

## VNS Therapy Epilepsy Literature

(Quarterly Update)

### Summary

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This reference list for VNS Therapy was collected from PubMed (supplemented with key book chapters, electronic comments, Google alerts, Table of Contents subscriptions, and EMBASE searches) through the date listed above using the search terms below. Each reference is listed only once, categorized under the most relevant heading/tab.

### What's New?

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- Letters to the Editor (comments, author replies) have been included with the original reference.
- New headings and subheadings have been added along with additional descriptors as to the content of each tab.
- All heading assignments have been confirmed, and some may have changed; however, the document is completely searchable, making specific articles easy to locate.
- [Foreign language articles] are now listed under the most relevant heading, unless there is no English abstract. References without an English abstract are listed together in one tab.

### Search Terms

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Search terms used for this update are:

1. ((vagal OR vagus) AND stimulation) NOT ((depression OR bipolar) AND ("mood" OR symptom))
2. (seizure AND (detection[title] OR prediction[title])) OR ((ictal OR seizure) AND (\*cardia[title] OR \*rhythmia[title] OR heart[title] OR cardiac[title]))
3. (((magnet OR magnetic OR electric\* OR deep) AND brain) OR (trigeminal OR cranial) AND nerve) AND (stimulation OR neurostimulation OR neuromodulation) AND (epilepsy OR seizure OR epileptic)

For more information, please contact Natasha Green ([Natasha.Green@cyberonics.com](mailto:Natasha.Green@cyberonics.com)),  
Sr. Manager, Market Development, Cyberonics Inc.

**AEDs (VNS and/versus...)**

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1. **Rocha L. Interaction between electrical modulation of the brain and pharmacotherapy to control pharmaco-resistant epilepsy. *Pharmacol Ther.* 2013;138(2):211-28.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23353099>  
**Abstract** In spite of the high success rate of many surgical procedures for pharmaco-resistant epilepsy, a substantial number of patients do not become seizure-free. Different strategies for electrical modulation of the brain such as Deep Brain Stimulation, Vagal Nerve Stimulation and Transcranial Magnetic Stimulation have gained considerable interest in the last decade as alternative therapies for patients with medically refractory epilepsy. Research into the mechanism of action of the strategies for electrical modulation of the brain suggests a crucial role of different molecules and channels such as glutamate, gamma-aminobutyric acid, adenosine, brain-derived neurotrophic factor, calcium channels, sodium channels as well as extracellular potassium. Electrical modulation of the brain may reduce the overexpression of P-glycoprotein, a drug efflux transporter that reduces the absorption of antiepileptic drugs. Electrical modulation of the brain induces long-term effects associated with beneficial consequences on clinical symptoms observed during the postictal state. In addition, electrical modulation of the brain might also promote the neurogenesis in subjects with pharmaco-resistant epilepsy in whom this process is decreased. Targeting the regulatory pathways in charge of the effects of electrical modulation of the brain is discussed as a means to improve its efficacy. Electrical modulation of the brain combined with pharmacotherapy may represent an innovative approach to avoid epileptogenesis, reduce seizure activity, induce beneficial effects during the postictal state, diminish the amount of antiepileptic drugs, and improve alertness, memory and mood in pharmaco-resistant epilepsy.
  
2. **Englot DJ. Vagus nerve stimulation versus "best drug therapy" in epilepsy patients who have failed best drug therapy. *Seizure.* 2013.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23506645>

3. **Ben-Menachem E, French JA. VNS Therapy versus the latest antiepileptic drug. *Epileptic Disord.* 2005;7 Suppl 1:S22-6.**

<http://www.ncbi.nlm.nih.gov/pubmed/16120490>

**Abstract** Pro AED: The central issue in medical decision-making is risk-benefit assessment. Surgery of any type is still considered to be a major undertaking. To warrant these risks, the patient has a right to expect that they have a greater chance of a good outcome with an invasive therapy than with a non-invasive one. The main question is when, if ever, this becomes the case when comparing implantation of a VNS Therapy System versus adding an antiepileptic drug (AED)? After the first drug? The second? After all AEDs have failed? To date, no randomized trial comparing the addition of an AED against vagus nerve stimulation (VNS Therapy) has been undertaken, although several are currently being contemplated. Without this information, it is more difficult to make a case for early implementation of VNS Therapy. Unfortunately, few data are available regarding the potential for patients to become seizure-free after implantation of a VNS Therapy System. Another issue is side effects. It is important to remember that VNS Therapy also produces adverse events, albeit very different in character than those associated with AEDs, to which physicians have become accustomed. These include cough, dyspnea, pharyngitis, voice alteration and sleep apnea. A less frequently discussed, potentially negative consequence of VNS Therapy relates to the ability to obtain imaging of the patient. Patients who have undergone VNS Therapy System implantation are not candidates for imaging of the chest, breast, or abdomen. A second issue is that imaging of the brain can only be performed with MRI scanners that meet certain requirements, and as MRI technology develops, scanners meeting these requirements may become harder to find. However, to summarize, VNS Therapy is an excellent and useful treatment choice. Fortunately, the choice between AEDs and VNS Therapy is not an "either/or" decision. Each has a role in the treatment of patients with epilepsy, and the advantages and disadvantages of each should be kept in perspective. Pro VNS Therapy: VNS Therapy is no longer a new treatment for patients with refractory epilepsy. The first implant was performed in 1988, and since then more than 30,000 patients have received this therapy. It is no longer considered an unusual or dangerous procedure, but it is still used almost exclusively for refractory epilepsy patients and it has not been generally accepted for use as a first line or even second line therapy. However, compared to the new AEDs, VNS Therapy has similar efficacy results in clinical trials and in many epilepsy syndromes and the long-term efficacy results are even more positive, with continued improvement in seizure reduction for up to two years. Two of the major reasons for not using VNS Therapy early are that it is a surgical procedure, and its safety during MRI procedures, especially with 3 Tesla, has not yet been elucidated. The safety profile of VNS Therapy is very favorable; the side effects being totally different from those seen with AEDs. The most important aspects are that there have been no pharmacological interactions, cognitive or sedative side effects reported, and it is safe for use in all age groups. Side effects are restricted to local irritation, hoarseness, coughing and, in a few cases, swallowing difficulties when the stimulator is on, but these tend to disappear with time. No idiosyncratic side effect has emerged during the 16 years of use. Compliance is guaranteed. The cost of the implantation of the VNS Therapy System, when spread out over 8 years (battery life), is actually less than the cost of using a new AED over an eight-year period, and real savings as regards hospital costs due to seizures can be expected.

4. **Labar DR. Antiepileptic drug use during the first 12 months of vagus nerve stimulation therapy: a registry study. *Neurology*. 2002;59(6 Suppl 4):S38-43.**

<http://www.ncbi.nlm.nih.gov/pubmed/12270967>

**Abstract** Understanding interrelationships between antiepileptic drugs (AEDs) and vagus nerve stimulation (VNS) therapy can guide research into epilepsy treatment. A constant cohort of patients with data available at baseline and 12 months were drawn from the VNS patient outcome registry and analyzed for changes in AEDs and seizure rates. Of the 1,407 patients, group 1 (n = 896) took fewer (n = 228) or the same (n = 668) AEDs at 12 months compared to baseline. Group 2 (n = 511) took additional (n = 251) or different (n = 260) AEDs. Median seizure rate reductions after 12 months of VNS therapy were 58% in group 1 and 55% in group 2. The number of and specific AEDs remained unchanged for 668 patients and dosages remained the same for 269 (40%) of these patients. The most commonly discontinued drugs were topiramate (n = 115), tiagabine (n = 78), carbamazepine (n = 62), lamotrigine (n = 56), and gabapentin (n = 52). Changes in seizure rates were not significantly different among patients who added levetiracetam (n = 151), zonisamide (n = 71), or oxcarbazepine (n = 46) to VNS. Changes in seizure rates were not significantly different among patients whose baseline AEDs were carbamazepine (n = 273), lamotrigine (n = 238), valproate (n = 201), topiramate (n = 190), or phenytoin (n = 151). Our results suggest the following: (a) patients commonly stay on the same AEDs during 12 months of treatment with VNS; (b) the registry cohort who had reduced AEDs by month 12 did not appear to experience any seizure exacerbation; and (c) no specific AED shows promise of unique additive antiepileptic effects in combination with VNS.

5. **Tatum WO, Johnson KD, Goff S, Ferreira JA, Vale FL. Vagus nerve stimulation and drug reduction. *Neurology*. 2001;56(4):561-3.**

<http://www.ncbi.nlm.nih.gov/pubmed/11261422>

<http://www.neurology.org/content/56/4/561.full.pdf>

**Abstract** The authors prospectively assessed drug reduction and patient satisfaction in 21 patients using vagus nerve stimulation (VNS) for refractory epilepsy and compared results to a case-matched control group with a mean follow-up of 13.2 months. Significant antiepileptic drug (AED) reduction occurred in 9/21 (42.9%) of VNS patients averaging 0.43 AED/patient, with dose reduction in four patients (19.0%). For 12/21 (57.1%) patients not reducing AED, dose reduction occurred in 6/21 (28.6%). Drug and dose reduction of AED is possible in patients using VNS for refractory epilepsy without loss of seizure control and with improved patient satisfaction.

**Animal Models (of VNS Efficacy in Epilepsy)**

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- 1. Pineda R, Beattie CE, Hall CW. Closed-loop neural stimulation for pentylenetetrazole-induced seizures in zebrafish. *Dis Model Mech.* 2013;6(1):64-71.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22822044>  
<http://dmm.biologists.org/content/6/1/64.full.pdf>

**Abstract** Neural stimulation can reduce the frequency of seizures in persons with epilepsy, but rates of seizure-free outcome are low. Vagus nerve stimulation prevents seizures by continuously activating noradrenergic projections from the brainstem to the cortex. Cortical norepinephrine then increases GABAergic transmission and increases seizure threshold. Another approach, responsive nervous stimulation, prevents seizures by reactively shocking the seizure onset zone in precise synchrony with seizure onset. The electrical shocks abort seizures before they can spread and manifest clinically. The goal of this study was to determine whether a hybrid platform in which brainstem activation triggered in response to impending seizure activity could prevent seizures. We chose the zebrafish as a model organism for this study because of its ability to recapitulate human disease, in conjunction with its innate capacity for tightly controlled high-throughput experimentation. We first set out to determine whether electrical stimulation of the zebrafish hindbrain could have an anticonvulsant effect. We found that pulse train electrical stimulation of the hindbrain significantly increased the latency to onset of pentylenetetrazole-induced seizures, and that this apparent anticonvulsant effect was blocked by noradrenergic antagonists, as is also the case with rodents and humans. We also found that the anticonvulsant effect of hindbrain stimulation could be potentiated by reactive triggering of single pulse electrical stimulations in response to impending seizure activity. Finally, we found that the rate of stimulation triggering was directly proportional to pentylenetetrazole concentration and that the stimulation rate was reduced by the anticonvulsant valproic acid and by larger stimulation currents. Taken as a whole, these results show that the anticonvulsant effect of brainstem activation can be efficiently utilized by reactive triggering, which suggests that alternative stimulation paradigms for vagus nerve stimulation might be useful. Moreover, our results show that the zebrafish epilepsy model can be used to advance our understanding of neural stimulation in the treatment of epilepsy.
  
- 2. Alexander GM, McNamara JO. Vagus nerve stimulation elevates seizure threshold in the kindling model. *Epilepsia.* 2012;53(11):2043-52.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22958190>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2012.03646.x/asset/j.1528-1167.2012.03646.x.pdf?v=1&t=hekhyk63&s=c06ba1225aac8677d7f7aadd61dda2ea07bfacd0>

**Abstract** PURPOSE: Vagus nerve stimulation (VNS) provides partial relief of medically refractory partial seizures in a subset of patients. The optimal pattern of stimulation and the mechanism of the antiseizure effects are uncertain. Establishing the efficacy of VNS in an animal model of epilepsy would provide an experimental preparation with which to address these questions. We sought to determine whether VNS exerted antiseizure effects in the kindling model of epilepsy. METHODS: We implanted adult rats with bipolar stimulating electrodes in the right amygdala and VNS devices around the left vagus nerve. Following induction of kindling, electrographic seizure threshold (EST) was determined by quantifying the amygdala electrode current required to evoke a seizure. Once stable ESTs were established, VNS devices were programmed to deliver U.S. Food and Drug Administration (FDA)-approved, clinically used (standard) or an experimental (microburst) pattern of stimulation of variable intensity. VNS devices were programmed identically in control animals except that no current was delivered. EST was examined at 60 min and 1 week in the control and vagus nerve stimulated groups. KEY FINDINGS: Significant reductions of EST values were detected in control animals when tested both 60 min and 1 week following device programming. Both clinically used and experimental patterns of VNS prevented the reduction of EST evident in control animals when tested either 60 min or 1 week after device programming. SIGNIFICANCE: These findings establish an experimental preparation with which to elucidate the antiseizure mechanisms of VNS and to determine patterns of VNS most effective at elevating seizure threshold.

3. **Aalbers M, Vles J, Klinkenberg S, Hoogland G, Majoie M, Rijkers K. Animal models for vagus nerve stimulation in epilepsy. *Exp Neurol.* 2011;230(2):167-75.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21565191>  
**Abstract** Vagus nerve stimulation (VNS) is a moderately effective adjunctive treatment for patients suffering from medically refractory epilepsy and is explored as a treatment option for several other disorders. The present review provides a critical appraisal of the studies on VNS in animal models of seizures and epilepsy. So far, these studies mostly applied short-term VNS in seizure models, demonstrating that VNS can suppress and prevent seizures and affect epileptogenesis. However, the mechanism of action is still largely unknown. Moreover, studies with a clinically more relevant setup where VNS is chronically applied in epilepsy models are scarce. Future directions for research and the application of this technology in animal models of epilepsy are discussed.
4. **De Herdt V, De Waele J, Raedt R, Wyckhuys T, El Tahry R, Vonck K, et al. Modulation of seizure threshold by vagus nerve stimulation in an animal model for motor seizures. *Acta Neurol Scand.* 2010;121(4):271-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20003088>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0404.2009.01223.x/abstract>  
**Abstract** OBJECTIVE: The precise mechanism of action of vagus nerve stimulation (VNS) in suppressing epileptic seizures remains to be elucidated. This study investigates whether VNS modulates cortical excitability by determining the threshold for provoking focal motor seizures by cortical electrical stimulation before and after VNS. MATERIAL AND METHODS: Male Wistar rats (n = 8) were implanted with a cuff-electrode around the left vagus nerve and with stimulation electrodes placed bilaterally on the rat motor cortex. Motor seizure threshold (MST) was assessed for each rat before and immediately after 1 h of VNS with standard stimulation parameters, during two to three sessions on different days. RESULTS: An overall significant increase of the MST was observed following 1 h of VNS compared to the baseline value (1420 microA and 1072 microA, respectively; P < 0.01). The effect was reproducible over time with an increase in MST in each experimental session. CONCLUSIONS: VNS significantly increases the MST in a cortical stimulation model for motor seizures. These data indicate that VNS is capable of modulating cortical excitability.
5. **Rijkers K, Aalbers M, Hoogland G, van Winden L, Vles J, Steinbusch H, et al. Acute seizure-suppressing effect of vagus nerve stimulation in the amygdala kindled rat. *Brain Res.* 2010;1319:155-63.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20079342>  
**Abstract** PURPOSE: Vagus nerve stimulation (VNS) is a moderately effective anti-epileptic treatment. Clinically relevant animal models that are suitable to study the mechanism of action of VNS are not available. The aim of the current study was to develop a clinically relevant animal model for VNS-treated epilepsy that can be used to study the mechanism of action of VNS. METHODS: The anticonvulsive effect of VNS was studied in fully kindled rats by measuring behavioral and electrophysiological parameters. Afferent vagus nerve activation was confirmed by quantifying nNOS immunoreactive cells in the nucleus of the solitary tract (NTS). RESULTS: VNS rats had more nNOS immunoreactive cells/mm(2) in the NTS than shams. VNS induced a >25% decrease in stage 5 duration (S5D) in 32% of rats. Prior to VNS this type of responders suffered from seizures with a longer total seizure duration (TSD) than non-responders. In 21% of rats VNS resulted in a >25% decrease in TSD. This type of responders had a shorter TSD prior to VNS than non-responders. In 29% of rats VNS resulted in >200% increase in stage 5 latency (S5L). This type of responders had higher kindling rates than non-responders. CONCLUSION: The VNS-treated kindled rat is a clinically relevant animal model because it is a chronic epilepsy model that responds to VNS with effects that are comparable to the effects of VNS in epilepsy patients. In addition, this study demonstrates that VNS-treated kindled rats can be used to study the mode of action of VNS using immunohistochemical techniques.

6. **Sahin D, Ilbay G, Imal M, Bozdogan O, Ates N. Vagus nerve stimulation suppresses generalized seizure activity and seizure-triggered postictal cardiac rhythm changes in rats. *Physiol Res.* 2009;58(3):345-50.** <http://www.ncbi.nlm.nih.gov/pubmed/18657001>

**Abstract** In the present study, we investigated the effects of vagus nerve stimulation (VNS), a proposed treatment for patients with intractable epilepsy, on cardiac rhythm following seizures induced by pentylenetetrazole (PTZ) in Wistar rats. After a baseline recording of electroencephalogram (EEG), electrocardiogram (ECG) and blood pressure (BP), rats in the first group received a single convulsive dose of PTZ (70 mg/kg) (Group 1). In the other two groups, the Wistar rats were implanted with a cuff electrode on the left cervical vagus nerve. One day after surgery, rats in the second group were treated with VNS (Group 2), whereas rats in the third group were connected to the stimulator but did not receive VNS (Group 3). Ten minutes after VNS onset, 70 mg/kg dose of PTZ was injected. EEG, ECG and BP were continuously recorded during post-injection period. Seizure severity was scored behaviorally. Then, baseline, ictal and postictal periods were analyzed for cardiac rhythms, seizure severity and blood pressure variability. PTZ treatment induced tonic-clonic seizure activity in all animals of Group 1 and Group 3. In these groups a marked increase of mean arterial blood pressure (MABP) but a significant decrease in heart rate and PP interval fluctuations was observed at postictal period. However, in the VNS-treated group the seizure scores and cardiac parameter returned to the baseline level. Present results emphasize that VNS effectively reduces seizure severity and suppress the seizure-induced cardiac rhythm changes.

7. **Yang HJ, Peng KR, Hu SJ, Liu Y. Inhibiting effect of vagal nerve stimulation to seizures in epileptic process of rats. *Neurosci Bull.* 2007;23(6):336-40.**

<http://www.ncbi.nlm.nih.gov/pubmed/18064063>  
<http://link.springer.com/article/10.1007%2Fs12264-007-0050-x>

**Abstract** **OBJECTIVE:** Our previous work suggested that sensitivity of hippocampal neurons is changed in process of epileptic activities, and closely parallel to the dynamic characteristic of epileptic activity of the neurons. This study investigated the sensitivity of epileptic brain to vagal nerve stimulation (VNS) in epileptic process. **METHODS:** Epileptic model was evoked by penicillin. Left vagal nerves were stimulated to inhibit the seizures induced by penicillin. The electrocorticography (ECoG) and electromyography (EMG) were recorded to analyze inhibiting effect of VNS in epileptic process. **RESULTS:** It was found that VNS could inhibit the seizures caused by penicillin, and the inhibiting effect of VNS to seizures increased as the vagal nerve stimulating time prolonged. It was also found that the inhibiting effect of VNS to seizures decreased in epileptic process. **CONCLUSION:** The results suggested that the sensitivity of epileptic brain to VNS was different in epileptic process. The inhibiting effect of VNS to seizure decreased as the development of seizures.

8. **Dedeurwaerdere S, Vonck K, De Herdt V, Waterschoot L, De Smedt T, Raedt R, et al. Neuromodulation with levetiracetam and vagus nerve stimulation in experimental animal models of epilepsy. *Acta Neurol Belg.* 2006;106(2):91-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/16898260>

**Abstract** Epilepsy is a neurological disorder consisting of recurrent seizures, resulting from excessive, uncontrolled electrical activity in the brain. Epilepsy treatment is successful in the majority of the cases; however, still one third of the epilepsy patients are refractory to treatment. Besides the ongoing research on the efficacy of antiepileptic treatments in suppressing seizures (anti-seizure effect), we want to seek for therapies that can lead to plastic, neuromodulatory changes in the epileptic network. Neuropharmacological therapy with levetiracetam (LEV) and vagus nerve stimulation (VNS) are two novel treatments for refractory epilepsy. LEV acts rapidly on seizures in both animal models and humans. In addition, preclinical studies suggest that LEV may have antiepileptogenic and neuroprotective effects, with the potential to slow or arrest disease progression. VNS as well can have an immediate effect on seizures in epilepsy models and patients with, in addition, a cumulative effect after prolonged treatment. Studies in man are hampered by the heterogeneity of patient populations and the difficulty to study therapy-related effects in a systematic way. Therefore, investigation was performed utilizing two rodent models mimicking epilepsy in humans. Genetic absence epilepsy rats from Strasbourg (GAERS) have inborn absence epilepsy and Fast rats have a genetically determined sensitivity for electrical amygdala kindling, which is an excellent model of temporal lobe epilepsy. Our findings support the hypothesis that treatment with LEV and VNS can be considered as neuromodulatory: changes are induced in central nervous system function or organization as a result of influencing and initiating neurophysiological signals.

9. **Dedeurwaerdere S, Vonck K, Van Hese P, Wadman W, Boon P. The acute and chronic effect of vagus nerve stimulation in genetic absence epilepsy rats from Strasbourg (GAERS). *Epilepsia.* 2005;46 Suppl 5:94-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/15987260>

**Abstract** **PURPOSE:** The aim of this study was to evaluate the efficacy of acute and chronic vagus nerve stimulation (VNS) in genetic absence epilepsy rats from Strasbourg (GAERS). This is a validated model for absence epilepsy, characterized by frequent spontaneous absences concomitant with spike and wave discharges (SWD) on the EEG. Although absences are a benign form of seizures, it is conceptually important to investigate the efficacy of VNS in a controlled study by using this chronic epilepsy model. **METHODS:** Both control and stimulated GAERS were implanted with five epidural EEG electrodes and a stimulation electrode around the left vagus nerve. In the first experiment, VNS was given when SWD occurred in the EEG; this was repeated the next day. A randomized crossover design ( $n = 8$ ) was used. In the chronic experiment, GAERS underwent EEG monitoring during a first baseline week. During the second week, the treated group ( $n = 18$ ) received VNS; controls ( $n = 13$ ), on the other hand, only underwent EEG recordings. **RESULTS:** On day 1 of the acute VNS experiment, the mean duration of the SWD when VNS was applied was higher than in baseline conditions ( $p < 0.05$ ). However, on day 2, there was no difference in mean duration of the SWD. In the chronic VNS experiment, no statistically significant differences were found between control and stimulated GAERS. **CONCLUSIONS:** Acute VNS applied shortly after the onset of SWD prolonged the mean duration of SWD in GAERS at least during the first day of VNS. Chronic stimulation hardly affected SWD in GAERS.

10. **Takaya M, Terry WJ, Naritoku DK. Vagus nerve stimulation induces a sustained anticonvulsant effect. *Epilepsia*. 1996;37(11):1111-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/8917063>  
**Abstract** PURPOSE: Stimulation of the vagus nerve can effectively abort several types of experimentally induced seizures in animals when administered near the time of seizure onset. Indirect evidence from human trials and animal studies suggests that the anticonvulsant effects of vagus nerve stimulation (VNS) extend beyond the duration of stimulation. We used the pentylenetetrazol model to determine whether VNS exerts a persistent anticonvulsant effect. METHODS: VNS (1 mA, 30 Hz, 500 microseconds pulse width) was administered continuously for 0.1, or 60 min, or intermittently (30 s on, 5 min off) for 60 min, to awake and freely moving animals. After the end of stimulation, pentylenetetrazol (50 mg/kg i.p.) was administered to induce seizures. Time-course studies were also performed, consisting of 60 min of VNS followed by pentylenetetrazol injection after 0, 3-, 5-, and 10-min intervals. RESULTS: The greatest anticonvulsant effect occurred after 60 min of continuous VNS, which prevented convulsions in four of 12 rats and reduced significantly seizure duration, the total number of seizures, and number of tonic seizures. Intermittent VNS was less effective than continuous stimulation for 60 min, but more effective than that for 1 min. The anticonvulsant effect declined in a time-dependent fashion after discontinuation of VNS, with return to nonstimulated control values by 10 min. CONCLUSIONS: The results of this study verify a persistent VNS-induced anticonvulsant effect and indicate that its efficacy is dependent on the cumulative stimulus duration.
11. **McLachlan RS. Suppression of interictal spikes and seizures by stimulation of the vagus nerve. *Epilepsia*. 1993;34(5):918-23.**  
<http://www.ncbi.nlm.nih.gov/pubmed/8404747>  
**Abstract** The effects of electrical stimulation of the vagus nerve, a proposed treatment for patients with intractable epilepsy, on focal interictal spikes produced by penicillin and EEG secondarily generalized seizures induced by pentylenetetrazol were assessed in rats. Interictal spike frequency was reduced by 33% during 20 s of stimulation ( $p < 0.001$ ) and remained low for  $< \text{or} = 3$  min. Amplitude of residual spikes was also decreased. Cardiac and respiratory rates were suppressed. Cooling the nerve proximal to the point of stimulation abolished the EEG and respiratory effects. A similar reduction in spike frequency of 39% was obtained by heating the animals' tail ( $p < 0.01$ ). Vagal stimulation at onset of seizures reduced mean seizure duration from 30.2  $\pm$  15.7 s without stimulation to 5.0  $\pm$  1.8 s ( $p < 0.01$ ). Only the EEG equivalent of the clonic phase of the seizure was affected. These findings suggest that vagus nerve stimulation can be a potent but nonspecific method to reduce cortical epileptiform activity, probably through an indirect effect mediated by the reticular activating system.
12. **Zabara J. Inhibition of experimental seizures in canines by repetitive vagal stimulation. *Epilepsia*. 1992;33(6):1005-12.**  
<http://www.ncbi.nlm.nih.gov/pubmed/1464256>  
**Abstract** Repetitive electrical stimulation of the canine cervical vagus nerve interrupts or abolishes motor seizures induced by strychnine and tremors induced by pentylenetetrazol (PTZ). Tremors were defined as rhythmic alternating contractions of opposing muscle groups, exerting much less force than seizure contractions. Seizures were induced by injection boluses of strychnine or PTZ at 1- to 4-min intervals until sustained muscle activity was observed electromyographically (EMG). Vagal stimulation terminated seizures in 0.5-5 s. There were prolonged periods with no spontaneous EMG activity after stimulation. The period of protection was approximately four times the stimulation period. The antiseizure actions of vagal stimulation were not altered by transection of the vagus distal to the stimulating electrode. Optimal stimulus parameters were estimated: strength, approximately 20 V (electrode resistance 1-5  $\Omega$ ); frequency 20-30 Hz; duration, approximately 0.2 ms. These data suggest that the antiseizure effects derive from stimulation of small-diameter afferent unmyelinated fibers in the vagus nerve. These results may form the basis of a new therapeutic approach to epilepsy.

13. **Woodbury JW, Woodbury DM. Vagal stimulation reduces the severity of maximal electroshock seizures in intact rats: use of a cuff electrode for stimulating and recording. *Pacing Clin Electrophysiol.* 1991;14(1):94-107.**

<http://www.ncbi.nlm.nih.gov/pubmed/1705342>

**Abstract** J. Zabara showed that repetitive vagal stimulation (VS) prevents or ameliorates convulsive seizures in dogs. We have studied the effects of VS on maximal electroshock seizures (MES) in intact rats: (1) A 5 wire cuff electrode was developed for stimulating and recording from the vagus. Compound action potentials (AP) were recorded and strength-duration curves obtained for A and C fibers. There is a monotonic relationship with a negative slope between heart rate (HR) and AP amplitude. C fibers remain excitable for 25 days after cuff implant. (2) The anticonvulsant efficacy of VS is directly related to the fraction of vagal C fibers stimulated and the frequency of stimulation. (3) The anticonvulsant efficacy of VS has been established using two rat models of human epilepsy. VS abolishes the extensor component of the tonic phase of a MES and shortens or prevents tonic seizures induced by pentylentetrazol (PTZ). (4) VS appears to act via release of large quantities of the inhibitory mediators GABA and glycine throughout large volumes of the brain. (5) It is rational to test VS in man as a treatment for intractable seizures.

14. **Woodbury DM, Woodbury JW. Effects of vagal stimulation on experimentally induced seizures in rats. *Epilepsia.* 1990;31 Suppl 2:S7-19.**

<http://www.ncbi.nlm.nih.gov/pubmed/2226368>

**Abstract** Repetitive stimulation of the vagus nerve inhibits chemically induced seizures in dogs. We report here the results and conclusions from studies designed to answer some of the immediate questions raised by this finding. (1) Maximal stimulation of vagal C fibers at frequencies greater than 4 Hz prevents or reduces chemically and electrically induced seizures in young male rats. (2) Antiepileptic potency is directly related to the fraction of vagal C fibers stimulated. (3) Vagal stimulation shortens but does not shut down a chemical seizure once it has begun. (4) In rats, optimal stimulus frequency is approximately 10-20 Hz; duration of stimulus, 0.5-1 ms; and stimulus strength, 0.2-0.5 mA/mm<sup>2</sup> of nerve cross-section. These results, when taken together with similar results obtained from dogs, monkeys, and humans, strongly suggest that periodic stimulation of the vagus nerve using appropriate stimulation parameters is a powerful method for preventing seizures. The data from the literature suggest that the antiepileptic actions of vagal stimulation are largely mediated by widespread release of GABA and glycine in the brainstem and cerebral cortex. The probable pathway is via projections from the nucleus of the solitary tract to the reticular formation and thence by diffuse projections to the cortex and other areas. Intermittent vagal stimulation has the potentiality of reducing the number and/or the intensity of seizures in patients with intractable epilepsy. These results indicate that feasibility studies in humans should be continued and expanded.

15. **Lockard JS, Congdon WC, DuCharme LL. Feasibility and safety of vagal stimulation in monkey model. *Epilepsia*. 1990;31 Suppl 2:S20-6.**

<http://www.ncbi.nlm.nih.gov/pubmed/2226362>

**Abstract** The feasibility, safety, and preliminary effects of chronic vagal stimulation were studied in an aluminum monkey model. Pilot studies to perfect the equipment, determine stimulation thresholds, and insure the comfort and safety of the animals preceded this study. Four monkeys were equipped with an indwelling, 2-electrode cuff (titanium bands spaced 7 mm apart; silicone encased; 1.5 cm total length) in contact around the right vagus nerve; avoidance of the cardiac branch was confirmed by electrocardiograms. After postsurgical recovery, the intact and awake animals received constant-current stimulation (5 mA; 83 Hz, 143 Hz, or 50-250 Hz randomly; 0.5-ms pulse width) at the onset of every spontaneous seizure for the duration of the seizure or every 3 h for 40 s if stimulation had not occurred in the preceding hour. Stimulation periods of 2-6 weeks, with differing levels of stimulation, were preceded and followed by at least a 2-week baseline period of no stimulation. During the stimulation periods, the seizure rate decreased to zero in two monkeys and the interseizure intervals became invariable in the remaining two monkeys. These effects carried over temporarily into the poststimulation baseline periods. Vagal stimulation had no consistent effects on seizure severity or EEG interictal spikes. Histological studies of six vagus nerves were unable to separate electrode cuff damage from any direct effects stimulation may have had on the nerves. Although it appears that chronic vagal stimulation is feasible and that epileptogenic processes are influenced, the safety and efficacy of the procedure are still in question.

**Autism and Landu-Kleffner Syndrome (Epilepsy/VNS in...)**

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1. **Roberts JE, Tonnsen B, Robinson A, Shinkareva SV. Heart activity and autistic behavior in infants and toddlers with fragile X syndrome. *Am J Intellect Dev Disabil.* 2012;117(2):90-102.**

<http://www.ncbi.nlm.nih.gov/pubmed/22515825>

<http://www.aaidjournals.org/doi/abs/10.1352/1944-7558-117.2.90>

**Abstract** The present study contrasted physiological arousal in infants and toddlers with fragile X syndrome to typically developing control participants and examined physiological predictors early in development to autism severity later in development in fragile X syndrome. Thirty-one males with fragile X syndrome (ages 8-40 months) and 25 age-matched control participants were included. The group with fragile X syndrome showed shorter interbeat intervals (IBIs), lower vagal tone (VT), and less modulation of IBI. Data suggested a nonlinear effect with IBI and autistic behavior; however, a linear effect with VT and autistic behavior emerged. These findings suggest that atypical physiological arousal emerges within the first year and predicts severity of autistic behavior in fragile X syndrome. These relationships are complex and dynamic, likely reflecting endogenous factors assumed to reflect atypical brain function secondary to reduced fragile X mental retardation protein. This research has important implications for the early identification and treatment of autistic behaviors in young children with fragile X syndrome.

2. **Kaartinen M, Puura K, Makela T, Rannisto M, Lemponen R, Helminen M, et al. Autonomic arousal to direct gaze correlates with social impairments among children with ASD. *J Autism Dev Disord.* 2012;42(9):1917-27; comment *Auton Neurosci.* 2012;171(1-2):4-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/22215435>

**Abstract** The present study investigated whether autonomic arousal to direct gaze is related to social impairments among children with autism spectrum disorder (ASD). Arousal was measured through skin conductance responses (SCR) while the participants (15 children with ASD and 16 control children) viewed a live face of another person. Impairments in social skills was assessed with the Developmental, Dimensional and Diagnostic Interview. The level of arousal enhancement to direct gaze in comparison to arousal to faces with averted gaze or closed eyes was positively associated with impairments in social skills (use of language and other social communication skills and use of gesture and non-verbal play) among children with ASD. There was no similar association among children without ASD. The role of arousal-related factors in influencing eye contact behaviour in ASD is discussed.

3. **Sansa G, Carlson C, Doyle W, Weiner HL, Bluvstein J, Barr W, et al. Medically refractory epilepsy in autism. *Epilepsia*. 2011;52(6):1071-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21671922>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2011.03069.x/asset/j.1528-1167.2011.03069.x.pdf?v=1&t=hekiixn&s=b7cb04a02e0f1b979a5e0ed803261133068ef5e3>  
**Abstract** PURPOSE: Epilepsy and electroencephalographic abnormalities are frequent in idiopathic autism, but there is little information regarding treatment-resistant epilepsy (TRE) in this group. We sought to define the clinical and electrophysiologic characteristics and treatment outcomes in these patients. METHODS: We retrospectively reviewed clinical and laboratory data of patients with idiopathic autism evaluated at NYU Epilepsy Center during a 20-year period. KEY FINDINGS: One hundred twenty-seven patients had idiopathic autism and at least one epileptic seizure; 33.9% had TRE and 27.5% were seizure free. The remaining 38.6% of patients had infrequent seizures or insufficient data to categorize. Patients with TRE had a significantly earlier onset of seizures than seizure-free patients, and a trend for more developmental regression and motor and language delays. Three patients had surgical resection (two had limited improvement and one had no improvement) and one had an anterior callosotomy (no improvement). Vagus nerve stimulator (VNS) implantation provided limited improvement (2 patients) and no improvement (7). SIGNIFICANCE: This study found that TRE is common in idiopathic autism and more common with early age of seizure onset. Relatively few patients underwent surgical resection due to multifocal partial epilepsy, comorbid generalized epilepsy, or limited impact of ongoing partial seizures given other problems related to autism. Our small sample suggests that surgical and VNS outcomes in this group are less favorable than in other TRE populations.
4. **Kinsbourne M. The Immune system's moderating response to inflammation relieves autistic behavior: response to Peter Good. *Neuropsychol Rev*. 2011;21(1):68-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21240676>  
[http://download.springer.com/static/pdf/204/art%253A10.1007%252Fs11065-011-9158-x.pdf?auth66=1365201744\\_1fc75a6b4f18d97c2393262cf9defbdf&ext=.pdf](http://download.springer.com/static/pdf/204/art%253A10.1007%252Fs11065-011-9158-x.pdf?auth66=1365201744_1fc75a6b4f18d97c2393262cf9defbdf&ext=.pdf)
5. **Levy ML, Levy KM, Hoff D, Amar AP, Park MS, Conklin JM, et al. Vagus nerve stimulation therapy in patients with autism spectrum disorder and intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. *J Neurosurg Pediatr*. 2010;5(6):595-602.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20515333>  
**Abstract** OBJECT: The purpose of this study was to determine the effectiveness of vagus nerve stimulation (VNS) therapy on quality-of-life (QOL) variables among patients with both autism spectrum disorder (ASD) and persistent or recurrent intractable epilepsy. METHODS: Data were obtained from the VNS therapy patient outcome registry, which was established after US FDA approval of the VNS device in 1997 as a means of capturing open-label clinical data outside of protocol. The integrity of the systems for collecting and processing registry data was authenticated by an independent auditing agency. The effect of potential selection bias, however, remains uncertain. RESULTS: Two cohorts were compared: 1) patients with epilepsy but without ASD (non-ASD [NASD] Group, 315 patients) who were being tracked in the registry (this cohort, which was controlled for age, included patients 20 years of age or younger); and 2) patients with a diagnosis of ASD who underwent implantation of the VNS device (ASD Group, 77 patients). Differences between the ASD and NASD groups were noted in the following categories: sex (male preponderance in ASD); normal imaging results (MR imaging results normal in ASD); depression (less common in ASD); behavioral problems (more common in ASD); neurological deficit (more common in ASD); mental retardation (more common in ASD); and developmental delay. The only QOL difference between the ASD and NASD groups was noted in mood at 12 months postimplant (mood was improved in ASD) ( $p = 0.04$ ). There were no other differences in the QOL variables. CONCLUSIONS: Patients with ASD and intractable epilepsy respond as favorably as all other patients receiving VNS therapy. In addition, they may experience a number of QOL improvements, some of which exceed those classically observed following placement of a VNS device.

**CBSD (Physiological basis/Devices based on...)**

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1. **Van de Vel A, Cuppens K, Bonroy B, Milosevic M, Jansen K, Van Huffel S, et al. Non-EEG seizure-detection systems and potential SUDEP prevention: State of the art. *Seizure*. 2013. <http://www.ncbi.nlm.nih.gov/pubmed/23506646>**

**Abstract** PURPOSE: There is a need for a seizure-detection system that can be used long-term and in home situations for early intervention and prevention of seizure related side effects including SUDEP (sudden unexpected death in epileptic patients). The gold standard for monitoring epileptic seizures involves video/EEG (electro-encephalography), which is uncomfortable for the patient, as EEG electrodes are attached to the scalp. EEG analysis is also labour-intensive and has yet to be automated and adapted for real-time monitoring. It is therefore usually performed in a hospital setting, for a few days at the most. The goal of this article is to provide an overview of body signals that can be measured, along with corresponding methods, state-of-art research, and commercially available systems, as well as to stress the importance of a good detection system. METHOD: Narrative literature review. RESULTS: A range of body signals can be monitored for the purpose of seizure detection. It is particularly interesting to include monitoring of autonomic dysfunction, as this may be an important patho-physiological mechanism of SUDEP, and of movement, as many seizures have a motor component. CONCLUSION: The most effective seizure detection systems are multimodal. Such systems should also be comfortable and low-power. The body signals and modalities on which a system is based should take account of the user's seizure types and personal preferences.
2. **Conradsen I, Beniczky S, Wolf P, Kjaer TW, Sams T, Sorensen HB. Automatic multi-modal intelligent seizure acquisition (MISA) system for detection of motor seizures from electromyographic data and motion data. *Comput Methods Programs Biomed*. 2012;107(2):97-110. <http://www.ncbi.nlm.nih.gov/pubmed/21724291>**

**Abstract** The objective is to develop a non-invasive automatic method for detection of epileptic seizures with motor manifestations. Ten healthy subjects who simulated seizures and one patient participated in the study. Surface electromyography (sEMG) and motion sensor features were extracted as energy measures of reconstructed sub-bands from the discrete wavelet transformation (DWT) and the wavelet packet transformation (WPT). Based on the extracted features all data segments were classified using a support vector machine (SVM) algorithm as simulated seizure or normal activity. A case study of the seizure from the patient showed that the simulated seizures were visually similar to the epileptic one. The multi-modal intelligent seizure acquisition (MISA) system showed high sensitivity, short detection latency and low false detection rate. The results showed superiority of the multi-modal detection system compared to the uni-modal one. The presented system has a promising potential for seizure detection based on multi-modal data.
3. **Conradsen I, Beniczky S, Wolf P, Jennum P, Sorensen HB. Evaluation of novel algorithm embedded in a wearable sEMG device for seizure detection. *Conf Proc IEEE Eng Med Biol Soc*. 2012;2012:2048-51. <http://www.ncbi.nlm.nih.gov/pubmed/23366322> <http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6346361>**

**Abstract** We implemented a modified version of a previously published algorithm for detection of generalized tonic-clonic seizures into a prototype wireless surface electromyography (sEMG) recording device. The method was modified to require minimum computational load, and two parameters were trained on prior sEMG data recorded with the device. Along with the normal sEMG recording, the device is able to set an alarm whenever the implemented algorithm detects a seizure. These alarms are annotated in the data file along with the signal. The device was tested at the Epilepsy Monitoring Unit (EMU) at the Danish Epilepsy Center. Five patients were included in the study and two of them had generalized tonic-clonic seizures. All patients were monitored for 2-5 days. A double-blind study was made on the five patients. The overall result showed that the device detected four of seven seizures and had a false detection rate of 0.003/h or one in twelve days.

- 4. Reinsberger C, Perez DL, Murphy MM, Dworetzky BA. Pre- and postictal, not ictal, heart rate distinguishes complex partial and psychogenic nonepileptic seizures. *Epilepsy Behav.* 2012;23(1):68-70. <http://www.ncbi.nlm.nih.gov/pubmed/22100065>**  
**Abstract** Psychogenic nonepileptic seizures (PNES) remain poorly understood neurobiologically. Previously reported work suggests that adjunct ictal heart rates (HRs) may differentiate PNES from complex partial seizures (CPS). We retrospectively reviewed and compared preictal, ictal, and postictal HR differences in patients with PNES (n=42) and CPS controls (n=46) electively admitted for video/EEG monitoring to further characterize PNES autonomic patterns. Statistically significant preictal HR increases (P=0.006) and postictal (P=0.015) HR reductions normalized to baseline were identified in subjects with PNES compared with CPS controls. Ictal HRs were not found to differentiate between PNES and CPS events. This pattern of pre-event HR increases and postevent HR decreases in patients with PNES compared with those with CPS suggests frontolimbic neural circuit dysfunction and merits further exploration.
- 5. Conradsen I, Beniczky S, Hoppe K, Wolf P, Sorensen HB. Automated algorithm for generalized tonic-clonic epileptic seizure onset detection based on sEMG zero-crossing rate. *IEEE Trans Biomed Eng.* 2012;59(2):579-85. <http://www.ncbi.nlm.nih.gov/pubmed/22156944> <http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6095334>**  
**Abstract** Patients are not able to call for help during a generalized tonic-clonic epileptic seizure. Our objective was to develop a robust generic algorithm for automatic detection of tonic-clonic seizures, based on surface electromyography (sEMG) signals suitable for a portable device. Twenty-two seizures were analyzed from 11 consecutive patients. Our method is based on a high-pass filtering with a cutoff at 150 Hz, and monitoring a count of zero crossings with a hysteresis of +/-50 muV . Based on data from one sEMG electrode (on the deltoid muscle), we achieved a sensitivity of 100% with a mean detection latency of 13.7 s, while the rate of false detection was limited to 1 false alarm per 24 h. The overall performance of the presented generic algorithm is adequate for clinical implementation.
- 6. Yerdelen D, Erol T, Koc F. Heart rate recovery in epilepsy. *Int J Neurosci.* 2012;122(9):515-8. <http://www.ncbi.nlm.nih.gov/pubmed/22510003> <http://informahealthcare.com/doi/abs/10.3109/00207454.2012.683218>**  
**Abstract** Autonomic manifestations regarding cardiac function in epilepsy are not rare and are being recognized with increasing frequency. The aim of this study was to assess autonomic function by measuring heart rate recovery (HRR), an index of vagal activity, in patients with epilepsy who were not taking any medication. Fourteen patients (eight with primary generalized epilepsy, four with secondary generalized epilepsy, and two with complex partial epilepsy) and 14 control subjects underwent exercise tolerance tests according to the modified Bruce protocol. HRR at 1 and 3 min (HRR1 and HRR3) were calculated. HRR1 and HRR3 were increased in patients with epilepsy. These results suggest increased parasympathetic function in epilepsy and support results of previous studies indicating autonomic dysfunction in epilepsy.

7. **Conradsen I, Beniczky S, Hoppe K, Wolf P, Sams T, Sorensen HB. Seizure onset detection based on one sEMG channel. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:7715-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22256126>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6091901>  
**Abstract** We present a new method to detect seizure onsets of tonic-clonic epileptic seizures based on surface electromyography (sEMG) data. The proposed method is generic and based on a single channel making it ideal for a small detection or monitoring device. The sEMG signal is high-pass filtered with a Butterworth filter with a cut-off frequency of 150 Hz. The number of zero-crossings with a hysteresis of +/- 50 muV is the only feature extracted. The number of counts in a window of 1 second and the number of windows to make a detection is tested with a leave-one-out method. On 6 patients the method performs with a sensitivity of 100%, a median latency of 7.6 seconds and a median false detection rate of 0.04/h.
8. **Ponnusamy A, Marques JL, Reuber M. Heart rate variability measures as biomarkers in patients with psychogenic nonepileptic seizures: potential and limitations. *Epilepsy Behav.* 2011;22(4):685-91.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21975299>  
**Abstract** Heart rate variability (HRV) metrics provide reliable information about the functioning of the autonomic nervous system (ANS) and have been discussed as biomarkers in anxiety and personality disorders. We wanted to explore the potential of various HRV metrics (VLF, LF, HF, SDNN, RMSSD, cardiovagal index, cardiosympathetic index, approximate entropy) as biomarkers in patients with psychogenic nonepileptic seizures (PNES). HRV parameters were extracted from 3-minute resting single-lead ECGs of 129 subjects (52 with PNES, 42 with refractory epilepsy and 35 age-matched healthy controls). Compared with healthy controls, both patient groups had reduced HRV (all measures P<0.03). Binary logistic regression analyses yielded significant models differentiating between healthy controls and patients with PNES or patients with epilepsy (correctly classifying 86.2 and 93.5% of cases, respectively), but not between patients with PNES and those with epilepsy. Interictal resting parasympathetic activity and sympathetic activity differ between healthy controls and patients with PNES or those with epilepsy. However, resting HRV measures do not differentiate between patients with PNES and those with epilepsy.
9. **Panchani J, Adjei P, Henneberger C, Scott CA, Thompson AJ, Diehl B, et al. Asymmetric hemispheric representation of periictal heart rate modulation is individually lateralised. *Epileptic Disord.* 2011;13(2):172-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21561842>  
**Abstract** Asymmetric cortical representation of cardiac function is a matter of debate and large inter-individual variability of cortical autonomic networks and different study designs may contribute to this controversy. Lateralised seizure activity in individual patients may provide valuable insights into cortical regulation of cardiac function. We report two patients with focal epilepsy who had seizures arising from both hemispheres. In Patient 1, heart rate increased over two-fold with seizures arising from the right hemisphere, whereas heart rate increased invariably less with seizures arising from the left hemisphere. In Patient 2, heart rate increased 1.3 fold or less with seizures arising from the left hemisphere, whereas a seizure with right-sided onset was followed by bradycardia and asystole. Our findings support the notion that effects on autonomic function are lateralised, although lateralisation varies from patient to patient. This may partially explain the difficulty in determining cortical representation of cardiac autonomic function.

10. **Harreby KR, Sevcencu C, Struijk JJ. Ictal and peri-ictal changes in cervical vagus nerve activity associated with cardiac effects. *Med Biol Eng Comput.* 2011;49(9):1025-33.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21544670>  
<http://link.springer.com/article/10.1007%2Fs11517-011-0782-7>  
**Abstract** The vagus nerves convey both afferent and efferent information about autonomic activity related to cardiovascular functions. Those functions have been shown to change due to epileptic seizures, which suggests that ictal events might be detected via the vagus electroneurogram (VENG). In this study, we characterize the association of ictal and peri-ictal VENG with cardiac parameters. The electrocorticogram (ECoG), electrocardiogram, and the VENG were recorded in anesthetized rats, which were intravenously infused with either a pentylenetetrazole (PTZ) solution (PTZ-lot, n = 11) or saline (control-lot, n = 6). Control animals were subsequently vagotomized and also infused with a PTZ solution (n = 5, V-PTZ-lot). Cardiac and VENG parameters were assessed during different ECoG stages of ictal activity. None of the parameters changed in the control-lot. PTZ infusion induced seizures in all rats. Cardiac-related VENG showed distinctive firing patterns for the left and right vagus nerves. Significant ictal and post-ictal changes were seen in both the left and the right VENG in association with cardiac changes and increased parasympathetic influence on the heart. Changes in VENG parameters might provide a new way to assess the ictal state of patients, which could be suitable for triggering on-demand vagus nerve stimulation.
11. **Katona PG. Biomedical engineering in heart-brain medicine: a review. *Cleve Clin J Med.* 2010;77 Suppl 3:S46-50.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20622076>  
[http://www.ccm.org/content/77/Suppl\\_3/S46.full.pdf](http://www.ccm.org/content/77/Suppl_3/S46.full.pdf)  
**Abstract** New reports have emerged exploring the use of electrical stimulation of peripheral nerves in patients for the treatment of depression, heart failure, and hypertension. Abolishing renal sympathetic nerve activity in resistant hypertension has also been described. Since nerve bundles carry a variety of signals to multiple organs, it is necessary to develop technologies to stimulate or block targeted nerve fibers selectively. Mathematical modeling is a major tool for such development. Purposeful modeling is also needed to quantitatively characterize complex heart-brain interactions, allowing an improved understanding of physiological and clinical measurements. Automated control of therapeutic devices is a possible eventual outcome.

**Cranial Surgery (VNS versus/after...)**

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1. **Cukiert A, Cukiert CM, Burattini JA, Lima AM, Forster CR, Baise C, et al. Long-term outcome after callosotomy or vagus nerve stimulation in consecutive prospective cohorts of children with Lennox-Gastaut or Lennox-like syndrome and non-specific MRI findings. *Seizure*. 2013.**

<http://www.ncbi.nlm.nih.gov/pubmed/23490456>

**Abstract** PURPOSE: There is currently no resective (potentially curative) surgical option that is useful in patients with Lennox-Gastaut syndrome. Palliative procedures such as callosotomy (Cx), vagus nerve stimulation (VNS) or deep brain stimulation have been offered. We compared the outcomes after Cx or VNS in two consecutive prospective cohorts of patients with generalised epilepsy. METHODS: Twenty-four patients underwent callosotomy from 2006 to 2007 (Group 1); 20 additional patients were submitted to VNS from 2008 to 2009 (Group 2). They had generalised epilepsy of the Lennox-Gastaut or Lennox-like type. They were submitted to a neurological interview and examination, interictal and ictal video-EEG, high resolution 1.5T MRI, and cognitive and quality of life evaluations. The two-year post-operative follow-up results were evaluated for each patient. RESULTS: The final mean stimuli intensity was 3.0mA in the Group 2 patients. Seizure-free patients accounted for 10% in Group 1 and none in Group 2. Ten and sixteen percent of the Group 1 and 2 patients, respectively, were non-responders. Improvements in attention and quality of life were noted in 85% of both Group 1 and 2 patients. Rupture of the secondary bilateral synchrony was noted in 85% of Group 1 patients; there was no EEG modification after VNS in Group 2. Both procedures were effective regarding the control of atypical absences and generalised tonic-clonic seizures. Both procedures were not effective in controlling tonic seizures. Callosotomy was very effective in reducing the frequency of atonic seizures, but VNS was ineffective. In contrast, callosotomy was not effective in reducing myoclonic seizures, whereas VNS was. DISCUSSION: Callosotomy might be preferred as the primary treatment in children with Lennox-Gastaut syndrome, and no specific findings on MRI if atonic seizures prevail in the patient's clinical picture; when myoclonic seizures prevail, the same might hold true in favour of VNS. When atypical absence or generalised tonic-clonic seizures are the main concern, although both procedures carry similar effectiveness, VNS might be considered a good option as an initial approach, taking into account the adverse event profile. Patients should be advised that both procedures are not very effective in the treatment of tonic seizures.

2. **Lancman G, Virk M, Shao H, Mazumdar M, Greenfield JP, Weinstein S, et al. Vagus nerve stimulation vs. corpus callosotomy in the treatment of Lennox-Gastaut syndrome: a meta-analysis. *Seizure*. 2013;22(1):3-8.**

<http://www.ncbi.nlm.nih.gov/pubmed/23068970>

**Abstract** PURPOSE: Lennox-Gastaut syndrome (LGS) is an epileptogenic disorder that arises in childhood and is typically characterized by multiple seizure types, slow spike-and-wave complexes on EEG and cognitive impairment. If medical treatment fails, patients can proceed to one of two palliative surgeries, vagus nerve stimulation (VNS) or corpus callosotomy (CC). Their relative seizure control rates in LGS have not been well studied. The purpose of this paper is to compare seizure reduction rates between VNS and CC in LGS using meta-analyses of published data. METHODS: A systematic search of Pubmed, Ovidsp, and Cochrane was performed to find articles that met the following criteria: (1) prospective or retrospective study, (2) at least one patient diagnosed with Lennox-Gastaut syndrome, and (3) well-defined measure of seizure frequency reduction. Seizure reduction rates were divided into seizure subtypes, as well as total seizures, and categorized as 100%, >75%, and >50%. Patient groups were compared using chi-square tests for categorical variables and t-test for continuous measures. Pooled proportions with 95% confidence interval (95% CI) of seizure outcomes were estimated for total seizures and seizure subtypes using random effects methods. RESULTS: 17 VNS and 9 CC studies met the criteria for inclusion. CC had a significantly better outcome than VNS for >50% atonic seizure reduction (80.0% [67.0-90.0%] vs. 54.1% [32.1-75.4%],  $p < 0.05$ ) and for >75% atonic seizure reduction (70.0% [48.05-87.0%] vs. 26.3% [5.8-54.7%],  $p < 0.05$ ). All other seizure types, as well as total number of seizures, showed no statistically significant difference between VNS and CC. CONCLUSIONS: CC may be more beneficial for LGS patients whose predominant disabling seizure type is atonic. For all other seizure types, VNS offers comparable rates to CC.

3. **Benedetti-Isaac JC, Torres-Zambrano M, Fandino-Franky J, Polo-Verbel LM, Bolano-Esquirol M, Villa-Delgado R, et al. [Vagus nerve stimulation therapy in patients with drug-resistant epilepsy and previous corpus callosotomy]. *Neurocirugia (Astur)*. 2012;23(6):244-9. Spanish.**

<http://www.ncbi.nlm.nih.gov/pubmed/23046918>

**Abstract** OBJECTIVE: To analyse the results of vagus nerve stimulation in patients with drug-resistant epilepsy and previous corpus callosotomy. MATERIALS AND METHODS: We prospectively reviewed data from patients with drug-resistant epilepsy who showed persistence of disabling seizures after undergoing corpus callosotomy, in whom it was not possible to identify an epileptogenic focus and who were subsequently treated with vagus nerve stimulation. Variables analysed included: age, gender, aetiology of epilepsy, frequency and characteristics of the crises and Engel scale classification, before and after vagal stimulator implant. Furthermore, the percentage differences in seizure frequency changes were also calculated. RESULTS: Four patients were identified: two male and two female. The total seizure frequency had decreased between 20% and 81% after corpus callosotomy in three patients and one of them did not show any favourable response (Engel IVB). Following implantation of the stimulator they became reduced to between 57% and 100% after a mean follow-up period of 8.3 months (range: 3 to 12 months). Generalised seizures decreased between 71.4% and 100%, and focal seizures between 57.7% and 100%. CONCLUSIONS: Vagus nerve stimulation therapy proved to be an alternative for the reduction of seizure frequency in patients with drug-resistant epilepsy who suffered disabling seizures despite undergoing corpus callosotomy as primary surgery.

4. **Elliott RE, Morsi A, Geller EB, Carlson CC, Devinsky O, Doyle WK. Impact of failed intracranial epilepsy surgery on the effectiveness of subsequent vagus nerve stimulation. *Neurosurgery*. 2011;69(6):1210-7. <http://www.ncbi.nlm.nih.gov/pubmed/21558973>**  
**Abstract** BACKGROUND: Using the Cyberonics registry, Amar and colleagues reported poorer efficacy of vagus nerve stimulation (VNS) in patients who failed intracranial epilepsy surgery (IES). OBJECTIVE: To study the impact of failed IES and other surrogate marker of severe epilepsy on VNS effectiveness in a large cohort with treatment-resistant epilepsy (TRE). METHODS: We retrospectively reviewed 376 patients (188 female patients; 265 adults; mean age, 29.4 years at implantation) with TRE who underwent VNS implantation between 1997 and 2008 and had at least 1 year of follow-up. One hundred ten patients (29.3%) had failed  $\geq 1$  prior craniotomies for TRE, and 266 (70.7%) had no history of IES. RESULTS: The mean duration of VNS therapy was 5.1 years. Patients with prior IES were more commonly male and adult, had a greater number of seizure types, and more commonly had focal or multifocal vs generalized seizures ( $P < .05$ ). There was no significant difference in the mean percentage seizure reduction between patients with and without a history of IES (59.1% vs 56.5%;  $P = .42$ ). There was no correlation between type of failed IES (callosotomy vs resection) and seizure reduction with VNS therapy. CONCLUSION: Failed IES did not affect the response to VNS therapy. Unlike prior reports, patients with callosotomy did not respond better than those who had resective surgery. Nearly 50% of patients experienced at least 50% reduction in seizure frequency. For patients with TRE, including patients who failed cranial epilepsy surgeries, VNS should be considered a palliative treatment option.
5. **Vale FL, Ahmadian A, Youssef AS, Tatum WO, Benbadis SR. Long-term outcome of vagus nerve stimulation therapy after failed epilepsy surgery. *Seizure*. 2011;20(3):244-8. <http://www.ncbi.nlm.nih.gov/pubmed/21196125> [http://ac.els-cdn.com/S1059131110003109/1-s2.0-S1059131110003109-main.pdf?\\_tid=313cec82-927a-11e2-8782-00000aab0f6b&acdnat=1363906608\\_af6af5d93ad486554c87c5489fe2a7a8](http://ac.els-cdn.com/S1059131110003109/1-s2.0-S1059131110003109-main.pdf?_tid=313cec82-927a-11e2-8782-00000aab0f6b&acdnat=1363906608_af6af5d93ad486554c87c5489fe2a7a8)**  
**Abstract** OBJECTIVE: Adequate control of intractable epilepsy continues to be a challenge. Little is known about the role of VNS therapy in intractable epilepsy in patients who failed to respond to surgical management. The objective of the present study is to determine the efficacy of vagus nerve stimulation therapy in patients with intractable epilepsy who have failed surgical and medical therapy. METHODS: All the patients who had persistent seizures after cranial surgery who subsequently underwent vagus nerve stimulator (VNS) placement at our institution from 1998 to 2008 were included in the study. Thirty-seven consecutive patients were enrolled and followed for the outcome measures of seizure burden, anti-epileptic drug (AED) burden and quality of life (QoL). Minimum follow-up was 18 months. RESULTS: Overall, 24 (64.9%), 9 (24.3%), 4 (10.8%) patients reported less than 30%, between 30% and 60% and greater than 60% reduction in seizure frequency after VNS placement, respectively at a mean of 5 years follow-up period. Post-VNS anti-epileptic requirement exhibited a decreasing trend. 17 patients (45.9%) report an improvement in QoL (better or much better). CONCLUSION: VNS therapy in patients who have failed medical and surgical therapies only provides marginal improvement in seizure control but has greater likelihood to improve subjective QoL issues. In addition, VNS has the potential to reduce AED burden without adversely impacting seizure management. Given the low surgical risk of VNS placement, vagus nerve stimulation as a therapeutic modality should be individualized to achieve best clinical response and fewest side effects.

6. **Rosenfeld WE, Roberts DW. Tonic and atonic seizures: what's next--VNS or callosotomy? *Epilepsia*. 2009;50 Suppl 8:25-30.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19702730>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2009.02232.x/asset/j.1528-1167.2009.02232.x.pdf?v=1&t=he942pfr&s=ef0d96108100600c273a20948ab6de4860e3cfb4>  
**Abstract** Medically intractable tonic and atonic seizures may be responsive to either vagus nerve stimulation (VNS) or corpus callosum section. VNS has been shown to be effective and is associated with very low morbidity. Callosotomy is a more ambitious procedure, with a higher risk of complications but greater likelihood of seizure improvement.
7. **You SJ, Kang HC, Ko TS, Kim HD, Yum MS, Hwang YS, et al. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. *Brain Dev*. 2008;30(3):195-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17825516>  
**Abstract** PURPOSE: To compare the efficacy of corpus callosotomy and vagus nerve stimulation (VNS) for long-term adjunctive therapy in children with Lennox-Gastaut syndrome (LGS). METHOD: Fourteen patients underwent a total corpus callosotomy and 10 patients received VNS implantation. The patients were monitored for more than 12 months after treatment, and seizure rates and complications were retrospectively evaluated. RESULTS: Seizure types among the 24 patients included atonic or tonic seizures with head-drops in 17 patients, generalized tonic seizures in two patients, atypical absence seizures in one patient, generalized tonic-clonic seizures in one patient, and myoclonic seizures in three patients. Of the 14 patients who underwent a corpus callosotomy, nine (64.3%) had a greater than 50% reduction in seizure frequency and five (35.7%) had a greater than 75% reduction. Of the 10 patients who underwent VNS implantation, seven (70.0%) had a greater than 50% reduction in seizure frequency and two (20.0%) had a greater than 75% reduction. There was no significant difference between the two procedures in terms of final efficacy. Complications of corpus callosotomy included aphasia in one patient, ataxia in another, and paresis in a third. Among patients receiving VNS, one patient experienced dyspnea while sleeping and one patient suffered from drooling. These complications were transient and tolerable, and were controlled by simple adjustments of VNS treatment parameters. CONCLUSION: The efficacy and safety of corpus callosotomy and VNS were comparable in children with LGS.
8. **Nei M, O'Connor M, Liporace J, Sperling MR. Refractory generalized seizures: response to corpus callosotomy and vagal nerve stimulation. *Epilepsia*. 2006;47(1):115-22.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16417539>  
**Abstract** PURPOSE: The vagal nerve stimulator (VNS) and corpus callosotomy can reduce seizure frequency when seizures are refractory to medications. However, the efficacy and safety of these two procedures have not been compared. This study evaluates the two procedures for generalized seizures. METHODS: All patients with refractory generalized seizures (generalized tonic-clonic, tonic, or atonic) who underwent a corpus callosotomy (anterior or complete) (n = 53) without other forms of epilepsy surgery and those who underwent VNS placement (n = 25) were evaluated for this study. Seizure response and procedure complications were evaluated. RESULTS: For those with a corpus callosotomy and generalized tonic-clonic seizures (n = 50), 79.5% had  $\geq$ 50% decrease in the frequency of generalized tonic-clonic seizures, and 60% had  $\geq$ 80% seizure reduction. For those with a VNS and generalized tonic-clonic seizures (n = 21), 50% had  $\geq$ 50% seizure reduction, and 33% had  $\geq$ 80% seizure reduction. Tonic and atonic seizures decreased after either VNS or a corpus callosotomy. The complication rate for corpus callosotomy was higher (21% all complications, 3.8% permanent) than that for VNS (8%; none permanent), but complications for both corpus callosotomy and VNS were rarely permanent. CONCLUSIONS: Both corpus callosotomy and VNS are effective in reducing generalized seizures. Corpus callosotomy is associated with greater efficacy but higher risk for complications, although these were generally transient.

9. **Schmidt D. Should VNS be considered before corpus callosotomy? . In: Miller JW, Silbergeld DL, Eds. *Epilepsy Surgery: Principles and Controversies*. New York, NY: Taylor & Francis; 2006:614-9.**  
<http://www.amazon.com/Epilepsy-Surgery-Principles-Controversies-Neurological/dp/0824725913>
  
10. **Amar AP, Apuzzo ML, Liu CY. Vagus nerve stimulation therapy after failed cranial surgery for intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. *Neurosurgery*. 2004;55(5):1086-93.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15509315>  
**Abstract** OBJECTIVE: To determine the effectiveness of vagus nerve stimulation (VNS) therapy among patients with persistent or recurrent seizures after lobar resection, callosotomy, and other cranial operations for intractable epilepsy. METHODS: Data were obtained from the VNS therapy patient outcome registry, which was established after United States Food and Drug Administration approval of the VNS device in 1997 as a means of capturing open-label clinical data outside of protocol. The integrity of the systems for collecting and processing registry data was authenticated by an independent auditing agency. The effect of potential selection bias, however, remains uncertain. RESULTS: Two nonconsecutive cohorts were compared: patients tracked in the registry who had previously undergone cranial surgery for epilepsy (CS group, n = 921) and those who had not (non-CS group, n = 3822). For the CS group, the median reduction in seizure frequency was 42.5% after 3 months of VNS therapy, 42.9% at 6 months, 45.7% at 12 months, 52.0% at 18 months, and 50.5% at 24 months. For the non-CS group, analogous rates were 47.0%, 52.9%, 60.0%, 62.7%, and 66.7%, respectively. In the CS group, seizures were reduced by at least 50% in 55.1% of patients, at least 75% in 31.4% of patients, at least 90% in 17.3% of patients, and 100% in 5.1% of patients after 24 months of VNS therapy. Response rates were more pronounced in the non-CS group: at least 50% in 62.2% of patients, at least 75% in 43.7% of patients, at least 90% in 26.8% of patients, and 100% in 8.3% of patients. Patients in both groups experienced marked improvements in quality of life parameters. CONCLUSION: The effectiveness of VNS is maintained during prolonged stimulation, and overall seizure control continues to improve with time. Patients in whom prior cranial surgery had failed did not respond as favorably as all other patients receiving VNS therapy. Nonetheless, many of the former group improved substantially. Thus, on the basis of these open-label data, VNS therapy represents a potentially palliative treatment option for patients with refractory seizures after failed cranial surgery.
  
11. **Koutroumanidis M, Binnie CD, Hennessy MJ, Alarcon G, Elwes RD, Toone BK, et al. VNS in patients with previous unsuccessful resective epilepsy surgery: antiepileptic and psychotropic effects. *Acta Neurol Scand*. 2003;107(2):117-21.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12580861>  
<http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0404.2003.01211.x/abstract>  
**Abstract** OBJECTIVES: To assess the efficacy of vagus nerve stimulation (VNS) in patients with medically and surgically intractable complex partial seizures (CPS). PATIENTS AND METHODS: Sixteen patients with previous temporal [15] and frontal [one] resections were treated with VNS between 1994 and 1999 at King's College Hospital, London, UK. Post-operative video-electroencephalogram telemetry had shown that CPS started from the operated side in 12 patients, contralaterally in three and bilaterally independently in one. RESULTS: Three patients (18.75%) had 50% or more reduction in seizure frequency, but one showed severe worsening of epilepsy, which remitted upon VNS discontinuation. The antiepileptic effect of VNS was not different with respect to the type of operation (anterior temporal lobectomy vs amygdalohippocampectomy), the side of operation, or the side of seizure onset. We observed psychotropic effects in two patients with post-ictal psychosis, in two others with depression, and in a child with severe behavioral disorder. CONCLUSIONS: VNS may have a rather limited antiepileptic role to play in patients with persistent seizures following epilepsy surgery, but may independently possess useful antipsychotic and mood-stabilizing properties.

12. **Amar AP, Apuzzo ML. Vagus nerve stimulation therapy for patients with persistent seizures after epilepsy surgery. *Stereotact Funct Neurosurg.* 2003;80(1-4):9-13.**

<http://www.ncbi.nlm.nih.gov/pubmed/14745201>

<http://www.karger.com/Article/FullText/75152>

**Notes** This extended Abstract was presented by Dr. Amar at the American Society of Stereotactic and Functional Neurosurgery meeting in May 2003 and is a shortened version of the full article (currently submitted to Neurosurgery as of 2/6/04) that compares outcomes of VNS registry patients who had failed cranial surgery before they were implanted with those who had not previously undergone cranial surgery. Although patients without previous cranial surgery achieved greater reductions in seizure frequency from baseline, patients who had failed previous cranial surgery did experience seizure reductions exceeding 40% at each interval reported.

**Abstract** BACKGROUND: This study reports the effectiveness of vagus nerve stimulation (VNS) among patients who failed cranial surgery for intractable epilepsy. METHODS: Data were obtained from the Cyberonics VNS therapy patient outcome registry. The integrity of the systems for collecting and processing registry data was authenticated by an independent auditing agency. RESULTS: Two nonconsecutive cohorts were compared: patients who had had prior cranial surgery (CS group, n = 921) and those who had not (non-CS group, n = 3,822). For the CS group, the median reduction in seizure frequency was 42.5% after 3 months of VNS therapy, 42.9% at 6 months, 45.7% at 12 months, 52.0% at 18 months and 50.5% at 24 months. For the non-CS group, analogous rates were 47.0, 52.9, 60.0, 62.7 and 66.7%, respectively. CONCLUSION: The effectiveness of VNS is maintained during prolonged stimulation. Patients who failed prior cranial surgery did not respond quite as favorably as all other patients receiving VNS therapy.

13. **Schwartz TH, Spencer DD. Strategies for reoperation after comprehensive epilepsy surgery. *J Neurosurg.* 2001;95(4):615-23.**

<http://www.ncbi.nlm.nih.gov/pubmed/11596956>

**Abstract** OBJECT: Prior reports of seizure control following reoperation for failed epilepsy surgery have shown good results. These studies included patients who presented during the era preceding magnetic resonance (MR) imaging, and the patients were often not monitored intracranially or underwent subtotal hippocampal resections. In this study, the authors hypothesized that reoperation for recurrent seizures following a more comprehensive initial workup and surgery would not yield such good results. METHODS: The authors examined a consecutive series of patients who underwent two operations at Yale-New Haven Hospital for medically intractable epilepsy and in whom there was a minimum of 1-year follow up after the second surgery. All patients were evaluated and treated according to a standard protocol, including preoperative MR imaging, a low threshold for invasive monitoring, and a radical amygdalohippocampectomy when indicated. Twenty-seven patients were identified (five with mesial temporal sclerosis, 20 with neocortical disease, and two with multifocal sites of seizure onset) of whom six (22%) underwent intentionally palliative second surgery (corpus callostomy or placement of a vagus nerve stimulator [VNS]). Of the remaining 21 patients, only four (19%) became seizure free after a second resective operation. The most common causes of treatment failure were dual pathology, recurrent tumor, limited resection to preserve function, widespread developmental abnormalities, and electrographic sampling error. Successful outcomes resulted from removal of recurrent tumors, completion of a functional hemispherectomy, or repeated invasive monitoring to correct a sampling error. Five (83%) of the six intentionally palliative second operations resulted in more than a 50% decrease in seizure frequency. CONCLUSIONS: If an aggressive preoperative evaluation and surgical resection are performed, reoperation for recurrent seizures has a much lower likelihood of cure than previously reported. Intentionally palliative surgery such as placement of a VNS unit may be considered for patients in whom the initial operation fails to decrease seizure frequency.

**Early Use (of VNS; early in disease course)**

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1. **Helmert SL, Griesemer DA, Dean JC, Sanchez JD, Labar D, Murphy JV, et al. Observations on the use of vagus nerve stimulation earlier in the course of pharmacoresistant epilepsy: patients with seizures for six years or less. *Neurologist*. 2003;9(3):160-4.**

<http://www.ncbi.nlm.nih.gov/pubmed/12808412>

**Abstract** BACKGROUND: This study retrospectively compared the effectiveness of vagus nerve stimulation (VNS) therapy among a constant cohort of patients in the patient outcome registry, which systematically monitors outcomes of patients receiving VNS therapy. Patients in the study had pharmacoresistant seizures for 6 years or less (early treatment group) or more than 6 years (late treatment group) before initiation of VNS therapy, and results are provided after both 3 and 12 months. REVIEW SUMMARY: Of 405 patients, 51 were in the early and 354 in the late treatment groups. Median age at onset of seizures was 7 years in the early and 4.5 years in the late treatment group. Seizure reduction of 100% was reported in 7.8% (early) and 3.7% (late) patients at 3 months and 11.8% (early) and 4.5% (late) at 12 months (P = 0.033). Reductions in seizure frequency greater than or equal to 90% for early and late treatment groups were similar: 11.8% (early) and 11.0% (late) at 3 months and 23.5% (early) and 17.0% (late) at 12 months. CONCLUSIONS: Patients treated earlier with VNS therapy were twice as likely to report no seizures as patients who had seizures for more than 6 years before they received VNS therapy. The effectiveness of VNS therapy should be assessed among other patients with pharmacoresistant seizures and lesser cumulative seizure loads.

2. **Renfroe JB, Wheless JW. Earlier use of adjunctive vagus nerve stimulation therapy for refractory epilepsy. *Neurology*. 2002;59(6 Suppl 4):S26-30.**

<http://www.ncbi.nlm.nih.gov/pubmed/12270965>

**Abstract** Recent studies suggest that epilepsy that is unresponsive to medical therapy is likely to be refractory from the onset. Identifying such patients early and treating them with nonpharmacologic therapies may improve their outcome. We hypothesized that patients who had adjunctive therapy with vagus nerve stimulation (VNS) earlier in the course of their epilepsy would have a better response compared with patients who had VNS therapy instituted later in the course. Patients in the VNS patient outcome registry who were more than 5 years post onset of their seizure disorder at implantation and had seizure frequency data available at both baseline and 3 months comprised the control group (n = 2785). These data were obtained retrospectively. Patients who were implanted between August 15, 2000 and July 31, 2001 who had epilepsy for 5 years or less at implantation or who had tried four or fewer standard antiepileptic drugs (AEDs) before implantation, and who were evaluated at baseline and at 3-month intervals for seizure frequency and quality of life, comprised the early adjunctive registry (EAR group; n = 120). This group was identified prospectively by participating physicians at multiple centers. The data describe patient demographics, medical history, seizure frequency, and physician-graded quality of life measures. The two populations were demographically similar except for statistically significant differences in age, duration of epilepsy, institutionalized patients, and seizure type (partial and generalized). Although the median reduction in seizure frequency for all patients at 3 months was similar between groups (48.2% control versus 50.0% EAR), 15.0% of the patients in the EAR group reported no seizures at 3 months compared with 4.4% of those in the control group (p < 0.001). In addition, significantly more patients in the EAR group (20% versus 8%; p < 0.001) reported no seizures with alteration or loss of consciousness, and 32% of EAR patients reported no complex partial seizures compared with 17% in the control group (p = 0.002). Improvements in all areas of quality of life were reported by both populations, but more patients in the EAR group were reported as "much better/better" for postictal state (p = 0.030) and seizure clustering (p = 0.002). Typically, 5% of patients report having no seizures after 3 months of VNS therapy. The proportion increased threefold, from 5% to 15%, for patients who received VNS therapy earlier in the treatment process. Patients reported even higher rates of no seizures when simple partial seizures were excluded from the analysis or when only complex partial seizures were considered. Although these results are preliminary, they offer promise of success in achieving seizure control among patients with refractory seizures who have been diagnosed with epilepsy for less than 5 years or who have tried four or fewer AEDs. We suggest future prospective studies evaluating VNS therapy versus best medical therapy after the first two to three AEDs have failed, which typically occurs within 2 years of seizure onset.

**End of Service (including VNS battery depletion/removal or replacement)**

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1. **Giulioni M, Martinoni M, Naldi I, Bisulli F, Pozzati E, Tinuper P. Successful removal and reimplant of vagal nerve stimulator device after 10 years. *Ann Indian Acad Neurol.* 2012;15(2):128-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22566727>  
<http://www.annalsofian.org/article.asp?issn=0972-2327;year=2012;volume=15;issue=2;spage=128;epage=129;aulast=Giulioni>

**Abstract** The number of implanted vagal nerve stimulators is growing and the need for removal or revision of the devices will become even more frequent. A significant concern about Vagus Nerve Stimulation (VNS) therapy is the presence of the spiral stimulating electrodes, wrapped around the nerve, once treatment is considered ineffective or is no longer desired. Our purpose is to demonstrate the feasibility of complete removal and replacement of the vagal nerve stimulator electrodes using microsurgical technique even after a long period, without damaging the nerve. We attempted removal and replacement of spiral stimulating electrodes from a patient who received a 10-year long VNS therapy for drug-resistant epilepsy. Our results indicate that the spiral electrodes may be safely removed from the vagus nerve, even after several years. The reversibility of lead implantation may enhance the attractiveness of VNS therapy. Furthermore, with a correct microsurgical technique, it is possible to respect the normal anatomy and functionality of vagal nerve and to reimplant a new VNS system with all its components, maintaining the same therapeutic efficacy after many years.
  
2. **Donahue D, Sanchez R, Hernandez A, Malik S, Black CT, Honeycutt J. Preservation of a subcutaneous pocket for vagus nerve stimulation pulse generator during magnetoencephalography. *Technical note. J Neurosurg.* 2007;107(6 Suppl):519-20; comment *J Neurosurg Pediatr.* 2008;2(5):375; author reply *J Neurosurg Pediatr.* 2008;2(5):375; comment *J Neurosurg Pediatr.* 2008;2(5):375-7; author reply *J Neurosurg Pediatr.* 2008;2(5):377.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18154026>

**Abstract** Patients with epilepsy and an implanted vagus nerve stimulation (VNS) device who are referred for consideration of definitive epilepsy surgery (removal of the epileptogenic cortex) may require magnetoencephalography (MEG), a study requiring explantation of the pulse generator, as part of their evaluation. Nonetheless, these patients may not wish to abandon palliative VNS therapy should definitive surgery prove unsuccessful or impossible. To avoid obliteration of the pocket by scar tissue after the pulse generator is explanted, the authors have preserved the dead space in several patients with insertion of a similarly sized silicone block. This block is easily replaced with the pulse generator if continued VNS therapy is appropriate, and is left in place in patients who appear to no longer require VNS therapy. Upon completion of MEG, if pulse generator replacement proves desirable, atraumatic retrieval of the electrode connector pin and body is easy. Silicone block implantation during what may prove to be temporary device explantation facilitates reuse of the original pulse generator implantation site and atraumatic distal electrode wire retrieval.

3. **Vonck K, Dedeurwaerdere S, De Groote L, Thadani V, Claeys P, Gossiaux F, et al. Generator replacement in epilepsy patients treated with vagus nerve stimulation. *Seizure*. 2005;14(2):89-99.**

<http://www.ncbi.nlm.nih.gov/pubmed/15694561>

**Abstract** PURPOSE: In epilepsy patients treated with vagus nerve stimulation (VNS), the occurrence of end of battery life (EOBL), when the generator will no longer deliver any stimulation, was investigated with regard to seizure control. EOBL is preceded by end of effective stimulation (EOES) when irregular stimulation may occur. METHODS: In 14/78 patients, treated with VNS at Ghent University Hospital, generators were replaced at different times following EOES or EOBL. We retrospectively analysed the time of occurrence of EOES and EOBL and seizure control before and after generator replacement. RESULTS: EOES or EOBL was indicated by loss of seizure control, decreased perception of stimulation and recurrence of depression in 3, 3 and 1/14 patient(s), respectively. In 2 and 1/14 patient(s), EOBL and premature generator failure, respectively, were detected during routine check-up at the epilepsy clinic. In 4/14 patients, generator replacement was performed before estimated EOES. Pre-replacement seizure control could not be regained in 2/14 patients in whom replacement had been postponed for several months. Estimation of EOES and EOBL occurrence proved difficult in individual patients. CONCLUSION: EOES or EOBL may be indicated by loss of seizure control, decreased or irregular perception of stimulation by the patient and loss of other VNS-induced effects. Postponing generator replacement may result into permanent loss of seizure control. In responders we suggest generator replacement before EOBL. Our results call for performance of prospective studies in larger patient groups that may eventually lead to general guidelines on the indication and timing of generator replacement.

4. **Tatum WO, Ferreira JA, Benbadis SR, Heriaud LS, Gieron M, Rodgers-Neame NT, et al. Vagus nerve stimulation for pharmaco-resistant epilepsy: clinical symptoms with end of service. *Epilepsy Behav*. 2004;5(1):128-32; comment *Epilepsy Behav*. 2004;5(1):612-3; author reply *Epilepsy Behav*. 2004;5(1):613-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/14751218>

**Abstract** PURPOSE: Limited capability exists to predict when vagus nerve stimulation (VNS) battery deterioration becomes significant. Initial models last 2-5 years. We evaluated the first 18 patients with pharmaco-resistant epilepsy after reimplantation to examine the clinical course observed during VNS end of service (EOS). METHODS: Of 72 patients with VNS, 18 patients had generator replacement. EOS was estimated based on duration of use and stimulus parameters in accordance with manufacturer guidelines. Eight males and ten females had pharmaco-resistant epilepsy for a mean of 17.9 years. Thirteen with localization-related epilepsy (LRE) and 5 nonverbal patients with symptomatic generalized epilepsy (SGE) failed a mean of 11.1 antiepileptic drugs (AEDs) over 21.5 years. Seven had intracranial evaluations and five failed epilepsy surgery. Reimplantation was performed after a mean of 34.4 months. Symptoms at end of service (EOS) were addressed by postoperative survey submitted at initial reprogramming within 2 weeks of reimplantation. Stimulus parameters were compared before and after surgery. RESULTS: Nine of thirteen (69.2%) verbal patients and 11 of 18 (61.1%) total patients had signs or symptoms prior to replacement, suggesting clinical EOS, and 4 of 18 (22.2%) failed interrogation denoting battery failure without symptoms; however, this did not reach significance ( $\chi^2=0.359, p=0.54$ ). Increased seizures were the most frequent sign in 8 of 18 (44.4%), with intensification in 7 of 18 (38.9%). Irregular stimulation was detected in 5 of 18 (27.7%), with less intense stimulation in 4 of 18 (22.2%). Painful stimulation and behavioral worsening each occurred in 2 of 18 (11.1%). A subjective improvement in function after reimplantation was noted in 12 of 13 (92.3%) verbal patients, with greater intensity and consistency. Maximally tolerated reimplant current averaged -0.56 mA less. All but one (94.4%) felt surgery should be performed before clinical EOS occurred. CONCLUSIONS: We conclude that clinical signs and symptoms may arise during VNS EOS and following replacement. Seizure increase or a change in seizure pattern was most frequently observed. The tolerated reimplant current was less than the preoperative output current in most cases. Battery replacement before EOS appears desirable from a patient perspective.

5. **Tarver WB. Response to Letter to the Editor Wenneberg R [E-Letter]. *J Neurol Neurosurg Psychiatry*. 2004. [http://jnnp.bmj.com/content/75/6/939.long/reply#jnnp\\_el\\_205](http://jnnp.bmj.com/content/75/6/939.long/reply#jnnp_el_205). Published July 12, 2004. Accessed March 13, 2013.**  
**Abstract** Electronic letter published on the journal's web site in response to the Wennberg letter published in JNNP 2004;75:939.
6. **Wennberg RA. Seizure frequency after battery depletion of the VNS device - a reply to Tarver [E-Letter]. *J Neurol Neurosurg Psychiatry*. 2004. [http://jnnp.bmj.com/content/75/6/939.long/reply#jnnp\\_el\\_205](http://jnnp.bmj.com/content/75/6/939.long/reply#jnnp_el_205). Published September 15, 2004. Accessed March 13, 2013.**  
**Abstract** Electronic letter in response to Tarver's electronic letter in response to the original Wennberg letter published in JNNP 2004;75:939.
7. **Wennberg R. Short term benefit of battery depletion in vagus nerve stimulation for epilepsy. *J Neurol Neurosurg Psychiatry*. 2004;75(6):939.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15146025>  
**Notes** In this Letter to the Editor, the author misinterprets data from the VNS Therapy Manual. The information provided in the VNS Therapy physician's manual states that the information provided was referenced to BASELINE, not to the time just before battery depletion. Therefore the data do not indicate that 58% of subjects improved after battery depletion, but that 58% of subjects had not yet returned to their baseline seizure rates within 4 weeks after VNS Therapy battery depletion. As such, Wennberg's conclusion is incorrect. The data discussed by Wennberg has been previously presented by Ristanovic in Abstract form. This information clearly indicates no significant rebound after battery depletion, but a loss of benefit within 4 weeks after battery depletion. Letters to the Editor are not usually peer reviewed; as such, they represent the opinion of the author. Cyberonics will submit a response to this Letter to the Editor. Short term benefit of battery depletion in vagus nerve stimulation for epilepsy.
8. **Labar D, Ponticello L. Persistent antiepileptic effects after vagus nerve stimulation ends? *Neurology*. 2003;61(12):1818.**  
<http://www.ncbi.nlm.nih.gov/pubmed/14694061>  
**Notes** This brief report describes the case of a man who continued to show a persistent reduction in seizure frequency for up to 16 months after stopping VNS therapy. The patient had received VNS therapy for 6 years and had experienced a significant reduction in seizures while on the treatment as well as a reduction in AEDs early in the treatment course. Following surgery to replace the battery, the device was explanted because of an infection and was not reimplanted at the family's request. However, the seizures did not return. Although some cases of persistent antiepileptic effects after the end of stimulator battery life have been reported, persistent effects from VNS are not the norm. The authors point out that stopping VNS therapy among responders is not normal clinical practice, but that "the possibility of permanent remodeling of neural systems by the neurostimulation treatment approach needs to be considered when mechanisms of action, clinical trial designs, and outcome measures are discussed."

**Epilepsy Monitoring (Video/Intracranial EEG)**

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1. **Bower MR, Stead M, Van Gompel JJ, Bower RS, Sulc V, Asirvatham SJ, et al. Intravenous recording of intracranial, broadband EEG. *J Neurosci Methods*. 2013;214(1):21-6.**

<http://www.ncbi.nlm.nih.gov/pubmed/23313850>

**Abstract** The most direct evaluation of human brain activity has been obtained from intracranial electrodes placed either on the surface of the brain or inserted into the brain to record from deep brain structures. Currently, the placement of intracranial electrodes implies transcranial surgery, either through a burr hole or a craniotomy, but the high degree of invasiveness and potential for morbidity of such major surgical procedures limits the applicability of intracranial recording. The vascular system provides a natural avenue to reach many brain regions that currently are reached by transcranial approaches, along with deep brain structures that cannot be reached via a transcranial approach without significant risk. To determine the applicability of intravascular approaches to high-frequency intracranial monitoring, a catheter containing multiple macro- and micro-electrodes was placed into the superior sagittal sinus of anesthetized pigs in parallel with clinical, subdural electrode grids to record epileptiform activity induced by direct, cortical injection of penicillin and to record responses to electrical stimulation. Intravascular electrodes recorded epileptiform spikes with similar magnitudes and waveshapes to those obtained by surface electrodes, both for macroelectrodes and microelectrodes, including the spatiotemporal evolution of epileptiform activity, suggesting that intravascular electrodes might provide localizing information regarding seizure foci. Sinusoidal electrical stimulation showed that intravascular electrodes provide sufficient broadband fidelity to record high-frequency, physiological events that may also prove useful in localizing seizure onset zones. As intravascular techniques have transformed cardiology, so intravascular neurophysiology may transform intracranial monitoring, in general, and the treatment of epilepsy, in particular.

2. **Lee CH, Lim SN, Lien F, Wu T. Duration of electroencephalographic recordings in patients with epilepsy. *Seizure*. 2013.**

<http://www.ncbi.nlm.nih.gov/pubmed/23587866>

**Abstract** **PURPOSE:** Previous studies have demonstrated different diagnostic yields with electroencephalography (EEG). Due to the small sample sizes or different patient populations (outpatients or inpatients only) in these previous studies, the clinical use of routine EEG and outpatient/inpatient video-EEG monitoring (VEM) needs further clarification. In this study, we investigated EEGs obtained from patients referred by epileptologists; by comparing the results of different EEG methods, we sought to determine the optimal durations and specific types of EEG recordings for different clinical situations. **METHODS:** The data from 335 routine EEGs, 281 3h outpatient VEMs, and 247 inpatient VEMs (>48h) were reviewed. We analyzed the latency to the first epileptiform discharge or clinical event. **RESULTS:** In patients undergoing outpatient VEMs, 48% of the first epileptiform discharges appeared within 20min, and 64% appeared within 30min. In patients undergoing inpatient VEMs, 21.2% had their first attack within 3h. The second peak of event occurrence was during the 33rd-36thh. Only 3.5% of the seizures were recorded after 57h. The detection rate of epileptiform discharges was higher for 3h outpatient VEM than for routine EEG (54.1% versus 16.4%,  $p<0.01$ ). Epileptic and/or nonepileptic events were recorded in 45.8% of the inpatient VEMs, the diagnostic yield of which was higher than for outpatient VEMs ( $p<0.01$ ). Since the patients in this study had been selected to limit the bias between each group, the diagnostic yield of EEGs in this study are likely to have been higher than those found in routine practice. Patients with generalized epilepsy had a shorter latency to the first epileptiform discharge compared to patients with localization-related epilepsy (mean, 22.1min versus 33.9min,  $p<0.05$ ). **CONCLUSIONS:** Two-thirds of epileptiform discharges were detected within 30min of VEM. A 30-min recording is recommended for routine EEG examinations that aim to detect epileptiform discharges. A 3h outpatient VEM is a reasonable option when a routine EEG fails to detect epileptiform discharges. The latency to the first epileptiform discharge was shorter in patients with generalized epilepsy than in patients with localization-related epilepsy. 48h of inpatient VEM might be adequate for detecting the target events.

3. **Cuppens K, Chen CW, Wong KB, Van de Vel A, Lagae L, Ceulemans B, et al. Using Spatio-Temporal Interest Points (STIP) for myoclonic jerk detection in nocturnal video. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:4454-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/23366916>

<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6346955>

**Abstract** In this study we introduce a method for detecting myoclonic jerks during the night with video. Using video instead of the traditional method of using EEG-electrodes, permits patients to sleep without any attached sensors. This improves the comfort during sleep and it makes long term home monitoring possible. The algorithm for the detection of the seizures is based on spatio-temporal interest points (STIPs), proposed by Ivan Laptev, which is the state-of-the-art in action recognition. We applied this algorithm on a group of patients suffering from myoclonic jerks. With an optimal parameter setting this resulted in a sensitivity of over 75% and a PPV of over 85%, on the patients' combined data.

4. **Agbenu J, Newton RW, Martland T, Ismayl O, Hargreaves S. Effect of reducing the recording time of standard EEGs on the detection of EEG-abnormalities in the management of the epilepsies of childhood. *Seizure.* 2012;21(6):422-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/22579242>

**Abstract** PURPOSE: The ILAE recommends baseline recordings of 30 min to detect abnormalities supporting a clinical diagnosis of epilepsy in children. A shorter recording time may be better tolerated by children and be more resource-efficient. Our aim was to determine how many abnormalities supporting a diagnosis of epilepsy would be missed by reducing the recording time of paediatric standard electroencephalograms (EEGs) from 20 to 15 min. METHODS: We evaluated standard EEGs of 300 patients aged 2 months to 17 years referred consecutively with confirmed or suspected epilepsy. EEGs were recorded for 20 min on digital media. A digital copy of each EEG was truncated to give consecutive sequences of 10 min (sequence "A") and 5 min duration (sequences "B" and "C" respectively). A panel of EEG raters blinded to the children's' details other than age identified these sequences as "normal" or "abnormal" if they contained spike waves, discrete sharp waves or notched slow waves in the respective EEG period. RESULTS: EEGs of 297 children were analysed (three were omitted for technical reasons). 109 out of 297 EEGs (37%) had specific abnormalities supportive of a diagnosis of an epilepsy. 17 of these EEGs showed the abnormality in EEG sequences "B" or "C" and 7 (95% CI: 1.9-12.2) out of these demonstrated the abnormality in sequence "C" only. 105 out of 297 EEGs had non-specific findings. CONCLUSION: We conclude that reducing the recording time of standard EEGs to 15 min may miss abnormalities in 2.36% [95% CI: 0.63-4.09%] overall and 6.42% [95% CI: 2.2-11.8%] of those with an abnormality supportive of an epilepsy to explain the reported symptoms. This result should inform any future discussions on seeking resource-efficiencies.

5. **Kanazawa K, Matsumoto R, Kinoshita M, Ikeda A. [Novel electrophysiological approaches to clinical epilepsy: diagnosis and treatment]. *Brain Nerve*. 2011;63(4):355-64. Japanese.**

<http://www.ncbi.nlm.nih.gov/pubmed/21441638>

**Abstract** Seizure onset zone (SOZ) is currently defined by ictal epileptiform discharges, which are most commonly recorded as regional low-voltage fast waves or repetitive spikes. Interictal epileptiform discharges, on the other hand, are not specific enough for SOZ as they are recorded at zones other than the SOZ; they are also recorded from areas that do not generate the ictal pattern and from areas to which ictal discharges propagate. Besides spikes and sharp waves, a novel index of human epileptogenicity has been investigated in association with wide-band electroencephalography (EEG) analysis. We primarily noted the following during clinical neurophysiological analysis for clinical epilepsy. (1) Recent development of digital EEG technology enabled us to record wide-band EEG in a clinical setting. Thus, high frequency (>200 Hz) and low frequency (<1 Hz) components can be reliably recorded using subdural electrodes. Direct current shift, slow shift, ripple, and fast ripple can be well delineated, and they will be potentially useful in the diagnosis and management of epileptic patients. (2) Fiber tractography (morphological parameter) and cortico-cortical-evoked potentials with single cortical stimulation (electrophysiological parameter) elucidated cortico-cortical connections in human brain. The data thus obtained can help us understand the mechanism of seizure propagation and normal cortical functional connectivity. (3) Non-invasive simultaneous recording of EEG and functional magnetic resonance imaging (fMRI) provided information on the roles of deep brain structures associated with scalp-recorded epileptiform discharges. Interventional neurophysiology can shed light on the non-pharmacological treatment of epilepsy. In this report, we discuss these novel electrophysiological approaches to the diagnosis and treatment of clinical epilepsy.

6. **Chamberlain AC, Viventi J, Blanco JA, Kim DH, Rogers JA, Litt B. Millimeter-scale epileptiform spike patterns and their relationship to seizures. *Conf Proc IEEE Eng Med Biol Soc*. 2011;2011:761-4.**

<http://www.ncbi.nlm.nih.gov/pubmed/22254422>

<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090174>

**Abstract** Advances in neural electrode technology are enabling brain recordings with increasingly fine spatial and temporal resolution. We explore spatio-temporal (ST) patterns of local field potential spikes using a new high-density active electrode array with 500  $\mu\text{m}$  resolution. We record subdural micro-electrocorticographic ( $\mu\text{ECoG}$ ) signals in vivo from a feline model of acute neocortical epileptiform spikes and seizures induced with local administration of the GABA antagonist, picrotoxin. We employ a clustering algorithm to separate 2-dimensional (2-D) spike patterns to isolate distinct classes of spikes unique to the interictal and ictal states. Our findings indicate that the 2-D patterns can be used to distinguish seizures from non-seizure state. We find two statistically significant ST patterns that uniquely characterize ictal epochs. We conclude that millimeter-scale ST spike dynamics contain useful information about ictal state. This finding may be important to understanding mechanisms underlying local circuit activity during seizure generation. Further work will investigate whether patterns we identify can increase our understanding of seizure dynamics and their underlying mechanisms and inform new electrical stimulation protocols for seizure termination.

7. **Dobesberger J, Walser G, Unterberger I, Seppi K, Kuchukhidze G, Larch J, et al. Video-EEG monitoring: safety and adverse events in 507 consecutive patients. *Epilepsia*. 2011;52(3):443-52.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21087243>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2010.02782.x/asset/j.1528-1167.2010.02782.x.pdf?v=1&t=heki2yj8&s=d0c05d88f55bd3ed099ada6f2733801ea624de4a>  
**Abstract** PURPOSE: Video-electroencephalography (EEG) monitoring plays a central role in the presurgical evaluation of medically refractory epilepsies and the diagnosis of nonepileptic attack disorders (NEADs). The aim of this study was to analyze safety and adverse events (AEs) during video-EEG monitoring. METHODS: We retrospectively evaluated 596 video-EEG sessions in 507 patients (233 men, mean age 36 years, standard deviation = 14, range 9-80 years) within a 6-year period. AEs were examined in detail and their risk factors were assessed using multiple logistic regression analysis. Key FINDINGS: Forty-four patients (9%) experienced 53 AEs: 20 had psychiatric events (17 postictal psychosis, 2 panic attacks, 1 interictal psychosis), 15 had injuries (14 falls with minor injuries, 2 falls with fractures, 2 fractures without fall, 1 fall with epidural hematoma), 10 patients had 13 episodes of status epilepticus (SE), and one AE was treatment-related (valproic acid--induced encephalopathy). Patients with AEs were older ( $p = 0.036$ ) and had a longer duration of epilepsy ( $p = 0.019$ ). All AEs resulted in a prolonged hospital stay ( $p < 0.001$ ). Ninety-one percent of the AEs occurred within the first 4 days of monitoring. Independent risk factors were duration of epilepsy  $>17$  years [odds ratio (OR) 3.096; 95% confidence interval (CI) 1.548-6.189], a previous history of psychiatric illness (OR 16.882; 95% CI 5.469-52.110), a history of seizure-related injuries (OR 3.542; 95% CI 1.069-11.739), or a history of SE (OR 3.334; 95% CI 1.297-8.565). Significance: The most common AEs were postictal psychosis, falls, and SE. Patients with an older age, long disease duration, psychiatric comorbidity, history of injuries, and SE have a higher risk.
8. **Arain AM, Song Y, Bangalore-Vittal N, Ali S, Jabeen S, Azar NJ. Long term video/EEG prevents unnecessary vagus nerve stimulator implantation in patients with psychogenic nonepileptic seizures. *Epilepsy Behav*. 2011;21(4):364-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21737353>  
**Abstract** OBJECTIVE: Psychogenic nonepileptic seizures (PNES) are common paroxysmal events that mimic and can often be misdiagnosed as epileptic seizures. PNES account for 10 to 40% of patients referred to epilepsy centers. Patients with uncontrolled PNES are at times subjected to vagus nerve stimulator (VNS) implantation. We report a series of such referred patients studied with video/EEG monitoring at our institution. METHODS: We evaluated patients who were implanted with a VNS by their primary neurologist for refractory seizures and who were referred to the Vanderbilt University epilepsy monitoring unit for a second opinion. The presumed diagnosis of epilepsy was based on abnormal routine EEG studies obtained by their primary neurologist. We evaluated these patients and recorded their typical spells between 2005 and 2009. We describe the results of 13 patients with VNS who were found to have PNES. The total number of patients with a VNS studied during this time was 60. RESULTS: None of the patients had undergone prior long-term video/EEG monitoring to document the nature of their events. A total of 13 patients with an implanted VNS had exclusive PNES, 9 women and 4 men with a mean age of  $38.2 \pm 10.4$  years. Mean age at seizure onset was  $28.5 \pm 15.4$  years. Patients were taking two to four antiepileptic medications in addition to VNS at the time of video/EEG monitoring. The average latency from the time of VNS implantation to the confirmatory diagnosis was 2.8 years. One to ten (median=3) of these patients' typical seizures were recorded during video/EEG monitoring. All patients were subsequently discharged off antiepileptic medications, and five of these patients were discharged home with the VNS turned off. CONCLUSION: A VNS may be implanted inappropriately in patients with PNES. As video/EEG monitoring may help in excluding the diagnosis of PNES and preventing unnecessary VNS implants, it should be a requirement before VNS implantation.

9. **Van den Berg PJ, Brekelmans GJ. Rhythmic heart beat artefacts mimicking an ictal EEG pattern with abundant interictal epileptiform activity in both mother and child. *Epileptic Disord.* 2011;13(2):177-80. <http://www.ncbi.nlm.nih.gov/pubmed/21561833>**  
**Abstract** We present the EEG findings in a two-year-old girl with cryptogenic localisation-related epilepsy. The electroencephalogram showed fronto-temporal spike-wave discharges. In addition, the EEG repeatedly showed activity at different electrodes consisting of spikes with varying amplitude, rhythmicity and frequency, mimicking polyspikes. Both low- and high-amplitude spikes were generated from the same electrodes, however, only the low-amplitude spikes coincided with features of the child's electrocardiogram. Video monitoring showed the child's head resting on her mother's chest. This spike pattern was shown to be a heart beat artefact originating from the mother, as implied by the rhythmicity and the shift to other electrodes by moving the child's head, causing electrocardiogram artefacts on the posterior electrodes. This case study underscores the importance of routine use of simultaneous electroencephalogram and video monitoring. [Published with video sequences].
10. **Lareau E, Lesage F, Pouliot P, Nguyen D, Le Lan J, Sawan M. Multichannel wearable system dedicated for simultaneous electroencephalography-near-infrared spectroscopy real-time data acquisitions. *J Biomed Opt.* 2011;16(9):096014. <http://www.ncbi.nlm.nih.gov/pubmed/21950928> [http://biomedicaloptics.spiedigitallibrary.org/data/Journals/BIOMEDO/23536/096014\\_1.pdf](http://biomedicaloptics.spiedigitallibrary.org/data/Journals/BIOMEDO/23536/096014_1.pdf)**  
**Abstract** Functional neuroimaging is becoming a valuable tool in cognitive research and clinical applications. The clinical context brings specific constraints that include the requirement of a high channel count to cover the whole head, high sensitivity for single event detection, and portability for long-term bedside monitoring. For epilepsy and stroke monitoring, the combination of electroencephalography (EEG) and functional near-infrared spectroscopy (NIRS) is expected to provide useful clinical information, and efforts have been deployed to create prototypes able to simultaneously acquire both measurement modalities. However, to the best of our knowledge, existing systems lack portability, NIRS sensitivity, or have low channel count. We present a battery-powered, portable system with potentially up to 32 EEG channels, 32 NIRS light sources, and 32 detectors. Avalanche photodiodes allow for high NIRS sensitivity and the autonomy of the system is over 24 h. A reduced channel count prototype with 8 EEG channels, 8 sources, and 8 detectors was tested on phantoms. Further validation was done on five healthy adults using a visual stimulation protocol to detect local hemodynamic changes and visually evoked potentials. Results show good concordance with literature regarding functional activations and suggest sufficient performance for clinical use, provided some minor adjustments were made.
11. **Benbadis SR, O'Neill E, Tatum WO, Heriaud L. Outcome of prolonged video-EEG monitoring at a typical referral epilepsy center. *Epilepsia.* 2004;45(9):1150-3. <http://www.ncbi.nlm.nih.gov/pubmed/15329081>**  
**Abstract** PURPOSE: When seizures do not respond to medications, video-EEG monitoring is the best available diagnostic tool and is the principal activity of epilepsy centers. The purpose of this study was to analyze the eventual disposition of patients who undergo video-EEG monitoring at a typical referral epilepsy center. METHODS: We reviewed the diagnoses and dispositions of all patients (adults and children) who underwent inpatient video-EEG monitoring (> or = 24 h) at our center (University of South Florida-Tampa General Hospital) over a 1-year period (2002). RESULTS: In total, 251 inpatient video-EEG monitoring sessions were performed. Nonepileptic seizures were diagnosed in 75 (30%); 58 (23%) were found to be surgical candidates; seven were implanted with the vagus nerve stimulator. In 47 (19%) patients, seizures were recorded, and the diagnosis of epilepsy was confirmed and clarified (symptomatic/cryptogenic generalized epilepsy, seven; localization-related epilepsy, 35; idiopathic generalized epilepsy, five). CONCLUSIONS: The eventual outcome of video-EEG monitoring is diverse. The largest groups, as expected, are psychogenic nonepileptic seizures (30%), and surgery (23%).

12. **Jaseja H. Intractable epilepsy management: an EEG-oriented approach. *Med Hypotheses*. 2003;61(2):231-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12888310>  
**Abstract** Intractable epilepsy has always posed a challenge to management; conventional, surgical and alternative techniques available so far (e.g., vagal nerve stimulation, i.e. VNS). The author has attempted to search for a novel alternative (drug-regime) approach to its management to minimise any invasive technique or surgery. The drug-regime is based primarily on EEG-background picture (namely synchronisation and de-synchronisation), which the author claims plays a crucial role in epileptogenesis and/or enhancement of epileptic recruitment. Thus an EEG (both in wake and sleep states) shall be a pre-requisite. The novel drug-regime promises to alter the cortical background-activity in a manner to render it un-favorable for epileptogenesis/enhancement of epileptic recruitment, thereby attempting to produce control over Intractable Epilepsy. The new drug-regime, by virtue of its properties to alter the EEG-background activity, thus could enhance the efficacy of conventional treatment and together, they could form a highly effective management for Intractable Epilepsy, thus minimising the intervention of invasive techniques like VNS and epilepsy brain surgery.
13. **Attarian H, Dowling J, Carter J, Gilliam F. Video EEG monitoring prior to vagal nerve stimulator implantation. *Neurology*. 2003;61(3):402-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12913209>  
**Abstract** Vagal nerve stimulation (VNS) is a safe alternative therapy for epilepsy but may have rare significant complications. There is no consensus regarding the necessity of video-EEG monitoring to characterize events before the VNS implantation. The authors discuss four patients who were inappropriately referred for or implanted with VNS without any previous video-EEG monitoring, in the context of their entire case experience.

14. **Boon P, Michielsen G, Goossens L, Drieghe C, D'Have M, Buyle M, et al. Interictal and ictal video-EEG monitoring. *Acta Neurol Belg.* 1999;99(4):247-55.**

<http://www.ncbi.nlm.nih.gov/pubmed/10674142>

**Abstract** PURPOSE: The purpose of this paper is to demonstrate the diagnostic efficacy and therapeutic relevance of video-EEG monitoring in a large patient population with long-term follow-up. PATIENTS AND METHODS: Between October 1990 and May 1997, 400 patients were monitored at the Epilepsy Monitoring Unit (EMU) of the University Hospital in Gent. In all patients, the following parameters were retrospectively examined: reason for referral, tentative diagnosis, prescribed antiepileptic drugs (AEDs), seizure frequency, number of admission days, number of recorded seizures, ictal and interictal EEG, clinical and electroencephalographic diagnosis following the monitoring session. During follow-up visits at the Epilepsy Clinic, we prospectively collected data on different types of treatment and post-monitoring seizure control. RESULTS: 255/400 (64%) patients were referred for refractory epilepsy. 145/400 (36%) patients were evaluated for attacks of uncertain origin. Mean follow-up, available in 225 patients, was 28 months (range: 6-80 months). Mean duration of a single monitoring session was 4 days (range: 2-7 days). Prolonged interictal EEG was recorded in all patients and ictal EEG in 258 (65%) patients. Following the monitoring session, the diagnosis of epilepsy was confirmed in 217 patients. Pseudoseizures were diagnosed in 31 patients (8%). AEDs were started in 19 patients, stopped in 6 and left unchanged in 110. The type and/or number of AEDs was changed in 111 patients. Sixty patients underwent epilepsy surgery. In 48 surgery patients, follow-up data were available, 29 of whom became seizure-free, and 16 of whom experienced a greater than 90% seizure reduction. Vagus nerve stimulation was performed in 11 patients, 2 became seizure-free, and 7 improved markedly. Of the non-invasively treated patients in whom follow-up was available (n = 135), 70 became seizure-free or experienced a greater than 50% reduction in seizure frequency; 51 patients experienced no change in seizure frequency. Outcome was unrelated to the availability of ictal video-EEG recording. In patients with complex partial seizures, seizure control was significantly improved when a well-defined ictal onset zone could be defined during video-EEG monitoring. CONCLUSION: Prolonged interictal EEG monitoring is mandatory in the successful management of patients with refractory epilepsy. Ictal video-EEG monitoring is very helpful but not indispensable, except in patients enrolled for presurgical evaluation or suspected of having pseudoseizures.

**Epileptic Encephalopathies (VNS efficacy in...)**

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1. **McTague A, Cross JH. Treatment of Epileptic Encephalopathies. *CNS Drugs*. 2013;27(3):175-84.**

<http://www.ncbi.nlm.nih.gov/pubmed/23397290>

<http://link.springer.com/article/10.1007%2Fs40263-013-0041-6>

**Abstract** Epileptic encephalopathy is defined as a condition where the epileptic activity itself may contribute to the severe neurological and cognitive impairment seen, over and above that which would be expected from the underlying pathology alone. The epilepsy syndromes at high risk of this are a disparate group of conditions characterized by epileptic seizures that are difficult to treat and developmental delay. In this review, we discuss the ongoing debate regarding the significance of inter-ictal discharges and the impact of the seizures themselves on the cognitive delay or regression that is a common feature of these syndromes. The syndromes also differ in many ways and we provide a summary of the key features of the early-onset epileptic encephalopathies including Ohtahara and West syndromes in addition to later childhood-onset syndromes such as Lennox Gastaut and Doose syndromes. An understanding of the various severe epilepsy syndromes is vital to understanding the rationale for treatment. For example, the resolution of hypsarrhythmia in West syndrome is associated with an improvement in cognitive outcome and drives treatment choice, but the same cannot be applied to frequent inter-ictal discharges in Lennox Gastaut syndrome. We discuss the evidence base for treatment where it is available and describe current practice where it is not. For example, in West syndrome there is some evidence for preference of hormonal treatments over vigabatrin, although the choice and duration of hormonal treatment remains unclear. We describe the use of conventional and newer anti-epileptic medications in the various syndromes and discuss which medications should be avoided. Older possibly forgotten treatments such as sulthiame and potassium bromide also have a role in the severe epilepsies of childhood. We discuss hormonal treatment with particular focus on the treatment of West syndrome, continuous spike wave in slow wave sleep (CSWS)/electrical status epilepticus in slow wave sleep (ESES) and Landau Kleffner syndrome. The role of the ketogenic diet has in recent years come to the fore of the management of these severe epilepsies and we describe successful use in myoclonic astatic epilepsy, Lennox Gastaut syndrome and Dravet syndrome. It is important that resective epilepsy surgery is not ignored in the management of these children, particularly those with hemi-pathology who may present with ESES and respond well to hemispheric disconnection. Adjunctive and symptomatic surgical treatments such as vagal nerve stimulation and corpus callosotomy may improve seizure burden. Finally, it is vital that the identification and treatment of developmental, behavioural and psychiatric co-morbidities are not neglected and that a rational, holistic approach is taken to the management of epileptic encephalopathies.

2. **Cersosimo RO, Bartuluchi M, De Los Santos C, Bonvehi I, Pomata H, Caraballo RH. Vagus nerve stimulation: effectiveness and tolerability in patients with epileptic encephalopathies. *Childs Nerv Syst.* 2011;27(5):787-92.**

<http://www.ncbi.nlm.nih.gov/pubmed/21038079>

<http://link.springer.com/article/10.1007%2Fs00381-010-1314-8>

**Abstract** PURPOSE: We discuss the effectiveness, tolerability, and safety of vagus nerve stimulation (VNS) as adjunctive therapy in 26 patients with refractory epileptic encephalopathies (EEs). MATERIAL AND METHODS: Twenty-six patients (17 male and 9 female) with electroclinical features compatible with Lennox-Gastaut syndrome (LGS) in 20 patients, Dravet syndrome (DS) in 3 patients, and epilepsy with myoclonic-astatic seizures (EMAS) in 3 patients implanted with the NCP system were analyzed. RESULTS: In our series of patients with LGS, 17 cases showed a significant improvement in seizure control, with a reduction in seizure frequency of at least 50%. Seven of them previously had epileptic spasms. Three patients with EMAS and two patients with DS showed a significant improvement in seizure control, with a reduction in seizure frequency of at least 50%. A good clinical response was evident early and efficacy progressively improved with the duration of treatment up to 36 months. In patients who had a reduction in seizure frequency of at least 50%, quality of life (QOL) and neuropsychological performance improved. VNS was well-tolerated in all patients. CONCLUSION: VNS is an effective and well-tolerated treatment for patients with epileptic encephalopathies EEs, improving QOL and neuropsychological performance.

3. **Grujic J, Bien CG, Pollo C, Rossetti AO. Vagus nerve stimulator treatment in adult-onset Rasmussen's encephalitis. *Epilepsy Behav.* 2011;20(1):123-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/21130042>

**Abstract** We describe a patient with adult-onset Rasmussen's encephalitis (RE) responsive to vagus nerve stimulation. This previously healthy woman developed RE in the right hemisphere at the age of 27. Despite antiepileptic drug polytherapy, she continued to experience subcontinuous, simple-partial left-sided motor seizures and slowly progressive cognitive impairment. Resective surgery was not considered owing to the preservation of left motor skills. She was implanted with a vagus nerve stimulator at the age of 41; after 6 months she experienced a greater than 50% reduction in seizure frequency, which persisted over 2 years together with improvement of her neurological and cognitive status.

4. **Tharp BR. Epileptic encephalopathies and their relationship to developmental disorders: do spikes cause autism? *Ment Retard Dev Disabil Res Rev.* 2004;10(2):132-4.**

<http://www.ncbi.nlm.nih.gov/pubmed/15362170>

<http://onlinelibrary.wiley.com/doi/10.1002/mrdd.20025/abstract>

<http://onlinelibrary.wiley.com/doi/10.1002/mrdd.20025/abstract>

**Abstract** Epileptic encephalopathies are progressive clinical and electroencephalographic syndromes where deterioration is thought to be caused by frequent seizures and abundant EEG epileptiform activity. Seizures occur in approximately 10-15% of children with pervasive developmental disorders (PDD) and 8-10% have epileptiform EEG abnormalities without seizures. Thirty percent of children with PDD have regression of social behavior and language at 2-3 years of age. Some authors speculate that the regression is caused by epileptiform activity even in the absence of overt clinical seizures ("autism with epileptic regression") and suggest that elimination of the epileptiform activity, either medically or surgically, should lead to improvement in behavior. This review examines the data showing that interictal epileptiform discharges are associated with transient clinical dysfunction and discusses the implications of these observations for autistic behavioral abnormalities. The results of resective surgery, vagal nerve stimulation, and multiple subpial transaction on children with autism and epileptiform EEG abnormalities are also discussed. I conclude that there is no evidence that interictal discharges per se cause (or contribute to) the complex behavioral phenotype of autism. There is no justification to support the use of anticonvulsant medication or surgery in children with PDD without seizures; that is, there is no evidence that treatment to eliminate EEG spikes will have a therapeutic effect on the behavioral abnormalities of PDD and autism.

5. **Parker AP, Polkey CE, Binnie CD, Madigan C, Ferrie CD, Robinson RO. Vagal nerve stimulation in epileptic encephalopathies. *Pediatrics.* 1999;103(4 Pt 1):778-82; comment 821-2.**

<http://www.ncbi.nlm.nih.gov/pubmed/10103302>

<http://pediatrics.aappublications.org/content/103/4/778.long>

**Abstract** **OBJECTIVE:** To study the effect of vagal nerve stimulation (VNS) in children with epileptic encephalopathies. **METHODS AND MATERIALS:** All children receiving VNS during a 2-year period at our center were studied prospectively for changes in seizure frequency, electroencephalogram (EEG), adaptive behavior, quality of life, and where appropriate, verbal/nonverbal performance. Assessments were made before and for at least 1 year after implant. **RESULTS:** Sixteen children were studied. One device was removed because of infection. Of the remaining 15 children, 4 had a >50% reduction and 2 had a >50% increase in seizure frequency at 1 year after implant. Median reduction in seizure frequency was 17%. There was no trend toward improvement of the EEG or adaptive behavior. Quality of life was unchanged in most areas, except in perceived treatment side effects and general behavior that were improved. In 6 children undergoing further assessment, there was a significant improvement in verbal performance; this did not correlate with reduction in seizure frequency. **CONCLUSION:** VNS did not significantly improve seizure frequency, severity, adaptive behavior, or the EEG during the first year of treatment for the group as a whole, although 4 children (27%) had a worthwhile reduction in seizure frequency. There were significant improvements in perceived treatment side effects and general behavior.

**Focal/Partial Onset Seizures (VNS efficacy in...)**

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- 1. Maguire M, Marson AG, Ramaratnam S. Epilepsy (partial). *Clin Evid (Online)*. 2011;2011. <http://www.ncbi.nlm.nih.gov/pubmed/21549021>**  
**Abstract** INTRODUCTION: About 3% of people will be diagnosed with epilepsy during their lifetime, but about 70% of people with epilepsy eventually go into remission. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of starting antiepileptic drug treatment following a single seizure? What are the effects of drug monotherapy in people with partial epilepsy? What are the effects of additional drug treatments in people with drug-resistant partial epilepsy? What is the risk of relapse in people in remission when withdrawing antiepileptic drugs? What are the effects of behavioural and psychological treatments for people with epilepsy? What are the effects of surgery in people with drug-resistant temporal lobe epilepsy? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2009 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 83 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antiepileptic drugs after a single seizure; monotherapy for partial epilepsy using carbamazepine, gabapentin, lamotrigine, levetiracetam, phenobarbital, phenytoin, sodium valproate, or topiramate; addition of second-line drugs for drug-resistant partial epilepsy (allopurinol, eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, losigamone, oxcarbazepine, retigabine, tiagabine, topiramate, vigabatrin, or zonisamide); antiepileptic drug withdrawal for people with partial or generalised epilepsy who are in remission; behavioural and psychological treatments for partial or generalised epilepsy (biofeedback, cognitive behavioural therapy (CBT), educational programmes, family counselling, relaxation therapy (alone or plus behavioural modification therapy, yoga); and surgery for drug-resistant temporal lobe epilepsy (lesionectomy, temporal lobectomy, vagus nerve stimulation as adjunctive therapy).
- 2. Burakgazi AZ, Burakgazi-Dalkilic E, Caputy AJ, Potolicchio SJ. The correlation between vagus nerve stimulation efficacy and partial onset epilepsies. *J Clin Neurophysiol*. 2011;28(4):380-3. <http://www.ncbi.nlm.nih.gov/pubmed/21811127>**  
**Abstract** PURPOSE: To evaluate the correlation between vagus nerve stimulation (VNS) efficacy and partial seizures originating from different brain regions. MATERIALS AND METHODS: The authors retrospectively analyzed the data of 46 subjects with medically intractable epilepsy who had insertion of VNS between April 1999 and July 2005. The clinical outcome was assessed with Engel classification. Subjects were divided into group A (Engel I, II, and III) and group B (Engel IV) for statistical analysis. Group A was referred as a satisfactory outcome. The statistical analysis of the data was assessed whether these parameters such as age, type of seizure, age at insertion of VNS, and lengths of follow-up affect the outcome. RESULTS: Nineteen patients (41.3%) had a satisfactory outcome (Engel II, III). The analysis of VNS efficacy demonstrated that 65% of the patients with frontal lobe epilepsy and only 15% of the patients with temporal lobe epilepsy (TLE) had a satisfactory outcome. There was a statistically significant difference between these types of epilepsy and VNS outcomes (Fisher exact test,  $P = 0.004$ ). CONCLUSION: VNS is more effective in frontal lobe epilepsy than in temporal lobe epilepsy. Further studies are warranted to verify our findings and the correlation between types of epilepsy and VNS outcome.
- 3. Bokkala-Pinninti S, Pinninti N, Jossen S. Vagus nerve stimulation effective for focal motor seizures and focal interictal parkinsonian symptoms. A case report. *J Neurol*. 2008;255(2):301-2. <http://www.ncbi.nlm.nih.gov/pubmed/17994309> <http://link.springer.com/article/10.1007%2Fs00415-007-0723-4>**

4. Landre E. [Vagus nerve stimulation and refractory partial epilepsies]. *Rev Neurol (Paris)*. 2004;160 Spec No 1:5S280-7. French.  
<http://www.ncbi.nlm.nih.gov/pubmed/15331976>  
**Abstract** Since 1988, intermittent electric stimulation of the cervical portion of the left vagus nerve is proposed as additive treatment of epilepsy. The effects of vagus nerve stimulation (VNS) on the modulation of cerebral activity, shown in animals and confirmed by the data of functional imagery in human beings, can be apprehended by the anatomic and functional characteristics of this nerve, whereas the anti-epileptic mode of action remains unknown. Following five controlled multicentric studies, including 440 patients presenting refractory epilepsy, 20,000 patients worldwide have been treated by VNS for this indication. Proposed as additive symptomatic treatment of refractory epilepsies, VNS has proven effective and well tolerated by both children and adults with refractory partial epilepsy. After 2 years of treatment, patients achieve an overall average of 40 p. 100 reduction of seizure frequency. In 40 to 50 p. 100 of the patients, the frequency of seizure can even be decreased by 50 p. 100. Moreover, even in the absence of a significant reduction of seizure, patients subjected to this treatment have reported an improvement in their quality of life. The economic surveys also show a favorable impact of VNS on the management of refractory partial epilepsies.
5. Privitera MD, Welty TE, Ficker DM, Welge J. Vagus nerve stimulation for partial seizures. *Cochrane Database Syst Rev*. 2002(1):CD002896.  
<http://www.ncbi.nlm.nih.gov/pubmed/11869641>  
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002896/abstract>  
**Abstract** BACKGROUND: Vagus nerve stimulation (VNS) has recently been introduced as an adjunct for treating patients with seizures. The aim of this systematic review was to overview the current evidence for the effects of vagus nerve stimulation, when used as an adjunctive treatment for patients with drug-resistant partial epilepsy. OBJECTIVES: To determine the effects of VNS high-level stimulation compared to low-level (presumed subtherapeutic dose) stimulation. SEARCH STRATEGY: We searched the Cochrane Epilepsy Group trials register, MEDLINE (January 1966 to October 2000) and The Cochrane Controlled Trials Register (Cochrane Library Issue 4, 2000). SELECTION CRITERIA: Randomized, double-blind controlled trials of VNS comparing high and low stimulation paradigms. Studies in adults or children with drug-resistant partial seizures. DATA COLLECTION AND ANALYSIS: Two reviewers independently selected trials for inclusion and extracted data. The following outcomes were assessed: (a) 50% or greater reduction in total seizure frequency; (b) treatment withdrawal (any reason); (c) side effects. Primary analyses were intention to treat. Sensitivity best and worst case analyses were also undertaken. Summary odds ratios (ORs) were estimated for each outcome. MAIN RESULTS: Results of the overall efficacy analysis show that VNS stimulation using the high stimulation paradigm was significantly better than low stimulation. The overall OR (95% Confidence Interval (CI)) for 50% responders across all studies is 1.93 (1.1,3.3). This effect did not vary substantially and remained statistically significant for both the best and worst case scenarios. Results for the outcome "withdrawal of allocated treatment" suggest that VNS is well tolerated as no significant difference was found between the high and low stimulation groups, and withdrawals were rare. Statistically significant adverse effects associated with implantation (low versus baseline) were hoarseness, cough, pain and paresthesia. Statistically significant adverse effects associated with stimulation (high versus low) were hoarseness and dyspnea, suggesting the implantation is associated with hoarseness, but the stimulation produces additional hoarseness. REVIEWER'S CONCLUSIONS: VNS for partial seizures appears to be an effective and well tolerated treatment. Adverse effects of hoarseness, cough, pain, paresthesias and dyspnea are associated with the treatment but appear to be reasonably well tolerated as dropouts were rare. Typical central nervous system adverse effects of antiepileptic drugs such as ataxia, dizziness, fatigue, nausea and somnolence were not statistically significantly associated with VNS treatment.

6. **Neufeld M, Quaknine G, Korczyn A. [Vagus nerve stimulation for partial seizures]. *Harefuah*. 1995;129(1-2):5-7, 80. Hebrew.**

<http://www.ncbi.nlm.nih.gov/pubmed/7557711>

**Abstract** Cerebellar and thalamic stimulation has been known for many years to improve control of epileptic seizures. In the past few years electrical vagus nerve stimulation (VNS) has been introduced and has been effective in controlling seizures in animal models. These encouraging results led to the development of a transcutaneous programmable pulse generator and electrode lead for human use. 2 pilot studies and a multicenter, prospectively-randomized, parallel, double-blind study of patients with refractory partial seizures were performed. In a 3-22 month follow-up, in about 50% of patients seizures were reduced by 30-50%. There were no significant complications of the implant. Side-effects associated with VNS included intermittent hoarseness, coughing and throat pain. Additional controlled clinical trials with many patients and long follow-up are needed. We report 2 patients, the first in Israel, who underwent VNS.

**Foreign Language Articles (No English Abstract)**

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1. Jin K, Nakasato N, Iwasaki M, Tominaga T. [Recent advances in epilepsy management]. *No Shinkei Geka*. 2012;40(1):5-14. Japanese.  
<http://www.ncbi.nlm.nih.gov/pubmed/22223517>
2. Kawai K. [Vagus nerve stimulation for intractable epilepsy: implantation of vagus nerve stimulator]. *No Shinkei Geka*. 2008;36(11):979-89. Japanese.  
<http://www.ncbi.nlm.nih.gov/pubmed/19048916>
3. Engelsen BA. [Vagus nerve stimulation]. *Tidsskr Nor Laegeforen*. 2006;126(7):895. Norwegian.  
<http://www.ncbi.nlm.nih.gov/pubmed/16554877>
4. Hajnsek S, Poljakovic Z. [A new minimally invasive neurosurgery method in the treatment of refractory epilepsy: vagus nerve stimulator implantation]. *Lijec Vjesn*. 1999;121(1-2):42. Croatian.  
<http://www.ncbi.nlm.nih.gov/pubmed/10377700>
5. Mauguiere F. [Intermittent chronic stimulation of the vagus nerve: a last chance for palliative treatment of drug-resistant epileptic seizures?]. *Rev Neurol (Paris)*. 1996;152(4):231-3. French.  
<http://www.ncbi.nlm.nih.gov/pubmed/8763650>
6. Tomovic M. [Therapy of epilepsy with stimulation of the vagus nerve]. *Vojnosanit Pregl*. 1994;51(2):143-6. Serbian.  
<http://www.ncbi.nlm.nih.gov/pubmed/8560825>

**Generalized Epilepsy (VNS efficacy in...)**

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1. **Erdem A, Acik V, Leventoglu A, Sarilar C, Cansu A. Effect of vagal nerve stimulation in Dyke-Davidoff-Masson syndrome with refractory generalized seizures - case report. *Turk Neurosurg.* 2009;19(2):197-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19431136>  
**Abstract** We report a case of Dyke-Davidoff-Masson syndrome (DDMS) in whom left vagal nerve stimulation (VNS) resulted in worthwhile seizure reduction (Engel's Classification Class III). A 20-year-old woman with DDMS whose seizures were medically intractable was successfully treated using left VNS. She was born at term by unsuccessful forceps-assisted vaginal delivery. Her seizures started at the age of 4. There was no detectable mental retardation. Her seizures were intractable although she had been receiving three medications for sixteen years. She underwent left vagal nerve stimulator placement. Pre-stimulation seizure frequency was three seizures per month. This case shows that VNS is an alternative treatment procedure for medically intractable seizures in DDMS. To our knowledge, this is the first case in the world literature reporting worthwhile seizure reduction in DDMS after VNS.
  
2. **Kostov H, Larsson PG, Roste GK. Is vagus nerve stimulation a treatment option for patients with drug-resistant idiopathic generalized epilepsy? *Acta Neurol Scand Suppl.* 2007;187:55-8; comment *Epilepsy Curr.* 2007;187:55-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17419830>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0404.2007.00848.x/abstract>  
**Abstract** BACKGROUND: The value of vagus nerve stimulation (VNS) for treating patients with drug-resistant idiopathic generalized epilepsy (IGE) is not well documented. PATIENTS AND METHODS: Twelve patients (2 males, 10 females) with a mean age of 31 years (11-48 years) and with drug-resistant IGE had VNS implanted in the period 1995-2006. All had generalized seizures documented by video-electroencephalogram. Mean follow-up period was 23 months (9-54 months). RESULTS: There was a total seizure reduction of 61% (P = 0.0002). There was 62% reduction of generalized tonic-clonic seizures (P = 0.0020), 58% of absences (P = 0.0003) and 40% of myoclonic seizures (P = 0.0156). Eight patients were considered responders (>50% seizure reduction); two of these patients became seizure-free. Five out of seven patients with juvenile myoclonic epilepsy were responders. At the last follow-up visit, the patients had reduced the anti-epileptic drug (AED) usage from an average of 2.3 to 1.7 AED per patient (P = 0.0625). Two patients are currently being treated with VNS therapy only. Nine patients reported side effects, which were mostly mild and tended to diminish over time. CONCLUSION: Our results indicate that adjunctive VNS therapy is a favourable treatment option for patients with drug-resistant IGE. Rapid cycling seems worth trying in some of the non-responders.
  
3. **Holmes MD. Is vagus nerve stimulation therapy effective for generalized epilepsy? In: Miller JW, Silbergeld DL, Eds. *Epilepsy Surgery: Principles and Controversies*. New York, NY: Taylor & Francis; 2006:620-3.**  
<http://www.amazon.com/Epilepsy-Surgery-Principles-Controversies-Neurological/dp/0824725913#>
  
4. **Faught E. Treatment of refractory primary generalized epilepsy. *Rev Neurol Dis.* 2004;1 Suppl 1:S34-43.** <http://www.ncbi.nlm.nih.gov/pubmed/16400293>  
**Abstract** Although complete seizure control is achievable in 54% to 82% of patients with primary (idiopathic) generalized epilepsy syndromes, there remains a substantial group with inadequate control. Valproate has been considered the drug of choice but is not always effective and might produce unacceptable adverse effects. Several newer drugs have emerged as potential alternatives to valproate, including lamotrigine, levetiracetam, topiramate, and zonisamide. Sedation and tolerance limit the utility of benzodiazepines. For severely refractory patients, drug combinations, vagal nerve stimulation, or felbamate might be considered. Only a few controlled clinical trials have been conducted for these syndromes; more are needed.

5. **Ng M, Devinsky O. Vagus nerve stimulation for refractory idiopathic generalised epilepsy. *Seizure*. 2004;13(3):176-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15010055>  
**Abstract** We reviewed our experience with vagus nerve stimulation (VNS) in 165 patients with medically refractory epilepsy (138 partial epilepsy (PE), 13 symptomatic generalised epilepsy (SGE), 14 idiopathic generalised epilepsy (IGE)). Average duration of VNS therapy was 21.6 months. A 50% or greater reduction in seizure frequency was achieved in 47.1% of the PE group, 46.1% of the SGE group, and 57.1% of the IGE group. A 50% or greater reduction in seizure frequency and reduced antiepileptic drug (AED) regimen were achieved in: PE (9.4%), SGE (7.7%), and IGE (35.7%). These preliminary results suggest that VNS is an effective therapy for some patients with medically refractory IGE.
  
6. **Holmes MD, Silbergeld DL, Drouhard D, Wilensky AJ, Ojemann LM. Effect of vagus nerve stimulation on adults with pharmaco-resistant generalized epilepsy syndromes. *Seizure*. 2004;13(5):340-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15158706>  
**Abstract** INTRODUCTION: Although vagus nerve stimulation (VNS) therapy is approved for the treatment of partial onset seizures, its efficacy for generalized seizures has not been fully evaluated. This Investigational Device Exemption assessed the outcome of VNS therapy among patients with generalized epilepsy syndromes. METHODS: Sixteen patients with pharmaco-resistant generalized epilepsy syndromes and stable antiepileptic drug (AED) regimens were implanted with the VNS therapy device and were evaluated for changes in seizure frequency and type between baseline and follow-up of 12-21 months. RESULTS: The patients experienced a statistically significant overall median seizure frequency reduction of 43.3% (P = 0.002, Wilcoxon signed rank test) after 12-21 months of VNS therapy. Types of seizures that may involve a fall or collapse decreased with reductions in the frequency of myoclonic (60% reduction, n = 9; P = 0.016, Wilcoxon signed rank test), tonic (75% reduction, n = 8, NS), atonic (98.6%, n = 3, NS), and clonic seizures (86.7%, n = 1, NS). Conclusion: The benefits of reduced seizure frequency and reduced risk of injury merit consideration of VNS therapy for patients with pharmaco-resistant generalized seizure syndromes.
  
7. **Labar D, Nikolov B, Tarver B, Fraser R. Vagus nerve stimulation for symptomatic generalized epilepsy: a pilot study. *Epilepsia*. 1998;39(2):201-5; comment *Epilepsia*. 1998;39(9):1018.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9578001>  
**Abstract** PURPOSE: Patients with symptomatic generalized epilepsy (SGE) may have antiepileptic drug (AED)-resistant mixed generalized seizures. Vagus nerve stimulation (VNS) reduces partial seizures and may help SGE. METHODS: We added VNS to stable AED therapy in five SGE patients. Nine-month postoperative VNS treatment seizure rates were compared to a 1-month preoperative baseline. RESULTS: All patients had mixed generalized seizures, EEG generalized slow spike-and-wave and behavioral abnormalities. Median number of previous AEDs taken was 6 (range 5-12). Median baseline seizure rate was 75/month (range 29-110). VNS produced a median seizure rate production of -41% (range -40% - -85%). Adverse events reported in one patient each were: incisional infection, choking sensation and voice change; and coughing (noted by two patients). One patient discontinued VNS due to coughing. CONCLUSIONS: We conclude that VNS may be useful add-on therapy for SGE. A larger, controlled, and blinded trial may be warranted.

**Geriatric Population (Epilepsy/VNS in...)**

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1. **Gallo BV. Epilepsy, surgery, and the elderly. *Epilepsy Res.* 2006;68 Suppl 1:S83-6.** <http://www.ncbi.nlm.nih.gov/pubmed/16380232>  
**Abstract** Treatment of elderly patients with epilepsy may present unique challenges to physicians. Co-morbid conditions and drugs to treat such conditions are common in elderly patients, possibly complicating epilepsy therapies that are dependent on drugs alone. For this reason, surgical intervention may be an attractive option for elderly patients with epilepsy, particularly for medically intractable patients with key disease features, such as lateralization and precisely localized epileptic foci. Curative procedures, including lobectomy and lesionectomy, are most likely to lead to seizure freedom, but not all patients are candidates for such procedures. When a curative surgical procedure is not an option, palliative procedures, including vagus nerve stimulation and deep brain stimulation, may be viable options. Vagus nerve stimulation has been reported to reduce seizure rates and improve quality of life in elderly patients with epilepsy. Currently, widespread therapeutic application of deep brain stimulation is limited by risks, costs, and pending studies.
  
2. **LaRoche SM, Helmers SL. Epilepsy in the elderly. *Neurologist.* 2003;9(5):241-9.** <http://www.ncbi.nlm.nih.gov/pubmed/12971835>  
**Abstract** BACKGROUND: Epilepsy is one of the most common neurologic diseases that affect the elderly population. Underlying etiologies as well as diagnostic and treatment issues vary from that of younger adults and deserve special consideration. REVIEW SUMMARY: The substantially increased risk of seizures and epilepsy in the elderly is associated with medical conditions that affect this group such as stroke, dementia, and metabolic disturbances. In addition, there is an increased incidence and associated mortality of status epilepticus among seniors. Distinguishing epilepsy from paroxysmal nonepileptic events can be a particular challenge. As in the general adult population, EEG and MRI are the cornerstones of diagnostic assessment; however, the clinician must be aware of nonspecific changes associated with aging that do not necessarily indicate an underlying predisposition for epilepsy. Finally, there are unique challenges to the treatment of epilepsy in this population, but fortunately there are multiple treatment options available, including nonpharmacological therapies. CONCLUSIONS: Knowledge of the unique challenges in identifying and treating the elderly patient with epilepsy is important for effective management as well as maximizing quality of life. However, further studies in this area are still needed to establish optimal treatment strategies.
  
3. **Sirven JI, Sperling M, Naritoku D, Schachter S, Labar D, Holmes M, et al. Vagus nerve stimulation therapy for epilepsy in older adults. *Neurology.* 2000;54(5):1179-82.** <http://www.ncbi.nlm.nih.gov/pubmed/10720294>  
**Abstract** The authors assessed the efficacy, safety, and tolerability of vagus nerve stimulation (VNS) for refractory epilepsy in 45 adults 50 years of age and older. They determined seizure frequency, adverse effects, and quality of life. At 3 months, 12 patients had a >50% decrease in seizure frequency; at 1 year, 21 of 31 studied individuals had a >50% seizure decrease. Side effects were mild and transient. Quality of life scores improved significantly with time.

**Healthcare Utilization/Costs (with VNS in epilepsy)**

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1. **Forbes R. Cost-utility of vagus nerve stimulation (VNS) therapy for medically refractory epilepsy--an update. *Seizure*. 2008;17(4):387-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18584780>
  
2. **Bernstein AL, Hess T. Vagus nerve stimulation therapy for pharmaco-resistant epilepsy: effect on health care utilization. *Epilepsy Behav*. 2007;10(1):134-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17084676>  
**Abstract** We retrospectively analyzed the effects of vagus nerve stimulation (VNS) therapy on utilization of medical services by 138 patients in a large staff-model health maintenance organization. We compared average quarterly rates for 12 months before device implantation with quarterly rates during 48 months of follow-up. Wilcoxon matched-pairs signed-ranks tests comparing pre-VNS with post-VNS utilization rates showed statistically significant reductions in numbers of emergency department visits, hospitalizations, and hospital lengths of stay, beginning with the first quarter after implantation ( $P < 0.05$  for all post-implantation quarters for these three aspects). For the first two quarters after implantation, the average number of outpatient visits was significantly greater than the pre-implant quarterly average (quarter 1:  $P < 0.0001$ ; quarter 2:  $P = 0.0067$ ), but the average was 12.2% less by the fourth quarter of the first year after implantation and significantly less beginning with the first quarter of the second year ( $P = 0.0017$ ) and continuing through the end of the study ( $P < 0.0001$  for all subsequent quarters). A comparison of time spent on epilepsy-related tasks during the year before implantation with the year after implantation also revealed significant decreases in the average number of days on which patients could not work because of health-related concerns, from 3.67 to 1.04 days ( $P = 0.002$ , paired Student's *t* test) and the average time spent caring for health problems, from 352.6 to 136.1 minutes per week ( $P < 0.001$ ). VNS therapy had a positive effect on both the utilization of health care services and the time spent on epilepsy-related tasks for these patients with pharmaco-resistant epilepsy.
  
3. **Forbes RB, Macdonald S, Eljamel S, Roberts RC. Cost-utility analysis of vagus nerve stimulators for adults with medically refractory epilepsy. *Seizure*. 2003;12(5):249-56.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12810336>  
**Abstract** INTRODUCTION: The cost-utility of vagus nerve stimulator (VNS) devices for medically refractory epilepsy has yet to be estimated. METHODS: Using a meta-analysis of randomised controlled trials of VNS, we estimate that six people require implantation in order for one person to experience a 50% reduction in seizure frequency. Costs averted from improved epilepsy control were ascertained from published literature. Values for health states were obtained from a series of 42 seizure clinic attenders using time trade-off techniques and the EQ-5D health status instrument. The cost per quality adjusted life year gained was estimated and the values obtained were tested in a sensitivity analysis. RESULTS: Improved epilepsy control averted, on average, 745 pounds sterling health care costs per annum. People with epilepsy had great difficulty performing the time trade-off experiment, but those who managed to complete the task valued a 50% reduction in their own seizure frequency at 0.285 units. For a programme of six implants, the baseline model estimated the cost per quality adjusted life year gained at 28,849 pounds sterling. The most favourable estimate was equal to 4785 pounds sterling per quality adjusted life year gained, assuming that the number needed to treat was similar to published series in which one response was obtained for every three implants. The least favourable estimate was equal to 63,000 pounds sterling per quality adjusted life year gained, when EQ-5D utility values were used. The cost per quality adjusted life year gained was not sensitive to changes in length of stay, nor complication rates, but was significantly influenced by cost of device and device battery life expectancy. CONCLUSION: There is not a strong economic argument against a programme of VNS implantation, although care should be taken to try and identify and treat those most likely to benefit.

4. **Boon P, D'Have M, Van Walleghem P, Michielsen G, Vonck K, Caemaert J, et al. Direct medical costs of refractory epilepsy incurred by three different treatment modalities: a prospective assessment. *Epilepsia*. 2002;43(1):96-102.**

<http://www.ncbi.nlm.nih.gov/pubmed/11879393>

**Abstract** PURPOSE: More than 20% of epilepsy patients have refractory seizures. Treatment options for these patients include continued polytherapy with/without novel antiepileptic drugs (AEDs), epilepsy surgery (ES), or vagus nerve stimulation (VNS). The purpose of this study was prospectively to compare epilepsy-related direct medical costs (ERDMCs) incurred by these different treatment modalities. METHODS: Eighty-four patients underwent a complete presurgical evaluation protocol at our institution. As a result, 24 (29%) patients were treated with continued AED polytherapy only; 35 (40%) underwent ES; and 25 (30%) had VNS. In each patient, annual costs in the 2 years preceding the therapeutic decision (ERDMC-pre) and during the follow-up afterward (ERDMC-post) were prospectively calculated. Furthermore, frequency of complex partial seizures with/without secondary generalization (CPS+/-SG), dosage and number of AEDs, number of hospital admission days, clinic visits, and laboratory tests before and after the therapeutic decision also were prospectively assessed. ERDMC-pre and ERDMC-post were compared in and among the three treatment groups. RESULTS: In patients conservatively treated with AEDs, mean frequency of CPSs decreased from 12 per month to nine per month, whereas mean ERDMCs decreased from \$2,525 U.S. to \$2,421 U.S. In surgical patients, mean seizure frequency decreased from six to fewer than one per month; mean ERDMCs per year decreased from \$1,465 U.S. preoperatively to \$1,186 U.S. postoperatively. In the VNS group, mean seizure frequency decreased from 21 per month to seven per month. ERDMCs in this subgroup decreased from \$4,826 U.S. to \$2,496 U.S. Mean seizure frequency changes were significant when conservatively treated patients were compared with surgically treated and VNS patient groups (chi2 test,  $p < 0.001$  and  $p = 0.0019$ , respectively). ERDMC changes in conservatively treated patients also were statistically significant when compared with surgically treated and VNS patients (chi2 test,  $p = 0.0007$  and  $p = 0.0036$ , respectively). No statistically significant differences were found in ERDMC changes between the surgical and VNS groups (chi2 test,  $p = 0.387$ ). CONCLUSIONS: Ongoing daily treatment of patients who underwent resective surgery costs significantly less than conservative treatment. For patients in whom resective surgery is not an option, ERDMC show a significant decrease in VNS-treated patients compared with conservatively treated patients.

5. **Ben-Menachem E, Hellstrom K, Verstappen D. Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients. *Neurology*. 2002;59(6 Suppl 4):S44-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/12270968>

**Abstract** Vagus nerve stimulation (VNS) therapy is an established method for treating patients with refractory seizures. Although the initial cost of the device is about 10,000 US dollars, the battery life of the model 100 implanted in the patients in this analysis can exceed 5 years at standard settings. It is important to understand what type of cost-benefit can be expected after implantation. Our aim was to assess unplanned hospital costs 18 months before and 18 months after VNS implantation in 43 patients. The VNS therapy system was implanted according to standard procedures and stimulation of 0.75 to 2.0 mA was delivered either as 30 seconds on and 5 minutes off or 7 seconds on and 14 seconds off. Seizure frequency was calculated before and after 18 months of treatment. During this time no changes were made with other therapies for epilepsy. Hospitalization for emergency room (ER) visits, ward stays, and intensive care days were calculated according to the costs at Sahlgrenska University Hospital in Sweden. Therapy response was defined as 25% or greater reduction in seizure frequency. For all patients, intensive care unit (ICU) costs were reduced from 46,875 to 0 US dollars, ER visits from 13,000 to 9,000 US dollars, and ward stays from 151,125 to 21,375 US dollars. Total hospital costs for the 43 patients studied before VNS therapy were 211,000 US dollars and after 18 months of treatment were reduced to 30,375 US dollars, an average annual cost savings of approximately 3,000 US dollars per patient. The cost savings applied to all patients, irrespective of whether they responded to VNS therapy. VNS therapy resulted in annual reductions of approximately 3000 US dollars in unplanned hospital costs per study patient. Such direct savings sustained over the battery life of the VNS therapy system can equal or exceed the purchase price of the device.

6. **Boon P, Vonck K, Vandekerckhove T, D'Have M, Nieuwenhuis L, Michielsen G, et al. Vagus nerve stimulation for medically refractory epilepsy; efficacy and cost-benefit analysis. *Acta Neurochir (Wien)*. 1999;141(5):447-52; discussion 453.**

<http://www.ncbi.nlm.nih.gov/pubmed/10392199>

<http://link.springer.com/article/10.1007%2Fs007010050324>

**Abstract** INTRODUCTION: Vagus nerve stimulation is a novel treatment for patients with medically refractory epilepsy, who are not candidates for conventional epilepsy surgery, or who have had such surgery without optimal outcome. To date only studies with relatively short follow-up are available. In these studies efficacy increased with time and reached a maximum after a period of 6 to 12 months. Implantation of a vagus nerve stimulator requires an important financial investment but a cost-benefit analysis has not been published. PATIENTS AND METHODS: Our own experience with VNS in Gent comprises 15 patients with mean age of 29 years (range: 17-44 years) and mean duration of epilepsy of 18 years (range: 4-32 years). All patients underwent a comprehensive presurgical evaluation and were found not to be suitable candidates for resective epilepsy surgery. Mean post-implantation follow-up is 24 months (range: 7-43 months). In patients with follow-up of at least one year, efficacy of treatment in terms of seizure control and seizure severity was assessed one year before and after the implantation of a vagus nerve stimulator. Epilepsy-related direct medical costs (ERDMC) before and after the implantation were also compared. RESULTS: A mean reduction of seizure frequency from 14 seizures/month (range: 2-40/month) to 8 seizures/month (range: 0-30/month) was achieved (Wilcoxon signed rank test  $n = 14$ ;  $p = 0.0016$ ). Five patients showed a marked seizure reduction of  $> \text{ or } = 50\%$ ; 6 became free of complex partial seizures, 3 of whom became entirely seizure free for more than 12 months; 2 patients had a worthwhile reduction of seizure frequency between 30-50%; in 2 patients seizure frequency reduction has remained practically unchanged. Seizure freedom or  $> \text{ or } = 50\%$  seizure reduction was achieved within the first 4 months after implantation in 6/11 patients. Before the implantation, the mean yearly epilepsy-related direct medical costs per patient were estimated to be 8830 US\$ ( $n = 13$ ; range: 1879-31,129 US\$;  $sd = 7667$ ); the average number of hospital admission days per year was 21 (range: 4-100;  $sd = 25.7$ ). In the 12 months after implantation, ERDMC had decreased to 4215 US\$ (range: 615-11,794 US\$;  $sd = 3558$ ) (Wilcoxon signed rank test  $n = 13$ ;  $p = 0.018$ ) and the average number of admission days to 8 (range: 0-35) (Wilcoxon signed rank test  $n = 13$ ;  $p = 0.023$ ). CONCLUSION: VNS is an effective treatment of refractory epilepsy and remains effective during long-term follow-up. Cost-benefit analysis suggests that the cost of VNS is saved within two years following implantation.

7. **Boon P, Vonck K, D'Have M, O'Connor S, Vandekerckhove T, De Reuck J. Cost-benefit of vagus nerve stimulation for refractory epilepsy. *Acta Neurol Belg*. 1999;99(4):275-80.**

<http://www.ncbi.nlm.nih.gov/pubmed/10674145>

**Abstract** PURPOSE: Vagus nerve stimulation (VNS) is an established treatment for patients with medically refractory epilepsy who are unsuitable candidates for conventional epilepsy surgery. VNS requires an initial financial investment but apart from our own previous study there are no reports on cost-benefit published to date. The purpose of this paper is to assess prospectively the cost-benefit ratio of VNS in a series of patients with long term follow-up. METHODS: Our experience with VNS comprises 25 patients of whom 20 with sufficient follow-up will be further discussed. These 20 patients have a mean post-implantation follow-up of 26 months (range: 6-50 months). Mean age was 30 years (range: 12-45 years); mean duration of epilepsy 17 years (range: 5-35 years). We prospectively assessed seizure frequency, prescribed AEDs, number of hospital admission days and side effects and calculated the epilepsy related direct medical cost and compared this with pre-implantation data. RESULTS: Mean seizure frequency decreased from 14 seizures/month (range: 2-40) to 9 seizures/month (range: 0-30) ( $p = 0.0003$ ). The mean yearly epilepsy related direct medical costs per patient dropped from 6,682 USD (range: 829-21,888 USD) to 3,635 USD (range: 684-12,486 USD) ( $p = 0.0046$ ). The mean number of hospital admission days was reduced from 16 days/year (range: 0-60) to 4 days/year (range: 0-30) ( $p = 0.0029$ ). CONCLUSION: VNS is an efficacious and cost-beneficial treatment for refractory partial seizures.

**Ketogenic Diet (VNS and/versus...)**

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- 1. Caraballo RH. Nonpharmacologic treatments of Dravet syndrome: focus on the ketogenic diet. *Epilepsia*. 2011;52 Suppl 2:79-82.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21463287>

**Abstract** We present an update of our experience with the ketogenic diet (KD) in patients with Dravet syndrome (DS) to evaluate the efficacy and tolerability and our short experience with vagus nerve stimulation (VNS) in the treatment of this syndrome. Between March 1, 1990 and May 31, 2007, 59 patients who met diagnostic criteria for DS were studied in our department. Twenty-four of them were placed on the KD and were followed up for a minimum of 2 years. Three patients were treated with VNS. Sixteen (66.6%) of 24 patients remained on the diet. Two patients (12.5%) became seizure free, 10 children (62.5%) had a 75-99% decrease in seizures, and the remaining 4 children (25%) had a 50-74% decrease in seizures. Six patients have been off the diet for >2 years; one of them is seizure free, two have sporadic seizures, and three, who abandoned the diet after 3 years of adhering to it, relapsed. As to the efficacy of VNS, two patients had a 50-74% decrease in seizures and in the other seizure frequency remained unchanged. The device was well tolerated in all patients without significant complications. Considering the severity and refractoriness of seizures in patients with DS, the fact that 12 of 16 children who remained on the diet had a significant reduction in number of seizures shows that the KD is at present an interesting therapeutic option. VNS may be a good alternative treatment for DS.
  
- 2. Kossoff EH, Pyzik PL, Rubenstein JE, Bergqvist AG, Buchhalter JR, Donner EJ, et al. Combined ketogenic diet and vagus nerve stimulation: rational polytherapy? *Epilepsia*. 2007;48(1):77-81.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17241211>

**Abstract** OBJECTIVE: The concept of "rational polypharmacy" has been associated with anticonvulsant management for decades, but the term has not been applied to nonpharmacologic therapies. METHODS: We conducted a multicenter, retrospective study of children who received concurrent diet (ketogenic or modified Atkins) and vagus nerve stimulation (VNS) treatment for medically intractable epilepsy. RESULTS: Thirty children in total from six epilepsy centers were treated over a 6-yr period. The median age at the initiation of combination therapy was 10 yr (range, 4-24 yr). Sixteen (53%) received dietary therapy followed by VNS; no differences were noted between centers. After 3 months, 21 (70%) had seizure reduced by >50% over the previous single nonpharmacologic treatment, of whom 13 (62%) had improvement within the first month. A 5-min VNS off-time correlated with >90% seizure reduction ( $p = 0.02$ ). The median duration of nonpharmacologic polytherapy was 12 months (range, 0.5-96 months); 17 (57%) remain on dual therapy at this time. No side effects were noted. Most patients who discontinued combination therapy did so because of a lack of efficacy rather than restrictiveness. CONCLUSIONS: In this small group, the combined use of diet and VNS appeared synergistic and yielded rapid benefits. It may be more effective with longer VNS off-times. Further prospective studies of this combination in refractory pediatric epilepsy are needed to help guide optimal use.

3. **Marsh EB, Freeman JM, Kossoff EH, Vining EP, Rubenstein JE, Pyzik PL, et al. The outcome of children with intractable seizures: a 3- to 6-year follow-up of 67 children who remained on the ketogenic diet less than one year. *Epilepsia*. 2006;47(2):425-30.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16499771>  
**Abstract** PURPOSE: To determine the long-term outcome of children with difficult-to-control seizures who remained on the ketogenic diet for <1 year. METHODS: Between 1994 and 1996, 150 children with epilepsy, refractory to at least two medications, initiated the ketogenic diet according to the Hopkins protocol. Three to six years after diet initiation, all the families were contacted by telephone or questionnaire to assess their child's current seizure status, medications, and therapies. RESULTS: Sixty-seven children discontinued the diet within 1 year of initiation. Follow-up data were available for 54 of these children. Ten subsequently had surgery, and three underwent VNS implantation. These operated-on children were significantly more likely to be >50% controlled at follow-up than were those managed with medications alone ( $p < 0.05$ ). A statistically significant difference in long-term outcome was noted between those who responded while on the diet, even if they discontinued it before 1 year, and those who did not ( $p < 0.05$ ), but no statistical correlation was found between length of time that they had remained on the diet and long-term prognosis. CONCLUSIONS: Almost half of the children who discontinued the diet during the first year had a decrease in seizures when assessed 3-6 years later. Twenty-two percent of these had become seizure free without surgery. We were unable to ascertain whether this may have been due to new medications. Those who saw some improvement while on the diet were more likely to have a favorable long-term outcome. Resective surgery, in children who were candidates, or vagal nerve stimulation (VNS) implantation, was more likely to result in significant seizure improvement than was management with medications alone. Whether or not the diet was effective, most families did not regret trying it and would recommend it to others.
4. **Stafstrom CE. Dietary approaches to epilepsy treatment: old and new options on the menu. *Epilepsy Curr*. 2004;4(6):215-22.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16059506>  
**Abstract** Dietary therapies represent a potentially valuable adjunct to other epilepsy treatments, such as anticonvulsant medications, epilepsy surgery, and vagus nerve stimulation. Although the ketogenic diet (high fat, adequate protein, low carbohydrate) is the most well-established dietary therapy for epilepsy, other possible approaches include the Atkins diet (high fat, high protein, low carbohydrate), a diet enriched in polyunsaturated fatty acids, or overall restriction of calorie intake. This review discusses the current clinical status of each of these dietary approaches and suggests possible mechanisms by which they might suppress neuronal hyperexcitability and seizures.
5. **Sheth RD, Stafstrom CE. Intractable pediatric epilepsy: vagal nerve stimulation and the ketogenic diet. *Neurol Clin*. 2002;20(4):1183-94.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12616687>  
**Abstract** The KD has been proven an effective alternative epilepsy treatment in children refractory to standard anticonvulsants. Children to be placed on the diet must be carefully selected, monitored, and followed. The diet is to be regarded as a strict medical regimen and requires a comprehensive medical team approach in concert with intensive parental involvement. With better understanding of the scientific principles underlying brain ketosis, we should be able to optimize the KD to achieve even better results.

6. **Wheless JW, Baumgartner J, Ghanbari C. Vagus nerve stimulation and the ketogenic diet. *Neurol Clin.* 2001;19(2):371-407.**

<http://www.ncbi.nlm.nih.gov/pubmed/11358749>

**Abstract** Antiepileptic drugs are the primary form of treatment for patients with epilepsy. In the United States, hundreds of thousands of people do not achieve seizure control, or have significant side effects, or both. Only a minority of patients with intractable epilepsy are candidates for traditional epilepsy surgery. Vagus nerve stimulation is now the second most common treatment for epilepsy in the United States. Additionally, the ketogenic diet has established itself as a valid treatment. This article discusses the history, mechanism of action, patient selection, efficacy, initiation, complications, and advantages of vagus nerve stimulation and the ketogenic diet.

**Lennox-Gastaut Syndrome (VNS efficacy in...)**

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- 1. Lemmon ME, Kossoff EH. New Treatment Options for Lennox-Gastaut Syndrome. *Curr Treat Options Neurol.* 2013.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23471536>  
<http://link.springer.com/article/10.1007%2Fs11940-013-0223-z>  
**Abstract** OPINION STATEMENT: Lennox-Gastaut syndrome (LGS) is one of the most difficult epilepsy syndromes to treat, and many children are refractory to standard treatment regimens. Valproic acid, topiramate, and lamotrigine are considered first-line therapies. Newer agents, including clobazam and rufinamide, are promising additions to the current treatment options. The ketogenic diet and vagus nerve stimulation are important adjuncts, with increasing evidence to support their use. Corpus callosotomy should be considered in refractory cases. Finally, focal resective surgery should be considered in patients with lesional disease, although for most patients with LGS this is unlikely to be the case.
- 2. VanStraten AF, Ng YT. Update on the management of Lennox-Gastaut syndrome. *Pediatr Neurol.* 2012;47(3):153-61.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22883278>  
**Abstract** Lennox-Gastaut syndrome is a severe childhood epilepsy disorder characterized by encephalopathy and multiple, often intractable, seizure types. The drop attack is the most frequently recognizable seizure type in this patient population, and is also the most dangerous physically, thus severely limiting quality of life. The diagnosis is confirmed by electroencephalography, for which the classic pattern is a slow 2.5 Hz generalized spike-and-wave. Newer pharmacologic treatments include rufinamide and clobazam. However, antiepileptic drugs are often exhausted in pursuit of seizure control requiring nonpharmacologic interventions. These include dietary therapies, vagus nerve stimulation, and epilepsy surgery, including corpus callosotomy and focal curative resection. Although large lobar resections are often required, very localized, discrete resections may be possible, as in symptomatic Lennox-Gastaut syndrome (specifically, hypothalamic hamartoma). We review the history of the disease and current management options.
- 3. Montouris GD. Rational approach to treatment options for Lennox-Gastaut syndrome. *Epilepsia.* 2011;52 Suppl 5:10-20.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21790561>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2011.03178.x/asset/j.1528-1167.2011.03178.x.pdf?v=1&t=hekiekhj&s=850aaeac33a47a0b6578cc02453cc3b874a53782>  
**Abstract** Lennox-Gastaut syndrome (LGS) is an intractable childhood-onset epileptic encephalopathy. Seizure freedom is rare in LGS. One of the hallmarks of LGS is medical intractability, with generally poor response to antiepileptic drugs (AEDs). Nevertheless, several treatment options are available that can mitigate the severity of seizures and curtail their frequency. New AEDs have been validated in randomized, controlled trials for the treatment of seizures in LGS. In some cases, nonpharmacologic options may be effective, although more data are needed to confirm efficacy outcomes. Comprehensive patient assessments are critical to achieve an optimal AED treatment regimen and minimize the potential for adverse effects.

4. **Crumrine PK. Management of seizures in Lennox-Gastaut syndrome. *Paediatr Drugs*. 2011;13(2):107-18.** <http://www.ncbi.nlm.nih.gov/pubmed/21351810> <http://link.springer.com/article/10.2165%2F11536940-000000000-00000>
- Abstract** Lennox-Gastaut syndrome is an epilepsy syndrome that begins in childhood (between 1 and 8 years of age), worsens during latency and persists frequently into adulthood, is refractory to antiepileptic medications, and results in cognitive decline and behavioral problems in affected individuals. Seizure types consist primarily of axial tonic, atonic, and atypical absence; nocturnal tonic seizures are the most common seizure pattern in this population, but often are not one of the initial seizure patterns. Some patients also have myoclonic seizures; this seizure pattern is less frequent than the three preceding types. Although there are some cases that are cryptogenic, most are symptomatic, arising during prenatal and perinatal periods from intrauterine infections, and vascular insults to the brain. Examples of causes of Lennox-Gastaut syndrome include migrational abnormalities of the brain, late effects of CNS infections, certain genetic disorders such as tuberous sclerosis, and inherited metabolic disorders. The difficulty early in the course of Lennox-Gastaut syndrome is distinguishing this diagnosis from severe myoclonic epilepsy of infancy (Dravet syndrome) or from myoclonic-astatic epilepsy (Doose syndrome), as the seizure patterns in these three syndromes may overlap at the onset. EEG is a helpful diagnostic tool in the diagnosis of Lennox-Gastaut syndrome, usually demonstrating high voltage, bifrontal 1.5-2.5 Hz spike and wave complexes interictally, and attenuation with paroxysmal fast activity (10-13 Hz) during the ictal phase. Treatment options for Lennox-Gastaut syndrome have been less than optimal. In recent years, several drugs have been tested and approved for the treatment of this syndrome; these include felbamate, lamotrigine, topiramate, and rufinamide. The long-term outcome does not appear to be any better with the newer antiepileptic drugs than when using earlier prescribed antiepileptic drugs or polytherapy. Treatment options other than antiepileptic drugs include a ketogenic diet, vagus nerve stimulation, and corpus callosotomy. Long-term outcome of these patients relative to seizure control and cognition is poor. Most develop moderate intellectual disability within a few years of onset of the syndrome. Many develop behavioral problems with inattention, hyperactivity, and aggression.
5. **Rychlicki F, Zamponi N, Trignani R, Ricciuti RA, Iacoangeli M, Scerrati M. Vagus nerve stimulation: clinical experience in drug-resistant pediatric epileptic patients. *Seizure*. 2006;15(7):483-90.** <http://www.ncbi.nlm.nih.gov/pubmed/16899378>
- Abstract** INTRODUCTION: Vagus nerve stimulation (VNS) is an effective alternative treatment for patients with partial refractory epilepsy. Nevertheless, information regarding VNS in children is still limited. MATERIALS AND METHODS: The clinical efficacy, safety and neuropsychological effects of VNS in 34 children (mean age 11.5 years) with drug-resistant epilepsy were studied. Mean follow-up was 30.8 months. Nine patients have been diagnosed with Lennox-Gastaut Syndrome, nine patients were affected by severe partial epilepsy with bisynchronous EEG and drop attacks, and 16 patients suffered from partial epilepsy without bisynchronous EEG and fall seizures. Forms were designed for prospective data collection on each patient's history, seizures, implants, device settings, quality of life (QOL), neuropsychological assessment and adverse events. Surgical technique was performed both by standard two incisions and single neck incision. RESULTS: Mean reduction in total seizures was 39% at 3 months, 38% at 6 months, 49% at 12 months, 61% at 24 months and 71% at 36 months. Significant better results were obtained in partial epilepsy, with and without drop attacks, than in Lennox-Gastaut syndrome--three patients being seizure-free. No operative morbidity was reported. Side-effects were minor and transient--the most common were voice alteration and coughing during stimulation. In two patients, electrode breakage occurred 3 years after surgical procedure; in both cases, a new device was implanted after removing the vagal electrode coils and generator. CONCLUSION: VNS can be considered an appropriate strategy as an add-on treatment in children affected by drug-resistant partial epilepsy and ineligible for resective epilepsy surgery.

6. **Majoie HJ, Berfelo MW, Aldenkamp AP, Renier WO, Kessels AG. Vagus nerve stimulation in patients with catastrophic childhood epilepsy, a 2-year follow-up study. *Seizure*. 2005;14(1):10-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15642494>  
**Abstract** PURPOSE: To establish the long-term efficacy and tolerability of vagus nerve stimulation (VNS) in children with a Lennox-like syndrome. METHOD: This study was a longitudinal observational prospective cohort analysis. Baseline: 6 months. Follow-up: 24 months. Screening (baseline and every 6 months): MRI (baseline only), EEG, neuropsychological evaluation, ECG and blood sampling for antiepileptic drug levels. Nineteen children are included. RESULTS: A seizure frequency reduction of 20.6% was found at the end of the follow-up period. No relationship was detected between the length of the stimulation period and the reduction in the seizure frequency. 21% of the patients showed a reduction in seizure frequency of 50% or more. The seizure severity showed improvement in the first 12 months of treatment. The largest seizure reduction was found in the patients with highest frequency of background activity at the baseline EEG. Neuropsychological findings: no negative impact on behaviour, moderate improvement in function, behaviour and mood. Largest seizure reduction was found in the group with the highest baseline mental function. The scores for mental age improved independently of the seizure control. Twelve patients (63%) experienced minor side effects, which subsided after 1 month. CONCLUSION: (1) There was a significant reduction in seizure frequency and severity. (2) No serious side effects were recorded. (3) No negative effects on cognition or quality of life were apparent. (4) Patients with highest baseline mental functioning showed the highest seizure reduction. (5) Those patients with less disturbed EEG (high background activity and less interictal epileptic activity) showed the highest seizure reduction.
  
7. **Duric M. [Therapies for Lennox-Gastaut syndrome]. *Srp Arh Celok Lek*. 2005;133(5-6):283-7.**  
**Serbian.** <http://www.ncbi.nlm.nih.gov/pubmed/16392289>  
**Abstract** The treatment of Lennox-Gastaut Syndrome (LGS) has been improved with the introduction of the new anti-epileptic drugs: lamotrigine and topiramate, the employment of a ketogenic diet, and the availability of vagal nerve stimulation. It is difficult to provide recommendations for the treatment of LGS, in the absence of comparative trials. However, suggestions can be made on the basis of the best evidence available. Treatment should commence with valproate and continue with lamotrigine or topiramate. If seizure control is not sufficient, felbamate, a ketogenic diet, and vagal nerve stimulation are recommended. A partial callosotomy may be performed for the treatment of frequent drop attacks. Other anti-epileptic drugs may be used after a risks-benefits evaluation.
  
8. **Buoni S, Zannolli R, Macucci F, Pieri S, Galluzzi P, Mariottini A, et al. Delayed response of seizures with vagus nerve stimulation in Lennox-Gastaut syndrome. *Neurology*. 2004;63(8):1539-40.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15505192>

9. **Aldenkamp AP, Majoie HJ, Berfelo MW, Evers SM, Kessels AG, Renier WO, et al. Long-term effects of 24-month treatment with vagus nerve stimulation on behaviour in children with Lennox-Gastaut syndrome. *Epilepsy Behav.* 2002;3(5):475-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12609271>  
**Abstract** The long-term effects of vagus nerve stimulation (VNS) on behaviour were studied in 19 children with Lennox-Gastaut syndrome. We used the following stimulation parameters: output current: 112 to 2mA; signal frequency: 30Hz frequency; signal pulse width: 500µs; signal 'on and off' time: 30s 'on,' 3min 'off.' The test battery consisted of cognitive tests assessing mental age and quality of life measurements assessing independency, behavioural problems, and mood. The results show relatively small changes in the behavioural outcomes, concurrent with the modest effects of VNS on seizure frequency (an average of 20.6% seizure reduction). When baseline measurements are compared with the follow-up measures, neither the cognitive measure nor the quality of life measures show any deterioration and the cognitive measure (mental age) showed mild positive changes (gain of 4.2 months mental age during the follow-up period). None of the changes were statistically significant. Treatment effect was most prominent in the group with the highest mental age at baseline, which suggests that mental retardation is a negative prognostic factor for VNS treatment. Moreover, in this specific patient group, treatment effect did not increase with treatment duration. Some evidence during follow-up suggests a direct positive effect of VNS on behavioural function, independent of changes in seizure frequency. Long-term treatment with VNS is not associated with adverse behavioural effects. Mental retardation is a negative prognostic factor for the efficacy of VNS.
10. **Trevathan E. Infantile spasms and Lennox-Gastaut syndrome. *J Child Neurol.* 2002;17 Suppl 2:2S9-22.** <http://www.ncbi.nlm.nih.gov/pubmed/11952036>  
**Abstract** Infantile spasms and Lennox-Gastaut syndrome are rare but are important to child neurologists because of the intractable nature of the seizures and the serious neurologic comorbidities. New antiepileptic drugs offer more alternatives for treating both infantile spasms and Lennox-Gastaut syndrome. Selected children with infantile spasms are candidates for epilepsy surgery. Vagus nerve stimulation, corpus callosotomy, and the ketogenic diet are all options for selected children with Lennox-Gastaut syndrome. The epidemiology, clinical manifestations of the seizures, electroencephalographic characteristics, prognosis, and treatment options are reviewed for infantile spasms and Lennox-Gastaut syndrome. Additional therapies are needed for both infantile spasms and Lennox-Gastaut syndrome as many children fail to achieve adequate seizure control in spite of newer treatments.
11. **Karceski S. Vagus nerve stimulation and Lennox-Gastaut syndrome: a review of the literature and data from the VNS patient registry. *CNS Spectr.* 2001;6(9):766-70.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15489825>  
**Abstract** Lennox-Gastaut syndrome (LGS) is a severe form of childhood epilepsy that is usually refractory to medical management. When medication fails, alternative therapies are considered. Among these are two surgical options: corpus callosotomy and vagus nerve stimulation (VNS). Safety and efficacy are two important factors to consider when selecting an appropriate treatment. VNS is safer than callosotomy, but its efficacy is more difficult to assess. Available studies evaluate its effectiveness using a mixed population of patients (some with prior epilepsy surgery), a multitude of VNS settings, and variable endpoints. To estimate the efficacy of VNS in patients with LGS, a review of the medical literature and the VNS Patient Registry was performed. Within the limits of this type of study, the results showed that VNS appears to be equally as effective as callosotomy. Because VNS has a lower potential for adverse effects, these results suggest that VNS should be considered first in appropriately selected patients.

12. **Frost M, Gates J, Helmers SL, Wheless JW, Levisohn P, Tardo C, et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. *Epilepsia*. 2001;42(9):1148-52. <http://www.ncbi.nlm.nih.gov/pubmed/11580762>**  
**Abstract** PURPOSE: Vagus nerve stimulation (VNS) is approved for use for refractory partial seizures. Nevertheless, information regarding VNS therapy for special populations, including Lennox-Gastaut syndrome (LGS) is limited. We discuss the effectiveness, tolerability, and safety of VNS therapy in patients with LGS. METHODS: A six-center, retrospective study evaluated the effectiveness of VNS therapy in patients with LGS at 3 and 6 months and compared preimplant and postimplant seizure frequency. Adverse effects and quality of life (QOL) were included as secondary measures. RESULTS: Fifty patients, median age 13 years, with medically refractory epilepsy, were implanted. Median age at onset of seizures was 1.4 years, and a median of nine anticonvulsants (AEDs) had been tried before implantation. Data-collection forms were designed for retrospectively gathering data on each patient's preimplant history, seizures, implants, device settings, QOL, and adverse events. Median reductions in total seizures were 42% at 1 month, 58.2% at 3 months, and 57.9% at 6 months. The most common adverse events reported were voice alteration and coughing during stimulation. Other uncommon adverse events included increased drooling and behavioral changes. Investigators noted that QOL had improved for some patients in the study. CONCLUSIONS: VNS is an effective treatment for medically refractory epilepsy in LGS. This treatment is well tolerated, safe, and may improve QOL.
13. **Aldenkamp AP, Van de Veerdonk SH, Majoie HJ, Berfelo MW, Evers SM, Kessels AG, et al. Effects of 6 months of treatment with vagus nerve stimulation on behavior in children with lennox-gastaut syndrome in an open clinical and nonrandomized study. *Epilepsy Behav*. 2001;2(4):343-50. <http://www.ncbi.nlm.nih.gov/pubmed/12609211>**  
**Abstract** The effect of vagus nerve stimulation (VNS) on behavior outcomes was studied in 16 children with Lennox-Gastaut syndrome. We used the following stimulation parameters: output current, 11.2 to 20 mA; signal frequency, 30 Hz; signal pulse width, 500 microseconds; signal on and off times, 30 seconds on and 3 minutes off. The test battery consisted of cognitive tests measuring mental age, attention, language, psychomotor function, and cognitive style, and quality-of-life measurements assessing independence, behavioral problems, symptoms of pervasive development disorders (PDDs) and mood. The results show relatively small changes in behavioral outcomes concurrently with modest effects on seizure frequency (an average of 26.9% seizure reduction). When baseline and endpoint measurements are compared none of the cognitive measures show any deterioration and three of five cognitive measures show slight positive changes. Among the quality-of-life measures, one measure showed a slight worsening of scores and three showed slight improvement. When the group is divided into subgroups on the basis of treatment effect the most prominent improvements are observed in the group without any effects of VNS on seizure frequency. These patients gained, on average, 9.5 months in mental age and showed more independent behavior, mood improvements and fewer PDD symptoms. This suggests an effect of VNS on behavioral function independent of changes in seizure frequency.

14. **Majoie HJ, Berfelo MW, Aldenkamp AP, Evers SM, Kessels AG, Renier WO. Vagus nerve stimulation in children with therapy-resistant epilepsy diagnosed as Lennox-Gastaut syndrome: clinical results, neuropsychological effects, and cost-effectiveness. *J Clin Neurophysiol.* 2001;18(5):419-28.** <http://www.ncbi.nlm.nih.gov/pubmed/11709647>  
**Abstract** We studied the clinical efficacy and tolerability, neuropsychological effects, and cost-effectiveness (direct medical costs, direct nonmedical costs, and indirect costs) of vagus nerve stimulation (VNS) in children with Lennox-like syndrome (n = 16). The situation 6 months before implantation of the device is compared with that 6 months after surgery. Seizure frequency and severity are significantly reduced during VNS: 25% of the patients show a reduction in seizure frequency of 50% or greater; overall seizure reduction is 26.9%. Measures of neuropsychological outcome show a moderate improvement in mental functioning, behavior, and mood. The scores for mood and mental age improve independently of seizure control. Side effects are minor and transient. There is a significant reduction in direct non-health care costs, ergotherapy, and the number of days of sub-optimal functioning of the child. The costs during the 6 postoperative months are 2,876.06 Euros less than the costs during the 6 months before VNS; the payback period is 2.3 years.
15. **Hosain S, Nikalov B, Harden C, Li M, Fraser R, Labar D. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. *J Child Neurol.* 2000;15(8):509-12.** <http://www.ncbi.nlm.nih.gov/pubmed/10961788>  
**Abstract** Lennox-Gastaut syndrome is a severe age-specific epilepsy syndrome that presents with medication-resistant seizures in childhood. Antiepileptic drugs are the mainstay of treatment. Nonpharmacologic treatments include corpus callosum section and the ketogenic diet. However, no single treatment is safe and effective. We treated 13 patients with Lennox-Gastaut syndrome between the ages of 4 and 44 years (mean, 16.7 years) with vagus nerve stimulation. During the first 6 months of treatment, vagus nerve stimulation produced a median seizure rate reduction of 52% (range, 0% to 93%; P = .04). At 6 months of follow-up, three patients had a greater than 90% reduction in seizures, two had a greater than 75% reduction, one had a greater than 50% reduction, and six had at least a 25% reduction. One patient did not improve. No patient worsened after initial improvement. Side effects, including hoarseness, coughing, and pain in the throat, were transient and tolerable. No patient discontinued vagus nerve stimulation. Our results suggest that vagus nerve stimulation could be an effective and safe adjunct therapy for the treatment of Lennox-Gastaut syndrome.
16. **Archila R, Papazian O. [Lennox-Gastaut syndrome]. *Rev Neurol.* 1999;29(4):346-9.**  
**Spanish.** <http://www.ncbi.nlm.nih.gov/pubmed/10797925>  
**Abstract** INTRODUCTION: The Lennox-Gestaut syndrome is classified as an epileptic syndrome shown by the presence of various types of generalized seizures (tonic, atonic and atypical absences) which appear at a certain age (1-8 years), with an interictal EEG showing an abnormally slow basic rhythm interrupted by slow spike-and-wave complexes (< 3 Hz) and progressive mental deterioration. DEVELOPMENT: From the aetiological point of view there are cryptogenic (25%) and symptomatic (75%) forms. There is a previous history of West syndrome in 9.4-30% of the symptomatic cases. The commonest types of seizures are tonic (17-95%), atypical absences (17-60%) and atonic (25-56%). The mixed form of an epileptic state with typical absences and tonic seizures is the most frequent (27%). Follow-up studies show that in 90% and 100% of cryptogenic and symptomatic patients, respectively, mental retardation develops and the initial seizures persist in 67% and 45% of the patients with cryptogenic and symptomatic forms respectively, when they become adults. CONCLUSIONS: There is still no successful treatment for these seizures and progressive mental deterioration occurs even when using the newer anti-epileptic drugs. Electrical stimulation of the vagus nerve seems a promising possibility but further experience is necessary.

**Magnet Mode (VNS efficacy in...)**

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1. **Majkowska-Zwolinska B, Zwolinski P, Roszkowski M, Drabik K. Long-term results of vagus nerve stimulation in children and adolescents with drug-resistant epilepsy. *Childs Nerv Syst.* 2012;28(4):621-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22222361>  
<http://link.springer.com/article/10.1007%2Fs00381-011-1670-z>  
**Abstract** PURPOSE: The purpose of this study was to evaluate long-term seizure reduction and on-demand magnet use in children and adolescents with drug-resistant epilepsy who were treated with vagus nerve stimulation therapy. METHODS: Fifty-seven children and adolescents under 18 years of age with drug-resistant epilepsy were implanted with a vagus nerve stimulation therapy device. Seizure reduction was evaluated at 6, 12, 24, 36, and 48 months after implantation. Magnet effect on seizure frequency was evaluated during the first week after implantation and after 6, 12, 24, 36, and 48 months of treatment. RESULTS: The mean reduction in seizure frequency compared with baseline was significant at all time points up to 48 months post-implantation. At 12 months, the average reduction in seizure frequency was 52.4%, and at 48 months, it was 53.1% (observed case analysis). The use of a magnet to deliver extra "on-demand" stimulation between cycles resulted in cessation of seizures in 16.1% of patients, partial effect in 73.2%, and no effect in 10.7%, when evaluated within 1 week of implantation. The magnet effect decreased slightly with increasing time after implantation. A sub-analysis of children <math>\leq 12</math> years of age (N = 34) showed similar results after 36 months of follow-up. The therapy was well tolerated regardless of age. CONCLUSION: Vagus nerve stimulation therapy is a safe and effective adjunctive treatment for children and adolescents of all ages with drug-resistant epilepsy.
  
2. **Morris GL, 3rd. A retrospective analysis of the effects of magnet-activated stimulation in conjunction with vagus nerve stimulation therapy. *Epilepsy Behav.* 2003;4(6):740-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/14698710>  
**Abstract** Vagus nerve stimulation (VNS) therapy offers two methods to help control seizures, automatic stimulation delivered at programmed intervals and on-demand stimulation initiated with a magnet. This study retrospectively analyzes magnet use during the E03 and E04 clinical trials of VNS therapy. Magnet activation that aborted, decreased, terminated, or diminished a seizure was classified as an improvement; for purposes of evaluation, the patient was considered to have received a benefit. When patients in the E03 trial used magnets to activate stimulation, patients with active magnets were more likely to report seizure improvement than patients with inactive magnets (P=0.0479, Fisher's test). In the E04 trial, 22% of patients using the magnet reported seizure termination and 31% reported seizure diminution. Unrelated to seizure reduction with programmed VNS therapy, approximately half of the patients who used the magnet in this study received some benefit. Additional studies can provide a better understanding of this unique mode of delivering antiseizure therapy.

3. **Boon P, Vonck K, Van Walleghem P, D'Have M, Caemaert J, De Reuck J. Vagus nerve stimulation for epilepsy, clinical efficacy of programmed and magnet stimulation. *Acta Neurochir Suppl.* 2002;79:93-8. <http://www.ncbi.nlm.nih.gov/pubmed/11974997>**

**Abstract** RATIONALE: Vagus nerve stimulation (VNS) by intermittent and programmed electrical stimulation of the left vagus nerve in the neck, has become widely available. It is an effective treatment for patients with refractory epilepsy. Patients can be provided with a magnet that allows to deliver additional stimulation trains. Since earlier studies have demonstrated the persistence of a stimulation effect after discontinuation of the stimulation train, we evaluated the clinical efficacy of VNS both in the programmed intermittent stimulation mode and magnet stimulation mode. METHODS: A group of 30 patients (16 F, 14 M) with medically refractory partial epilepsy, who were unsuitable candidates for resective surgery, were included in the study. The patients, their companions and caregivers were instructed on how to administer additional stimulation trains using a hand-held magnet when an aura or a seizure onset occurred. Patients or caregivers could recognize habitual seizures and were able to evaluate sudden interruption of these seizures. Using seizure diaries, detailed accounts of magnet use and regular clinic follow-up visits, data on seizure frequency and severity and number of magnet applications were collected. Patients who provided unreliable information were excluded from the analysis. RESULTS: Forty-seven percent of all patients had an improvement in seizure control with a reduction in seizure frequency of more than 50% during a mean follow-up of 33 months (range: 4-67 months). More than half of the patients used the magnet and provided reliable information. In 63% of patients who were able to self-administer or receive additional magnet stimulation, seizures could be interrupted, be it consistently or occasionally. More than half of the patients who reported a positive effect of magnet stimulation became responders. In most cases the magnet was applied by a caregiver. CONCLUSIONS: To our knowledge, this study is the first to explore the efficacy of magnet-induced vagus nerve stimulation. Results suggest that the magnet is a useful tool that provides patients and mainly caregivers with an additional means of controlling refractory seizures. Additional controlled studies comparing programmed stimulation and magnet-induced stimulation in monitoring conditions are warranted.

4. **Boon P, Vonck K, Van Walleghem P, D'Have M, Goossens L, Vandekerckhove T, et al. Programmed and magnet-induced vagus nerve stimulation for refractory epilepsy. *J Clin Neurophysiol.* 2001;18(5):402-7. <http://www.ncbi.nlm.nih.gov/pubmed/11709644>**

**Abstract** Vagus nerve stimulation (VNS) is an effective alternative treatment for patients with refractory epilepsy. The generator produces intermittent stimulation trains and does not require patient intervention. Using currently available technology, continuous stimulation is incompatible with a reasonable battery life. Because earlier studies have demonstrated the persistence of a stimulation effect after discontinuation of the stimulation train, we intended to evaluate the clinical efficacy of VNS in both the programmed intermittent stimulation mode and the magnet stimulation mode. Patients, companions, and caregivers were instructed on how to administer additional stimulation trains when an aura or a seizure onset occurred. We assumed that patients or caregivers could recognize habitual seizures and were able to evaluate sudden interruption of these seizures. During a mean follow-up of 35 months, 46% of patients became responders, with a reduction in seizure frequency of more than 50%. Twenty-nine percent of patients stopped having convulsive seizures. In two thirds of patients who were able to self-administer or receive additional magnet stimulation, seizures could be interrupted consistently or occasionally. More than half of the patients who reported a positive effect of magnet stimulation became responders. Only three patients were able to use the magnet themselves. In most cases, support from caregivers was necessary. This study is the first to document the efficacy of magnet-induced VNS in a larger patient population during long-term follow-up. The magnet is a useful tool that provides patients who are treated with VNS and mainly caregivers of such patients with an additional means of controlling seizures. To further confirm the self-reported results from our patients, additional studies comparing programmed stimulation and magnet-induced stimulation during monitoring conditions are needed.

**MoA - Animal Studies (of VNS in epilepsy)**

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1. **Ura H, Sugaya Y, Ohata H, Takumi I, Sadamoto K, Shibasaki T, et al. Vagus nerve stimulation induced long-lasting enhancement of synaptic transmission and decreased granule cell discharge in the hippocampal dentate gyrus of urethane-anesthetized rats. *Brain Res.* 2013;1492:63-71.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23183039>  
**Abstract** Vagus nerve stimulation (VNS) ameliorates deficits of hippocampal functions, such as contextual learning and memory, probably through direct modulation of neuronal activity. Previous studies showed that VNS enhanced excitatory synaptic transmission in the hippocampal CA3 area via activation of beta-adrenergic receptors. However, effects of VNS on excitatory synaptic transmission and action potential (AP) discharge of granule cells (GCs) in the dentate gyrus have not been studied. Urethane-anesthetized rats were used to investigate whether VNS influences synaptic transmission efficacy at perforant path-GC synapses and population spike discharge in the dentate gyrus. Intermittent burst stimulation of the left vagus nerve (30Hz for 30s at an inter-train interval of 5min for 1h) significantly enhanced the perforant path-GC synaptic transmission efficacy in the dentate gyrus for at least 2h, indicating that VNS can induce a long-lasting enhancement of synaptic transmission in this area, similar to the situation observed in the CA3 area. In contrast, a 60-min period of VNS significantly reduced population spike amplitude (a parameter reflecting synchronized AP discharge of GCs) for a given excitatory postsynaptic potential. These findings suggest that acute VNS enhances the excitatory synaptic transmission and reduces synchronized AP discharge of GCs in the dentate gyrus. It is likely that enhancement of excitatory synaptic transmission and reduction of GC excitability contribute VNS treatment efficacy for learning deficits and intractable epilepsy, respectively.
  
2. **Yoo PB, Lubock NB, Hincapie JG, Ruble SB, Hamann JJ, Grill WM. High-resolution measurement of electrically-evoked vagus nerve activity in the anesthetized dog. *J Neural Eng.* 2013;10(2):026003.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23370017>  
<http://iopscience.iop.org/1741-2552/10/2/026003/>  
**Abstract** Objective. Not fully understanding the type of axons activated during vagus nerve stimulation (VNS) is one of several factors that limit the clinical efficacy of VNS therapies. The main goal of this study was to characterize the electrical recruitment of both myelinated and unmyelinated fibers within the cervical vagus nerve. Approach. In anesthetized dogs, recording nerve cuff electrodes were implanted on the vagus nerve following surgical excision of the epineurium. Both the vagal electroneurogram (ENG) and laryngeal muscle activity were recorded in response to stimulation of the right vagus nerve. Main results. Desheathing the nerve significantly increased the signal-to-noise ratio of the ENG by 1.2 to 9.9 dB, depending on the nerve fiber type. Repeated VNS following nerve transection or neuromuscular block (1) enabled the characterization of A-fibers, two sub-types of B-fibers, and unmyelinated C-fibers, (2) confirmed the absence of stimulation-evoked reflex compound nerve action potentials in both the ipsilateral and contralateral vagus nerves, and (3) provided evidence of stimulus spillover into muscle tissue surrounding the stimulating electrode. Significance. Given the anatomical similarities between the canine and human vagus nerves, the results of this study provide a template for better understanding the nerve fiber recruitment patterns associated with VNS therapies.

3. **Kaya M, Orhan N, Karabacak E, Bahceci MB, Arican N, Ahishali B, et al. Vagus nerve stimulation inhibits seizure activity and protects blood-brain barrier integrity in kindled rats with cortical dysplasia. *Life Sci.* 2013;92(4-5):289-97.**

<http://www.ncbi.nlm.nih.gov/pubmed/23333826>

**Abstract** AIMS: This study investigates the effects of vagus nerve stimulation (VNS) on seizure severity and blood-brain barrier (BBB) integrity in kindled rats with cortical dysplasia (CD). MAIN METHODS: Pregnant rats were exposed to 145cGy of gamma-irradiation on day 17 of pregnancy. In offsprings, kindling was induced by giving subconvulsive doses of pentylenetetrazole. Left VNS was performed for 48h at output currents of 0.5 or 1mA. Horseradish peroxidase (HRP) was used to study the BBB permeability. Immunohistochemistry for occludin and P-glycoprotein (P-gp) was also performed. KEY FINDINGS: Kindled rats with CD exhibited seizures with mean Racine's scores of 3.57+/-1.2 during video EEG recording. Kindled animals with CD receiving VNS at 0.5 and 1.0mA did not exhibit either clinical or electrophysiological signs of seizure. Immunostaining for occludin, a tight junction protein, in hippocampus remained relatively intact in all groups. VNS-treated and -untreated kindled animals with CD revealed intense immunostaining for P-gp in hippocampal formation (P<0.01). Electron microscopic observations revealed frequent transport vesicles containing electron-dense HRP reaction products in the cytoplasm of brain capillary endothelial cells in both cerebral cortex and hippocampus of kindled animals with CD. Those which were exposed to 1mA VNS were observed to have brain capillary endothelial cells largely devoid of HRP reaction products in both cerebral cortex and hippocampus. SIGNIFICANCE: The results of this study suggest that VNS therapy at 1mA inhibits seizure activity and protects BBB integrity by limiting the enhancement of transcellular pathway in kindled animals with CD.

4. **Maggio N, Segal M. Stress and corticosteroid modulation of seizures and synaptic inhibition in the hippocampus. *Exp Neurol.* 2012;234(1):200-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/22227061>

**Abstract** The role of stress hormones in the initiation of epileptic seizures has been studied extensively in the past decade, with conflicting observations, from suppression to exacerbation of spontaneous seizures. We have now studied the effects of an acute stress on reactivity of juvenile rats to kainic acid (KA), which produces epileptic seizures. With a short (30s) stress-KA delay, stress exacerbated epilepsy via activation of mineralocorticosterone receptors (MR). With a long (60 min) stress-KA delay, seizures were suppressed through activation of a glucocorticosterone receptor (GR). In a parallel study with CA1 pyramidal neurons in acute hippocampal slices, activation of MRs reduced the frequency of mIPSCs, whereas activation of GRs produced a slow onset, 2.5 fold increase in amplitudes of mIPSCs. GR effects were not mediated by protein synthesis, but did require activation of some protein kinases. These experiments suggest that stress can either facilitate or suppress seizures, in a time and receptor dependent manner.

5. **Gnatek Y, Zimmerman G, Goll Y, Najami N, Soreq H, Friedman A. Acetylcholinesterase loosens the brain's cholinergic anti-inflammatory response and promotes epileptogenesis. *Front Mol Neurosci.* 2012;5:66.**

<http://www.ncbi.nlm.nih.gov/pubmed/22639569>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3355593/pdf/fnmol-05-00066.pdf>

**Abstract** Recent studies show a key role of brain inflammation in epilepsy. However, the mechanisms controlling brain immune response are only partly understood. In the periphery, acetylcholine (ACh) release by the vagus nerve restrains inflammation by inhibiting the activation of leukocytes. Recent reports suggested a similar anti-inflammatory effect for ACh in the brain. Since brain cholinergic dysfunctions are documented in epileptic animals, we explored changes in brain cholinergic gene expression and associated immune response during pilocarpine-induced epileptogenesis. Levels of acetylcholinesterase (AChE) and inflammatory markers were measured using real-time RT-PCR, in-situ hybridization and immunostaining in wild type (WT) and transgenic mice over-expressing the "synaptic" splice variant AChE-S (TgS). One month following pilocarpine, mice were video-monitored for spontaneous seizures. To test directly the effect of ACh on the brain's innate immune response, cytokines expression levels were measured in acute brain slices treated with cholinergic agents. We report a robust up-regulation of AChE as early as 48 h following pilocarpine-induced status epilepticus (SE). AChE was expressed in hippocampal neurons, microglia, and endothelial cells but rarely in astrocytes. TgS mice overexpressing AChE showed constitutive increased microglial activation, elevated levels of pro-inflammatory cytokines 48 h after SE and accelerated epileptogenesis compared to their WT counterparts. Finally we show a direct, muscarine-receptor dependant, nicotine-receptor independent anti-inflammatory effect of ACh in brain slices maintained ex vivo. Our work demonstrates for the first time, that ACh directly suppresses brain innate immune response and that AChE up-regulation after SE is associated with enhanced immune response, facilitating the epileptogenic process. Our results highlight the cholinergic system as a potential new target for the prevention of seizures and epilepsy.

6. **Shen H, Fuchino Y, Miyamoto D, Nomura H, Matsuki N. Vagus nerve stimulation enhances perforant path-CA3 synaptic transmission via the activation of beta-adrenergic receptors and the locus coeruleus. *Int J Neuropsychopharmacol.* 2012;15(4):523-30.**

<http://www.ncbi.nlm.nih.gov/pubmed/21733240>

<http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=8536940>

**Abstract** Vagus nerve stimulation (VNS) is an approved treatment for epilepsy and depression and has cognition-enhancing effects in patients with Alzheimer's disease. The hippocampus is widely recognized to be related to epilepsy, depression, and Alzheimer's disease. One possible mechanism of VNS involves its effect on the hippocampus; i.e. it increases the release of noradrenaline in the hippocampus. However, the effect of VNS on synaptic transmission in the hippocampus is unknown. To determine whether VNS modulates neurotransmission in the hippocampus, we examined the effects of VNS on perforant path (PP)-CA3 synaptic transmission electrophysiologically in anaesthetized rats. VNS induces a persistent enhancement of PP-CA3 field excitatory post-synaptic potentials (fEPSPs). Arc, an immediate early gene, was used to identify active brain regions after VNS. The locus coeruleus (LC), which contains the perikarya of noradrenergic projections, harboured more Arc-positive cells, as measured by in-situ hybridization, after 10-min VNS. In addition, electrical lesions of LC neurons or intraventricular administration of the beta-adrenergic receptor antagonist timolol prevented the enhancement of PP-CA3 responses by VNS. In conclusion, the protracted increase in PP-CA3 synaptic transmission that is induced by VNS entails activation of the LC and beta-adrenergic receptors. Our novel findings suggest that information from the periphery modulates synaptic transmission in the CA3 region of the hippocampus.

7. **Rijkers K, Majoie HJ, Aalbers MW, Philippens M, Doenni VM, Vles JS, et al. Rat vagus nerve stimulation model of seizure suppression: nNOS and DeltaFos B changes in the brainstem. *J Chem Neuroanat.* 2012;46(1-2):1-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23022956>  
**Abstract** Vagus nerve stimulation (VNS) is a moderately effective treatment for intractable epilepsy. However, the mechanism of action is poorly understood. The effect of left VNS in amygdala kindled rats was investigated by studying changes in nNOS and DeltaFos B expression in primary and secondary vagus nerve projection nuclei: the nucleus of the solitary tract (NTS), dorsal motor nucleus of the vagus nerve (DMV), parabrachial nucleus (PBN) and locus coeruleus (LC). Rats were fully kindled by stimulation of the amygdala. Subsequently, when the fully kindled state was reached and then maintained for ten days, rats received a single 3-min train of VNS starting 1min prior to the kindling stimulus and lasting for 2min afterwards. In control animals the vagus nerve was not stimulated. Animals were sacrificed 48h later. The brainstems were stained for neuronal nitric oxide synthase (nNOS) and DeltaFos B. VNS decreased seizure duration with more than 25% in 21% of rats. No VNS associated changes in nNOS immunoreactivity were observed in the NTS and no changes in DeltaFos B were observed in the NTS, PBN, or LC. High nNOS immunopositive cell densities of >300cells/mm(2) were significantly more frequent in the left DMV than in the right ( $\chi^2(1)=26.2$ ,  $p<0.01$ ), independent of whether the vagus nerve was stimulated. We conclude that the observed nNOS immunoreactivity in the DMV suggests surgery-induced axonal damage. A 3-min train of VNS in fully kindled rats does not affect DeltaFos B expression in primary and secondary projection nuclei of the vagus nerve.
8. **Fornai F, Ruffoli R, Giorgi FS, Paparelli A. The role of locus coeruleus in the antiepileptic activity induced by vagus nerve stimulation. *Eur J Neurosci.* 2011;33(12):2169-78.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21535457>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1460-9568.2011.07707.x/abstract>  
**Abstract** Stimulation of the vagus nerve produces antiepileptic effects. This is used clinically to treat drug-refractory epilepsies. The mechanisms responsible for these effects depend on the activation of vagal afferents reaching the nucleus of the solitary tract. This review focuses on the neuroanatomy of the nucleus of the solitary tract and its relation with the nucleus locus coeruleus as a preferential anatomical substrate in producing antiepileptic effects. In fact, following the transient or permanent inactivation of locus coeruleus neurons, some antiepileptic effects of vagus nerve stimulation are lost. The activation of locus coeruleus per se is known to limit the spread of a seizure and the duration of a variety of seizure types. This is due to the fine chemical neuroanatomy of norepinephrine pathways that arise from the locus coeruleus, which produce widespread changes in cortical areas. These changes may be sustained by norepinephrine alone, or in combination with its co-transmitters. In addition, vagus nerve stimulation may prevent seizures by activating the serotonin-containing dorsal raphe neurons.

9. **Raedt R, Clinckers R, Mollet L, Vonck K, El Tahry R, Wyckhuys T, et al. Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model. *J Neurochem.* 2011;117(3):461-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21323924>  
**Abstract** Vagus nerve stimulation (VNS) is an effective adjunctive treatment for medically refractory epilepsy. In this study, we measured VNS-induced changes in hippocampal neurotransmitter levels and determined their potential involvement in the anticonvulsive action of VNS, to elucidate the mechanism of action responsible for the seizure suppressing effect of VNS in an animal model for limbic seizures. We used in vivo intracerebral microdialysis to measure VNS-induced changes in hippocampal extracellular concentrations of noradrenaline, dopamine, serotonin and GABA in freely moving, male Wistar rats. During the same experiment, the effect of VNS on pilocarpine-induced limbic seizures was assessed using video-EEG monitoring. The involvement of VNS-induced increases in hippocampal noradrenaline in the mechanisms of action of VNS was evaluated by blocking hippocampal alpha(2)-receptors. VNS produced a significant increase in hippocampal noradrenaline concentration (69 +/- 16% above baseline levels). VNS also increased the latency between pilocarpine infusion and the onset of epileptiform discharges, and reduced the duration and severity of pilocarpine-induced limbic seizures. A strong positive correlation was found between the noradrenergic and anticonvulsive effects of VNS. Blockade of hippocampal alpha(2)-receptors reversed the seizure-suppressing effect of VNS. VNS induces increases in extracellular hippocampal noradrenaline, which are at least partly responsible for its seizure-suppressing effect in a model for limbic seizures, and constitute a potential biomarker for the efficacy of VNS in temporal lobe epilepsy.
10. **Nichols JA, Nichols AR, Smirnakis SM, Engineer ND, Kilgard MP, Atzori M. Vagus nerve stimulation modulates cortical synchrony and excitability through the activation of muscarinic receptors. *Neuroscience.* 2011;189:207-14.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21627982>  
**Abstract** Vagus nerve stimulation (VNS) is an FDA approved treatment for drug-resistant epilepsy and depression. Recently, we demonstrated the capacity for repeatedly pairing sensory input with brief pulses of VNS to induce input specific reorganization in rat auditory cortex. This was subsequently used to reverse the pathological neural and perceptual correlates of hearing loss induced tinnitus. Despite its therapeutic potential, VNS mechanisms of action remain speculative. In this study, we report the acute effects of VNS on intra-cortical synchrony, excitability, and sensory processing in anesthetized rat auditory cortex. VNS significantly increased and decorrelated spontaneous multi-unit activity, and suppressed entrainment to repetitive noise burst stimulation at 6-8 Hz but not after application of the muscarinic antagonist scopolamine. Collectively, these experiments demonstrate the capacity for VNS to acutely influence cortical synchrony and excitability and strengthen the hypothesis that acetylcholine and muscarinic receptors are involved in VNS mechanisms of action. These results are discussed with respect to their possible implications for sensory processing, neural plasticity, and epilepsy.

11. **Momose-Sato Y, Nakamori T, Sato K. Functional development of the vagal and glossopharyngeal nerve-related nuclei in the embryonic rat brainstem: optical mapping with a voltage-sensitive dye. *Neuroscience*. 2011;192:781-92.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21718760>  
**Abstract** We investigated functional organization of the vagus nerve (N. X)- and glossopharyngeal nerve (N. IX)-related nuclei in the embryonic rat brainstem and compared their development and spatial distribution patterns, using multiple-site optical recording with a fast voltage-sensitive dye, NK2761. Intact brainstem preparations with N. X and N. IX attached were dissected from E13-E16 rat embryos, and electrical responses evoked by N. X/N. IX stimulation were optically recorded from many loci of the stained preparations. We analyzed optical waveforms and separated fast and slow optical signals corresponding to the antidromic/orthodromic action potentials and the excitatory postsynaptic potentials (EPSPs), respectively. We constructed contour line maps of signal amplitudes and identified motor and sensory nuclei of N. X and N. IX. In the N. X-related motor nucleus (the dorsal motor nucleus of the vagus nerve: DMNV), the fast signals were distributed in multiple-peak patterns, suggesting that the neurons and/or their activity are not distributed uniformly within the motor nuclei at early developmental stages. In the sensory nucleus (the nucleus of the tractus solitarius: NTS), the EPSPs were first detected from E15 in normal physiological solution for both N. X and N. IX. The N. IX-related NTS partially overlapped with the N. X-related NTS, but the peak locations were different between these two nerves. The results obtained in this study suggest that functional organization of the N. X- and N. IX-related nuclei changes dynamically with development in the embryonic rat brainstem.
12. **Hotta H, Watanabe N, Orman R, Stewart M. Efferent and afferent vagal actions on cortical blood flow and kainic acid-induced seizure activity in urethane anesthetized rats. *Auton Neurosci*. 2010;156(1-2):144-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20510656>  
**Abstract** Autonomic dysfunction during seizures can induce bradyarrhythmia via efferent vagal overactivity. We studied cardiovascular, brain blood flow, and electroencephalographic consequences of vagal stimulation during seizures in rats. Efferent vagal stimulation reduced seizure activity, completely suppressing it at high frequencies, by reducing heart rate, arterial pressure, and cortical blood flow. Afferent vagal activation was more variable, and the highest stimulation frequencies also appeared to reduce cortical blood flow. We conclude that efferent vagal activity can arrest ongoing seizure activity by ultimately decreasing hippocampal blood flow. Afferent vagal activity (which does not occur during seizures) may have a similar action.

13. **Magdaleno-Madrigal VM, Martinez-Vargas D, Valdes-Cruz A, Almazan-Alvarado S, Fernandez-Mas R. Preemptive effect of nucleus of the solitary tract stimulation on amygdaloid kindling in freely moving cats. *Epilepsia*. 2010;51(3):438-44.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19817809>  
**Abstract** PURPOSE: The nucleus of the solitary tract (NTS) is a primary site where vagal afferents terminate. The aim of this study was to analyze the preemptive effect of NTS electrical stimulation on daily amygdaloid kindling (AK) in freely moving cats. METHODS: Seven adult male cats were used. Bipolar electrodes were stereotaxically implanted into both amygdalae, lateral geniculate bodies, hippocampi, and prefrontal cortices. In addition, a bipolar stainless steel electrode was implanted in the left NTS. Cats were recorded under the following experimental conditions: The NTS was stimulated for 6 days before the initiation of AK (1 min on/5 min off, 1 h total). AK was performed by stimulating the amygdala every 24 h (1 s, 60 Hz, 1 ms) until behavioral stage VI was reached. RESULTS: The number of stimulations to reach stage VI in control animals was 23.4 +/- 3.7, in lateral tegmental field (LTF) animals was 17.0 +/- 2.1 days. Animals subjected to preemptive NTS stimulation showed a significant increase (53.8 +/- 5.9). In addition, behavioral development was retarded, with an increase in the number of stimulations required to reach stage III. In this group, overall kindling development was delayed, and amygdaloid afterdischarge duration did not show a progressive increase as was observed in the control group. DISCUSSION: Our results indicate that preemptive NTS electrical stimulation interferes with epileptogenesis. This anticonvulsive effect could be related to the activation of certain structures that inhibit seizure development. Therefore, results suggest that NTS mediates the anticonvulsive effect of vagus nerve stimulation.
14. **Reyt S, Picq C, Sinniger V, Clarencon D, Bonaz B, David O. Dynamic Causal Modelling and physiological confounds: a functional MRI study of vagus nerve stimulation. *Neuroimage*. 2010;52(4):1456-64.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20472074>  
**Abstract** Dynamic Causal Modelling (DCM) has been proposed to estimate neuronal connectivity from functional magnetic resonance imaging (fMRI) using a biophysical model that links synaptic activity to hemodynamic processes. However, it is well known that fMRI is sensitive not only to neuronal activity, but also to many other psychophysiological responses which may be task-related, such as changes in cardio-respiratory activity. They are not explicitly taken into account in the generative models of DCM and their effects on estimated neuronal connectivity are not known. The main goal of this study was to report the face validity of DCM in the presence of strong physiological confounds that presumably cannot be corrected for, using an fMRI experiment of vagus nerve stimulation (VNS) performed in rats. First, a simple simulation was used to evaluate the principled ability of DCM to recover directed connectivity in the presence of a confounding factor. Second, we tested the experimental validity using measures of the BOLD correlates of left 5Hz VNS. Because VNS mostly activates the central autonomic regulation system, fMRI signals were likely to represent both direct and indirect vascular responses to such activation. In addition to the inference of standard statistical parametric maps, DCM was thus used to estimate directed neural connectivity in a small brain network including the nucleus tractus solitarius (NTS) known to receive vagal afferents. Though blood pressure changes may constitute a major physiological confound in this dataset, model comparison of DCMs still allowed the identification of the NTS as the input station of the VNS pathway to the brain. Our study indicates that current developments of DCM are robust to psychophysiological responses to some extent, but does not exclude the need to develop specific models of brain - body interactions within the DCM framework to better estimate neuronal connectivity from fMRI time series.

15. **Zhang JL, Zhang SP, Zhang HQ. Antiepileptic effects of electroacupuncture vs vagus nerve stimulation on cortical epileptiform activities. *J Neurol Sci.* 2008;270(1-2):114-21.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18394652>  
**Abstract** Introduced about two decades ago, vagus nerve stimulation (VNS) therapy has been increasingly used for the treatment of refractory epilepsy recently. This study was set out to compare the effects between VNS and electroacupuncture (EA) on pentylenetetrazole (PTZ) induced epileptiform activities in the rat cerebral cortex. Under general anesthesia, the parietal cortex of the rat (n=20) was exposed to record the cortical epileptiform activities. The left vagus nerve was stimulated at 30 Hz, 1 mA or 3 mA for 5 min. For EA, "Dazhui" acupoint (GV14) was stimulated with a pair of acupuncture needles with the same parameters. The results show that both VNS and EA at either 1 mA or 3 mA could inhibit the PTZ-induced cortical epileptiform activities, and higher stimulation (3 mA) was not associated with a greater inhibition. In the cases that showed inhibitory responses, there were no statistically significant differences between the two modalities, implying that EA could be comparable to VNS in the treatment of epilepsy. Thus, under current experimental settings, the antiepileptic effect induced by electrical stimulation appeared not vagal specific, and EA could be a good alternative to VNS in the management of epilepsy.
16. **Zhang JL, Zhang SP, Zhang HQ. Antiepileptic effect of electroacupuncture vs. vagus nerve stimulation in the rat thalamus. *Neurosci Lett.* 2008;441(2):183-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18577420>  
**Abstract** Our previous study has shown that both electroacupuncture (EA) and vagus nerve stimulation (VNS) can inhibit cortical epileptiform activities induced by pentylenetetrazole (PTZ). The current study compared the effects of EA and VNS on thalamic neuronal responses to PTZ-induced epileptiform activities. Under general anesthesia, extracellular single unit recordings were made from 49 single neurons in the rat ventrobasal (VB) thalamus. The left vagus nerve was stimulated at 30 Hz, 1 or 3 mA for 5 min. For EA, "Dazhui" acupoint (GV14) was stimulated with the same parameters. It was found that (1) the VB thalamic neurons showed epileptiform activities after PTZ injection; (2) VNS and EA could predominantly inhibit the PTZ-induced epileptiform activities in the thalamic neurons. The higher intensity stimulation (3 mA) in either VNS or EA was, however, not associated with a greater inhibition. Our study suggests that both EA and VNS reduce epileptiform activities at the thalamic level, and EA may be an alternative to VNS.
17. **Osharina V, Bagaev V, Wallois F, Larnicol N. Autonomic response and Fos expression in the NTS following intermittent vagal stimulation: importance of pulse frequency. *Auton Neurosci.* 2006;126-127:72-80.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16713370>  
**Abstract** Chronic intermittent stimulation of the vagus nerve (VNS) is an approved adjunctive therapy of refractory epilepsy. Nevertheless, the circuits triggered by VNS under the variable conditions used in patients are not well understood. We analyzed the effect of increasing pulse frequency on physiological variables (intra-gastric pressure, cardiac and respiratory frequencies) and neuronal activation in the solitary tract nucleus (NTS), the entry level of peripheral vagal afferents, in the rat. For this purpose, we compared the subnuclear distribution of Fos-like immunoreactivity within the NTS following VNS at frequencies selected for their low (1 Hz) or high (10 Hz) therapeutic efficacy. In addition, NADPH diaphorase histochemistry was conducted in double-labeling experiments to check whether activated neurons may express nitric oxide (NO). We demonstrated that increasing pulse frequency had a major influence on the cardiorespiratory response to VNS and on the amount of activated neurons within NTS subdivisions engaged in cardiorespiratory control. These data, in line with clinical observations, suggested that within the range of therapeutic frequency, VNS may favor the regulation by vagal inputs of cortical activities within limbic areas involved in both epileptogenesis and cardiorespiratory afferent control. Furthermore, we did not find any evidence that anticonvulsant VNS might trigger NOergic neurons in the NTS.

18. **Roosevelt RW, Smith DC, Clough RW, Jensen RA, Browning RA. Increased extracellular concentrations of norepinephrine in cortex and hippocampus following vagus nerve stimulation in the rat. *Brain Res.* 2006;1119(1):124-32.**

<http://www.ncbi.nlm.nih.gov/pubmed/16962076>

**Abstract** The vagus nerve is an important source of afferent information about visceral states and it provides input to the locus coeruleus (LC), the major source of norepinephrine (NE) in the brain. It has been suggested that the effects of electrical stimulation of the vagus nerve on learning and memory, mood, seizure suppression, and recovery of function following brain damage are mediated, in part, by the release of brain NE. The hypothesis that left vagus nerve stimulation (VNS) at the cervical level results in increased extracellular NE concentrations in the cortex and hippocampus was tested at four stimulus intensities: 0.0, 0.25, 0.5, and 1.0 mA. Stimulation at 0.0 and 0.25 mA had no effect on NE concentrations, while the 0.5 mA stimulation increased NE concentrations significantly in the hippocampus (23%), but not the cortex. However, 1.0 mA stimulation significantly increased NE concentrations in both the cortex (39%) and hippocampus (28%) bilaterally. The increases in NE were transient and confined to the stimulation periods. VNS did not alter NE concentrations in either structure during the inter-stimulation baseline periods. No differences were observed between NE levels in the initial baseline and the post-stimulation baselines. These findings support the hypothesis that VNS increases extracellular NE concentrations in both the hippocampus and cortex.

19. **Dedeurwaerdere S, Gilby K, Vonck K, Delbeke J, Boon P, McIntyre D. Vagus nerve stimulation does not affect spatial memory in fast rats, but has both anti-convulsive and pro-convulsive effects on amygdala-kindled seizures. *Neuroscience.* 2006;140(4):1443-51.**

<http://www.ncbi.nlm.nih.gov/pubmed/16650602>

**Abstract** Vagus nerve stimulation (VNS) is an adjunctive treatment for refractory epilepsy. Using a seizure-prone Fast-kindling rat strain with known comorbid behavioral features, we investigated the effects of VNS on spatial memory, epileptogenesis, kindled seizures and body weight. Electrodes were implanted in both amygdalae and around the left vagus nerve of 17 rats. Following recovery, rats were tested in the Morris water-maze utilizing a fixed platform paradigm. The VNS group received 2 h of stimulation prior to entering the Morris water-maze. Rats were then tested in the kindling paradigm wherein the VNS group received 2 h of stimulation prior to daily kindling stimulation. Finally, the abortive effects of acute VNS against kindling-induced seizures were determined in fully kindled rats by applying VNS immediately after the kindling pulse. Body weight, water consumption and food intake were measured throughout. Memory performance in the Morris water-maze was not different between control and vagus nerve stimulation rats. Similarly, kindling rate was unaffected by antecedent VNS. However, pro-convulsive effects ( $P < 0.05$ ) were noted, when VNS was administered prior to the kindling pulse in fully kindled rats. Yet, paradoxically, VNS showed anti-convulsant effects ( $P < 0.01$ ) in those rats when applied immediately after the kindling stimulus. Body weight was significantly lower throughout kindling ( $P < 0.01$ ) in VNS-treated rats compared with controls, which was associated with reduced food intake ( $P < 0.05$ ), but without difference in water consumption. VNS appears to be devoid of significant cognitive side effects in the Morris water-maze in Fast rats. Although VNS exhibited no prophylactic effect on epileptogenesis or seizure severity when applied prior to the kindling stimulus, it showed significant anti-convulsant effects in fully kindled rats when applied after seizure initiation. Lastly, VNS prevented the weight gain associated with kindling through reduced food intake.

20. **Dedeurwaerdere S, Cornelissen B, Van Laere K, Vonck K, Achten E, Slegers G, et al. Small animal positron emission tomography during vagus nerve stimulation in rats: a pilot study. *Epilepsy Res.* 2005;67(3):133-41.**

<http://www.ncbi.nlm.nih.gov/pubmed/16289508>

**Abstract** Vagus nerve stimulation (VNS) is an effective neurophysiological treatment for patients with refractory epilepsy, however, the mechanism of action remains unclear. Small animal positron emission tomography (PET) permits the monitoring of biochemical processes during multiple scans in the same animal. The aim of this pilot study was to explore the potential of 2-[18F]-fluoro-2-deoxy-d-glucose (FDG)-PET to investigate the effect of acute and chronic VNS on glucose metabolism in the rat brain. One week after EEG and VNS electrode implantation, a baseline FDG-PET scan was acquired during which animals were not stimulated. Secondly, scans were taken after first activation of the VNS electrode (acute VNS) and after one week of continuous VNS (chronic VNS). On the same time points, images were obtained in a control group. After acquisition, PET images were manually fused with MRI data. Normalized brain activities and left/right activity ratios of different brain structures were compared between control measurements and VNS group. During acute VNS, glucose metabolism was significantly decreased in the left hippocampus ( $P < 0.05$ ). Significant increases were found in both olfactory bulbs ( $P < 0.05$ ). During chronic VNS, a significant decrease in left/right ratio in the striatum ( $P < 0.05$ ) was found. Acute and chronic VNS induced changes in glucose metabolism in regions important for seizure control (hippocampus and striatum). Our results promote further brain research on VNS using small animal PET in rats.

21. **Ito S, Craig AD. Vagal-evoked activity in the parafascicular nucleus of the primate thalamus. *J Neurophysiol.* 2005;94(4):2976-82.**

<http://www.ncbi.nlm.nih.gov/pubmed/15928062>

**Abstract** The physiological effects of ascending vagal afferent activity in the primate forebrain have not been established, and because vagus nerve stimulation (VNS) is useful clinically for treatment of epilepsy and depression, these actions need to be identified. We used a roving microelectrode to record vagal-evoked potentials in the thalamus of the macaque monkey. In addition to the anticipated activation in the gustatory/visceral thalamic relay nucleus, we found an unexpectedly larger and earlier response focus with multi-unit discharges in the adjacent parafascicular nucleus. These data reveal a potent vagal input to this intralaminar nucleus, which is normally considered to be involved in motor control. This finding indicates that a role for this vagal activation site in the anti-epileptic effects of VNS needs to be considered.

22. **Tubbs RS, Killingsworth CR, Rollins DL, Smith WM, Ideker RE, Wellons JC, 3rd, et al. Vagus nerve stimulation for induced spinal cord seizures: insights into seizure cessation. *J Neurosurg.* 2005;102(2 Suppl):213-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16156232>  
**Abstract** OBJECT: Vagus nerve stimulation is known to decrease the frequency, duration, and intensity of some types of intracranial seizures in both humans and animals. Although many theories abound concerning the mechanism for this action, the true cause remains speculative. To potentially elucidate a pathway in which vagus nerve stimulation aborts seizure activity, seizures were initiated not in the cerebral cortex but in the spinal cord and then vagus nerve stimulation was performed. METHODS: Ten pigs were anesthetized and placed in the lateral position, and a small laminectomy was performed in the lumbar region. Topical penicillin, a known epileptogenic drug to the cerebral cortex and spinal cord, was applied to the dorsal surface of the exposed cord. With the exception of two animals that were used as controls, once seizure activity was discernible via motor convulsion or increased electrical activity the left vagus nerve, which had been previously isolated in the neck, was stimulated. Following multiple stimulations of the vagus nerve and with seizure activity confirmed, the cord was transected in the midthoracic region and vagus nerve stimulation was performed. Vagus nerve stimulation resulted in cessation of spinal cord seizure activity in all (87.5%) but one experimented animal. Transection of the spinal cord superior to the site of seizure induction resulted in the ineffectiveness of vagus nerve stimulation to cause cessation of seizure activity in all study animals. CONCLUSIONS: The effects of vagus nerve stimulation on induced spinal cord seizures involve descending spinal pathways. The authors believe that this experiment is the first to demonstrate that spinal cord neuronal hyperactivity can be suppressed by stimulation of a cranial nerve. These data may aid in the development of alternative mechanisms for electrical stimulation in patients with medically intractable seizures. Further studies are now necessary to isolate which specific tracts, nuclei, and neurotransmitters are involved in this process.
23. **Groves DA, Bowman EM, Brown VJ. Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetised rat. *Neurosci Lett.* 2005;379(3):174-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15843058>  
**Abstract** Vagal nerve stimulation (VNS) is used as a treatment for Epilepsy and is currently under investigation as a treatment for depression (see [M.S. George, Z. Nahas, X. Li, F.A. Kozel, B. Anderson, K. Yamanaka, J.H. Chae, M.J. Foust, Novel treatments of mood disorders based on brain circuitry (ECT, MST, TMS, VNS, DBS), *Semin. Clin. Neuropsychiatry* 7 (2002) 293-304; M.S. George, A.J. Rush, H.A. Sackeim, L.B. Marangell, Vagus nerve stimulation (VNS): utility in neuropsychiatric disorders, *Int. J. Neuropsychopharmacol.* 6 (2003) 73-83] for reviews). The mechanism of action of VNS is not fully understood [E. Ben-Menachem, Vagus-nerve stimulation for the treatment of epilepsy, *Lancet Neurol.* 1 (2002) 477-482] despite numerous imaging investigations (see [E. Ben-Menachem, Vagus-nerve stimulation for the treatment of epilepsy, *Lancet Neurol.* 1 (2002) 477-482; M.S. George, Z. Nahas, X. Li, F.A. Kozel, B. Anderson, K. Yamanaka, J.H. Chae, M.J. Foust, Novel treatments of mood disorders based on brain circuitry (ECT, MST, TMS, VNS, DBS), *Semin. Clin. Neuropsychiatry* 7 (2002) 293-304; M.S. George, A.J. Rush, H.A. Sackeim, L.B. Marangell, Vagus nerve stimulation (VNS): utility in neuropsychiatric disorders, *Int J Neuropsychopharmacol* 6 (2003) 73-83; M.S. George, H.A. Sackeim, L.B. Marangell, M.M. Husain, Z. Nahas, S.H. Lisanby, J.C. Ballenger, A.J. Rush, Vagus nerve stimulation. A potential therapy for resistant depression? *Psychiatr. Clin. North Am.* 23 (2000) 757-783] for reviews). However, there is some evidence to suggest that the locus coeruleus may play a role modulating the effects of VNS. This study investigated the effects of VNS (0.3mA), of sufficient intensity to recruit the A and B fibre components of the vagus [D.M. Woodbury, J.W. Woodbury, Effects of vagal stimulation on experimentally induced seizures in rats, *Epilepsia* 31 (Suppl. 2) (1990) S7-S19], on the discharge rate of single neurons from the locus coeruleus. This study is the first to demonstrate a direct neuronal response from the locus coeruleus following acute challenge of VNS in the anaesthetised rat. The results of this study indicate that neuronal activity of the locus coeruleus is modulated by VNS. This pathway through the locus coeruleus may be significant for mediating the clinical effects of VNS.

24. **Dedeurwaerdere S, Vonck K, Claeys P, Van Hese P, D'Have M, Grisar T, et al. Acute vagus nerve stimulation does not suppress spike and wave discharges in genetic absence epilepsy rats from Strasbourg. *Epilepsy Res.* 2004;59(2-3):191-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15246120>  
**Abstract** We evaluated the efficacy of vagus nerve stimulation (VNS) in Genetic Absence Epilepsy Rats from Strasbourg (GAERS), a validated model for absence epilepsy. In the first experiment, we investigated whether VNS applied at seizure onset can interrupt spike and wave discharges (SWD). In the second experiment, we investigated whether SWD are suppressed or shortened in duration when VNS is applied several hours per day. Both control and VNS groups underwent EEG and VNS electrode implantation. For the first experiment, a randomized crossover design was used. Stimuli (amplitude: 3 V; frequency: 30 Hz; pulse duration: 500 micros) were given when an SWD occurred on the EEG. The experiment was repeated the next day. In the second experiment, treated animals were stimulated (amplitude: 1.5 mA; frequency: 30 Hz; pulse duration: 500 micros; on/off time cycle: 30 s / 5 min) for 3h per day, during five consecutive days. In the first experiment, the duration of the SWD was increased on day 1, ( $P < 0.05$ ). There was no difference in SWD duration on Day 2. In the second experiment, no significant differences could be found in number, duration and EEG frequency of SWD. VNS applied at the onset of an SWD can prolong the duration of SWD in GAERS. As a 5-day stimulation protocol had no effect, long-term VNS might be necessary to affect SWD.
25. **Zhang J, Zhang J. [The influence of vagus nerve stimulation on NMDAR1 mRNA and GABAAR alpha 1 mRNA in thalamic reticular nucleus of pentylentetrazole-induced epileptic rats]. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi.* 2002;19(4):566-8. Chinese.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12561348>  
**Abstract** To study the antiepileptic mechanism of vagus nerve stimulation (VNS), we used the methods of in situ hybridization and image analysis to detect the expression of NMDAR1 mRNA and GABA $\alpha$ 1 receptor alpha 1 subunit mRNA (GABAAR alpha 1 mRNA) in the thalamic reticular nucleus. The results show that the NMDAR1 mRNA expression of rats administered pentylentetrazole (PTZ) is higher than that of control group. By treating with VNS, it decreased. On the contrary, the expression of GABAAR alpha 1 mRNA in the thalamic reticular nucleus of PTZ group rats is lower than that of control group. For rats treated with VNS, it increased. Therefore, it is concluded that VNS may reduce the excitability of cerebral cortices by depressing the activities of glutamic acid receptors (GluR) and by promoting the activities of gamma-aminobutyric acid receptors (GABAAR) in thalamic reticular nucleus. So the formation and development of seizures are inhibited.

26. **Sunderam S, Osorio I, Watkins JF, 3rd, Wilkinson SB, Frei MG, Davis RE. Vagal and sciatic nerve stimulation have complex, time-dependent effects on chemically-induced seizures: a controlled study. *Brain Res.* 2001;918(1-2):60-6.**

<http://www.ncbi.nlm.nih.gov/pubmed/11684042>

**Abstract** Previous studies of the effects of electrical vagus stimulation on experimental seizures were without suitable controls or statistical validation, and ignored the potential role of vagally-induced hemodynamic depression on seizure expression. This study addresses these limitations. The effects of periodic left vagus nerve stimulation (LVNS) on chemically-induced seizures in rats were compared with control groups receiving no stimulation (NoS), left sciatic nerve stimulation (LSNS) and LVNS after pretreatment with methyl atropine (MA-LVNS). Stimulation followed a 30 s on-120 s off cycle over 130 min. Seizures were scored visually and the temporal variation of their probability P(s) across the stimulation cycle was measured statistically. P(s) was significantly different ( $P < 0.01$ ) for all groups: LSNS had the highest and MA-LVNS the lowest seizure probability; LVNS and NoS had intermediate values. While LVNS blocked seizures, it also precipitated them, explaining why its anti-seizure effect was only slightly greater than NoS. Neither LVNS nor MA-LVNS induced changes in cortical rhythms ('activation') associated with decreased P(s), unlike LSNS which increased cortical rhythm synchrony and with it, P(s). LVNS alone induced marked bradycardia and moderate hypoxemia. In conclusion, cranial and peripheral nerve stimulation have complex, time-varying effects on cerebral excitability: low frequency LSNS facilitated seizures, while LVNS both suppressed and facilitated them. The anti-seizure effect of LVNS was small and may have, in part, been due to a hemodynamically-induced deficit in energy substrates. The effects of MA-LVNS on seizure duration and P(s) raise the possibility that, in the absence of hemodynamic depression, stimulation of this nerve does not have a strong anti-seizure effect.

27. **Krahl SE, Senanayake SS, Handforth A. Destruction of peripheral C-fibers does not alter subsequent vagus nerve stimulation-induced seizure suppression in rats. *Epilepsia.* 2001;42(5):586-9.**

<http://www.ncbi.nlm.nih.gov/pubmed/11380564>

**Abstract** PURPOSE: Early animal studies of the therapeutic mechanisms of vagus nerve stimulation (VNS) suggested that seizure suppression requires maximal activation of small, unmyelinated vagal C fibers. However, effective therapeutic stimulation parameters appear to be subthreshold for these fibers in humans, and there are no clinical reports of the autonomic side effects that would be expected if these fibers were maximally activated. We report here that selective destruction of C fibers with capsaicin does not affect VNS-induced seizure suppression in rats. METHODS: Rats were pretreated with capsaicin or vehicle in three injections over a 2-day period. A cuff electrode was later implanted on the left cervical vagus nerve. Two days after surgery, VNS was given to half of the capsaicin- and vehicle-treated rats. The remaining rats were connected to the stimulator but did not receive VNS. Thirty seconds after VNS onset, seizures were induced by pentylenetetrazol (PTZ), and seizure severity was measured. Two days later, the reciprocal VNS treatment was given, and PTZ-induced seizure severity was again measured. RESULTS: VNS effectively reduced seizure severity in both capsaicin- and vehicle-treated rats as compared with their non-VNS baselines. CONCLUSIONS: These results indicate that activation of vagal C fibers is not necessary for VNS-induced seizure suppression.

28. **Zagon A, Kemeny AA. Slow hyperpolarization in cortical neurons: a possible mechanism behind vagus nerve simulation therapy for refractory epilepsy? *Epilepsia*. 2000;41(11):1382-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11077451>  
**Abstract** PURPOSE: Recent studies have shown that chronic, intermittent stimulation of the left vagus nerve (VNS) decreases the frequency, duration, and/or intensity of seizures in some patients with medically refractory focal seizures. Although VNS is being used in an increasing number of patients, the neuronal mechanism behind VNS therapy of refractory epileptic seizures is yet unclear. METHODS: In vivo intracellular recordings were used to study responses elicited by the VNS in pyramidal neurons of the parietal association cortex in anesthetized rats. RESULTS: Low-intensity trains of VNS, which activated predominantly myelinated fibers (100 microA, 30 Hz, 0.5 millisecond, 20 seconds), elicited a slow hyperpolarization (onset latency 17.4 +/- 2.0 seconds, amplitude -4.7 +/- 0.6 mV, duration 35 +/- 3.2 seconds; n = 19). Increasing the intensity of VNS to recruit nonmyelinated vagal fibers (200 microA) led to an increase in the magnitude of the response in some neurons while failed to evoke a response in others. On increasing the stimulus intensity to 500 microA, only one in nine neurons exhibited a visible response. All recorded and visualised neurons were pyramidal cells in cortical layer V. CONCLUSIONS: Stimulus intensities that activate predominantly myelinated fibers (less than 200 microA) were most effective to induce slow vagal hyperpolarization. It is suggested that slow hyperpolarization may be one of the mechanisms that underlie the seizure-reducing effect of VNS, by means of reducing the excitability in neurons that would be involved in propagation of seizure activity. As the balance of activity in myelinated and nonmyelinated primary vagal afferents influenced the effect of VNS stimulation, it is likely that the effect of VNS is modulated as changes occur in the underlying vagal tone.
29. **Fernandez-Guardiola A, Martinez A, Valdes-Cruz A, Magdaleno-Madrigal VM, Martinez D, Fernandez-Mas R. Vagus nerve prolonged stimulation in cats: effects on epileptogenesis (amygdala electrical kindling): behavioral and electrographic changes. *Epilepsia*. 1999;40(7):822-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10403204>  
**Abstract** PURPOSE: To analyze the effect of prolonged (daily) electrical vagus nerve stimulation (VNS) on daily amygdaloid kindling (AK) in freely moving cats. METHODS: Fifteen adult male cats were implanted in both temporal lobe amygdalae, both lateral geniculate bodies, and prefrontal cortices. A bipolar hook (5-mm separation) stainless steel electrode also was implanted in the unsectioned left vagus nerve. AK only was performed on five of the cats as a control. The remaining 10 cats were recorded under the following experimental conditions: VNS (1.2-2.0 mA, 0.5-ms pulses, 30 Hz) for 1 min along with AK (1-s train, 1-ms pulses, 60 Hz, 300-600 microA), followed by VNS alone for 1 min, four times between 11:00 a.m. and 2 p.m. At different times, VNS was arrested, and AK was continued until stage VI kindling was reached. RESULTS: The behavioral changes evoked by VNS were as follows: left miosis, blinking, licking, abdominal contractions, swallowing, and eventually yawning, meowing, upward gaze, and short head movements. Compulsive eating also was present with a variable latency. Outstanding polygraphic changes consisted of augmentation of eye movements and visual evoked potentials while the animal was awake and quiet, with immobility and upward gaze. An increase of the pontogeniculooccipital (PGO) wave density in rapid eye movement (REM) sleep also was noticeable. AK was completed (to stage VI) in the control animals without a vagus nerve implantation in 23.4 +/- 3.7 trials. In animals with VNS, the AK was significantly delayed, remaining for a long time in the behavioral stages I-III and showing a reduction of afterdischarge duration and frequency. Stage VI was never reached despite 50 AK trials, except when the vagus nerve electrodes were accidentally broken or vagal stimulation was intentionally arrested. Under these circumstances, 24.4 +/- 8.16 AK trials alone were necessary to reach stage VI of kindling. CONCLUSIONS: Our results indicate that left, electrical VNS interferes with AK epileptogenesis. This anticonvulsant effect could be related to the increase of REM sleep.

**30. Walker BR, Easton A, Gale K. Regulation of limbic motor seizures by GABA and glutamate transmission in nucleus tractus solitarius. *Epilepsia*. 1999;40(8):1051-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/10448815>

**Notes** This paper demonstrates the anticonvulsant effects of VNS in rats by either activating or deactivating the nucleus tractus solitarius (NTS) and then inducing seizures. The authors note that the vagus terminates into the NTS and the NTS is important in seizure regulation. VNS protects against seizures by sending signals directly into the NTS. The paper supports the idea that VNS gets better over time by noting that chronic VNS can alter the 'net charge' status of the NTS, thereby resetting the brain's equilibrium. Abstract: **PURPOSE:** The nucleus of the solitary tract (NTS) is a primary site at which vagal afferents terminate. Because afferent vagal nerve stimulation has been demonstrated to have anticonvulsant effects, it is likely that changes in synaptic transmission in the NTS can regulate seizure susceptibility. We tested this hypothesis by examining the influence of gamma-aminobutyric acid (GABA) ergic and glutamatergic transmission in the NTS on seizures evoked by systemic and focal bicuculline and systemic pentylenetetrazol (PTZ) in rats. **METHODS:** Muscimol (256 pmol), a GABA(A)-receptor agonist, bicuculline methiodide (177 pmol), a GABA(A)-receptor antagonist, kynurenate (634 pmol), a glutamate-receptor antagonist, or lidocaine (100 nl; 5%), a local anesthetic, was microinjected into the mediocaudal (m)NTS. Ten minutes later, seizure activity was induced by either a focal microinfusion of bicuculline methiodide (177 pmol) into the rostral piriform cortex, systemic PTZ (50 mg/kg, i.p.), or systemic bicuculline (0.35 mg/kg, i.v.). **RESULTS:** Muscimol in mNTS (but not in adjacent regions of NTS) attenuated seizures in all seizure models tested, whereas bicuculline methiodide into mNTS did not alter seizure responses. Kynurenate infusions into mNTS significantly reduced the severity of seizures evoked both systemically and focally. Anticonvulsant effects also were obtained with lidocaine application into the same region of mNTS. Unilateral injections were sufficient to afford seizure protection. **CONCLUSIONS:** Our results demonstrate that an increase in GABA transmission or a decrease in glutamate transmission in the rat mNTS reduces susceptibility to limbic motor seizures. This suggests that inhibition of mNTS outputs enhances seizure resistance in the forebrain and provides a potential mechanism for the seizure protection obtained with vagal stimulation.

**Abstract** **PURPOSE:** The nucleus of the solitary tract (NTS) is a primary site at which vagal afferents terminate. Because afferent vagal nerve stimulation has been demonstrated to have anticonvulsant effects, it is likely that changes in synaptic transmission in the NTS can regulate seizure susceptibility. We tested this hypothesis by examining the influence of gamma-aminobutyric acid (GABA) ergic and glutamatergic transmission in the NTS on seizures evoked by systemic and focal bicuculline and systemic pentylenetetrazol (PTZ) in rats. **METHODS:** Muscimol (256 pmol), a GABA(A)-receptor agonist, bicuculline methiodide (177 pmol), a GABA(A)-receptor antagonist, kynurenate (634 pmol), a glutamate-receptor antagonist, or lidocaine (100 nl; 5%), a local anesthetic, was microinjected into the mediocaudal (m)NTS. Ten minutes later, seizure activity was induced by either a focal microinfusion of bicuculline methiodide (177 pmol) into the rostral piriform cortex, systemic PTZ (50 mg/kg, i.p.), or systemic bicuculline (0.35 mg/kg, i.v.). **RESULTS:** Muscimol in mNTS (but not in adjacent regions of NTS) attenuated seizures in all seizure models tested, whereas bicuculline methiodide into mNTS did not alter seizure responses. Kynurenate infusions into mNTS significantly reduced the severity of seizures evoked both systemically and focally. Anticonvulsant effects also were obtained with lidocaine application into the same region of mNTS. Unilateral injections were sufficient to afford seizure protection. **CONCLUSIONS:** Our results demonstrate that an increase in GABA transmission or a decrease in glutamate transmission in the rat mNTS reduces susceptibility to limbic motor seizures. This suggests that inhibition of mNTS outputs enhances seizure resistance in the forebrain and provides a potential mechanism for the seizure protection obtained with vagal stimulation.

31. **Krahl SE, Clark KB, Smith DC, Browning RA. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia*. 1998;39(7):709-14.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9670898>  
**Abstract** PURPOSE: Although vagus nerve stimulation (VNS) is now marketed throughout most of the world as a treatment for drug-resistant epilepsy, the therapeutic mechanism of action of VNS-induced seizure suppression has not yet been established. Elucidation of this mechanism is an important first step in the development of strategies to improve VNS efficacy. Because the locus coeruleus (LC) has been implicated in the antinociceptive effects of VNS, we chemically lesioned the LC in the present study to determine if it is a critical structure involved in the anticonvulsant mechanisms of VNS. METHODS: Rats were chronically depleted of norepinephrine (NE) by a bilateral infusion of 6-hydroxydopamine (6-OHDA) into the LC. Two weeks later, they were tested with maximal electroshock (MES) to assess VNS-induced seizure suppression. In another experiment, the LC was acutely inactivated with lidocaine, and seizure suppression was tested in a similar fashion. RESULTS: VNS significantly reduced seizure severities of control rats. However, in animals with chronic or acute LC lesions, VNS-induced seizure suppression was attenuated. CONCLUSIONS: Our data indicate that the LC is involved in the circuitry necessary for the anticonvulsant effects of VNS. Seizure suppression by VNS may therefore depend on the release of NE, a neuromodulator that has anticonvulsant effects. These data suggest that noradrenergic agonists might enhance VNS-induced seizure suppression.
32. **Naritoku DK, Terry WJ, Helfert RH. Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. *Epilepsy Res*. 1995;22(1):53-62.**  
<http://www.ncbi.nlm.nih.gov/pubmed/8565967>  
**Abstract** Electrical stimulation of the vagus nerve exerts an antiepileptic effect on human partial-onset epilepsy, but little is known about the brain structures that mediate this phenomenon. Fos is a nuclear protein that is expressed under conditions of high neuronal activity. We utilized fos immunolabeling techniques on Sprague-Dawley rat brains to identify regions that are activated by antiepileptic stimulation of the left vagus nerve. Vagus nerve stimulation (VNS) induced specific nuclear fos immunolabeling in several forebrain structures, including the posterior cortical amygdaloid nucleus, cingulate and retrosplenial cortex, ventromedial and arcuate hypothalamic nuclei. In the brainstem, there was specific immunolabeling in vagus nerve nuclei, in the A5 and locus ceruleus noradrenergic nuclei, and in the cochlear nucleus. No labeling of these structures occurred in sham-operated, unstimulated control animals. Intense labeling also occurred in habenular nucleus of thalamus after vagus nerve stimulation, whereas only mild staining occurred in unstimulated animals. Several of the brain structures activated by VNS are important for genesis or regulation of seizures in the forebrain. These structures may mediate the antiepileptic effect of VNS.
33. **Foley JO, DuBois FS. Quantitative studies of the vagus nerve in the cat. *J Comp Neurol*. 1937;67(1):49-87.**  
<http://onlinelibrary.wiley.com/doi/10.1002/cne.900670104/abstract>

**MoA - Human Studies (of VNS in epilepsy)**

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1. **Muller HH, Kornhuber J, Sperling W. Resting motor threshold changes in vagus nerve stimulation-treated patients during on/off-stimulation conditions. *Psychiatry Clin Neurosci.* 2013;67(1):64-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23331290>  
<http://onlinelibrary.wiley.com/store/10.1111/pcn.12000/asset/pcn12000.pdf?v=1&t=hekieobl&s=255f2a861c0a1cd1a9a24808b0a3a9bed21439ae>
  
2. **Aalbers MW, Klinkenberg S, Rijkers K, Verschuure P, Kessels A, Aldenkamp A, et al. The effects of vagus nerve stimulation on pro- and anti-inflammatory cytokines in children with refractory epilepsy: an exploratory study. *Neuroimmunomodulation.* 2012;19(6):352-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23038102>  
**Abstract** OBJECTIVES: The vagus nerve has important immunological and anti-inflammatory actions that might be relevant to the beneficial effects of vagus nerve stimulation (VNS). Therefore, we conducted an exploratory study on VNS effects on cytokine levels in plasma and cerebrospinal fluid of children suffering from refractory epilepsy. Moreover, as predictors of the response are lacking, we also aimed to determine if cytokine changes predict the clinical response. METHODS: VNS was performed according to a randomized double-blind design: plasma levels were compared between patients who received 20 weeks of high output (therapeutic) (n = 21) or low output (active control) stimulation (n = 20). Thereupon, all patients received high output stimulation for another 19 weeks; levels during this period were compared to baseline. Interictal interleukin-1beta, interleukin-6, and interleukin-10 were determined by ELISA. RESULTS: No significant changes were found between high and low output groups and between the last 19 weeks of stimulation and baseline. Changes in interleukin-1beta correlated with improved IQ (tau = 0.42, p < 0.01). Lower baseline plasma levels of interleukin-6 were associated with more seizure frequency reduction [R(2) = 0.105 (1, 35), p = 0.050]. CONCLUSION: Interictal cytokine levels were not altered by VNS but baseline interleukin-6 predicted the clinical response. In the future, patient selection may be aided by determination of the cytokine profile of the patient.
  
3. **Majoie HJ, Rijkers K, Berfelo MW, Hulsman JA, Myint A, Schwarz M, et al. Vagus nerve stimulation in refractory epilepsy: effects on pro- and anti-inflammatory cytokines in peripheral blood. *Neuroimmunomodulation.* 2011;18(1):52-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20639683>  
**Abstract** OBJECTIVE: The vagus nerve has important immunological functions that may be relevant for its anticonvulsive action. We postulate that this anticonvulsive action is activated by a shift in the immune system resulting in a reduction of neurotoxic and an increase of neuroprotective tryptophan metabolites. METHODS: Eleven patients with refractory epilepsy and 11 controls matched for age and gender were included in this study. The primary outcome measure was a 50% seizure reduction. Other variables were pro-inflammatory cytokines IL-6 and TNF-alpha, anti-inflammatory cytokine IL-10, cortisol, and the tryptophan metabolites 3-hydroxykynurenine (3-OH-KYN), kynurenic acid (KYNA), kynurenine, serotonin (5-HT) and 5-hydroxyindol acetic acid (5-HIAA). Blood samples were scheduled during baseline, and in week 28 of add-on treatment. RESULTS: IL-6 levels were higher in the responders than in the control group, and decreased after vagus nerve stimulation (VNS), whereas IL-10 was low and increased after VNS. In nonresponders, VNS resulted in an increase of IL-6 plasma levels and in a decrease of IL-10. Cortisol concentrations are higher in the epilepsy group than in the control group. After VNS, these concentrations decreased. The concentrations of the tryptophan metabolites were lower in the epilepsy group than in the control group. The KYNA ratios are defined as the ratio of neuroprotective KYNA versus neurotoxic 3-OH-KYN and KYNA versus neurotoxic kynurenine: these ratios were lower in epilepsy patients than in controls, and they both moderately increased after VNS. CONCLUSION: The outcome of this preliminary study indicates that VNS causes a rebalancing of the immune system. This results in: (1) a reduction of neurotoxic and an increase of neuroprotective kynurenine metabolites and (2) in the normalization of cortisol levels.

4. **Wang H, Chen X, Lin Z, Shao Z, Sun B, Shen H, et al. Long-term effect of vagus nerve stimulation on interictal epileptiform discharges in refractory epilepsy. *J Neurol Sci.* 2009;284(1-2):96-102.**

<http://www.ncbi.nlm.nih.gov/pubmed/19427651>

**Abstract** BACKGROUND: Vagus nerve stimulation (VNS) therapy has been widely recognized as an effective alternative for the treatment of refractory epilepsy. However, the precise mechanism of VNS is poorly understood. The purpose of this study was to observe the long-term interictal EEG changes induced by VNS, and to investigate the probable mechanism of action of VNS in achieving seizure control. METHODS: Eight patients with VNS were selected from two epilepsy centers in China (Harbin and Shanghai) between 2001 and 2004. We studied the clinical efficacy by long-term follow-up, ranging from 37 to 81 months (mean 55.8 months). Moreover, serial EEGs were performed at the different time (preoperative baseline, 3, 6, 12, and 24 months after VNS initiation) and the different states of VNS stimulator ("activation", "deactivation" and "reactivation"). RESULTS: A  $\geq$  50% seizure reduction was achieved in 12.5%, 62.5%, 75%, 62.5% and 75% of the total patients (n=8) at 6, 12, 18, 24 and 36 months of post-VNS, respectively. The results revealed a statistically significant progressive decrease in the number of IEDs (interictal epileptiform discharges) on EEG with time ( $P < 0.01$ ). Significant correlation had been highlighted after 6 months of VNS stimulation, between the reduction of seizure frequency and the decreasing of IEDs ( $P < 0.01$ ). Furthermore, statistically significant difference of IEDs was seen when comparing the state of "deactivation" with the states of "activation" and "reactivation", respectively ( $P < 0.01$ ). However, there was no significant difference in IEDs between "activation" and "reactivation" ( $P > 0.05$ ). CONCLUSIONS: VNS is an efficient, well-tolerated therapy for refractory epilepsy. It can induce progressive electrophysiological effect on epileptiform activity over time. This may reflect the mechanism of chronic action of VNS with desynchronization of EEG in achieving seizure control.

5. **Conte MM, Victor JD. VEP indices of cortical lateral interactions in epilepsy treatment. *Vision Res.* 2009;49(9):898-906.**

<http://www.ncbi.nlm.nih.gov/pubmed/18572221>

**Abstract** We extend Spekreijse's strategy for analyzing lateral interactions in visual evoked potentials (VEPs) to clinical neurophysiologic testing of patients with epilepsy. Stimuli consisted of the radial windmill/dartboard pattern [Ratliff, F., & Zemon, V. (1982). Some new methods for the analysis of lateral interactions that influence the visual evoked potential. In: Bodis-Wollner (Ed.), *Evoked potentials*, Vol. 388. (pp. 113-124). New York: Annals of the New York Academy of Sciences.] and conventional checkerboards. The fundamental and 2nd-harmonic components of the steady-state responses were used to calculate indices reflecting facilitatory (FI) and suppressive (SI) cortical interactions. We carried out two studies. In the first, VEPs in 38 patients receiving antiepileptic drug (AED) therapy were compared to those of age-matched controls. For three AEDs (tiagabine, topiramate, and felbamate), addition of the drug did not change the FI and SI compared to baseline values or those of normal controls. However, the addition of gabapentin was associated with an increase of the FI, and this change was reversed when the medication was withdrawn. This suggested a medication-specific change in cortical lateral interactions. The second study focused on the effects of neurostimulation therapy. Eleven epilepsy patients receiving chronic vagus nerve stimulation (VNS) treatment were tested. By comparing VEPs recorded with the stimulator on (Stim-ON) and turned off (Stim-OFF) in the same session, we determined that VNS did not have a short-acting effect on lateral interactions. However, when compared with normal controls, the VNS patients had a significantly smaller SI ( $p < .05$ ), but no difference in the FI, demonstrating the presence of a chronic effect. We conclude that with the appropriate stimuli, VEPs can be used as a measure of cortical lateral interactions in normals and epileptic patients, and demonstrate specific changes in these interactions associated with certain treatment modalities.

6. **Vonck K, De Herdt V, Bosman T, Dedeurwaerdere S, Van Laere K, Boon P. Thalamic and limbic involvement in the mechanism of action of vagus nerve stimulation, a SPECT study. *Seizure*. 2008;17(8):699-706.**

<http://www.ncbi.nlm.nih.gov/pubmed/18556220>

**Abstract** PURPOSE: To unravel the mechanism of action of neurostimulation as a treatment for seizures, functional neuroimaging tools allow minimally invasive research in humans. We performed single-photon emission computed tomography (SPECT) in patients with epilepsy, treated with vagus nerve stimulation (VNS). Changes in regional cerebral blood flow (rCBF) at the time of initial stimulation as well as after chronic treatment were correlated with long-term clinical efficacy. METHODS: In this pilot study, 27 patients (14 female and 13 male) who were treated with VNS at Ghent University Hospital for refractory epilepsy underwent a (99m)Tc-ECD (ethyl cystein dimer) SPECT activation study at the time the first stimulation train was administered. 12 patients underwent an additional (99m)Tc-ECD SPECT activation study 6 months later. Image acquisition was performed on a high-resolution triple-headed gamma camera. Significant rCBF changes were correlated with prospectively assessed clinical efficacy data. RESULTS: Significant rCBF changes were found in the thalamus, the hippocampus and the parahippocampal gyrus. Acute limbic hyper-perfusion and chronic thalamic hypo-perfusion correlate with positive clinical efficacy. CONCLUSIONS: Acute and chronic electrical stimulation of the vagus nerve induces rCBF changes that can be measured by SPECT on a group-basis. The thalamus and the limbic system are thought to play a key role in the mechanism of action of VNS.

7. **Marrosu F, Santoni F, Puligheddu M, Barberini L, Maleci A, Ennas F, et al. Increase in 20-50 Hz (gamma frequencies) power spectrum and synchronization after chronic vagal nerve stimulation. *Clin Neurophysiol*. 2005;116(9):2026-36.**

<http://www.ncbi.nlm.nih.gov/pubmed/16055378>

**Abstract** OBJECTIVE: Though vagus nerve stimulation (VNS) is an important option in pharmaco-resistant epilepsy, its mechanism of action remains unclear. The observation that VNS desynchronised the EEG activity in animals suggested that this mechanism could be involved in VNS antiepileptic effects in humans. Indeed VNS decreases spiking bursts, whereas its effects on the EEG background remain uncertain. The objective of the present study is to investigate how VNS affects local and inter regional synchronization in different frequencies in pharmaco-resistant partial epilepsy. METHODS: Digital recordings acquired in 11 epileptic subjects 1 year and 1 week before VNS surgery were compared with that obtained 1 month and 1 year after VNS activation. Power spectrum and synchronization were then analyzed and compared with an epileptic group of 10 patients treated with AEDs only. RESULTS: VNS decreases the synchronization of theta frequencies ( $P < 0.01$ ), whereas it increases gamma power spectrum and synchronization ( $< 0.001$  and  $0.01$ , respectively). CONCLUSIONS: The reduction of theta frequencies and the increase in power spectrum and synchronization of gamma bands can be related to VNS anticonvulsant mechanism. In addition, gamma modulation could also play a seizure-independent role in improving attentional performances. SIGNIFICANCE: These results suggest that some antiepileptic mechanisms affected by VNS can be modulated by or be the reflection of EEG changes.

8. **Corcoran C, Connor TJ, O'Keane V, Garland MR. The effects of vagus nerve stimulation on pro- and anti-inflammatory cytokines in humans: a preliminary report. *Neuroimmunomodulation*. 2005;12(5):307-9.**

<http://www.ncbi.nlm.nih.gov/pubmed/16166810>

**Abstract** OBJECTIVE: Vagus nerve stimulation (VNS) is a novel therapy in resistant epilepsy, and is undergoing clinical trials in resistant depression. The mechanism of action of VNS is assumed to be due to modulation of deep brain structures via its afferent connections. As the vagus nerve has potentially important immunological actions that may have relevance to its therapeutic effects, we hypothesised that an additional mechanism may occur via vagally mediated actions on cytokine synthesis. METHODS: Patients (n=10) with resistant depression were studied in the weeks prior to, and 3 months following, implantation of a vagus nerve stimulator. No medication changes were made during the course of the study. High-sensitivity ELISA kits were used to measure plasma IL-1 beta, IL-6, TNF-alpha, IL-10 and TGF-beta concentrations. C-reactive protein (CRP) was measured using a high sensitivity immunonephelometry assay. RESULTS: There were highly significant increases in the plasma levels of IL-6, TNF-alpha and TGF-beta. Increases seen with IL-10 and IL-1 beta were not significant. Plasma CRP levels were unchanged. CONCLUSION: VNS is associated with marked peripheral increases in pro- and anti-inflammatory circulating cytokines. Such changes are unlikely to be non-specific inflammatory reactions, reflected by CRP levels. In view of gathering evidence supporting a role for the immune system in modulating affect, as well as seizure activity, these effects of VNS may be therapeutically relevant.

9. **Henry TR, Bakay RA, Pennell PB, Epstein CM, Votaw JR. Brain blood-flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: II. prolonged effects at high and low levels of stimulation. *Epilepsia*. 2004;45(9):1064-70.**

<http://www.ncbi.nlm.nih.gov/pubmed/15329071>

**Abstract** PURPOSE: To measure vagus nerve stimulation (VNS)-induced cerebral blood flow (CBF) effects after prolonged VNS and to compare these effects with immediate VNS effects on CBF. METHODS: Ten consenting partial epilepsy patients had positron emission tomography (PET) with intravenous [<sup>15</sup>O]H<sub>2</sub>O. Each had three control scans without VNS and three scans during 30 s of VNS, within 20 h after VNS began (immediate-effect study), and repeated after 3 months of VNS (prolonged study). After intrasubject subtraction of control from stimulation scans, images were anatomically transformed for intersubject averaging and superimposed on magnetic resonance imaging (MRI) for anatomic localization. Changes on t-statistical maps were considered significant at  $p < 0.05$  (corrected for multiple comparisons). RESULTS: During prolonged studies, CBF changes were not observed in any regions that did not have CBF changes during immediate-effect studies. During both types of studies, VNS-induced CBF increases were similarly located in the bilateral thalami, hypothalami, inferior cerebellar hemispheres, and right postcentral gyrus. During immediate-effect studies, VNS decreased bilateral hippocampal, amygdalar, and cingulate CBF and increased bilateral insular CBF; no significant CBF changes were observed in these regions during prolonged studies. Mean seizure frequency decreased by 25% over a 3-month period between immediate and prolonged PET studies, compared with 3 months before VNS began. CONCLUSIONS: Seizure control improved during a period over which some immediate VNS-induced CBF changes declined (mainly over cortical regions), whereas other VNS-induced CBF changes persisted (mainly over subcortical regions). Altered synaptic activities at sites of persisting VNS-induced CBF changes may reflect antiseizure actions.

- 10. Tatum WO, Malek A, Recio M, Orlowski J, Murtagh R. Diffusion-weighted imaging and status epilepticus during vagus nerve stimulation. *Epilepsy Behav.* 2004;5(3):411-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15145313>

**Abstract** PURPOSE: Transient abnormalities have been reported on diffusion-weighted imaging (DWI) during status epilepticus. Vagus nerve stimulation (VNS) is a therapy for epilepsy that has previously demonstrated alteration in regional cerebral blood flow on functional neuroimaging. We describe the peri-ictal DWI abnormalities in a patient with status epilepticus. METHODS: A 21-year-old woman with pharmaco-resistant localization-related epilepsy was treated with VNS and underwent brain magnetic resonance imaging (MRI) with DWI for clinical purposes. RESULTS: Transient and reversible hyperintense signal abnormalities were noted on DWI at the site of seizure onset, in addition to the thalamus and midbrain bilaterally. A concomitant decrease in the apparent diffusion coefficient mimicked ischemia, yet complete clinical, and electrographic resolution occurred following successful termination of status. CONCLUSIONS: High-energy brain MRI sequences using DWI were safely performed in our epilepsy patient with a vagus nerve stimulator who experienced status epilepticus. This case highlights the bilateral and robust involvement of subcortical structures present immediately following status epilepticus. Additionally, bilateral abnormalities in the thalamus and midbrain in addition to the region of seizure origin, were observed in our patient implanted with a vagus nerve stimulator. Modulation of regional cerebral blood flow is one potential mechanism of action for VNS in humans; therefore, these regions of involvement could reflect the effects of status epilepticus, activation or facilitation by VNS, or both.
- 11. Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Dileone M, Meglio M, et al. Effects of vagus nerve stimulation on cortical excitability in epileptic patients. *Neurology.* 2004;62(12):2310-2.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15210904>

**Abstract** Vagus nerve stimulation (VNS) is used as adjunctive treatment for medically refractory epilepsy, but little is known about its mechanisms of action. The effects of VNS on the excitatory and inhibitory circuits of the motor cortex were evaluated in five patients with epilepsy using single- and paired-pulse transcranial magnetic stimulation (TMS). Patients were examined with the stimulator on and off. VNS determined a selective and pronounced increase in the inhibition produced by paired-pulse TMS with no effects on the excitability by single-pulse TMS.
- 12. Petrucci M, Hoh C, Alksne JF. Thalamic hypometabolism in a patient undergoing vagal nerve stimulation seen on F-18 FDG PET imaging. *Clin Nucl Med.* 2003;28(9):784-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12973011>

**Abstract** A 31-year-old man with a vagal nerve stimulator for seizure control was noted to have decreased metabolism within the thalamus as visualized by F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET). Some investigators think the thalamus plays an important role in the regulation of seizure activity. Vagal nerve stimulation (VNS) may reduce thalamic activity, which in turn may reduce seizure activity. However, because the thalamus has diffuse connections throughout the brain, its role in seizure activity is likely complex. Observing decreased thalamic activity during VNS is just 1 small step toward understanding this role.

13. **Holmes MD, Miller JW, Voipio J, Kaila K, Vanhatalo S. Vagal nerve stimulation induces intermittent hypocapnia. *Epilepsia*. 2003;44(12):1588-91.**  
<http://www.ncbi.nlm.nih.gov/pubmed/14636333>  
**Abstract** PURPOSE: To study whether respiratory alteration caused by vagal nerve stimulation (VNS) can change end-tidal carbon dioxide (EtCO<sub>2</sub>) levels. METHODS: We performed polygraphic recordings including capnographic monitoring during daytime sleep on adults with VNS therapy. RESULTS: Ten of 13 patients showed VNS-induced alterations in the frequency or amplitude of respiration. Five patients had a consistent increase in respiratory rate with a simultaneous, consistent and significant decrease ( $p < 0.01$ ; 5-22%) in EtCO<sub>2</sub> during VNS. Three subjects showed occasional decreases in EtCO<sub>2</sub> during VNS, and two showed no clearly detectable VNS-related EtCO<sub>2</sub> changes. CONCLUSIONS: Our findings suggest that VNS may alter brain CO<sub>2</sub> levels through changes in respiration. Because carbon dioxide (CO<sub>2</sub>) has potent effects on various brain functions, it is possible that these transient CO<sub>2</sub> changes may have an effect on the state transitions between interictal and preictal states.
14. **Marrosu F, Serra A, Maleci A, Puligheddu M, Biggio G, Piga M. Correlation between GABA(A) receptor density and vagus nerve stimulation in individuals with drug-resistant partial epilepsy. *Epilepsy Res*. 2003;55(1-2):59-70.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12948617>  
**Abstract** Vagus nerve stimulation (VNS) is an important option for the treatment of drug-resistant epilepsy. Through delivery of a battery-supplied intermittent current, VNS protects against seizure development in a manner that correlates experimentally with electrophysiological modifications. However, the mechanism by which VNS inhibits seizures in humans remains unclear. The impairment of gamma-aminobutyric acid (GABA)-mediated neuronal inhibition associated with epilepsy has suggested that GABA(A) receptors might contribute to the therapeutic efficacy of VNS. We have now applied single photon emission computed tomography (SPECT) with the benzodiazepine receptor inverse agonist [<sup>123</sup>I]iomazenil to examine cortical GABA(A) receptor density (GRD) before and 1 year after implantation of a VNS device in 10 subjects with drug-resistant partial epilepsy. VNS therapeutic responses resulted significantly correlated with the normalization of GRD. Moreover, a comparable control group, scheduled for a possible VNS implant, failed to show significant GRD variations after 1 year of a stable anti-epileptic treatment. These results suggest that VNS may modulate the cortical excitability of brain areas associated with epileptogenesis and that GABA(A) receptor plasticity contributes to this effect.

15. **Barnes A, Duncan R, Chisholm JA, Lindsay K, Patterson J, Wyper D. Investigation into the mechanisms of vagus nerve stimulation for the treatment of intractable epilepsy, using 99mTc-HMPAO SPET brain images. *Eur J Nucl Med Mol Imaging*. 2003;30(2):301-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/12552350>

<http://link.springer.com/article/10.1007%2Fs00259-002-1026-8>

**Abstract** Vagus nerve stimulation (VNS) has gained recognition as a treatment for refractory epilepsies where surgical treatment is not possible. While it appears that this treatment is effective in some patients, the mechanism of action is not clearly understood. The purpose of this study was to clarify findings of other positron emission tomography and single-photon emission tomography (SPET) investigations by measuring the acute effect of VNS on patients who have normal cerebral anatomy on magnetic resonance imaging and who have not previously been exposed to VNS. We investigated six subjects (two males and four females, mean age 29.5 years, range 21-39 years) with intractable epilepsy. One patient had primary generalised epilepsy causing generalised tonic-clonic seizures; the remaining five patients had localisation-related epilepsy causing complex partial seizures. SPET imaging was performed using 250 MBq of (99m)Tc-HMPAO and a four-scan paradigm - two with and two without stimulation. The stimulation began at VNS current levels of 0.25 mA and was increased according to the limit of patients' tolerance, usually defined by coughing or discomfort. The stimulating waveform was of continuous square wave pulses of 500 micro s duration at 30 Hz. Image analysis was by SPM99. Reduced perfusion during stimulation was observed in the ipsilateral brain stem, cingulate, amygdala and hippocampus and contralateral thalamus and cingulate. The study provides further evidence of the involvement of the limbic system in the action of vagal nerve stimulation.

16. **Liu WC, Mosier K, Kalnin AJ, Marks D. BOLD fMRI activation induced by vagus nerve stimulation in seizure patients. *J Neurol Neurosurg Psychiatry*. 2003;74(6):811-3.**

<http://www.ncbi.nlm.nih.gov/pubmed/12754361>

**Notes** This short report of five patients with complex partial seizures showed that all patients had activation in the frontal and occipital lobes with VNS, but only the two responders to VNS Therapy had activation in the thalamus. The patient with greater seizure control had a more robust thalamic activation pattern. The authors conclude that there may be a relation between thalamic activation (both spatial extent and peak intensity) and a favorable clinical outcome with VNS. Their findings are similar to those of other imaging studies.

**Abstract** **OBJECTIVE:** To identify the cerebral activated regions associated with the vagus nerve stimulation in epilepsy patients. **DESIGN:** Blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) was employed to detect areas of the brain activated by vagus nerve stimulation in five patients with documented complex partial seizures. **METHODS:** Functional MRI was done on a GE 1.5T Echosped horizon scanner. Before each patient entered the scanner, the vagal nerve stimulator was set to a specific ON-OFF paradigm so that the data could be analysed using a box-car type of design. The brains were scanned both anatomically and functionally. The functional images were corrected for head motion and co-registered to the anatomical images. Maps of the activated areas were generated and analysed using the brain mapping software, SPM99. The threshold for activation was chosen as  $p < 0.001$ . **RESULTS:** All patients showed activation in the frontal and occipital lobes. However, activation in the thalamus was seen only in the two patients with improved seizure control. **CONCLUSIONS:** BOLD fMRI can detect activation associated with vagus nerve stimulation. There may be a relation between thalamic activation and a favourable clinical outcome.

17. **Rysz A, Koszewski W. [The effect of chronic Vagus Nerve Stimulation (VNS) on the central conduction time assessed by multimodal evoked potentials in patients with drug resistant epilepsy: preliminary report]. *Neurol Neurochir Pol.* 2003;37(5):1113-25. Polish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15174257>  
**Abstract** Changes over time in evoked potentials of various modality (VEP, SSEP and BAEP) were analyzed in 3 patients, submitted to chronic Vagus Nerve Stimulation (VNS) due to drug resistant epilepsy. The aim of a study was to establish which cerebral structures are most prone to change their baseline electrophysiological status in consequence of chronic VNS. Evoked potentials were examined before the Vagus Nerve Stimulator implantation and at arbitrarily defined follow-ups several months after the implantation. Preliminary results obtained in a small group of 3 patients suggest a possible prolongation of the central conduction time in the examined modalities of evoked potentials due to the VNS treatment. A hypothetical mechanism of antiepileptic VNS action might be related to the permanent stimulation of brainstem and cortical structures that limit seizures propagation through hyperpolarisation both at the cortical level and in subcortical structures.
18. **Narayanan JT, Watts R, Haddad N, Labar DR, Li PM, Filippi CG. Cerebral activation during vagus nerve stimulation: a functional MR study. *Epilepsia.* 2002;43(12):1509-14.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12460253>  
**Abstract** PURPOSE: To study the short-term effects of vagus nerve stimulation (VNS) on brain activation and cerebral blood flow by using functional magnetic resonance imaging (fMRI). METHODS: Five patients (three women, two men; mean age, 35.4 years) who were treated for medically refractory epilepsy with VNS, underwent fMRI. All patients had a nonfocal brain MRI. The VNS was set at 30 Hz, 0.5-2.0 mA for intervals of activation of 30 s on and 30 s off, during which the fMRI was performed. Statistical parametric mapping (SPM) was used to determine significant areas of activation or inhibition during vagal nerve stimulation ( $p < 0.05$ ). RESULTS: VNS-induced activation was detected in the thalami bilaterally (left more than right), insular cortices bilaterally, ipsilateral basal ganglia and postcentral gyri, right posterior superior temporal gyrus, and inferomedial occipital gyri (left more than right). The most robust activation was seen in the thalami (left more than right) and insular cortices. Conclusions: VNS-induced thalamic and insular cortical activation during fMRI suggests that these areas may play a role in modulating cerebral cortical activity, and the observed decrease in seizure frequency in patients who are given VNS may be a consequence of this increased activation.

19. Van Laere K, Vonck K, Boon P, Versijpt J, Dierckx R. Perfusion SPECT changes after acute and chronic vagus nerve stimulation in relation to prestimulus condition and long-term clinical efficacy. *J Nucl Med.* 2002;43(6):733-44.

<http://www.ncbi.nlm.nih.gov/pubmed/12050316>

**Abstract** Left-sided vagus nerve stimulation (VNS) is an efficacious treatment for patients with refractory epilepsy. Previous studies have implicated thalamic and mesial temporal involvement in acute stimulation. In this study, acute and chronic effects of VNS in patients with refractory complex partial seizures with or without secondary generalization (CPS +/- SG) were evaluated with respect to the prestimulus condition and long-term follow-up. **METHODS:** Twenty-three patients (12 females, 11 males; mean age, 32.4 +/- 10.6 y; mean CPS +/- SG duration, 21.0 +/- 11.7 y) were prospectively included. All patients were considered unsuitable candidates for resective surgery because of nonlocalizing findings in the presurgical evaluation. All underwent a split-dose (99m)Tc-ethyl cysteinate dimer activation study before and immediately after their initial stimulation (0.25 or 0.5 mA, 30 Hz) on a high-resolution triple-head gamma camera. Ten patients also underwent a SPECT activation study 5.7 +/- 1.6 mo after implantation with an additional 0.25-mA stimulus superposed on a therapeutic intensity of 1.5 +/- 0.3 mA. Data were analyzed by an automated semiquantitative volume-of-interest analysis after stereotactic anatomic standardization. **RESULTS:** In the acute, initial setting, the left thalamus, right parahippocampal gyrus, and right hippocampus were deactivated by VNS ( $P < 0.011$ ). Acute stimulation in the chronic state resulted in a significant left thalamic activation ( $P < 0.001$ ). When chronic perfusion was compared with the initial pre-VNS baseline, perfusion decreases were found in both thalami (-5.3% on the left and -3.4% on the right,  $P < \text{or} = 0.04$ ). Perfusion changes in chronic VNS correlated negatively with the prestimulus perfusion pattern, indicating the tendency toward decreased brain activity on VNS. Initial stimulation changes in the right amygdala in the group of 10 patients with chronic assessment were predictive of therapeutic response ( $P = 0.018$ ); in addition, right chronic hippocampal perfusion changes correlated strongly with the long-term clinical efficacy of VNS ( $P = 0.004$ ). **CONCLUSION:** Under initial and chronic conditions, acute VNS stimulation produces different perfusion changes that are related to the interictal perfusion pattern before stimulation. The long-term mechanism of clinically effective VNS may rely on mainly hippocampal/amygdala and thalamic inhibition. Acute amygdala and chronic hippocampal perfusion changes are predictive of long-term therapeutic response in specific patient subgroups.

20. Olejniczak PW, Fisch BJ, Carey M, Butterbaugh G, Happel L, Tardo C. The effect of vagus nerve stimulation on epileptiform activity recorded from hippocampal depth electrodes. *Epilepsia*. 2001;42(3):423-9.

<http://www.ncbi.nlm.nih.gov/pubmed/11442163>

**Abstract** PURPOSE: To assess the effect of vagus nerve stimulation (VNS) on interictal epileptiform activity in the human hippocampus. Clinical studies have established the efficacy of vagus nerve stimulation in patients with epilepsy (VNS Study Group, 1995), although the electrophysiologic effects of VNS on the human hippocampus and mesial temporal lobe structures remain unknown. METHODS: We report a case study in which a patient with an implanted VNS underwent intracranial electrode recording before temporal lobectomy for intractable complex partial seizures. Epileptiform spikes and sharp waves were recorded from a depth electrode placed in the patient's left hippocampus. Spike frequencies and sharp-wave frequencies before and during VNS were compared using both a 5- and a 30-Hz stimulus. Different stimulation rates were tested on different days, and all analyses were performed using a Student's t test. RESULTS: We found no significant differences in spike frequency between baseline periods and stimulation at 5 and 30 Hz. In contrast, stimulation at 30 Hz produced a significant decrease in the occurrence of epileptiform sharp waves compared with the baseline, whereas stimulation at 5 Hz was associated with a significant increase in the occurrence of epileptiform sharp waves. CONCLUSIONS: VNS produces a measurable electrophysiologic effect on epileptiform activity in the human hippocampus. Although a clinical response to VNS did not occur in our patient before surgery, 30-Hz VNS suppressed interictal epileptiform sharp waves that were similar in appearance to those seen during the patient's actual seizures. In contrast, 5-Hz stimulation appeared to increase the appearance of interictal sharp waves.

21. Dasheiff RM, Sandberg T, Thompson J, Arrambide S, E03 and E05 Cooperative Study Group. Vagal nerve stimulation does not unkindle seizures. *J Clin Neurophysiol*. 2001;18(1):68-74.

<http://www.ncbi.nlm.nih.gov/pubmed/11290941>

**Abstract** The purpose of this study was to investigate a mechanism of action for the effect of vagal nerve stimulation on reducing seizures in patients with complex partial epilepsy. The hypothesis tested was that vagal nerve stimulation has an anticonvulsant effect on epilepsy. The databases of two large clinical trials (E03, E05) were accessed, and statistical methods were applied using logarithmic transforms and regression analysis. Two parameters--duration of a patient's epilepsy before entering the clinical trial and the patient's seizure density before entering the clinical trial--were used as markers of subsequent seizure control during vagal nerve stimulation. In general, there was not a good fit to the regression lines, and the slope of the lines did not conform to the hypothesis. The hypothesis that vagal nerve stimulation may unkindle epileptic seizures was not supported.

22. **Koo B. EEG changes with vagus nerve stimulation. *J Clin Neurophysiol.* 2001;18(5):434-41. <http://www.ncbi.nlm.nih.gov/pubmed/11709649>**  
**Abstract** Vagus nerve stimulation (VNS) has been shown to induce EEG changes in animals, but human studies have not shown any significant acute EEG changes. This study is to determine the long-term effect of VNS on EEG. Twenty-one patients aged 4 to 31 years (mean: 14.1 +/- 7.0 years) were studied for a mean duration of 16.8 months with serial EEGs performed at baseline and at 3 months, 6 months, and 12 months after receiving a VNS implant. Five patients who showed active spikes/spike and wave activity on baseline EEGs were found to have synchronization of epileptiform activity, progressive increase in duration of spike-free intervals ( $P < 0.05$ ), and progressive decrease in duration and frequency of spikes/spike and wave activity ( $P < 0.01$ ) with time. The remaining 16 patients with less active baseline EEGs did not show obvious synchronization or clustering of spikes but also showed a statistically significant progressive decrease in the number of spikes on EEG with time ( $P < 0.004$  at 3 months,  $P < 0.008$  at 6 months, and  $P < 0.004$  at 1 year). Vagus nerve stimulation induces progressive EEG changes in the form of clustering of epileptiform activity followed by progressively increased periods of spike-free intervals. This may reflect the mechanism of action of VNS in achieving seizure control: alternating synchronization and desynchronization of EEG, with the latter being progressively the dominant feature.
23. **Henry TR. Functional imaging studies of epilepsy therapies. *Adv Neurol.* 2000;83:305-17. <http://www.ncbi.nlm.nih.gov/pubmed/10999213>**
24. **Vonck K, Boon P, Van Laere K, D'Have M, Vandekerckhove T, O'Connor S, et al. Acute single photon emission computed tomographic study of vagus nerve stimulation in refractory epilepsy. *Epilepsia.* 2000;41(5):601-9. <http://www.ncbi.nlm.nih.gov/pubmed/10802767>**  
**Abstract** PURPOSE: Left-sided vagus nerve stimulation (VNS) is an efficacious treatment for patients with refractory epilepsy. The precise mechanism of action remains to be elucidated. Only limited data on VNS-induced changes in regional cerebral blood flow (rCBF) are available. The aim of this study was to investigate rCBF changes during initial VNS with single-photon emission computed tomography (SPECT). METHODS: In 12 patients (8 women, 4 men) with mean age of 32 years and mean duration of epilepsy of 19 years, VNS-induced rCBF changes were studied by means of a  $^{99m}\text{Tc}$ -ethyl cysteinate dimer activation study with a single-day split-dose protocol before and immediately after initial stimulation. Images were acquired on a triple-head camera with fan-beam collimators and were reconstructed with scatter and attenuation correction. After coregistration to a standardized template, both a semiquantitative analysis using predefined volumes-of-interest (VOIs) as well as voxel-by-voxel analysis of the intrasubject activation were performed. During follow-up, efficacy of VNS in terms of seizure-frequency reduction was studied. RESULTS: The semiquantitative analysis, with reference to the total counts in all VOIs, revealed a significant decrease of activity in the left thalamus immediately after the initial stimulation train. These results agreed with voxel-by-voxel analysis. In our study ipsilateral thalamic hypoperfusion was the most significant finding. Mean frequency of complex partial seizures was reduced from 30 per month before implantation to six per month after implantation. CONCLUSIONS: VNS induces rCBF changes immediately after initial stimulation that can be studied with SPECT. VNS-induced changes in the thalamus may play an important role in suppression of seizures. However, no significant relation between the level of hypoperfusion and subsequent clinical efficacy was found.

25. **Van Laere K, Vonck K, Boon P, Brans B, Vandekerckhove T, Dierckx R. Vagus nerve stimulation in refractory epilepsy: SPECT activation study. *J Nucl Med.* 2000;41(7):1145-54.**

<http://www.ncbi.nlm.nih.gov/pubmed/10914903>

**Abstract** Left-sided vagus nerve stimulation (VNS) is an efficacious treatment for patients with refractory epilepsy. The exact mechanism of action remains to be elucidated. This study investigated the acute effects of initial VNS in patients with refractory complex partial epilepsy with or without secondary generalization (complex partial seizures [CPS] +/- SG) by means of a perfusion activation study with SPECT. **METHODS:** Twelve patients (mean age, 32.2 +/- 10.2 y; age range, 12-47 y) with a mean duration of CPS +/- SG of 19.8 +/- 10.0 y (range, 5-33 y) received VNS. All patients were considered unsuitable candidates for resective surgery because of nonlocalizing findings on presurgical evaluation. VNS efficacy was evaluated for patients with at least 4-mo follow-up. VNS-induced regional cerebral blood flow alterations were studied by a (99m)Tc-ethyl cysteinyl dimer activation study with a single-day split-dose protocol before and immediately after an initial stimulation. Images were acquired on a triple-head camera with fanbeam collimators. After coregistration to a standardized template, both a semiquantitative analysis using predefined volumes of interest and a voxel-by-voxel analysis of the intrasubject activation (statistical parametric mapping) were performed. **RESULTS:** Seizure-frequency changes ranged from 100% decrease to 0% after VNS. The semiquantitative analysis revealed a consistent decrease of activity in the left thalamus (ratio stimulator on/off = 0.94 +/- 0.04; P = 0.005). These results were concordant with the voxel-by-voxel analysis in which a significant deactivation in the left thalamus was found with spread to the ipsilateral hippocampus. There was no statistically significant correlation between initial VNS-induced thalamic hypoperfusion and seizure reduction at maximum follow-up. **CONCLUSION:** Our findings are consistent with the hypothesis that acute VNS reduces seizure onset or propagation through inhibition of the thalamic relay center. Differences with limited H<sub>2</sub>(<sup>15</sup>O) PET data may be associated with temporal effects caused by a stimulation-induced local hemodynamic response and need further investigation. SPECT allows study of cerebral physiopathologic effects of vagus nerve electrostimulation in complex partial epilepsy.

26. **Ring HA, White S, Costa DC, Pottinger R, Dick JP, Koeze T, et al. A SPECT study of the effect of vagal nerve stimulation on thalamic activity in patients with epilepsy. *Seizure.* 2000;9(6):380-4.**

<http://www.ncbi.nlm.nih.gov/pubmed/10985992>

**Abstract** The mechanism by which vagal nerve stimulation (VNS) exerts an anticonvulsant effect in humans is unknown. This study used (99m)Tc-HMPAO single photon emission tomography (SPECT) to examine the effects of VNS on regional cerebral activity in thalamic and insular regions. Seven subjects with epilepsy who had been receiving vagal nerve stimulation for at least 6 months underwent SPECT scanning with simultaneous scalp electroencephalographic (EEG) recording. Subjects were studied in two states; during VNS activity and during a comparison condition of VNS inactivity. A region of interest analysis demonstrated that rapid cycling stimulation (7 seconds on, 12 seconds off) was associated with relatively decreased activity in left and right medial thalamic regions. No systematic stimulation-related changes were observed on visual or spectral analysis of EEG data. The thalamus is involved in modulation of ongoing cortical EEG activity in animals. Our results support the hypothesis that VNS may exert an antiepileptic action by an effect on thalamic activity.

27. **Henry TR, Votaw JR, Pennell PB, Epstein CM, Bakay RA, Faber TL, et al. Acute blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy. *Neurology*. 1999;52(6):1166-73.**

<http://www.ncbi.nlm.nih.gov/pubmed/10214738>

**Notes** This is the second substantial mechanism of action (MOA) paper on VNS in humans (and a follow up to the previous Henry et al article). Findings were similar to those in the previous paper. In addition, increased regional blood flow in the right and left thalami were correlated with a statistically significant seizure decrease demonstrating a very nice cause and effect in an epileptogenic structure.

**Abstract** **OBJECTIVE:** To determine possible sites of therapeutic action of vagus nerve stimulation (VNS), by correlating acute VNS-induced regional cerebral blood flow (rCBF) alterations and chronic therapeutic responses. **BACKGROUND:** We previously found that VNS acutely induces rCBF alterations at sites that receive vagal afferents and higher-order projections, including dorsal medulla, somatosensory cortex (contralateral to stimulation), thalamus and cerebellum bilaterally, and several limbic structures (including hippocampus and amygdala bilaterally). **METHODS:** VNS-induced rCBF changes were measured by subtracting resting rCBF from rCBF during VNS, using [<sup>15</sup>O]water and PET, immediately before ongoing VNS began, in 11 partial epilepsy patients. T-statistical mapping established relative rCBF increases and decreases for each patient. Percent changes in frequency of complex partial seizures (with or without secondary generalization) during three months of VNS compared with pre-VNS baseline, and T-thresholded rCBF changes (for each of the 25 regions of previously observed significant CBF change), were rank ordered across patients. Spearman rank correlation coefficients assessed associations of seizure-frequency change and t-thresholded rCBF change. **RESULTS:** Seizure-frequency changes ranged from 71% decrease to 12% increase during VNS. Only the right and left thalami showed significant associations of rCBF change with seizure-frequency change. Increased right and left thalamic CBF correlated with decreased seizures ( $p < 0.001$ ). **CONCLUSIONS:** Increased thalamic synaptic activities probably mediate some antiseizure effects of VNS. Future studies should examine neurotransmitter-receptor alterations in reticular and specific thalamic nuclei during VNS.

28. **Henry TR, Bakay RA, Votaw JR, Pennell PB, Epstein CM, Faber TL, et al. Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: I. Acute effects at high and low levels of stimulation. *Epilepsia*. 1998;39(9):983-90.**

<http://www.ncbi.nlm.nih.gov/pubmed/9738678>

**Notes** This article is the first substantial mechanism of action (MOA) paper on VNS in humans. Henry et al conclude that NS directly changes cerebral blood flow in seizure-related areas as determined by PET scans before VNS and PET scans during VNS using the magnet (10 patients). Changes were seen with both high and low stimulation parameters, but were more prominent in the high stimulation group of patients. The findings suggest that left cervical VNS acutely increases synaptic activity in structures directly innervated by central vagal structures and areas that process left-sided somatosensory information, but VNS also acutely alters synaptic activity in multiple limbic system structures bilaterally. The effects of VNS may outlast the actual On time of the VNS pulse.

**Abstract** PURPOSE: Left cervical vagus nerve stimulation (VNS) decreases complex partial seizures (CPS) by unknown mechanisms of action. We hypothesized that therapeutic VNS alters synaptic activities at vagal afferent terminations and in sites that receive polysynaptic projections from these medullary nuclei. METHODS: Ten patients with partial epilepsy underwent positron emission tomographic (PET) measurements of cerebral blood flow (BF) three times before and three times during VNS. Parameters for VNS were at high levels for 5 patients and at low levels for 5. Resting BF measurements were subtracted from measurements during VNS in each subject. Subtraction data were averaged in each of 2 groups of 5 patients. t Tests were applied to BF changes in brain regions that receive vagal afferents and projections (significant at  $p < 0.05$ , corrected for repeated measures). RESULTS: In both the low- and high-stimulation groups during VNS, brain BF was (a) increased in the rostral, dorsal-central medulla; (b) increased in the right postcentral gyrus, (c) increased bilaterally in the hypothalamus, thalamus, and insular cortices, and in cerebellar hemispheres inferiorly; and (d) decreased bilaterally in hippocampus, amygdala, and posterior cingulate gyri. The high-stimulation group had greater volumes of activation and deactivation sites. CONCLUSIONS: Our findings suggest that left cervical VNS acutely increases synaptic activity in structures directly innervated by central vagal structures and areas that process left-sided somatosensory information, but VNS also acutely alters synaptic activity in multiple limbic system structures bilaterally. These findings may reflect sites of therapeutic actions of VNS.

29. **Uysal H, Inan LE, Kuli P. Vagal stimulation. *Neurology*. 1996;47(5):1355-6.** <http://www.ncbi.nlm.nih.gov/pubmed/8909471>

30. **Ko D, Heck C, Grafton S, Apuzzo ML, Couldwell WT, Chen T, et al. Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H2(15)O blood flow imaging. *Neurosurgery*. 1996;39(2):426-30; discussion *Neurosurgery*. 1996;39(2):430-1; comment *Neurosurgery*. 1998;42(5):1196.**

<http://www.ncbi.nlm.nih.gov/pubmed/8832691>

**Abstract** OBJECTIVE: To determine the central areas of activation by vagal nerve stimulation (VNS) in epilepsy. VNS is a promising neurosurgical method for treating patients with partial and secondary generalized epilepsy. The anti-epileptic mechanism of action from VNS is not well understood. METHODS: We performed H2(15)O PET blood flow functional imaging on three patients with epilepsy in a vagal nerve stimulation study (E04 Protocol with Cyberonics). The three patients included two that had previous epilepsy surgery but continued to have frequent seizures. Seizure onset was frontal in two patients and bitemporal in the third patient. Twelve PET scans per subject were acquired every 10 minutes with a Siemens 953/A scanner. In 6 stimulus scans, VNS was activated for 60 seconds (2 mA, 30 Hz) commensurate with isotope injection. In 6 control scans no VNS was administered. No clinical seizures were present during any scan. Three way ANOVA with linear contrasts subject, task, repetition) of coregistered images identified significant treatment effects. RESULTS: The difference between PET with VNS and without revealed that left VNS activated right thalamus ( $P < 0.0006$ ), right posterior temporal cortex ( $P < 0.0003$ ), left putamen ( $P < 0.0002$ ), and left inferior cerebellum ( $P < 0.0009$ ). CONCLUSIONS: VNS causes activation of several central areas including contralateral thalamus. Localization to the thalamus suggests a possible mechanism to explain the therapeutic benefit, consistent with the role of the thalamus as a generator and modulator of cerebral activity.

31. **Ben-Menachem E, Hamberger A, Hedner T, Hammond EJ, Uthman BM, Slater J, et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. *Epilepsy Res*. 1995;20(3):221-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/7796794>

**Abstract** Electrical stimulation of the vagus nerve (VNS) is a new method for the treatment of patients with medically intractable epilepsy. Sixteen patients, ten of whom participated in a larger multicenter double-blind trial on the efficacy of VNS in epilepsy, and six who participated in pilot studies, consented to participate in the present study. Ten patients received HIGH stimulation and six patients LOW stimulation for the 3-month trial. Cerebrospinal fluid (CSF) samples (16 ml) were collected both before and after 3 months of VNS. Amino acid and neurotransmitter metabolites were analyzed. Four patients responded to VS with more than a 25% seizure reduction after 3 months. Mean and median concentrations of phosphoethanolamine (PEA) increased in responders and decreased in nonresponders. Free GABA increased in both groups but more so in the nonresponders. After 9 months of VS (6-9 months on HIGH stimulation) 4 of 15 patients had more than 40% seizure reduction. There were significant correlations between seizure reduction and increases in asparagine, phenylalanine, PEA, alanine and tryptophan concentrations. Comparison between patients with HIGH or LOW stimulation showed a significant increase in ethanolamine (EA) in the HIGH group and a decrease in glutamine in the LOW group. All patients regardless of response or stimulation intensity showed significantly increased total and free GABA levels. A decrease in CSF aspartate was marginally significant. Other trends were decreases in glutamate and increases in 5-hydroxyindoleacetic acid. Chronic VNS appears to have an effect on various amino acids pools in the brain.(ABSTRACT TRUNCATED AT 250 WORDS)

32. **Hammond EJ, Uthman BM, Wilder BJ, Ben-Menachem E, Hamberger A, Hedner T, et al. Neurochemical effects of vagus nerve stimulation in humans. *Brain Res.* 1992;583(1-2):300-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/1504837>  
**Abstract** An implanted stimulating device chronically stimulated the left cervical vagus nerve in epileptic patients. Cerebrospinal fluid concentrations of free and total gamma-aminobutyric acid, homovanillic acid, 5-hydroxyindoleacetic acid, aspartate, glutamate, asparagine, serine, glutamine, glycine, phosphoethanolamine, taurine, alanine, tyrosine, ethanolamine, valine, phenylalanine, isoleucine, vasoactive intestinal peptide, beta-endorphin, and somatostatin were measured before and after 2 months of chronic stimulation in six patients. Significant increases were seen in homovanillic acid and 5-hydroxyindoleacetic acid in three patients, and significant decreases in aspartate were seen in five patients. These changes were associated with a decrease in seizure frequency.
33. **Hammond EJ, Uthman BM, Reid SA, Wilder BJ. Electrophysiological studies of cervical vagus nerve stimulation in humans: I. EEG effects. *Epilepsia.* 1992;33(6):1013-20.**  
<http://www.ncbi.nlm.nih.gov/pubmed/1464257>  
**Abstract** Evidence from studies of experimental animals indicates that electrical stimulation of the vagus nerve alters EEGs under certain stimulus parameters. We report EEG effects of electrical stimulation of the vagus nerve in 9 patients with medically intractable seizures as part of a clinical trial of chronic vagal stimulation for control of epilepsy. The mechanism of action of the vagal antiepileptic effect is unknown, and we believed that analysis of electrophysiologic effects of vagal nerve stimulation would help elucidate the brain areas affected. The left vagus nerve in the neck was stimulated with a programmable implanted stimulator. Stimulation at various stimulus frequencies and amplitudes had no noticeable effect on EEG activity whether the patient was under general anesthesia, awake, or asleep, but vagus nerve stimulation may interrupt ongoing ictal EEG activity.
34. **Hammond EJ, Uthman BM, Reid SA, Wilder BJ. Electrophysiologic studies of cervical vagus nerve stimulation in humans: II. Evoked potentials. *Epilepsia.* 1992;33(6):1021-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/1464258>  
**Abstract** Evidence from studies of experimental animals indicates that electrical stimulation of the vagus nerve not only can alter the EEG but evokes activity in specific brain areas. We report effects of electrical stimulation of the vagus nerve in 9 patients with medically intractable seizures as part of a clinical trial of chronic vagal stimulation for control of epilepsy. The left vagus nerve in the neck was stimulated with a programmable implanted stimulator. Effects of stimulus amplitude, duration, and rate were studied. Noncephalic reference recording of the vagus nerve evoked potential showed some unusual properties: a scalp negative component occurred with a latency of 12 ms, very high amplitude (< or = 60 microV), and widespread scalp distribution. Field distribution studies indicated that this potential was myogenic in origin and generated in the region of the stimulating electrodes in the neck area. Chemically induced muscle paralysis confirmed this observation. Bipolar scalp recording showed several small-amplitude topographically distinct potentials occurring in 30 ms. No effect, either acute or chronic, could be detected on pattern-reversal evoked potentials, auditory brainstem evoked potentials, auditory 40-Hz potentials, or cognitive evoked potentials.
35. **Garnett ES, Nahmias C, Scheffel A, Firnau G, Upton AR. Regional cerebral blood flow in man manipulated by direct vagal stimulation. *Pacing Clin Electrophysiol.* 1992;15(10 Pt 2):1579-80.**  
<http://www.ncbi.nlm.nih.gov/pubmed/1383972>
36. **Upton AR, Tougas G, Talalla A, White A, Hudoba P, Fitzpatrick D, et al. Neurophysiological effects of left vagal stimulation in man. *Pacing Clin Electrophysiol.* 1991;14(1):70-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/1705339>

37. **Hammond EJ, Uthman BM, Reid SA, Wilder BJ, Ramsay RE. Vagus nerve stimulation in humans: neurophysiological studies and electrophysiological monitoring. *Epilepsia*. 1990;31 Suppl 2:S51-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/2226367>

**Abstract** Evidence from studies of experimental animals indicates that electrical stimulation of the vagus nerve alters behavioral and electrographic seizure activity. We report on effects of electrical stimulation of the vagus nerve in five patients with medically intractable seizures as part of a clinical trial of chronic vagal stimulation for control of epilepsy. The mechanism of action of the vagal antiepileptic effect is unknown, and it is hoped that analysis of electrophysiological effects of vagal nerve stimulation will help elucidate which brain areas are affected. Stimulation of the left vagus nerve in the neck was accomplished with a programmable implanted stimulator. Effects of stimulus amplitude, duration, and rate were studied. Noncephalic reference recording of the vagus-nerve-evoked potential showed some unusual properties: a scalp negative component occurred with latency of 12 ms, very high amplitude (up to 60 microV), and widespread scalp distribution. Field distribution studies indicate that this potential is generated in the neck, in the region of the stimulating electrodes. Muscle paralysis confirms this observation. Stimulation at various frequencies had no noticeable effect on electroencephalographic (EEG) activity regardless of whether the patient was under general anesthesia, awake, or asleep.

**MoA - Review Articles (of VNS in epilepsy)**

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- 1. Witcher MR, Ellis TL. Astroglial networks and implications for therapeutic neuromodulation of epilepsy. *Front Comput Neurosci.* 2012;6:61.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22952462>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3429855/pdf/fncom-06-00061.pdf>  
**Abstract** Epilepsy is a common chronic neurologic disorder affecting approximately 1% of the world population. More than one-third of all epilepsy patients have incompletely controlled seizures or debilitating medication side effects in spite of optimal medical management. Medically refractory epilepsy is associated with excess injury and mortality, psychosocial dysfunction, and significant cognitive impairment. Effective treatment options for these patients can be limited. The cellular mechanisms underlying seizure activity are incompletely understood, though we here describe multiple lines of evidence supporting the likely contribution of astroglia to epilepsy, with focus on individual astrocytes and their network functions. Of the emerging therapeutic modalities for epilepsy, one of the most intriguing is the field of neuromodulation. Neuromodulatory treatment, which consists of administering electrical pulses to neural tissue to modulate its activity leading to a beneficial effect, may be an option for these patients. Current modalities consist of vagal nerve stimulation, open and closed-loop stimulation, and transcranial magnetic stimulation. Due to their unique properties, we here present astrocytes as likely important targets for the developing field of neuromodulation in the treatment of epilepsy.
- 2. Krahl SE. Vagus nerve stimulation for epilepsy: A review of the peripheral mechanisms. *Surg Neurol Int.* 2012;3(Suppl 1):S47-52.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22826811>  
**Abstract** Vagus nerve stimulation (VNS) is a unique epilepsy treatment in that a peripheral intervention is used to treat a disease that is entirely related to pathological events occurring within the brain. To understand how stimulation of the vagus nerve can be used to stop seizures, an understanding of the peripheral anatomy and physiology of the vagus nerve is essential. The peripheral aspects of the vagus nerve are discussed in this review, with an explanation of which fibers and branches are involved in producing these antiepileptic effects, along with speculation about the potential for improving the therapy.
- 3. Krahl SE, Clark KB. Vagus nerve stimulation for epilepsy: A review of central mechanisms. *Surg Neurol Int.* 2012;3(Suppl 4):S255-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23230530>  
<http://www.surgicalneurologyint.com/article.asp?issn=2152-7806;year=2012;volume=3;issue=5;spage=255;epage=259;aulast=Krahl>  
**Abstract** In a previous paper, the anatomy and physiology of the vagus nerve was discussed in an attempt to explain which vagus nerve fibers and branches are affected by clinically relevant electrical stimulation. This companion paper presents some of vagus nerve stimulation's putative central nervous system mechanisms of action by summarizing known anatomical projections of vagal afferents and their effects on brain biogenic amine pathways and seizure expression.

4. **Jaseja H. EEG-desynchronization as the major mechanism of anti-epileptic action of vagal nerve stimulation in patients with intractable seizures: clinical neurophysiological evidence. *Med Hypotheses*. 2010;74(5):855-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20005054>  
**Abstract** Vagal nerve stimulation (VNS) has emerged as an effective and acceptable alternative therapy for patients with intractable seizures. Despite its reported efficacy in several studies, the precise mechanism of its anti-epileptic action remains elusive and requires to be established. Based on neurophysiological alterations induced by VNS, it has been proposed earlier that a major mechanism of its anti-epileptic action could be EEG-desynchronization, which is known to be associated with increased resistance to seizures. This brief paper attempts to support the proposed mechanism with clinical neurophysiological evidence that has emerged in recent times.
  
5. **Vonck K, Boon P, Van Roost D. Anatomical and physiological basis and mechanism of action of neurostimulation for epilepsy. *Acta Neurochir Suppl*. 2007;97(Pt 2):321-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17691318>  
**Abstract** Neurostimulation is an emerging treatment for neurological diseases. Different types of neurostimulation exist mainly depending of the part of the nervous system that is being affected and the way this stimulation is being administered. Vagus nerve stimulation (VNS) is a neurophysiological treatment for patients with medically or surgically refractory epilepsy. Over 30,000 patients have been treated with VNS. No clear predictive factors for responders have been identified. To date, the precise mechanism of action remains to be elucidated. Better insight in the mechanism of action may identify seizure types or syndromes that respond better to VNS and may guide the search for optimal stimulation parameters and finally improve clinical efficacy. Deep brain stimulation (DBS) has been used extensively as a treatment for movement disorders. Several new indications such as obsessive compulsive behaviour and cluster headache are being investigated with promising results. The vast progress in biotechnology along with the experience in other neurological diseases in the past ten years has led to a renewed interest in intracerebral stimulation for epilepsy. Epilepsy centers around the world have recently reinitiated trials with deep brain stimulation in different intracerebral structures such as the thalamus, the hippocampus and the subthalamic nucleus.
  
6. **Henry TR. The antiseizure effect of VNS is mediated by ascending pathways. In: Miller JW, Silbergeld DL, Eds. *Epilepsy Surgery: Principles and Controversies*. New York, NY: Taylor & Francis; 2006:624-9.**

7. **Magdaleno-Madrigal VM. [Electrical stimulation of the vagal nerve: from experimental to clinical aspects]. *Rev Neurol.* 2004;39(10):971-7. Spanish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15573317>  
**Abstract** INTRODUCTION AND AIMS: This review focuses its attention on the studies that have been conducted to determine the influence of electrical stimulation of the vagal nerve on experimentally induced convulsive activity and its application in the clinical field. The literature published to date describes an anticonvulsive effect on the seizures triggered by pharmacological agents and by electrical stimulation such as electroshock, and in the amygdaline electrical kindling model a delay in the generalisation of the convulsive activity is observed. DEVELOPMENT: The first experimental observations showed that electrical stimulation of the vagal nerve can have effects on EEG activity, including synchronisation and desynchronisation of the electrical activity of the brain, as well as promoting an increase in the amount of REM sleep. These observations served as the basis for the renewed interest in the electrical stimulation of the vagal nerve in experimental models and testing its effectiveness in patients with medication-resistant epilepsy. Nevertheless, the mechanisms accounting for the anticonvulsive effect remain unknown. CONCLUSIONS: These observations open up the possibility of studying the role played by neurotransmitters and neuromodulators in the anticonvulsive process of the electrical stimulation of the vagal nerve in experimental models of epilepsy and offer evidence of its possible action in the human brain.
8. **Chae JH, Nahas Z, Lomarev M, Denslow S, Lorberbaum JP, Bohning DE, et al. A review of functional neuroimaging studies of vagus nerve stimulation (VNS). *J Psychiatr Res.* 2003;37(6):443-55.**  
<http://www.ncbi.nlm.nih.gov/pubmed/14563375>  
**Abstract** Vagus nerve stimulation (VNS) is a new method for preventing and treating seizures, and shows promise as a potential new antidepressant. The mechanisms of action of VNS are still unknown, although the afferent direct and secondary connections of the vagus nerve are well established and are the most likely route of VNS brain effects. Over the past several years, many groups have used functional brain imaging to better understand VNS effects on the brain. Since these studies differ somewhat in their methodologies, findings and conclusions, at first glance, this literature may appear inconsistent. Although disagreement exists regarding the specific locations and the direction of brain activation, the differences across studies are largely due to different methods, and the results are not entirely inconsistent. We provide an overview of these functional imaging studies of VNS. PET (positron emission tomography) and SPECT (single photon emission computed tomography) studies have implicated several brain areas affected by VNS, without being able to define the key structures consistently and immediately activated by VNS. BOLD (blood oxygen level dependent) fMRI (functional magnetic resonance imaging), with its relatively high spatio-temporal resolution, performed during VNS, can reveal the location and level of the brain's immediate response to VNS. As a whole, these studies demonstrate that VNS causes immediate and longer-term changes in brain regions with vagus innervations and which have been implicated in neuropsychiatric disorders. These include the thalamus, cerebellum, orbitofrontal cortex, limbic system, hypothalamus, and medulla. Functional neuroimaging studies have the potential to provide greater insight into the brain circuitry behind the activity of VNS.

9. **Henry TR. Therapeutic mechanisms of vagus nerve stimulation. *Neurology*. 2002;59(6 Suppl 4):S3-14.** <http://www.ncbi.nlm.nih.gov/pubmed/12270962>  
**Abstract** Experiments in acute and chronic animal models of epilepsy provide mechanistic insight into the acute abortive, acute prophylactic, and chronic progressive prophylactic, anti-seizure effects of vagus nerve stimulation (VNS) observed in human epilepsies, and demonstrate antiepileptogenic effects of VNS in the kindling model. Anatomic-physiologic studies, experimental epilepsy studies, and human imaging, EEG, and CSF studies suggest that multiple mechanisms underlie the antiseizure effects of VNS and that alterations of vagal parasympathetic efferent activities do not underlie these antiseizure effects. Putative antiseizure mechanisms are mediated by altered vagal afferent activities, and probably include altered activities in the reticular activating system, the central autonomic network, the limbic system, and the diffuse noradrenergic projection system. Anatomic-physiologic studies fully account for the common and rare adverse effects of VNS. Current understandings of antiepileptic drug (AED) and VNS therapeutic mechanisms strongly support the "common sense" interpretation of the clinical studies: i.e., adjunctive VNS can add antiseizure effect to any AED regimen, with no interactive toxicity and no effect on drug distribution and elimination.
10. **Weinstein S. The anticonvulsant effect of electrical fields. *Curr Neurol Neurosci Rep*. 2001;1(2):155-61.** <http://www.ncbi.nlm.nih.gov/pubmed/11898511>  
**Abstract** The use of electrical fields to treat epilepsy is undergoing increased scrutiny as an alternative to medications and resective surgery. Much recent attention has been focused on ionic channels and seizure control; however, nonsynaptic mechanisms may be crucial for seizure onset, raising the possibility of using electrical field application to abort seizures. Furthermore, the inhibitory effects may outlast the immediate treatment and possibly be a prophylactic intervention. This paper reviews the use of brain stimulation for treatment of epilepsy, but also cites instances where the antithetical results occur. The greatest detail focuses on disrupting the onset or shortening the seizure. The paper does not extensively review deep brain or vagal nerve stimulation.
11. **Vonck K, Van Laere K, Dedeurwaerdere S, Caemaert J, De Reuck J, Boon P. The mechanism of action of vagus nerve stimulation for refractory epilepsy: the current status. *J Clin Neurophysiol*. 2001;18(5):394-401.** <http://www.ncbi.nlm.nih.gov/pubmed/11709643>  
**Abstract** Vagus nerve stimulation (VNS) is a neurophysiologic treatment for patients with medically or surgically refractory epilepsy. Since the first human implant in 1989, more than 10,000 patients have been treated with VNS. The precise mechanism of action remains to be elucidated. Animal experiments with VNS were initially performed to demonstrate efficacy and safety preceding the clinical trials in human patients. Mechanism of action research involving animal experiments can provide essential clues. Animal experiments are often labor-intensive even in the hands of experienced researchers, however, and the results remain only a reflection of the complicated pathophysiologic systems of the human brain. Mechanism of action research in human patients treated with VNS is particularly challenging because of safety concerns, the large number of patients required, and the heterogeneous nature of various small patient series. This study provides an overview of the progress that has been made in the past 10 years through neurophysiologic, neuroanatomic, neurochemical, and cerebral blood flow studies in animals and patients treated with VNS. Further elucidation of the mechanism of action of VNS may increase its clinical efficacy. It may also provide inspiration for the development of new therapeutic modalities for refractory epilepsy.

12. **Rutecki P. Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. *Epilepsia*. 1990;31 Suppl 2:S1-6.**

<http://www.ncbi.nlm.nih.gov/pubmed/2226360>

**Abstract** The vagus is a mixed nerve carrying somatic and visceral afferents and efferents. The majority of vagal nerve fibers are visceral afferents and have a wide distribution throughout the central nervous system (CNS) either monosynaptically or via the nucleus of the solitary tract. Besides activation of well-defined reflexes, vagal stimulation produces evoked potentials recorded from the cerebral cortex, the hippocampus, the thalamus, and the cerebellum. Activation of vagal afferents can depress monosynaptic reflexes, decrease the activity of spinothalamic neurons, and increase pain threshold. Depending on the stimulation parameters, vagal afferent stimulation in experimental animals can produce electroencephalographic (EEG) synchronization or desynchronization and has been shown to affect sleep states. The desynchronization of the EEG appears to depend on activation of afferent fibers that have conduction velocities of less than or equal to 15 m/s. Vagal afferent stimulation can also influence the activity of interictal cortical spikes produced by topical strychnine application, and either attenuate or stop seizures produced by pentylenetetrazol, 3-mercaptopropionic acid, maximal electroshock, and topical alumina gel. The mechanisms for the antiepileptic effects of vagal stimulation are not fully understood but probably relate to effects on the reticular activating system. The vagus provides an easily accessible, peripheral route to modulate CNS function.

**MR/DD Population (VNS/Epilepsy in...)**

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1. **Lund C, Kostov H, Blomskjold B, Nakken KO. Efficacy and tolerability of long-term treatment with vagus nerve stimulation in adolescents and adults with refractory epilepsy and learning disabilities. *Seizure*. 2011;20(1):34-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21035358>  
**Abstract** The long-term effects of vagus nerve stimulation (VNS) on seizure frequency were studied in 50 patients with epilepsy and learning disabilities. Mean observation time was 4.6 years. At follow-up, none of the patients was seizure-free, 25% had more than 50% seizure reduction, and 46% had some seizure reduction, but less than 50%. The discontinuation rate was 18%. Our results indicate that, like antiepileptic drugs, VNS does not have such a good seizure-reducing effect in patients with epilepsy and learning disabilities compared with the general epilepsy population.
2. **Huber B, Seidel M. Update on treatment of epilepsy in people with intellectual disabilities. *Curr Opin Psychiatry*. 2006;19(5):492-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16874122>  
**Abstract** PURPOSE OF REVIEW: On the basis of the relevance of adequate epilepsy treatment (antiepileptic drugs, surgery and vagus nerve stimulation) for people with intellectual disabilities, all articles, published from the beginning of 2005 to March 2006 and searched by MEDLINE, on this topic were reviewed. RECENT FINDINGS: On pharmacological treatment of epilepsy in people with intellectual disabilities, there were two articles on topiramate and one on levetiracetam. Two studies described the effect of surgical interventions, one of epilepsy surgery in the narrow sense and one of vagus nerve stimulation. Two papers were published on clinical conditions and therapeutic aspects of Angelman syndrome. They highlight the importance of gamma-aminobutyric acidergic mechanism in Angelman syndrome and the antiepileptic drug effects in this syndrome. SUMMARY: A contradiction exists between the relevance of epilepsy treatment in people with intellectual disabilities and the small number of published studies on pharmacological treatment. Some of the reasons are addressed and some alternatives are proposed.
3. **Huf RL, Mamelak A, Kneedy-Cayem K. Vagus nerve stimulation therapy: 2-year prospective open-label study of 40 subjects with refractory epilepsy and low IQ who are living in long-term care facilities. *Epilepsy Behav*. 2005;6(3):417-23.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15820352>  
**Abstract** Treating seizures among patients with mental retardation/developmental disabilities (MR/DD) is difficult owing in large part to the presence of additional comorbidities and the resulting need for polytherapy. Therefore, a nonpharmacological treatment option is needed for this population. This prospective, open-label study documented the long-term outcome of 40 low-IQ (<70) patients living in long-term care facilities who received vagus nerve stimulation (VNS) therapy for pharmacoresistant epilepsy. Subjects were seen every 1 to 3 months by their neurologist (R.H.). Seizure frequency, antiepileptic medication, and quality-of-life information were documented preimplantation and quarterly thereafter through 2 years. The surgery and therapy were well tolerated. Seizures were reduced by at least 50% for 11 subjects. Antiepileptic medications were reduced from 3.3 per subject at baseline to an average of 2.3 per subject after 2 years. According to caregiver reports, overall quality of life improved for the majority of subjects; also, using the Client Development Evaluation Report (CDER), statistically significant improvements were reported at both 1 and 2 years in attention span, word usage, clarity of speech, standing balance, washing dishes, and household chores. VNS is a viable treatment option for low-IQ patients with pharmacoresistant epilepsy who are living in long-term care facilities.

- 4. Shields WD. Management of epilepsy in mentally retarded children using the newer antiepileptic drugs, vagus nerve stimulation, and surgery. *J Child Neurol.* 2004;19 Suppl 1:S58-64.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15526971>  
**Abstract** Clusters of seizures, prolonged seizures, and status epilepticus occur more frequently in children with multiple disabilities, and chronic seizures are more likely to be refractory to treatment. In many patients, the seizures appear to contribute to the mental retardation. Thus, if the lives of these children are to improve, seizure control is essential. However, medical treatment can interfere with cognition and cause behavioral disturbances, making life very difficult for the child and the child's family. With the introduction of 10 new antiepileptic drugs in the last decade, the treatment of epilepsy in multiply handicapped children has significantly advanced. These new antiepileptic drugs may improve seizure control, medication tolerance, or both. Although the ultimate therapeutic goal is to keep children seizure free and alert, compromises regarding medication choice and dosage are still necessary in many cases. Novel treatment options, such as the vagus nerve stimulator, may decrease seizure frequency without behavioral or cognitive side effects. In carefully selected children with specific epilepsy syndromes, epilepsy surgery can provide partial or complete relief from seizures.
- 5. Devinsky O. What do you do when they grow up? Approaches to seizures in developmentally delayed adults. *Epilepsia.* 2002;43 Suppl 3:71-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12060009>  
<http://onlinelibrary.wiley.com/store/10.1046/j.1528-1157.43.s.3.2.x/asset/j.1528-1157.43.s.3.2.x.pdf?v=1&t=he9407bj&s=e33167c543e762a678db4a12946fd8d6ab6a9bb1>  
**Abstract** Epilepsy and developmental disabilities (DD) often occur together but affect individuals differently and have a complex causal relationship. Most epilepsy in the population with DD is partial or symptomatic generalized. Seizures and antiepileptic drugs (AEDs) can further delay development, and the DD can complicate treatment and adjustment to epilepsy. Medical care and decision making require careful coordination of health care providers and the family, especially because of the trend for the patients to live in group homes. Behavioral and psychiatric disorders are difficult to diagnose but common in those with DD and epilepsy; psychiatric disorders are perhaps up to sevenfold higher in this group than in the general population. Psychotropic medications-antidepressants, anxiolytics (but use caution with benzodiazepines), antipsychotics, and stimulants-are appropriate for those with psychiatric disorders. Diagnostic difficulties may lead to undertreatment, and the motivation to lessen certain behaviors may lead to overtreatment. Because those with DD may be unusually sensitive to adverse effects of both seizures and AEDs, cognitive and behavioral side effects must be carefully monitored. Few relevant studies exist. For some patients, comorbid psychiatric disorders may be treated with one AED, such as carbamazepine, lamotrigine, or valproate. Phenobarbital and phenytoin may be inappropriate for those with epilepsy and DD. Studies have shown some success with oxcarbazepine (for partial and generalized epilepsy) and with adjunctive lamotrigine. For those on medication regimens, perhaps taking combinations of drugs for numerous years, queries about earlier attempts to reduce AEDs and gradual efforts to substitute less toxic medications are worthwhile. Vagus nerve stimulation and epilepsy surgery for those with medically refractory epilepsy may be options after careful evaluation.
- 6. Wilfong AA. Treatment considerations: role of vagus nerve stimulator. *Epilepsy Behav.* 2002;3(6S1):41-44.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12609311>  
**Abstract** Epilepsy is considerably more common in individuals with mental retardation and developmental delays than in the general population. Compared with other groups with epilepsy, these individuals have higher seizure burdens, more often experience multiple seizure types, and more frequently have seizures that are medically refractory. The majority of these patients with refractory epilepsy will not have a surgically amenable epilepsy syndrome. For these individuals, the vagus nerve stimulator offers the potential for improved seizure control, abortive treatment of seizures, and medication reduction, which may lead to greater independence and other improvements in quality of life.

7. **Andriola MR, Vitale SA. Vagus Nerve Stimulation in the Developmentally Disabled. *Epilepsy Behav.* 2001;2(2):129-134.**

<http://www.ncbi.nlm.nih.gov/pubmed/12609196>

**Abstract** Vagus nerve stimulation (VNS) with the neuro cybernetic prosthesis (NCP) is an approved treatment of partial seizures for patients 12 years and older. Developmentally disabled or mentally retarded patients with epilepsy may also benefit from VNS; however, their evaluation and management pose greater problems. A retrospective chart review was conducted on all patients diagnosed with mild to severe mental retardation who had an NCP implanted. Records of these 21 patients, ranging in age from 3 to 56 years, were reviewed regarding VNS efficacy, side effects, behavioral changes, and alterations in antiepileptic drugs (AEDs). Seizure types included partial onset and generalized. Sixteen patients had clearly evaluable seizures both pre- and postimplant, with a greater than 50% reduction in seizures noted in 68% (11/16) after 6 months of implant. There were no adverse events that prevented chronic stimulation. Institutional staff and family members were provided with both pre- and postoperative education on VNS and magnet use. VNS appeared to be an effective and well-tolerated therapy in this group of developmentally disabled patients with refractory epilepsy.

8. **Gates J, Huf R, Frost M. Vagus Nerve Stimulation for Patients in Residential Treatment Facilities. *Epilepsy Behav.* 2001;2(6):563-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/12609390>

**Abstract** THIS ANALYSIS COMPARED THE EFFECTIVENESS OF VAGUS NERVE STIMULATION (VNS) THERAPY AMONG PATIENTS WITH INTRACTABLE SEIZURES: a group living in residential treatment facilities (RTF) with a group not living in RTFs (non-RTF). Among a constant cohort of patients with baseline, 3-month, and 12-month data, the RTF group had significantly ( $P < 0.05$ ) larger numbers of patients with generalized seizures, previous callosotomy, psychiatric disorders, behavioral problems, and Rett's syndrome. Median seizure reductions after 3 months were 33% in the RTF group and 49% in the non-RTF group ( $P < 0.001$ ); after 12 months, 50% (RTF) and 56% (non-RTF). After both 3 and 12 months, alertness, mood, postictal recovery, and cluster seizures improved in more than a third of patients in both groups. Because VNS therapy does not interact with medications and is delivered automatically, it should be seriously considered for patients with intractable epilepsy who reside in RTFs.

**Myoclonic Seizures (Pediatric; VNS efficacy in...)**

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1. Fujimoto A, Yamazoe T, Yokota T, Enoki H, Sasaki Y, Nishimura M, et al. Clinical utility of vagus nerve stimulation for progressive myoclonic epilepsy. *Seizure*. 2012;21(10):810-2.  
<http://www.ncbi.nlm.nih.gov/pubmed/22999567>
2. Wheless JW, Sankar R. Treatment strategies for myoclonic seizures and epilepsy syndromes with myoclonic seizures. *Epilepsia*. 2003;44 Suppl 11:27-37.  
<http://www.ncbi.nlm.nih.gov/pubmed/14641568>  
<http://onlinelibrary.wiley.com/store/10.1046/j.1528-1157.44.s.2.1.x/asset/j.1528-1157.44.s.2.1.x.pdf?v=1&t=he94393d&s=a72e44b33341981cc72c3b095f0dc2c6d7afdce3>

**Abstract** Despite the availability of numerous treatment options, the diagnosis and treatment of myoclonic seizures continue to be challenging. Based on clinical experience, valproate and benzodiazepines have historically been used to treat myoclonic seizures. However, many more treatment options exist today, and the clinician must match the appropriate treatment with the patient's epilepsy syndrome and its underlying etiology. Comorbidities and other medications must also be considered when making decisions regarding treatment. Rarely, some antiepileptic drugs may exacerbate myoclonic seizures. Most epileptic myoclonus can be treated pharmacologically, but some cases respond better to surgery, the ketogenic diet, or vagus nerve stimulation. Because myoclonic seizures can be difficult to treat, clinicians should be flexible in their approach and tailor therapy to each patient.

**Nursing Perspectives (on VNS)**

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1. **Kennedy PA, Schallert G. Practical issues and concepts in vagus nerve stimulation: a nursing review. *J Neurosci Nurs*. 2001;33(2):105-12.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11326619>  
**Abstract** Estimates of epilepsy incidence among the U.S. population range between 0.5% and 1%. The most common type of seizure in adult patients is partial onset. Approximately 20% of these patients are refractory to antiepileptic drug therapy and experience intolerable side effects such as confusion, dizziness, weight gain, lethargy, and ataxia. The ketogenic diet appears to be beneficial for children but is not considered a standard option for adults. Epilepsy surgery can be an option for many and may offer control or a reduction in seizures. However, many patients are opposed to cranial surgery or may not tolerate the ketogenic diet. Recent advances in biomedical technology and perfection in surgical techniques have shown vagus nerve stimulation (VNS) using the Neuro Cybernetic Prosthesis (NCP) system is an effective new treatment option in reducing seizure frequency. On July 16, 1997, the U.S. Food and Drug Administration (FDA) approved the use of the NCP for vagus nerve stimulation, as an adjunctive treatment for refractory partial onset seizures in adults and adolescents over 12 years of age. Murphy et al. and Wheless have reported similar results in children younger than 12 years. VNS represents the first therapy using a medical device approved by the FDA for the treatment of refractory seizures. An estimated 10,000 patients have been implanted with the device.
2. **Doerksen K, Klassen L. Vagus nerve stimulation therapy: nurses role in a collaborative approach to a program. *Axone*. 1998;20(1):6-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9849135>  
**Abstract** Approximately 300,000 Canadians have epilepsy. Of those 30 percent fail to achieve satisfactory seizure control with current antiepileptic drug therapy (Vagus Nerve Stimulator Study Group, 1995). The development and availability of new therapeutic options cannot be overlooked for medically intractable patients. Chronic Vagus Nerve Stimulation (VNS) has demonstrated a 50 percent reduction in seizure frequency in 1/3 of patients with refractory partial onset seizures (Uthman, et al, 1993). Individuals undergoing this procedure require the attention of health care professionals from both the neurological and neurosurgical programs. This unique intervention demands that the patient's device be tested intra-operative, and programming begin during the immediate post-operative phase. Assessment of tolerance and side effects to vagus nerve stimulation therapy, as well as continued evaluation of the patients seizure control are necessary to direct staged programming of the device. This poster will demonstrate how the nurses from the neurology and neurosurgery clinics have been able to collaborate to ensure patients needs are met. Patient education is crucial to assisting the patient through this procedure, and key points will be identified. The implementation of coordinating the approach for programming the patient's device will be depicted. Future recommendations for long-term outcome measurement will be addressed.
3. **Harkins M, Thomas T, Cooper H. Vagal nerve stimulation: nursing implications. *Clin Nurs Pract Epilepsy*. 1997;4(3):11-2.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9450427>
4. **Michael JE. Vagal nerve stimulation in treatment of intractable partial seizures: nursing implications. *J Neurosci Nurs*. 1992;24(1):19-23.**  
<http://www.ncbi.nlm.nih.gov/pubmed/1532006>  
**Abstract** Seizures are the result of abnormal synchronization of electrical activity in the brain. Medical therapy is unsuccessful in controlling seizures for many patients with partial seizures and surgery may not be a viable option. An alternate mode of treatment of intractable partial seizures is needed. Vagal nerve stimulation is a treatment modality under investigation. Stimulating the vagus nerve is hypothesized to desynchronize cerebral electrical activity, yielding an antiepileptic effect. A multicenter vagal nerve stimulation study is currently underway.

**Other Neurostimulation in Epilepsy - Cortical Stimulation**

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1. **Alarcon G, Valentin A. Cortical stimulation with single electrical pulses in human epilepsy. *Clin Neurophysiol.* 2012;123(2):223-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21831707>
  
2. **Blauwblomme T, Piallat B, Fourcade A, David O, Chabardes S. Cortical stimulation of the epileptogenic zone for the treatment of focal motor seizures: an experimental study in the nonhuman primate. *Neurosurgery.* 2011;68(2):482-90; discussion 490.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21135746>  
**Abstract** BACKGROUND: Cortical stimulation is under investigation in clinical trials of drug-resistant epilepsy. Results are heterogeneous; therefore, more evidence from animal studies is required. OBJECTIVE: To investigate the therapeutic effects of parameters of direct stimulation of the cortical focus in a *Macaca fascicularis* presenting focal motor epilepsy. METHODS: We developed a model of motor seizures after intracortical injection of penicillin G in the primary motor cortex of a *Macaca fascicularis*. We performed electric epidural cortical stimulation at low, medium, and high frequency using continuous or short-term stimulation. Short-term stimulation was triggered on seizure onset, either visually or automatically with a seizure detection algorithm connected to a programmable stimulator. RESULTS: Automated detection could detect 100% of the seizures, but ensuing cortical electric stimulation failed to abort seizures. CONCLUSION: This study demonstrates the inefficacy of the stimulation of the cortical focus to prevent seizures induced by local injection of penicillin G. Because this model may be too severe to allow comparison to human epilepsies, further work is required in other monkey models of focal epilepsy.

**Other Neurostimulation in Epilepsy - Cranial Nerve Stimulation**

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1. Fanselow EE. Central mechanisms of cranial nerve stimulation for epilepsy. *Surg Neurol Int.* 2012;3(Suppl 4):S247-54.

<http://www.ncbi.nlm.nih.gov/pubmed/23230529>

<http://www.surgicalneurologyint.com/article.asp?issn=2152-7806;year=2012;volume=3;issue=5;spage=247;epage=254;aulast=Fanselow>

**Abstract** Stimulation of peripheral cranial nerves has been shown to exert anticonvulsant effects in animal models as well as in human patients. Specifically, stimulation of both the trigeminal and vagus nerves has been shown in multiple clinical trials to be anticonvulsant, and stimulation of these nerves at therapeutic levels does not cause pain or negatively affect brain function. However, the neuronal mechanisms by which such stimulation exerts therapeutic effects are not well understood. In this review, the possible locations of action for trigeminal nerve stimulation (TNS) and vagus nerve stimulation (VNS) are explored. Additionally, the multiple time scales on which TNS and VNS function are discussed.

**Other Neurostimulation in Epilepsy - DBS**

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1. **Pekkonen E. [Deep brain stimulation in neurological illnesses]. *Duodecim*. 2013;129(5):481-8. Finnish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23520891>  
**Abstract** Advanced Parkinson's disease, essential tremor and dystonia are the most common indications for deep brain stimulation (DBS). The patients having this disease should be referred to DBS assessment at a stage where a satisfactory response to motor symptoms is no longer obtained with conventional medication. DBS therapy is acceptable also in epilepsy, when standard epilepsy surgery is out of question. To date, about 500 patients have had a deep brain stimulator implanted in Finland.
2. **Min B, Guoming L, Jian Z. Treatment of mesial temporal lobe epilepsy with amygdalohippocampal stimulation: A case series and review of the literature. *Exp Ther Med*. 2013;5(4):1264-1268.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23596499>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3627467/pdf/etm-05-04-1264.pdf>  
**Abstract** Deep brain stimulation (DBS) is being used with increasing frequency for the treatment of mesial temporal lobe epilepsy (MTLE). Here, we report two patients treated with amygdalohippocampal (AH)-DBS for drug-resistant temporal lobe epilepsy. Two patients with temporal lobe epilepsy were admitted to Beijing Sanbo Brain Hospital. The first patient was a 34-year-old male with a 31-year history of epileptic seizures. The second patient was a 27-year-old male with a 19-year history of drug-resistant epilepsy. The patients received a comprehensive presurgical workup and were considered unsuitable candidates for resective surgery. AH-DBS was recommended for the two patients. The last follow-up for patient 1 was 36 months after surgery and the final parameter settings were 3.6 mA, 450 msec, 130 Hz and cycling with 60 sec on, 180 sec off. The last follow-up for patient 2 was 18 months after surgery and the final parameter settings were 2.6 mA, 450 msec, 130 Hz and cycling with 60 sec on, 180 sec off. The patients experienced a seizure frequency reduction of 90 and 65%, respectively, with respect to the baseline. AH-DBS is a safe, micro-invasive alternative in patients with MTLE who are not candidates for resective surgery. It effectively reduces seizures without a negative effect on memory performance.
3. **Vonck K, Sprengers M, Carrette E, Dauwe I, Miatton M, Meurs A, et al. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. *Int J Neural Syst*. 2013;23(1):1250034.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23273130>  
**Abstract** In this study, we present long-term results from patients with medial temporal lobe (MTL) epilepsy treated with deep brain stimulation (DBS). Since 2001, 11 patients (8M) with refractory MTL epilepsy underwent MTL DBS. When unilateral DBS failed to decrease seizures by > 90%, a switch to bilateral MTL DBS was proposed. After a mean follow-up of 8.5 years (range: 67-120 months), 6/11 patients had a >= 90% seizure frequency reduction with 3/6 seizure-free for > 3 years; three patients had a 40%-70% reduction and two had a < 30% reduction. In 3/5 patients switching to bilateral DBS further improved outcome. Uni- or bilateral MTL DBS did not affect neuropsychological functioning. This open study with an extended long-term follow-up demonstrates maintained efficacy of DBS for MTL epilepsy. In more than half of the patients, a seizure frequency reduction of at least 90% was reached. Bilateral MTL DBS may herald superior efficacy in unilateral MTL epilepsy.

- 4. Bondallaz P, Boex C, Rossetti AO, Foletti G, Spinelli L, Vulliemoz S, et al. Electrode location and clinical outcome in hippocampal electrical stimulation for mesial temporal lobe epilepsy. *Seizure*. 2013.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23540624>

**Abstract** PURPOSE: To study the clinical outcome in hippocampal deep brain stimulation (DBS) for the treatment of patients with refractory mesial temporal lobe epilepsy (MTLE) according to the electrode location. METHODS: Eight MTLE patients implanted in the hippocampus and stimulated with high-frequency DBS were included in this study. Five underwent invasive recordings with depth electrodes to localize ictal onset zone prior to chronic DBS. Position of the active contacts of the electrode was calculated on postoperative imaging. The distances to the ictal onset zone were measured as well as atlas-based hippocampus structures impacted by stimulation were identified. Both were correlated with seizure frequency reduction. RESULTS: The distances between active electrode location and estimated ictal onset zone were 11+/-4.3 or 9.1+/-2.3mm for patients with a >50% or <50% reduction in seizure frequency. In patients (N=6) showing a >50% seizure frequency reduction, 100% had the active contacts located <3mm from the subiculum (p<0.05). The 2 non-responders patients were stimulated on contacts located >3mm to the subiculum. CONCLUSION: Decrease of epileptogenic activity induced by hippocampal DBS in refractory MTLE: (1) seems not directly associated with the vicinity of active electrode to the ictal focus determined by invasive recordings; (2) might be obtained through the neuromodulation of the subiculum.
- 5. DeLong M, Wichmann T. Deep brain stimulation for movement and other neurologic disorders. *Ann N Y Acad Sci*. 2012;1265:1-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22823512>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1749-6632.2012.06608.x/asset/j.1749-6632.2012.06608.x.pdf?v=1&t=hfzqvzj5&s=524ac81009dc02785f46a38780fdabb329673094>

**Abstract** Deep brain stimulation (DBS) was introduced as a treatment for patients with parkinsonism and other movement disorders in the early 1990s. The technique rapidly became the treatment of choice for these conditions, and is now also being explored for other diseases, including Tourette syndrome, gait disorders, epilepsy, obsessive-compulsive disorder, and depression. Although the mechanism of action of DBS remains unclear, it is recognized that DBS works through focal modulation of functionally specific circuits. The fact that the same DBS parameters and targets can be used in multiple diseases suggests that DBS does not counteract the pathophysiology of any specific disorder, but acts to replace pathologic activities in disease-affected brain circuits with activity that is more easily tolerated. Despite the progress made in the use of DBS, much remains to be done to fully realize the potential of this therapy. We describe some of the most active areas of research in this field, both in terms of exploration of new targets and stimulation parameters, and in terms of new electrode or stimulator designs.
- 6. Tykocki T, Mandat T, Kornakiewicz A, Koziara H, Nauman P. Deep brain stimulation for refractory epilepsy. *Arch Med Sci*. 2012;8(5):805-16.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23185188>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3506228/pdf/AMS-8-19589.pdf>

**Abstract** Deep brain stimulation (DBS) is a method of treatment utilized to control medically refractory epilepsy (RE). Patients with medically refractory epilepsy who do not achieve satisfactory control of seizures with pharmacological treatment or surgical resection of the epileptic focus and those who do not qualify for surgery could benefit from DBS. The most frequently used stereotactic targets for DBS are the anterior thalamic nucleus, subthalamic nucleus, central-medial thalamic nucleus, hippocampus, amygdala and cerebellum. The DBS is believed to be an effective method of treatment for various types of epilepsy among adults and adolescents. Side effects may be associated with implantation of electrodes and with the stimulation itself. An increasing number of publications and growing interest in DBS application for RE may result in standardization of the qualification and treatment protocol for RE with DBS.

7. **Mandzia J, Andrade D, Burneo JG, Jenkins ME, University Of Western Ontario Evidence Based Neurology Group. Critically appraised topic. Temporal lobe epilepsy and hippocampal stimulation. *Can J Neurol Sci.* 2012;39(6):830-2.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23041406>
8. **Oluigbo CO, Salma A, Rezai AR. Deep brain stimulation for neurological disorders. *IEEE Rev Biomed Eng.* 2012;5:88-99.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23231991>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6257420>  
**Abstract** Deep brain stimulation (DBS) involves the delivery of precise electrical signals to specific deep anatomical structures of the central nervous system, with the objective of altering or modulating neural functioning and achieving a reversible, adjustable and therapeutic or clinically beneficial effect. The exact mechanism of action of DBS is still the subject of ongoing investigations. However, based on extensive clinical investigations, it has become an established modality for the surgical treatment of advanced and medication intractable movement disorders such as Parkinson's disease, essential tremor and dystonia. DBS is also being investigated for conditions such as intractable epilepsy, neurobehavioral and psychiatric disorders such as treatment resistant depression, obsessive compulsive disorders, addiction, obesity, Alzheimer's disease and traumatic brain injury. The advantage of DBS over older deep brain lesioning procedures is its reversibility and adjustability. The design of the DBS systems allows for dynamic adjustment of the effects of electrical stimulation by altering the contacts at which electrical pulses are delivered to the brain and changing the stimulation parameters of those pulses. The clinical results from studies on DBS show that it has great potential making it one of most promising fields which could be used to address challenging neurological problems.
9. **Pereira EA, Green AL, Stacey RJ, Aziz TZ. Refractory epilepsy and deep brain stimulation. *J Clin Neurosci.* 2012;19(1):27-33.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22172283>  
**Abstract** Up to one-third of all patients with epilepsy have epilepsy refractory to medical therapy. Surgical options include temporal lobectomy, focal neocortical resection, stereotactic lesioning and neurostimulation. Neurostimulatory options comprise vagal nerve stimulation, trigeminal nerve stimulation and deep brain stimulation (DBS). DBS enables structures in the brain to be stimulated electrically by an implanted pacemaker after a minimally invasive neurosurgical procedure and has become the therapy of choice for Parkinson's disease refractory to or complicated by drug therapy. Here we review DBS for epilepsy, a powerful emerging treatment in the surgical armamentarium for drug refractory epilepsy, with a focus on extratemporal epilepsy.
10. **Bakay RA, Vannemreddy PS. Deep brain stimulation and seizures. *J Neurosurg.* 2012;116(4):926; author reply 926-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22242674>

11. **Carron R, Chabardes S, Hammond C. [Mechanisms of action of high-frequency deep brain stimulation. A review of the literature and current concepts]. *Neurochirurgie*. 2012;58(4):209-17. French.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22465140>  
**Abstract** High-frequency deep brain stimulation (HF-DBS) has become a widely used therapeutic method in the field of movement disorders for the treatment of Parkinson's disease, essential tremor or dystonia. New targets and indications are under evaluation in several other conditions such as cluster headache, obesity, epilepsy or psychiatric diseases (depression, OCD). However, the mechanisms of action of HF-DBS remain poorly understood. Herein we present a review of the literature and our current view of the question. The first part deals with the effects of stimulation itself on the different parts of the neuron and tries to answer the question of what is actually stimulated by DBS (cell bodies, dendrites or axons). The second part is devoted to the ortho- and antidromic effects of the stimulation. The third part more specifically focuses on the case of subthalamic nucleus stimulation. The target axons in the subthalamic area are discussed in the light of recent optogenetic studies. In conclusion, HF-DBS leads to a kind of functional deafferentation of the stimulated structure and to the modulation of cortical activity (both ortho and antidromically). Which effects are relevant to the therapeutic effects of DBS is still unclear. Further investigations are required especially regarding the corticosubthalamic pathways.
12. **Oh YS, Kim HJ, Lee KJ, Kim YI, Lim SC, Shon YM. Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. *Seizure*. 2012;21(3):183-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22209542>  
**Abstract** INTRODUCTION: The cognitive and behavioral effect of deep brain stimulation (DBS) administered to the deep cerebral nuclei for epilepsy treatment is unknown. We investigated the cognitive outcomes at least 12 months after DBS to the bilateral anterior thalamic nucleus (ATN) for controlling intractable epilepsy. METHODS: Nine patients with intractable epilepsy who were not candidates for resective surgery, but who were treated by bilateral ATN DBS underwent cognitive and behavioral assessments before implantation and more than 1 year after DBS surgery. Postoperative cognitive assessments were carried out under a continuous stimulation mode. RESULTS: The mean seizure-reduction rate of these patients after ATN DBS was 57.9% (35.6-90.4%). Cognitive testing showed favorable results for verbal fluency tasks (letter and category,  $p < 0.05$ ), and a significant improvement in delayed verbal memory was observed ( $p = 0.017$ ). However, we did not observe any significant changes in general abilities (IQ, MMSE), information processing (digit forward and backward, Trail A, and Digit Symbol), or executive function (Trail B and WCST). Interestingly, we did not observe any significant cognitive decline approximately 1 year (mean, 15.9 months) after ATN DBS surgery. CONCLUSIONS: We showed that ATN DBS not only resulted in promising clinical effects but was also associated with improvements in both verbal recall and oral information processing, which may be related to the bilateral activation of the fronto-limbic circuit following DBS surgery. Further controlled, long-term studies with larger populations are warranted for elucidating the clinical effects of ATN DBS.

13. **Lee KJ, Shon YM, Cho CB. Long-term outcome of anterior thalamic nucleus stimulation for intractable epilepsy. *Stereotact Funct Neurosurg.* 2012;90(6):379-85.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22922474>  
**Abstract** BACKGROUND: Many patients with epilepsy have persistent seizures despite treatment with maximal antiepileptic drug therapy and are not candidates for resective brain surgery. Objectives: We investigated the effectiveness of seizure reduction after anterior thalamic nucleus (ATN) stimulation in patients with intractable epilepsy undergoing deep brain stimulation (DBS) of the thalamus. METHODS: Patients included in this study had poorly controlled seizures, despite anticonvulsant medication, and were not candidates for surgical resection of an identifiable seizure focus. Fifteen patients with medically refractory epilepsy underwent the placement of bilateral DBS electrodes in the anterior thalamus. The seizure frequency was monitored and compared with the preimplantation baseline. RESULTS: The treatment demonstrated a statistically significant decrease in the seizure frequency, with a mean reduction of 70.4% (mean follow-up, 27 months). Two of the patients had a remarkable reduction of seizure frequency. CONCLUSION: It seems to be important that the short-term outcome of ATN DBS reflects the long-term outcome directly. The correlation between the seizure type, characteristics and anticonvulsant effects of ATN DBS did not exhibit significance because of the small number of cases. Therefore, a longer-term follow-up with a larger group of patients is required to fully evaluate the safety and effectiveness of this treatment modality.
14. **Sankar T, Tierney TS, Hamani C. Novel applications of deep brain stimulation. *Surg Neurol Int.* 2012;3(Suppl 1):S26-33.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22826807>  
**Abstract** The success of deep brain stimulation (DBS) surgery in treating medically refractory symptoms of some movement disorders has inspired further investigation into a wide variety of other treatment-resistant conditions. These range from disorders of gait, mood, and memory to problems as diverse as obesity, consciousness, and addiction. We review the emerging indications, rationale, and outcomes for some of the most promising new applications of DBS in the treatment of postural instability associated with Parkinson's disease, depression, obsessive-compulsive disorder, obesity, substance abuse, epilepsy, Alzheimer's-type dementia, and traumatic brain injury. These studies reveal some of the excitement in a field at the edge of a rapidly expanding frontier. Much work still remains to be done on basic mechanism of DBS, optimal target and patient selection, and long-term durability of this technology in treating new indications.
15. **Akamatsu N, Tsuji S. [Deep brain stimulation for epilepsy]. *Brain Nerve.* 2011;63(4):365-9. Japanese.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21441639>  
**Abstract** Despite the advances in pharmacologic treatments for epilepsy, approximately one-third of patients with epilepsy continue to have seizures, and alternative treatment approaches are necessary in such cases. For many patients, resective surgery can be an alternative for achieving seizure freedom; however, its success depend on identifying seizure foci before surgery. Many patients with medically intractable epilepsy are not suitable candidates for surgery. The therapeutic effect of electrical stimulation on the brain has been studied for decades. Currently, the thalamus, subthalamic nucleus, hippocampus, cerebellar nuclei, and cortical seizure foci are stimulated for treating epilepsy. In 2010, the results of the first, multicenter randomized double-blinded controlled study were published. This report documents a clinical trial involving stimulation of the anterior nucleus of the thalamus for epilepsy (SANTE). These results showed bilateral stimulation of the anterior nucleus of the thalamus reduces seizures. The responsive neurostimulator, which can be called a brain pacemaker, is another stimulation device for the treatment of epilepsy. A clinical trial involving the Neuropace system is in progress in the USA. Preliminary results indicating the efficacy of the Neuropace study were presented at the annual American Epilepsy Society meeting in 2010; the final results of this study are awaited.

16. **Zhong XL, Yu JT, Zhang Q, Wang ND, Tan L. Deep brain stimulation for epilepsy in clinical practice and in animal models. *Brain Res Bull.* 2011;85(3-4):81-8.** <http://www.ncbi.nlm.nih.gov/pubmed/21457763>  
**Abstract** Given the tremendous success of deep brain stimulation (DBS) for the treatment of movement and neuropsychiatric disorders, clinicians have begun to open up to the possible use of electrical stimulation for the treatment of patients with uncontrolled seizures. DBS of various neural targets has been investigated in clinical studies and animal studies, including the anterior nucleus of thalamus (ANT), cerebellum, hippocampus, subthalamic nucleus (STN), centromedian nucleus of the thalamus (CMT), caudate nucleus (CN). Recently, a large and multicenter trial (SANTE: Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) was conducted and subsequently with encouraging results, making ANT the most well-established target for DBS in the treatment of epilepsy to date. Here, we endeavor to review mainly the animal studies and clinical studies of ANT DBS to further explore the more reliable target.
17. **Fisher RS. Benefits of trigeminal nerve stimulation. *Epilepsy Behav.* 2011;22(4):615-6.** <http://www.ncbi.nlm.nih.gov/pubmed/22019017>
18. **Miatton M, Van Roost D, Thiery E, Carrette E, Van Dycke A, Vonck K, et al. The cognitive effects of amygdalohippocampal deep brain stimulation in patients with temporal lobe epilepsy. *Epilepsy Behav.* 2011;22(4):759-64.** <http://www.ncbi.nlm.nih.gov/pubmed/22030536>  
**Abstract** The aim of this study was to examine the effects of amygdalohippocampal deep brain stimulation (AH-DBS) on cognitive functioning in patients with refractory temporal lobe epilepsy. The population consisted of 10 patients (7 men) who underwent ipsilateral (n=8) or bilateral (n=2) AH-DBS. Intellectual and neuropsychological evaluation was performed before and 6 months after initiation of AH-DBS. Group analyses revealed no overall pattern of change in cognitive measures, but improvement was seen in emotional well-being. Individual results varied over a broad spectrum ranging from no cognitive effects to negative effects on intelligence capacities, divided attention, and concept formation, to positive effects on speed of information processing and speed of finger movements. AH-DBS is a valuable treatment alternative for patients with refractory epilepsy that appears to have no major adverse neuropsychological consequences and enhances emotional well-being on the group level. Individual results are too diverse at this moment to allow viable interpretation. Additional studies are needed to confirm these preliminary results.
19. **Sironi VA. Origin and evolution of deep brain stimulation. *Front Integr Neurosci.* 2011;5:42.** <http://www.ncbi.nlm.nih.gov/pubmed/21887135> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3157831/pdf/fnint-05-00042.pdf>  
**Abstract** This paper briefly describes how the electrical stimulation, used since antiquity to modulate the nervous system, has been a fundamental tool of neurophysiologic investigation in the second half of the eighteenth century and was subsequently used by the early twentieth century, even for therapeutic purposes. In mid-twentieth century the advent of stereotactic procedures has allowed the drift from lesional to stimulating technique of deep nuclei of the brain for therapeutic purposes. In this way, deep brain stimulation (DBS) was born, that, over the last two decades, has led to positive results for the treatment of medically refractory Parkinson's disease, essential tremor, and dystonia. In recent years, the indications for therapeutic use of DBS have been extended to epilepsy, Tourette's syndrome, psychiatric diseases (depression, obsessive-compulsive disorder), some kinds of headache, eating disorders, and the minimally conscious state. The potentials of the DBS for therapeutic use are fascinating, but there are still many unresolved technical and ethical problems, concerning the identification of the targets for each disease, the selection of the patients and the evaluation of the results.

20. **Sarem-Aslani A, Mullett K. Industrial perspective on deep brain stimulation: history, current state, and future developments. *Front Integr Neurosci.* 2011;5:46.**

<http://www.ncbi.nlm.nih.gov/pubmed/21991248>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3180671/pdf/fnint-05-00046.pdf>

**Abstract** Deep brain stimulation (DBS) emerged in the late 1960s as a possible therapeutic alternative to lesioning in patients with severe, chronic, intractable pain. DBS devices in the era were based on cardiac pacing technology but were greatly modified in implementation due to the unique needs of DBS. Clinical studies in the 1970s and early 1980s have revealed a technique with modest results which did not lead to regulatory approval for the treatment of pain. In the 1980s a new application for DBS emerged in the treatment of movement disorders. Clinical trials confirmed the robustness of the therapy leading to approvals by regulatory authorities in the US and Europe for the treatment of tremor and the symptoms of Parkinson's disease. Technology based on that used for earlier clinical research in pain was improved by leveraging advances in cardiac pacing technology resulting in the sophisticated and reliable systems available today. In the 1990s scientific exploration began in the treatment of psychiatric disorders which is ongoing today. Simultaneously, studies into the treatment of epilepsy were begun which resulted in regulatory approval in Europe. Suggestions have been made to expand these scientific explorations to other central nervous system dysfunctions. Opportunity remains to improve the technology including individualized and symptom specific stimulation patterns, more physician and patient friendly programming, and possibly closed-loop systems for more situation dependent and effective therapy.

21. **Janszky J, Balas I, Kovacs N. [Role of deep brain stimulation in epilepsy]. *Ideggyogy Sz.* 2011;64(9-10):317-20. Hungarian.**

<http://www.ncbi.nlm.nih.gov/pubmed/22059367>

**Abstract** The deep brain stimulation (DBS) is an emerging treatment option in brain disorders in which randomized multicenter trials proved its efficacy leading to licensing different DBS methods in various brain diseases. More recently more and more brain structures have become candidates for being "target" in a possible DBS treatment of epilepsy. At present, only the DBS of the anterior nucleus of the thalamus (ANT) can be considered as a proved method for epilepsy treatment. Other potential targets for DBS treatment in epilepsy are the subthalamic nuclei, and the amygdala-hippocampus complex. There are some ongoing randomized studies to investigating their therapeutical role. The therapeutical outcome of ANT-DBS treatment in drug-resistant epilepsy seems to be better than the new antiepileptic drugs, but much worse than the results of a potential epilepsy surgery. At about 10% of patients may become seizure-free and 50% of patients may have a significant improvement. Nowadays ANT-DBS should be considered as an "ultima ratio" in those adult drug-resistant epilepsy patients with normal intelligence in which neither new antiepileptic drugs nor resective epilepsy surgery are a reasonable therapeutical options.

22. **Pouratian N, Reames DL, Frysingher R, Elias WJ. Comprehensive analysis of risk factors for seizures after deep brain stimulation surgery. Clinical article. *J Neurosurg.* 2011;115(2):310-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21548744>  
**Abstract** OBJECT: The aim of this study was to assess risk factors for postoperative seizures after deep brain stimulation (DBS) lead implantation surgery and the impact of such seizures on length of stay and discharge disposition. METHODS: The authors reviewed a consecutive series of 161 cases involving patients who underwent implantation of 288 electrodes for treatment of movement disorders at a single institution to determine the absolute risk of postoperative seizures, to describe the timing and type of seizures, to identify statistically significant risk factors for seizures, and to determine whether there are possible indications for seizure prophylaxis after DBS lead implantation. The electronic medical records were reviewed to identify demographic details, medical history, operative course, and postoperative outcomes and complications. To evaluate significant associations between potential risk factors and postoperative seizures, both univariate and multivariate analyses were performed. RESULTS: Seven (4.3%) of 161 patients experienced postoperative seizures, all of which were documented to have been generalized tonic-clonic seizures. In 5 (71%) of 7 cases, patients only experienced a single seizure. Similarly, in 5 of 7 cases, patients experienced seizures within 24 hours of surgery. In 6 (86%) of the 7 cases, seizures occurred within 48 hours of surgery. Univariate analysis identified 3 significant associations (or risk factors) for postoperative seizures: abnormal findings on postoperative imaging (hemorrhage, edema, and or ischemia;  $p < 0.001$ ), age greater than 60 years ( $p = 0.021$ ), and transventricular electrode trajectories ( $p = 0.023$ ). The only significant factor identified on multivariate analysis was abnormal findings on postoperative imaging ( $p < 0.0001$ , OR 50.4, 95% CI 5.7-444.3). Patients who experienced postoperative seizures had a significantly longer length of stay than those who were seizure free (mean  $\pm$  SD 5.29  $\pm$  3.77 days vs 2.38  $\pm$  2.38 days;  $p = 0.002$ , Student 2-tailed t-test). Likewise, final discharge to home was significantly less likely in patients who experienced seizures after implantation (43%) compared with those patients who did not (92%;  $p = 0.00194$ , Fisher exact test). CONCLUSIONS: These results affirm that seizures are an uncommon complication of DBS surgery and generally occur within 48 hours of surgery. The results also indicate that hemorrhage, edema, or ischemia on postoperative images ("abnormal" imaging findings) increases the relative risk of postoperative seizures by 30- to 50-fold, providing statistical credence to the long-held assumption that seizures are associated with intracranial vascular events. Even in the setting of a postimplantation imaging abnormality, long-term anticonvulsant therapy will not likely be required because none of our patients developed chronic epilepsy.
23. **Lyons MK. Deep brain stimulation: current and future clinical applications. *Mayo Clin Proc.* 2011;86(7):662-72.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21646303>  
[http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3127561/pdf/mayoclinproc\\_86\\_7\\_009.pdf](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3127561/pdf/mayoclinproc_86_7_009.pdf)  
**Abstract** Deep brain stimulation (DBS) has developed during the past 20 years as a remarkable treatment option for several different disorders. Advances in technology and surgical techniques have essentially replaced ablative procedures for most of these conditions. Stimulation of the ventralis intermedialis nucleus of the thalamus has clearly been shown to markedly improve tremor control in patients with essential tremor and tremor related to Parkinson disease. Symptoms of bradykinesia, tremor, gait disturbance, and rigidity can be significantly improved in patients with Parkinson disease. Because of these improvements, a decrease in medication can be instrumental in reducing the disabling features of dyskinesias in such patients. Primary dystonia has been shown to respond well to DBS of the globus pallidus internus. The success of these procedures has led to application of these techniques to multiple other debilitating conditions such as neuropsychiatric disorders, intractable pain, epilepsy, camptocormia, headache, restless legs syndrome, and Alzheimer disease. The literature analysis was performed using a MEDLINE search from 1980 through 2010 with the term deep brain stimulation, and several double-blind and larger case series were chosen for inclusion in this review. The exact mechanism of DBS is not fully understood. This review summarizes many of the current and potential future clinical applications of this technology.

24. **Fisher RS. Direct brain stimulation is an effective therapy for epilepsy. *Neurology*. 2011;77(13):1220-1.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21917779>  
<http://www.neurology.org/content/77/13/1220.full.pdf>

25. **Ooi YC, Styliaras JC, Sharan A. Thalamic stimulation for epilepsy. *Neurosurg Clin N Am*. 2011;22(4):457-64, v-vi.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21939844>

**Abstract** With the growing applications for deep brain stimulators (DBS) in recent years, interest in using DBS as an option for patients with epilepsy has increased. Thalamic DBS appears to be a viable minimally invasive treatment for patients experiencing medically intractable seizures. Thalamic DBS has been associated with significant reduction in seizure frequency and an improvement in overall quality of life, especially in patients who have failed maximal antiepileptic drugs or other surgical alternatives. However, further work is necessary to identify the subgroups of patients experiencing medically intractable seizures who may benefit from DBS, and also to identify optimal stimulation parameters and mode of stimulation.

26. **Gautschi OP, Haegele S, Cadosch D, Hildebrandt G, Bauer R. [Deep brain stimulation - options and limits]. *Praxis (Bern 1994)*. 2011;100(8):469-77. German.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21484710>

**Abstract** Deep brain stimulation (DBS) is meanwhile an established procedure. It has been employed for several neurological diseases with impressive therapeutic responses to some extent. Stimulation of the ventral intermediate nucleus of the thalamus can distinctively improve tremor associated with essential tremor or Parkinson disease. Similarly, stimulation of the subthalamic nucleus or the globus pallidus internus can substantially diminish bradykinesia, rigidity, and tremor. Additionally, by means of a reduced dopaminergic therapy, it can lead to an improvement of the L-Dopa induced dyskinesias in patients with Parkinson disease. In recent years, DBS has also been used for other neurological and psychiatric diseases. Yet, the exact mechanism of action on a neuronal level remains uncertain. Regardless of the underlying disease and the surgical electrode positioning, a meticulous patient selection and correct indication is of paramount importance for the therapeutic success.

27. **Torres CV, Pastor J, Navarrete EG, Sola RG. [Thalamic deep brain stimulation for refractory epilepsy]. *Rev Neurol*. 2011;53(2):99-106. Spanish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21720980>

**Abstract** Epilepsy is a neurological disorder that affects 1-2% of the population. Despite the available treatments (drug therapy, resective surgery, vagus nerve stimulation), there is a significant subgroup of patients that continues to have disabling seizures. The indications of deep brain stimulation are exponentially growing, and there is a wide experience with deep brain stimulation (DBS) for the treatment of abnormal movements. DBS for epilepsy may be a new therapy for the subgroup of patients that remain disabled despite other treatments. Experiments with animal models, and the new advances in our knowledge about the neurophysiological processes that govern the genesis of epilepsy, have led to the selection of various brain targets for stimulation. The thalamus is a fundamental relay centre in the corticothalamic and corticostriatal thalamocortical circuits, and it has been studied with this purpose. Studies on epileptic patients have shown various degrees of effectiveness; however, controlled studies do not permit definitive conclusions about the role of DBS in the treatment of epilepsy. Probably a better patient selection would lead to more decisive conclusions. Further randomised studies are needed to draw reliable conclusions and scientific evidence on the effectiveness of DBS for refractory epilepsy.

28. **Torres CV, Pastor J, Navarrete EG, Sola RG. [Deep brain stimulation for refractory epilepsy: extrathalamic targets]. *Rev Neurol.* 2011;53(3):153-64. Spanish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21748713>  
**Abstract** Epilepsy is a neurological disorder that affects 1-2% of the population. The majority of epileptic patients achieve a good seizure control with the current available treatments. However, there is a subgroup of patients that remain severely disabled despite the variety of anti-epileptic drugs, the possibility of surgery for resection of the epileptogenic foci in selected patients, and vagal nerve stimulation; various lines of research are being carried out to look for new treatment alternatives. Deep brain stimulation (DBS) of the thalamus has emerged as a therapeutic alternative for patients who remain in-capacitated; the efficacy of this new therapy is subject of several studies, and its effectiveness and safety has not been established yet. There are other targets for deep brain stimulation that may be useful for drug-resistant epilepsy. Experiments with animal models and preliminary human studies have shown encouraging results with DBS on cerebellum, subthalamic nucleus, substantia nigra, hippocampus and cerebral cortex, among others. The purpose of this review is to revisit the studies that have been carried out on these brain nuclei, as targets for DBS for drug-resistant epilepsy. Studies have shown varying degrees of effectiveness, and there is a need for controlled trials to draw any definite conclusions.
29. **Boex C, Seeck M, Vulliemoz S, Rossetti AO, Staedler C, Spinelli L, et al. Chronic deep brain stimulation in mesial temporal lobe epilepsy. *Seizure.* 2011;20(6):485-90.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21489828>  
**Abstract** The objective of this study was to evaluate the efficiency and the effects of changes in parameters of chronic amygdala-hippocampal deep brain stimulation (AH-DBS) in mesial temporal lobe epilepsy (TLE). Eight pharmacoresistant patients, not candidates for ablative surgery, received chronic AH-DBS (130 Hz, follow-up 12-24 months): two patients with hippocampal sclerosis (HS) and six patients with non-lesional mesial TLE (NLES). The effects of stepwise increases in intensity (0-Off to 2 V) and stimulation configuration (quadripolar and bipolar), on seizure frequency and neuropsychological performance were studied. The two HS patients obtained a significant decrease (65-75%) in seizure frequency with high voltage bipolar DBS ( $\geq 1$  V) or with quadripolar stimulation. Two out of six NLES patients became seizure-free, one of them without stimulation, suggesting a microlesional effect. Two NLES patients experienced reductions of seizure frequency (65-70%), whereas the remaining two showed no significant seizure reduction. Neuropsychological evaluations showed reversible memory impairments in two patients under strong stimulation only. AH-DBS showed long-term efficiency in most of the TLE patients. It is a valuable treatment option for patients who suffer from drug resistant epilepsy and who are not candidates for resective surgery. The effects of changes in the stimulation parameters suggest that a large zone of stimulation would be required in HS patients, while a limited zone of stimulation or even a microlesional effect could be sufficient in NLES patients, for whom the importance of the proximity of the electrode to the epileptogenic zone remains to be studied. Further studies are required to ascertain these latter observations.

30. **Akman T, Erken H, Acar G, Bolat E, Kizilay Z, Acar F, et al. Effects of the hippocampal deep brain stimulation on cortical epileptic discharges in penicillin - induced epilepsy model in rats. *Turk Neurosurg.* 2011;21(1):1-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21294084>  
**Abstract** AIM: Experimental and clinical studies have revealed that hippocampal DBS can control epileptic activity, but the mechanism of action is obscure and optimal stimulation parameters are not clearly defined. The aim was to evaluate the effects of high frequency hippocampal stimulation on cortical epileptic activity in penicillin-induced epilepsy model. MATERIAL and METHODS: Twenty-five Sprague-Dawley rats were implanted DBS electrodes. In group-1 (n=10) hippocampal DBS was off and in the group-2 (n=10) hippocampal DBS was on (185 Hz, 0.5V, 1V, 2V, and 5V for 60 sec) following penicillin G injection intracortically. In the control group hippocampal DBS was on following 8 mul saline injection intracortically. EEG recordings were obtained before and 15 minutes following penicillin-G injection, and at 10th minutes following each stimulus for analysis in terms of frequency, amplitude, and power spectrum. RESULTS: High frequency hippocampal DBS suppressed the acute penicillin-induced cortical epileptic activity independent from stimulus intensity. In the control group, hippocampal stimulation alone lead only to diffuse slowing of cerebral bioelectrical activity at 5V stimulation. CONCLUSION: Our results revealed that continuous high frequency stimulation of the hippocampus suppressed acute cortical epileptic activity effectively without causing secondary epileptic discharges. These results are important in terms of defining the optimal parameters of hippocampal DBS in patients with epilepsy.
31. **Lega BC, Halpern CH, Jaggi JL, Baltuch GH. Deep brain stimulation in the treatment of refractory epilepsy: update on current data and future directions. *Neurobiol Dis.* 2010;38(3):354-60.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19631750>  
**Abstract** Deep brain stimulation for epilepsy has garnered attention from epileptologists due to its well-documented success in treating movement disorders and the low morbidity associated with the implantation of electrodes. Given the large proportion of patients who fail medical therapy and are not candidates for surgical amelioration, as well as the suboptimal seizure control offered by vagus nerve stimulation, the search for appropriate brain structures to serve as targets for deep brain stimulation has generated a useful body of evidence to serve as the basis for larger investigations. Early results of the SANTE trial should lay the foundation for widespread implementation of DBS for epilepsy targeting the anterior thalamic nucleus. Other targets also offer promise, including the caudate nucleus, the subthalamic nucleus, the cerebellum, the centromedian nucleus of the thalamus, and the hippocampus. This paper reviews the logic which underlies these potential targets and recapitulates the current data from limited human trials supporting each one. It also provides a succinct overview of the surgical procedure used for electrode implantation.

32. **Vesper J, Steinhoff B, Rona S, Wille C, Bilic S, Nikkhah G, et al. Chronic high-frequency deep brain stimulation of the STN/SNr for progressive myoclonic epilepsy. *Epilepsia*. 2007;48(10):1984-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17561948>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2007.01166.x/asset/j.1528-1167.2007.01166.x.pdf?v=1&t=he9433si&s=650b2742c0f191f0ff17e21d48598d31af5f0fd1>

**Abstract** Chronic high-frequency deep brain stimulation (DBS) may also be effective in patients with refractory epilepsy. A possible benefit has been postulated because of the connections that exist between the subthalamic nucleus (STN) and the superior colliculus. Individual case reports and pilot studies of successful DBS in different types of epilepsy have already been presented. Here, the case of a 39-year-old male with progressive myoclonic epilepsy is reported who remained severely impaired despite VNS and combined antiepileptic drug therapy. Bilateral DBS electrodes were implanted into the STN, followed by implantation of a neurostimulation system under general anesthesia. Adjustment and testing of the remaining contacts was done over several months postoperatively. Bilateral monopolar DBS reduced the intensity and frequency of seizures by 50%. The patient has so far been followed for 12 months. This is the first report of positive effects of DBS in progressive myoclonic epilepsy in an adult patient. A subsequent prospective study will have to investigate whether the STN or other target nuclei are most suitable for DBS in these types of epilepsy and which long-term results can be obtained.

**Other Neurostimulation in Epilepsy - TMS**

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1. **Kimiskidis VK, Kugiumtzis D, Papagiannopoulos S, Vlaikidis N. Transcranial magnetic stimulation (TMS) modulates epileptiform discharges in patients with frontal lobe epilepsy: a preliminary EEG-TMS study. *Int J Neural Syst.* 2013;23(1):1250035.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23273131>  
**Abstract** BACKGROUND: TMS is being increasingly used as a noninvasive brain stimulation technique for the therapeutic management of partial epilepsies. However, the acute effects of TMS on epileptiform discharges (EDs, i.e. interictal epileptiform activity and subclinical electrographic seizure patterns) remain unexplored. OBJECTIVE: To investigate whether TMS can modulate EDs in partial epilepsy. METHODS: In Experiment Set 1, the safety of the TMS protocol was investigated in 10 well-controlled by anti-epileptic drugs (AEDs) epileptic patients. In Experiment Set 2, the effects of TMS on EDs were studied in three subjects with intractable frontal lobe epilepsies, characterized by particularly frequent EDs. TMS was applied over the electrographic focus with a circular and a figure of eight coil while recording EEG with a 60-channel TMS-compatible EEG system. The effectiveness of TMS in aborting EDs was investigated using survival analysis and brain connectivity analysis. RESULTS: The TMS protocol was well-tolerated. TMS was an effective method to abort EDs even when adjusting for its latency with respect to ED onset (CMH test,  $p < 0.0001$ ). While the effective brain connectivity around the epileptic focus increased significantly during EDs ( $p < 0.01$ ), with TMS administration the increase was not statistically significant. CONCLUSION: TMS can modulate EDs in patients with epileptogenic foci in the cortical convexity and is associated with reversal of ED-induced changes in brain connectivity.
  
2. **DeGiorgio CM, Soss J, Cook IA, Markovic D, Gornbein J, Murray D, et al. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. *Neurology.* 2013;80(9):786-91; comment 780-1, e95-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23365066>  
<http://www.neurology.org/content/80/9/786.full.pdf>  
**Abstract** OBJECTIVE: To explore the safety and efficacy of external trigeminal nerve stimulation (eTNS) in patients with drug-resistant epilepsy (DRE) using a double-blind randomized controlled trial design, and to test the suitability of treatment and control parameters in preparation for a phase III multicenter clinical trial. METHODS: This is a double-blind randomized active-control trial in DRE. Fifty subjects with 2 or more partial onset seizures per month (complex partial or tonic-clonic) entered a 6-week baseline period, and then were evaluated at 6, 12, and 18 weeks during the acute treatment period. Subjects were randomized to treatment (eTNS 120 Hz) or control (eTNS 2 Hz) parameters. RESULTS: At entry, subjects were highly drug-resistant, averaging 8.7 seizures per month (treatment group) and 4.8 seizures per month (active controls). On average, subjects failed 3.35 antiepileptic drugs prior to enrollment, with an average duration of epilepsy of 21.5 years (treatment group) and 23.7 years (active control group), respectively. eTNS was well-tolerated. Side effects included anxiety (4%), headache (4%), and skin irritation (14%). The responder rate, defined as >50% reduction in seizure frequency, was 30.2% for the treatment group vs 21.1% for the active control group for the 18-week treatment period (not significant,  $p = 0.31$ , generalized estimating equation [GEE] model). The treatment group experienced a significant within-group improvement in responder rate over the 18-week treatment period (from 17.8% at 6 weeks to 40.5% at 18 weeks,  $p = 0.01$ , GEE). Subjects in the treatment group were more likely to respond than patients randomized to control (odds ratio 1.73, confidence interval 0.59-0.51). eTNS was associated with reductions in seizure frequency as measured by the response ratio ( $p = 0.04$ , analysis of variance [ANOVA]), and improvements in mood on the Beck Depression Inventory ( $p = 0.02$ , ANOVA). CONCLUSIONS: This study provides preliminary evidence that eTNS is safe and may be effective in subjects with DRE. Side effects were primarily limited to anxiety, headache, and skin irritation. These results will serve as a basis to inform and power a larger multicenter phase III clinical trial. CLASSIFICATION OF EVIDENCE: This phase II study provides Class II evidence that trigeminal nerve stimulation may be safe and effective in reducing seizures in people with DRE.

- 3. Manganotti P, Del Felice A. New perspectives in transcranial magnetic stimulation: Epilepsy, consciousness and the perturbational approach. *Behav Neurol*. 2012.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23001632>  
**Abstract** Transcranial magnetic stimulation (TMS) evolved from a simple method to stimulate the motor cortex to an invaluable tool for multiple diagnostic, research, and therapeutic applications. A further development of this noninvasive brain stimulation technique is concomitant electroencephalographic (EEG) recording during TMS. The theoretical underpinnings and the technological innovation of TMS-EEG co-registration have opened new ways to study brain excitability in neurological conditions previously investigated with conventional EEG alone. A further advance in TMS research applications is the perturbational approach: magnetic pulses can interfere not only with dynamic, often pathological rhythms in epilepsy or altered consciousness states, but also modulate physiological states such as sleep and sleep deprivation. So applied, TMS-EEG co-registration can reveal different neurophysiological and behavioral patterns in the awake state, sleep or sleep deprivation. In this review, we discuss the use of TMS and TMS-EEG co-registration in epilepsy, a still rather limited although promising area of study.
- 4. Hsu WY, Cheng CH, Lin MW, Shih YH, Liao KK, Lin YY. Antiepileptic effects of low frequency repetitive transcranial magnetic stimulation: A meta-analysis. *Epilepsy Res*. 2011;96(3):231-40.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21715144>  
**Abstract** PURPOSE: To evaluate the antiepileptic efficacy of low frequency repetitive transcranial magnetic stimulation (rTMS) in medically intractable epilepsy. METHODS: A comprehensive literature search was performed on articles published from 1990 to 2010 in Medline, Pubmed, CINAHL, and Cochrane using the following keywords: epilepsy, seizure, transcranial magnetic stimulation, repetitive transcranial magnetic stimulation. Two reviewers assessed article eligibility and extracted the data independently. For outcome measures, effect size and 95% confidence interval (CI) were calculated for seizure frequency, spike number, duration of epileptiform abnormalities (EAs), and resting motor threshold (RMT) by using fixed and random effect models. RESULTS: Eleven articles were identified, with a total of 164 participants. Based on seizure frequency, a significant effect size was found (effect size: 0.34, with a 95% CI at 0.10-0.57). Considering between-study heterogeneity, we conducted a second meta-analysis, and the underlying etiology was considered important for the treatment effect. Cortical dysplasia or neocortical epilepsy showed an effect size of 0.71, with a 95% CI at 0.30-1.12. In contrast, other epileptic disorders showed an effect size of 0.22. CONCLUSION: Low frequency rTMS has a favorable effect on seizure reduction, particularly evident in patients with neocortical epilepsy or cortical dysplasia.
- 5. Oberman L, Edwards D, Eldaief M, Pascual-Leone A. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. *J Clin Neurophysiol*. 2011;28(1):67-74.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21221011>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3260517/pdf/nihms272818.pdf>  
**Abstract** Theta burst stimulation (TBS) protocols have recently emerged as a method to transiently alter cortical excitability in the human brain through repetitive transcranial magnetic stimulation. TBS involves applying short trains of stimuli at high frequency repeated at intervals of 200 milliseconds. Because repetitive transcranial magnetic stimulation is known to carry a risk of seizures, safety guidelines have been established. TBS has the theoretical potential of conferring an even higher risk of seizure than other repetitive transcranial magnetic stimulation protocols because it delivers high-frequency bursts. In light of the recent report of a seizure induced by TBS, the safety of this new protocol deserves consideration. We performed an English language literature search and reviewed all studies published from May 2004 to December 2009 in which TBS was applied. The adverse events were documented, and crude risk was calculated. The majority of adverse events attributed to TBS were mild and occurred in 5% of subjects. Based on this review, TBS seems to be a safe and efficacious technique. However, given its novelty, it should be applied with caution. Additionally, this review highlights the need for rigorous documentation of adverse events associated with TBS and intensity dosing studies to assess the seizure risk associated with various stimulation parameters (e.g., frequency, intensity, and location).

6. **Azizi SA. Of sleep, seizures and networks. *Neurosci Lett.* 2011;493(3):61-2. <http://www.ncbi.nlm.nih.gov/pubmed/21352895>**  
**Abstract** A common property of sleep and epileptic seizures is that both occur because of alteration in network activity within the nervous system. This is represented by an oscillating synchronization of spiking in large groups of neurons from the ever evanescent chaotic yet coherent patterns of activity that underlie sensory and motor operations of the brain. The idea that both slow wave sleep and epileptic seizures may have similar functions in brain homeostasis by purging and consolidating environmental cues is discussed. TMS can be used as a tool to investigate these patterns.
7. **Najib U, Bashir S, Edwards D, Rotenberg A, Pascual-Leone A. Transcranial brain stimulation: clinical applications and future directions. *Neurosurg Clin N Am.* 2011;22(2):233-51, ix. <http://www.ncbi.nlm.nih.gov/pubmed/21435574> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547606/pdf/nihms263566.pdf>**  
**Abstract** Noninvasive brain stimulation is a valuable investigative tool and has potential therapeutic applications in cognitive neuroscience, neurophysiology, psychiatry, and neurology. Transcranial magnetic stimulation (TMS) is particularly useful to establish and map causal brain-behavior relations in motor and nonmotor cortical areas. Neuronavigated TMS is able to provide precise information related to the individual's functional anatomy that can be visualized and used during surgical interventions and critically aid in presurgical planning, reducing the need for riskier and more cumbersome intraoperative or invasive mapping procedures. This article reviews methodological aspects, clinical applications, and future directions of TMS-based mapping.
8. **DeGiorgio CM, Faselow EE, Schrader LM, Cook IA. Trigeminal nerve stimulation: seminal animal and human studies for epilepsy and depression. *Neurosurg Clin N Am.* 2011;22(4):449-56, v. <http://www.ncbi.nlm.nih.gov/pubmed/21939843>**  
**Abstract** The unique ability to stimulate bilaterally, extracranially, and non-invasively may represent a significant advantage to invasive neuromodulation therapies. In humans thus far the technique has been applied noninvasively, and is termed external trigeminal nerve stimulation (eTNSTM).

**Other Neurostimulation in Epilepsy - TNS**

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1. **Pop J, Murray D, Markovic D, DeGiorgio CM. Acute and long-term safety of external trigeminal nerve stimulation for drug-resistant epilepsy. *Epilepsy Behav.* 2011;22(3):574-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21959083>  
**Abstract** Trigeminal nerve stimulation (TNS) is a novel therapy for drug-resistant epilepsy. We report in detail the safety of external TNS (eTNS), focusing on acute and long-term heart rate and systolic and diastolic blood pressure in response to TNS from the pilot feasibility study. The data indicate that eTNS of the infraorbital and supraorbital branches of the trigeminal nerve is safe and well tolerated.
2. **DeGiorgio CM, Shewmon DA, Whitehurst T. Trigeminal nerve stimulation for epilepsy. *Neurology.* 2003;61(3):421-2.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12913219>
3. **Fanselow EE, Reid AP, Nicoletis MA. Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation. *J Neurosci.* 2000;20(21):8160-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11050139>  
**Abstract** Stimulation of the vagus nerve has become an effective method for desynchronizing the highly coherent neural activity typically associated with epileptic seizures. This technique has been used in several animal models of seizures as well as in humans suffering from epilepsy. However, application of this technique has been limited to unilateral stimulation of the vagus nerve, typically delivered according to a fixed duty cycle, independently of whether ongoing seizure activity is present. Here, we report that stimulation of another cranial nerve, the trigeminal nerve, can also cause cortical and thalamic desynchronization, resulting in a reduction of seizure activity in awake rats. Furthermore, we demonstrate that providing this stimulation only when seizure activity begins results in more effective and safer seizure reduction per second of stimulation than with previous methods. Seizure activity induced by intraperitoneal injection of pentylenetetrazole was recorded from microwire electrodes in the thalamus and cortex of awake rats while the infraorbital branch of the trigeminal nerve was stimulated via a chronically implanted nerve cuff electrode. Continuous unilateral stimulation of the trigeminal nerve reduced electrographic seizure activity by up to 78%, and bilateral trigeminal stimulation was even more effective. Using a device that automatically detects seizure activity in real time on the basis of multichannel field potential signals, we demonstrated that seizure-triggered stimulation was more effective than the stimulation protocol involving a fixed duty cycle, in terms of the percent seizure reduction per second of stimulation. In contrast to vagus nerve stimulation studies, no substantial cardiovascular side effects were observed by unilateral or bilateral stimulation of the trigeminal nerve. These findings suggest that trigeminal nerve stimulation is safe in awake rats and should be evaluated as a therapy for human seizures. Furthermore, the results demonstrate that seizure-triggered trigeminal nerve stimulation is technically feasible and could be further developed, in conjunction with real-time seizure-predicting paradigms, to prevent seizures and reduce exposure to nerve stimulation.

**Other Neurostimulation in Epilepsy - Transcranial Ultrasound**

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1. **Yang T, Chen J, Yan B, Zhou D. Transcranial ultrasound stimulation: a possible therapeutic approach to epilepsy. *Med Hypotheses*. 2011;76(3):381-3.**

<http://www.ncbi.nlm.nih.gov/pubmed/21144673>

**Abstract** Epilepsy threatens the health of more than 50 million people all over the world. Many patients with epilepsy, especially temporal lobe epilepsy, are resistant to the current therapeutic drugs. Different strategies for these patients are therefore necessary to achieve maximum therapeutic effect. Neuromodulation techniques have gained widespread attention due to their therapeutic utility in managing numerous neurological/psychiatric diseases. Transcranial ultrasound stimulation (TUS) is an emerging non-invasive neurostimulation tool that can both excite and reversibly suppress neuronal activity effectively within the brain. TUS can transmit through the skull with millimeter spatial resolutions. In the current work, we propose that TUS may be a promising alternative therapy for the suppression of seizure activity in epilepsy patients, minimizing poor post-seizure outcomes and improving life quality. Further investigation into stimulation parameters, including waveform parameters such as tone burst duration (pulse length), pulse repetition frequency, exposure time, acoustic frequency, and the acoustic intensity of TUS, is needed to verify the efficacy of this intervention in epilepsy.

2. **Tyler WJ. Noninvasive neuromodulation with ultrasound? A continuum mechanics hypothesis. *Neuroscientist*. 2011;17(1):25-36.**

<http://www.ncbi.nlm.nih.gov/pubmed/20103504>

<http://nro.sagepub.com/content/17/1/25>

**Abstract** Deep brain stimulation and vagal nerve stimulation are therapeutically effective in treating some neurological diseases and psychiatric disorders. Optogenetic-based neurostimulation approaches are capable of activating individual synapses and yield the highest spatial control over brain circuit activity. Both electrical and light-based neurostimulation methods require intrusive procedures such as surgical implantation of electrodes or photon-emitting devices. Transcranial magnetic stimulation has also shown therapeutic effectiveness and represents a recent paradigm shift towards implementing less invasive brain stimulation methods. Magnetic-based stimulation, however, has a limited focusing capacity and lacks brain penetration power. Because ultrasound can be noninvasively transmitted through the skull to targeted deep brain circuits, it may offer alternative approaches to currently employed neuromodulation techniques. Encouraging this idea, literature spanning more than half a century indicates that ultrasound can modulate neuronal activity. In order to provide a comprehensive overview of potential mechanisms underlying the actions of ultrasound on neuronal excitability, here, I propose the continuum mechanics hypothesis of ultrasonic neuromodulation in which ultrasound produces effects on viscoelastic neurons and their surrounding fluid environments to alter membrane conductance. While further studies are required to test this hypothesis, experimental data indicate ultrasound represents a promising platform for developing future therapeutic neuromodulation approaches.

**Outcome Measures (for assessing VNS)**

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- 1. Rodgers WP, Durnford AJ, Kirkham FJ, Whitney A, Mullee MA, Gray WP. Interrater reliability of Engel, International League Against Epilepsy, and McHugh seizure outcome classifications following vagus nerve stimulator implantation. *J Neurosurg Pediatr.* 2012;10(3):226-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22816604>  
**Abstract** OBJECT: Interrater reliability as measured by the kappa (kappa) statistic is a widely used and valuable tool to measure the robustness of a scoring system. Seizure frequency reduction is a central outcome measure following vagus nerve stimulation (VNS). A specific VNS scoring system has been proposed by McHugh, but its interrater reliability has not been tested. The authors assessed its interrater reliability and compared it with that of the Engel and International League Against Epilepsy (ILAE) systems. METHODS: Using the Engel, ILAE, and McHugh scoring systems, 3 observers independently rated the medical records of children who had undergone vagus nerve stimulator implantation between January 2001 and April 2011 at the Southampton University Hospital. The interrater agreements were then calculated using the kappa statistic. RESULTS: Interrater reliability for the McHugh scale (kappa0.693) was very good and was superior to those of the Engel (kappa0.464) and ILAE (kappa0.491) systems for assessing outcome in patients undergoing VNS. CONCLUSIONS: The authors recommend considering the McHugh scoring system when assessing outcomes following VNS.
  
- 2. McHugh JC, Singh HW, Phillips J, Murphy K, Doherty CP, Delanty N. Outcome measurement after vagal nerve stimulation therapy: proposal of a new classification. *Epilepsia.* 2007;48(2):375-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17295633>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2006.00931.x/asset/j.1528-1167.2006.00931.x.pdf?v=1&t=he941xly&s=cf4b40ade23f522e9272a08b942182820db681ae>  
**Abstract** PURPOSE: Vagal nerve stimulation (VNS) is an adjunctive palliative therapy for refractory epilepsy. Effects of treatment are varied and some, such as the use of an external magnet for seizure termination, are unique to VNS. No accepted standard exists for outcome measurement after VNS treatment. We present a novel classification for outcome, which includes assessment of both seizure frequency and severity in VNS-treated patients. METHODS: We devised a classification system modeled on the Engel classification for surgically treated patients, but tailored for use in VNS therapy, which incorporates five classes of outcome. We retrospectively reviewed VNS-treated patients in our centre, and used the data to illustrate our system and compare it with the Engel model. RESULTS: With this system, 48 patients (mean age, 30 years) were followed up over a median of 18 months. Seventy-eight percent had partial epilepsy. Sixteen and a half percent experienced class I outcome (>80% seizure-frequency reduction). Twenty percent had class II improvement (50-79% seizure-frequency reduction). One-third had no improvement (class V). The remaining patients comprised class III (seizure-frequency reduction <50%) or class IV (magnet benefit alone) outcomes. Class I-III outcomes were further subdivided according to effects on ictal or postictal severity. CONCLUSIONS: We propose a new classification, which can be used for all epilepsies and which reflects outcome measures beyond seizure-frequency reduction alone. Use of this system would allow greater comparison between future studies of VNS therapy.

3. Clarke BM, Upton AR, Griffin H, Fitzpatrick D, DeNardis M. Seizure control after stimulation of the vagus nerve: clinical outcome measures. *Can J Neurol Sci.* 1997;24(3):222-5; comment *Can J Neurol Sci.* 2011;38(6):804-5.

<http://www.ncbi.nlm.nih.gov/pubmed/9276107>

**Abstract** BACKGROUND: Currently, decreases in seizure frequency are the accepted efficacy outcome measure of therapeutic interventions in the management of patients with epilepsy. In a longitudinal randomized controlled trial of 10 subjects with intractable complex partial seizures who received left vagal nerve stimulation (VNS) to control seizures, it was found that the total number of consecutive seizure-free days is a significant efficacy outcome measure. Unlike measures in which percentage decreases in seizure frequency are calculated, measures of consecutive seizure days indicate improvement in the amount of time for which patients may function at a higher level in activities of daily living. METHODS: Fourteen day blocks of consecutive seizure-free days and 14 day blocks of consecutive days in which subjects had seizures were tabulated. RESULTS: A Pearson correlation coefficient showed that prior to VNS subjects had few, if any, seizure free blocks of time and after VNS they had more blocks of time seizure free  $r = -1.00$  and  $r = -0.99$ . The blocks of seizure-free days increased tenfold (mean 0.85 to mean 8.00) from 1991-1995 while mean seizure frequency in those blocks in which subjects had seizures only decreased from (mean 20.14 to mean 17.59) for the same time period. Correlations between total number of seizures after 24 months of VNS and after 50 months of VNS were  $r = 0.85$  showing a consistency in the effect of VNS. CONCLUSIONS: Monitoring the number of consecutive seizure-free days is a significant clinical outcome measure of VNS.

**Parameters/Dosing (Optimizing VNS therapy)**

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1. **Helmert SL, Begnaud J, Cowley A, Corwin HM, Edwards JC, Holder DL, et al. Application of a computational model of vagus nerve stimulation. *Acta Neurol Scand.* 2012;126(5):336-43.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22360378>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0404.2012.01656.x/abstract>  
**Abstract** OBJECTIVES: The most widely used and studied neurostimulation procedure for medically refractory epilepsy is vagus nerve stimulation (VNS) Therapy. The goal of this study was to develop a computational model for improved understanding of the anatomy and neurophysiology of the vagus nerve as it pertains to the principles of electrical stimulation, aiming to provide clinicians with a systematic and rational understanding of VNS Therapy. MATERIALS AND METHODS: Computational modeling allows the study of electrical stimulation of peripheral nerves. We used finite element electric field models of the vagus nerve with VNS Therapy electrodes to calculate the voltage field for several output currents and studied the effects of two programmable parameters (output current and pulse width) on optimal fiber activation. RESULTS: The mathematical models correlated well with strength-duration curves constructed from actual patient data. In addition, digital constructs of chronic versus acute implant models demonstrated that at a given pulse width and current combination, presence of a 110-mum fibrotic tissue can decrease fiber activation by 50%. Based on our findings, a range of output current settings between 0.75 and 1.75 mA with pulse width settings of 250 or 500 mus may result in optimal stimulation. CONCLUSIONS: The modeling illustrates how to achieve full or nearly full activation of the myelinated fibers of the vagus nerve through output current and pulse width settings. This knowledge will enable clinicians to apply these principles for optimal vagus nerve activation and proceed to adjust duty cycle and frequency to achieve effectiveness.
  
2. **Bhat S, Lysenko L, Neiman ES, Rao GK, Chokroverty S. Increasing off-time improves sleep-disordered breathing induced by vagal nerve stimulation. *Epileptic Disord.* 2012;14(4):432-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23247901>  
**Abstract** Vagal nerve stimulation (VNS) has been reported to adversely impact breathing in sleep. While continuous positive airway pressure is often employed to treat these patients, little data exist on the effects of adjusting various settings on VNS-induced sleep-disordered breathing. We describe a patient in whom increasing off-time caused resolution of VNS-induced arterial oxygen desaturations in sleep, which we believe is a novel observation.

- 3. Hoffmann TJ, Simon BJ, Zhang Y, Emala CW. Low voltage vagal nerve stimulation reduces bronchoconstriction in guinea pigs through catecholamine release. *Neuromodulation*. 2012;15(6):527-36.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22551486>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1525-1403.2012.00454.x/abstract>  
**Abstract** OBJECTIVE: Electrical stimulation of the vagus nerve at relatively high voltages (e.g., >10 V) can induce bronchoconstriction. However, low voltage (<math>\leq 2</math> V) vagus nerve stimulation (VNS) can attenuate histamine-invoked bronchoconstriction. Here, we identify the mechanism for this inhibition. METHODS: In urethane-anesthetized guinea pigs, bipolar electrodes were attached to both vagus nerves and changes in pulmonary inflation pressure were recorded in response to i.v. histamine and during VNS. The attenuation of the histamine response by low-voltage VNS was then examined in the presence of pharmacologic inhibitors or nerve ligation. RESULTS: Low-voltage VNS attenuated histamine-induced bronchoconstriction (4.4 +/- 0.3 vs. 3.2 +/- 0.2 cm H<sub>2</sub>O,  $p < 0.01$ ) and remained effective following administration of a nitric oxide synthase inhibitor, NG-nitro-L-arginine methyl ester, and after sympathetic nerve depletion with guanethidine, but not after the beta-adrenoceptor antagonist propranolol. Nerve ligation caudal to the electrodes did not block the inhibition but cephalic nerve ligation did. Low-voltage VNS increased circulating epinephrine and norepinephrine without but not with cephalic nerve ligation. CONCLUSION: These results indicate that low-voltage VNS attenuates histamine-induced bronchoconstriction via activation of afferent nerves, resulting in a systemic increase in catecholamines likely arising from the adrenal medulla.
- 4. Yoo PB, Hincapie JG, Hamann JJ, Ruble SB, Wolf PD, Grill WM. Selective control of physiological responses by temporally-patterned electrical stimulation of the canine vagus nerve. *Conf Proc IEEE Eng Med Biol Soc*. 2011;2011:3107-10.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22254997>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090848>  
**Abstract** Vagus nerve stimulation (VNS) is effective for treating epilepsy and depression, and has emerging indications for anxiety and heart failure. However, stimulation-evoked side effects remain a challenge for long-term compliance. We investigated the feasibility of reducing VNS side effects by using a temporally-modified stimulation pattern. In 4 anesthetized canines, we measured changes in both the heart rate and evoked laryngeal muscle activity. Compared to baseline, we found that a 5% duty cycle (measured by the number of pulses per second of stimulation) could still evoke a 21% reduction in heart rate; whereas compared to continuous stimulation (3 mA, 300  $\mu$ s pulsewidth, 20 Hz) the same 5% duty cycle reduced the evoked laryngeal muscle activity by 90%. The results of this study indicate that temporally-patterned stimulation may provide an effective tool for optimizing VNS therapy.

5. **Castoro MA, Yoo PB, Hincapie JG, Hamann JJ, Ruble SB, Wolf PD, et al. Excitation properties of the right cervical vagus nerve in adult dogs. *Exp Neurol*. 2011;227(1):62-8.**

<http://www.ncbi.nlm.nih.gov/pubmed/20851118>

**Abstract** Vagus nerve stimulation (VNS) is an approved treatment for epilepsy and depression, and it is currently under investigation for applications in Alzheimer's disease, anxiety, heart failure, and obesity. However, the mechanism(s) by which VNS has its effects are not clear, and the stimulation parameters for obtaining therapeutic outcomes appear highly variable. The purpose of this study was to quantify the excitation properties of the right cervical vagus nerve in adult dogs anesthetized with propofol and fentanyl. Input-output curves of the right cervical vagus nerve compound action potential and laryngeal muscle electromyogram were measured in response to VNS across a range of stimulation parameters: amplitudes of 0.02-50mA, pulsewidths of 10, 50, 100, 200, 300, 500, and 1,000µs, frequencies of 1-2Hz, and train lengths of 20 pulses with 3 different electrode configurations: monopolar cathode, proximal anode/distal cathode, and proximal cathode/distal anode. Electrode configuration and stimulation waveform (monophasic vs. asymmetric charge-balanced biphasic) did not affect the threshold or recruitment of the vagal nerve fibers that were activated. The rheobase currents of A- and B-fibers were 0.4mA and 0.7mA, respectively, and the chronaxie of both components was 180µs. Pulsewidth had little effect on the normalized threshold difference between activation of A- and B-fibers. The results provide insight into the complement of nerve fibers activated by VNS and guidance to clinicians for the selection of optimal stimulation parameters.

6. **Vuckovic A, Tosato M, Struijk JJ. A comparative study of three techniques for diameter selective fiber activation in the vagal nerve: anodal block, depolarizing prepulses and slowly rising pulses. *J Neural Eng*. 2008;5(3):275-86.**

<http://www.ncbi.nlm.nih.gov/pubmed/18566504>

<http://iopscience.iop.org/1741-2552/5/3/002/>

**Abstract** The paper shows selective smaller fiber activation in the left and right vagal nerve in in vivo experiments in pigs using three different techniques: anodal block, depolarizing prepulses and slowly rising pulses. All stimulation techniques were performed with the same experimental setup. The techniques have been compared in relation to maximum achievable suppression of nerve activity, maximum required current, maximum achievable stimulation frequency and the required charge per phase. Suppression of the largest fiber activity (expressed as a percentage of the maximum response) was 0-40% for anodal block, 10-25% for depolarizing prepulses and 40-50% for slowly rising pulses (duration up to 5 ms). Incomplete suppression of activation was mainly attributed to the large size of the vagal nerve (3.0-3.5 mA) which resulted in a large difference of the excitation thresholds of nerve fibers at different distances from the electrode, as well as a relatively short duration of slowly rising pulses. The technique of anodal block required the highest currents. The techniques of slowly rising pulses and anodal block required comparable charge per phase that was larger than for the technique of depolarizing prepulses. Depolarizing prepulses were an optimal choice regarding maximum required current and charge per phase but were very sensitive to small changes of the current amplitude. The other two techniques were more robust regarding small changes of stimulation parameters. The maximum stimulation frequency, using typical values of stimulation parameters, was 105 Hz for depolarizing prepulses, 30 Hz for anodal block and 28 Hz for slowly rising pulses. Only a technique of depolarizing prepulses had a charge per phase within the safe limits. For the other two techniques it would be necessary to optimize the shape of a stimulation pulse in order to reduce the charge per phase.

7. **Labiner DM, Ahern GL. Vagus nerve stimulation therapy in depression and epilepsy: therapeutic parameter settings. *Acta Neurol Scand.* 2007;115(1):23-33.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17156262>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0404.2006.00732.x/abstract>  
**Abstract** Vagus nerve stimulation (VNS) therapy is an effective adjunctive treatment for chronic or recurrent treatment-resistant depression in adults, and for pharmaco-resistant epilepsy in adults and adolescents. VNS therapy is administered through an implanted pulse generator that delivers programmed electrical pulses through an implanted lead to the left vagus nerve. Programmable pulse parameters include output current, frequency, pulse width, and ON/OFF times. Within a range of typical values, individual patients respond best to different combinations of parameter settings. The physician must identify the optimum settings for each patient while balancing the goals of maximizing efficacy, minimizing side effects, and preserving battery life. Output current is gradually increased from 0.25 mA to the maximum tolerable level (maximum, 3.5 mA); typical therapeutic settings range from 1.0 to 1.5 mA. Greater output current is associated with increased side effects, including voice alteration, cough, a feeling of throat tightening, and dyspnea. Frequency is typically programmed at 20 Hz in depression and 30 Hz in epilepsy. Pulse width is typically 250 or 500 microseconds. The recommended initial ON time is 30 s, followed by 5 min OFF; OFF time > ON time is recommended. As with pharmacotherapy, VNS therapy must be adjusted in a gradual, systematic fashion to individualize therapy for each patient.
8. **Bunch S, DeGiorgio CM, Krahl S, Britton J, Green P, Lancman M, et al. Vagus nerve stimulation for epilepsy: is output current correlated with acute response? *Acta Neurol Scand.* 2007;116(4):217-20.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17824897>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0404.2007.00878.x/abstract>  
**Abstract** OBJECTIVES: Vagus nerve stimulation (VNS) is an effective treatment for intractable epilepsy. It is unknown whether acute response is correlated with the amplitude of output current. The purpose of this study was to determine if the output current of VNS is correlated with percent reductions in seizure frequency and response. MATERIALS AND METHODS: Retrospective analysis of a multicenter randomized trial of three unique paradigms of VNS was carried out in patients with intractable partial onset epilepsy. Output current at 1 and 3 months was correlated with percent reduction in seizure frequency and response rates. RESULTS: Sixty-one subjects were enrolled and completed the study. Output current, ranging from 0.25 to 1.5 mA, was not correlated with reductions in seizure frequency, or with > or = 50% reduction in seizures. Six of seven initial non-responders did experience > or = 50% reductions in seizures after current was increased. CONCLUSIONS: The output current is not a major determinant of acute response to VNS for epilepsy. Many patients respond to low current (<1 mA). Some (20%) initial non-responders may respond to an increase in output current.

9. **Santiago-Rodriguez E, Alonso-Vanegas M, Cardenas-Morales L, Harmony T, Bernardino M, Fernandez-Bouzas A. Effects of two different cycles of vagus nerve stimulation on interictal epileptiform discharges. *Seizure*. 2006;15(8):615-20.**

<http://www.ncbi.nlm.nih.gov/pubmed/17049887>

[http://ac.els-cdn.com/S1059131106001725/1-s2.0-S1059131106001725-main.pdf?\\_tid=eacd67ce-8cc3-11e2-8886-00000aab0f6b&acdnat=1363278567\\_86044287ca4802ae5b9cfcc3565685f3](http://ac.els-cdn.com/S1059131106001725/1-s2.0-S1059131106001725-main.pdf?_tid=eacd67ce-8cc3-11e2-8886-00000aab0f6b&acdnat=1363278567_86044287ca4802ae5b9cfcc3565685f3)

**Abstract** PURPOSE: To evaluate the effects of two cycles of vagus nerve stimulation (VNS), 30 s/5 min and 7 s/18 s on the interictal epileptiform discharges (IEDs). METHODS: Twenty patients were studied, 12 with generalized and 8 with partial seizures. An EEG of 120 channels was performed during 3 different conditions, each one lasting 30 min: basal state (BS), 30 s/5 min and 7 s/18 s VNS cycles. The number and duration of IEDs, time of IEDs in 1 min (TIEDM), IEDs/NIEDs index and the spike-free period (SFP) were determined. RESULTS: In 16 patients (80%), IED decreased during 30 s/5 min cycle (Group 1) and increased in 4 (Group 2). In Group 1, during the 30 s/5 min cycle the following variables showed a decrease: TIEDM, from 12.64 s to 9.62 s ( $p=0.001$ ); IED/NIED index, from 0.53 to 0.31 ( $p=0.021$ ), and IED duration, from 1.57 s to 1.05 s ( $p=0.015$ ); whereas SFP duration increased from 20.06 s to 37.73 s ( $p=0.008$ ). The decrease in IED was 41% and the increase in SFP 88%. In the 7s/18s cycle, only SFP had an increase, 72% ( $p<0.043$ ). In Group 2, an increase in IED during both cycles was found. In the 30 s/5 min cycle, TIEDM increased 56% ( $p=0.042$ ) and IED/NIED index 259% ( $p=0.040$ ). CONCLUSION: VNS modifies IED in an acute form, in 80% of patients the 30 s/5 min cycle decreases the epileptiform activity and it is not modified by 7 s/18 s cycle. In 20% of patients, both cycles increase the epileptiform activity.

10. **Vuckovic A, Struijk JJ, Rijkhoff NJ. Influence of variable nerve fibre geometry on the excitation and blocking threshold. A simulation study. *Med Biol Eng Comput*. 2005;43(3):365-74.**

<http://www.ncbi.nlm.nih.gov/pubmed/16035225>

**Abstract** The aim of the study was to investigate how variable fibre geometry influences the excitation and blocking threshold of an undulating peripheral nerve fibre. The sensitivity of the excitation and blocking thresholds of the nerve fibres to various geometric and stimulation parameters was examined. The nerve fibres had a spiral shape (defined by the undulation wavelength, undulation amplitude and phase), and the internodal length varied. Diameter-selective stimulation of nerve fibres was obtained using anodal block. Simulation was performed using a two-part simulation model: a volume conductor model to calculate the electrical potential distribution inside a tripolar cuff electrode and a model of a peripheral undulating human nerve fibre to simulate the fibre response to stimulation. The excitation threshold of the undulating fibres was up to 100% higher than the excitation threshold of the straight fibres. When a nerve was stimulated with long pulses, which are typically applied for anodal block (> 400 micros), the blocking threshold of the undulating fibres was up to four times higher than the blocking threshold of the straight fibres. Dependencies of the excitation threshold on geometric and stimulation parameters were the same as for a straight fibre. Dependencies of the blocking threshold on geometric and stimulation parameters were different compared with a straight fibre. Owing to the fibre undulation and variable internodal length, the blocking threshold and the minimum pulse duration to obtain anodal block were generally different in the proximal and distal directions. Owing to variable fibre geometry, the excitation threshold varied by up to +/- 40% of the mean value, and the blocking threshold varied by up to +/- 60 % of the mean value. Owing to undulation, the blocking threshold of large fibres could be higher than the blocking threshold of small-diameter fibres, even if they had the same geometry. The results indicate that, during skeletal muscle stretching and contracting or during variation in joint angle, the excitation and blocking thresholds of the nerve fibres change owing to variations in fibre geometry. A straight fibre model could be too simple for modelling the response of peripheral nerve fibres to electrical stimulation.

11. **DeGiorgio C, Heck C, Bunch S, Britton J, Green P, Lancman M, et al. Vagus nerve stimulation for epilepsy: randomized comparison of three stimulation paradigms. *Neurology*. 2005;65(2):317-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16043810>  
<http://www.neurology.org/content/65/2/317.full.pdf>  
**Abstract** Vagus nerve stimulation (VNS) is an effective adjunctive treatment for intractable epilepsy. However, the optimal range of device duty-cycles [on/(on + off times)] is poorly understood. The authors performed a multicenter, randomized trial of three unique modes of VNS, which varied primarily by duty-cycle. The results indicate that the three duty-cycles were equally effective. The data support the use of standard duty-cycles as initial therapy.
  
12. **Evans MS, Verma-Ahuja S, Naritoku DK, Espinosa JA. Intraoperative human vagus nerve compound action potentials. *Acta Neurol Scand*. 2004;110(4):232-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15355486>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0404.2004.00309.x/abstract>  
**Abstract** OBJECTIVE: Although electrical stimulation of vagus nerve is used widely for treatment of epilepsy the electrophysiological properties of human vagus nerve are not well characterized. Our objective was to measure compound action potentials of human vagus nerve fiber groups intraoperatively by stimulation using a commercially available generator and electrode system (Neurocybernetic Prosthesis System, NCP). MATERIAL AND METHODS: During NCP implantation we recorded compound action potentials evoked by stimulating the left vagus nerve through the NCP bipolar lead. Current intensities were varied from 0.25 to 3.0 mA. RESULTS: Vagus nerve compound action potential components conducting in the A, Adelta, and C velocity ranges could be elicited using either the NCP pulse generator or by a standard evoked potential instrument. A fiber potentials were recordable in all nerves, and were activated by very low stimulus currents. Adelta and C fibers were less reliably elicited, with C fibers requiring the highest currents. CONCLUSIONS: Three clearly identified fiber populations can be identified using therapeutic electrical stimulation of the human vagus. Intraoperative measurements of NCP-induced action potentials may potentially provide a marker for therapeutic stimulation and better insight into mechanisms of vagus nerve stimulation (VNS) efficacy.
  
13. **Mu Q, Bohning DE, Nahas Z, Walker J, Anderson B, Johnson KA, et al. Acute vagus nerve stimulation using different pulse widths produces varying brain effects. *Biol Psychiatry*. 2004;55(8):816-25.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15050863>  
**Abstract** BACKGROUND: Vagus nerve stimulation (VNS) is an approved treatment for epilepsy and has been investigated in clinical trials of depression. Little is known about the relationship of VNS parameters to brain function. Using the interleaved VNS /functional magnetic resonance imaging (fMRI) technique, we tested whether variations of VNS pulse width (PW) would produce different immediate brain activation in a manner consistent with single neuron PW studies. METHODS: Twelve adult patients with major depression, treated with VNS, underwent three consecutive VNS/fMRI scans, each randomly using one of three PWs (130 micros, 250 micros, or 500 micros). The data were analyzed with SPM2. RESULTS: Global activations induced by PWs 250 and 500 were both significantly greater than that induced by PW 130 but not significantly different from each other. For global deactivation, PWs 130 and 250 were both significantly greater than PW 500 but not significantly different from each other. Regional similarities and differences were also seen with the various PWs. CONCLUSIONS: The data confirm our hypothesis that VNS at PW 500 globally produces no more activation than does PW 250, and PW 130 is insufficient for activation of some regions. These data suggest that PW is an important variable in producing VNS brain effects.

- 14. Heck C, Helmers SL, DeGiorgio CM. Vagus nerve stimulation therapy, epilepsy, and device parameters: scientific basis and recommendations for use. *Neurology*. 2002;59(6 Suppl 4):S31-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12270966>  
**Abstract** Our understanding of a precise dose-response relationship for vagus nerve stimulation (VNS) therapy in the treatment of seizures is still evolving. Because several parameters are involved in VNS therapy, the individual contribution of each is not well understood. This review discusses the efficacy of stimulation parameters used in the VNS clinical trials. The background, influence on safety and efficacy, and role in helping to achieve seizure control are discussed for each VNS device parameter: output current, pulse duration, frequency, and duty cycle. Finally, we provide an algorithm for the adjustment of VNS device settings (see Appendices).
- 15. Helmstaedter C, Hoppe C, Elger CE. Memory alterations during acute high-intensity vagus nerve stimulation. *Epilepsy Res*. 2001;47(1-2):37-42.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11673019>  
**Abstract** Left cervical vagus nerve stimulation (VNS) is an accepted add-on treatment for pharmaco-resistant epilepsy. However, it also allows the investigation of the effects of peripheral nerve stimulation on central nervous functions. The impact of 4.5 min high intensity VNS (>1 mA) on material-specific memory and decision times was evaluated in an experimental 'box car' design in 11 patients with pharmaco-resistant epilepsy. Results indicate reversible deterioration of figural but not verbal memory and a trend of accelerated decision times during VNS. Thus, further support of cognitive effects of VNS is provided. There are indications of a major projection of VNS to activating brain structures of and the right hemisphere. Significant cognitive side effects in clinical application are unlikely because of the reversibility of the effect and differences between experimental and therapeutic stimulation conditions. However, since the effectors and the direction of the cognitive effects of VNS seem to depend strongly on stimulation conditions, we recommend future experimental research covering a larger range of stimulation conditions.
- 16. Koo B, Ham SD, Sood S, Tarver B. Human vagus nerve electrophysiology: a guide to vagus nerve stimulation parameters. *J Clin Neurophysiol*. 2001;18(5):429-33.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11709648>  
**Abstract** The authors studied human vagus nerve electrophysiology intraoperatively on 21 patients (age range: 4 to 31 years) during implantation of a vagus nerve stimulator for seizure control. The study was performed with direct electrical stimulation of the vagus nerve with various stimulation parameters resembling those employed by the Cyberonics NeuroCybernetic Prosthesis System (Houston, TX), which is used clinically for vagus nerve stimulation for treatment of seizures. Recordings were made directly from the rostral end of the vagus nerve. The response of the vagus nerve to various stimulus parameters in patients of different ages was studied. Based on the vagus nerve characteristics, age-related adjustments for stimulus parameters were recommended.
- 17. Liporace J, Hucko D, Morrow R, Barolat G, Nei M, Schnur J, et al. Vagal nerve stimulation: adjustments to reduce painful side effects. *Neurology*. 2001;57(5):885-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11552021>  
<http://www.neurology.org/content/57/5/885.full.pdf>  
**Abstract** Vagal nerve stimulation is an approved adjunctive treatment for medically intractable epilepsy. Although it is generally well tolerated, some patients experience pain, coughing, or hoarseness during stimulation. Lowering the pulse width in these patients alleviates pain and reduces voice alteration without loss of efficacy. This allows more optimal programming of stimulation intensities.

18. **Binks AP, Paydarfar D, Schachter SC, Guz A, Banzett RB. High strength stimulation of the vagus nerve in awake humans: a lack of cardiorespiratory effects. *Respir Physiol.* 2001;127(2-3):125-33.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11504585>  
**Abstract** Vagus nerve stimulation is used to reduce the frequency and intensity of seizures in patients with epilepsy. In the present study four such patients were studied while awake. We analyzed the physiological responses to vagus nerve stimulation over a broad range of tolerable stimulus parameters to identify vagal A-fiber threshold and to induce respiratory responses typical of C-fiber activation. A-fiber threshold was determined by increasing stimulation current until laryngeal motor A-fibers were excited (frequency=30 Hz). With A-fiber threshold established, C-fiber excitation was attempted with physiologically appropriate stimulus parameters (low frequency and high amplitude). RESULTS: A-fiber thresholds were established in all patients, threshold currents ranged between 0.5 and 1.5 mA. Stimulation at lower frequency (2-10 Hz) and higher amplitudes (2.75-3.75 mA) did not produce cardiorespiratory effects consistent with C-fiber activation. It is possible that such effects were not observed because vagal C-fibers were not excited, because C-fiber effects were masked by the 'wakeful drive' to breathe, or because epilepsy or the associated therapy had altered central processing of the vagal afferent inputs.
19. **Banzett RB, Guz A, Paydarfar D, Shea SA, Schachter SC, Lansing RW. Cardiorespiratory variables and sensation during stimulation of the left vagus in patients with epilepsy. *Epilepsy Res.* 1999;35(1):1-11.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10232789>  
**Abstract** We studied physiological and sensory effects of left cervical vagal stimulation in six adult patients receiving this stimulation as adjunctive therapy for intractable epilepsy. Stimulus strength varied among subjects from 0.1 to 2.1 microCoulomb (microC) per pulse, delivered in trains of 30-45 s at frequencies from 20 to 30 Hz; these stimulation parameters were standard in a North American study. The stimulation produced no systematic changes in ECG, arterial pressure, breathing frequency tidal volume or end-expiratory volume. Five subjects experienced hoarseness during stimulation. Three subjects with high stimulus strength (0.9-2.1 microC) recalled shortness of breath during stimulation when exercising; these sensations were seldom present during stimulation at rest. No subjects reported the thoracic burning sensation or cough previously reported with chemical stimulation of pulmonary C fibers. Four of six subjects (all those receiving stimuli at or above 0.6 microC) experienced a substantial reduction in monthly seizure occurrence at the settings used in our studies. Although animal models of epilepsy suggest that C fibers are the most important fibers mediating the anti-seizure effect of vagal stimulation, our present findings suggest that the therapeutic stimulus activated A fibers (evidenced by laryngeal effects) but was not strong enough to activate B or C fibers.

**Pediatric Population - Epilepsy Management**

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1. **Cross JH, Kluger G, Lagae L. Advancing the management of childhood epilepsies. *Eur J Paediatr Neurol.* 2013.**

<http://www.ncbi.nlm.nih.gov/pubmed/23558251>

**Abstract** Childhood epilepsies comprise a heterogeneous group of disorders and syndromes that vary in terms of severity, prognosis and treatment requirements. Effective management requires early, accurate recognition and diagnosis, and a holistic approach that addresses each individual's medical and psychosocial needs within the context of their overall health status and quality of life. With increasing understanding of underlying aetiologies, new approaches to management and treatment are emerging. For example, genetic testing is beginning to provide a tool to aid differential diagnosis and a means of predicting predisposition to particular types of epilepsy. Despite the availability of an increasing number of antiepileptic drugs (AEDs) - due not only to the development of new AEDs, but also to changes in regulatory requirements that have facilitated clinical development - seizure control and tolerability continue to be suboptimal in many patients, and there is therefore a continuing need for new treatment strategies. Surgery and other non-pharmacological treatments (e.g. vagus nerve stimulation, ketogenic diet) are already relatively well established in paediatric epilepsy. New pharmacological treatments include generational advances on existing AEDs and AEDs with novel modes of action, and non-AED pharmacological interventions, such as immunomodulation. Emerging technologies include novel approaches allowing the delivery of medicinal agents to specific areas of the brain, and 'closed-loop' experimental devices employing algorithms that allow treatment (e.g. electrical stimulation) to be targeted both spatially and temporally. Although in early stages of development, cell-based approaches (e.g. focal targeting of adenosine augmentation) and gene therapy may also provide new treatment choices in the future.

2. **Joshi SM, Singh RK, Shellhaas RA. Advanced treatments for childhood epilepsy: beyond antiseizure medications. *JAMA Pediatr.* 2013;167(1):76-83.**

<http://www.ncbi.nlm.nih.gov/pubmed/23147598>

<http://archpedi.jamanetwork.com/article.aspx?articleid=1390785>

**Abstract** A substantial minority of children with epilepsy have continued seizures despite adequate trials of standard antiseizure medications. To maximize seizure control and thereby optimize their neurodevelopmental outcomes, alternate nonmedication therapies should be considered for these patients. Dietary therapies, including the ketogenic diet and its variations, have been available for years. With a recent resurgence in popularity and expansion of indications, these treatments can lead to freedom from seizures or a significantly reduced seizure burden for a large number of patients. For carefully selected individuals, resective epilepsy surgery may offer the best hope for a cure. For others, palliation may be achieved through additional surgical approaches, such as corpus callosotomy and multiple subpial transections, or through neurostimulation techniques, such as the vagus nerve stimulator. In this review, we present these nonmedication approaches to treatment-resistant childhood epilepsy, with attention to patient selection and the potential risks and benefits.

3. **Mantoan L, Walker M. Treatment options in juvenile myoclonic epilepsy. *Curr Treat Options Neurol.* 2011;13(4):355-70.**

<http://www.ncbi.nlm.nih.gov/pubmed/21494841>

<http://link.springer.com/article/10.1007%2Fs11940-011-0131-z>

**Abstract** OPINION STATEMENT: Juvenile myoclonic epilepsy (JME) is characterized by excellent response to treatment, if diagnosed correctly. Lifestyle advice is an integral part of the treatment of JME; it should include recommendations on avoidance of common triggers such as sleep deprivation and alcohol excess and emphasis on the importance of compliance with medication. The drug of first choice in the treatment of JME is sodium valproate, which has a response rate of up to 80%. Valproate should be avoided in women of childbearing age because of significantly increased risks of fetal malformations and neurodevelopmental delay. Levetiracetam or lamotrigine are alternative first-line options if valproate is contraindicated. With limited data from trials to support either of these drugs, the choice should take into account comorbidity factors and patient priorities. Because of its low side effect profile, excellent tolerability, and lack of interactions with other drugs, levetiracetam is our preferred alternative first-line agent. Lamotrigine is another first-line option but may exacerbate myoclonus. The failure of valproate or failure of two first-line antiepileptic drugs suggests that combination therapy is indicated. Drug interactions and the patient's gender, age, and comorbidities need to be considered. Levetiracetam, lamotrigine, and valproate are suitable adjuncts, with a synergistic effect reported from the combination of valproate and lamotrigine. Clonazepam is a useful adjunct for myoclonus and can be used in combination with lamotrigine to avoid lamotrigine's myoclonic effects. In women of childbearing potential, valproate should be considered if levetiracetam and lamotrigine have failed to control seizures at this stage. Topiramate is a cost-effective alternative monotherapy, but because of its poor tolerability, we recommend it as add-on treatment only. Zonisamide should remain a second-line adjunct in the treatment of JME, owing to the lack of supportive data. Phenobarbital is the most cost-effective drug and can be used to control the seizures of JME when antiepileptic drugs are limited or too costly. Carbamazepine, oxcarbazepine, and phenytoin can exacerbate absences and myoclonus and are therefore contraindicated, although they can improve control of tonic-clonic seizures when these are refractory to other medication. Gabapentin, pregabalin, tiagabine, and vigabatrin are contraindicated and can worsen seizures. (Tiagabine and vigabatrin have been reported to induce absence status epilepticus.) Surgical alternatives in refractory cases are rarely contemplated but may include vagus nerve stimulation and callosotomy. Deep brain stimulation is an experimental technique that may prove useful in managing refractory cases of JME.

4. **Coppola G. Treatment of partial seizures in childhood : an overview. *CNS Drugs*. 2004;18(3):133-56.**

<http://www.ncbi.nlm.nih.gov/pubmed/14871158>

**Abstract** The treatment of partial seizures in children is based on the use of first generation and recently introduced antiepileptic drugs as well as nonpharmacological treatments such as the ketogenic diet, vagus nerve stimulation and surgical therapy. The present review discusses the efficacy and tolerability of different treatment options for partial seizures in childhood. Few adjunctive or monotherapy, placebo-controlled or comparative trials of the first-generation antiepileptic drugs and some of the more recently introduced antiepileptic drugs have been performed in children. This can be explained by the fact that it is only relatively recently (1989) that the International League against Epilepsy proposed that randomised, controlled trials be included among the required criteria for assessing the efficacy and tolerability of an antiepileptic agent. This led to controlled, comparative trials among older antiepileptic drugs (phenobarbital, phenytoin, carbamazepine and valproic acid), both in adults and in paediatric patients, being performed relatively 'late', based on when these drugs were first introduced. Carbamazepine and valproic acid may still be considered as first-line antiepileptic therapies for children with partial seizures. Phenobarbital and phenytoin are mostly considered as last choice drugs because of their adverse event profiles. The new generation of antiepileptic agents has added to the first- and second-line treatment options for paediatric partial seizures. To date, there are sufficient data to support the clinical use of some of the recently introduced antiepileptic drugs (e.g. oxcarbazepine, topiramate, gabapentin and lamotrigine) as adjunctive or first-line monotherapy. Because of the risk of visual field constriction with vigabatrin, the use of this drug is currently limited to patients refractory to other medications. Tiagabine, felbamate, levetiracetam and zonisamide have been shown to be effective in adults with partial seizures; however, at present there are not yet enough data on the efficacy of these drugs in children to support consideration of their use as either first-line or add-on therapy in this patient population, although controlled studies are expected shortly. Furthermore, the use of felbamate is considerably limited by rare, but severe, hepatic and haematological toxicity. Controlled trials for paediatric partial seizures are still lacking for the ketogenic diet and vagus nerve stimulation, though they may represent, in given patients, useful adjunctive alternative treatments for refractory partial seizures. In conclusion, further trials are needed to determine an optimal sequence of first- and second-line therapies and to establish whether other newer antiepileptic drugs merit consideration as initial therapy in children with partial seizures.

5. **Buchhalter JR, Jarrar RG. Therapeutics in pediatric epilepsy, Part 2: Epilepsy surgery and vagus nerve stimulation. *Mayo Clin Proc.* 2003;78(3):371-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12630591>  
**Notes** This is a good review article describing the studies relating to the efficacy and adverse effects of using epilepsy surgery and VNS Therapy to treat pediatric epilepsies. Both options should be considered earlier rather than later in the treatment process to improve results after noninvasive therapies (AEDs and ketogenic diet) have failed to control seizures.  
**Abstract** When antiepileptic drugs fail to relieve seizures adequately in children and adolescents, more invasive therapies such as epilepsy surgery and an implanted device to stimulate the vagus nerve should be considered. Temporal lobectomy is an effective treatment of complex partial and secondarily generalized tonic-clonic seizures arising in the mesial structures or lateral temporal neocortex. Excellent outcomes (seizure free or rare, nondisabling seizures) are achieved in at least 70% of children. The most common adverse effect is a superior quadrant field cut that is usually asymptomatic. Transient and more long-lasting language difficulties have been reported when the surgery involves the dominant temporal lobe. The excellent outcome rate for extratemporal surgery ranges from approximately 20% to 80%, with better results seen in patients with an identifiable lesion. Potential morbidity is related to the region of resected neocortex. Corpus callosotomy is an excellent procedure for palliation but is not a cure for seizures that cause falls, with substantial improvement seen in more than 80% of patients. Potential adverse effects include more intense focal seizures and dysphasia, depending on the developmental level of the individual. Hemispherectomy provides seizure relief in 60% to 80% of patients with hemispherical pathologies such as Sturge-Weber or Rasmussen syndromes. Operative mortality has been reported in the range of 0% to 6%; other morbidities include infection and hydrocephalus. Stimulation of the vagus nerve has reduced partial seizures by 50% or more in approximately one third of patients. No adverse cognitive or systemic effects are associated with use of the implanted vagus nerve stimulator.
  
6. **Cuellar R, Molinero M. [The treatment of children with difficult to control epilepsy]. *Rev Neurol.* 2003;37(4):371-5. Spanish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/14533115>  
**Notes** A review written in Spanish that discusses epilepsy treatments (including VNS therapy) particularly among the pediatric population.  
**Abstract** A survey is conducted of the way difficult-to-control epileptic seizures are currently managed in paediatric practice. We also highlight the alternative means of therapy available, such as epilepsy surgery, a ketogenic diet, the use of hormones, steroids, gamma globulin and the stimulation of the vagal nerve, together with their indications, their efficiency in the different types of epilepsy and their contraindications. Mention is also made of the new antiepileptic drugs that have appeared since the nineties, as well as the reappearance of others that had fallen into disuse.
  
7. **Bednarek N, Motte J. [Treatment and followup of epilepsy in children]. *Rev Prat.* 1999;49(14):1532-9. French.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10887600>  
**Abstract** The decision to treat and the choice of the right antiepileptic drug depend on frequency, severity, type of seizures, epileptic syndrome, familial and school life, impact of seizures. On the other hand it is important to know the pediatric characteristics of pharmacology, tolerance, possible side effects and efficacy of each antiepileptic drug. Some antiepileptic drugs could also worsen some types of seizures. Other therapies can be efficient in refractory epilepsies: steroids, vague nerve stimulation, ketogenic diet and surgery. Clinical informations are essential to appreciate drugs efficacy and safety. Physician could be very important for the social and school insertion of epileptic children.

**Pediatric Population - QoL in Epilepsy (VNS and...)**

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- 1. Klinkenberg S, van den Bosch CN, Majoie HJ, Aalbers MW, Leenen L, Hendriksen J, et al. Behavioural and cognitive effects during vagus nerve stimulation in children with intractable epilepsy - a randomized controlled trial. *Eur J Paediatr Neurol.* 2013;17(1):82-90.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22878130>

**Abstract** BACKGROUND/AIMS: In addition to effects on seizure frequency in intractable epilepsy, multiple studies report benefits of vagus nerve stimulation (VNS) on behavioural outcomes and quality of life. The present study aims to investigate the effects of VNS on cognition, mood in general, depression, epilepsy-related restrictions and psychosocial adjustment in children with intractable epilepsy, as well as the relation between these effects and seizure reduction. METHODS: We conducted a randomized, active-controlled, double-blinded, add-on study in 41 children (age 4-18) with medically refractory epilepsy. We performed cognitive and behavioural testing at baseline (12 weeks), at the end of the blinded phase (20 weeks) in children receiving either high-output or low-output (active control) stimulation, and at the end of the open label phase (19 weeks) with all children receiving high-output stimulation. Seizure frequency was recorded using seizure diaries. RESULTS: VNS did not have a negative effect on cognition nor on psychosocial adjustment. At the end of the follow-up phase we noted an improvement of mood in general and the depression subscale for the entire group, unrelated to a reduction of seizure frequency. At the end of the blinded phase a  $\geq 50\%$  reduction of seizure frequency occurred in 16% of the high-stimulation group and 21% of the low-stimulation group. At the end of the open-label follow-up phase, 26% of the children experienced a seizure frequency reduction of 50% or more (responders). CONCLUSIONS: VNS has additional beneficial effects in children with intractable epilepsy. As opposed to anti-epileptic drugs, there are no negative effects on cognition. Moreover, we observed an improvement of mood in general and depressed feelings in particular, irrespective of a reduction in seizure frequency. These beneficial effects should be taken into account when deciding whether to initiate or continue VNS treatment in these children.
  
- 2. Hallbook T, Lundgren J, Kohler S, Blennow G, Stromblad LG, Rosen I. Beneficial effects on sleep of vagus nerve stimulation in children with therapy resistant epilepsy. *Eur J Paediatr Neurol.* 2005;9(6):399-407.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16257548>

**Abstract** The study purpose was to evaluate sleep structure following Vagus Nerve Stimulation (VNS) in 15 children with therapy resistant epilepsy and to correlate possible alterations with changes in epileptiform activity and clinical effects. Fifteen children were examined with ambulatory polysomnographic recordings initially, and after 3 and 9 months of VNS-treatment. Sleep parameters, all-night delta power activity and movement times (MTs), used to account for arousals were estimated. Epileptiform activity was evaluated by spike detection. Seizure frequency was recorded in a diary. The severity of the seizures was scored with the National Hospital Seizure Severity Scale (NHS3). Quality of life (QOL) was assessed by a visual analogue scale. Behaviour problems were quantified by using the total score of the Child Behaviour Checklist (CBCL). VNS induces a significant increase in slow wave sleep (SWS) and a decrease in sleep latency and in stage 1 sleep. The number and density of MTs during total night sleep were significantly increased. There was also a significant increase in the number of MTs immediately related to the VNS stimulation periods. Of the 14 children with increased MTs, 10 had a reduction in epileptiform activity, and in clinical seizures, all had an improvement in NHS3, and 11 in QOL. Of the 10 children with increased SWS, eight also improved in QOL and eight in behaviour. Our findings indicate that VNS counteracts known adverse effects of epilepsy on sleep and increases slow wave sleep. This possibly contributes to the reported improvement in well-being. We also see an increase in MTs. This arousal effect seems to be of minor importance for QOL and could possibly be related to the antiepileptic mechanisms in VNS.

3. **Hallbook T, Lundgren J, Stjernqvist K, Blennow G, Stromblad LG, Rosen I. Vagus nerve stimulation in 15 children with therapy resistant epilepsy; its impact on cognition, quality of life, behaviour and mood. *Seizure*. 2005;14(7):504-13.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16176878>  
[http://ac.els-cdn.com/S1059131105001500/1-s2.0-S1059131105001500-main.pdf?\\_tid=50d1123c-8cc4-11e2-9fb0-0000aacb360&acdnat=1363278737\\_2e78259ffe2a3c3947eec4c63fcbf090](http://ac.els-cdn.com/S1059131105001500/1-s2.0-S1059131105001500-main.pdf?_tid=50d1123c-8cc4-11e2-9fb0-0000aacb360&acdnat=1363278737_2e78259ffe2a3c3947eec4c63fcbf090)  
**Abstract** PURPOSE: Vagus nerve stimulation (VNS) is a neurophysiologic treatment for patients with refractory epilepsy. There is growing evidence of additional quality of life (QOL) benefits of VNS. We report the effects of VNS on seizure frequency and severity and how these changes are related to cognitive abilities, QOL, behaviour and mood in 15 children with medically refractory and for surgery not eligible epilepsy. METHODS: Initially, and after 3 and 9 months of VNS-treatment, 15 children were investigated with Bayley Scales of Infant Development (BSID), Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R), Wechsler Intelligence Scales for Children (WISC-III) depending on the child's level of functioning, a Visual Analogue Scale for validating QOL, Child Behaviour Checklist (CBCL) for quantifying behaviour problems, Dodrill Mood Analogue Scale and Birlerson Depression Self-Rating Scale, and the National Hospital Seizure Severity Scale (NHS3). A diary of seizure frequency was collected. RESULTS: Six of 15 children showed a 50% or more reduction in seizure frequency; one of these became seizure-free. Two children had a 25-50% seizure reduction. Two children showed increased seizure frequency. In 13 of 15 children there was an improvement in NHS3. The parents reported shorter duration of seizure and recovery phase. There were no changes in cognitive functioning. Twelve children showed an improvement in QOL. Eleven of these also improved in seizure severity and mood and five also in depressive parameters. CONCLUSION: This study has shown a good anti-seizure effect of VNS, an improvement in seizure severity and in QOL and a tendency to improvement over time regarding behaviour, mood and depressive parameters. The improvement in seizure severity, QOL, behaviour, mood and depressive parameters was not related to the anti-seizure effect.
4. **Kossoff EH, Pyzik PL. Improvement in alertness and behavior in children treated with combination topiramate and vagus nerve stimulation. *Epilepsy Behav*. 2004;5(2):256-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15123029>  
**Abstract** It has been reported that vagus nerve stimulation (VNS) improves behavior in children, whereas topiramate has a less clear effect. Three boys, aged 5-12 years, with generalized slow spike-wave discharges and refractory epilepsy, were treated with combination therapy of topiramate and VNS. All three had a significant reduction in seizures, but even more dramatic improvement in aggression, social interaction, and ambulation. The Cyberonics Patient Outcome Registry was subsequently queried and a beneficial effect of this combination therapy on behavior (specifically alertness) beyond that of VNS and other anticonvulsants was noted. This did not appear to be due solely to seizure reduction, which was observed only differentially at 12 months.

**Pediatric Population - Real-World Outcomes (VNS in...)**

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- 1. Ryzi M, Brazdil M, Novak Z, Chrastina J, Oslejskova H, Rektor I, et al. Long-term vagus nerve stimulation in children with focal epilepsy. *Acta Neurol Scand.* 2013;127(5):316-22.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22994298>

**Abstract** OBJECTIVES: The aim of the study was to evaluate the long-term efficacy and hospitalization rates in children with refractory focal epilepsy treated by vagus nerve stimulation. MATERIALS AND METHODS: We retrospectively analyzed 15 children with intractable focal epilepsy treated by vagus nerve stimulation (mean age of 14.6 +/- 2.5 years at the time of implantation). We analyzed the treatment effectiveness at 1, 2, and 5 year follow-up visits. We counted the average number of urgent hospitalizations and number of days of urgent hospitalization per year for each patient before and after the VNS implantation. RESULTS: The mean seizure reduction was 42.5% at 1 year, 54.9% at 2 years, and 58.3% at 5 years. The number of responders was 7 (46.7%) at 1 year and 9 (60%) at both 2 and 5 years. The mean number of urgent hospitalizations per patient was 1.0 +/- 0.6 per year preoperatively and 0.3 +/- 0.5 per year post-operatively (P < 0.0001). The mean number of days of urgent hospitalization per patient was 9.3 +/- 6.1 per year preoperatively and 1.3 +/- 1.8 per year post-operatively (P < 0.0001). CONCLUSIONS: Vagus nerve stimulation is an effective method of treating children with refractory focal epilepsy. It leads to a substantial decrease in the number and duration of urgent hospitalizations.
  
- 2. Helmers SL, Duh MS, Guerin A, Sarda SP, Samuelson TM, Bunker MT, et al. Clinical outcomes, quality of life, and costs associated with implantation of vagus nerve stimulation therapy in pediatric patients with drug-resistant epilepsy. *Eur J Paediatr Neurol.* 2012;16(5):449-58.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22261080>

**Abstract** BACKGROUND: VNS (Vagus Nerve Stimulation Therapy) is approved in the USA to treat refractory epilepsy as adjunctive to antiepileptic drugs (AEDs) in patients >=12 years with complex partial seizures. AIMS: To evaluate clinical outcomes, quality-adjusted life years (QALY), and costs associated with VNS in pediatric patients with drug-resistant epilepsy in a real-world setting. METHODS: A retrospective analysis was conducted using Medicaid data (USA). Patients had >=1 neurologist visits with epilepsy diagnosis (ICD-9 345.xx, 780.3x), >=1 procedure claims for VNS implantation, >=1 AEDs, >=6-months of Pre- and Post-VNS continuous enrollment. Pre-VNS period was 6-months and Post-VNS period extended from implantation until device removal, death, Medicaid disenrollment, or study end (up to 3 years). Incidence rate ratios (IRR) and costs (\$2010) were estimated. QALYs were estimated using number of seizure-related events. RESULTS: For patients 1-11 years old (N = 238), hospitalizations and emergency room visits were reduced Post-VNS vs. Pre-VNS (adjusted IRR = 0.73 [95% CI: 0.61-0.88] and 0.74 [95% CI: 0.65-0.83], respectively). Average total healthcare costs were lower Post-VNS vs. Pre-VNS (\$18,437 vs. \$18,839 quarterly [adjusted p = 0.052]). For patients 12-17 years old (N = 207), hospitalizations and status epilepticus events were reduced Post-VNS vs. Pre-VNS (adjusted IRR = 0.43 [95% CI: 0.34-0.54] and 0.25 [95% CI: 0.16-0.39], respectively). Average total healthcare costs were lower Post-VNS vs. Pre-VNS period (\$14,546 vs. \$19,695 quarterly [adjusted p = 0.002]). Lifetime QALY gain after VNS was 5.96 (patients 1-11 years) and 4.82 years (patients 12-17 years). CONCLUSIONS: VNS in pediatric patients is associated with decreased resource use and epilepsy-related events, cost savings, and QALY gain.

- 3. Thompson EM, Wozniak SE, Roberts CM, Kao A, Anderson VC, Selden NR. Vagus nerve stimulation for partial and generalized epilepsy from infancy to adolescence. *J Neurosurg Pediatr.* 2012;10(3):200-5. <http://www.ncbi.nlm.nih.gov/pubmed/22768964>**

**Abstract** OBJECT: Vagus nerve stimulation (VNS) is approved by the FDA for the treatment of partial epilepsy in patients older than 12 years. Authors of the current study performed a large retrospective analysis and comparison of VNS outcomes in children with an age  $\geq$  and  $<$  12 years, including those with partial and generalized epilepsy. METHODS: A retrospective review of the records of pediatric patients (age  $<$  18 years) who had undergone primary VNS system implantation between 2001 and 2010 by a single pediatric neurosurgeon was undertaken. Considered data included demographics, epilepsy type (partial vs generalized), seizure frequency, seizure duration, postictal period duration, and antiepileptic medication use. RESULTS: One hundred forty-six patients (49% female) were followed up for a mean of 41 months after VNS implantation. Thirty-two percent of patients had partial epilepsy and 68% had generalized epilepsy. After VNS system implantation, seizure frequency was reduced in 91% of patients, seizure duration in 50%, postictal period in 49%, and antiepileptic medication use in 75%. There was no significant difference in age, sex, or duration of follow-up according to epilepsy type. Neither was there any significant difference in seizure frequency reduction, seizure duration, postictal period, medication use, overall clinical improvement, or improvement in quality of life based on an age  $\geq$  or  $<$  12 years or epilepsy type. CONCLUSIONS: Vagus nerve stimulation reduced both seizure frequency and antiepileptic medication use in the majority of pediatric patients regardless of sex, age cohort, or epilepsy type. Vagus nerve stimulation also reduced seizure duration and postictal period in approximately half of the pediatric patients. Contrary to expectation, children with partial epilepsy do not benefit from VNS at higher rates than those with generalized epilepsy.
  
- 4. Chen CY, Lee HT, Chen CC, Kwan SY, Chen SJ, Hsieh LP, et al. Short-term results of vagus nerve stimulation in pediatric patients with refractory epilepsy. *Pediatr Neonatol.* 2012;53(3):184-7; comment 155-6. <http://www.ncbi.nlm.nih.gov/pubmed/22770107>**

**Abstract** BACKGROUND: Vagus nerve stimulation (VNS), an alternative method to manage patients with medically intractable epilepsy, has shown favorable results in reducing seizure relapse and improvements in quality of life. In 1997, the U.S. Food and Drug Administration approved the use of this device as an adjunctive therapy for intractable seizure in adults and adolescents older than 12 years of age. METHODS: We present a preliminary study of pediatric patients, who suffered from medically intractable seizure and underwent VNS implantation after observation of the baseline seizure frequency. Classification of epileptic syndrome, seizure patterns, age of onset, seizure frequency reduction and adverse effects were recorded. RESULTS: Patients who underwent VNS implantation included four adolescents and four children. The follow-up duration ranged from 9-33 months. All the patients were responders after the beginning of the stimulation. Five of the eight patients responded to VNS with a seizure frequency reduction rate  $>$  50%, and four of the eight patients experienced a  $\geq$  90% seizure reduction. No significant adverse effects were noted in all patients during the observation period. CONCLUSION: The effective management of medically intractable seizure remains challenging to most clinical physicians. In addition to ketogenic diet and epilepsy surgery, VNS provides an alternative way to manage this issue. Our results suggest that VNS is well tolerated in pediatric patients, and is a favorable and safe method of treating intractable seizure in common clinical practice.

5. **Cersosimo RO, Bartuluchi M, Fortini S, Soraru A, Pomata H, Caraballo RH. Vagus nerve stimulation: effectiveness and tolerability in 64 paediatric patients with refractory epilepsies. *Epileptic Disord.* 2011;13(4):382-8.**

<http://www.ncbi.nlm.nih.gov/pubmed/22258042>

**Abstract** AIM: We discuss the effectiveness, tolerability, and safety of vagus nerve stimulation (VNS) as adjunctive therapy in 64 paediatric patients with refractory epilepsies. MATERIALS AND METHODS: Sixty-four patients (34 male and 30 female) implanted with VNS for refractory epilepsy were analysed. Electroclinical features were compatible with Lennox-Gastaut syndrome in 46 patients, focal epilepsies in 10 patients, Dravet syndrome in three patients, epilepsy with myoclonic-astatic seizures in three patients, and West syndrome in two. The NeuroCybernetic Prosthesis (NCP) system (Cyberonics, Webster, TX, USA) was employed and the following stimulation parameters were used: output current of 1 to 2.5mA, signal frequency of 30Hz, signal pulse width of 500mus, and signal "on" and "off" times of 30 seconds and 5 minutes, respectively. RESULTS: Of 46 patients with LGS, 30 cases showed a significant improvement in seizure control, with a reduction in seizure frequency of at least 50%. Ten patients with focal epilepsy, three patients with myoclonic-astatic seizures, two patients with Dravet, and two patients with West showed a significant improvement in seizure control, with a reduction in seizure frequency of at least 50%. A good clinical response was evident early and efficacy progressively improved with the duration of treatment up to 36 months. In a significant number of patients, reduced seizure severity and shorter recovery time and hospital stay were also observed. VNS was well tolerated in all patients. CONCLUSION: VNS is an effective and well-tolerated treatment for paediatric patients with refractory epilepsies, improving quality of life and neuropsychological performance.

6. **Zamponi N, Passamonti C, Cappanera S, Petrelli C. Clinical course of young patients with Dravet syndrome after vagal nerve stimulation. *Eur J Paediatr Neurol.* 2011;15(1):8-14.**

<http://www.ncbi.nlm.nih.gov/pubmed/20971664>

**Abstract** Medical treatment of Dravet syndrome is disappointing. Ketogenic Diet and neurostimulation procedures as Vagus Nerve Stimulation (VNS) and Deep Brain Stimulation are in ongoing evaluation. In the present study, the long-term effectiveness of VNS on seizures, cognition and behavior was retrospectively evaluated in eight young patients with DS and medically refractory epilepsy (mean age at VNS implant: 10.28 years, range: 5-25). The average duration of treatment was 54 months (range: 12-120). Compared to baseline (mean: 55; standard deviation: 83, range: 4-200), the mean number of monthly seizures after VNS implantation was 39 +/- 67 at 3 months, 42 +/- 67 at 6 months and 38 +/- 69 at twelve months (not significant comparisons). In particular, VNS produced a mean seizure rate reduction of 12% at three months, 6% at six months, and 31% at twelve months. All patients but three experienced some reduction in seizure burden (range: 33-61%) at twelve months. Seizure outcome after one year of stimulation was rated as Mc Hugh class II (50-79% reduction in seizure frequency) in four patients, class III (<50% reduction) in one patient and class V (no improvement) in three patients. In this small case series of patients with DS, VNS therapy had a clinically significant effect in reducing seizures at twelve months in four of the eight patients. Even in patients in whom seizure reduction was not dramatic, a slight improvement in alertness and communicative skills was seen. The long-term clinical course of two selected cases is discussed.

7. Elliott RE, Rodgers SD, Bassani L, Morsi A, Geller EB, Carlson C, et al. Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases. *J Neurosurg Pediatr.* 2011;7(5):491-500.

<http://www.ncbi.nlm.nih.gov/pubmed/21529189>

**Abstract** OBJECT: The authors undertook this study to analyze the efficacy of vagus nerve stimulation (VNS) in a large consecutive series of children 18 years of age and younger with treatment-resistant epilepsy and compare the safety and efficacy in children under 12 years of age with the outcomes in older children. METHODS: The authors retrospectively reviewed 141 consecutive cases involving children (75 girls and 66 boys) with treatment-resistant epilepsy in whom primary VNS implantation was performed by the senior author between November 1997 and April 2008 and who had at least 1 year of follow-up since implantation. The patients' mean age at vagus nerve stimulator insertion was 11.1 years (range 1-18 years). Eighty-six children (61.0%) were younger than 12 years at time of VNS insertion (which constitutes off-label usage of this device). RESULTS: Follow-up was complete for 91.8% of patients and the mean duration of VNS therapy in these patients was 5.2 years (range 25 days-11.4 years). Seizure frequency significantly improved with VNS therapy (mean reduction 58.9%,  $p < 0.0001$ ) without a significant reduction in antiepileptic medication burden (median number of antiepileptic drugs taken 3, unchanged). Reduction in seizure frequency of at least 50% occurred in 64.8% of patients and 41.4% of patients experienced at least a 75% reduction. Major (3) and minor (6) complications occurred in 9 patients (6.4%) and included 1 deep infection requiring device removal, 1 pneumothorax, 2 superficial infections treated with antibiotics, 1 seroma/hematoma treated with aspiration, persistent cough in 1 patient, severe but transient neck pain in 1 patient, and hoarseness in 2 patients. There was no difference in efficacy or complications between children 12 years of age and older (FDA-approved indication) and those younger than 12 years of age (off-label usage). Linear regression analyses did not identify any demographic and clinical variables that predicted response to VNS. CONCLUSIONS: Vagus nerve stimulation is a safe and effective treatment for treatment-resistant epilepsy in young adults and children. Over 50% of patients experienced at least 50% reduction in seizure burden. Children younger than 12 years had a response similar to that of older children with no increase in complications. Given the efficacy of this device and the devastating effects of persistent epilepsy during critical developmental epochs, randomized trials are needed to potentially expand the indications for VNS to include younger children.

8. Pastrana EA, Estronza S, Sosa JJ. Vagus nerve stimulation for intractable seizures in children: the University of Puerto Rico experience. *P R Health Sci J.* 2011;30(3):128-31.

<http://www.ncbi.nlm.nih.gov/pubmed/21932713>

**Abstract** OBJECTIVE: Vagus nerve stimulation (VNS) is considered an alternative treatment for patients with medically refractory epilepsy who are not candidates for resective surgery. It consists of intermittent electrical stimulation of the left vagus nerve in the neck. Such stimulation has been demonstrated to be efficacious, safe, and well tolerated, offering these patients another option for seizure control. The aim of this study was to evaluate the experience of VNS at the University of Puerto Rico, and to examine demographic data, types of seizures, and seizure-control outcomes among treated subjects. This study is the first account of VNS in a pediatric population living in the Caribbean area. METHODS: A retrospective analysis of 13 patients treated at the University Pediatric Hospital in San Juan, Puerto Rico, was undertaken. Different types of seizures were identified and managed. RESULTS: The mean age at implantation was 12 years; 77% of patients were female. The most common type of seizure treated was generalized tonic-clonic (24%), followed by complex partial (23%). Sixty-nine percent of patients demonstrated a reduction in monthly seizure frequency. Ninety-three percent of caregivers reported improvements in alertness and communication. CONCLUSION: Vagus nerve stimulation is a safe and effective way to treat medically refractory epilepsy and should be considered as a non-pharmacological treatment for select patients with medically refractory epilepsy.

9. **Abd-El-Barr MM, Joseph JR, Schultz R, Edmonds JL, Wilfong AA, Yoshor D. Vagus nerve stimulation for drop attacks in a pediatric population. *Epilepsy Behav.* 2010;19(3):394-9.**

<http://www.ncbi.nlm.nih.gov/pubmed/20800554>

**Abstract** A retrospective analysis of 43 patients with drop attack seizures who were treated with vagus nerve stimulation (VNS) was undertaken to determine the efficacy of VNS and to determine pre-implantation characteristics associated with VNS success. It was found that on last follow-up, 46% of patients had at least a 75% reduction in drops per day. Forty-six percent of patients had less than a 50% reduction in drops per day and were considered nonresponders. Univariate analysis failed to uncover significant associations between pre-implantation characteristics and VNS success. It was found that atonic head nods were more amenable to VNS treatment as compared with atonic or tonic drop attacks. In addition, patients with focal or lateralized epileptiform abnormalities responded better to VNS compared with those with more diffuse or poorly localized findings on ictal and/or interictal recordings. Our data suggest that VNS offers significant palliative benefit to many children with medically intractable drop attack seizures.

10. **Arhan E, Serdaroglu A, Kurt G, Bilir E, Durdag E, Erdem A, et al. The efficacy of vagal nerve stimulation in children with pharmaco-resistant epilepsy: practical experience at a Turkish tertiary referral center. *Eur J Paediatr Neurol.* 2010;14(4):334-9.**

<http://www.ncbi.nlm.nih.gov/pubmed/19850501>

**Abstract** BACKGROUND: Vagus nerve stimulation (VNS) is an effective therapy for pharmaco-resistant epilepsy. Nevertheless, information regarding the long-term outcome of VNS in children is limited. AIM: To describe the long-term outcome of VNS in patients with pharmaco-resistant epilepsy treated at the Gazi University Medical Faculty Epilepsy Center, Turkey. PATIENTS AND METHODS: The study included 24 patients - all younger than 18 years of age (mean age: 14.31 years). Median age at the time of VNS device implantation was 11 years. Median age at onset of epilepsy was 21 months and median duration of epilepsy was 126 months. All the patients' seizures were intractable with antiepileptic drug treatment and all had been treated with an average of 6+/-2 antiepileptic medications. In all, 12 patients had secondary generalized seizures and 12 had partial seizures. Because this was a retrospective open study, the number of seizures could not be enumerated in most of these cases. RESULTS: The only factor that was associated with seizure reduction was duration of follow-up. Age at seizure onset and age at VNS device implantation were not associated with seizure reduction. The difference in seizure reduction between patients >12 years of age and patients <12 years of age was not significant. Mean percentage of seizure reduction after 6 months-7 years of treatment was, respectively, 22.5% (n=24) (6th month), 32% (n=20) (1st year), 42% (n=16) (2nd year), 50.45% (n=11) (3rd year), 52% (n=10) (4th year), 60% (n=8) (5th year), 61.25% (n=8) (6th year), and 61.6% (n=6) (7th year). The positive effect of VNS persisted throughout the follow-up period. CONCLUSIONS: Although it is an expensive method, VNS is an effective treatment method. This series shows the necessity of long-term follow-up series for understanding the efficacy and advantages of VNS. Prospective, long-term double-blind studies with large samples are needed to confirm the present study's findings.

- 11. Tsao CY. The efficacy of vagus nerve stimulation in intractable epilepsy associated with nonketotic hyperglycinemia in two children. *J Child Neurol.* 2010;25(3):375-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19841478>  
<http://jcn.sagepub.com/content/25/3/375>

**Abstract** Nonketotic hyperglycinemia is an inborn error of glycine metabolism and these patients frequently suffer from intractable epilepsy despite treatment with sodium benzoate, dextromethophan, and multiple anticonvulsants. We encountered 2 infants with nonketotic hyperglycinemia whose intractable generalized convulsive seizures were difficult to control with sodium benzoate, dextromethophan, and multiple anticonvulsants. However, after the addition of vagus nerve stimulation, their intractable generalized seizures were >75% reduced in frequency, the numbers of multiple anticonvulsants were reduced, and the quality of life significantly improved. The efficacy in seizure reduction persists for at least 3 years in both children.
- 12. Coykendall DS, Gauderer MW, Blouin RR, Morales A. Vagus nerve stimulation for the management of seizures in children: an 8-year experience. *J Pediatr Surg.* 2010;45(7):1479-83.**  
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**Abstract** BACKGROUND: Medication-resistant seizure disorder is a challenging, debilitating, and expensive condition. Although multiple interventions are now available, none is universally effective. In 1997, vagus nerve stimulation (VNS) was approved for treatment of refractory seizures in patients older than 12 years. Vagus nerve stimulation has shown some benefit for these individuals, but less is known about its use in patients younger than 12 years. This review analyzes the safety and efficacy of VNS in young children. METHODS: From March 2000 to February 2008, patients with medication-resistant seizures were implanted with a neurocybernetic prosthesis. Two weeks later, the device was activated. The children were followed for at least 3 months, and adjustments were made. Retrospective chart review was performed to collect data. RESULTS: Of 28 patients, the mean age at implantation was 8 years and 5 months. Twenty-one (75%) children were younger than 12 years. There were no surgical complications. Two children were reimplanted for lead malfunction, and 4 generators were replaced. Two children had transitory adverse effects (hoarseness and stridor). Mean follow-up was 3 years and 5 months. At 1 year, 52% of children had greater than 50% reduction in seizures. CONCLUSIONS: Although the effectiveness of VNS is variable and unpredictable, safety is high even in young children. Because of the potential benefit for these complex patients, the implantation of this nerve stimulation device should be included in the armamentarium of pediatric surgeons.
- 13. Kabir SM, Rajaraman C, Rittey C, Zaki HS, Kemeny AA, McMullan J. Vagus nerve stimulation in children with intractable epilepsy: indications, complications and outcome. *Childs Nerv Syst.* 2009;25(9):1097-100.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19263056>  
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**Abstract** PURPOSE: To analyze the indication, complications and outcome of vagus nerve stimulation in intractable childhood epilepsy. MATERIALS AND METHODS: We retrospectively reviewed the data of 69 children who had insertion of vagal nerve stimulator (VNS) between June 1995 and August 2006 for medically intractable epilepsy. Outcome was based on the Engel's classification. Statistical analysis of the data was also done to see if any of the parameters significantly influenced the outcome. RESULT: Thirty-eight patients (55.08 %) had a satisfactory outcome (Engel class I, II or III), and in 31 patients (44.92 %), there was no worthwhile improvement of seizures (Engel class IV). There was no statistical significance between the type of seizure and outcome (Fisher's exact test,  $p = 0.351$ ). Statistical analysis also showed that the following parameters did not significantly influence the outcome ( $p > 0.05$ ): age at insertion of VNS, age of first fit, duration between first fit and insertion of VNS and the length of follow-up. Complications included infection, lead fracture, fluid collection around the stimulator, neck pain and difficulty swallowing. CONCLUSION: Vagus nerve stimulation is a relatively safe and potentially effective treatment for children with medically intractable epilepsy.

14. **Shahwan A, Bailey C, Maxiner W, Harvey AS. Vagus nerve stimulation for refractory epilepsy in children: More to VNS than seizure frequency reduction. *Epilepsia*. 2009;50(5):1220-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19170732>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2008.01940.x/asset/j.1528-1167.2008.01940.x.pdf?v=1&t=he942skb&s=d5dc4b7fb54c84acb95f5520d8ef711b857f59c3>  
**Abstract** PURPOSE: Vagus nerve stimulation (VNS) is used increasingly as adjunctive therapy for refractory epilepsy. Studies of VNS in children report mainly seizure frequency reduction as a measure of efficacy and clinical details are often scanty. We report our experience with VNS in children with refractory epilepsy and emphasize the positive effects of VNS in terms of seizure severity. METHODS: We reviewed 26 consecutive children who had VNS with a minimum follow-up period of 18 months. We examined their clinical characteristics, seizure types, seizure frequency, epilepsy syndrome diagnosis, and response to VNS in terms of seizure frequency and seizure severity. RESULTS: Fifty-four percent of patients responded to VNS with  $\geq 50\%$  seizure frequency reduction. Patients with Lennox-Gastaut syndrome (LGS) and tonic seizures had a higher responder rate; 78% (seven of nine patients) ( $p < 0.01$ ). Status epilepticus (SE) episodes were reduced or ceased in the four patients with recurrent SE. Seizure severity, duration, and recovery time decreased in all responders. Increased alertness was reported in all responders and three nonresponders. CONCLUSION: Decreased seizure severity, recovery time, abolition of daytime drop attacks, and reduced hospitalization due to SE improved patients' lives over and above the benefit from seizure frequency reduction.
15. **Sherman EM, Connolly MB, Slick DJ, Eyrl KL, Steinbok P, Farrell K. Quality of life and seizure outcome after vagus nerve stimulation in children with intractable epilepsy. *J Child Neurol*. 2008;23(9):991-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18474931>  
<http://jcn.sagepub.com/content/23/9/991>  
**Abstract** This study examined the effect of vagus nerve stimulation on quality of life in children with epilepsy using a validated quality-of-life scale and an empirical technique that accounts for measurement error in assessing individual change (the reliable change index). Participants were 34 children with severe intractable epilepsy who underwent vagus nerve stimulation and 19 children with intractable epilepsy who received medical management. Parent-completed epilepsy-specific and global ratings at baseline and after 1 year indicated that most children had no changes in quality of life following vagus nerve stimulation (52%-77%), similar to the comparison group. There was a trend for decreases to be less common in the vagus nerve stimulation group (14% vs 37%,  $P < .07$ ), but there was no relation between improved quality of life and seizure control. The results raise questions about the mechanisms that underlie changes in quality of life after vagus nerve stimulation in this group of children.

16. **Larysz D, Larysz P, Mandera M. Evaluation of quality of life and clinical status of children operated on for intractable epilepsy. *Childs Nerv Syst.* 2007;23(1):91-7.**  
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<http://link.springer.com/article/10.1007%2Fs00381-006-0200-x>  
**Abstract** AIM: The aim of the study was evaluation of surgical treatment of epilepsy measured by changes in quality of life (QOL) and in seizure frequency and severity. MATERIALS AND METHODS: Examined group consists of 24 boys and 9 girls. We performed corpus callosotomy, lesionectomy, vagal nerve stimulation, temporal lobectomy and multiple subpial transections. Age at surgery ranged from 5 months to 19 years, with mean follow-up of 11.9 months. QOL was evaluated on the basis of the questionnaire created by us, in which parents were asked to assess the following variables before and after the surgical procedure: communication, socialization, daily living skills, movement abilities and behavioural problems. The seizure frequency was assessed with the Engel's scale, the modified Engel's scale and the Seizure Scoring System. Clinical state of all the patients was evaluated as well. RESULTS: There were no patients with stable and worsening QOL status. In the whole group treated with callosotomy, the considerable improvement in QOL concerned 36.4% of cases. In more than 95% of cases, the reduction in seizures frequency is greater than 75%. In more than 43% of patients, there are no seizures after surgery. CONCLUSIONS: Surgical treatment of intractable epilepsy is an effective method in terms of both seizure control and QOL improvement. Our results indicate the improvement in QOL of all operated patients. The improvement in QOL was accompanied by decrease in frequency and 'positive' changes in morphology of seizures. Improvement in QOL, as equivalent to seizure reduction rate, may influence further differentiation of qualification methods and surgical procedures of epilepsy.
17. **Arthur TM, Saneto RP, de Menezes MS, Devinsky O, Lajoie J, Murphy PJ, et al. Vagus nerve stimulation in children with mitochondrial electron transport chain deficiencies. *Mitochondrion.* 2007;7(4):279-83.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17513178>  
**Abstract** We retrospectively investigated outcome data for vagus nerve stimulation (VNS) in children less than 12 years of age with intractable seizures and mitochondrial disease. Five children with a mitochondrial disease, due to electron transport chain deficiency, were studied. Information was collected from clinic visits prior to, and subsequent to, VNS implantation. Data were collected by type and frequency of seizures, encephalogram and neuroimaging findings, and medication history. Four of the children had predominantly myoclonic seizures, while the other child had focal seizures with secondary generalization and myoclonic seizures. All five children did not have significant reduction in seizure frequency with VNS. VNS may not be an effective method to control myoclonic seizures in children with electron transport chain disorders.
18. **Kang HC, Hwang YS, Kim DS, Kim HD. Vagus nerve stimulation in pediatric intractable epilepsy: a Korean bicentric study. *Acta Neurochir Suppl.* 2006;99:93-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17370772>  
**Abstract** OBJECTIVE: To present our experience with vagus nerve stimulation (VNS) and to evaluate the long-term efficacy and safety of the procedure in pediatric intractable epilepsy. METHODS: This study included sixteen patients, who were implanted with a vagus nerve stimulator and could be followed up for at least more than 12 months in two epilepsy centers. Data including seizure frequency, EEG, quality of life measures and adverse events were prospectively filed over a 5-year period. RESULTS: VNS resulted in a > 50% reduction in seizure frequency in 50.0% (8/16) of children with 31.3% (5/16) of patients achieving a > 90% reduction. Additionally, enhancements in quality of life were as follows: memory in 50.0% (8/16), mood in 62.5% (10/16), behavior in 68.8% (11/16), alertness in 68.8% (11/16), achievement in 37.5% (6/16), and verbal skills in 43.8% (7/16) of the patients. Adverse events included hoarseness in two patients, dyspnea during sleep in two patients, and sialorrhoea in one patient. However, these events were tolerable or could be controlled by the adjustment of output currents. In one patient, wound revision was required. CONCLUSION: Our data supports the role of VNS as an alternative therapy for pediatric intractable epilepsy.

19. **Benifla M, Rutka JT, Logan W, Donner EJ. Vagal nerve stimulation for refractory epilepsy in children: indications and experience at The Hospital for Sick Children. *Childs Nerv Syst.* 2006;22(8):1018-26.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16816981>  
<http://link.springer.com/article/10.1007%2Fs00381-006-0123-6>  
**Abstract** OBJECTIVES: The management of intractable epilepsy in children is a challenging problem. For those patients who do not respond to antiepileptic drugs and are not candidates for epilepsy surgery, vagal nerve stimulation (VNS), can be a viable alternative for reducing seizure frequency. We have reviewed the historical and clinical background of VNS treatment. We also include our experience at The Hospital for Sick Children in children who underwent VNS implantation. METHODS: Forty-one children underwent VNS implantation for epilepsy over 6 years. After a mean follow-up of 31 months, 15 (38%) patients had a seizure frequency reduction of more than 90%. Fifteen (38%) children failed to respond to the VNS treatment. The device was removed in five children: in one, due to late infection; the other four could not tolerate the side effects of chronic VNS therapy. Two patients required reimplantation due to electrode failure. The most common side effects in our series were cough and vocal disturbances. CONCLUSIONS: Our results show that VNS implantation can be a safe and effective alternative therapy for children with drug-resistant epilepsy who are not candidates for epilepsy surgery.
20. **Blount JP, Tubbs RS, Kankirawatana P, Kiel S, Knowlton R, Grabb PA, et al. Vagus nerve stimulation in children less than 5 years old. *Childs Nerv Syst.* 2006;22(9):1167-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16718501>  
<http://link.springer.com/article/10.1007%2Fs00381-006-0104-9>  
**Abstract** INTRODUCTION: Vagus nerve stimulation (VNS) has been used in both adults and older children with varying success. MATERIALS AND METHODS: We retrospectively reviewed our experience with VNS in very young children (below 5 years old). The mean age at stimulator implantation was 20.5 months. Two patients were below 2 years old at implantation and two patients were below 1 year old at their initial surgery. The average follow up time for this group was 22 months. RESULTS: Of the six patients (three males and three females) with long-term follow up, 83% had a significant decrease in the frequency of their seizure. Of these, two are seizure-free (33%), three are improved (50%), and one (17%) has had no change in seizure status at their most recent clinical examination. Age at implantation of the vagus nerve stimulator did not seem to correlate with patient success. In this group, atonic seizures were found to best respond to VNS with cessation of this type of seizure in two patients. No patients were made worse by the procedure and no morbidity was observed related to VNS. CONCLUSIONS: Based on our small patient cohort, it appears that VNS in very young children with life-threatening epilepsy can be efficacious. Larger groups and other institutional experiences are now needed to verify our findings.
21. **Saneto RP, Sotero de Menezes MA, Ojemann JG, Bournival BD, Murphy PJ, Cook WB, et al. Vagus nerve stimulation for intractable seizures in children. *Pediatr Neurol.* 2006;35(5):323-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17074602>  
**Abstract** Forty-three children less than 12 years of age having intractable seizures were treated with vagus nerve stimulation. Five children were monitored for <12 months, 16 children for 12 to 17 months, and 22 children for > or =18 months with overall median seizure reduction of 55%. Thirty-seven percent had at least 90% reduction. Vagus nerve stimulation was effective in children with generalized, mixed, and partial medically refractory seizures.

22. **Alexopoulos AV, Kotagal P, Loddenkemper T, Hammel J, Bingaman WE. Long-term results with vagus nerve stimulation in children with pharmaco-resistant epilepsy. *Seizure*. 2006;15(7):491-503.**

<http://www.ncbi.nlm.nih.gov/pubmed/16859931>

**Abstract** PURPOSE: To retrospectively review our experience with VNS in pediatric patients with pharmaco-resistant epilepsy and examine the seizure-frequency outcome and rates of discontinuation in two age groups: adolescent and pre-adolescent children. RESULTS: Complete pre- and post-VNS data were available for 46/49 patients. Median age at implantation was 12.1 (range 2.3-17.9) and median duration of epilepsy 8.0 (1.9-16.9) years. Twenty-one patients (45.6%) were under 12 years at the time of surgery. Median follow-up was 2 years; follow-up exceeded 4 years in 9/46 patients. As compared to baseline, median seizure-frequency reduction in the setting of declining numbers was 56% at 3 months, 50% at 6, 63% at 12, 83% at 24 and 74% at 36 months. When a last observation carried forward analysis was employed median seizure-frequency reduction in the range of 60% was observed at 1, 2 and 3 years post-VNS. Twenty patients (43.5%) had >75% seizure-frequency reduction. No response (increase or <50% reduction) was observed in 19/46 (41.3%). Five patients (10.1%) were seizure-free for more than 6 months by their last follow-up. There was no difference in the number of AEDs used before and after VNS. The long-term discontinuation rate was 21.7% and reflected a lack of clinical response or infection. CONCLUSIONS: In this series VNS was well-tolerated and effective as add-on therapy for refractory seizures in children of all ages. Response was even more favorable in the younger group (<12 years at implantation). Infection and lack of efficacy were the most common reasons for discontinuation of long-term VNS therapy in this group.

23. **Bremer A, Eriksson AS, Roste GK, Knudtzen B, Nakken KO. [Vagal nerve stimulation in children with drug-resistant epilepsy]. *Tidsskr Nor Laegeforen*. 2006;126(7):896-8. Norwegian.**

<http://www.ncbi.nlm.nih.gov/pubmed/16554878>

**Abstract** BACKGROUND: To evaluate the clinical efficacy and side effects of vagal nerve stimulation (VNS) in Norwegian children with difficult-to-treat epilepsy. MATERIAL AND METHODS: We have performed an open retrospective study of 60 children with pharmaco-resistant epilepsy who had a VNS implantation between October 1996 and May 2003. The effects and side effects of VNS were evaluated on the basis of the medical records and a questionnaire filled in by the patients and/or their relatives. RESULTS: Forty-six patients (77%), 25 females and 21 males, aged 4-16 years at the time of implantation, filled in the questionnaire. All patients had tried > or = 6 antiepileptic drugs prior to the implantation. Five of them had undergone resective epilepsy surgery. After a mean of 2.5 years of follow up, 33 patients (72 %) reported positive effects of VNS. Twenty-nine patients (63%) reported decreased seizure frequency and/or less severe seizures, 20 (43%) achieved > or = 50 % seizure reduction, but only two became seizure free. Sixteen (35%) experienced a shorter and milder postictal phase. In 10 patients (22%) the need of diazepam treatment to terminate seizures was considerably reduced. Twenty-eight of the children (61%) experienced a positive effect of magnet activation. Twenty-three patients (50%) reported minor and waning side effects. Because most of the patients (32) had their antiepileptic medication changed after the implantation, the results should be interpreted with caution. CONCLUSIONS: A majority of the patients (72%) reported positive effects on seizure frequency and/or epilepsy-related symptoms. The side effects were modest. Our findings support previous reports about VNS being an effective additional treatment in children with refractory epilepsy.

24. **Hallbook T, Lundgren J, Blennow G, Stromblad LG, Rosen I. Long term effects on epileptiform activity with vagus nerve stimulation in children. *Seizure*. 2005;14(8):527-33.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16098769>  
[http://ac.els-cdn.com/S1059131105001238/1-s2.0-S1059131105001238-main.pdf?\\_tid=54b2c080-8cc4-11e2-bf77-00000aab0f6c&acdnat=1363278743\\_600d3a48566d19d5d6a072b8a50ae0c8](http://ac.els-cdn.com/S1059131105001238/1-s2.0-S1059131105001238-main.pdf?_tid=54b2c080-8cc4-11e2-bf77-00000aab0f6c&acdnat=1363278743_600d3a48566d19d5d6a072b8a50ae0c8)  
**Abstract** PURPOSE: We report long-term effects of vagus nerve stimulation (VNS) on epileptiform activity in 15 children, and how these changes are related to activity stage and to clinical effects on seizure reduction, seizure severity (NHS3) and quality of life (QOL). METHODS: Initially, and after 3 and 9 months of VNS-treatment, 15 children were investigated with 24 h ambulatory EEG monitoring for spike detection. The number of interictal epileptiform discharges (IEDs) and the inter spike intervals (ISIs) were analysed during 2 h in the awake state, and 1h of rapid eye movement (REM)-, spindle- and delta-sleep, respectively. Total number and duration of electrographic seizure episodes were also analysed. RESULTS: At 9 months the total number of IEDs was significantly reduced ( $p=0.04$ ). There was a tendency of reduction in all activity stages, and significantly so in delta-sleep ( $p=0.008$ ). Total electrographic seizure number was significantly reduced in the 24 h EEG at 3 and 9 months ( $p=0.03$ ,  $0.05$ ). There was a significant concordance in direction of changes in epileptiform activity and electrographic seizures at 9 months ( $p=0.04$ ). Concordance in direction of changes was seen in 9 of 15 children between clinical seizures and IED ( $p>0.3$ ), in 10 of 15 children between QOL and IED ( $p=0.3$ ) and in 8 of 15 children between NHS3 and IED ( $p>0.3$ ). There was no direct correlation between the extent of improvement in these clinical data and the degree of spike reduction. CONCLUSION: This study shows that VNS reduces IEDs especially in REM and delta sleep, as well as the number of electrographic seizures. It also shows a concordance between reduction in IEDs and electrographic seizures.
25. **Buoni S, Mariottini A, Pieri S, Zalaffi A, Farnetani MA, Strambi M, et al. Vagus nerve stimulation for drug-resistant epilepsy in children and young adults. *Brain Dev*. 2004;26(3):158-63.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15030903>  
**Abstract** We present our experience with the use of intermittent vagal nerve stimulation in 13 patients with medically intractable epilepsy. A surgical approach, with the exception of callosotomy, was impossible. The age range was 6-28 years (median 17 years). In all patients the epilepsy was severe and in six of them was symptomatic. Seven patients had Lennox-Gastaut syndrome, one epilepsy with myoclonic-astatic seizures, four localization-related and one symptomatic generalized epilepsy. The length of the follow-up averaged 22 months (range 8 months-3 years). Of the 13 patients, five (38.4%) had a 50% or more reduction in the number of seizures compared with preimplantation. Of these patients, one with a localization-related epilepsy had a 90% reduction as well as a significant improvement in alertness. Three patients showed no improvement with regard to the number of seizures but there was an improvement in alertness and, in one case in hyperactivity. Some seizure types responded better than others did: complex partial seizures with secondary generalization and atonic seizures. All our responsive patients improved in the first 2 months of VNS activation and only one case with further improvement was observed after this period. Considering the severity of the epilepsy the results can be considered satisfactory. We think that this treatment appears to be a safe adjunctive therapy for children and adults with medically and surgically intractable epilepsy.

26. **Murphy JV, Torkelson R, Dowler I, Simon S, Hudson S. Vagal nerve stimulation in refractory epilepsy: the first 100 patients receiving vagal nerve stimulation at a pediatric epilepsy center. *Arch Pediatr Adolesc Med.* 2003;157(6):560-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12796236>  
[http://archpedi.jamanetwork.com/data/Journals/PEDS/11795/poa20261\\_560\\_564.pdf](http://archpedi.jamanetwork.com/data/Journals/PEDS/11795/poa20261_560_564.pdf)  
**Notes** This paper is one of only two reports on the outcome of VNS Therapy among pediatric patients (mean age, 10.4 years) treated at a single center (Children's Mercy Hospital, Kansas City, MO). The study compares the treatment's effectiveness between age groups and with the magnet and includes accounts of the 24 patients who discontinued VNS Therapy as well as the outcomes of patients with previous epilepsy surgeries. Experience with rapid cycling and device end of service also is discussed. Adverse effects were few, particularly among patients aged younger than 12 years. AEDs were not significantly reduced. The authors conclude that "VNS Therapy appears to be a relatively safe and potentially effective treatment for children with severely intractable epilepsy."  
**Abstract** **OBJECTIVE:** To determine the outcome of intermittent left vagal nerve stimulation on the first 100 consecutive patients treated at our pediatric epilepsy center. **METHODS:** Patients were identified by means of operating room records. Data collected described the patient's epilepsy, previous and subsequent therapies, adverse events, nonepileptic changes, and outcomes. **RESULTS:** Average age was 10.4 years; years of epilepsy, 8.5; total number of antiepileptic therapies, 8.4; and median monthly seizure frequency, 120. Data on seizure frequency at follow-up were available for 96 of the 100 patients. Forty-five percent of patients achieved greater than 50% reduction; and 18% had had no seizures for the last 6 months. Response was similar in patients with more than 7 years of refractory epilepsy as compared with patients with a shorter history. Magnet-generated, on-demand current reduced seizure intensity in almost half of the patients with available data. Generator infections occurred in 3 patients. Twenty-four patients had their generators removed. Subsequently, 2 of these patients died. **CONCLUSIONS:** Seizure reduction was the same in patients younger than 12 years and 12 years or older and in patients with shorter and longer histories of refractory epilepsy. Adverse effects were few in this population, particularly in those younger than 12 years. Vagal nerve stimulation appears to be a relatively safe and potentially effective treatment for children with severely intractable epilepsy.
27. **Nagarajan L, Walsh P, Gregory P, Lee M. VNS therapy in clinical practice in children with refractory epilepsy. *Acta Neurol Scand.* 2002;105(1):13-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11903103>  
<http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0404.2002.00129.x/abstract>  
**Abstract** **OBJECTIVES:** To study the efficacy, tolerability and safety of the vagus nerve stimulation (VNS) therapy in clinical practice, in 16 children and adolescents with refractory epilepsy. **METHODOLOGY:** We assessed the efficacy of VNS therapy, retrospectively by comparing seizure frequency, duration and severity at the time of most recent follow up (av: 24.9 months) to that in the 4 weeks prior to VNS surgery. Changes in quality of life, sleep and behaviour at last review was compared with that prior to VNS. Adverse effects elicited by specific questioning, spontaneous reporting and clinical examination are described. **RESULTS:** Vagus nerve stimulation resulted in a >50% reduction in seizure frequency in 62.5% of children with 25% achieving a >90% reduction. Vagus nerve stimulation was well tolerated in all but one of our cohort, with no serious side-effects. **CONCLUSION:** Our results support its role as one of the options in intractable childhood epilepsy.

28. **Zamponi N, Rychlicki F, Cardinali C, Luchetti A, Trignani R, Ducati A. Intermittent vagal nerve stimulation in paediatric patients: 1-year follow-up. *Childs Nerv Syst.* 2002;18(1-2):61-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11935246>  
<http://link.springer.com/article/10.1007%2Fs00381-001-0548-x>  
**Abstract** OBJECT: Vagal nerve stimulation (VNS) has recently been proposed as a valid treatment for adult patients with drug-resistant partial epilepsy. Little experience in children has been reported. In order to evaluate the clinical efficacy and tolerance of VNS, we studied 13 paediatric patients with drug-resistant partial epilepsy. METHODS: Improvement in seizure frequency was estimated by calculating the percentage of change in seizure frequency during each 3-month period following initiation of VNS, compared with the 3-month period prior to the implantation of the VNS device. The improvement in quality of life (QOL) was evaluated with the Vineland Behavior Adaptive Scale (VBAS). RESULTS: In all patients, the surgical procedure was well tolerated. A recent modification of the implantation technique needing only a single cervical incision, has further reduced the aesthetic damage, particularly in small children who have a reduced muscular mass. Three months after the surgical procedure, 10 of the 13 patients demonstrated a seizure reduction rate greater than 50%. At the 1-year follow-up these positive results were maintained: 6 out of 8 patients continued to demonstrate a seizure reduction rate greater than 50%. Comparison with the pre-implantation period also showed a significant improvement in QOL in 4 out of 8 patients. We conclude that VNS is a valid treatment modality in children with drug-resistant partial epilepsy.
29. **Farooqui S, Boswell W, Hemphill JM, Pearlman E. Vagus nerve stimulation in pediatric patients with intractable epilepsy: case series and operative technique. *Am Surg.* 2001;67(2):119-21.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11243532>  
**Abstract** Patients with epilepsy refractory to medical therapy or who experience intolerable side effects from the medication may benefit from placement and activation of a vagus nerve stimulator (VNS) (Cyberonics, Houston, TX). We present our experience with the VNS implanted by a pediatric surgeon and its activation managed by a pediatric neurologist. Six patients (one male and five females) with average age 11 years, 10 months (range 7 years, 4 months to 18 years, 1 month) received VNS implants at a community-based teaching hospital. One patient developed a self-inflicted wound complication secondary to persistent trauma at the implant site that led to removal of the implant. Before VNS implantation the frequency of seizures among the remaining five patients averaged 73 per patient per month (range 20-165). Length of follow-up averaged 6.5 months (range 1.5-11 months). At most recent follow-up seizure frequency averaged 14 per month (range 1-42); this represents an average reduction of 78 per cent (range 30-99%). We conclude that a pediatric surgeon with pediatric neurologic support can safely and effectively perform the VNS implantation at a hospital equipped to administer anesthesia to pediatric patients.
30. **Helmers SL, Wheless JW, Frost M, Gates J, Levisohn P, Tardo C, et al. Vagus nerve stimulation therapy in pediatric patients with refractory epilepsy: retrospective study. *J Child Neurol.* 2001;16(11):843-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11732771>  
**Abstract** This six-center, retrospective study evaluated the effectiveness, tolerability, and safety of vagus nerve stimulation in children. Data were available for 125 patients at baseline, 95 patients at 3 months, 56 patients at 6 months, and 12 patients at 12 months. The typical patient, aged 12 years, had onset of seizures at age 2 years and had tried nine anticonvulsants before implantation. Collected data included preimplant history, seizures, implant, device settings, quality of life, and adverse events. Average seizure reduction was 36.1% at 3 months and 44.7% at 6 months. Common adverse events included voice alteration and coughing during stimulation. Rare adverse events, unique to this age group, included increased drooling and increased hyperactivity. Quality of life improved in alertness, verbal communication, school performance, clustering of seizures, and postictal periods. We concluded that vagus nerve stimulation is an effective treatment for medically refractory epilepsy in children.

31. **Wakai S, Kotagal P. Vagus nerve stimulation for children and adolescents with intractable epilepsies.**

*Pediatr Int.* 2001;43(1):61-5.

<http://www.ncbi.nlm.nih.gov/pubmed/11208002>

<http://onlinelibrary.wiley.com/doi/10.1046/j.1442-200x.2001.01326.x/abstract>

**Abstract** BACKGROUND: Vagus nerve stimulation (VNS) has been shown to be efficacious in the treatment of patients > 12 years of age with refractory partial epilepsies and it is suggested that VNS should be considered as one of the treatment options for these patients. METHODS: Four patients had partial epilepsies and one had symptomatic generalized epilepsy. After observation of the baseline seizure frequency and the average seizure frequency for 3 months, the VNS system was implanted. Thereafter, seizure frequency, average seizure frequency of each seizure type during the month just before the evaluation, seizure severity, side effects and quality of life were recorded. RESULTS: In four of five patients, overall seizure frequency was reduced > 50% after VNS treatment. The seizure types that showed a > 50% reduction in frequency were auras, focal clonic, generalized tonic clonic seizures, astatic, versive, hypomotor, generalized tonic and generalized clonic seizures according to Luders' classification. In two patients, as major convulsive seizures were reduced in number after VNS treatment, dialeptic seizures (non-convulsive seizure with lapse of consciousness) gradually appeared. In one patient without significant seizure reduction, quick recovery from postictal periods after generalized tonic seizure was seen after treatment. In one patient with generalized epilepsy, improvement of cognitive function was reported by his guardians. After VNS, the number of antiepileptic drugs was reduced from three to one in one patient. No significant adverse effects were noted in any patients. CONCLUSIONS: Our results suggest that VNS is well tolerated in young patients with intractable epilepsies and it may be an important non-pharmacologic treatment option for children with severe epilepsies who cannot tolerate medical therapy and/or are not candidates for epilepsy surgery.

32. **Patwardhan RV, Stong B, Bebin EM, Mathisen J, Grabb PA. Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. *Neurosurgery.* 2000;47(6):1353-7; discussion 1357-8.**

<http://www.ncbi.nlm.nih.gov/pubmed/11126906>

**Abstract** OBJECTIVE: The effects of vagal nerve stimulation (VNS) on seizure frequency and quality of life were analyzed retrospectively in children with medically refractory epilepsy. METHODS: Thirty-eight children aged 11 months to 16 years underwent implantation of vagal nerve stimulators. Age of seizure onset, duration of epilepsy, and seizure type and frequency were recorded preoperatively. Age at implantation, length of follow-up, seizure type and frequency, and change in quality of life (QOL) were recorded postoperatively. Changes in QOL were assigned a QOL score by the caretakers on a visual analog scale of -1 (much worse) to +1 (much improved). RESULTS: The median follow-up period was 12 months (range, 10-18 mo). Eleven (29%), 15 (39%), 5 (13%), and 7 (18%) children had greater than 90% reduction, 50 to 90% reduction, less than 50% reduction, and no reduction in seizure frequency, respectively. For all children, seizure reduction by seizure type was as follows: atonic (80%), absence (65%), complex partial (48%), and generalized tonicoclonic (45%). The mean change in QOL score was 0.61. Eighty-six percent of the children had QOL scores of 0.5 (improved) or higher. Follow-up of at least 6 months was associated with greater seizure reduction ( $P = 0.05$ ) and higher QOL score ( $P < 0.01$ ). Seizure reduction was greater in children with onset of epilepsy after 1 year of age ( $P < 0.05$ ). The age of the child and duration of epilepsy were not associated with greater or lesser degrees of seizure reduction. CONCLUSION: VNS provided improvements in seizure control for the majority of children regardless of age. QOL was improved in the majority of children with VNS. VNS should be considered for children with medically refractory epilepsy who have no surgically resectable focus.

33. **Lundgren J, Amark P, Blennow G, Stromblad LG, Wallstedt L. Vagus nerve stimulation in 16 children with refractory epilepsy. *Epilepsia*. 1998;39(8):809-13.**

<http://www.ncbi.nlm.nih.gov/pubmed/9701369>

**Abstract** PURPOSE: Vagus nerve stimulation (VNS) has been reported to produce >90% reduction in the number of seizures in children with intractable epilepsy. These encouraging results need confirmation. METHODS: Sixteen children, 10 boys and 6 girls aged 4-19 years, were treated with VNS (Cyberonics, Webster, TX, U.S.A.) for 12-24 months. Seizure frequency, seizure severity, changes in quality of life (QOL: visual analogue scale), and side effects were recorded. Eight children had partial and 8 had generalized seizures; 4 of the latter had Lennox-Gastaut syndrome (LGS). RESULTS: During the tenth to twelfth month of VNS, 6 of 16 children experienced > or =50% reduction in seizure frequency. One girl became seizure-free. Seizure severity showed an average decrease in the score from 15 to 11. After 10 months of treatment, QOL was estimated to have improved > or =50% in 6 of 16 children. Reduction in seizure frequency, decreased seizure severity, and reported improvement in QOL did not entirely coincide. Six children experienced hoarseness, 1 had neck pain, 2 had hypersalivation, 2 experienced tiredness, 2 had aspiration episodes during liquid intake, and 6 had electrical transmission problems; in 4 the problem has been surgically corrected. Five stimulators were turned off due to lack of efficacy. CONCLUSIONS: Six of 16 children with refractory epilepsy treated with VNS improved, with a reduction not only in seizure frequency but also in seizure severity and in QOL.

34. **Hornig GW, Murphy JV, Schallert G, Tilton C. Left vagus nerve stimulation in children with refractory epilepsy: an update. *South Med J*. 1997;90(5):484-8.**

<http://www.ncbi.nlm.nih.gov/pubmed/9160063>

**Abstract** This report updates previous reports regarding the tolerance and efficacy of periodic vagus nerve stimulation in a group of 19 children with medically and surgically intractable epilepsy. After vagal stimulator implantation, follow-up continued from 2 months to 30 months, with the study period ending in October 1995. Of the 19 patients, 6 (32%) had more than a 90% reduction in the number of monthly seizures, and 10 (53%) had more than a 50% reduction. Global evaluation scores indicated that only 1 patient had deterioration from baseline, 5 had no change, and the remainder had modest to remarkable improvement. All 3 children with unsuccessful corpuscallosotomy had improvement after implantation of the stimulator, and 5 of 6 children with Lennox-Gastaut syndrome had a 90% reduction of seizures. Five patients required fewer antiepileptic medications, and 1 patient had an increase in medication. Adversities included 2 possible wound infections, 1 instance of generator failure, and hoarseness during stimulation in all patients. Changing stimulation parameters to increase the rate of stimulation and reduce the interval between stimulations resulted in improved seizure control in 4 of 5 patients. Periodic VNS was well tolerated by these children and may have a role in the management of refractory epilepsy.

**Pediatric Population - Review Articles, VNS in Epilepsy**

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1. **Hauptman JS, Mathern GW. Vagal nerve stimulation for pharmacoresistant epilepsy in children. *Surg Neurol Int.* 2012;3(Suppl 4):S269-74.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23230532>  
<http://www.surgicalneurologyint.com/article.asp?issn=2152-7806;year=2012;volume=3;issue=5;spage=269;epage=274;aulast=Hauptman>  
**Abstract** Vagus nerve stimulation (VNS) is an adjunctive treatment for adult patients with pharmacoresistant epilepsy. Little is known about VNS therapy for children with epilepsy. This article will: (1) Review the contemporary medical literature related to VNS therapy in children with epilepsy, (2) describe the experience of VNS treatment in 153 children less than 18 years of age, in the University of California, Los Angeles (UCLA) Pediatric Epilepsy Surgery Program, from 1998 to 2012, and (3) describe the surgical technique used for VNS implantation at UCLA. Review of the literature finds that despite different etiologies and epilepsy syndromes in children, VNS appears to show a similar profile of efficacy for seizure control compared to adults, and low morbidity and mortality. The UCLA experience is similar to that reported in the literature for children. VNS constitutes about 21% of our pediatric epilepsy surgery volume. We have implanted VNS in infants as young as six months of age and the most common etiology is the Lennox-Gastaut Syndrome. About 5% of the patients are seizure-free with VNS therapy and there is a low rate of surgically related complications. The UCLA surgical approach emphasizes minimal direct manipulation of the vagus nerve and adequate wire loops, to prevent a lead fracture. In summary, VNS is a viable palliative treatment for medically refractory epilepsy in children, with outcomes and complications equal to adult patients. Being a small child is not a contraindication for VNS therapy, if needed for refractory epilepsy.
2. **Heyman E, Lahat E, Lotan G. [Vagal nerve stimulation for refractory epilepsy in children]. *Harefuah.* 2008;147(2):136-8, 182. Hebrew.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18357671>  
**Abstract** Epileptic disease is defined as recurrent seizures not as a result of fever or acute cerebral insult. It is very common in all age groups. In the majority of cases, satisfactory control is being achieved, leading to normal life. However, in some cases, the disease is resistant to a variety of medications. In these cases, an attempt to decrease the number of epileptic episodes is done by trying other methods such as a ketogenic diet or neurosurgical interventions. Recently, a new modality of treatment with vagal nerve stimulation was introduced, particularly for cases resistant to medications and are not candidates for neurosurgical intervention.
3. **Wheless JW, Maggio V. Vagus nerve stimulation therapy in patients younger than 18 years. *Neurology.* 2002;59(6 Suppl 4):S21-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12270964>  
**Abstract** Nonpharmacologic treatment options are effective in reducing seizures and improving quality of life without the negative side effects associated with antiepileptic drug (AED) therapy among pediatric epilepsy patients. One such treatment, vagus nerve stimulation (VNS) therapy, appears to be particularly effective among pediatric patients with refractory seizures. Seizure severity and frequency, as well as quality of life, are improved with VNS therapy.

4. **Valencia I, Holder DL, Helmers SL, Madsen JR, Riviello JJ, Jr. Vagus nerve stimulation in pediatric epilepsy: a review. *Pediatr Neurol.* 2001;25(5):368-76.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11744311>  
**Abstract** Therapeutic options for intractable epilepsy include new and investigational antiepileptic drugs, ketogenic diet, epilepsy surgery, and, now, vagus nerve stimulation, which is approved by the U.S. Food and Drug Administration for the treatment of refractory partial seizures in adolescents and adults. The exact mechanisms of action are unknown. Although the use of vagus nerve stimulation in children has increased, including those younger than 12 years of age or those with generalized epilepsy, there has been no large controlled pediatric study to date. The identification of favorable prognostic indicators, especially in children, would be useful. Preliminary results suggest that children with Lennox-Gastaut syndrome may have a favorable response, with improvement in both seizure control and global evaluation scores. Improved global evaluation scores have occurred even without an associated improvement in seizure control.
5. **Amar AP, Levy ML, McComb JG, Apuzzo ML. Vagus nerve stimulation for control of intractable seizures in childhood. *Pediatr Neurosurg.* 2001;34(4):218-23.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11359116>  
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**Abstract** Vagus nerve stimulation (VNS) is gaining increasing popularity and credibility as a treatment option for children with intractable epilepsy. VNS offers several advantages over extant treatments. Its efficacy is maintained during prolonged stimulation, and seizure control actually improves with time. There is no associated cognitive impairment and no adverse drug interactions. Unlike cerebral surgery, VNS is a potentially reversible form of therapy. The computer-controlled characteristic of the device permits complete and involuntary treatment compliance. VNS is safe and well-tolerated. Its side effects are generally transient and mild, and no physiologic perturbations have been reported despite extensive monitoring. Serious adverse events are rare, and no deaths have been attributed to VNS therapy itself or to the technique of surgical insertion. In this article, we discuss the theoretical background behind VNS and review the clinical studies that substantiate its long-term safety, feasibility, tolerability and potential efficacy in children with refractory epilepsy.
6. **Labar D. Vagal nerve stimulation for intractable epilepsy in children. *Dev Med Child Neurol.* 2000;42(7):496-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10972424>  
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7. **Crumrine PK. Vagal nerve stimulation in children. *Semin Pediatr Neurol.* 2000;7(3):216-23.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11023179>  
**Abstract** Vagal nerve stimulation is a new therapeutic option for patients with medically refractory epilepsy. The FDA approved the NeuroCybernetic Prosthesis (NCP) in July 1997 for use in adults and adolescents over the age of 12 years with medically refractory epilepsy. Most of the patients in the initial pilot studies and subsequent extended longitudinal and randomized controlled studies were adults. There were small numbers of children who received the NCP system. However, these were not part of controlled studies. As the system has had greater exposure in the United States and Europe, there are more children who are receiving vagal nerve stimulation (VNS). Initial data from open-label, uncontrolled studies suggest that VNS does have some efficacy and safety for those children with refractory epilepsy who have not responded to appropriate trials of antiepileptic drugs. The questions to be asked and answered are as follows: (1) When is a child medically refractory? (2) What are the criteria for selection for VNS? (3) Which seizure types or syndromes will benefit most from the treatment? and (4) What are the most effective and safe stimulation parameters, and do these vary depending on the seizure type?

**Pediatric Population - VNS Efficacy in Epilepsy**

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- 1. Gyires K, Nemeth J, Zadori ZS. Gastric mucosal protection and central nervous system. *Curr Pharm Des.* 2013;19(1):34-9.**  
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**Abstract** Several human and experimental data suggest the particular importance of gastric protective processes in maintaining mucosal integrity. Both peripheral and central mechanisms are involved in this process. In the periphery, pre-epithelial mucus-bicarbonate layer, mucus, phospholipids, trefoil peptides, prostaglandins, heat shock proteins, sensory neuropeptides, nitric oxide, and hydrogen sulfide may mediate mucosal protection. In the central nervous system hypothalamus and dorsal vagal complex (DVC) have particular important role in the regulation of centrally-induced gastroprotection. Stimulation of paraventricular nuclei either aggravates or inhibits the mucosal injury depending on the ulcer model. Vagal nerve also has a dual role, its activation can induce mucosal injury (by high dose of thyrotropin-releasing hormone (TRH), electrical stimulation), however, integrity of vagal nerve is necessary for gastroprotection induced either peripherally (by PGE2, prostacyclin, adaptive cytoprotection), or centrally (e.g. by neuropeptides). The centrally induced gastroprotection is likely to be vagal dependent, though vagal independent pathways have also been shown. Endomorphin-1 and endomorphin-2, selective mu-opioid receptor ligands, proved to be highly potent and effective gastroprotective agents in ethanol ulcer model (0.03-3 pmol intracerebroventricularly). Inhibition of the degradation of endomorphins by diprotin A resulted in gastroprotective effect, indicating the potential role of these endogenous opioids in the regulation of gastric mucosal integrity. Endomorphin-2 injected intracerebroventricularly restored the reduced levels of CGRP and somatostatin in gastric mucosa induced by ethanol. In conclusion, neuropeptides expressed in dorsal vagal complex and hypothalamus may have a regulatory role in maintaining gastric mucosal integrity by stimulating the formation of mucosal protective compounds.
  
- 2. Engineer ND, Moller AR, Kilgard MP. Directing neural plasticity to understand and treat tinnitus. *Hear Res.* 2013;295:58-66.**  
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**Abstract** The functional organization of cortical and subcortical networks can be altered by sensory experience. Sensory deprivation destabilizes neural networks resulting in increased excitability, greater neural synchronization and increased spontaneous firing in cortical and subcortical neurons. This pathological activity is thought to generate the phantom percept of chronic tinnitus. While sound masking, pharmacotherapy and cortical stimulation can temporarily suppress tinnitus for some patients, these interventions do not eliminate the pathological activity that is responsible for tinnitus. A treatment that could reverse the underlying pathology would be expected to be effective in alleviating the symptoms, if not curative. Targeted neural plasticity can provide the specificity required to restore normal neural activity in dysfunctional neural circuits that are assumed to underlie many forms of tinnitus. The forebrain cholinergic system and the noradrenergic system play a significant role in modulating cortical plasticity. Stimulation of the vagus nerve is known to activate these neuromodulatory pathways. Our earlier studies have demonstrated that pairing sounds with either nucleus basalis of Meynert (NB) stimulation or vagus nerve stimulation (VNS) generates highly specific and long-lasting plasticity in auditory cortex neurons. Repeatedly pairing tones with brief pulses of VNS reversed the physiological and behavioral correlates of tinnitus in noise exposed rats. We also recently demonstrated that VNS modulates synchrony and excitability in the auditory cortex at least in part by activation of muscarinic acetylcholine receptors, suggesting that acetylcholine is involved in the mechanism of action of VNS. These results suggest that pairing sounds with VNS provides a new avenue of treatment for some forms of tinnitus. This paper discusses neuromodulation as treatment for tinnitus with a focus on the potential value of pairing VNS with sound stimulation as a treatment of chronic tinnitus.

3. **Miner JR, Lewis LM, Mosnaim GS, Varon J, Theodoro D, Hoffmann TJ. Feasibility of percutaneous vagus nerve stimulation for the treatment of acute asthma exacerbations. *Acad Emerg Med.* 2012;19(4):421-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22506946>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1553-2712.2012.01329.x/abstract>  
**Abstract** OBJECTIVES: This study assessed the feasibility of an investigational vagus nerve stimulation (VNS) device for treating acute asthma exacerbations in patients not responding to at least 1 hour of initial standard care therapy. METHODS: This was a prospective, nonrandomized study of patients treated in the ED for moderate to severe acute asthma (forced expiratory volume in 1 second [FEV(1)] 25% to 70% of predicted). Treatment entailed percutaneous placement of an electrode near the right carotid sheath and 60 minutes of VNS and continued standard care. VNS voltage was adjusted to perceived improvement, muscle twitching, or adverse events (AEs). All AEs, vital signs, FEV(1), perceived work of breathing (WOB), and final disposition were recorded. RESULTS: Twenty-five subjects were enrolled. There were no serious AEs and no significant changes in vital signs. No subject required terminating VNS. One patient had minor bleeding from the procedure, and one had a hematoma and withdrew prior to VNS. AEs related to VNS were temporary and included cough (1 of 24), swallowing difficulty (2 of 24), voice change (2 of 24), and muscle twitching (14 of 24). These resolved when VNS ended. The FEV(1) improved at 15 minutes (median = 15.8%, 95% confidence interval [CI] = 9.3% to 22.4%), 30 minutes (median = 21.3%, 95% CI = 8.1% to 36.5%), and 60 minutes (median = 27.5%, 95% CI = 11.3% to 43.5%). WOB improved at 15 minutes (median = 53.9%, 95% CI = 33.7% to 73.9%), 30 minutes (median = 69.1%, 95% CI = 56.4% to 81.8%), and 60 minutes (median = 81.0%, 95% CI = 68.5% to 93.5%). CONCLUSIONS: Percutaneous VNS did not result in serious AEs and was associated with improvements in FEV(1) and perceived dyspnea. Percutaneous VNS appears to be feasible for use in the treatment of moderate to severe acute asthma in patients unresponsive to initial standard care treatment.
4. **Porter BA, Khodaparast N, Fayyaz T, Cheung RJ, Ahmed SS, Vrana WA, et al. Repeatedly pairing vagus nerve stimulation with a movement reorganizes primary motor cortex. *Cereb Cortex.* 2012;22(10):2365-74.**  
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<http://cercor.oxfordjournals.org/content/22/10/2365.long>  
**Abstract** Although sensory and motor systems support different functions, both systems exhibit experience-dependent cortical plasticity under similar conditions. If mechanisms regulating cortical plasticity are common to sensory and motor cortices, then methods generating plasticity in sensory cortex should be effective in motor cortex. Repeatedly pairing a tone with a brief period of vagus nerve stimulation (VNS) increases the proportion of primary auditory cortex responding to the paired tone (Engineer ND, Riley JR, Seale JD, Vrana WA, Shetake J, Sudanagunta SP, Borland MS, Kilgard MP. 2011. Reversing pathological neural activity using targeted plasticity. *Nature.* 470:101-104). In this study, we predicted that repeatedly pairing VNS with a specific movement would result in an increased representation of that movement in primary motor cortex. To test this hypothesis, we paired VNS with movements of the distal or proximal forelimb in 2 groups of rats. After 5 days of VNS movement pairing, intracranial microstimulation was used to quantify the organization of primary motor cortex. Larger cortical areas were associated with movements paired with VNS. Rats receiving identical motor training without VNS pairing did not exhibit motor cortex map plasticity. These results suggest that pairing VNS with specific events may act as a general method for increasing cortical representations of those events. VNS movement pairing could provide a new approach for treating disorders associated with abnormal movement representations.

5. **Klinkenberg S, Aalbers MW, Vles JS, Cornips EM, Rijkers K, Leenen L, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. *Dev Med Child Neurol.* 2012;54(9):855-61; comment *Dev Med Child Neurol.* 2012;54(9):782-3; comment *Dev Med Child Neurol.* 2013;55(2):195; author reply *Dev Med Child Neurol.* 2013;55(2):195-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22540141>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8749.2012.04305.x/abstract>  
**Abstract** AIM: The aim of this study was to evaluate the effects of vagus nerve stimulation (VNS) in children with intractable epilepsy on seizure frequency and severity and in terms of tolerability and safety. METHOD: In this study, the first randomized active controlled trial of its kind in children, 41 children (23 males; 18 females; mean age at implantation 11y 2mo, SD 4y 2mo, range 3y 10mo-17y 8mo) were included. Thirty-five participants had localization-related epilepsy (25 symptomatic; 10 cryptogenic), while six participants had generalized epilepsy (four symptomatic; two idiopathic). During a baseline period of 12 weeks, seizure frequency and severity were recorded using seizure diaries and the adapted Chalfont Seizure Severity Scale (NHS3), after which the participants entered a blinded active controlled phase of 20 weeks. During this phase, half of the participants received high-output VNS (maximally 1.75mA) and the other half received low-output stimulation (0.25mA). Finally, all participants received high-output stimulation for 19 weeks. For both phases, seizure frequency and severity were assessed as during the baseline period. Overall satisfaction and adverse events were assessed by semi-structured interviews. RESULTS: At the end of the randomized controlled blinded phase, seizure frequency reduction of 50% or more occurred in 16% of the high-output stimulation group and in 21% of the low-output stimulation group (p=1.00). There was no significant difference in the decrease in seizure severity between participants in the stimulation groups. Overall, VNS reduced seizure frequency by 50% or more in 26% of participants at the end of the add-on phase. The overall seizure severity also improved (p<0.001). INTERPRETATION: VNS is a safe and well-tolerated adjunctive treatment of epilepsy in children. Our results suggest that the effect of VNS on seizure frequency in children is limited. However, the possible reduction in seizure severity and improvement in well-being makes this treatment worth considering in individual children with intractable epilepsy.
  
6. **Matteoli G, Boeckxstaens GE. The vagal innervation of the gut and immune homeostasis. *Gut.* 2012.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23023166>  
<http://gut.bmj.com/content/early/2012/09/28/gutjnl-2012-302550>  
**Abstract** The central nervous system interacts dynamically with the immune system to modulate inflammation through humoral and neural pathways. Recently, in animal models of sepsis, the vagus nerve (VN) has been proposed to play a crucial role in the regulation of the immune response, also referred to as the cholinergic anti-inflammatory pathway. The VN, through release of acetylcholine, dampens immune cell activation by interacting with alpha-7 nicotinic acetylcholine receptors. Recent evidence suggests that the vagal innervation of the gastrointestinal tract also plays a major role controlling intestinal immune activation. Indeed, VN electrical stimulation potently reduces intestinal inflammation restoring intestinal homeostasis, whereas vagotomy has the reverse effect. In this review, we will discuss the current understanding concerning the mechanisms and effects involved in the cholinergic anti-inflammatory pathway in the gastrointestinal tract. Deeper investigation on this counter-regulatory neuroimmune mechanism will provide new insights in the cross-talk between the nervous and immune system leading to the identification of new therapeutic targets to treat intestinal immune disease.

7. **Kox M, Vaneker M, van der Hoeven JG, Scheffer GJ, Hoedemaekers CW, Pickkers P. Effects of vagus nerve stimulation and vagotomy on systemic and pulmonary inflammation in a two-hit model in rats. *PLoS One*. 2012;7(4):e34431.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22493690>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3321011/pdf/pone.0034431.pdf>  
**Abstract** Pulmonary inflammation contributes to ventilator-induced lung injury. Sepsis-induced pulmonary inflammation (first hit) may be potentiated by mechanical ventilation (MV, second hit). Electrical stimulation of the vagus nerve has been shown to attenuate inflammation in various animal models through the cholinergic anti-inflammatory pathway. We determined the effects of vagotomy (VGX) and vagus nerve stimulation (VNS) on systemic and pulmonary inflammation in a two-hit model. Male Sprague-Dawley rats were i.v. administered lipopolysaccharide (LPS) and subsequently underwent VGX, VNS or a sham operation. 1 hour following LPS, MV with low (8 mL/kg) or moderate (15 mL/kg) tidal volumes was initiated, or animals were left breathing spontaneously (SP). After 4 hours of MV or SP, rats were sacrificed. Cytokine and blood gas analysis was performed. MV with 15, but not 8 mL/kg, potentiated the LPS-induced pulmonary pro-inflammatory cytokine response (TNF-alpha, IL-6, KC: p<0.05 compared to LPS-SP), but did not affect systemic inflammation or impair oxygenation. VGX enhanced the LPS-induced pulmonary, but not systemic pro-inflammatory cytokine response in spontaneously breathing, but not in MV animals (TNF-alpha, IL-6, KC: p<0.05 compared to SHAM), and resulted in decreased pO<sub>2</sub> (p<0.05 compared to sham-operated animals). VNS did not affect any of the studied parameters in both SP and MV animals. In conclusion, MV with moderate tidal volumes potentiates the pulmonary inflammatory response elicited by systemic LPS administration. No beneficial effects of vagus nerve stimulation performed following LPS administration were found. These results questions the clinical applicability of stimulation of the cholinergic anti-inflammatory pathway in systemically inflamed patients admitted to the ICU where MV is initiated.
8. **Jaseja H. Efficacy of vagal nerve stimulation in patients with cerebral palsy: emerging corroborative evidence. *Clin Neurol Neurosurg*. 2011;113(7):603.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21420784>
9. **Das UN. Vagus nerve stimulation as a strategy to prevent and manage metabolic syndrome. *Med Hypotheses*. 2011;76(3):429-33.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21144670>  
**Abstract** An increase in pro-inflammatory cytokines, decrease in endothelial nitric oxide (eNO) and adiponectin levels and an alteration in hypothalamic peptides and gastrointestinal hormones such as incretins and cholecystokinin that regulate satiety, hunger, and food intake occur in metabolic syndrome. Thus, metabolic syndrome is a low-grade systemic inflammatory condition and could be due to inappropriate cross-talk between the peripheral tissues and the hypothalamic centers implying that methods designed to restore these two abnormalities to normal could be of significant benefit in metabolic syndrome. Vagus nerve stimulation has been shown to suppress inflammation and acetylcholine, the principal vagal neurotransmitter, modulates the actions of several hypothalamic peptides and incretins and cholecystokinin. Based on these evidences, it is proposed that vagus nerve stimulation could be of significant benefit in the management of the metabolic syndrome.

10. **Liu H, Liu Y, Yu J, Lai M, Zhu H, Sun A, et al. Vagus nerve stimulation inhibits heroin-seeking behavior induced by heroin priming or heroin-associated cues in rats. *Neurosci Lett.* 2011;494(1):70-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21362452>  
**Abstract** Vagus nerve stimulation has been used for the treatment of neuropsychiatric disorders, such as epilepsy. However, little is known whether it is also effective for the treatment of heroin dependence, in particular for relapse to heroin seeking. In the present study, we investigated the effects of vagus nerve stimulation on reinstatement (relapse) of heroin-seeking behavior induced by heroin priming or heroin-associated cues. The rats were trained for heroin self-administration for 14 days and followed by extinction training in which heroin was replaced by saline and heroin-associated cues were turned off. In addition, animals were also received daily electric stimulation of vagus nerve (30Hz, pulse width of 0.5ms, 0.5mA (low-intensity) or 1mA (high-intensity); 30s on, 5min off; 10 continuous cycle per day) or false stimulation during extinction training. We found that such vagus nerve stimulation significantly inhibited heroin priming (0.25mg/kg, s.c.) - or heroin-associated conditioned cue-induced reinstatement of drug-seeking behavior, when compared to false stimulation control. Further, such a behavioral inhibition was correlated to a reduction in the expression of FosB and an increase in the expression of phosphorylation of cAMP response element binding protein (p-CREB) in nucleus accumbens. The data suggest that vagus nerve stimulation may inhibit heroin- or heroin cue-induced relapse, possibly by regulation of the expression of Fos and CREB in nucleus accumbens.
11. **Biermann T, Kreil S, Groemer TW, Maihofner C, Richter-Schmiedinger T, Kornhuber J, et al. Time perception in patients with major depressive disorder during vagus nerve stimulation. *Pharmacopsychiatry.* 2011;44(5):179-82.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21751128>  
**Abstract** BACKGROUND: Affective disorders may affect patients' time perception. Several studies have described time as a function of the frontal lobe. The activating effects of vagus nerve stimulation on the frontal lobe might also modulate time perception in patients with major depressive disorder (MDD). METHODS: Time perception was investigated in 30 patients with MDD and in 7 patients with therapy-resistant MDD. In these 7 patients, a VNS system was implanted and time perception was assessed before and during stimulation. A time estimation task in which patients were asked "How many seconds have passed?" tested time perception at 4 defined time points (34 s, 77 s, 192 s and 230 s). The differences between the estimated and actual durations were calculated and used for subsequent analysis. RESULTS: Patients with MDD and healthy controls estimated the set time points relatively accurately. A general linear model revealed a significant main effect of group but not of age or sex. The passing of time was perceived as significantly slower in patients undergoing VNS compared to patients with MDD at all time points (T34:  $t = -4.2$ ;  $df = 35$ ;  $p < 0.001$ ; T77:  $t = -4.8$ ;  $df = 35$ ;  $p < 0.001$ ; T192:  $t = -2.0$ ;  $df = 35$ ;  $p = 0.059$ ; T230  $t = -2.2$ ;  $df = 35$ ;  $p = 0.039$ ) as well as compared to healthy controls (at only T77:  $t = 4.1$ ;  $df = 35$ ;  $p < 0.001$ ). There were no differences in time perception with regard to age, sex or polarity of depression (uni- or bipolar). CONCLUSIONS: VNS is capable of changing the perception of time. This discovery furthers the basic research on circadian rhythms in patients with psychiatric disorders.
12. **Longatti P, Basaldella L, Moro M, Ciccarino P, Franzini A. Refractory central supratentorial hiccup partially relieved with vagus nerve stimulation. *J Neurol Neurosurg Psychiatry.* 2010;81(7):821-2.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20581144>  
<http://jnnp.bmj.com/content/81/7/821.long>

13. **Rossignol E, Lortie A, Thomas T, Bouthiller A, Scavarda D, Mercier C, et al. Vagus nerve stimulation in pediatric epileptic syndromes. *Seizure*. 2009;18(1):34-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18657451>  
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**Abstract** Vagal nerve stimulation (VNS) has shown promising results in various cohorts of non-surgical refractory epilepsy in adults and children. However studies report a significant delay between implantation and clinical response. We describe a cohort of 28 children and adolescents prospectively followed, classified by epileptic syndromes and treated with VNS using a 6-week rapid ramping protocol between January 2000 and March 2005. Our cohort showed favorable outcome within 6 months which was sustained at 24 months: 68% (19/28) showing  $\geq 50\%$  reduction in seizure frequency, including 14% (4/28) who became seizure-free. VNS was particularly efficacious in children with cryptogenic generalized and partial epilepsies. Although adverse events occurred in 68% (19/28) of patients, most were transient. In conclusion, rapid ramping is associated with an early and lasting response in most children but with a slightly higher side-effect rate.
14. **You SJ, Kang HC, Kim HD, Ko TS, Kim DS, Hwang YS, et al. Vagus nerve stimulation in intractable childhood epilepsy: a Korean multicenter experience. *J Korean Med Sci*. 2007;22(3):442-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17596651>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2693635/pdf/jkms-22-442.pdf>  
**Abstract** We evaluated the long-term outcome of vagus nerve stimulation (VNS) in 28 children with refractory epilepsy. Of these 28 children, 15 (53.6%) showed a  $>50\%$  reduction in seizure frequency and 9 (32.1%) had a  $>75\%$  reduction. When we compared seizure reduction rates according to seizure types (generalized vs. partial) and etiologies (symptomatic vs. cryptogenic), we found no significant differences. In addition, there was no correlation between the length of the stimulation period and treatment effect. The seizure reduction rate, however, tended to be inversely related to the seizure duration before VNS implantation and age at the time of VNS therapy. VNS also improved quality of life in this group of patients, including improved memory in 9 (32.1%), improved mood in 12 (42.9%), improved behavior in 11 (39.3%), improved alertness in 12 (42.9%), improved achievement in 6 (21.4%), and improved verbal skills in 8 (28.6%). Adverse events included hoarseness in 7 patients, dyspnea at sleep in 2 patients, and wound infection in 1 patient, but all were transient and successfully managed by careful follow-up and adjustment of parameters. These results indicate that VNS is a safe and effective alternative therapy for pediatric refractory epilepsy, without significant adverse events.

15. **Kuramoto H, Kadowaki M. Vagus nerve stimulation preferentially induces Fos expression in nitrergic neurons of rat esophagus. *Cell Tissue Res.* 2006;324(3):361-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16450125>  
<http://link.springer.com/article/10.1007%2Fs00441-005-0124-x>  
**Abstract** To identify neurochemical phenotypes of esophageal myenteric neurons synaptically activated by vagal preganglionic efferents, we immunohistochemically detected the expression of Fos, an immediate early gene product, in whole-mount preparations of the entire esophagus of rats following electrical stimulation of the vagus nerves. When electrical stimulation was applied to either the cervical left (LVN) or right vagus nerve (RVN), neurons with nuclei showing Fos immunoreactivity (IR) were found to comprise approximately 10% of the total myenteric neurons in the entire esophagus. These neurons increased from the oral toward the gastric end of the esophagus, with the highest frequency in the abdominal portion of the esophagus. A significant difference was not found in the number of Fos neurons between the LVN-stimulated and RVN-stimulated esophagus. Double-immunolabeling showed that nitric oxide synthase (NOS)-IR occurred in most (86% and 84% in the LVN-stimulated and RVN-stimulated esophagus, respectively) of the Fos neurons in the entire esophagus. Furthermore, the stimulation of either of the vagus nerves resulted in high proportions (71%-90%) of Fos neurons with NOS-IR, with respect to the total Fos neurons in each segment, in the entire esophagus. However, a small proportion (8% and 7% in the LVN-stimulated and RVN-stimulated esophagus, respectively) of the Fos neurons in the esophagus exhibited choline acetyltransferase (ChAT)-IR. The occurrence-frequency of Fos neurons with ChAT-IR was less than 4% of the total Fos neurons in any segment of the LVN-stimulated and RVN-stimulated esophagus. Some of the Fos neurons with ChAT-IR appeared to be innervated by numerous varicose ChAT-positive nerve terminals. The present results showing that electrical stimulation of the vagus nerves induces a high proportion of Fos neurons with NOS-IR suggests the preferential activation of NOS neurons in the esophagus by vagal preganglionic efferents. This connectivity between the vagal efferents and intrinsic nitrergic neurons might be involved in inhibitory actions on esophageal motility.
16. **Peitl B, Dobronte R, Nemeth J, Mezey G, Kovacs P, Paragh G, et al. The prandial insulin sensitivity-modifying effect of vagal stimulation in rats. *Metabolism.* 2005;54(5):579-83.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15877286>  
**Abstract** The effect of left cervical vagal nerve stimulation was studied on insulin sensitivity to test the proposed permissive insulin-sensitizing role of hepatic vagal parasympathetic efferent pathways in fasted and fed anesthetized rats. In fed animals, electrical stimulation (square impulses: 25 V, 5 Hz, 0.5 milliseconds over 15 minutes) of the vagal nerve induced hyperglycemia and an increase in plasma insulin immunoreactivity. Atropine (1.0 mg/kg intravenously) induced insulin resistance estimated by rapid insulin sensitivity testing. This was amplified when the vagal nerve was stimulated. The insulin-resistant state developed by fasting was not modified by either treatment with atropine or electrical stimulation. We conclude that both parasympathetic cholinergic and noncholinergic vagal efferents modulate postprandial neurogenic insulin sensitivity adjustments.

17. **Bentham L, Mundinger TO, Taborsky GJ, Jr. Parasympathetic inhibition of sympathetic neural activity to the pancreas. *Am J Physiol Endocrinol Metab.* 2001;280(2):E378-81.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11158944>  
**Abstract** The present study tested the hypothesis that activation of the parasympathetic nervous system could attenuate sympathetic activation to the pancreas. To test this hypothesis, we measured pancreatic norepinephrine (NE) spillover (PNESO) in anesthetized dogs during bilateral thoracic sympathetic nerve stimulation (SNS; 8 Hz, 1 ms, 10 mA, 10 min) with and without (randomized design) simultaneous bilateral cervical vagal nerve stimulation (VNS; 8 Hz, 1 ms, 10 mA, 10 min). During SNS alone, PNEO increased from the baseline of 431 +/- 88 pg/min to an average of 5,137 +/- 1,075 pg/min ( $P < 0.05$ ) over the stimulation period. Simultaneous SNS and VNS resulted in a significantly ( $P < 0.01$ ) decreased PNEO response [from 411 +/- 61 to an average of 2,760 +/- 1,005 pg/min ( $P < 0.05$ ) over the stimulation period], compared with SNS alone. Arterial NE levels increased during SNS alone from 130 +/- 11 to approximately 600 pg/ml ( $P < 0.05$ ); simultaneous SNS and VNS produced a significantly ( $P < 0.05$ ) smaller response (142 +/- 17 to 330 pg/ml). Muscarinic blockade could not prevent the effect of VNS from reducing the increase in PNEO or arterial NE in response to SNS. It is concluded that parasympathetic neural activity opposes sympathetic neural activity not only at the level of the islet but also at the level of the nerves. This neural inhibition is not mediated via muscarinic mechanisms.
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19. **Murphy JV. Left vagal nerve stimulation in children with medically refractory epilepsy. The Pediatric VNS Study Group. *J Pediatr.* 1999;134(5):563-6; comment 532-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10228290>  
**Notes** First major paper on 60 adolescent patients (<18 years of age, with 16 younger than 12 years of age) taken from all of the VNS clinical studies (E01-E05). VNS reported to be safe and effective among this population, with results similar to those seen in adult patients.  
**Abstract** **OBJECTIVE:** To assess the use of intermittent left vagal nerve stimulation in a large population of children with pharmacoresistant epilepsy. **STUDY DESIGN:** Sixty children who were entered into controlled or compassionate use protocols of left vagal nerve stimulation all had been monitored for at least 3 months after their left vagal nerve stimulators were activated. **RESULTS:** The age range was 3 to 18 years (median 15 years). Sixteen of these 60 patients were younger than 12 years. Fifty-seven percent of the patients had partial complex seizures, and generalized tonic clonic seizures occurred in 27%. After 3 months of intermittent stimulation of the left vagal nerve, a median reduction in seizure frequency of 23% occurred in 60 patients. At 6 months the median reduction was 31% in 55 patients, at 12 months 34% in 51 patients, and at 18 months 42% in 46 patients. Improvement was not associated with any seizure type or seizure cause. Adverse events during stimulation included fever, coughing, colds, and voice alteration. None of these necessitated cessation of stimulation. Complications included aspiration pneumonia and necrosis of skin overlying the generator. **CONCLUSIONS:** Intermittent stimulation of the left vagal nerve appears to be a safe, adjunctive therapy for the treatment of children with epilepsy intractable to available antiepileptic drugs. The reduction in seizure frequency in children was similar to that reported in adults.

20. **Murphy JV, Hornig G, Schallert G. Left vagal nerve stimulation in children with refractory epilepsy. Preliminary observations. *Arch Neurol.* 1995;52(9):886-9.**

<http://www.ncbi.nlm.nih.gov/pubmed/7661726>

<http://archneur.jamanetwork.com/article.aspx?articleid=593629>

**Abstract** OBJECTIVE: To observe the tolerance and efficacy of periodic left vagal nerve stimulation in a group of children with medically intractable epilepsies. DESIGN: A vagal nerve stimulator (Cyberonics Inc, Webster, Tex) was implanted in 12 children with medically and surgically refractory epilepsies. These children were followed up for 2 to 14 months. OUTCOME MEASUREMENTS: (1) The number of seizures recorded during the final month of observation was compared with the number recorded during the month before the implantation of the vagal nerve stimulator. (2) Parents were asked to compare overall status of their child, relative to the period prior to using the vagal nerve stimulator, on a global rating scale. (3) The number of antiepileptic drugs at the last visit was compared with the number before the use of this device. (4) Adverse events were recorded. RESULTS: Five of the 12 patients had a greater than 90% reduction in the number of monthly seizures. Global evaluation scores indicated that there were no deteriorations from baseline and that there was a considerable number with improved status. Four patients were able to reduce the number of antiepileptic drugs used. No significant adversities were noted. CONCLUSIONS: The vagal nerve stimulator is well tolerated in children with intractable epilepsies, and it may have a role in their medical management. We were unable to determine specific epilepsies or seizures that were sensitive to this intervention.

**Pre-Approval Studies (of VNS in Epilepsy)**

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- 1. DeGiorgio CM, Thompson J, Lewis P, Arrambide S, Naritoku D, Handforth A, et al. Vagus nerve stimulation: analysis of device parameters in 154 patients during the long-term XE5 study. *Epilepsia*. 2001;42(8):1017-20.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11554887>  
<http://onlinelibrary.wiley.com/store/10.1046/j.1528-1157.2001.0420081017.x/asset/j.1528-1157.2001.0420081017.x.pdf?v=1&t=he9402rg&s=5d03b973ae5d4cf99b263af6e2414e9bfa65bd79>

**Abstract** PURPOSE: To determine the effect of changes in device settings and duty cycle (on and off times) on the efficacy of vagus nerve stimulation (VNS) for refractory epilepsy. In the long-term XE5 study of VNS for intractable epilepsy, the median reduction in seizure frequency improved significantly after 1 year of follow-up. A central question is whether device changes improve efficacy. We analyzed the effects of device parameter changes on seizure frequency in 154 subjects who completed the study and who had complete data for analysis. METHODS: Retrospective analysis of device changes during the XE5 long-term study of VNS. During the XE5 long-term follow-up study, the subject's device settings were modified within a Food and Drug Administration (FDA)-approved range of output current, pulse duration, frequency, on time, and off time. Significant changes in device settings occurred after 3 months. We investigated the relationship between percentage reduction in seizures and changes in device parameters between the 3- and 12-month visits. Within-group comparisons were performed for those who continued on standard on/off cycle of 30 s on and 5 min off, and those with the most common off times of 3, 1.8, and < 1.1 min. RESULTS: Output current, pulse duration, frequency, and off time changed significantly between the 3- and 12-month long-term follow-ups. For the group as a whole, changes in device settings were not correlated with an improvement in efficacy. However, a significant improvement in efficacy occurred in a subgroup whose off time was reduced to < or = 1.1 min. In this group, the median reduction in seizures improved from 21% before the change in off time, to 39% after the change in off time (Wilcoxon Signed-Rank,  $p = 0.011$ ). The responder rate (> 50% reduction in seizures) also significantly improved from 19 to 35% (McNemar's test,  $p = 0.046$ ). CONCLUSIONS: The data from this retrospective analysis indicate that device changes were not the primary determinant of increased efficacy at 12 months of long-term follow-up. In general, patients who remained on the original settings of 30 s on and 5 min off continued to respond or improve in their response over the 1-year period. However, some patients may benefit from reductions in off time (increases in duty cycle). In a subgroup initially resistant to VNS, a change in off time to < or = 1.1 min off did result in significant improvements in efficacy.
  
- 2. DeGiorgio CM, Schachter SC, Handforth A, Salinsky M, Thompson J, Uthman B, et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. *Epilepsia*. 2000;41(9):1195-200.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10999559>

**Abstract** PURPOSE: To determine the long-term efficacy of vagus nerve stimulation (VNS) for refractory seizures. VNS is a new treatment for refractory epilepsy. Two short-term double-blind trials have demonstrated its safety and efficacy, and one long-term study in 114 patients has demonstrated a cumulative improvement in efficacy at 1 year. We report the largest prospective long-term study of VNS to date. METHODS: Patients with six or more complex partial or generalized tonic-clonic seizures enrolled in the pivotal EO5 study were prospectively evaluated for 12 months. The primary outcome variable was the percentage reduction in total seizure frequency at 3 and 12 months after completion of the acute EO5 trial, compared with the preimplantation baseline. Subjects originally randomized to low stimulation (active-control group) were crossed over to therapeutic stimulation settings for the first time. Subjects initially randomized to high settings were maintained on high settings throughout the 12-month study. RESULTS: The median reduction at 12 months after completion of the initial double-blind study was 45%. At 12 months, 35% of 195 subjects had a >50% reduction in seizures, and 20% of 195 had a >75% reduction in seizures. CONCLUSIONS: The efficacy of VNS improves during 12 months, and many subjects sustain >75% reductions in seizures.

3. **Labar D, Murphy J, Tecoma E. Vagus nerve stimulation for medication-resistant generalized epilepsy. E04 VNS Study Group. *Neurology*. 1999;52(7):1510-2.**

<http://www.ncbi.nlm.nih.gov/pubmed/10227649>

**Notes** First major paper on VNS among patients with generalized seizures (patients taken from the E04 study; n=24). VNS was reported safe and effective in this population, with results slightly better than those seen in patients with partial seizures and VNS. No patients became seizure free.

**Abstract** We treated 24 generalized epilepsy patients with vagus nerve stimulation (VNS), comparing seizure rates during a 1-month baseline with 3 months of VNS. Median seizure rate reduction was -46%. Sixteen of the 24 patients had better than a -30% reduction and 11 of the 24 patients had better than a -50% reduction in seizure rate. A mild cough during stimulation occurred in six patients. Patients with higher baseline seizure rates and later ages at epilepsy onset had the best responses to VNS. Our findings suggest VNS is an effective treatment for medication-resistant generalized epilepsy even in patients as young as 4 years.

4. **Morris GL, 3rd, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. *Neurology*. 1999;53(8):1731-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/10563620>

**Notes** Second major article on long-term treatment (after the 1-year E03 article by Salinsky et al) and the first that includes data after 1 year (3-year data reported). The paper covers all patients implanted during the clinical trials (E01-E05; n=454), with evaluable data for 440 patients. This is the paper on long-term follow up for the clinical studies.

**Abstract** **OBJECTIVE:** To perform an open-label, long-term efficacy and safety/tolerability study of vagus nerve stimulation (VNS) of 454 patients with refractory epilepsy. **METHODS:** Subjects were enrolled from five clinical trials of VNS between 1988 and 1995 after undergoing an implantation of a pulse generator in the chest and a left cervical vagus nerve-stimulating lead coil. Patients were assessed at 6-month intervals until device approval. Seizure frequencies, medication treatment, and adverse events (AEs) were recorded and entered into a database. **RESULTS:** A total of 454 patients were implanted, and 440 patients yielded assessable data. A > or =50% seizure reduction postimplantation occurred in 36.8% of patients at 1 year, in 43.2% at 2 years, and in 42.7% at 3 years. Median seizure reductions compared with baseline were 35% at 1 year, 44.3% at 2 years, and 44.1% at 3 years. Most common AEs postimplantation at 1 year were hoarseness (28%) and paraesthesias (12%), at 2 years were hoarseness (19.8%) and headache (4.5%), and at 3 years was shortness of breath (3.2%). Continuation rates were 96.7% at 1 year, 84.7% at 2 years, and 72.1% at 3 years. **CONCLUSION:** Long-term, open-label vagus nerve stimulation (VNS) provided seizure reduction similar to or greater than acute studies, for median reductions and for those reaching a > or =50% seizure reduction. VNS remained safe and well tolerated, with nearly three-quarters of the patients choosing to continue therapy.

5. **Amar AP, DeGiorgio CM, Tarver WB, Apuzzo ML. Long-term multicenter experience with vagus nerve stimulation for intractable partial seizures: results of the XE5 trial. *Stereotact Funct Neurosurg.* 1999;73(1-4):104-8.**

<http://www.ncbi.nlm.nih.gov/pubmed/10853111>

**Abstract** OBJECTIVE: Intermittent stimulation of the left cervical vagus nerve trunk (VNS) with the NeuroCybernetic Prosthesis (NCP) is emerging as a novel adjunct in the management of medically refractory epilepsy. We review the safety and efficacy of VNS 1 year after completion of the E05 study, the largest controlled clinical trial of VNS to date. METHODS: One hundred and ninety-nine patients with intractable epilepsy and at least 6 complex partial or secondarily generalized seizures per month enrolled in a randomized, double-blinded, partial crossover trial of high versus low parameters of stimulation (E05). After 3 months, all patients received high stimulation during an open-label, nonblinded extension trial (XE5). Seizure frequency, adverse events and multiple physiologic variables were monitored at regular intervals. RESULTS: At 3 months, the mean reduction in seizure frequency among patients receiving high stimulation during E05 was 28%. Of the 199 subjects participating in this acute-phase trial, 195 continued in the long-term protocol. Among the latter patients, 21 subsequently exited the study due to lack of efficacy, and 2 others died from causes unrelated to VNS. Complete data were obtained for 164 of the remaining subjects. Using a declining N analysis, the mean and median reduction in seizure frequency at 15 months was 37 and 45%, respectively. A last visit carried forward analysis, which controls for dropouts and incomplete follow-up, yielded comparable results (34 and 45%, respectively), indicating little potential for selection bias. At 15 months, 39% of the subjects had a greater than 50% reduction in seizures, including 21% who had a greater than 75% reduction, and 2% have remained seizure free. Few serious adverse events, physiological perturbation or device failures were reported. CONCLUSIONS: The long-term multicenter safety, efficacy, feasibility and tolerability of VNS, as well as the durability of the NCP device have been confirmed. Unlike chronic therapy with antiepileptic medication, the efficacy of VNS is maintained during prolonged stimulation, and overall seizure control continues to improve with time.

6. **Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology*. 1998;51(1):48-55.**

<http://www.ncbi.nlm.nih.gov/pubmed/9674777>

**Notes** Seminal paper on VNS as it reports the results of the pivotal E05 study, which conclude that VNS is safe and effective as confirmed by this multicenter, randomized, active-control trial (n=199; 20 centers). No changes in physiologic indicators of gastric, cardiac, or pulmonary functions occurred. VNS is associated with greater improvements on global evaluation scores and does not interact or conflict with other AED therapies. High stimulation was associated with more voice alteration and dyspnea. Data suggests that VNS results improve over the long term. 99% of patients completed the 3-month study. VNS represents the advent of a new, nonpharmacologic treatment for epilepsy.

**Abstract** **OBJECTIVE:** The purpose of this multicenter, add-on, double-blind, randomized, active-control study was to compare the efficacy and safety of presumably therapeutic (high) vagus nerve stimulation with less (low) stimulation. **BACKGROUND:** Chronic intermittent left vagus nerve stimulation has been shown in animal models and in preliminary clinical trials to suppress the occurrence of seizures. **METHODS:** Patients had at least six partial-onset seizures over 30 days involving complex partial or secondarily generalized seizures. Concurrent antiepileptic drugs were unaltered. After a 3-month baseline, patients were surgically implanted with stimulating leads coiled around the left vagus nerve and connected to an infraclavicular subcutaneous programmable pacemaker-like generator. After randomization, device initiation, and a 2-week ramp-up period, patients were assessed for seizure counts and safety over 3 months. The primary efficacy variable was the percentage change in total seizure frequency compared with baseline. **RESULTS:** Patients receiving high stimulation (94 patients, ages 13 to 54 years) had an average 28% reduction in total seizure frequency compared with a 15% reduction in the low stimulation group (102 patients, ages 15 to 60 year; p = 0.04). The high-stimulation group also had greater improvements on global evaluation scores, as rated by a blinded interviewer and the patient. High stimulation was associated with more voice alteration and dyspnea. No changes in physiologic indicators of gastric, cardiac, or pulmonary functions occurred. **CONCLUSIONS:** Vagus nerve stimulation is an effective and safe adjunctive treatment for patients with refractory partial-onset seizures. It represents the advent of a new, nonpharmacologic treatment for epilepsy.

7. **Salinsky MC, Uthman BM, Ristanovic RK, Wernicke JF, Tarver WB. Vagus nerve stimulation for the treatment of medically intractable seizures. Results of a 1-year open-extension trial. Vagus Nerve Stimulation Study Group. *Arch Neurol.* 1996;53(11):1176-80.**  
<http://www.ncbi.nlm.nih.gov/pubmed/8912492>  
<http://archneur.jamanetwork.com/article.aspx?articleid=594305>  
**Abstract** BACKGROUND: Chronic vagus nerve stimulation (VNS) continues to be evaluated as an adjunctive treatment for medically intractable seizures. A previous randomized controlled trial of 114 patients demonstrated a significant decrease in seizure frequency during 3 months of VNS at effective stimulation levels. OBJECTIVE: To evaluate the efficacy of 1 year of VNS therapy for the treatment of medically refractory partial seizures and the relationship between initial and long-term response. PATIENTS AND METHODS: All patients exiting the randomized controlled study of VNS for treatment of medically refractory partial seizures were offered indefinite treatment extension as part of an open-label trial. One hundred (88%) of 114 patients completed 12 months of VNS treatment at effective stimulation levels. Fourteen patients discontinued VNS treatment prior to 1 year, principally because of the treatment's lack of efficacy. These 14 patients were retained in the present analysis using an intent-to-treat approach. Antiepileptic drug use was monitored throughout the trial. Seizure frequency was analyzed in 4 sequential 3-month treatment periods. RESULTS: Compared with pretreatment baseline, there was a significant decrease in seizure frequency during each of the 3-month treatment periods. Seizure frequency was reduced by a median of 20% during the first 3 months of VNS treatment and by 32% during stimulation months 10 through 12. Response during the first 3 months of VNS treatment was a statistically significant predictor of response at months 10 through 12. The observed reduction in seizure frequency was not explained by overall changes in antiepileptic drug use. CONCLUSIONS: The results indicate that VNS remains an effective adjunctive therapy for medically refractory partial seizures over a period of at least 1 year. Response during the first 3 months of treatment is predictive of long-term response.
8. **A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. *Neurology.* 1995;45(2):224-30.**  
<http://www.ncbi.nlm.nih.gov/pubmed/7854516>  
**Abstract** Preliminary reports have suggested that chronic, intermittent stimulation of the vagus nerve (VNS) is an alternative treatment for patients with medically refractory seizures. We performed a multicenter, randomized, controlled trial to evaluate the efficacy and safety of adjunctive VNS in patients with poorly controlled partial seizures. An implanted, programmable pacemaker-like device was connected to two stimulating electrodes wrapped around the left vagus nerve. One hundred fourteen patients were randomized to receive 14 weeks of high-level stimulation (presumed therapeutic dose) or low-level stimulation (presumed subtherapeutic dose) using a blinded, parallel study design. Seizure frequency was compared with a 12-week baseline. Mean reduction in seizure frequency was 24.5% for the "high" stimulation group versus 6.1% for the "low" stimulation group ( $p = 0.01$ ). Thirty-one percent of patients receiving high stimulation had a seizure frequency reduction of  $\geq 50\%$ , versus 13% of patients in the low group ( $p = 0.02$ ). Treatment emergent side effects were largely limited to a transient hoarseness occurring during the stimulation train. One patient with no previous history of cardiac disease experienced a myocardial infarction during the third month of vagal stimulation. VNS may be an effective alternative treatment for patients who have failed antiepileptic drug therapy and are not optimal candidates for epilepsy surgery.

9. **Ben-Menachem E, Manon-Espaillet R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. *Epilepsia*. 1994;35(3):616-26.**

<http://www.ncbi.nlm.nih.gov/pubmed/8026408>

**Abstract** Vagus nerve stimulation (VNS) was shown to reduce seizure frequency in refractory epilepsy patients in two pilot studies. Based on these results, a multicenter, prospectively randomized, parallel, double-blind study of patients with refractory partial seizures was initiated. After a 12-week baseline period, identical vagus nerve stimulators were implanted and patients randomized to either a high or low 14-week VNS treatment paradigm. The primary objective was to demonstrate that high VNS (therapeutic parameters) was more effective in reducing partial seizure frequency than was low VNS (less or noneffective parameters). Patients continued receiving antiepileptic drugs (AEDs) with plasma concentrations held constant throughout the study. We report results of the first 67 patients to exit the 14-week acute phase. After 14 weeks of VNS, 31 patients receiving high VNS experienced a mean seizure frequency percentage reduction of 30.9%, which was statistically significant as compared with the mean seizure frequency percentage reduction of 11.3% in 36 patients receiving low VNS ( $p = 0.029$ ,  $t$  test;  $p = 0.036$ , Wilcoxon rank-sum test). In addition to the significant intragroup  $p$ -values, mean seizure frequency percentage change reached statistical significance for high VNS ( $p < 0.001$ ) but not low VNS ( $p = 0.072$ ) as compared with baseline. Twelve of 31 (38.7%) patients receiving high VNS achieved at least 50% reduction in seizure frequency whereas 7 of 36 (19.4%) patients receiving low VNS experienced at least 50% reduction after 14 weeks. The implant procedure and VNS therapy were well tolerated. Our study confirmed the effectiveness of VNS as treatment for epilepsy patients with refractory partial seizures.

10. **Ramsay RE, Uthman BM, Augustinsson LE, Upton AR, Naritoku D, Willis J, et al. Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side effects, and tolerability. First International Vagus Nerve Stimulation Study Group. *Epilepsia*. 1994;35(3):627-36.**

<http://www.ncbi.nlm.nih.gov/pubmed/8026409>

**Abstract** Vagus nerve stimulation (VNS) significantly reduces the frequency of partial seizures in refractory epilepsy patients. We examined the serious adverse events, side effects, and tolerability as they relate to the surgical implant procedure and the stimulating device. We also reviewed potential drug interactions, device output complications, and impact of the therapy on overall health status. We analyzed the first 67 patients to exist the acute phase of the EO3 VNS trial comparing high (therapeutic) VNS to low (less or noneffective) VNS. Data were collected from case report forms used at each of the four visits during the 12-week baseline and at each of the four visits during the 14-week randomized phase of the trial. No significant complications were reported as a result of the implant procedure. Serious adverse events included 1 patient who experienced direct current to the vagus nerve owing to generator malfunction resulting in left vocal cord paralysis and withdrawal of the patient from the study. No clinically significant effects on vital signs, cardiac function, or gastric function were detected. Side effects associated with VNS in the high group were hoarseness (35.5%), coughing (13.9%), and throat pain (12.9%). In the low group, only hoarseness (13.9%) and throat pain (13.9%) were associated with VNS. These effects generally were not considered clinically significant and occurred primarily during the stimulation pulses. No patients discontinued VNS therapy during the acute phase because of side effects associated with normal stimulation. Except for the one instance of a short circuit in the system resulting in a direct current, stimulating system complications were minor, limited to programming, unscheduled stimulation, and high lead impedance. Patients, investigators, and patient companions rated patients receiving high stimulation as more "improved" than those receiving low stimulation in regards to overall health status. Antiepileptic drug (AED) plasma concentrations were not affected by VNS. The implant procedure, stimulating system, and therapy proved safe and tolerable during the study. The high percentage (67 of 68) of patients completing the study reflects patient acceptance and tolerability of this mode of therapy.

11. **George R, Salinsky M, Kuzniecky R, Rosenfeld W, Bergen D, Tarver WB, et al. Vagus nerve stimulation for treatment of partial seizures: 3. Long-term follow-up on first 67 patients exiting a controlled study. First International Vagus Nerve Stimulation Study Group. *Epilepsia*. 1994;35(3):637-43.**

<http://www.ncbi.nlm.nih.gov/pubmed/8026410>

**Abstract** Vagus nerve stimulation (VNS) has demonstrated a significant anticonvulsant effect in preclinical studies, in pilot studies in humans, and in the acute phase of a multicenter, double-blinded, randomized study. After completion of a 14-week, blinded, randomized study, with 31 receiving high (therapeutic) VNS and 36 receiving low (less or noneffective) VNS, 67 patients elected to continue in an open extension phase. During the extension phase, all 67 patients received high VNS. Seizure frequency during the 3-month treatment blocks was compared with a 12-week baseline. For both groups, all periods of high VNS demonstrated a significant decrease in seizure frequency ( $p < 0.01$  level) as compared with baseline. For the 16-18-month period of VNS, data were available for 26 of the 31 patients randomized to high VNS. This group achieved a 52.0% mean seizure frequency percentage reduction as compared with baseline. For those converted from low to high VNS, data were available for 24 of the 36 patients at the 16-18-month time period. This group reported a mean seizure frequency percentage reduction of 38.1% as compared with baseline. No significant change in the safety/side effect profile was reported during long-term follow-up. The previously reported side effects of hoarseness/voice change, coughing, and paresthesia (sensation in neck and jaw) continued to occur during VNS. These side effects were well tolerated. During the follow-up period, 1 patient died of thrombotic thrombocytopenic purpura (TTP) and 5 patients discontinued treatment because of unsatisfactory efficacy.

12. **Michael JE, Wegener K, Barnes DW. Vagus nerve stimulation for intractable seizures: one year follow-up. *J Neurosci Nurs*. 1993;25(6):362-6.**

<http://www.ncbi.nlm.nih.gov/pubmed/8106830>

**Abstract** Even with the best health care available, many patients with epilepsy still suffer from poorly controlled seizures. Patients with intractable partial seizures are often inhibited from realizing their full potential and may experience a less than optimal quality of life. Vagus nerve stimulation (VNS) is being studied in a double-blind, controlled, randomized trial at 17 epilepsy centers throughout the U.S. and Europe as a potential therapy for patients with refractory seizures. During a 14-week controlled phase in three of the centers, the therapeutic group ( $N = 10$ ) experienced a mean seizure frequency percent reduction (SFPR) of 33.1% as compared to baseline ( $p = 0.0084$ ) while the subtherapeutic group ( $N = 12$ ) experienced an SFPR of 0.6% as compared to baseline ( $p = 0.9183$ ). After the controlled phase, all patients were switched into the therapeutic group in an open extension phase. Results after one year of therapeutic stimulation ( $N = 15$ ) reveal a mean SFPR of 35.6% ( $p = 0.0088$ ) with 6 of the 15 patients (40%) achieving at least a 50% seizure reduction. Adverse effects included hoarseness, coughing and nausea. There were no deaths or serious injuries related to the device. Based on these limited data, VNS appears to be a safe and efficacious new therapy for refractory partial seizures.

13. **Uthman BM, Wilder BJ, Penry JK, Dean C, Ramsay RE, Reid SA, et al. Treatment of epilepsy by stimulation of the vagus nerve. *Neurology*. 1993;43(7):1338-45.**

<http://www.ncbi.nlm.nih.gov/pubmed/8327135>

**Notes** This paper discusses the outcomes from a subset of the patients from the singleblind pilot studies. This paper was written 4 years before VNS became an approved therapy and is written on a small n (14 subjects), but showed that the therapy was well tolerated and no permanent adverse events were seen. The article discusses the three types of responses seen with VNS Therapy: rapid-sustained, gradual, and nonresponse.

**Abstract** We treated 14 patients with medically refractory partial seizures by stimulation of the vagus nerve in two single-blind pilot studies. Patients received stimulation through an implantable, programmable NeuroCybernetic Prosthesis, consisting of a pulse generator and a lead-electrode assembly. The mean reduction in seizure frequency after 14 to 35 months of vagal stimulation was 46.6%. Of the 14 patients, five (35.7%) had a 50% or greater reduction in seizure frequency. Two patients, one of whom had had 10 to 100 seizures per day before stimulation, have been seizure-free for over 1 year. Adverse events were primarily limited to initial hoarseness and a tingling sensation at the electrode site in the neck when the device was activated. Most patients tolerated the device and stimulation well. There were no permanent adverse events. Some cases of medically refractory partial seizures are improved by vagal stimulation.

14. **Holder LK, Wernicke JF, Tarver WB. Treatment of refractory partial seizures: preliminary results of a controlled study. *Pacing Clin Electrophysiol*. 1992;15(10 Pt 2):1557-71.**

<http://www.ncbi.nlm.nih.gov/pubmed/1383970>

**Abstract** Vagus nerve stimulation for the treatment of epilepsy has been studied in medically refractory patients with partial seizures in a randomized, blinded, parallel study. After a 3-month baseline period, the patients were implanted with the Neurocybernetic Prosthesis (NCP) system consisting of the NCP Generator and the Bipolar Vagal Stimulation Lead. Two stimulation paradigms were used, HIGH, which delivers what is considered to be optimal stimulation parameters and LOW, which is considered to be less or noneffective. The system and vagus nerve stimulation were well tolerated and few adverse events have been attributed to either. One patient experienced a period of direct current to the nerve due to a generator malfunction. This results in paralysis of the left vocal cord. Efficacy analysis on the first 37 patients to complete the controlled portion of the study has shown that the patients in the HIGH group experienced a mean reduction in seizure frequency of 33.3% and patients in the LOW group experienced a mean reduction in seizure frequency of 8.4%. The difference between the groups is statistically significant with a P value of 0.025. Analysis of seizure duration and intensity does not show any significant change. Ratings of the patient's overall condition by the patient, investigator, and companion as a measurement of "quality of life" also show improvement in the HIGH group. The results of this interim study demonstrate that vagus nerve stimulation is a safe and effective method of treating partial epileptic seizures.

15. **Wilder BJ, Uthman BM, Hammond EJ. Vagal stimulation for control of complex partial seizures in medically refractory epileptic patients. *Pacing Clin Electrophysiol.* 1991;14(1):108-15.**  
<http://www.ncbi.nlm.nih.gov/pubmed/1705324>  
**Abstract** Chronic intermittent stimulation of the vagus nerve is a new method currently being tested for the treatment of medically intractable complex partial seizures (CPS). We have studied the effects of vagal stimulation in nine patients with CPS for 4-16 months to determine its safety and efficacy. With the patients maintained on constant dosages of antiepileptic drugs, we recorded the electroencephalogram and electrocardiogram, and performed clinical laboratory tests and gastric analysis over a 6-week baseline period. The neurocybernetic prosthesis (NCP) was then implanted and connected to two spiral electrodes wound around the left vagus nerve. After a 4-week placebo period, vagal stimulation was started. Stimulation parameters were increased stepwise at monthly intervals until patients were being stimulated for 30-second periods at 20-50 Hz with 1-2 mA of current at 250-500 microseconds pulses. A second 4-week placebo period was added 3 months after the implantation. Thereafter, vagal stimulation was resumed and self-stimulation with magnetic activation was allowed for a 1-minute period at the onset of an aura. Six patients had a significant reduction in the frequency, intensity, or duration of seizures. All patients tolerated the implantation and stimulation well and none reported pain, discomfort, or important changes in their daily activities, sleep habits, eating, swallowing, or breathing. There were no remarkable changes in blood pressure or heart rate.
16. **Penry JK, Dean JC. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. *Epilepsia.* 1990;31 Suppl 2:S40-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/2121469>  
**Abstract** Intermittent stimulation of the vagus nerve in four patients resulted in complete seizure control in two, a 40% reduction of seizure frequency in one, and no change in seizure frequency in the other. Side effects (hoarseness, stimulation sensation in the neck, and hiccups) were transient and occurred concomitantly with stimulation. All patients tolerated increasing stimulation parameters well. The results, however, are inconclusive because of the brief duration (6-12 months) of follow-up. Vagal stimulation represents a novel approach for seizure control in patients who have intractable epilepsy, but additional studies are needed to clarify the efficacy and safety of the procedure and to define selection criteria for patients.
17. **Uthman BM, Wilder BJ, Hammond EJ, Reid SA. Efficacy and safety of vagus nerve stimulation in patients with complex partial seizures. *Epilepsia.* 1990;31 Suppl 2:S44-50.**  
<http://www.ncbi.nlm.nih.gov/pubmed/2226366>  
**Abstract** A clinical trial of chronic intermittent vagal stimulation in five patients suggests that the procedure may be safe and effective as adjunctive treatment of medically intractable seizures of partial onset. Patients tolerated well the implantation of the neurocybernetic prosthesis and the vagal stimulation without serious physiological or lifestyle changes. Stimulation of the vagus nerve either reduced the seizure frequency or decreased the duration or intensity of seizures. Adverse side effects were limited to a tingling sensation in the throat and hoarseness during stimulation. A major complication was mechanical interruption of the wire-electrode circuitry, with consequent cessation of stimulation. The small number of patients and the relatively short follow-up period make this a pilot study, but the results are promising.

**Predictors/Markers of Response (to VNS)**

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- 1. Fraschini M, Puligheddu M, Demuru M, Polizzi L, Maleci A, Tamburini G, et al. VNS induced desynchronization in gamma bands correlates with positive clinical outcome in temporal lobe pharmacoresistant epilepsy. *Neurosci Lett*. 2013;536:14-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23333601>

**Abstract** The vagus nerve stimulation (VNS) represents a diffuse non-pharmacological low-risk surgical option for epilepsy treatment. The aim of this study is to investigate the correlation between variations of global EEG synchronization and the clinical outcome in pharmacoresistant epileptic subjects implanted with VNS. Ten subjects affected by pharmacoresistant epilepsy were recruited on the basis of a clear-cut successful or unsuccessful outcome of the VNS add-on treatment. After five years from VNS surgery we examined the EEG in five subjects in each group. The investigation was led with the method of the phase lag index (PLI), which allows for the study of the global rate of synchronicity among the EEG signals before and after VNS implantation. The results of this study show that after five years from VNS surgery, in subjects whose seizures show a significant reduction, the desynchronization in the gamma frequency band is statistically decreased in comparison with patients who failed to show variations in the frequency and characteristics of their seizures. The other frequency bands are unaffected. This finding suggests that long lasting variations in gamma band desynchronization can be a new tool in assessing the efficacy of VNS. The possibility that GABA-mediated VNS-induced effects can also play a role in this result is discussed.
  
- 2. Colicchio G, Montano N, Fuggetta F, Papacci F, Signorelli F, Meglio M. Vagus nerve stimulation in drug-resistant epilepsies. Analysis of potential prognostic factors in a cohort of patients with long-term follow-up. *Acta Neurochir (Wien)*. 2012;154(12):2237-40.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23086106>  
<http://link.springer.com/article/10.1007%2Fs00701-012-1524-9>

**Abstract** BACKGROUND: The results of vagus nerve stimulation (VNS) for the treatment of drug-resistant epilepsies are highly variable due to the lack of defined patient's selection criteria and a follow-up of published studies being generally too short. Here we report the outcome of VNS in a series with long-term follow-up and try to identify subgroups of patients who could be better candidates for this procedure. METHOD: We studied 53 patients (33 male, 20 female) with a prospectively recorded follow-up (mean, 55.96 +/- 43.53 months). The monthly average seizure frequency for each patient at baseline, 3, 6, 12 months, and each year until the latest follow-up after implant was measured and the percentage of "responders" and response time (RT) were calculated. We investigated the following potential prognostic role of these factors: age of onset of epilepsy, pre-implant epilepsy duration, etiology, and age at implant. RESULTS: Globally, 40 % of patients responded to VNS (mean RT, 14.85 +/- 16.85 months). Lesional etiology (p = 0.0179, logrank test), particularly ischemia (p = 0.011, Fisher exact test) and tuberous sclerosis (p = 0.0229, Fisher exact test), and age at implant <18 years (p = 0.0242, logrank test) were associated to better response to VNS. In the lesional subgroup the best results were observed in patients with a pre-implant epilepsy duration <15 years (p = 0.0204, logrank test) and an age at implant <18 years (p = 0.0187 logrank test). CONCLUSIONS: The best candidate to VNS seems to be a patient with lesional etiology epilepsy (particularly post-ischemic and tuberous sclerosis) and a short duration of epilepsy who undergo VNS younger than 18 years.

- 3. Usami K, Kawai K, Sonoo M, Saito N. Scalp-recorded evoked potentials as a marker for afferent nerve impulse in clinical vagus nerve stimulation. *Brain Stimul.* 2012.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23088852>  
**Abstract** BACKGROUND: Vagus nerve stimulation (VNS) is a palliative treatment for drug resistant epilepsy for which the efficacy and safety are well established. Accumulating evidence suggests that ascending vagal signals modulate abnormal cortical excitability via various pathways. However, there is no direct evidence for an ascending conduction of neural impulses in a clinical case of VNS. OBJECTIVE: We recorded and analyzed the short-latency components of the vagus nerve (VN) evoked potential (EP) from the viewpoint of determining whether or not it is a marker for the ascending neural conduction. METHODS: EPs within 20 ms were prospectively recorded simultaneously from a surgical wound in the neck and at multiple scalp sites during implantation surgery in 25 patients with drug-resistant epilepsy. Electrical stimulation was delivered using the clinical VNS Therapy system. A recording was made before and after a muscle relaxant was administered, when changing the rostrocaudal position of stimulation, or when stimulating the ansa cervicalis instead of the VN. RESULTS: The short-latency components consisted of four peaks. The early component around 3 ms, which was most prominent in A1-Cz, remained unchanged after muscle relaxation while the later peaks disappeared. Rostral transition of the stimulation resulted in an earlier shift of the early component. The estimated conduction velocity was 27.4 +/- 10.2 m/s. Stimulation of the ansa cervicalis induced no EP. CONCLUSIONS: The early component was regarded as directly resulting from ascending neural conduction of A fibers of the VN, probably originating around the jugular foramen. Recording of VN-EP might document the cause of treatment failure in some patients.
  
- 4. de Vos CC, Melching L, van Schoonhoven J, Ardesch JJ, de Weerd AW, van Lambalgen HC, et al. Predicting success of vagus nerve stimulation (VNS) from interictal EEG. *Seizure.* 2011;20(7):541-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21514181>  
[http://ac.els-cdn.com/S1059131111001051/1-s2.0-S1059131111001051-main.pdf?\\_tid=7c52cc44-8cc3-11e2-b9c1-00000aab0f01&acdnat=1363278380\\_d7183de51f116184c963d14200421308](http://ac.els-cdn.com/S1059131111001051/1-s2.0-S1059131111001051-main.pdf?_tid=7c52cc44-8cc3-11e2-b9c1-00000aab0f01&acdnat=1363278380_d7183de51f116184c963d14200421308)  
**Abstract** PURPOSE: Vagus nerve stimulation (VNS) has shown to be an effective treatment for drug resistant epilepsy in numerous patients, however, not in all. It is still not possible to predict which patients will profit from VNS. In this pilot study, we explore predictive interictal EEG features for seizure reduction after VNS. METHODS: 19 Patients with medically refractory epilepsy and an implanted VNS system were included. Interictal EEG registrations, recorded before implantation, were retrospectively analysed. A quantitative symmetry measure, the pair wise derived brain symmetry index (pdBSI), was tested to predict VNS outcome. Reduction in seizure frequency was used to define the responders. RESULTS: 10 Patients did respond to VNS, of whom 7 patients had a seizure reduction of at least 50% in a follow-up period of 2 years. On average, we find higher pdBSI values for delta, theta, alpha and beta bands for non-responders than for responders. The average pdBSI of the theta and alpha bands could significantly discriminate between responders and non-responders. CONCLUSION: In this study, quantifying EEG symmetry using the pdBSI shows promising results in predicting the reduction of seizure frequency after VNS treatment.

5. **Colicchio G, Policicchio D, Barbati G, Cesaroni E, Fuggetta F, Meglio M, et al. Vagal nerve stimulation for drug-resistant epilepsies in different age, aetiology and duration. *Childs Nerv Syst.* 2010;26(6):811-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20091042>  
<http://link.springer.com/article/10.1007%2Fs00381-009-1069-2>  
**Abstract** PURPOSE: The aim of the study was to compare the outcome with respect to age of implant, aetiology and duration of epilepsy. METHODS: One hundred thirty-five drug-resistant epileptic patients, excluded from ablative surgery, were submitted to vagal nerve stimulation (1995-2007). Aetiology was cryptogenic in 57 and symptomatic in 78 patients. Ages of implant were 0.5-6 years (18 patients), 7-12 years (32 patients), 13-18 years (31 patients) and more than 18 years (54 patients). Epilepsy types were Lennox-Gastaut (18 patients), severe multifocal epilepsy (33 patients) and partial (84 patients). Duration of epilepsy is 3 months to 57 years. Clinical outcome was determined by comparing the seizure frequency after stimulation at 3-6-12-18-24-36 months with the previous 3 months. 'Responders' were the patients experiencing a seizure frequency reduction of 50% or more during follow-up. In statistical analysis, Wilcoxon and McNemar tests, general linear model for repeated measures, logistic regression and survival analysis were used. RESULTS: The seizure frequency reduction was significant in the group as a whole between baseline and the first follow-up (Wilcoxon test). The percentage of responder increases with time (McNemar test  $p = 0.04$ ). Univariate analysis showed a significant effect of the age of implant on seizure frequency reduction: Adult patient had worst clinical outcome than children ( $p < 0.001$ ) and adolescents ( $p = 0.08$ ). Patients with severe multifocal epilepsy had better percentage seizure reduction compared with Lennox-Gastaut and partial ( $p = 0.03$ ). Lesser duration of epilepsy had positive influence on outcome. Multivariate analysis confirmed age of implant to be the strongest factor influencing prognosis. Furthermore, positive is the association between lesional aetiology and young age. CONCLUSIONS: The best responder could be a young lesional epileptic patient; after 3 years of follow-up, the percentage of responders is still in progress.
6. **Ghaemi K, Elsharkawy AE, Schulz R, Hoppe M, Polster T, Pannek H, et al. Vagus nerve stimulation: outcome and predictors of seizure freedom in long-term follow-up. *Seizure.* 2010;19(5):264-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20362466>  
[http://ac.els-cdn.com/S1059131110000567/1-s2.0-S1059131110000567-main.pdf?\\_tid=ce2aa50c-8cc6-11e2-9f1c-00000aab0f02&acdnat=1363279806\\_ca7d5d9f280f31d226c68bc5d8021b36](http://ac.els-cdn.com/S1059131110000567/1-s2.0-S1059131110000567-main.pdf?_tid=ce2aa50c-8cc6-11e2-9f1c-00000aab0f02&acdnat=1363279806_ca7d5d9f280f31d226c68bc5d8021b36)  
**Abstract** OBJECTIVES: To present long-term outcome and to identify predictors of seizure freedom after vagus nerve stimulation (VNS). METHODS: All patients who had undergone VNS implantation in the Epilepsy Centre Bethel were retrospectively reviewed. There were 144 patients who had undergone complete presurgical evaluation, including detailed clinical history, magnetic resonance imaging, and long-term video-EEG with ictal and interictal recordings. After implantation, all patients were examined at regular intervals of 4 weeks for 6-9 months. During this period the antiepileptic medication remained constant. All patients included in this study were followed up for a minimum of 2 years. RESULT: Ten patients remained seizure-free for more than 1 year after VNS implantation (6.9%). Seizures improved in 89 patients (61.8%) but no changes were observed in 45 patients (31.3%). The following factors were significant in the univariate analysis: age at implantation, multifocal interictal epileptiform discharges, unilateral interictal epileptiform discharge, cortical dysgenesis, and psychomotor seizure. Stepwise multivariate analysis showed that unilateral interictal epileptiform discharges (IEDs),  $P=0.014$ , HR=0.112 (95% CIs, 0.019-0.642), cortical dysgenesis  $P=0.007$ , HR=0.065 (95% CIs, 0.009-0.481) and younger age at implantation  $P=0.026$ , HR=7.533 (95% CIs 1.28-44.50) were independent predictors of seizure freedom in the long-term follow-up. CONCLUSION: VNS implantation may render patients with some forms of cortical dysgenesis (parietooccipital polymicrogyria, macrogyria) seizure-free. Patients with unilateral IEDs and earlier implantation achieved the most benefit from VNS.

7. **Casazza M, Avanzini G, Ferroli P, Villani F, Broggi G. Vagal nerve stimulation: relationship between outcome and electroclinical seizure pattern. *Seizure*. 2006;15(3):198-207.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16531077>  
[http://ac.els-cdn.com/S1059131106000288/1-s2.0-S1059131106000288-main.pdf?\\_tid=68aaed66-8cc3-11e2-bfdd-0000aacb35d&acdnat=1363278347\\_86e64842d9a4a56c1dc624b895750a40](http://ac.els-cdn.com/S1059131106000288/1-s2.0-S1059131106000288-main.pdf?_tid=68aaed66-8cc3-11e2-bfdd-0000aacb35d&acdnat=1363278347_86e64842d9a4a56c1dc624b895750a40)  
**Abstract** In recent years, vagal nerve stimulation (VNS) has been proposed as a possible way to improve the control of refractory (partial and generalized) seizures. To date, however, there is no complete understanding of the underlying mechanism for this action nor are there any available guidelines or criteria for the selection of those candidates that might be most suitable for this kind of neuromodulating surgery. This report presents evidence that should be helpful in defining the clinical criteria for using VNS for the treatment of refractory seizures. We report on 17 patients with severe partial refractory epilepsy and polymorphous seizures, who have been operated on previously or who were excluded from epilepsy surgery and for whom, at least, one seizure type has been electrographically recorded. Sixteen of these patients also had falling seizures. Our objective was to identify responders and to correlate the outcome of their seizures with the EEGraphic onset of their seizure. Follow-up ranged from 4 to 9 years. The results of this study indicate a significant reduction of seizures in only four patients and better outcome in patients where the onset of seizure activity occurred in the temporal area. Patients with frontal or frontocentral seizures resulted in the poorest outcomes. In four patients with Lennox-Gastaut syndrome VNS produced no significant reduction of seizures, while falling seizures decreased significantly in three patients with retropulsive falls. These results of this small series of patients suggest that VNS might be more suitable in patients with temporal rather than frontal or central seizure onset. Further studies are required to support this hypothesis.
8. **Janszky J, Hoppe M, Behne F, Tuxhorn I, Pannek HW, Ebner A. Vagus nerve stimulation: predictors of seizure freedom. *J Neurol Neurosurg Psychiatry*. 2005;76(3):384-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15716532>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1739542/pdf/v076p00384.pdf>  
**Abstract** OBJECTIVES: To identify predictive factors for the seizure-free outcome of vagus nerve stimulation (VNS). METHODS: All 47 patients who had undergone VNS implantation at one centre and had at least one year of follow up were studied. They underwent complete presurgical evaluation including detailed clinical history, magnetic resonance imaging, and long term video-EEG with ictal and interictal recordings. After implantation, adjustment of stimulation parameters and concomitant antiepileptic drugs were at the discretion of the treating physician. RESULTS: Mean (SD) age of the patients was 22.7 (11.6) years (range 7 to 53). Six patients (13%) became seizure-free after the VNS implantation. Only two variables showed a significant association with the seizure-free outcome: absence of bilateral interictal epileptiform discharges (IED) and presence of malformation of cortical development (MCD). Epilepsy duration showed a non-significant trend towards a negative association with outcome. By logistic regression analysis, only absence of bilateral IED correlated independently with successful VNS treatment ( $p < 0.01$ , odds ratio = 29.2 (95% confidence interval, 2.4 to 353)). Bilateral IED (independent or bilateral synchronous) was found in one of six seizure-free patients and in 33 of 41 non-seizure-free patients. When bilateral IED were absent, the sensitivity for seizure-free outcome was 0.83 (0.44 to 0.97), and the specificity was 0.80 (0.66 to 0.90). CONCLUSIONS: Bilateral IED was independently associated with the outcome of VNS. These results are preliminary because they were based on a small patient population. They may facilitate prospective VNS studies enrolling larger numbers of patients to confirm the results.

9. **Ebus SC, Majoie HJ, Arends JB, Boon PJ. Can spikes predict seizure frequency? Results of a pilot study in severe childhood epilepsies treated with vagus nerve stimulation. *Seizure*. 2004;13(7):494-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15324829>  
[http://ac.els-cdn.com/S1059131103002887/1-s2.0-S1059131103002887-main.pdf?\\_tid=7f0e7294-8cc3-11e2-bf77-0000aab0f6c&acdnat=1363278385\\_19faa7e819ee655c1fac3f340b20be38](http://ac.els-cdn.com/S1059131103002887/1-s2.0-S1059131103002887-main.pdf?_tid=7f0e7294-8cc3-11e2-bf77-0000aab0f6c&acdnat=1363278385_19faa7e819ee655c1fac3f340b20be38)  
**Abstract** We evaluated whether spike-rates are useful as an outcome parameter following vagus nerve stimulation (VNS). Spikes/minute and spikebursts/minute were counted in serial electroencephalograms before and after implantation of a vagus nerve stimulator in n = 19 patients with severe childhood epilepsies. In the period of 2 years post VNS, spike-rate and reported seizure frequency were significantly correlated (Spearman's R = 0.61); spikebursts and seizures were correlated with R = 0.74. The response rate, counted after 6 months, was too small to detect differences in responders and non-responders as to spike-reduction. Larger samples and effect sizes are necessary to prove the hypothesis that spike reduction is useful as outcome parameter after VNS or other interventions.
10. **Kuba R, Guzaninova M, Brazdil M, Novak Z, Chrastina J, Rektor I. Effect of vagal nerve stimulation on interictal epileptiform discharges: a scalp EEG study. *Epilepsia*. 2002;43(10):1181-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12366734>  
**Abstract** PURPOSE: To investigate the effects of acute vagal nerve stimulation (VNS) on interictal epileptiform discharges (IEDs). METHODS: Fifteen epilepsy patients, all of whom had been treated with VNS for > or =6 months, entered the study. In each subject, the absolute number of IEDs was counted at the baseline period (BP), the stimulation period (SP), six interstimulation periods (IPs), and the prestimulation period (PP), by using an original paradigm. The number of IEDs at the BP and the PP was compared with the number of IEDs at the SP and IPs. The results were correlated with other variables (the duration of VNS, the value of the output current, the duration of epilepsy, the type of epilepsy, the effect of VNS, and the effect of extrastimulation). RESULTS: We observed a significantly higher reduction in the number of IEDs in the SP and all the IPs as compared with the BP. We noticed a significantly higher reduction in the number of IEDs in the SP and in the first IP as compared with the PP. The reduction of IEDs was greater in patients who responded to VNS (>50% reduction of all seizures) and in patients who responded positively to magnetic extrastimulation. There were no other significant results in the reduction of IEDs when comparing other variables. CONCLUSIONS: Short-term VNS reduces IEDs significantly. The reduction is most prominent during the SP (i.e., when the pulse generator is active). The value of reduction of IEDs is higher in patients who respond to VNS and in patients with positive experiences with magnetic extrastimulation. These results can be useful in predicting the effect of VNS.
11. **Naritoku DK, Morales A, Pencek TL, Winkler D. Chronic vagus nerve stimulation increases the latency of the thalamocortical somatosensory evoked potential. *Pacing Clin Electrophysiol*. 1992;15(10 Pt 2):1572-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/1383971>  
**Abstract** The Neurocybernetic Prosthesis (NCP) is a pacemaker-like device that has been designed to provide chronic intermittent vagus nerve stimulation. It is currently under study for the treatment of refractory partial onset epilepsy, and preliminary studies have indicated that partial onset seizures are improved by this therapy. The mechanisms by which it exerts its antiepileptic effect are not well understood. Although there are extensive pathways to the forebrain from the nuclei of the vagus nerve, the evidence that the NCP alters neural transmission outside the vagal system is limited. We prospectively examined somatosensory and brain stem auditory evoked potentials (BAEPs) in three patients receiving NCP implantation to determine if changes in these studies occur as a result of chronic vagus nerve stimulation. The results demonstrate a significant prolongation of the cervicomedullary to thalamocortical potential (N13-N20) interval on somatosensory evoked potential (SSEP) studies following activation of the device. No other significant changes were seen on SSEP or BAEP in the NCP implanted patients or normal controls. The findings suggest that chronic vagus nerve stimulation does alter neuronal networks outside of the brain stem vagus system, and may potentially provide a means to clinically monitor and titrate this therapy.

**QoL - Alertness/Sleep in Epilepsy (VNS in...)**

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- 1. Rizzo P, Beelke M, De Carli F, Canovaro P, Nobili L, Robert A, et al. Modifications of sleep EEG induced by chronic vagus nerve stimulation in patients affected by refractory epilepsy. *Clin Neurophysiol.* 2004;115(3):658-64.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15036062>

**Abstract** OBJECTIVE: The aim of this study was to evaluate the impact of chronic vagus nerve stimulation (VNS) on sleep/wake background EEG and interictal epileptiform activity (IEA) of patients with medically refractory epilepsy. METHODS: From a broader sample of 10 patients subjected to baseline and treatment polysomnographies, spectral analysis and IEA count have been performed on 6 subjects' recordings, comparing the results by means of statistical analysis. RESULTS: An overall increase in EEG total power after VNS has been observed, more marked in NREM sleep; collapsing EEG power spectra into 5 frequency bands, we have found a statistically significant increase in delta and theta in NREM sleep, and of alpha in wakefulness and REM sleep. The incidence of IEA is diminished, although not significantly; only the duration of discharges is significantly diminished. CONCLUSIONS AND SIGNIFICANCE: Long-term VNS produces an enhancement in sleep EEG power of medically refractory epileptic patients. These results may be related to a better structured composition of EEG, and it is possible that chronic VNS may have a major role in enhancing the brain's ability to generate an electrical activity.
  
- 2. Galli R, Bonanni E, Pizzanelli C, Maestri M, Lutzemberger L, Giorgi FS, et al. Daytime vigilance and quality of life in epileptic patients treated with vagus nerve stimulation. *Epilepsy Behav.* 2003;4(2):185-91.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12697145>

**Abstract** OBJECTIVES: The goal of this study was to determine if vagus nerve stimulation (VNS) has any effect on daytime vigilance and perceived sense of well-being. METHODS: Multiple Sleep Latency Tests (MSLTs) were performed and visual reaction times (VRTs) obtained in eight epileptic patients before and during treatment with VNS. Prior to VNS initiation patients' baseline MSLT and VRT scores were recorded. Six months after VNS was initiated, treatment MSLT and VRT scores were obtained. A group of 12 age-matched healthy subjects served as controls. In addition, there was a global evaluation of well-being at baseline and during a follow-up of 6 months. RESULTS: As expected, patients evaluated both at baseline and during VNS showed more sleepiness than controls. In this group, baseline sleep latencies on the MSLT were significantly shorter, while VRT latencies were significantly longer than those of controls. After 6 months of VNS, MSLT scores in the eight patients did not change significantly with respect to baseline. However, if the single patient treated with relatively high stimulus intensities (1.75 mA) was excluded from the group and only the seven patients treated with low stimulus intensities ( $\leq 1.5$  mA) were considered, a significant effect of chronic VNS on MSLT scores could be observed. In fact, the mean sleep latency (MSL) average of the seven subjects significantly improved from 9.9+/-2.5 minutes during baseline to 10.9+/-2.3 minutes after 6 months of VNS ( $P < 0.05$ ). Conversely, the only patient treated with high stimulus intensities showed increased sleepiness, with MSL decreasing from 14.4 to 9.8 minutes. On the other hand, VRT latencies did not significantly change during VNS. Patients considered as a whole had significant improvements on global evaluation scores of quality of life. CONCLUSION: VNS at low stimulus intensities promotes daytime vigilance in adult epileptic patients and has a positive effect on quality of life.

3. **Rizzo P, Beelke M, De Carli F, Canovaro P, Nobili L, Robert A, et al. Chronic vagus nerve stimulation improves alertness and reduces rapid eye movement sleep in patients affected by refractory epilepsy. *Sleep*. 2003;26(5):607-11.**

<http://www.ncbi.nlm.nih.gov/pubmed/12938816>

**Notes** This study showed that VNS improved alertness and the quality of awakesness during the day, but reduced nocturnal rapid eye movement (REM) sleep. The authors suggest a correlation between sleep reduction and stimulus intensity. These results are similar to the findings of the Malow et al (2001) study in terms of the increase in alertness during the day, but Malow et al did not see a change in the amount of REM sleep among VNS patients. In addition, other sleep studies with VNS report and increase, not a decrease, of REM sleep with VNS. Therefore, in the literature, both sleep-facilitating and sleep-inhibiting effects have been reported.

**Abstract** **OBJECTIVE:** Our study aimed to evaluate the existence and entity of changes in sleep structure following vagus nerve stimulation in patients with refractory epilepsy. **METHOD:** A polysomnographic study was performed on the nocturnal sleep of 10 subjects with refractory epilepsy. Subjects were recorded both in baseline conditions and after chronic vagus nerve stimulation. Sleep parameters of the entire night were evaluated. Mean power value of slow-wave activity was computed in the first non-rapid eye movement sleep cycle. A sleep-wake diary evaluated quantity of both nocturnal and daytime sleep, while visual-analog scales assessed quality of sleep and wake. The differences between the 2 conditions underwent parametric and nonparametric statistical evaluation. **RESULTS:** Vagus nerve stimulation produced a significant reduction in REM sleep (in all subjects with vagus nerve stimulus intensity greater than 1.5 milliampere, but not in the only patient with a stimulus intensity less than 1.5 milliampere), along with an increase in the number of awakenings, percentage of wake after sleep onset, and stage 1 sleep. Data from a sleep-wake questionnaire show a decrease in both nocturnal sleep and daytime naps and an increased daytime alertness, while the quality of wakefulness is globally improved. Spectral analysis shows an enhancement of delta power during non-rapid eye movement sleep. **CONCLUSIONS:** Our data demonstrate major effects of vagus nerve stimulation on both daytime alertness (which is improved) and nocturnal rapid eye movement sleep (which is reduced). These effects could be interpreted as the result of a destabilizing action of vagus nerve stimulation on neural structures regulating sleep-wake and rapid eye movement/non-rapid eye movement sleep cycles. Lower intensity vagus nerve stimulation seems only to improve alertness; higher intensity vagus nerve stimulation seems able to exert an adjunctive rapid eye movement sleep-attenuating effect.

4. **Malow BA, Edwards J, Marzec M, Sagher O, Ross D, Fromes G. Vagus nerve stimulation reduces daytime sleepiness in epilepsy patients. *Neurology*. 2001;57(5):879-84.**

<http://www.ncbi.nlm.nih.gov/pubmed/11552020>

<http://www.neurology.org/content/57/5/879.full.pdf>

**Abstract** BACKGROUND: Given that vagal afferents project to brainstem regions that promote alertness, the authors tested the hypothesis that vagus nerve stimulation (VNS) would improve daytime sleepiness in patients with epilepsy. METHODS: Sixteen subjects with medically refractory seizures underwent polysomnography and multiple sleep latency tests (MSLT) and completed the Epworth Sleepiness Scale (ESS), a measure of subjective daytime sleepiness, before and after 3 months of VNS. Most subjects (>80%) were maintained on constant doses of antiepileptic medications. RESULTS: In the 15 subjects who completed baseline and treatment MSLT, the mean sleep latency (MSL) improved from 6.4 +/- 4.1 minutes to 9.8 +/- 5.8 minutes (+/- SD; p = 0.033), indicating reduced daytime sleepiness. All subjects with stimulus intensities of < or =1.5 mA showed improved MSL. In the 16 subjects who completed baseline and treatment ESS, the mean ESS score decreased from 7.2 +/- 4.4 to 5.6 +/- 4.5 points (p = 0.049). Improvements in MSLT and ESS were not correlated with reduction in seizure frequency. Sleep-onset REM periods occurred more frequently in treatment naps as compared to baseline naps (p < 0.008; Cochran-Mantel-Haenszel test). The amount of REM sleep or other sleep stages recorded on overnight polysomnography did not change with VNS treatment. CONCLUSIONS: Treatment with VNS at low stimulus intensities improves daytime sleepiness, even in subjects without reductions in seizure frequency. Daytime REM sleep is enhanced with VNS. These findings support the role of VNS in activating cholinergic and other brain regions that promote alertness.

**QoL - Cognition/Balance in Epilepsy (VNS in...)**

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- 1. Grill MF, Ng YT. Dramatic first words spoken in 2 children after vagus nerve stimulation. *Semin Pediatr Neurol.* 2010;17(1):54-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20434697>

**Abstract** Vagus nerve stimulation has become an accepted adjunctive treatment for refractory epilepsy with more recent FDA approval in the treatment of depression. Many "positive" effects have been noted in patients with epilepsy namely increased alertness, improved cognition, behavior and mood. These changes appear to be independent of seizure reduction and antiepileptic drug decrease. We present two children (aged 8 and 9 years) who were non-verbal and spoke their first words shortly after vagus nerve stimulators were implanted. The mechanism is unclear although vagus nerve stimulation has been clearly shown to induce neuronal, chemical and perfusion changes in both subcortical and cortical regions of the brain. There is likely a combined effect on primary speech areas as well subcortical and mamillothalamic tracts, and possibly even stimulation and changes at the local vocal cord level contributing to this phenomenon. Our observation has important implications in encephalopathic patients both with and without epilepsy.
  
- 2. Ghacibeh GA, Shenker JI, Shenal B, Uthman BM, Heilman KM. Effect of vagus nerve stimulation on creativity and cognitive flexibility. *Epilepsy Behav.* 2006;8(4):720-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16647302>

**Abstract** **OBJECTIVE:** The purpose of this study was to determine whether vagus nerve stimulation influences cognitive flexibility and creativity. **METHODS:** Ten subjects, in whom vagus nerve stimulators had been implanted for the treatment of intractable seizures, performed tasks that assessed cognitive flexibility (solving anagrams), creativity (Torrance Test), and memory (Hopkins Verbal Learning Test) during actual and sham vagus nerve stimulation. **RESULTS:** Vagus nerve stimulation impaired cognitive flexibility and creativity, but these results could not be explained by the induction of a general encephalopathy because VNS did not impair learning and improved retention. **CONCLUSIONS:** The means by which vagus nerve stimulation impairs cognitive flexibility and creative thinking is probably related to increased activity of the locus coeruleus-central adrenergic system that increases the signal-to-noise ratio and improves the brain's ability to attend to sensory input, but decreases its ability to recruit large-scale networks.
  
- 3. Hoppe C, Helmstaedter C, Scherrmann J, Elger CE. No evidence for cognitive side effects after 6 months of vagus nerve stimulation in epilepsy patients. *Epilepsy Behav.* 2001;2(4):351-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12609212>

**Abstract** Vagus nerve stimulation (VNS) can reduce seizure frequency in epilepsy patients and may affect central mechanisms of brain functioning. Experimental studies have provided evidence of cognitive alterations during VNS on phases. This single-arm follow-up study evaluates the potential of VNS to affect cognitive performance following long-term treatment. Thirty-six adult patients with medication-resistant epilepsies enrolled. Cognition was assessed before and at least 6 months after implantation of the stimulation device by a comprehensive neuropsychological assessment battery comprising tests on attention, motor functioning, short-term memory, learning and memory, and executive functions. Neither multiple testing of single score changes nor multivariate testing of cognitive domains revealed significant pre-post changes. Improvements in attentional performance were completely explained by practice effects as is usually expected. In particular, no negative side effects were revealed. These findings are in line with the clinical impression that VNS does not affect cognitive performance.

4. **Clarke BM, Upton AR, Griffin H, Fitzpatrick D, DeNardis M. Chronic stimulation of the left vagus nerve: cognitive motor effects. *Can J Neurol Sci.* 1997;24(3):226-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9276108>  
**Abstract** BACKGROUND: Early studies of cognitive motor control have shown deficits in complex reaction time tests of epileptic subjects. The purpose of this efficacy study was to determine whether chronic (28 months) stimulation of the left vagus nerve (VNS) to control seizures increased these deficits in 6 epileptic subjects with intractable complex partial seizures. METHODS: Subjects were assessed for simple reaction time, Test A, and subsequent Tests B and C which involved more complex cognitive strategies. Tests were done pre-operatively (S1) and at intervals, 6-8 weeks (S2-S3), and at 6 month intervals (S4-S6) over a 28 month period. Data were collected and collated on an Apple II E computer (Apple, Cupertino CA. U.S.A.) and on electronic switch pad. Data were analyzed using a repeated measures analysis of covariance technique with 2 within subject factors, day, and time of day. RESULTS: 2/11 cognitive measures showed a statistically significant difference. Error rate associated with Test A (simple reaction time) significantly decreased for the factor of day (repeated visits)  $p = .01$ . For Test C, error rates decreased in the afternoon ( $p = .03$ ). This test involved the subjects ability to respond quickly to one signal while simultaneously ignoring a second signal. Data analysis of the covariate showed that the effects of VNS are weak in comparison to baseline differences and the frequency of nerve stimulation negatively predicts the number of wrong errors. High frequency stimulation results showed fewer errors than low frequency stimulation  $T = -2.31$ ,  $p = .03$ . CONCLUSION: Chronic stimulation of the left vagus nerve to control seizure activity does not impair cognitive motor control.
5. **Clarke BM, Upton AR, Griffin H, Fitzpatrick D, DeNardis M. Chronic stimulation of the left vagus nerve in epilepsy: balance effects. *Can J Neurol Sci.* 1997;24(3):230-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9276109>  
**Abstract** BACKGROUND: Stimulation of the left vagus nerve (VNS) has been shown to control seizures in double blinded crossover studies in man. Animal studies have reported vagal afferent induced depression of nociceptive and motor reflexes which may be caused by an effect on the descending reticular system controlling spinal cord function. Anticonvulsant drug therapy may cause postural instability. The effects of VNS are assessed not only from the perspective of seizure control but also from the view of potential harm to other bodily systems. Long term (2 1/4 years) effects of VNS were compared to postural stability analyses. METHODS: 8 subjects, 2 were females, mean age 34.5 +/- 8.23 SD years, with intractable complex partial seizures, taking 3 anticonvulsant drugs were assessed for postural stability in quiet standing and while moving forwards, backwards and sideways with eyes open (EO) and eyes closed (EC). Data were collected and collated using an AMTI Biomechanics immovable forceplate, Newton M.A. U.S.A. The study design was longitudinal with pre-operative baseline data collected prior to neurostimulation and at intervals post operatively. RESULTS: 4/8 balance measures showed significant changes from pre-operative values and after 2 1/4 years of stimulation. Area of sway (EO) in quiet standing  $p = .022$  and total sway (EC) in the moving state  $p = .019$  and total sway (EC) in quiet standing showed an increase in sway  $p = .003$ . Area of sway (EC)  $p = .004$  tended to decrease. Regression analysis for frequency of stimulation showed an increase in sway with higher frequencies  $T = 1.99$ ,  $P = .05$ . CONCLUSION: Chronic VNS does not augment postural instability.

6. **Clarke BM, Upton AR, Griffin HM. Cognitive motor function after electrical stimulation of the vagus nerve. *Pacing Clin Electrophysiol.* 1992;15(10 Pt 2):1603-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/1383976>

**Abstract** Chronic stimulation of the vagus nerve does not seem to produce significant differences between high frequency and low frequency stimulation groups. Individuals within each group show significant changes between preoperative assessment and after 6-month stimulation. Some subjects showed significant improvement and some showed significant slowing of responses. Subjects who showed improvement are still considerably slower than normals, but all patients have a very long history of complex partial seizures and exposure to multiple medications. Larger homogeneous sample sizes are needed to delineate more clearly the correlation between cognitive performance, medication effects, and stimulation effects.

7. **Clarke BM, Upton AR, Griffin HM. Acute effects of high frequency vagal nerve stimulation on balance and cognitive motor performance in epilepsy: three case study reports. *Pacing Clin Electrophysiol.* 1992;15(10 Pt 2):1608-13.**

<http://www.ncbi.nlm.nih.gov/pubmed/1383977>

**Abstract** Quantitative measures of area of sway, total sway, and cognitive function failed to show significant differences in acute (50 minute) "ON-OFF-ON-OFF" studies of high frequency left vagal stimulation in three epileptic patients undergoing treatment for chronic complex partial seizures. Fluctuation in blood levels of anticonvulsants may have been associated with some clinical effects. There were no significant adverse effects of acute left vagal stimulation in these three subjects.

8. **Clarke BM, Upton AR, Kamath M, Griffin HM. Electrostimulation effects of the vagus nerve on balance in epilepsy. *Pacing Clin Electrophysiol.* 1992;15(10 Pt 2):1614-30.**

<http://www.ncbi.nlm.nih.gov/pubmed/1383978>

**Abstract** Preliminary results of selected postural measures in quiet standing indicate that stimulation of the vagus nerve appears not to be producing adverse effects. With this specific sample size, more testing is needed to determine long-term effects and future data analyses will examine correlations between electroencephalogram results, drug levels, and seizure frequency. In the present study three subjects have had old injuries to hips and ankles. Two subjects had normal values for postural control prior to stimulation, while other subjects were severely abnormal. In future, studies should include larger homogeneous sample sizes, as the current subjects show marked variability in age and premorbid health backgrounds. Future work should also control more vigorously for variables such as visual input (i.e., blindfolding subjects instead of simply closing the eyes). Evaluation of postural control mechanisms will be continued to assess stability changes in these patients as seizure frequency continues to subside.

9. **Clarke BM, Upton A, Griffin H, Hudoba P. Balance and cognitive impairment in two epileptic patients before and after vagal nerve stimulation. *Pacing Clin Electrophysiol.* 1991;14(1):77-85.**

<http://www.ncbi.nlm.nih.gov/pubmed/1705340>

**Abstract** Balance and cognition were assessed in two patients with uncontrolled complex partial seizures. The patients were on anticonvulsant medications and were treated with left vagal stimulation. Balance and cognition were assessed before and after vagal stimulation, and the results were compared with age matched controls and older patients with Parkinson's disease. Severe impairments of function were found in the epileptic patients, and such negative effects of medication make vagal stimulation a potentially practical alternative treatment for uncontrolled epilepsy.

**QoL - Depression/Mood in Epilepsy (VNS in...)**

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1. **Klinkenberg S, Majoie HJ, van der Heijden MM, Rijkers K, Leenen L, Aldenkamp AP. Vagus nerve stimulation has a positive effect on mood in patients with refractory epilepsy. *Clin Neurol Neurosurg.* 2012;114(4):336-40.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22130047>  
**Abstract** BACKGROUND: Preliminary research on the efficacy of vagus nerve stimulation (VNS) indicated additional effects on neuropsychological variables like mood and quality of life (QOL). OBJECTIVES: The objectives of this prospective longitudinal observational cohort study were to assess the effects of VNS on mood, QOL and cognition in patients with refractory epilepsy and to determine whether these effects occur dependent of seizure control. METHODS: We included 41 patients with refractory epilepsy; treated with VNS as part of usual patient care. A neuropsychological battery was performed during baseline and repeated after 6 months of VNS in order to compare neuropsychological variables before and after VNS. All patients completed seizure diaries. RESULTS: Significant improvements were observed for both mood and QOL after 6 months of VNS; based on the results in the POMS and QOLIE-89 questionnaires ( $p < 0.05$ ). There was no significant change in cognition. Mean percentage change in seizure frequency was -9.0%, while 20% of the patients achieved a seizure frequency reduction of 50% or more. No significant correlation was found between changes in seizure frequency and improvements in mood or QOL. CONCLUSIONS: VNS is associated with improvements in both mood and QOL in patients with refractory epilepsy. Since these improvements appeared to be independent of seizure control, the results of this study indicate an additional antidepressant effect of VNS, which can be of extra value in view of the high co-morbidity of mood disturbances in patients with epilepsy.
  
2. **Noe KH, Locke DE, Sirven JI. Treatment of depression in patients with epilepsy. *Curr Treat Options Neurol.* 2011;13(4):371-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21472437>  
<http://link.springer.com/article/10.1007%2Fs11940-011-0127-8>  
**Abstract** OPINION STATEMENT: In this article, we review the current best evidence for the treatment of depression in patients with epilepsy. Depression is a common epilepsy comorbidity, but it is often unrecognized. The most important step in appropriately managing mood disorders in this population is making the diagnosis. Clinical vigilance and routine use of a validated screening tool can improve detection and quality of care. As is increasingly the case for the general population, persons with epilepsy are often interested in exploring alternative therapies for chronic conditions, including depression. Unfortunately, the benefit of complementary and alternative therapies for depression currently is largely unproven for persons with a seizure history, although an early study of exercise for mild depression has shown some benefit. Concerns about drug interactions, side effects, and expense may be barriers to the prescription of antidepressant medications for people requiring chronic antiepileptic drug (AED) therapy. For this reason, use of an AED with mood-stabilizing properties has appeal and may be appropriate for selected individuals with mild depressive symptoms. Undue fear of lowering seizure threshold should not preclude the prescription of an antidepressant medication, as the perceived risks are often overestimated and rarely outweigh the risk of leaving depression untreated. At present, the best evidence for efficacy and safety support the use of citalopram, sertraline, or mirtazapine as initial pharmacotherapy, whereas bupropion should be avoided. Start low, go slow, and use the lowest effective dose. Cognitive behavioral therapy is a valuable adjunct to antidepressant therapy in this population. For people with refractory partial epilepsy and refractory depression, vagus nerve stimulation has some appeal, in that it may be beneficial for both conditions, but the efficacy of vagus nerve stimulation in improving mood in patients with epilepsy remains unclear.

3. **Kaplan PW. Obsessive-compulsive disorder in chronic epilepsy. *Epilepsy Behav.* 2011;22(3):428-32.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21889913>  
**Abstract** There is a long-recognized association between obsessive-compulsive disorder (OCD) and chronic epilepsy, most notably refractory temporal lobe epilepsy (TLE). The literature documents this association with case reports, patient series, and some larger controlled studies that reveal that almost a quarter of patients with TLE exhibit OCD features, which may go unrecognized. Obsession features with ordering, symmetry, exactness, handwashing, and religiosity occur more often in persons with right- or left-sided epileptic foci than in those with idiopathic generalized epilepsies or controls. Neurobiological and social factors suggest abnormalities of the frontal-thalamic-pallidal-striatal-anterior cingulate-frontal circuits stemming from the observation that certain diseases, damage, or surgery along these circuits may produce or, conversely, reduce OCD in TLE. This review explores the literature on case reports, case series, and larger retrospective controlled studies and looks at the associations of epilepsy with OCD. Contemporary speculation on the theoretical neurobiological underpinnings provides some basis on how and where to direct treatment. Invasive deep brain stimulation has triggered recent controversy on newer treatment modalities.
  
4. **Borghetti D, Pizzanelli C, Maritato P, Fabbrini M, Jensen S, Iudice A, et al. Mismatch negativity analysis in drug-resistant epileptic patients implanted with vagus nerve stimulator. *Brain Res Bull.* 2007;73(1-3):81-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17499640>  
**Abstract** It is well known that some epileptic patients does not respond to conventional treatments, despite multiple combination of antiepileptic drugs, and they are therefore considered drug-resistant. For these patients, vagal nerve stimulation (VNS) represents a successful alternative to traditional therapy, and it is generally well tolerated; beside benefits on seizure frequency, VNS showed positive effects on cognition and mood. Aim of this study was to investigate short-term memory changes in a group of 12 patients implanted with VNS, through Mismatch Negativity wave (MMN). After 1 year of follow-up, MMN latencies and amplitudes did not show significant changes following VNS implantation, independently on current intensity, as compared with pre-implantation values. In two patients, MMN values, which were abnormal before VNS implantation, showed a major reduction in latency and an increase in amplitude after implantation, suggesting a likely positive effect of VNS on pre-attentive processes investigated by MMN.

5. **Barry JJ. The recognition and management of mood disorders as a comorbidity of epilepsy. *Epilepsia*. 2003;44 Suppl 4:30-40.**

<http://www.ncbi.nlm.nih.gov/pubmed/12823567>

**Notes** As the incidence rate of one of the most pressing worldwide medical problems continues to increase, the need for early detection and adequate treatment for depressive disorders is greater than ever. The detection and treatment of comorbid mood disorders among patients with other chronic conditions such as epilepsy, however, is even more problematic. Comorbid mood disorders, including subsyndromal symptoms, are often untreated or undertreated despite the fact that they further increase patients' disability and result in increased morbidity and mortality. This recent article by Barry discusses the importance of mood disorders in epilepsy as well as how to recognize and treat those disorders.

Antidepressant drugs, ECT, and VNS Therapy are all potential treatments for comorbid mood disorders.

**Abstract** Mood disorders, especially as a comorbid finding in people with medical disorders in general, and in those with epilepsy in particular, have become increasingly recognized as a serious health concern. Unfortunately, affective disorders are underrecognized, and appropriate treatment is infrequent. The consequences of poor detection of mood disorders in people with epilepsy are discussed, along with a review of risk factors and the appearance of the disorder in this population. Prevalence rates of both depressive and bipolar spectrum disorders in people with epilepsy appear to be higher than in the general population. Recent data from community samples show elevated rates of both disorders in people with epilepsy, significantly above those in people with and without other chronic diseases. Assessment issues, including the positive and negative side effects of antiepileptic drugs, are reviewed. Treatment options are discussed, along with caveats concerning the use of antidepressants in people with epilepsy, with a focus on safety, utility, and drug interactions. Electroconvulsive therapy can also be used safely in people with epilepsy, and vagus nerve stimulation may have some utility in the treatment of depressive disorders as well. However, despite improved detection methods and effective treatments, implementation of this knowledge in neurology outpatient clinics is still problematic.

6. **Chavel SM, Westerveld M, Spencer S. Long-term outcome of vagus nerve stimulation for refractory partial epilepsy. *Epilepsy Behav*. 2003;4(3):302-9.**

<http://www.ncbi.nlm.nih.gov/pubmed/12791333>

**Notes** This long-term, prospective study assessed 1- and 2-year outcomes of specific seizure types, quality of life, depression, and anxiety among 30 patients treated with VNS for refractory partial epilepsy. Patients with more depressive symptoms were less likely to experience seizure reduction with VNS than were patients with less depressive symptoms. No statistically significant changes from baseline to 12 or 24 months were found in mean quality of life, depression, or anxiety measures in the overall study population. Patients with at least 50% reduction in seizures had significant improvement in anxiety at 12 and 24 months compared with patients who did not have the same degree of seizure reduction.

**Abstract** We assessed 1- and 2-year outcomes of specific seizure types, quality of life, depression, and anxiety among patients treated with vagus nerve stimulation (VNS) for refractory partial epilepsy. Patients completed a seizure questionnaire, the Quality of Life in Epilepsy-89 (QOLIE-89) questionnaire, the Beck Anxiety Inventory (BAI), and the Beck Depression Inventory (BDI) at baseline and 1 year, and 2 years after activation of VNS. VNS was associated with  $\geq 50\%$  reduction in total seizure frequency in 54% of patients at 1 year and 61% of patients 2 years post-VNS activation compared with baseline. No statistically significant changes from baseline to 12 or 24 months were found in mean quality of life, depression, or anxiety measures in the overall study population. Patients with at least 50% reduction in seizures had significant improvement in anxiety at 12 and 24 months compared with patients who did not have the same degree of seizure reduction.

7. **Krishnamoorthy ES. Treatment of depression in patients with epilepsy: problems, pitfalls, and some solutions. *Epilepsy Behav.* 2003;4 Suppl 3:S46-54.**

<http://www.ncbi.nlm.nih.gov/pubmed/14592640>

**Notes** The complex relationship between depression and epilepsy is discussed, with a special emphasis placed on “unique” syndromes of depression specific to patients with epilepsy. The management of depression among epilepsy patients also is presented, including the use of ECT, antidepressant drugs, psychological therapies, and combination treatments. VNS therapy, which may have the possibility of positive benefits for both disorders (depression and epilepsy), is one novel treatment option for this patient population that also is discussed. A cross-cultural perspective on these two comorbid disorders also is provided.

**Abstract** Many people with epilepsy suffer from comorbid depression. Despite this, there have been few studies addressing the treatment of depression in this population, and the literature on psychiatric management techniques in patients with epilepsy is composed largely of opinions rather than evidence from randomized, controlled trials or other systematic investigations. Antidepressant drugs, including tricyclics and selective serotonin reuptake inhibitors, can be used to treat patients with epilepsy and comorbid depression. Nonpharmacological treatment options include vagus nerve stimulation, transcranial magnetic stimulation, and psychological therapies including cognitive-behavioral therapy, individual or group psychotherapy, patient support groups, family therapy, and counseling. Another important area that remains largely uninvestigated is psychiatric research in patients with epilepsy in non-Western cultures (with the exception of Japan). Factors such as problems with access to and acceptability of therapies in many developing nations have further implications for the treatment of psychiatric disorders in epilepsy.

8. **Harden CL, Goldstein MA. Mood disorders in patients with epilepsy: epidemiology and management. *CNS Drugs.* 2002;16(5):291-302.**

<http://www.ncbi.nlm.nih.gov/pubmed/11994019>

**Abstract** Patients with epilepsy are at high risk for depression because of an incompletely understood combination of factors that may be both psychosocial and neurological. Interictal depression in patients with epilepsy is an undertreated condition, in part because of concern regarding drug interactions and the risk of exacerbating seizures with antidepressant treatment. Bipolar disorder is not described as occurring with a higher than expected frequency in the population with epilepsy, but high rates of depression and suicide are well recognised, highlighting the need for more emphasis on antidepressive treatment in this group of at-risk patients. Neurological factors, including site and lateralisation of seizure focus, may be important for the development of depression, with left-sided seizure foci having a higher association with depressive symptoms. Forced normalisation may be a factor in the paradoxical onset of depression in patients with epilepsy whose seizures suddenly become well controlled by anti-seizure treatment. Lowering of folic acid levels by some antiepileptic drugs (AEDs) may also influence the expression of depression in patients with epilepsy. New AEDs continue to emerge as beneficial treatments themselves for mood disorders, with lamotrigine, gabapentin and, to a lesser extent, topiramate having clinical trials data to support their use in patients with bipolar disease. Similar positive data are available for vagal nerve stimulation. Mood effects of AEDs can be complicated, however, as many of these drugs (e.g. tiagabine) have also been reported to cause depression as an adverse effect. Electroconvulsive therapy in depressed patients with epilepsy requires special consideration. The selective serotonin reuptake inhibitors (SSRIs) and antidepressants that act at multiple receptors (e.g. nefazodone, venlafaxine) are the most appropriate treatments for depressed patients with epilepsy. Among these agents, citalopram has a low risk of interactions with AEDs. Bupropion, clomipramine and maprotiline are associated with a greater risk of seizures compared with other antidepressants and consequently should be used with caution in the treatment of depression in patients with epilepsy.

9. **Harden CL. The co-morbidity of depression and epilepsy: epidemiology, etiology, and treatment. *Neurology*. 2002;59(6 Suppl 4):S48-55.**

<http://www.ncbi.nlm.nih.gov/pubmed/12270969>

**Abstract** Co-morbid depression is common in patients with epilepsy and is often undiagnosed. The manifestation of depression in epilepsy is multifaceted with many interacting neurobiological and psychosocial determinants, including clinical features of epilepsy (seizure frequency, type, foci, or lateralization of foci) and neurochemical or iatrogenic mechanisms. Depression is reported more frequently in patients with temporal lobe epilepsy (TLE) and left-sided foci, although not all studies support this finding. In patients with depression and epilepsy, optimal control of seizures should be attained first and foremost with appropriate anticonvulsant treatments including antiepileptic drugs (AEDs) and vagus nerve stimulation (VNS) therapy. Some anticonvulsant treatments (VNS, valproate, carbamazepine, lamotrigine, and gabapentin) have demonstrated mood improvement in epilepsy patients and may have therapeutic potential for this patient population. When antidepressants are necessary to treat depression in patients with epilepsy, selective serotonin reuptake inhibitors (SSRIs) and multireceptor antidepressants are considered first-line treatments. Electroconvulsive therapy is not contraindicated for treatment-resistant or psychotic depression. Depression must be recognized, diagnosed, and adequately treated in patients with epilepsy.

10. **Krishnamoorthy ES. Psychiatric issues in epilepsy. *Curr Opin Neurol*.**

**2001;14(2):217-24.** <http://www.ncbi.nlm.nih.gov/pubmed/11262739>

**Abstract** In recent years there has been considerable research interest at the interface between epilepsy and psychiatry. Topics of interest include the epidemiology of psychiatric co-morbidity in epilepsy; clinical syndromes at this interface and their classification; the relationship between cognitive dysfunction and psychiatric co-morbidity; biological mechanisms that mediate such co-morbidity, especially with developments in imaging and genetic research; the association between temporal lobe surgery, vagus nerve stimulation, and other non-pharmacological treatments, and the development of such co-morbidity; the contribution of anticonvulsant drugs towards the development of psychiatric co-morbidity; quality of life and other psychosocial issues; and non-epileptic attack disorder. In this review, papers on these psychiatric issues in epilepsy, with a focus on those published in the past year (October 1999 to October 2000) are critically evaluated, and some important current issues at this interface are considered in detail.

11. **Hoppe C, Helmstaedter C, Scherrmann J, Elger CE. Self-Reported Mood Changes following 6 Months of Vagus Nerve Stimulation in Epilepsy Patients. *Epilepsy Behav*. 2001;2(4):335-42.**

<http://www.ncbi.nlm.nih.gov/pubmed/12609210>

**Abstract** Vagus nerve stimulation (VNS) for treatment of drug-resistant epileptic seizures has been reported to have additional positive mood effects as obtained by psychiatric ratings. To avoid rater bias effects, this study used self-report questionnaires and examined changes in self-reported mood and health-related quality of life following 6 months of VNS treatment. From 40 adult patients treated with VNS since the beginning of the study, 28 patients (mean age: 35.4 years) with unchanged medication were included. Repeated-measures MANOVA revealed a significant general mood improvement. Post hoc univariate tests obtained improvements of tenseness and dysphoria but not of depression, level of activity, or health-related quality of life. Mood and seizure outcome were correlated. VNS may improve unspecific states of indisposition and dysphoria. Absolute seizure reduction contributes to this antidysphoric effect. Since baseline depression scores were low, findings do not contradict but complement earlier reports of an antidepressive effect of VNS.

12. **Harden CL. Mood changes in epilepsy patients treated with vagus nerve stimulation. *Epilepsy Behav.* 2001;2(3 Suppl):S17-20.**  
<http://www.sciencedirect.com/science/article/pii/S1525505001902033>  
**Abstract** Epilepsy treatments are often used by psychiatrists for their mood-stabilizing effects. Epilepsy patients treated with vagus nerve stimulation (VNS) have experienced improvements in mood and attentiveness. This anecdotal observation prompted several epileptologists to evaluate whether VNS has a quantifiable effect on mood improvement in epilepsy patients. The studies on mood changes in epilepsy patients are reviewed herein, and their implications regarding mood evaluation in epilepsy, the use of VNS in patients with psychiatric disorders, and the effect of seizure frequency on mood and anxiety are further discussed.
13. **Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper JP, Labar DR. A Pilot Study of Mood in Epilepsy Patients Treated with Vagus Nerve Stimulation. *Epilepsy Behav.* 2000;1(2):93-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12609137>  
**Abstract** Context. Antiepileptic drugs (AEDs) are frequently used for their beneficial mood effects.Objective. We sought to determine if there was a quantifiable effect on mood of the vagus nerve stimulator (VNS) when used as an antiseizure treatment.Design. Mood was assessed before and 3 months after VNS implantation in adult epilepsy patients. A group of adult epilepsy patients on stable AED regimens were used as a comparison group. AED regimens were unchanged during the study. The change in mood scale scores across time was assessed by t test (intragroup) and two-factor repeated-measures ANOVA (intergroup).Setting. An epilepsy center in a university hospital was the setting.Subjects. Twenty consecutive adult epilepsy patients undergoing VNS implantation to improve seizure control and twenty adult seizure patients with no intervention were enrolled.Main outcome measures. The mood scales used were the Cornell Dysthymia Rating Scale (CDRS) and the Hamilton Depression (Ham-D), Hamilton Rating Scale for Anxiety (Ham-A), and Beck Depression Inventory (BDI) scales.Results. The VNS group showed a significant decrease in mood scale scores across time (t test CDRS P = 0.001, Ham-D P = 0.017, BDI P = 0.045), indicating a decrease in depressive symptoms. The Ham-A scores in the VNS group and the comparison group scores did not significantly change across time. There were no significant differences between groups across time, although the BDI approached significance at P = 0.07. The VNS group had a significant decrease in seizure frequency compared with the comparison group (P = 0.01). There was no difference in mood scales over time between the VNS treatment responders (defined by >50% decrease in seizure frequency) and nonresponders, suggesting dissociation between seizure frequency reduction and mood change.Conclusion. VNS treatment is associated with mood improvement as measured by multiple scales, but differences in mood scale scores over time between the VNS and a comparison group were not found.

14. **Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res.* 2000;42(2-3):203-10.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11074193>  
**Abstract** Vagus nerve stimulation (VNS) has gained increasing acceptance for treatment of drug-resistant seizures. The aim of this study was to evaluate effects of VNS on depressed mood in epilepsy patients during the first 6 months after implantation of the stimulation device. This study was conducted as an addition to the international multisite randomized and double-blind controlled trial on anti-seizure effects of VNS (EO3). Only adult patients with >4/month medication-resistant complex-partial seizures were included (N=11). During the acute phase of the study (3 months after implantation), patients were randomly assigned to low (stimulation detection) versus high stimulation (maximal tolerability, maximum 1.75 mA). Mood and mood changes were recorded based on standardized psychiatric rating scales and self-report questionnaires. Patients were assessed 4 weeks before (baseline) as well as 3 and 6 months after implantation. Significant positive mood effects were observed in most scales and subscales at the 3-month follow-up (P<0.05). Mood improvements were sustained at the 6-month follow-up and were independent of effects on seizure activity (9/11 mood responders versus 2/11 seizure responders). Mood effects appeared more pronounced in the high stimulation group after the acute study phase, but findings were not significant (P<0.10). VNS is associated with mood improvements in patients with epilepsy, but to confirm VNS dose effects, studies with more statistical power are needed.
15. **Jobe PC, Dailey JW, Wernicke JF. A noradrenergic and serotonergic hypothesis of the linkage between epilepsy and affective disorders. *Crit Rev Neurobiol.* 1999;13(4):317-56.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11028680>  
**Abstract** Noradrenergic and/or serotonergic deficits, as well as other abnormalities, may contribute to predisposition to some epilepsies and depressions. Evidence for this hypothesis stems from several sources. Epidemiological investigations are intriguing but incomplete. Pharmacological studies show that noradrenergic and/or serotonergic transmission are both anticonvulsant and antidepressant. Therapeutically pertinent investigations show that antidepressant drugs have anticonvulsant properties, whereas antiepileptic drugs are effective in the management of affective disorders. Additional investigations demonstrate that seizures, whether spontaneously occurring or therapeutically induced, protect against depression. Through studies of innate pathophysiology, noradrenergic and serotonergic deficits have been identified in individuals with depression and in animal models of epilepsy, as well as in some humans with epilepsy. Vagal nerve stimulation, a treatment already known to be effective in the epilepsies, is presently under investigation for effectiveness in affective disorder. New evidence suggests that vagal nerve stimulation exerts at least some of its therapeutic effects through its capacity to increase noradrenergic and serotonergic transmission. Finally, emerging evidence supports the concept that some genetic mammalian models of the human epilepsies exhibit analogous manifestations of depression.

**QoL - Other (VNS and...)**

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1. **Sperling W, Biermann T, Spannenberger R, Clepce M, Padberg F, Reulbach U, et al. Changes in gustatory perceptions of patients with major depression treated with vagus nerve stimulation (VNS). *Pharmacopsychiatry*. 2011;44(2):67-71.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21157695>  
**Abstract** BACKGROUND: Olfactory and gustatory functions were investigated before and during vagus nerve stimulation (VNS) in a group of 9 patients with therapy-resistant depression, implanted with a VNS system. METHODS: Gustation and olfaction were tested using standard sniffing tests. Subjects participated in 2 sessions with the vagal stimulator switched on and off, respectively. RESULTS: Under conditions of stimulation of the VNS, there were statistically significant differences of the threshold of perception, with an intensification of the taste "sweet" ( $Z = -2.0$ ;  $p = 0.048$ ) and "bitter" ( $Z = -2.5$ ;  $p = 0.011$ ) compared to the "off-mode". A statistical trend ( $Z = -1.7$ ;  $p = 0.098$ ) for increased intensity of the taste "salty" was observed, however, these results would supposedly disappear after correction for multiple testing presumably due to the large number of variables and the small sample size. There were no statistically relevant differences concerning olfactory perception. CONCLUSIONS: The changes of gustatory perception under conditions of vagal nerve stimulation observed in this study show another important central nervous effect of vagal stimulation on the limbic system that might be of importance in the elucidation of mechanisms of action of VNS especially on refractory depression.
  
2. **Kaufman EL. Mu-metal magnetic shield box to improve the day-to-day quality of life for vagus nerve stimulator patients. *Epilepsy Behav*. 2009;14(2):432.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19032988>
  
3. **Kirchner A, Landis BN, Haslbeck M, Stefan H, Renner B, Hummel T. Chemosensory function in patients with vagal nerve stimulators. *J Clin Neurophysiol*. 2004;21(6):418-25.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15622128>  
**Abstract** Chemosensory function is determined by the interplay of numerous sensory modalities. The present study aimed to evaluate the possible influence of electrical stimulation of the left-sided vagal nerve on gustatory and olfactory function in patients with vagal nerve stimulation (VNS). Gustation and olfaction were tested using psychophysical techniques; olfactory function was additionally evaluated using event-related potentials. A total of 11 subjects participated (six men and five women, aged 21 to 56 years). The vagal stimulator was run in "rapid cycle mode" in 10 patients, whereas one patient was treated with "normal mode" VNS. Subjects participated in two sessions, with the vagal stimulator switched on and off, respectively. The sequence of the two sessions was randomized across all participants. Using air-dilution, olfactometry event-related potentials to the specific olfactory stimulant H<sub>2</sub>S were recorded. Psychophysical tests were performed using the "Sniffin' Sticks" test kit, a test for retronasal olfactory function, and a gustatory test based on impregnated filter paper. The study yielded the following major results: (1) VNS produced a prolongation of P2 latencies of olfactory ERP, and (2) patients with therapeutic benefit from VNS in terms of seizure control had larger amplitudes during the on period than during the off period. In conclusion, using electrophysiological measures of olfactory function, the present study indicated a significant role of VNS in the processing of olfactory information.

**QoL - Overall in Epilepsy (VNS in...)**

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- 1. Vonck K, Raedt R, Boon P. Vagus nerve stimulation and the postictal state. *Epilepsy Behav.* 2010;19(2):182-5. <http://www.ncbi.nlm.nih.gov/pubmed/20724218>**

**Abstract** Vagus nerve stimulation (VNS) is an established neurostimulation therapy used to treat refractory epilepsy. The effect of acute or chronic VNS on the postictal state as a separate entity is seldom reported in clinical or experimental studies. Apart from its antiseizure effects, VNS has several other beneficial effects. These effects may be of particular benefit for patients with postictal neuropsychiatric symptoms. The hypothesized mechanisms underlying the initiation and sustainment of the postictal phase, to some extent, overlap with mechanisms involved in the seizure-suppressing effects of VNS as well as other neurological and psychotropic effects of VNS. Both the clinical symptoms and the basic research hypotheses of the postictal state show similarities with clinical effects induced by VNS and its underlying mechanisms of action.
- 2. McGlone J, Valdivia I, Penner M, Williams J, Sadler RM, Clarke DB. Quality of life and memory after vagus nerve stimulator implantation for epilepsy. *Can J Neurol Sci.* 2008;35(3):287-96; comment 276-7. <http://www.ncbi.nlm.nih.gov/pubmed/18714795>**

**Abstract** **OBJECTIVE:** This prospective, case control study evaluates quality of life (QOL), depressive affect, and memory outcomes of epilepsy patients implanted with a vagus nerve stimulator (VNS). **METHODS:** Three groups of patients with epilepsy underwent assessment on two occasions: 1) patients with a VNS were tested before and 12 months after implantation (n = 16); 2) patients who underwent cerebral resective surgery were tested pre- and post-operatively (n = 10); and 3) patients under medical management (n = 9). Group means were compared on the QOLIE-89, Geriatric Depression Scale, Wechsler Memory Scale - III, and the Memory Observation Questionnaire. Secondary analyses calculated the reliable change index, providing information on change beyond measurement error and chance. **RESULTS:** Mean ratings of QOL, depression, and memory complaints and objective memory scores remained stable or improved in all the groups. The QOL improved more after cerebral resective surgery than VNS or medication controls, but the VNS and medication control groups did not differ. In the VNS group, QOL was not related to seizure reduction. The percentage of cases showing real change in memory was equivalent across groups, except in one of eight indices (i.e., verbal recognition memory). **CONCLUSIONS:** This first case controlled design found that vagus nerve stimulation as an adjunctive therapy for seizure control did not change QOL, depressive affect, or objective memory scores over one-year more so than medical management alone. We point out the need for larger case control, non-industry funded investigations.
- 3. Wheless JW. Intractable epilepsy: A survey of patients and caregivers. *Epilepsy Behav.* 2006;8(4):756-64. <http://www.ncbi.nlm.nih.gov/pubmed/16675306>**

**Abstract** The social and health consequences associated with epilepsy are often magnified among patients with refractory epilepsy. Despite recent advances in the treatment of seizure disorders, many people with epilepsy continue to suffer from uncontrolled seizures and adverse side effects from medical therapy. This survey is the first to focus solely on the experiences, attitudes, and quality of life of a refractory epilepsy population, both those with the condition and their caregivers. To participate in this survey, respondents had to currently be experiencing seizures or troubling treatment side effects and had to have tried at least two different epilepsy medications. These survey data represent three groups of participants (n = 903): those with epilepsy who self-reported on their condition (Group 1, n = 503), the caregivers of those with refractory epilepsy (Group 2, n = 200), and those with epilepsy who had their condition reported on by a caregiver (Group 3, n = 200). This survey revealed that the negative consequences associated with epilepsy tend to be greater among those experiencing treatment side effects and a greater number of seizures. Physicians must take into account medication side effects and quality-of-life issues when treating patients with epilepsy.

- 4. McLachlan RS, Sadler M, Pillay N, Guberman A, Jones M, Wiebe S, et al. Quality of life after vagus nerve stimulation for intractable epilepsy: is seizure control the only contributing factor? *Eur Neurol.* 2003;50(1):16-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12824707>  
<http://www.karger.com/Article/FullText/70853>

**Notes** This prospective, 1-year study (n=27) is one of the few to have used validated scales to evaluate the effects of VNS therapy on quality of life among patients with epilepsy. Consistent with previous findings, both objective and subjective improvements (some significant) in quality of life did not correlate with changes in seizure frequency, which were modest in this study. Adverse effects were absent or mild in two-thirds of the subjects, but several patients did experience adverse events in addition to the typical effects of hoarseness and coughing such as transient vocal cord paralysis, difficulty swallowing during stimulation, severe neck and throat pain, and intractable vomiting, which occurred in one patient but resolved when the stimulation current was reduced. At 1 year, one patient had discontinued the study owing to painful side effects in the throat and neck. This study is out of Canada and is a good resource for quality-of-life data with VNS therapy.

**Abstract** We assessed the impact of vagus nerve stimulation on a cohort of patients with intractable epilepsy. A 1-year prospective trial of vagus nerve stimulation for intractable epilepsy was done in 26 patients. Seizure frequency, anti-epileptic drugs, and quality of life were assessed using QOLIE-89, ELDQOL, and a Likert scale of impact of treatment. Seizures were reduced by more than 50% in 19% of the patients, by less than 50% in 46%, and were unchanged in 35% of them. Antiepileptic drugs were reduced in 43% of the patients. There was a significant improvement in the mean overall QOLIE-89 score and other measures of quality of life, but these did not correlate with changes in seizure frequency. Subjective improvement occurred in 84% of the patients. The quality of life improves in some patients following vagus nerve stimulation for intractable epilepsy. The favorable effects of this treatment may be attributable to additional factors besides seizure control which in this study was modest.
- 5. Farnalls SL, Rennick J. Parents' caregiving approaches: facing a new treatment alternative in severe intractable childhood epilepsy. *Seizure.* 2003;12(1):1-10.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12495642>  
[http://ac.els-cdn.com/S1059131102001693/1-s2.0-S1059131102001693-main.pdf?\\_tid=8c588548-8cc3-11e2-9d2e-00000aab0f26&acdnat=1363278407\\_cb013b014779814af83abf02cad48cc8](http://ac.els-cdn.com/S1059131102001693/1-s2.0-S1059131102001693-main.pdf?_tid=8c588548-8cc3-11e2-9d2e-00000aab0f26&acdnat=1363278407_cb013b014779814af83abf02cad48cc8)

**Abstract** Parents of children with severe and intractable epilepsy face profound caregiving challenges, dealing with their child's frequent and intense seizures, accompanying physical, social and psychological problems, and ongoing quest for seizure control through a variety of medications, diet and surgery. With the advent of a new, surgical treatment for epilepsy, vagus nerve stimulation (VNS), these parents have been presented with a renewed possibility of seizure control for their children. While many studies have investigated the effects of VNS on seizure frequency and intensity, none have looked at parents' experiences in facing this potentially life changing treatment for their child. This multiple-case study addresses this gap by exploring the experiences of nine parents of children receiving VNS. Collected over a 6-month period following parents in the hospital, clinic and in their homes, data from 22 in-depth interviews revealed that parents facing a new treatment alternative for their child experienced uncertainty around treatment efficacy and had a need to exert control over their expectations. Ongoing caregiving approaches adopted by these parents were consistent with existing literature on families living with childhood chronic illness, however, new insights were gained from parents' sharing of positive life perspectives gained through their experiences. These findings provide guidance for health care professionals working with the parents of children with severe, intractable epilepsy.
- 6. Wild D. Epilepsy therapies have similar impact on quality of life. *CNS News.* 2002;12.**

7. **Dodrill CB, Morris GL. Effects of Vagal Nerve Stimulation on Cognition and Quality of Life in Epilepsy. *Epilepsy Behav.* 2001;2(1):46-53.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12609181>  
**Abstract** To evaluate the cognitive and quality-of-life (QOL) impacts of vagal nerve stimulation (VNS), 160 patients with uncontrolled partial seizures from 20 sites were enrolled in a double-blind study. Patients were randomly assigned to low (minimal) stimulation (n = 82) or high (now clinically used) stimulation (n = 78) conditions and given a group of cognitive and QOL tests before implantation and after 12-16 weeks of VNS treatment. Results showed no clear cognitive changes. However, fewer emotional and physical problems were reported by the High Group than the Low Group at the end of the study. The 32 patients who had at least 50% seizure relief showed slightly more improvement in QOL variables than those patients who did not demonstrate this degree of seizure reduction. Overall, a small number of favorable QOL but no cognitive changes were associated with levels of VNS stimulation that are now typically used clinically.
8. **Labar D. Effects of Vagal Nerve Stimulation on Cognition and Quality of Life. To the Editor. *Epilepsy Behav.* 2001;2(2):161-2.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12609201>
9. **Dodrill CB, Morris GL. Reply. *Epilepsy Behav.* 2001;2(2):162.** <http://www.ncbi.nlm.nih.gov/pubmed/12609202>
10. **Ergene E, Behr PK, Shih JJ. Quality-of-Life Assessment in Patients Treated with Vagus Nerve Stimulation. *Epilepsy Behav.* 2001;2(3):284-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12609371>  
**Abstract** Vagus nerve stimulation (VNS) is a novel therapy used in patients with medically intractable epilepsy. We administered a Quality of Life in Epilepsy-10 (QOLIE-10) questionnaire consisting of questions designed to assess the patients' rating of their memory, level of physical and mental well-being, energy, depression, worries about seizures and work, social limitations, and overall quality of life on VNS treatment. The questionnaire was administered before and at 1-3 weeks, 5-7 weeks, 3 months, 6 months, and 9-12 months after the initiation of VNS in 17 patients. QOLIE-10 scores were significantly better after the initiation of the therapy as compared with baseline (P < 0.01). There was no correlation between the improvement in QOLIE-10 scores and the reduction in seizure frequency, decreased severity of seizures, or increased level of energy/alertness. We conclude that VNS therapy is associated with a significant improvement in subjective quality of life.
11. **Cramer JA. Exploration of Changes in Health-Related Quality of Life after 3 Months of Vagus Nerve Stimulation. *Epilepsy Behav.* 2001;2(5):460-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12609284>  
**Abstract** Purpose. The goal of this work was to explore changes in health-related quality of life (HRQOL) and reductions in seizure frequency among patients initiating vagus nerve stimulation (VNS) for medication-refractory epilepsy. Methods. Patients receiving VNS completed the Quality of Life in Epilepsy-10 (QOLIE-10) at baseline and after 3 months of stimulation. Patients were categorized as responders (>=50% seizure reduction) and nonresponders (<50% seizure reduction). Data were analyzed for change from baseline to 3 months within each group and between groups. Results. Both groups reported improvements in almost all aspects of HRQOL. Statistically significant improvements were reported by responders in energy, memory, social aspects, mental effects, and fear of seizures; and by nonresponders in downheartedness and overall QOL. Responders improved significantly more than nonresponders in energy. Conclusions. These exploratory analyses showed little difference in HRQOL between responders and nonresponders, with both reporting improvements after 3 months of VNS. Follow-up may determine whether improvements are sustained or attributable to placebo effect.

**Real-World Outcomes - Prospective Studies (VNS in...)**

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1. **Garcia-Navarrete E, Torres CV, Gallego I, Navas M, Pastor J, Sola RG. Long-term results of vagal nerve stimulation for adults with medication-resistant epilepsy who have been on unchanged antiepileptic medication. *Seizure*. 2013;22(1):9-13.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23041031>  
**Abstract** PURPOSE: Several studies suggest that vagal nerve stimulation (VNS) is an effective treatment for medication-resistant epileptic patients, although patients' medication was usually modified during the assessment period. The purpose of this prospective study was to evaluate the long-term effects of VNS, at 18 months of follow-up, on epileptic patients who have been on unchanged antiepileptic medication. METHODS: Forty-three patients underwent a complete epilepsy preoperative evaluation protocol, and were selected for VNS implantation. After surgery, patients were evaluated on a monthly basis, increasing stimulation 0.25mA at each visit, up to 2.5mA. Medication was unchanged for at least 18 months since the stimulation was started. The outcome was analysed in relation to patients' clinical features, stimulation parameters, epilepsy type, magnetic resonance imaging (MRI) results, and history of prior brain surgery. RESULTS: Of the 43 operated patients, 63% had a similar or greater than 50% reduction in their seizure frequency. Differences in the responder rate according to stimulation intensity, age at onset of epilepsy, duration of epilepsy before surgery, previous epilepsy surgery and seizure type, did not reach statistical significance. Most side effects were well tolerated. CONCLUSIONS: 62.8% of our series of 43 medication-resistant epileptic patients experienced a significant long-term seizure reduction after VNS, even in a situation of on unchanged medical therapy. Patient characteristics predictive of VNS responsiveness remain subject to investigation. Controlled studies with larger sample sizes, on VNS for patients with medication-resistant epilepsy on unchanged medication, are necessary to confirm VNS efficacy for drug-resistant epilepsy, and to identify predictive factors.
  
2. **Elliott RE, Morsi A, Kalthorn SP, Marcus J, Sellin J, Kang M, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. *Epilepsy Behav*. 2011;20(1):57-63.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21144802>  
**Abstract** OBJECTIVE: The goal of this study was to assess the efficacy and safety of vagus nerve stimulation in a consecutive series of adults and children with treatment-resistant epilepsy (TRE). METHODS: In this retrospective review of a prospectively created database of 436 consecutive patients who underwent vagus nerve stimulator implantation for TRE between November 1997 and April 2008, there were 220 (50.5%) females and 216 (49.5%) males ranging in age from 1 to 76 years at the time of implantation (mean: 29.0 +/- 16.5). Thirty-three patients (7.6%) in the primary implantation group had inadequate follow-up (<3 months from implantation) and three patients had early device removal because of infection and were excluded from seizure control outcome analyses. RESULTS: Duration of vagus nerve stimulation treatment varied from 10 days to 11 years (mean: 4.94 years). Mean seizure frequency significantly improved following implantation (mean reduction: 55.8%, P<0.0001). Seizure control >= 90% was achieved in 90 patients (22.5%), >= 75% seizure control in 162 patients (40.5%), >= 50% improvement in 255 patients (63.75%), and <50% improvement in 145 patients (36.25%). Permanent injury to the vagus nerve occurred in 2.8% of patients. CONCLUSION: Vagus nerve stimulation is a safe and effective palliative treatment option for focal and generalized TRE in adults and children. When used in conjunction with a multidisciplinary and multimodality treatment regimen including aggressive antiepileptic drug regimens and epilepsy surgery when appropriate, more than 60% of patients with TRE experienced at least a 50% reduction in seizure burden. Good results were seen in patients with non-U.S. Food and Drug Administration-approved indications. Prospective, randomized trials are needed for patients with generalized epilepsies and for younger children to potentially expand the number of patients who may benefit from this palliative treatment.

3. **Muller K, Fabo D, Entz L, Kelemen A, Halasz P, Rasonyi G, et al. Outcome of vagus nerve stimulation for epilepsy in Budapest. *Epilepsia*. 2010;51 Suppl 3:98-101.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20618411>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2010.02620.x/asset/j.1528-1167.2010.02620.x.pdf?v=1&t=he94215t&s=c92814dd88d56f68a74f4990721dca15685dd0e9>  
**Abstract** Vagus nerve stimulation (VNS) is a nonpharmacologic therapeutic option for patients with intractable epilepsy. Better clinical outcomes were recorded in nonfocal and Lennox-Gastaut syndrome (LGS). We conducted a 2-year, open label, prospective study to measure the seizure outcome of 26 VNS patients. The seizure numbers were assessed using clinician's global impression scale (CGI) and patient diaries. The average seizure reduction was 23% at the first year and 22% at the second year. Seizure reduction was more pronounced among patients with nonfocal than with focal epilepsy. The response rate was 50% at first year and 30% at the second year. The best CGI record for clinically significant improvement was 15% in the LGS group. The only statistically significant result was the reduction of the generalized tonic-clonic seizures (GTCS). The side-effect profile was good; however, the large number of mild and reversible effects influenced the stimulation parameters and thus probably the effectiveness of the therapy. We suggest that VNS is an optional treatment mostly in cases of therapy-resistant Lennox-Gastaut syndrome. Patients with GTCS may experience improvement such as reduction of seizure severity. We conclude that VNS is a safe neuromodulatory treatment, but future developments of neuromodulatory approaches are needed.
4. **Ardesch JJ, Buschman HP, Wagener-Schimmel LJ, van der Aa HE, Hageman G. Vagus nerve stimulation for medically refractory epilepsy: a long-term follow-up study. *Seizure*. 2007;16(7):579-85.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17543546>  
**Abstract** INTRODUCTION: Vagus nerve stimulation (VNS) is thought to have a cumulative effect in time on seizure frequency reduction. There also might be other variables than reduction of seizure frequency in order to determine VNS efficacy. In this study we describe the long-term outcome of the first group of vagus nerve stimulation patients with pharmaco-resistant epilepsy at the Medisch Spectrum Twente, The Netherlands. METHODS: This long-term descriptive prospective study included 19 patients, 11 males and 8 females, aged 17-46 years with pharmaco-resistant epilepsy. They had received 3-16 (mean 9) different anti-epileptic drugs and were not eligible for surgical resection of an epileptic focus. A vagus nerve stimulator was implanted in the period April 1999-October 2001. Follow-up ranges from 2 to 6 years (mean 4 years). Efficacy was measured as the percentage change in seizure rate during 1 year and then after each year follow-up of VNS compared to 5 months baseline before implantation. RESULTS: Mean seizure reduction at 1-6 years was, respectively, 14% (n = 19), 25% (n = 19), 29% (n = 16), 29% (n = 15), 43% (n = 9) and 50% (n = 7). Because of VNS two patients were able to start living without supervision. One patient died after 2 years of follow-up possibly as a result of SUDEP. Four patients had no apparent reduction in seizure frequency. Two of them had their stimulator removed. The other two patients however had significantly reduced post-ictal periods and seizure time and received a new pulse generator when the battery was depleted. One stimulator was switched off due to adverse effects, even though there was a positive effect on his seizure reduction. In six patients the medication regimen was changed during VNS by adding one anti-epileptic drug, however without significant change in seizure reduction. Adverse effects were hoarseness and coughing during stimulation. One patient had a temporary paralysis of his left vocal cord. CONCLUSION: We think that VNS is an effective treatment for pharmaco-resistant epilepsy and its positive effect persists during the years of follow-up. Our results suggest that seizure reduction should not be considered as the only variable of importance to describe the outcome of VNS on epilepsy and it is worthwhile to look at other outcome measures.

5. **Vonck K, Thadani V, Gilbert K, Dedeurwaerdere S, De Groote L, De Herdt V, et al. Vagus nerve stimulation for refractory epilepsy: a transatlantic experience. *J Clin Neurophysiol.* 2004;21(4):283-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15509917>

**Abstract** Vagus nerve stimulation (VNS) is an alternative treatment for medically or surgically refractory epilepsy. The long-term efficacy and safety of VNS were evaluated in a large patient series at Ghent University Hospital and Dartmouth-Hitchcock Medical Center. Between March 1995 and February 2003, seizure frequency and type as well as prescribed antiepileptic drugs and side effects were prospectively assessed in 131 patients treated with VNS in either center. Patients with a minimum follow-up duration of 6 months were included in the efficacy and safety analysis. A total of 118 of 131 implanted patients had a minimum postimplantation follow-up period of 6 months (mean, 33 months). The mean age of these patients was 32 years and the mean duration of refractory epilepsy was 22 years. The mean reduction in monthly seizure frequency in all patients was 55% (range, 0-100; SD = 31.6). Seven percent of patients were free of seizures with impaired consciousness, 50% of patients had a seizure frequency reduction of more than 50%, and 21% of patients were nonresponders. Fifteen patients reported stimulation-related side effects such as hoarseness or gagging. In a large patient series from two geographically distinct epilepsy centers located in two different continents, VNS proved to be efficacious and safe during long-term follow-up.

6. **Koszewski W, Bacia T, Rysz A. [Vagus nerve stimulation (VNS) in the treatment of drug-resistant epilepsy. A 4-year follow-up evaluation of VNS treatment efficacy]. *Neurol Neurochir Pol.* 2003;37(3):573-86. Polish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/14593753>

**Abstract** OBJECTIVES: Vagus nerve stimulation (VNS) is an alternative non-destructive surgical treatment for patients with medically intractable epilepsy. Neither the rationale nor proper indications for this treatment modality have been fully established yet. AIM OF THE STUDY: To assess the long-term efficacy of chronic VNS. MATERIAL: A series of 6 patients with drug-resistant epilepsy, subjected to VNS therapy. (4 females, 2 males, mean age 35.5 years, 3 patients with focal epilepsy, 3 with non-focal epilepsy, mean history of seizures 10 years, seizures frequency 10-400/per month). METHOD: An open-label prospective study with a 4-year follow-up. RESULTS: At a 4-year follow-up one patient (with non-focal epilepsy) was seizure-free, with only rare episodes of aura (Engel Ia), while in another one (with bitemporal epilepsy) seizures frequency remained unchanged with VNS (Engel IVb). In the remaining 4 cases (one with bitemporal, one with parietal, and two with non-focal epilepsy) the mean overall reduction in seizures frequency as compared to the baseline was 60% (Engel IIIa). VNS resulted in a reduction of seizures by 90% in a patient with a history of an unsuccessful anterior callosotomy. CONCLUSIONS: 1. VNS was found to reduce both the frequency of seizures (an overall 60% reduction in seizures frequency) and the duration of post-seizure consciousness disturbances in focal and non-focal epilepsies, but seizures-free state could be obtained in only one out of six patients. 2. A previous unsuccessful callosotomy did not prevent a good anticonvulsant effect in one patient. 3. The anticonvulsant effect of VNS was cumulative over time during the first 3 years postoperatively, then it tended to reach a plateau. 4. The best clinical outcome was positively correlated with the currents 1.5-2.0 mA. No significant correlation was noted for the current adjustments at the level of 2.0-3.5 mA. 5. Since no difference between the two stimulation patterns tested (30 s stimulation + 5 min break vs. 14 s + 3 min) was found as regards the anticonvulsant action of VNS, the latter pattern was subsequently used as the one more sparing the battery.

7. **Tanganelli P, Ferrero S, Colotto P, Regesta G. Vagus nerve stimulation for treatment of medically intractable seizures. Evaluation of long-term outcome. *Clin Neurol Neurosurg.* 2002;105(1):9-13.**

<http://www.ncbi.nlm.nih.gov/pubmed/12445916>

**Abstract** Vagus nerve stimulation (VNS) constitutes an adjunctive, modern management of medically intractable seizures, especially when surgery is inadvisable. **OBJECTIVE:** To evaluate the long-term results as regards efficacy, safety and tolerability of VNS in epileptic subjects, with focal and/or generalised seizures, refractory to old and new AEDs, without indication for resective surgery. **PATIENTS:** 51 epileptic subjects (30 males, 21 females), aged 7-49 years, have been implanted so far. **RESULTS:** The results refer to the 47 subjects with a follow-up longer than 6 months. 22 (46.8%) of them had a greater than 50% reduction in seizure frequency, with a more than 75% reduction in 6. No significant difference was found in relation to type of seizures. The efficacy maintained steadily over time during the follow-up (mean 26.4 months). Twelve out of the 47 subjects had an improvement in alertness, attention and psychomotor activity. Complications were observed in 5 cases, leading to removal of the stimulator in 2. A moderate vocal hoarseness (40.4%), paresthesia (6.3%), pharyngodinia and cough (4.3%) were the registered adverse events. **CONCLUSIONS:** Our results confirm that VNS is effective, safe and well tolerated and constitutes an alternative treatment for pharmaco-resistant epileptic seizures.

8. **Kawai K, Shimizu H, Maehara T, Murakami H. Outcome of long-term vagus nerve stimulation for intractable epilepsy. *Neurol Med Chir (Tokyo).* 2002;42(11):481-9; discussion 490.**

<http://www.ncbi.nlm.nih.gov/pubmed/12472212>

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**Abstract** The outcome of long-term vagus nerve stimulation (VNS) was evaluated in 13 Japanese patients with intractable epilepsy, all followed up for more than 4 years (48-91 months, median 56 months). VNS achieved a long-lasting and cumulative seizure-control effect in nine of 13 patients. The mean reduction of seizure frequency in the 1st to 4th year was 28%, 47%, 54%, and 63%, respectively. The percentage of patients with >60% seizure reduction in the 1st to 4th year was 15%, 46%, 54%, and 69%, respectively. One patient did not respond to the treatment at all. No patient became completely free from seizure or free from medication, but the number and/or dosage of antiepileptic drugs was reduced in five patients. Ten patients underwent exchange of the generator and continued treatment, and two patients underwent removal of the generator because of the unsatisfactory result. VNS controlled more disabling seizures earlier and more efficiently than less disabling seizures in seven patients. The cumulative reduction of seizures was partly associated with changes in the device setting toward increased stimulation. These effects were similar in patients with or without previous resective surgery. Long-term VNS therapy achieved a favorable outcome in a significant proportion of patients with intractable epilepsy.

9. **Morrow JJ, Bingham E, Craig JJ, Gray WJ. Vagal nerve stimulation in patients with refractory epilepsy. Effect on seizure frequency, severity and quality of life. *Seizure.* 2000;9(6):442-5.**

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**Abstract** Vagal nerve stimulation using an NCP (Cyberonics) device has been suggested as a potential treatment for patients with epilepsy that has previously proven refractory. Ten patients in Northern Ireland have had this device implanted and been fully audited pre- and post-operatively. Twelve months post-implantation, five patients have demonstrated a greater than 50% reduction in seizure frequency. A statistical reduction in seizure severity of the ictal phase of the major seizures has also been shown. Improvement in the patients' overall quality of life has, however, not been demonstrated in parallel to seizure reduction.

- 10. FineSmith RB, Zampella E, Devinsky O. Vagal nerve stimulator: a new approach to medically refractory epilepsy. *N J Med.* 1999;96(6):37-40.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10384766>  
**Abstract** Repetitive vagal nerve stimulation (VNS) is a new, FDA-approved treatment for medically refractory epilepsy. The device is implanted subcutaneously in the left chest and sends intermittent impulses to the left vagus nerve through communicating leads. Twelve patients have been implanted to date. The ages of the patients range from 8 to 36 years and the average followup at this point is five months. Five patients have achieved a greater than 50 percent reduction in seizure frequency with no serious adverse effects.
- 11. Ben-Menachem E, Hellstrom K, Waldton C, Augustinsson LE. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. *Neurology.* 1999;52(6):1265-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10214754>  
**Abstract** We assessed the long-term efficacy of vagus nerve stimulation (VNS) in 64 refractory epilepsy patients. After implantation, intermittent stimulation was delivered and seizure frequency and severity were counted. Average treatment time was 20 months. Nineteen of 47 patients with partial seizures, five of nine patients with idiopathic generalized seizures, and five of eight patients with Lennox-Gastaut syndrome had >50% seizure reduction. Side effects were mild. VNS is a safe and effective treatment for refractory epilepsy.
- 12. Vonck K, Boon P, D'Have M, Vandekerckhove T, O'Connor S, De Reuck J. Long-term results of vagus nerve stimulation in refractory epilepsy. *Seizure.* 1999;8(6):328-34.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10512772>  
[http://ac.els-cdn.com/S1059131199902996/1-s2.0-S1059131199902996-main.pdf?\\_tid=5cc93d1a-8c12-11e2-8180-00000aacb362&acdnat=1363202306\\_670e1c83af84bf6d66fd1dc89c9536a6](http://ac.els-cdn.com/S1059131199902996/1-s2.0-S1059131199902996-main.pdf?_tid=5cc93d1a-8c12-11e2-8180-00000aacb362&acdnat=1363202306_670e1c83af84bf6d66fd1dc89c9536a6)  
**Notes** Article of VNS results among patients at a leading Belgian epilepsy center led by Dr. Paul Boon; 15 of 25 patients had sufficient follow-up time (mean=29 months). Side effects occurred in six patients, three of whom required a temporary reduction of output current. Nine patients reported no side effects at all. Treatment with VNS remains effective in the long-term. In this series, 4/15 (27%) patients with highly refractory epilepsy experienced entirely seizure-free intervals of 12 months or more.  
**Abstract** Vagus nerve stimulation (VNS) is an adjunctive antiepileptic treatment for patients with refractory epilepsy. Limited information on long-term treatment with VNS is available. The purpose of this paper is to present our experience with VNS with a follow-up of up to 4 years. Twenty-five patients (13 females and 12 males) with refractory partial epilepsy were treated with VNS. The first 15 patients with a mean age of 30 years and a mean duration of epilepsy of 17.5 years have sufficient follow-up for analysis. Mean post-implantation follow-up was 29 months and mean stimulation output 2.25 mA. There was a mean seizure frequency reduction from 14 complex partial seizures (CPS) per month before implantation to 8 CPS per month after implantation (P = 0.0016; Wilcoxon signed-rank test (WSRT)). The mean maximum CPS-free interval changed from 9 to 312 days (P = 0.0007; WSRT). Six patients were free of CPS for at least one year. In one patient, one antiepileptic drug (AED) was tapered; in 10 patients, AEDs remained unchanged; in four, one adjunctive AED was administered. Side effects occurred in six patients, three of whom required a temporary reduction of output current. Nine patients reported no side effects at all. Treatment with VNS remains effective in the long-term. In this series 4 / 15 (27%) patients with highly refractory epilepsy experienced entirely seizure-free intervals of 12 months or more.

13. **Amar AP, Heck CN, Levy ML, Smith T, DeGiorgio CM, Oviedo S, et al. An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: rationale, technique, and outcome. *Neurosurgery*. 1998;43(6):1265-76; discussion 1276-80.**

<http://www.ncbi.nlm.nih.gov/pubmed/9848840>

**Notes** This article represents the first comprehensive and accurate VNS article in a neurosurgical journal and discusses the surgical outcomes, therapeutic efficacy, and therapeutic side effects of VNS for the 18 E05 patients at USC. The authors review the anatomic and physiological background arguing for clinical application of VNS, discuss salient aspects of patient selection and the nuances of surgical technique, and present observations of and results from application of the method. Overall, the article is very favorable and it provides an excellent reference on VNS for neurosurgeons. \*Seminal surgery article according to Andre

**Abstract** **OBJECTIVE:** Intermittent stimulation of the left cervical vagus nerve trunk is emerging as a novel adjunct in the treatment of medically refractory seizures. We sought to evaluate theoretical and practical issues attendant to this concept. We review the anatomic and physiological background arguing for clinical application of vagus nerve stimulation, discuss salient aspects of patient selection and the nuances of surgical technique, and present our observations of and results from application of the method. **METHODS:** Each of 18 patients with medically refractory epilepsy and at least six complex partial or secondarily generalized seizures per month underwent placement of a NeuroCybernetic Prosthesis pulse generator (Cyberonics, Webster, TX) in the chest, connected to helical platinum leads applied to the left cervical vagus nerve trunk. The patients were then randomized in a double-blinded fashion to receive either high (presumably therapeutic) or low (presumably less therapeutic) levels of vagus nerve stimulation. Reduction in seizure frequency, global assessments of quality of life, physiological measurements, and adverse events were recorded during a 3-month period. Patients in the low group were then crossed over to high-stimulation paradigms during a 15-month extension trial. **RESULTS:** All operations were successful, uneventful, and without adverse postoperative sequelae. One patient was excluded from analysis because of inadequate seizure calendars. Of the seven patients initially assigned to high stimulation, the mean reduction in seizure frequency was 71% at 3 months and 81% at 18 months. Five (72%) of these patients had a greater than 75% reduction in seizure frequency, and one (14%) remained seizure-free after more than 1.5 years of follow-up. The mean reduction in seizure frequency among the low-stimulation group was only 6% at 3 months. No serious complications, device failures, or physiological perturbations occurred. **CONCLUSION:** In our experience, vagus nerve stimulation has proven to be a safe, feasible, and potentially effective method of reducing seizures in select patient populations. However, the elements of strict definition for the application of the method require further study.

**Real-World Outcomes - Retrospective Studies (VNS in...)**

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- 1. Meneses MS, Rocha SF, Simao C, Santos HN, Pereira C, Kowacs PA. Vagus nerve stimulation may be a sound therapeutic option in the treatment of refractory epilepsy. *Arq Neuropsiquiatr.* 2013;71(1):25-30.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23338162>  
<http://www.scielo.br/pdf/anp/v71n1/a06v71n1.pdf>

**Abstract** INTRODUCTION: Refractory epilepsy accounts for 20 to 30% of epilepsy cases and remains a challenge for neurologists. Vagus nerve stimulation (VNS) is an option for palliative treatment. OBJECTIVE: It was to study the efficacy and tolerability of VNS in patients implanted with a stimulator at the Curitiba Institute of Neurology (INC). METHODS: A case study of six patients with refractory epilepsy submitted to a VNS procedure at the INC in the last four years was described and discussed. RESULTS: Mean age at time of implantation was 29 years. Mean follow-up was 26.6 months. Seizure frequency decreased in all patients (40-50% (n=2) and  $\geq$ 80% (n=4)). Three patients no longer required frequent hospitalizations. Two patients previously restricted to wheelchairs started to walk, probably because of improved mood. CONCLUSION: In this population, VNS proved to be a sound therapeutic option for treating refractory epilepsy.
  
- 2. Thygesen KS, Sabers A. Promising effect of vagal stimulation in Danish patients with epilepsy. *Dan Med J.* 2013;60(3):A4597.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23484615>

**Abstract** INTRODUCTION: Nervus vagus stimulation (VNS) is an option for additional surgical treatment for epilepsy. The aims of this study were to evaluate the effect of VNS on seizure frequency and to investigate patient satisfaction of and quality of life effects of VNS treatment. MATERIAL AND METHODS: We investigated 94 patients treated with VNS for intractable epilepsy in Denmark. The patients were operated in the 1996-2006 period. We performed a retrospective survey based on questionnaires which were adjusted to the following subgroups of patients: competent adults, children and mentally retarded adults. RESULTS: 46% of the patients reported a reduction in seizure frequency and 38% of adults reported a positive effect on quality of life with a benefit on long-term treatment. Around 20% also reported a positive effect on quality of life measures like coping, mood, self-confidence and social abilities. In the children's group, 21% reported a positive effect on quality of everyday life for the child and the family, 52-55% reported no change and 10% a negative effect. The patients had mild side effects, except for one case of vocal cord paralysis. CONCLUSION: VNS is a palliative add-on antiepileptic treatment in selected patients with medically intractable epilepsy. The effect may increase with long-term treatment. However, the impact on quality of life is modest. We found that side effects from VNS treatment were relatively mild. Future studies are needed. FUNDING: not relevant. TRIAL REGISTRATION: not relevant.

3. **Hoppe C, Wagner L, Hoffmann JM, von Lehe M, Elger CE. Comprehensive long-term outcome of best drug treatment with or without add-on vagus nerve stimulation for epilepsy: a retrospective matched pairs case-control study. *Seizure*. 2013;22(2):109-15.**

<http://www.ncbi.nlm.nih.gov/pubmed/23206433>

**Abstract** PURPOSE: In the treatment of epilepsy, the recommendation to add vagus nerve stimulation (VNS) to the best available drug therapy (BDT) mostly relies on uncontrolled studies which provide limited information about VNS-specific benefits. We report findings from a retrospective matched pairs case-control study comparing the long-term (>2 years) outcomes of BDT with or without VNS. METHODS: Included were adult patients with therapy-refractory epilepsy who had undergone the pre-surgical work-up (baseline) and subsequently received BDT with VNS (BDT+VNS) or BDT alone (BDT group). Patients were matched in pairs for age, gender and follow-up. Health outcomes were assessed at least 24 months after the baseline by comprehensive postal surveys and included established psychometric scales. RESULTS: We obtained data from 20 matched pairs of case and control patients. In both groups, seizures, health-related quality of life and mood improved over time. More BDT patients experienced a complete cessation of "major" seizures (12/20 vs. 4/20) whereas, in non-seizure free patients, BDT+VNS patients showed better seizure frequency reduction (>50% reduction: 12/19 vs. 7/16). BDT+VNS patients experienced equal drug related and additional VNS related side effects. No clinically relevant effect of VNS treatment was found on any psychological/psychosocial outcome measure. CONCLUSION: This retrospective study provided no positive evidence for therapeutic benefits of adding VNS to BDT. The follow-up health status of BDT+VNS patients was slightly worse than in patients receiving BDT alone. Despite minor group differences at baseline the two patient groups who had failed presurgical evaluation were comparable. Therapeutic improvements during long-term BDT alone are often underestimated resulting in a misattribution of positive changes to VNS in uncontrolled studies and reviews. Currently, there is no incontrovertible evidence for the clinical effectiveness of adding VNS to BDT.

4. **Arya R, Greiner HM, Lewis A, Mangano FT, Gonsalves C, Holland KD, et al. Vagus nerve stimulation for medically refractory absence epilepsy. *Seizure*. 2013;22(4):267-70.**

<http://www.ncbi.nlm.nih.gov/pubmed/23391567>

**Abstract** PURPOSE: A proportion of patients with childhood and juvenile absence epilepsies (CAE, JAE) are likely to be classified as medically refractory. In view of evidence gap for the treatment of such patients, this series is reported to generate estimate for efficacy of vagus nerve stimulation (VNS) in this patient population. METHODS: Patients were identified by a chart review of all VNS recipients between January 1, 2006 and December 31, 2011. The diagnosis of CAE and JAE was based on conventional criteria. Details of demography, epilepsy phenomenology, management and outcomes were extracted. The outcome measures included reduction in daily seizure frequency measured as a percentage of pre-VNS seizure frequency and classified on International League Against Epilepsy (ILAE) outcome scale. RESULTS: Nine patients (7 CAE, 2 JAE) with a mean age of seizure onset of 5.4 years (+/-3.9) were identified. Mean duration of epilepsy prior to VNS implant was found to be 3.9 years (+/-1.4). These patients had failed a median of 5 anti-epileptic drugs before being referred for consideration of surgical treatment. After a mean follow-up of 33.9 months (+/-25.5, minimum 4 months), 1 patient attained complete seizure freedom (ILAE class 1), 6 had ILAE class 4 and 2 had ILAE class 5 outcomes, respectively. Mean reduction in daily seizure frequency was found to be 53.5+/-60.3% (1-sided p-value for paired t-test=0.04), with a 50% responder rate of 55.6%. CONCLUSION: VNS may be considered as a therapeutic option in patients with medically refractory absence epilepsy.

5. **Ching J, Khan S, White P, Reed J, Ramnarine D, Sieradzan K, et al. Long-term effectiveness and tolerability of vagal nerve stimulation in adults with intractable epilepsy: a retrospective analysis of 100 patients. *Br J Neurosurg.* 2012;27(2):228-34.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23113878>  
<http://informahealthcare.com/doi/abs/10.3109/02688697.2012.732716>  
**Abstract** Abstract Data for 100 vagal nerve stimulation (VNS) patients were collected and analysed retrospectively. The mean seizure reduction was 17.86% (n = 67) at 6 months, 26.21% (n = 63) at 1 year, 30.43% (n = 53) at 2 years, 48.10% (n = 40) at 3 years, 49.44% (n = 32) at 4 years, 50.52% (n = 35) at 5 years, 45.85% (n = 31) at 6 years, 62.68% (n = 25) at 8 years, 76.41% (n = 9) at 10 years, 82.90% (n = 4) at 12 years. Evidence of statistical significance for mean seizure reduction over time was strong with all p values less than 0.05 except at 12 years (p = 0.125) where the sample size was small (n = 4). Mean seizure reduction was 49.04% and 51 (51%) patients were considered responders, defined as a 50% or more reduction in seizure frequency. Twenty-one (21%) patients suffered surgical complications. Of these 15 patients were self-limiting and 6 patients were irreversible or required a device revision. Fifty patients (50%) suffered from side-effects, while vagal stimulation cycled on (VNS on) post-operatively. However, of these, only one patient suffered from intolerable side effects requiring the device to be switched off temporarily. This study demonstrates the long-term efficacy in seizure reduction with the use of VNS. Complication rates and tolerability did not deviate greatly from that previously reported, indicating that VNS is a safe and effective treatment for seizure reduction in intractable epilepsy.
6. **Englot DJ, Rolston JD, Wang DD, Hassnain KH, Gordon CM, Chang EF. Efficacy of vagus nerve stimulation in posttraumatic versus nontraumatic epilepsy. *J Neurosurg.* 2012;117(5):970-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22978542>  
**Abstract** OBJECT: In the US, approximately 500,000 individuals are hospitalized yearly for traumatic brain injury (TBI), and posttraumatic epilepsy (PTE) is a common sequela of TBI. Improved treatment strategies for PTE are critically needed, as patients with the disorder are often resistant to antiepileptic medications and are poor candidates for definitive resection. Vagus nerve stimulation (VNS) is an adjunctive treatment for medically refractory epilepsy that results in a  $\geq 50\%$  reduction in seizure frequency in approximately 50% of patients after 1 year of therapy. The role of VNS in PTE has been poorly studied. The aim of this study was to determine whether patients with PTE attain more favorable seizure outcomes than individuals with nontraumatic epilepsy etiologies. METHODS: Using a case-control study design, the authors retrospectively compared seizure outcomes after VNS therapy in patients with PTE versus those with nontraumatic epilepsy (non-PTE) who were part of a large prospectively collected patient registry. RESULTS: After VNS therapy, patients with PTE demonstrated a greater reduction in seizure frequency (50% fewer seizures at the 3-month follow-up; 73% fewer seizures at 24 months) than patients with non-PTE (46% fewer seizures at 3 months; 57% fewer seizures at 24 months). Overall, patients with PTE had a 78% rate of clinical response to VNS therapy at 24 months (that is,  $\geq 50\%$  reduction in seizure frequency) as compared with a 61% response rate among patients with non-PTE (OR 1.32, 95% CI 1.07-1.61), leading to improved outcomes according to the Engel classification ( $p < 0.0001$ , Cochran-Mantel-Haenszel statistic). CONCLUSIONS: Vagus nerve stimulation should be considered in patients with medically refractory PTE who are not good candidates for resection. A controlled prospective trial is necessary to further examine seizure outcomes as well as neuropsychological outcomes after VNS therapy in patients with intractable PTE.

7. **Qiabi M, Bouthillier A, Carmant L, Nguyen DK. Vagus nerve stimulation for epilepsy: the notre-dame hospital experience. *Can J Neurol Sci.* 2011;38(6):902-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22030430>  
**Abstract** PURPOSE: Retrospective study assessing the efficacy and tolerability of vagus nerve stimulation (VNS) for the treatment of refractory epilepsy at Notre-Dame Hospital. METHODOLOGY: Chart review of all adult epileptic patients treated by VNS with  $\geq 1$  year follow-up. Responders were defined as patients with  $\geq 50\%$  reduction of baseline seizure frequency. RESULTS: Thirty-four patients (14M; mean age = 29.9 yrs) received a VNS. Sub-pectoralis implantation (n = 25) was more frequent than subcutaneous (n = 9). Most patients suffered from intractable partial epilepsy. After 6 months, 12 months, 24 months, and 36 months, 14/34 patients (41%), 16/34 patients (47%), 17/30 patients (57%) and 12/20 patients (60%) respectively were responders. Two patients (6%) became seizure-free. Complications related to implantation were minor: eight cases of limited cervical hypoesthesia, two minor scar infections and one Horner syndrome. Adverse events (voice hoarseness, throat paresthesia, coughing) related to stimulation were generally mild and tended to wane over time. However, a reduction in seizure frequency did not translate into a reduction in medication, as only 9% of responders had less antiepileptic medication at last follow-up compared to baseline. CONCLUSION: VNS as practiced at Notre-Dame hospital is an efficacious and safe treatment for refractory epilepsy. Quotas allotted to epilepsy centers in the province of Quebec should be lifted or increased to allow more patients to benefit from this therapeutic device.
8. **Bao M, Zhou J, Luan GM. Treatment of drug-resistant epilepsy with vagus nerve stimulation -- review of 45 cases. *Chin Med J (Engl).* 2011;124(24):4184-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22340384>  
**Abstract** BACKGROUND: Vagus nerve stimulation (VNS) is an alternative treatment for drug-resistant epilepsy (DRE). The study aimed to explore the potential factors of prognosis, safety and effect of VNS treatment in patients with DRE. METHODS: We retrospectively examined 45 cases of DRE that received VNS treatment in our center from June 2004 to June 2010 and analyzed the parameters (age of patient receiving VNS, seizure frequency before and after VNS as well as treatment duration) by Student's t test, Fisher's exact and Mann-Whitney U tests, and multivariate Logistic regression. RESULTS: The overall response rate was 64% (29/45), 67% (6/9) for adults and 64% (23/36) for children, with no significant difference (P = 0.28). Twenty-two cases had been in VNS therapy for over 1 year with a treatment efficacy of 73% (16/22), whereas 23 cases had been in VNS therapy no more than 1 year with a treatment efficacy of 57% (13/23), and has statistically significant difference (P = 0.03). The main side effect included hoarseness of voice and cough. One patient's device was removed due to infection. One patient's VNS was half-way terminated due to seizure aggravation. One patient died due to status epilepticus. CONCLUSIONS: VNS is a safe and effective treatment for DRE. Duration of VNS therapy may be a crucial factor on prognosis.

9. **Hajnsek S, Petelin Z, Poljakovic Z, Mrak G, Paladino J, Desnica A. Vagus nerve stimulation in the treatment of patients with pharmacoresistant epilepsy: our experiences. *Coll Antropol.* 2011;35(3):755-60.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22053552>  
**Abstract** Vagus nerve stimulation (VNS) for the treatment of refractory partial epileptic seizures with or without secondary generalisation in patients older than 12 years was approved in Europe in 1994 and in the United States in 1997. We have studied the efficacy of VNS in patients with pharmacoresistant epilepsy hospitalized in the Neurology Department of the University Hospital Centre Zagreb. From 1997 to 2001 we have implanted VNS in 11 patients with pharmacoresistant epilepsy, who were magnetic resonance imaging (MRI) negative and from May 2007 to May 2009 in 11 patients with pharmacoresistant epilepsy, 9 of them were MRI positive, and were inoperable due to localisation of the pathomorphologic changes (ganglioglioma, hamartoma, various types of cortical dysplasia, porencephalic cysts), 2 were MRI negative. In the group of MRI negative patients 1 patient had complex partial seizures (CPS), 6 patients had CPS with secondary generalisation, 2 patients had primary generalized epilepsy (PGE) including myoclonic, absence, atonic and tonic-clonic seizures, one patient had PGE and CPS, and 3 patients had Lennox-Gastaut syndrome (LGS). In the group of MRI positive patients one patient had elementary partial seizures (EPS) and CPS, two patients had EPS and CPS with secondary generalisation, one patient had CPS, 3 patients had CPS with secondary generalisation, and 2 patients had CPS with secondary generalisation as well as atonic seizures. After continuous follow-up of 11 MRI negative patients during 5 years and 2 MRI negative patients during one year there was decrease in mean-seizure frequency of 51.67%. After continuous follow-up of 9 MRI positive patients during 2 years there was decrease in mean-seizure frequency of 61.9%. The most frequent side effects were hoarseness, throat pain and cough in the "on phase" of the VNS, but they were mild and transitory. We can conclude that VNS was effective mode of therapy in our group of patients with pharmacoresistant epilepsy.
10. **Helmers SL, Duh MS, Guerin A, Sarda SP, Samuelson TM, Bunker MT, et al. Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy. *Epilepsy Behav.* 2011;22(2):370-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21872534>  
**Abstract** We evaluated long-term medical and economic benefits of vagus nerve stimulation (VNS) therapy in drug-resistant epilepsy. A pre-post analysis was conducted using multistate Medicaid data (January 1997-June 2009). One thousand six hundred fifty-five patients with one or more neurologist visits with epilepsy diagnoses (ICD-9 345.xx, 780.3, or 780.39), one or more procedures for vagus nerve stimulator implantation, one or more antiepileptic drugs (AEDs), and 6 or more months of continuous Medicaid enrollment pre- and post-VNS were selected. The pre-VNS period was 6 months. The post-VNS period extended from implantation to device removal, death, Medicaid disenrollment, or study end (up to 3 years). Incidence rate ratios (IRRs) and cost differences (\$2009) were estimated. Mean age was 29.4 years. Hospitalizations decreased post-VNS compared with pre-VNS (adjusted IRR=0.59, P<0.001). Grand mal status events decreased post-VNS compared with pre-VNS (adjusted IRR=0.79, P<0.001). Average total health care costs were lower post-VNS than pre-VNS (\$18,550 vs \$19,945 quarterly, P<0.001). VNS is associated with decreased resource utilization and epilepsy-related clinical events and net cost savings after 1.5 years.

11. Elliott RE, Morsi A, Tanweer O, Grobelny B, Geller E, Carlson C, et al. Efficacy of vagus nerve stimulation over time: review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS > 10 years. *Epilepsy Behav.* 2011;20(3):478-83.  
<http://www.ncbi.nlm.nih.gov/pubmed/21296622>  
**Abstract** OBJECTIVE: Studies have reported improved seizure control with increased duration of vagus nerve stimulation (VNS) but are prone to methodological biases. We analyzed the efficacy of VNS over time in patients with treatment-resistant epilepsy (TRE) who underwent VNS therapy 10 or more years. METHODS: We retrospectively reviewed 65 consecutive patients (29 females) who underwent VNS therapy  $\geq 10$  years. The mean age at VNS insertion was 30.0 years. Forty-four adults ( $\geq 18$  years; 67.7%) and 21 children (32.3%) were included. Seizure frequency and antiepileptic drug (AED) regimens were recorded prior to VNS and, following VNS insertion, at 6 months, 1 year, 2 years, and every 2 years thereafter. RESULTS: The mean duration of VNS therapy for this group was 10.4 years, and the mean decrease in seizure frequency at last follow-up was 76.3%. The mean reduction in seizures at 6 months and years 1, 2, 4, 6, 8, and 10 years was 35.7, 52.1, 58.3, 60.4, 65.7, 75.5, and 75.5%, respectively. Seizure frequency was significantly reduced from baseline at each of the recorded intervals ( $P < 0.001$ ). There was a trend toward increased AED burden in the latter years of the follow-up period. CONCLUSION: Following a "ramp-up" and accommodation period throughout the initial 24 months after VNS implantation, seizure control improved slightly over the subsequent years of therapy and eventually stabilized. Variation in seizure frequency, however, was common, and frequent changes in AED regimens or stimulation parameters were likely an important and possibly synergistic component of seizure control.
12. Englot DJ, Chang EF, Auguste KI. Efficacy of vagus nerve stimulation for epilepsy by patient age, epilepsy duration, and seizure type. *Neurosurg Clin N Am.* 2011;22(4):443-8, v.  
<http://www.ncbi.nlm.nih.gov/pubmed/21939842>  
**Abstract** Medically refractory epilepsy is a morbid condition, and many patients are poor candidates for surgical resection because of multifocal seizure origin or eloquence near epileptic foci. Vagus nerve stimulation (VNS) was approved in 1997 by the US Food and Drug Administration as an adjunctive treatment of intractable epilepsy for individuals aged 12 years and more with partial epilepsy. Controversy persists regarding the efficacy of VNS for epilepsy and about which patient populations respond best to therapy. In this article, the authors retrospectively studied a patient outcome registry and report the largest, to their knowledge, analysis of VNS outcomes in epilepsy.

13. **Wheeler M, De Herdt V, Vonck K, Gilbert K, Manem S, Mackenzie T, et al. Efficacy of vagus nerve stimulation for refractory epilepsy among patient subgroups: a re-analysis using the Engel classification. *Seizure*. 2011;20(4):331-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/21273097>

[http://ac.els-cdn.com/S1059131111000112/1-s2.0-S1059131111000112-main.pdf?\\_tid=a00dddac-8cc5-11e2-b3d7-00000aab0f02&acdnat=1363279299\\_15f18ba1384861e4e5fe456d9eb287cd](http://ac.els-cdn.com/S1059131111000112/1-s2.0-S1059131111000112-main.pdf?_tid=a00dddac-8cc5-11e2-b3d7-00000aab0f02&acdnat=1363279299_15f18ba1384861e4e5fe456d9eb287cd)

**Abstract** Optimal candidates for VNS as a treatment for refractory epilepsy have not been identified. In this retrospective two-center study, we used the Engel classification for evaluating seizure outcome, and tried to identify predictive factors for outcome by means of subgroup analysis. The medical records of patients who have been treated with VNS for at least one year at Dartmouth-Hitchcock Medical Center and Ghent University Hospital were evaluated. Seizure frequency outcome was assessed using the Engel classification for the study population as a whole, and for patient subgroups with regard to mental functioning, seizure type, predisposing factors for developing epilepsy, age at time of VNS implantation and epilepsy duration. 189 patients (102M/87F) were included in the study (mean FU: 41 months). 6% had a class I outcome (seizure-free), 13% a class II outcome (almost seizure-free), 49% a class III outcome (worthwhile improvement) and 32% had a class IV outcome (no improvement). When patients were divided into specific subgroups, a statistically significant better outcome was found patients with normal mental functioning ( $p=0.029$ ). In our series, results for VNS are clearly inferior to resective surgery, but comparable to other treatment modalities for refractory epilepsy. With combined class I and II outcomes around 20%, and another 50% of patients having worthwhile improvement, VNS is a viable alternative when resective surgery is not feasible.

14. **Alonso-Vanegas MA, Austria-Velasquez J, Lopez-Gomez M, Brust-Mascher E. Chronic intermittent vagal nerve stimulation in the treatment of refractory epilepsy: experience in Mexico with 35 cases. *Cir Cir*. 2010;78(1):15-23, 24.**

<http://www.ncbi.nlm.nih.gov/pubmed/20226124>

**Abstract** BACKGROUND: The role of vagal nerve stimulation (VNS) in the treatment of refractory epilepsy is still evolving and requires precision through extensive description of acute and chronic results, adverse effects and complications in specific populations. METHODS: We selected patients with refractory epilepsy subjected to VNS who had completed at least a 12-month followup. Descriptive and inferential statistics were used to review and assess the effects of VNS on seizure frequency/intensity, memory, alertness, mood, postictal recovery, and quality of life (subjective scale, QoL IE-31 inventory) as well as factors (gender, age, age of onset, time of surgery, stimulation parameters, seizure frequency and type) associated with clinical response. We describe stimulation parameters, complications and adverse effects compared to other series. RESULTS: We selected 35 patients with an age range of 5-48 years; 18 patients presented partial epilepsy and 17 generalized epilepsy. All procedures and wound healing were uneventful, and no infections were reported. Median reduction in seizure frequency was 55.65% ( $p < 0.001$ ). Four patients showed improvement of  $>90\%$ . Two patients became seizure free, whereas seizure frequency increased in two patients. The subjectively qualified response to treatment was good in 33 patients. The mean global increase in the QoLIE-31 Scale was 12.6 ( $p = 0.020$ ). Improvements in memory, mood, alertness and postictal recovery period were documented. Only seizure type showed statistically significant association with clinical response. Adverse effects were transitory and responded to changes in stimulation parameters. CONCLUSIONS: VNS is a safe, feasible, well-tolerated and effective palliative treatment in appropriately selected cases of refractory partial and multifocal generalized seizures.

15. **Siddiqui F, Herial NA, Ali, II. Cumulative effect of vagus nerve stimulators on intractable seizures observed over a period of 3years. *Epilepsy Behav.* 2010;18(3):299-302.**

<http://www.ncbi.nlm.nih.gov/pubmed/20580901>

**Abstract** OBJECTIVE: The objective of the study was to evaluate the efficacy of vagus nerve stimulator (VNS) therapy and identify factors associated with reduction of seizures. The VNS is an accepted therapeutic option for patients with refractory partial epilepsy. There are, however, limited data regarding efficacy in any specific group of patients with epilepsy. METHODS: This is a retrospective review of patients with epilepsy on VNS therapy initiated between January 2000 and December 2007 at a university medical center. Information collected included demographics, epilepsy type and duration, antiepileptic drug usage, stimulation parameters, and seizure frequency at baseline, 3months, 6months, 1year, 2years, and 3years after VNS therapy initiation. Seizure frequency at different follow-up intervals was compared with baseline frequency. Patients were stratified into three subsets based on VNS response. Relationships between VNS response and factors including demographics, location of seizure focus, type or duration of epilepsy, and VNS settings were examined as a whole as well as in subsets. RESULTS: Fifty-four patients were implanted with VNSs over a period of 7years. Four patients were excluded. A total of 50 patients (31 men, 19 women) with mean age 39years and on VNS therapy were included in this study. Average duration of VNS therapy was 4.5years. Baseline average frequency was 10 seizures per month. Significant decreases in median seizure frequency were noted at 3months ( $P<0.001$ ), 6months ( $P<0.001$ ), 1year ( $P=0.004$ ), 2years ( $P<0.001$ ), and 3years ( $P<0.0001$ ). Seventy-two percent of the patients reported a decrease in seizure frequency within the first 3months, which increased to 80% by the end of 3years. Overall, the percentage reduction in seizure frequency was 64% at 3months and increased to 86% at the end of 3years. In the subset of patients who responded to VNSs, reduction in seizure frequency improved from 80 to 89% by the end of 3years. There were no correlations between seizure frequency and specific VNS settings, epileptic focus, or duration or type of epilepsy, in the group as a whole or in its subsets. Data suggest a favorable VNS response in patients with higher baseline seizure frequency. CONCLUSIONS: Significant reductions in seizure frequency were noted with VNS therapy over a 3-year follow-up period with a possible cumulative effect. Lateralization or localization of epileptic focus or epilepsy subtype did not correlate with response to VNSs.

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**Notes** GENERAL NOTE: NLM: Original DateCompleted: 2010061  
**Abstract** BACKGROUND: In 1997 Vagus Nerve Stimulation (VNS) received approval from the US Food and Drug Administration (FDA) as an adjunctive therapy in the treatment of medically intractable partial epilepsy in people aged 12 years and older who are ineligible for resective epilepsy surgery. Although the exact mechanisms of action are unknown, the use of VNS with children has increased, including those younger than 12 years of age, or those with generalized epilepsy. METHODS: We describe the outcome for the first group of nine patients, aged 8-28 years, who had pharmaco-resistant epilepsy and were treated with VNS. During the follow up, we gradually and slowly increased the parameters of the stimulation in order to assess the efficacy of VNS even at parameters which would usually be considered "non-therapeutic", along with possible side effects and changes in quality of life. RESULTS: At the last follow up 1 patient was "seizures free", 3 were "very good responders", 3 were "good responders" and 2 were "non responders". We obtained an initial seizure reduction with low stimulation parameters, the highest current reached being 2.00 mA. This observation supports the possibility that, for younger patients, lower stimulation intensities than those commonly used in clinical practice for adults can be therapeutic. We also wanted to underline the reduction in seizure frequency (approximately 91.7%) and the reduction in seizure duration (> 50%) in the patients affected by drug-resistant absence epilepsy. Adverse effects were mild, tolerable and, in most of cases, easily resolved by adjusting the stimulation parameters. Hoarseness of voice was the most frequent side effect. The improvements in the quality of life are relevant and seem to be independent of the VNS effect in controlling seizures. CONCLUSIONS: Our small experience seems to confirm the efficacy and safety of VNS in drug resistant partial and generalized epilepsy in developing age groups.
17. **El Tahry R, De Herdt V, Raedt R, Van Dycke A, Meurs A, Dewaele F, et al. Evolution in VNS therapy for refractory epilepsy, experience with Demipulse devices at Ghent University Hospital. *Seizure.* 2010;19(9):531-5.**  
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**Abstract** RATIONALE: Vagus nerve stimulation (VNS) is a frequently used treatment for patients with refractory epilepsy who are unsuitable candidates for epilepsy surgery. There has been a steady evolution in VNS technology, as generators' volumes have become smaller and battery life expectancy longer. This pilot study is an open-label retrospective study that describes our experience with the latest commercially available generator, i.e. the VNS Therapy Demipulse Model 103. Treatment efficacy and side effects, as well as technical and practical enhancements useful for the patient and for the medical staff are discussed in this study. METHODS: Twenty patients (11F/9M) with a mean age of 40 years (range 8-61), who were considered unsuitable candidates for resective surgery, were implanted with a VNS Therapy Demipulse Model 103. Mean monthly seizure frequency reduction and side effects were evaluated 1 year after implantation. RESULTS: Mean monthly seizure frequency decreased significantly from 54 seizures/month (SEM 30; range 1-555) before treatment to 33 (SEM 24, range 0-445) following 12 months of treatment ( $p < 0.05$ ). Seven patients (39%) were considered responders with a reduction in seizure frequency of more than 50%. One of those seven patients became seizure free. Side effects were stimulation-related tingling sensation in the throat and/or hoarseness, a painful sensation in the left neck or ear region and a lead breakage. In addition; one case of SUDEP was reported. CONCLUSION: Patients treated with VNS Therapy Demipulse generators proved to have a significant decrease in seizure frequency. In this patient group, VNS was well tolerated. The main technical advances are the decrease in size and improved options for battery life follow-up.

18. **Kuba R, Brazdil M, Kalina M, Prochazka T, Hovorka J, Nezadal T, et al. Vagus nerve stimulation: longitudinal follow-up of patients treated for 5 years. *Seizure*. 2009;18(4):269-74.**  
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**Abstract** We performed a retrospective, multicenter, open-label study to evaluate the efficacy of vagus nerve stimulation (VNS) in all patients in the Czech Republic who have received this treatment for at least 5 years (n=90). The mean last follow-up was 6.6+/-1.1 years (79+/-13 months). The median number of seizures among all patients decreased from 41.2 seizures/month in the prestimulation period to 14.9 seizures/month at 5 years follow-up visit. The mean percentage of seizure reduction was 55.9%. The responder rate in these patients is in concordance with the decrease of overall seizure frequency. At 1 year after beginning the stimulation, 44.4% of patients were responders; this percentage increased to 58.7% after 2 years. At the 5 years last follow-up 64.4% of patients were responders, 15.5% experienced > or = 90% seizure reduction, and 5.5% were seizure-free. A separate analysis of patients younger than 16 years of age showed lower efficacy rates of VNS in comparison to the whole group. Complications and chronic adverse effects occurred in 13.3% of patients. VNS is an effective and safe method to refractory epilepsy in common clinical practice.
19. **Abubakr A, Wambacq I. Long-term outcome of vagus nerve stimulation therapy in patients with refractory epilepsy. *J Clin Neurosci*. 2008;15(2):127-9.**  
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**Abstract** We retrospectively assessed the long-term efficacy of vagus nerve stimulation (VNS) therapy in 31 patients with refractory partial and generalized seizures who were not candidates for resective epilepsy surgery. Following implantation of VNS there was significant improvement in seizure frequency at 6 months. Sixteen patients continued to have sustained response to VNS therapy 4 years later. Adverse effects of VNS therapy were transient and tolerable. The majority of the patients did not gain body weight and some of them had significant weight loss. Therefore VNS is safe and effective therapy and has a long-term sustained effect in refractory epilepsy.
20. **Roux FX, Turak B, Landre E. [Vagus nerve stimulation for the treatment of refractory epilepsy]. *Neurochirurgie*. 2008;54(3):332-9. French.**  
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**Abstract** Proposed as an additive symptomatic treatment of refractory epilepsy, vagus nerve stimulation (VNS) has proven to be effective and well-tolerated in patients presenting with refractory epilepsy for whom cortical resection is not indicated. After two years of treatment, the overall reduction of seizure frequency averaged 40%. In 50% of the patients, the frequency of seizures decreased by at least 50%. Moreover, even in absence of a significant reduction of seizures, patients who undergo this treatment reported an improvement in their quality of life. Economic surveys also demonstrate a favorable impact of VNS on the management of refractory epilepsy. Since 1988, 65,000 patients with refractory epilepsy throughout the world have been treated by VNS for this indication (1000 in France). The surgical implantation technique used in our department, the effects of vagus nerve stimulation reported in the literature, and our experience with a cohort of 70 patients with refractory epilepsy who received implants over the last 10 years are described.

21. **Sakas DE, Korfiatis S, Nicholson CL, Panourias IG, Georgakoulias N, Gatzonis S, et al. Vagus nerve stimulation for intractable epilepsy: outcome in two series combining 90 patients. *Acta Neurochir Suppl.* 2007;97(Pt 2):287-91.**

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**Abstract** Vagus nerve stimulation (VNS) is the most widely used non-pharmacological treatment for medically intractable epilepsy and has been in clinical use for over a decade. It is indicated in patients who are refractory to medical treatment or who experience intolerable side effects, and who are not candidates for resective surgery. VNS used in the acute setting can both abort seizures and have an acute prophylactic effect. This effect increases over time in chronic treatment to a maximum at around 18 months. The evidence base supporting the efficacy of VNS is strong, but its exact mechanism of action remains unknown. A vagus nerve stimulator consists of two electrodes embedded in a silastic helix that is wrapped around the cervical vagus nerve. The stimulator is always implanted on the left vagus nerve in order to reduce the likelihood of adverse cardiac effects. The electrodes are connected to an implantable pulse generator (IPG) which is positioned subcutaneously either below the clavicle or in the axilla. The IPG is programmed by computer via a wand placed on the skin over it. In addition, extra pulses of stimulation triggered by a hand-held magnet may help to prevent or abort seizures. VNS is essentially a palliative treatment and the number of patients who become seizure free is very small. A significant reduction in the frequency and severity of seizures can be expected in about one third of patients and efficacy tends to improve with time. Vagus nerve stimulation is well tolerated and has few significant side effects. We describe our experience on the use of VNS on drug-resistant epilepsy in 90 patients treated in two departments (in Athens, Greece and Newcastle, England).

22. **De Herdt V, Boon P, Ceulemans B, Hauman H, Lagae L, Legros B, et al. Vagus nerve stimulation for refractory epilepsy: a Belgian multicenter study. *Eur J Paediatr Neurol.* 2007;11(5):261-9.**

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**Abstract** INTRODUCTION: Vagus nerve stimulation (VNS) is a symptomatic add-on treatment for patients with medically refractory epilepsy. It consists of continuous electrical stimulation of the left vagus nerve by means of a helical electrode and an implantable, programmable pulse generator. Currently, over 50,000 patients are treated with VNS worldwide. AIM: This uncontrolled, open-label retrospective study evaluates long-term outcome in patients treated with VNS for refractory epilepsy in seven different epilepsy centres in Belgium. METHODS: For the purpose of this study, a minimum of essential inclusion criteria were defined to collect relevant data. This limited the results to basic findings with regards to efficacy on the long term. Inclusion criteria were a follow-up of at least 12 months and a documented seizure diary before implantation and at maximum follow-up. Primary outcome measures were the reduction in mean monthly seizure frequency and the percentage of patients with a seizure reduction of at least 50% (responder rate). RESULTS: About 138 patients (67M/71F) had a mean age of 30 years (range 4-59) at time of implantation and a mean post-implantation follow-up of 44 months (range 12-120). The mean number of AEDs before implantation was 3 (range 1-5). About 117/138 patients had focal epilepsy, 21 patients had symptomatic generalised epilepsy. About 117/138 patients were older than 16 years, 21 patients were 16 or younger. At maximum follow-up, mean stimulation output current was 1.84mA (range 0-3.25). Mean number of AEDs at maximum follow-up remained unchanged. The overall reduction in mean monthly seizure frequency was 51%. Mean seizure frequency before implantation was 41 seizures/month (SD=61; range 1-300), mean seizure frequency after implantation at maximum follow-up was 7 seizures/month (SD=25; range 0-120). Responder rate was 59%. 13% of patients had a seizure frequency decrease between 30% and 50%. About 28% had a seizure frequency decrease of <30%. Seizure freedom was obtained in 12/138 patients (9%). CONCLUSIONS: The long-term experience with VNS in Belgium confirms that VNS is an efficacious adjunctive antiepileptic treatment for patients with refractory epilepsy.

23. **Zwolinski P, Roszkowski M, Drabik K, Baczuk L, Majkowski J. [Vagus nerve stimulation in drug-resistant epilepsy. Experience with 23 patients]. *Neurol Neurochir Pol.* 2004;38(3):161-9; discussion 170-1. Polish. <http://www.ncbi.nlm.nih.gov/pubmed/15354227>**  
**Abstract** BACKGROUND: Vagal nerve stimulation (VNS) is a new non-pharmacological method of pharmacoresistant epilepsy treatment. The aim of this paper was to present effects of treatment in 23 patients with drug-resistant epilepsy with a different etiology. MATERIAL AND METHODS: Implantation and treatment was performed in two centers in 1998-2002. The effect of treatment was presented as a reduction of seizures during therapy. RESULTS: The lack of group homogeneity and a small number of patients (especially a small number of patients with a long follow-up period) did not allow a more detailed analysis to be made, although there seems to be a clear tendency to obtain better effects of treatment over follow-up time (at 24 month more than 50% seizure reduction or cease of seizures was observed in 80% of patients). The possibility to turn on the device "on demand" is an important advantage of this method. This raises the effectiveness of treatment in more than 80% of patients, and in more than 20% it stops the seizure. There were two groups of undesired side effects: frequent specific effects caused by local irritation of the vagal nerve in the cervical part of the neck and rare transient general effects. Both groups of effects rarely caused any treatment complications. CONCLUSIONS: VNS is an effective method of treatment, complementary to other epilepsy treatment methods and should be used in patients with drug-resistant epilepsy as an alternative to neurosurgical treatment. VNS improves the quality of life in treated patients.
24. **Uthman BM, Reichl AM, Dean JC, Eisenschenk S, Gilmore R, Reid S, et al. Effectiveness of vagus nerve stimulation in epilepsy patients: a 12-year observation. *Neurology.* 2004;63(6):1124-6. <http://www.ncbi.nlm.nih.gov/pubmed/15452317> <http://www.neurology.org/content/63/6/1124.full.pdf>**  
**Abstract** A retrospective review of the safety, tolerability, and efficacy of vagus nerve stimulation (VNS) in 48 patients with intractable partial epilepsy was performed. Side effects were few and mild to moderate. Mean seizure frequency decreased by 26% after 1 year, 30% after 5 years, and 52% after 12 years with VNS treatment.
25. **Labar D. Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs. *Seizure.* 2004;13(6):392-8. <http://www.ncbi.nlm.nih.gov/pubmed/15276142> [http://ac.els-cdn.com/S1059131103002334/1-s2.0-S1059131103002334-main.pdf?\\_tid=96866124-8cc4-11e2-9ad3-00000aabb0f02&acdnat=1363278854\\_4a8fac88351af44602953bb950ac0d9a](http://ac.els-cdn.com/S1059131103002334/1-s2.0-S1059131103002334-main.pdf?_tid=96866124-8cc4-11e2-9ad3-00000aabb0f02&acdnat=1363278854_4a8fac88351af44602953bb950ac0d9a)**  
**Abstract** PURPOSE: To study, in patients on unchanged antiepileptic drugs (AEDs): (1) seizure rates after 3 and 12 months of vagus nerve stimulation (VNS); (2) effects of VNS parameters; (3) patient characteristics versus VNS responsiveness. METHODS: We located in the VNS registry 269 patients treated for 1 year with no changes in AEDs. Seizure rates were calculated at 3 and 12 months. We analyzed: (1) 3 months versus 12 months seizure rates; (2) effects of changing duty cycles between 3 and 12 months; (3) effects of output current; (4) seizure rate changes associated with patient characteristics. RESULTS: Seizure rates improved between 3 months (median = -45%) and 12 months (median = -58%) ( $P < 0.0001$ ). There were no differences between patients who stayed on standard or rapid cycling, or changed from standard to rapid. Stimulation parameters did not affect seizure rates. VNS responsiveness was associated with older age ( $P = 0.016$ ), longer duration epilepsy ( $P = 0.033$ ), and syndromes other than Lennox-Gastaut ( $P = 0.003$ ). CONCLUSIONS: This was an analysis of treatment outcomes, not a prospective clinical trial. Nonetheless, our results suggest: (1) seizure rates decline with increasing VNS duration; (2) this decline occurs without AED changes; (3) this decline is not due to changes in stimulation parameters; (4) patient characteristics predictive of VNS responsiveness remain elusive.

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**Abstract** OBJECTIVE: This retrospective study documented long-term outcome of patients receiving vagus nerve stimulation (VNS) therapy for pharmacoresistant epilepsy. METHODS: Medical charts of 28 patients implanted for 5 years or longer were reviewed for changes in seizure frequency after 1 year of VNS therapy and at follow up, which ranged from 5 to 7 years. Numbers of antiepileptic drugs (AEDs) taken by the patients were also computed at 1 year and follow up. One patient had died and one had discontinued VNS therapy; data were available for 26 patients. Results: The median percent change in seizure frequency from baseline increased from -28% (P = 0.0053, Wilcoxon signed-rank test) at 12 months to -72% (P < 0.0001) at follow up. Some patients whose seizure frequency was not reduced during the initial 12 months of VNS therapy did experience reductions in seizure frequency during the follow-up period. CONCLUSION: In this retrospective study, the effectiveness of VNS therapy increased over time. Physicians should be aware that response to VNS therapy may be delayed for some patients.
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**Abstract** The purpose of this open retrospective study was to analyze the efficacy and tolerability of vagal nerve stimulation (VNS) in a Norwegian cohort of referral patients with refractory epileptic seizures. A total of 47 patients have been assessed after a mean follow-up time of 2.7 years. Mean age was 34.4 years, mean duration of epilepsy was 25.3 years. Forty-two patients (89%) had localization-related epilepsy, 36 patients (77%) had daily seizures. The patients had tried on average 9.5 antiepileptic drugs, and 12 patients (26%) had undergone epilepsy surgery. Sixteen patients (34%) had >50% reduction of seizure frequency with VNS, of which one patient became seizure free. The stimulation was generally well tolerated, but three patients requested the device removed because of troublesome side effects. We conclude that VNS is an efficacious and safe mode of treatment that should be offered to patients with medically and surgically refractory seizures.

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<http://www.ncbi.nlm.nih.gov/pubmed/11709645>  
**Abstract** During the last decade, intermittent electrical stimulation of the left cervical vagus nerve was established as a new add-on treatment of drug-resistant seizures. Particularly in Europe, the acceptance of vagus nerve stimulation (VNS) was tentative in the beginning because of unknown mechanisms of action. We report the outcome in a sample of 95 adult patients with drug-resistant seizures who have received implants since 1998. The last available follow-up data are included. Unavoidable medication changes (e.g., intoxication) were accepted to examine VNS under usual clinical conditions. Median percentage of reduction in seizure frequency as compared to baseline was 30%. The seizure responder rate (> or =50% reduction) was 45%. Four patients experienced total release from seizures. Adverse effects were mild in general. Seizure outcome was positively correlated with VNS duration. No potential clinical factor (e.g., syndrome, cause, or lesion) could be identified as an indicator of favorable outcome. Patients with on stimulation-on periods of 30 seconds (standard cycle) had a better outcome than patients with stimulation-on periods of 7 seconds (rapid cycle). During an embedded, randomized, controlled trial, no evidence was found for a differential outcome of initial standard cycle versus initial rapid cycle stimulation conditions. Taking into account the good cost-benefit ratio as well as positive effects on well-being, VNS has to be considered an appropriate strategy for the add-on treatment of drug-resistant seizures, particularly in cases not suitable for epilepsy surgery.
29. **Wagener-Schimmel LJ, Hageman G, van der Aa HE, Janssen AM, Buschman HP. [Vagus nerve stimulation in patients with drug-resistant epilepsy]. *Ned Tijdschr Geneeskd.* 2001;145(46):2229-34. Dutch.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11757247>  
**Abstract** **OBJECTIVE:** To describe the mechanism and first results of vagus nerve stimulation at the Medisch Spectrum Twente, the Netherlands, for the treatment of patients with drug-resistant epilepsy. **DESIGN:** Descriptive retrospective. **METHOD:** Fifteen patients, 8 male and 7 female, aged 18-45 years with drug-resistant epilepsy, who were not eligible for surgical resection of an epileptic focus, received a vagus nerve stimulator implant in the period April 1999-December 2000. Whilst the vagus nerve stimulator was being adjusted, the medication remained unchanged. **RESULTS:** Due to vagus nerve stimulation the mean seizure frequency decreased by 32% (range: +20% to -100%). In 6 patients there was a strong reduction in seizure frequency, in 3 there was a mild reduction, and in 6 patients there was no apparent effect. The most common adverse events during stimulation were a mild prickly cough and a change of voice during stimulation. In one patient a temporary left vocal cord paralysis was observed, which may possibly have been a result of the procedure. **CONCLUSION:** Vagus nerve stimulation is an effective means of treatment for drug-resistant epilepsy and is therefore a treatment option that deserves more attention in the Netherlands.

30. **Nakken KO, Henriksen O, Roste GK, Lossius R. [Chronic intermittent vagal nerve stimulation--a new therapeutic approach in epilepsy]. *Tidsskr Nor Laegeforen*. 2001;121(13):1582-5. Norwegian. <http://www.ncbi.nlm.nih.gov/pubmed/11446042>**

**Abstract** BACKGROUND: Vagal nerve stimulation is a new non-pharmacological therapy for patients with refractory epilepsy. Introduced in USA in 1988, the treatment is based on animal experiments demonstrating that intermittent stimulation of the vagal nerve could prevent or reduce the frequency and/or duration of seizures. MATERIAL AND METHODS: At the National Hospital in Norway, 47 therapy-resistant patients have had a vagal nerve stimulator implanted since June 1993. We have used the Neuro-Cybernetic Prosthesis system from Cyberonics, consisting of a programmable pulse generator, a bipolar vagal nerve stimulator lead, a programming wand with accompanying software, and a hand-held magnet. The mean age of the population was 34.4 years (12-70 years). All had a long-standing epilepsy with frequent seizures, 36 (77%) had seizures every day. The majority (89%) had localization-related epilepsy. Mean follow-up time was 2.7 years (0.4-6.5 years). RESULTS: 16 patients (34%) responded to the treatment with > 50% reduction in seizure frequency. No one, however, became seizure free. 20 patients (43%) had no seizure reduction. 24 of the patients (51%) benefited from extra stimulation triggered by the magnet. The stimulation affected several types of seizures; most often a reduction in frequency of secondary generalised tonic-clonic seizures was noted. Hoarseness, coughing and a tingling sensation in the throat were the most frequently reported side effects occurring during stimulation. The patients tended to habituate to these side effects. In 14 patients (30%), the device has been explanted, mostly due to lack of efficacy. INTERPRETATION: Considering the fact that this patient group belongs to the most refractory part of the epilepsy population, the results are regarded as promising and they are in keeping with results from other studies. However, the role of vagal nerve stimulation in the future treatment of epilepsy is still not settled. Several questions remain unanswered, e.g. what are the exact mechanisms of action behind the seizure reducing effect, and which patients are most suitable for this treatment?

**Reimbursement**

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1. **Chronic vagus nerve stimulation for treatment of seizures. *Tecnologica MAP Suppl.* 1998:3-5. <http://www.ncbi.nlm.nih.gov/pubmed/10183350>**

## Responsive Neurostimulation

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1. **Sillay KA, Rutecki P, Cicora K, Worrell G, Drazkowski J, Shih JJ, et al. Long-Term Measurement of Impedance in Chronically Implanted Depth And Subdural Electrodes During Responsive Neurostimulation in Humans. *Brain Stimul.* 2013.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23538208>  
**Abstract** Long-term stability of the electrode-tissue interface may be required to maintain optimal neural recording with subdural and deep brain implants and to permit appropriate delivery of neuromodulation therapy. Although short-term changes in impedance at the electrode-tissue interface are known to occur, long-term changes in impedance have not previously been examined in detail in humans. To provide further information about short- and long-term impedance changes in chronically implanted electrodes, a dataset from 191 persons with medically intractable epilepsy participating in a trial of an investigational responsive neurostimulation device (the RNS(R) System, NeuroPace, Inc.) was reviewed. Monopolar impedance measurements were available for 391 depth and subdural leads containing a total of 1564 electrodes; measurements were available for median 802 days post-implant (range 28-1634). Although there were statistically significant short-term impedance changes, long-term impedance was stable after one year. Impedances for depth electrodes transiently increased during the third week after lead implantation and impedances for subdural electrodes increased over 12 weeks post-implant, then were stable over the subsequent long-term follow-up. Both depth and subdural electrode impedances demonstrated long-term stability, suggesting that the quality of long-term electrographic recordings (the data used to control responsive brain stimulation) can be maintained over time.
  
2. **Panuccio G, Guez A, Vincent R, Avoli M, Pineau J. Adaptive control of epileptiform excitability in an in vitro model of limbic seizures. *Exp Neurol.* 2013;241:179-83.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23313899>  
**Abstract** Deep brain stimulation (DBS) is a promising tool for treating drug-resistant epileptic patients. Currently, the most common approach is fixed-frequency stimulation (periodic pacing) by means of stimulating devices that operate under open-loop control. However, a drawback of this DBS strategy is the impossibility of tailoring a personalized treatment, which also limits the optimization of the stimulating apparatus. Here, we propose a novel DBS methodology based on a closed-loop control strategy, developed by exploiting statistical machine learning techniques, in which stimulation parameters are adapted to the current neural activity thus allowing for seizure suppression that is fine-tuned on the individual scale (adaptive stimulation). By means of field potential recording from adult rat hippocampus-entorhinal cortex (EC) slices treated with the convulsant drug 4-aminopyridine we determined the effectiveness of this approach compared to low-frequency periodic pacing, and found that the closed-loop stimulation strategy: (i) has similar efficacy as low-frequency periodic pacing in suppressing ictal-like events but (ii) is more efficient than periodic pacing in that it requires less electrical pulses. We also provide evidence that the closed-loop stimulation strategy can alternatively be employed to tune the frequency of a periodic pacing strategy. Our findings indicate that the adaptive stimulation strategy may represent a novel, promising approach to DBS for individually-tailored epilepsy treatment.

3. **Paz JT, Davidson TJ, Frechette ES, Delord B, Parada I, Peng K, et al. Closed-loop optogenetic control of thalamus as a tool for interrupting seizures after cortical injury. *Nat Neurosci.* 2013;16(1):64-70.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23143518>  
<http://www.nature.com/neuro/journal/v16/n1/pdf/nn.3269.pdf>  
**Abstract** Cerebrocortical injuries such as stroke are a major source of disability. Maladaptive consequences can result from post-injury local reorganization of cortical circuits. For example, epilepsy is a common sequela of cortical stroke, but the mechanisms responsible for seizures following cortical injuries remain unknown. In addition to local reorganization, long-range, extra-cortical connections might be critical for seizure maintenance. In rats, we found that the thalamus, a structure that is remote from, but connected to, the injured cortex, was required to maintain cortical seizures. Thalamocortical neurons connected to the injured epileptic cortex underwent changes in HCN channel expression and became hyperexcitable. Targeting these neurons with a closed-loop optogenetic strategy revealed that reducing their activity in real-time was sufficient to immediately interrupt electrographic and behavioral seizures. This approach is of therapeutic interest for intractable epilepsy, as it spares cortical function between seizures, in contrast with existing treatments, such as surgical lesioning or drugs.
4. **Saillet S, Gharbi S, Charvet G, Deransart C, Guillemaud R, Depaulis A, et al. Neural adaptation to responsive stimulation: A comparison of auditory and deep brain stimulation in a rat model of absence epilepsy. *Brain Stimul.* 2012.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22727526>  
**Abstract** BACKGROUND: Responsive deep brain stimulation (rDBS) has been recently proposed to block epileptic seizures at onset. Yet, long-term stability of brain responses to such kind of stimulation is not known. OBJECTIVE: To quantify the neural adaptation to repeated rDBS as measured by the changes of anti-epileptic efficacy of bilateral DBS of the substantia nigra pars reticulata (SNr) versus auditory stimulation, in a rat model of spontaneous recurrent absence seizures (GAERS). METHODS: Local field potentials (LFP) were recorded in freely moving animals during 1 h up to 24 h under automated responsive stimulations (SNr-DBS and auditory). Comparison of seizure features was used to characterise transient (repetition-suppression effect) and long-lasting (stability of anti-epileptic efficacy, i.e. ratio of successfully interrupted seizures) effects of responsive stimulations. RESULTS: SNr-DBS was more efficient than auditory stimulation in blocking seizures (97% vs. 52% of seizures interrupted, respectively). Sensitivity to minimal interstimulus interval was much stronger for SNr-DBS than for auditory stimulation. Anti-epileptic efficacy of SNr-DBS was remarkably stable during long-term (24 h) recordings. CONCLUSIONS: In the GAERS model, we demonstrated the superiority of SNr-DBS to suppress seizures, as compared to auditory stimulation. Importantly, we found no long-term habituation to rDBS. However, when seizure recurrence was frequent, rDBS lack anti-epileptic efficacy because responsive stimulations became too close (time interval < 40 s) suggesting the existence of a refractory period. This study thus motivates the use of automated rDBS in patients having transient seizures separated by sufficiently long intervals.

5. **Makeyev O, Liu X, Wang L, Zhu Z, Taveras A, Troiano D, et al. Feasibility of recording high frequency oscillations with tripolar concentric ring electrodes during pentylenetetrazole-induced seizures in rats. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:4599-602.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23366952>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6346991>  
**Abstract** As epilepsy remains a refractory condition in about 30% of patients with complex partial seizures, electrical stimulation of the brain has recently shown potential for additive seizure control therapy. Previously, we applied noninvasive transcranial focal stimulation via novel tripolar concentric ring electrodes (TCREs) on the scalp of rats after inducing seizures with pentylenetetrazole (PTZ). We developed a close-loop system to detect seizures and automatically trigger the stimulation and evaluated its effect on the electrographic activity recorded by TCREs in rats. In our previous work the detectors of seizure onset were based on seizure-induced changes in signal power in the frequency range up to 100 Hz, while in this preliminary study we assess the feasibility of recording high frequency oscillations (HFOs) in the range up to 300 Hz noninvasively with scalp TCREs during PTZ-induced seizures. Grand average power spectral density estimate and generalized likelihood ratio tests were used to compare power of electrographic activity at different stages of seizure development in a group of rats (n= 8). The results suggest that TCREs have the ability to record HFOs from the scalp as well as that scalp-recorded HFOs can potentially be used as features for seizure onset detection.
  
6. **Makeyev O, Ding Q, Kay SM, Besio WG. Sensor integration of multiple tripolar concentric ring electrodes improves pentylenetetrazole-induced seizure onset detection in rats. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:5154-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23367089>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6347154>  
**Abstract** As epilepsy affects approximately one percent of the world population, electrical stimulation of the brain has recently shown potential for additive seizure control therapy. Previously, we applied noninvasive transcranial focal stimulation via tripolar concentric ring electrodes on the scalp of rats after inducing seizures with pentylenetetrazole. We developed a system to detect seizures and automatically trigger the stimulation and evaluated the system on the electrographic activity from rats. In this preliminary study we propose and validate a novel seizure onset detection algorithm based on exponentially embedded family. Unlike the previously proposed approach it integrates the data from multiple electrodes allowing an improvement of the detector performance.
  
7. **Enatsu R, Alexopoulos A, Bingaman W, Nair D. Complementary effect of surgical resection and responsive brain stimulation in the treatment of bitemporal lobe epilepsy: a case report. *Epilepsy Behav.* 2012;24(4):513-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22795315>  
**Abstract** We report a 39-year-old man with bilateral mesial temporal lobe epilepsy. He was implanted with a responsive brain stimulator (RNS System) with two depth electrodes placed in the bimesial temporal structures. After the implantation, his seizure frequency decreased by up to 50%. Electrocorticogram recorded by the RNS device revealed the right-sided predominance of seizure onset. He underwent a right temporal lobectomy, and his seizure significantly improved. After the RNS System was restarted 107 days after the temporal lobectomy, he has been seizure free for more than 1.5 years. However, the implanted device continued to record residual ictal activities at the posterior aspect of the right hippocampus and delivered electrical stimuli to suppress the seizure activities. Our report indicates the importance of electrocorticographic recordings by the RNS System to modify the treatment strategy and the complementary effect of surgical resection and brain stimulation in the treatment of epilepsy.

- 8. Modolo J, Beuter A, Thomas AW, Legros A. Using "smart stimulators" to treat Parkinson's disease: re-engineering neurostimulation devices. *Front Comput Neurosci.* 2012;6:69.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23060781>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3448062/pdf/fncom-06-00069.pdf>  
**Abstract** Let's imagine the cruise control of your car locked at 120 km/h on any road in any condition (city, country, highway, sunny or rainy weather), or your car air conditioner set on maximum cold in any temperature condition (even during a snowy winter): would you find it efficient? That would probably not be the most optimal strategy for a proper and comfortable driving experience. As surprising as this may seem, this is a pretty accurate illustration of how deep brain stimulation is used today to treat Parkinson's disease motor symptoms and other neurological disorders such as essential tremor, obsessive-compulsive disorder, or epilepsy.
- 9. Beverlin li B, Netoff TI. Dynamic control of modeled tonic-clonic seizure states with closed-loop stimulation. *Front Neural Circuits.* 2012;6:126.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23390413>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3565374/pdf/fncir-06-00126.pdf>  
**Abstract** Seizure control using deep brain stimulation (DBS) provides an alternative therapy to patients with intractable and drug resistant epilepsy. This paper presents novel DBS stimulus protocols to disrupt seizures. Two protocols are presented: open-loop stimulation and a closed-loop feedback system utilizing measured firing rates to adjust stimulus frequency. Stimulation suppression is demonstrated in a computational model using 3000 excitatory Morris-Lecar (M-L) model neurons connected with depressing synapses. Cells are connected using second order network topology (SONET) to simulate network topologies measured in cortical networks. The network spontaneously switches from tonic to clonic as synaptic strengths and tonic input to the neurons decreases. To this model we add periodic stimulation pulses to simulate DBS. Periodic forcing can synchronize or desynchronize an oscillating population of neurons, depending on the stimulus frequency and amplitude. Therefore, it is possible to either extend or truncate the tonic or clonic phases of the seizure. Stimuli applied at the firing rate of the neuron generally synchronize the population while stimuli slightly slower than the firing rate prevent synchronization. We present an adaptive stimulation algorithm that measures the firing rate of a neuron and adjusts the stimulus to maintain a relative stimulus frequency to firing frequency and demonstrate it in a computational model of a tonic-clonic seizure. This adaptive algorithm can affect the duration of the tonic phase using much smaller stimulus amplitudes than the open-loop control.

10. **Stanslaski S, Afshar P, Cong P, Giftakis J, Stypulkowski P, Carlson D, et al. Design and validation of a fully implantable, chronic, closed-loop neuromodulation device with concurrent sensing and stimulation. *IEEE Trans Neural Syst Rehabil Eng.* 2012;20(4):410-21.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22275720>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6135801>  
**Abstract** Chronically implantable, closed-loop neuromodulation devices with concurrent sensing and stimulation hold promise for better understanding the nervous system and improving therapies for neurological disease. Concurrent sensing and stimulation are needed to maximize usable neural data, minimize time delays for closed-loop actuation, and investigate the instantaneous response to stimulation. Current systems lack concurrent sensing and stimulation primarily because of stimulation interference to neural signals of interest. While careful design of high performance amplifiers has proved useful to reduce disturbances in the system, stimulation continues to contaminate neural sensing due to biological effects like tissue-electrode impedance mismatch and constraints on stimulation parameters needed to deliver therapy. In this work we describe systematic methods to mitigate the effect of stimulation through a combination of sensing hardware, stimulation parameter selection, and classification algorithms that counter residual stimulation disturbances. To validate these methods we implemented and tested a completely implantable system for over one year in a large animal model of epilepsy. The system proved capable of measuring and detecting seizure activity in the hippocampus both during and after stimulation. Furthermore, we demonstrate an embedded algorithm that actuates neural modulation in response to seizure detection during stimulation, validating the capability to detect bioelectrical markers in the presence of therapy and titrate it appropriately. The capability to detect neural states in the presence of stimulation and optimally titrate therapy is a key innovation required for generalizing closed-loop neural systems for multiple disease states.
11. **Makeyev O, Liu X, Luna-Munguia H, Rogel-Salazar G, Mucio-Ramirez S, Liu Y, et al. Toward a noninvasive automatic seizure control system in rats with transcranial focal stimulations via tripolar concentric ring electrodes. *IEEE Trans Neural Syst Rehabil Eng.* 2012;20(4):422-31.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22772373>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6231696>  
**Abstract** Epilepsy affects approximately 1% of the world population. Antiepileptic drugs are ineffective in approximately 30% of patients and have side effects. We are developing a noninvasive, or minimally invasive, transcranial focal electrical stimulation system through our novel tripolar concentric ring electrodes to control seizures. In this study, we demonstrate feasibility of an automatic seizure control system in rats with pentylenetetrazole-induced seizures through single and multiple stimulations. These stimulations are automatically triggered by a real-time electrographic seizure activity detector based on a disjunctive combination of detections from a cumulative sum algorithm and a generalized likelihood ratio test. An average seizure onset detection accuracy of 76.14% was obtained for the test set (n = 13). Detection of electrographic seizure activity was accomplished in advance of the early behavioral seizure activity in 76.92% of the cases. Automatically triggered stimulation significantly ( $p = 0.001$ ) reduced the electrographic seizure activity power in the once stimulated group compared to controls in 70% of the cases. To the best of our knowledge this is the first closed-loop automatic seizure control system based on noninvasive electrical brain stimulation using tripolar concentric ring electrode electrographic seizure activity as feedback.

12. **Santaniello S, Sherman DL, Thakor NV, Eskandar EN, Sarma SV. Optimal control-based bayesian detection of clinical and behavioral state transitions. *IEEE Trans Neural Syst Rehabil Eng.* 2012;20(5):708-19.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22893447>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6263308>  
**Abstract** Accurately detecting hidden clinical or behavioral states from sequential measurements is an emerging topic in neuroscience and medicine, which may dramatically impact neural prosthetics, brain-computer interface and drug delivery. For example, early detection of an epileptic seizure from sequential electroencephalographic (EEG) measurements would allow timely administration of anticonvulsant drugs or neurostimulation, thus reducing physical impairment and risks of overtreatment. We develop a Bayesian paradigm for state transition detection that combines optimal control and Markov processes. We define a hidden Markov model of the state evolution and develop a detection policy that minimizes a loss function of both probability of false positives and accuracy (i.e., lag between estimated and actual transition time). Our strategy automatically adapts to each newly acquired measurement based on the state evolution model and the relative loss for false positives and accuracy, thus resulting in a time varying threshold policy. The paradigm was used in two applications: 1) detection of movement onset (behavioral state) from subthalamic single unit recordings in Parkinson's disease patients performing a motor task; 2) early detection of an approaching seizure (clinical state) from multichannel intracranial EEG recordings in rodents treated with pentylenetetrazol chemoconvulsant. Our paradigm performs significantly better than chance and improves over widely used detection algorithms.
13. **Wang L, Guo H, Yu X, Wang S, Xu C, Fu F, et al. Responsive electrical stimulation suppresses epileptic seizures in rats. *PLoS One.* 2012;7(5):e38141.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22662277>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3360655/pdf/pone.0038141.pdf>  
**Abstract** BACKGROUND: A responsive electrical stimulation pattern based on our recently developed novel seizure prediction method was designed to suppress the penicillin-induced epileptic seizures. METHODOLOGY: Seizures were induced by Penicillin injection at rat cortex. A responsive electrical stimulation system was triggered prior to seizures predicted with phase synchronisation. Rats with induced seizures were stimulated by the electrical pulses at a responsive or 1 Hz periodic pattern of an open system. The effectiveness of stimulation on seizures suppression was assessed by measuring the average number and duration of seizures per hour. RESULTS: The prediction algorithm reliably identified seizures in real time and triggered the responsive stimulation. This type of electrical stimulation dramatically suppressed seizure activity and the performance was better than the open stimulation system with fewer and shorter seizures. CONCLUSIONS: A responsive electrical stimulation system triggered by the phase synchronisation prediction is able to significantly suppress seizures. SIGNIFICANCE: Responsive electrical stimulation could achieve superior treatment performance and reduce power consumption and side effects.
14. **Berenyi A, Belluscio M, Mao D, Buzsaki G. Closed-loop control of epilepsy by transcranial electrical stimulation. *Science.* 2012;337(6095):735-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22879515>  
<http://www.sciencemag.org/content/337/6095/735>  
**Abstract** Many neurological and psychiatric diseases are associated with clinically detectable, altered brain dynamics. The aberrant brain activity, in principle, can be restored through electrical stimulation. In epilepsies, abnormal patterns emerge intermittently, and therefore, a closed-loop feedback brain control that leaves other aspects of brain functions unaffected is desirable. Here, we demonstrate that seizure-triggered, feedback transcranial electrical stimulation (TES) can dramatically reduce spike-and-wave episodes in a rodent model of generalized epilepsy. Closed-loop TES can be an effective clinical tool to reduce pathological brain patterns in drug-resistant patients.

15. **Lee B, Liu CY, Apuzzo ML. Quantum computing: a prime modality in neurosurgery's future. *World Neurosurg.* 2012;78(5):404-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22846655>  
**Abstract** OBJECTIVE: With each significant development in the field of neurosurgery, our dependence on computers, small and large, has continuously increased. From something as mundane as bipolar cautery to sophisticated intraoperative navigation with real-time magnetic resonance imaging-assisted surgical guidance, both technologies, however simple or complex, require computational processing power to function. The next frontier for neurosurgery involves developing a greater understanding of the brain and furthering our capabilities as surgeons to directly affect brain circuitry and function. METHODS: This has come in the form of implantable devices that can electronically and nondestructively influence the cortex and nuclei with the purpose of restoring neuronal function and improving quality of life. RESULTS: We are now transitioning from devices that are turned on and left alone, such as vagus nerve stimulators and deep brain stimulators, to "smart" devices that can listen and react to the body as the situation may dictate. CONCLUSION: The development of quantum computers and their potential to be thousands, if not millions, of times faster than current "classical" computers, will significantly affect the neurosciences, especially the field of neurorehabilitation and neuromodulation. Quantum computers may advance our understanding of the neural code and, in turn, better develop and program implantable neural devices. When quantum computers reach the point where we can actually implant such devices in patients, the possibilities of what can be done to interface and restore neural function will be limitless.
16. **Stanslaski S, Giftakis J, Stypulkowski P, Carlson D, Afshar P, Cong P, et al. Emerging technology for advancing the treatment of epilepsy using a dynamic control framework. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:753-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22254420>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090172>  
**Abstract** We briefly describe a dynamic control system framework for neuromodulation for epilepsy, with an emphasis on its practical challenges and the preliminary validation of key prototype technologies in a chronic animal model. The current state of neuromodulation can be viewed as a classical dynamic control framework such that the nervous system is the classical "plant", the neural stimulator is the controller/actuator, clinical observation, patient diaries and/or measured bio-markers are the sensor, and clinical judgment applied to these sensor inputs forms the state estimator. Technology can potentially address two main factors contributing to the performance limitations of existing systems: "observability," the ability to observe the state of the system from output measurements, and "controllability," the ability to drive the system to a desired state. In addition to improving sensors and actuator performance, methods and tools to better understand disease state dynamics and state estimation are also critical for improving therapy outcomes. We describe our preliminary validation of key "observability" and "controllability" technology blocks using an implanted research tool in an epilepsy disease model. This model allows for testing the key emerging technologies in a representative neural network of therapeutic importance. In the future, we believe these technologies might enable both first principles understanding of neural network behavior for optimizing therapy design, and provide a practical pathway towards clinical translation.

17. **Makeyev O, Liu X, Koka K, Kay SM, Besio WG. Transcranial focal stimulation via concentric ring electrodes reduced power of pentylenetetrazole-induced seizure activity in rat electroencephalogram. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:7560-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22256088>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6091864>  
**Abstract** As epilepsy affects approximately one percent of the world population, electrical stimulation of the brain has recently shown potential for additive seizure control therapy. In this study we applied noninvasive transcranial focal stimulation (TFS) via concentric ring electrodes on the scalp of rats after inducing seizures with pentylenetetrazole (PTZ) to assess the effect of TFS on the electrographic activity. Grand average power spectral densities were calculated to compare different stages of seizure development. They showed a significant difference between the TFS treated group and the control group. In case of the TFS treated group, after TFS, the power spectral density was reduced further towards a pre-seizure "baseline" than it was for the control group. The difference is the most drastic in delta, theta and alpha frequency bands. Application of general likelihood ratio test showed that TFS significantly ( $p < 0.001$ ) reduced the power of electrographic seizure activity in the TFS treated group compared to controls in more than 86% of the cases. These results suggest that TFS may have an anticonvulsant effect.
18. **Spencer D, Gwinn R, Salinsky M, O'Malley JP. Laterality and temporal distribution of seizures in patients with bitemporal independent seizures during a trial of responsive neurostimulation. *Epilepsy Res.* 2011;93(2-3):221-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21256715>  
**Abstract** We describe seizure laterality and temporal seizure patterns in six subjects with bilateral temporal lobe epilepsy (bTLE) implanted with bilateral hippocampal depth electrodes and the NeuroPace RNS system over 84 consecutive days. Seizures were disproportionate in laterality in three subjects and disproportionate in time for two subjects. Clustering of seizures did not clearly affect laterality. Some but not all subjects with bTLE displayed nonrandom temporal or lateral clustering of seizures.
19. **Nelson TS, Suhr CL, Freestone DR, Lai A, Halliday AJ, McLean KJ, et al. Closed-loop seizure control with very high frequency electrical stimulation at seizure onset in the GAERS model of absence epilepsy. *Int J Neural Syst.* 2011;21(2):163-73.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21442779>  
**Abstract** A closed-loop system for the automated detection and control of epileptic seizures was created and tested in three Genetic Absence Epilepsy Rats from Strasbourg (GAERS) rats. In this preliminary study, a set of four EEG features were used to detect seizures and three different electrical stimulation strategies (standard (130 Hz), very high (500 Hz) and ultra high (1000 Hz)) were delivered to terminate seizures. Seizure durations were significantly shorter with all three stimulation strategies when compared to non-stimulated (control) seizures. We used mean seizure duration of epileptiform discharges persisting beyond the end of electrical stimulation as a measure of stimulus efficacy. When compared to the duration of seizures stimulated in the standard approach (7.0 s +/- 10.1), both very high and ultra high frequency stimulation strategies were more effective at shortening seizure durations (1.3 +/- 2.2 s and 3.5 +/- 6.4 s respectively). Further studies are warranted to further understand the mechanisms by which this therapeutic effect may be conveyed, and which of the novel aspects of the very high and ultra high frequency stimulation strategies may have contributed to the improvement in seizure abatement performance when compared to standard electrical stimulation approaches.

20. **Colic S, Zalay OC, Bardakjian BL. Responsive neuromodulators based on artificial neural networks used to control seizure-like events in a computational model of epilepsy. *Int J Neural Syst.* 2011;21(5):367-83.** <http://www.ncbi.nlm.nih.gov/pubmed/21956930>  
**Abstract** Deep brain stimulation (DBS) has been noted for its potential to suppress epileptic seizures. To date, DBS has achieved mixed results as a therapeutic approach to seizure control. Using a computational model, we demonstrate that high-complexity, biologically-inspired responsive neuromodulation is superior to periodic forms of neuromodulation (responsive and non-responsive) such as those implemented in DBS, as well as neuromodulation using random and random repetitive-interval stimulation. We configured radial basis function (RBF) networks to generate outputs modeling interictal time series recorded from rodent hippocampal slices that were perfused with low Mg(2+)/high K(+) solution. We then compared the performance of RBF-based interictal modulation, periodic biphasic-pulse modulation, random modulation and random repetitive modulation on a cognitive rhythm generator (CRG) model of spontaneous seizure-like events (SLEs), testing efficacy of SLE control. A statistically significant improvement in SLE mitigation for the RBF interictal modulation case versus the periodic and random cases was observed, suggesting that the use of biologically-inspired neuromodulators may achieve better results for the purpose of electrical control of seizures in a clinical setting.
21. **Rouse AG, Stanslaski SR, Cong P, Jensen RM, Afshar P, Ullestad D, et al. A chronic generalized bi-directional brain-machine interface. *J Neural Eng.* 2011;8(3):036018.** <http://www.ncbi.nlm.nih.gov/pubmed/21543839>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3146241/pdf/nihms310842.pdf>  
**Abstract** A bi-directional neural interface (NI) system was designed and prototyped by incorporating a novel neural recording and processing subsystem into a commercial neural stimulator architecture. The NI system prototype leverages the system infrastructure from an existing neurostimulator to ensure reliable operation in a chronic implantation environment. In addition to providing predicate therapy capabilities, the device adds key elements to facilitate chronic research, such as four channels of electrocortigram/local field potential amplification and spectral analysis, a three-axis accelerometer, algorithm processing, event-based data logging, and wireless telemetry for data uploads and algorithm/configuration updates. The custom-integrated micropower sensor and interface circuits facilitate extended operation in a power-limited device. The prototype underwent significant verification testing to ensure reliability, and meets the requirements for a class CF instrument per IEC-60601 protocols. The ability of the device system to process and aid in classifying brain states was preclinically validated using an in vivo non-human primate model for brain control of a computer cursor (i.e. brain-machine interface or BMI). The primate BMI model was chosen for its ability to quantitatively measure signal decoding performance from brain activity that is similar in both amplitude and spectral content to other biomarkers used to detect disease states (e.g. Parkinson's disease). A key goal of this research prototype is to help broaden the clinical scope and acceptance of NI techniques, particularly real-time brain state detection. These techniques have the potential to be generalized beyond motor prosthesis, and are being explored for unmet needs in other neurological conditions such as movement disorders, stroke and epilepsy.

22. Liang SF, Liao YC, Shaw FZ, Chang DW, Young CP, Chiueh H. Closed-loop seizure control on epileptic rat models. *J Neural Eng.* 2011;8(4):045001.

<http://www.ncbi.nlm.nih.gov/pubmed/21775786>

<http://iopscience.iop.org/1741-2552/8/4/045001/>

**Abstract** In this paper numerous alternative treatments in addition to pharmacological therapy are proposed for their use in epileptic patients. Epileptic animal models can play a crucial role in the performance evaluation of new therapeutic techniques. The objective of this research is to first develop various epileptic rat models; second, develop a portable wireless closed-loop seizure controller including on-line seizure detection and real-time electrical stimulation for seizure elimination; and third, apply the developed seizure controller to the animal models to perform on-line seizure elimination. The closed-loop seizure controller was applied to three Long-Evans rats with spontaneous spike-wave discharges (non-convulsive) and three Long-Evans rats with epileptiform activities induced by pentylenetetrazol (PTZ) injection (convulsive) for evaluation. The seizure detection accuracy is greater than 92% (up to 99%), and averaged seizure detection latency is less than 0.6 s for both spontaneous non-convulsive and PTZ-induced convulsive seizures. The average false stimulation rate is 3.1%. Near 30% of PTZ-induced convulsive seizures need more than two times of 0.5 s electrical stimulation for suppression and 90% of the non-convulsive seizures can be suppressed by only one 0.5 s electrical stimulation.

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<http://iopscience.iop.org/1741-2552/8/6/066008/>

**Abstract** A stimulus driver circuit for a micro-stimulator used in an implantable device is presented in this paper. For epileptic seizure control, the target of the driver was to output 30 microA stimulus currents when the electrode impedance varied between 20 and 200 k $\Omega$ . The driver, which consisted of the output stage, control block and adaptor, was integrated in a single chip. The averaged power consumption of the stimulus driver was 0.24-0.56 mW at 800 Hz stimulation rate. Fabricated in a 0.35 microm 3.3 V/24 V CMOS process and applied to a closed-loop epileptic seizure monitoring and controlling system, the proposed design has been successfully verified in the experimental results of Long-Evans rats with epileptic seizures.

24. **Morrell MJ, RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology*. 2011;77(13):1295-304.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21917777>  
<http://www.neurology.org/content/77/13/1295.full.pdf>  
**Abstract** OBJECTIVES: This multicenter, double-blind, randomized controlled trial assessed the safety and effectiveness of responsive cortical stimulation as an adjunctive therapy for partial onset seizures in adults with medically refractory epilepsy. METHODS: A total of 191 adults with medically intractable partial epilepsy were implanted with a responsive neurostimulator connected to depth or subdural leads placed at 1 or 2 predetermined seizure foci. The neurostimulator was programmed to detect abnormal electrocorticographic activity. One month after implantation, subjects were randomized 1:1 to receive stimulation in response to detections (treatment) or to receive no stimulation (sham). Efficacy and safety were assessed over a 12-week blinded period and a subsequent 84-week open-label period during which all subjects received responsive stimulation. RESULTS: Seizures were significantly reduced in the treatment (-37.9%, n = 97) compared to the sham group (-17.3%, n = 94; p = 0.012) during the blinded period and there was no difference between the treatment and sham groups in adverse events. During the open-label period, the seizure reduction was sustained in the treatment group and seizures were significantly reduced in the sham group when stimulation began. There were significant improvements in overall quality of life (p < 0.02) and no deterioration in mood or neuropsychological function. CONCLUSIONS: Responsive cortical stimulation reduces the frequency of disabling partial seizures, is associated with improvements in quality of life, and is well-tolerated with no mood or cognitive effects. Responsive stimulation may provide another adjunctive treatment option for adults with medically intractable partial seizures. Classification of evidence: This study provides Class I evidence that responsive cortical stimulation is effective in significantly reducing seizure frequency for 12 weeks in adults who have failed 2 or more antiepileptic medication trials, 3 or more seizures per month, and 1 or 2 seizure foci.
25. **Gigante PR, Goodman RR. Responsive neurostimulation for the treatment of epilepsy. *Neurosurg Clin N Am*. 2011;22(4):477-80, vi.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21939846>  
**Abstract** Neurostimulation in epilepsy has witnessed a century-long evolution that has resulted in the use of neurostimulation to both modulate and suppress abnormal neuronal firing. The recent development of advanced responsive stimulation via a closed-loop device (the RNS System) has provided evidence that surgical epilepsy treatment continues to move toward the possibility of reducing or eliminating seizures in medically refractory patients.
26. **Sohal VS, Sun FT. Responsive neurostimulation suppresses synchronized cortical rhythms in patients with epilepsy. *Neurosurg Clin N Am*. 2011;22(4):481-8, vi.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21939847>  
**Abstract** Deep brain stimulation (DBS) is an established treatment for Parkinson's disease, and is increasingly used for other neuropsychiatric conditions including epilepsy. Nevertheless, neural mechanisms for DBS and other forms of neurostimulation remain elusive. The authors measured effects of responsive neurostimulation on intracranially recorded activity from participants in a clinical investigation to assess the safety of an implantable responsive neurostimulation system in epilepsy (RNS System, NeuroPace, Inc.). Neurostimulation acutely suppressed gamma frequency (35-100 Hz) phase-locking. This may represent a therapeutic mechanism by which responsive neurostimulation can suppress epileptiform activity and disconnect stimulated regions from downstream targets in epilepsy and other neuropsychiatric conditions.

27. **Benabid AL, Costecalde T, Torres N, Moro C, Aksenova T, Eliseyev A, et al. Deep brain stimulation: BCI at large, where are we going to? *Prog Brain Res.* 2011;194:71-82.**

<http://www.ncbi.nlm.nih.gov/pubmed/21867795>

**Abstract** Brain-computer interfaces (BCIs) include stimulators, infusion devices, and neuroprostheses. They all belong to functional neurosurgery. Deep brain stimulators (DBS) are widely used for therapy and are in need of innovative evolutions. Robotized exoskeletons require BCIs able to drive up to 26 degrees of freedom (DoF). We report the nanomicrotechnology development of prototypes for new 3D DBS and for motor neuroprostheses. For this complex project, all compounds have been designed and are being tested. Experiments were performed in rats and primates for proof of concepts and development of the electroencephalogram (EEG) recognition algorithm. **METHODS:** Various devices have been designed. (A) In human, a programmable multiplexer connecting five tetrapolar (20 contacts) electrodes to one DBS channel has been designed and implanted bilaterally into STN in two Parkinsonian patients. (B) A 50-mm diameter titanium implant, telepowered, including a radioset, emitting ECoG data recorded by a 64-electrode array using an application-specific integrated circuit, is being designed to be implanted in a 50-mm trephine opening. Data received by the radioreceiver are processed through an original wavelet-based Iterative N-way Partial Least Square algorithm (INPLS, CEA patent). Animals, implanted with ECoG recording electrodes, had to press a lever to obtain a reward. The brain signature associated to the lever press (LP) was detected online by ECoG processing using INPLS. This detection allowed triggering the food dispenser. **RESULTS:** (A) The 3D multiplexer allowed tailoring the electrical field to the STN. The multiplication of the contacts affected the battery life and suggested different implantation schemes. (B) The components of the human implantable cortical BCI are being tested for reliability and toxicology to meet criteria for chronicle implantation in 2012. (C) In rats, the algorithm INPLS could detect the cortical signature with an accuracy of about 80% of LPs on the electrodes with the best correlation coefficient (located over the cerebellar cortex), 1% of the algorithm decisions were false positives. We aim to pilot effectors with DoF up to 3 in monkeys. **CONCLUSION:** We have designed multielectrodes wireless implants to open the way for BCI ECoG-driven effectors. These technologies are also used to develop new generations of brain stimulators, either cortical or for deep targets. This chapter is aimed at illustrating that BCIs are actually the daily background of DBS, that the evolution of the method involves a growing multiplicity of targets and indications, that new technologies make possible and simpler than before to design innovative solutions to improve DBS methodology, and that the coming out of BCI-driven neuroprostheses for compensation of motor and sensory deficits is a natural evolution of functional neurosurgery.

28. **Sun FT, Morrell MJ, Wharen RE, Jr. Responsive cortical stimulation for the treatment of epilepsy. *Neurotherapeutics*. 2008;5(1):68-74.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18164485>  
[http://download.springer.com/static/pdf/593/art%253A10.1016%252Fj.nurt.2007.10.069.pdf?auth66=1364573187\\_6fb89d7c6ac9da2d3d75744b0fdc7dcc&ext=.pdf](http://download.springer.com/static/pdf/593/art%253A10.1016%252Fj.nurt.2007.10.069.pdf?auth66=1364573187_6fb89d7c6ac9da2d3d75744b0fdc7dcc&ext=.pdf)  
**Abstract** Epilepsy is a common chronic neurological disorder affecting approximately 1-2% of the population. Despite the available treatment options (pharmacotherapy, surgery, and vagus nerve stimulation), a large percentage of patients continue to have seizures. With the success of deep brain stimulation for treatment of movement disorders, brain stimulation has received renewed attention as a potential treatment option for epilepsy. Responsive stimulation aims to suppress epileptiform activity by delivering stimulation directly in response to electrographic activity. Animal and human data support the concept that responsive stimulation can abort epileptiform activity, and this modality may be a safe and effective treatment option for epilepsy. Responsive stimulation has the advantage of specificity. In contrast to the typically systemic administration of pharmacotherapy, with the concomitant possibility of side effects, electrical stimulation can be targeted to the specific brain regions involved in the seizure. In addition, responsive stimulation provides temporal specificity. Treatment is provided as needed, potentially reducing the likelihood of functional disruption or habituation due to continuous treatment. Here we review current animal and human research in responsive brain stimulation for epilepsy and then discuss the NeuroPace RNS System, an investigational implantable responsive neurostimulator system that is being evaluated in a multicenter, randomized, double-blinded trial to assess the safety and efficacy of responsive stimulation for the treatment of medically refractory epilepsy.
29. **Jaseja H. Vagal nerve stimulation technique: enhancing its efficacy and acceptability by augmentation with auto activation and deactivation mode of operation. *Med Hypotheses*. 2004;63(1):76-9; comment *Med Hypothesis*. 2006;66(3):680-1.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15193352>  
**Abstract** The purpose of this article is to search for an additional modus operandi to improve the functioning of currently deployed vagal nerve stimulation (VNS) technique that is being used as an adjunctive therapy for intractable epilepsy, mainly complex partial seizures (partial onset with secondary generalization). The efficacy and success of current VNS technique is variable and limited, which can be attributed (to a considerable extent) to its present modi operandi. The mechanism of anti-epileptic action of VNS that has been hypothesized in the article is found to conform to observations and results in a large number of studies including those on VNS itself. Based on this mechanism in controlling seizures, the author proposes an additional mode of operation of the VNS device, (an auto activation and deactivation mode), designed to work on a feedback mechanism, which would deliver VNS as and when the brain requires it to abort/arrest the impending focal attack and/or its generalization, thus eliminating the limitations associated with the current VNS device. This mode should enhance its acceptability, efficacy and success.

**Rett Syndrome (VNS efficacy in...)**

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1. **Dolce A, Ben-Zeev B, Naidu S, Kossoff EH. Rett syndrome and epilepsy: an update for child neurologists. *Pediatr Neurol.* 2013;48(5):337-45.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23583050>  
**Abstract** Rett syndrome, a neurogenetic disorder predominantly affecting females, has many characteristic features including psychomotor retardation, impaired language development, hand stereotypies, gait dysfunction, and acquired microcephaly. Although each of these features undoubtedly contributes to the morbidity of this neurologic disorder, epilepsy is perhaps one of the most well-described and problematic, affecting as many as 50%-90% of patients. Seizures can often be refractory, requiring polytherapy and consideration of nonpharmacologic management (e.g., ketogenic diets and vagus nerve stimulation). In addition, many nonepileptic symptoms of Rett syndrome can occasionally be difficult to differentiate from seizures making clinical management and family counseling challenging. Our goal in this review is to better define the clinical and electrophysiological aspects of the epilepsy associated with Rett syndrome and provide practical guidance regarding management.
  
2. **Wilfong AA, Schultz RJ. Vagus nerve stimulation for treatment of epilepsy in Rett syndrome. *Dev Med Child Neurol.* 2006;48(8):683-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16836782>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1469-8749.2006.tb01340.x/asset/j.1469-8749.2006.tb01340.x.pdf?v=1&t=he93zbrm&s=0502afa4836e4119cbd414419256f186e9d672bd>  
**Abstract** This case series presents the outcomes of seven females with Rett syndrome and medically refractory epilepsy who were treated with adjunctive vagus nerve stimulation (VNS) therapy for a minimum of 12 months. Patients ranged in age from 1 to 14 years (median age 9 y) at the time of implantation, had experienced seizures for a median period of approximately 6 years, and had failed at least two trials of antiepileptic drugs before receiving VNS. The median number of seizures per month was 150 (range 12-3600). At 12 months, six females had  $\geq$ 50% reduction in seizure frequency. VNS was safe and well tolerated, with no surgical complications and no patients requiring explantation of the device. Quality of life outcomes of note among these patients included reports at 12 months of increased alertness among all seven patients. No change in mood or communication abilities was noted.

**Review Articles - Epilepsy, Devices**

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- 1. Fisher RS. Therapeutic devices for epilepsy. *Ann Neurol.* 2012;71(2):157-68. <http://www.ncbi.nlm.nih.gov/pubmed/22367987> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3296971/pdf/nihms322645.pdf>**

**Abstract** Therapeutic devices provide new options for treating drug-resistant epilepsy. These devices act by a variety of mechanisms to modulate neuronal activity. Only vagus nerve stimulation (VNS), which continues to develop new technology, is approved for use in the United States. Deep brain stimulation of anterior thalamus for partial epilepsy recently was approved in Europe and several other countries. Responsive neurostimulation, which delivers stimuli to 1 or 2 seizure foci in response to a detected seizure, recently completed a successful multicenter trial. Several other trials of brain stimulation are in planning or underway. Transcutaneous magnetic stimulation (TMS) may provide a noninvasive method to stimulate cortex. Controlled studies of TMS are split on efficacy, which may depend on whether a seizure focus is near a possible region for stimulation. Seizure detection devices in the form of shake detectors via portable accelerometers can provide notification of an ongoing tonic-clonic seizure, or peace of mind in the absence of notification. Prediction of seizures from various aspects of electroencephalography (EEG) is in early stages. Prediction appears to be possible in a subpopulation of people with refractory seizures, and a clinical trial of an implantable prediction device is underway. Cooling of neocortex or hippocampus reversibly can attenuate epileptiform EEG activity and seizures, but engineering problems remain in its implementation. Optogenetics is a new technique that can control excitability of specific populations of neurons with light. Inhibition of epileptiform activity has been demonstrated in hippocampal slices, but use in humans will require more work. In general, devices provide useful palliation for otherwise uncontrollable seizures, but with a different risk profile than with most drugs. Optimizing the place of devices in therapy for epilepsy will require further development and clinical experience.
  
- 2. Hunter TB, Yoshino MT, Dzioba RB, Light RA, Berger WG. Medical devices of the head, neck, and spine. *Radiographics.* 2004;24(1):257-85. <http://www.ncbi.nlm.nih.gov/pubmed/14730051> <http://radiographics.rsna.org/content/24/1/257.full.pdf>**

**Abstract** There are many medical devices used for head, neck, and spinal diseases and injuries, and new devices are constantly being introduced. Many of the newest devices are variations on a previous theme. Knowing the specific name of a device is not important. It is important to recognize the presence of a device and to have an understanding of its function as well as to be able to recognize the complications associated with its use. The article discusses the most common and important devices of the head, neck, and spine, including cerebrospinal fluid shunts and the Codman Hakim programmable valve; subdural drainage catheters, subdural electrodes, intracranial electrodes, deep brain stimulators, and cerebellar electrodes; coils, balloons, adhesives, particles, and aneurysm clips; radiation therapy catheters, intracranial balloons for drug installation, and carmustine wafers; hearing aids, cochlear implants, and ossicular reconstruction prostheses; orbital prostheses, intraocular silicone oil, and lacrimal duct stents; anterior and posterior cervical plates, posterior cervical spine wiring, odontoid fracture fixation devices, cervical collars and halo vests; thoracic and lumbar spine implants, anterior and posterior instrumentation for the thoracic and lumbar spine, vertebroplasty, and artificial disks; spinal column stimulators, bone stimulators, intrathecal drug delivery pumps, and sacral stimulators; dental and facial implant devices; gastric and tracheal tubes; vagus nerve stimulators; lumboperitoneal shunts; and temperature- and oxygen-sensing probes.

3. **Litt B. Evaluating devices for treating epilepsy. *Epilepsia*. 2003;44 Suppl 7:30-7.** <http://www.ncbi.nlm.nih.gov/pubmed/12919337>

**Notes** Evaluating implantable devices requires carefully executed clinical trials that take into account unique aspects of the devices. This article provides a good overview of the clinical trial process in the context of medical devices. Comparisons of drug trials versus device trials as well as special challenges and considerations, trial designs, device strategies, and the role of animal studies are discussed. The clinical trial experience with VNS therapy--the first device approved for the treatment of epilepsy--is highlighted throughout the article.

**Abstract** **PURPOSE:** Research into new implantable devices for treating epilepsy is expanding rapidly. Pilot studies suggest sufficient safety and potential efficacy to justify proceeding with larger scale clinical trials. Understanding the challenges presented by these trials, the testing and approval process for implantable devices, and how these differ from requirements for antiepileptic drugs (AEDs) is vital to evaluating when and where these new technologies will fit into the therapeutic armamentarium. **METHODS:** Important lessons regarding the limitations of uncontrolled pilot studies, patient registries, and how the Food and Drug Administration (FDA) approval process can influence trials are drawn from the implantable device literature. Some discussion of the role of animal experiments is presented, both as justification for investigational device exemptions and their potential role in establishing safety. Clinical trial experience with the vagal nerve stimulator, the first device approved for the treatment of epilepsy, is also discussed. **RESULTS:** New implantable devices hold great promise for medically refractory epilepsy patients who have no other therapeutic alternative. If effective, they may become a viable alternative to epilepsy surgery or multiple AED therapy in appropriate patients. **CONCLUSIONS:** The proper evaluation, use, and acceptance of antiepileptic devices will ultimately depend on carefully executed clinical trials that take into account unique aspects of these devices, such as the requirement for surgery, electrode placement, and navigation through FDA-monitored testing and approval.

**Review Articles - Epilepsy, Disease Management**

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1. **Yadegari S, Bahrami P. Idiopathic (primary) generalized epilepsy. Traditional versus new antiepileptic drugs. *Neurosciences (Riyadh)*. 2013;18(2):117-21.**

<http://www.ncbi.nlm.nih.gov/pubmed/23545607>

**Abstract** Idiopathic generalized epilepsies (IGE) are genetic based seizures with normal neurologic exam, intelligence, and imaging studies. Based on the age of onset and prominent seizure type, different syndromes were identified. The purpose of this study is to summarize the characteristics, prognosis, and choices of antiepileptic drugs (AED) in common syndromes of IGE. In addition, we review the updated role of new AEDs in specific syndromes of IGE. The first choice AED is usually valproate. Most drug trials on the effects of new AEDs compared them with placebo and not valproate. However, some of the broad spectrum new AEDs may be considered as the first choice in specific conditions. In true refractory patients, combination therapy and vagal nerve stimulation could be the next option. In the proper management of IGE, neurologists should consider the predominant seizure type, patient gender, co-morbidities, and antiepileptic drugs that may aggravate a specific seizure type.

2. **Rossetti AO, Vulliemoz S. [Treatment of pharmacoresistant epilepsy: stimulated refractoriness]. *Rev Med Suisse*. 2012;8(339):930, 932-4. French.**

<http://www.ncbi.nlm.nih.gov/pubmed/22675822>

**Abstract** Antiepileptic drugs allow controlling seizures in 70% of patients. For the others, a presurgical work-up should be undertaken, especially if a focal seizure origin is suspected; however, only a fraction of pharmacoresistant patients will be offered resective (curative) surgery. In the last 15 years, several palliative therapies using extra- or intracranial electrical stimulations have been developed. This article presents the vagal nerve stimulation, the deep brain stimulation (targeting the mesiotemporal region or the thalamus), and the cortical stimulation "on demand". All show an overall long-term responder rate between 30-50%, but less than 5% of patients becoming seizure free. It is to hope that a better understanding of epileptogenic mechanisms and of the implicated neuronal networks will lead to an improvement of these proportions.

3. **Prasad AN, Rupa CA, Prasad C. Methylenetetrahydrofolate reductase (MTHFR) deficiency and infantile epilepsy. *Brain Dev.* 2011;33(9):758-69.**

<http://www.ncbi.nlm.nih.gov/pubmed/21778025>

**Abstract** OBJECTIVES: A recessively inherited defect leading to deficiency of the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) underlies one form of hyperhomocysteinemia. We describe the association of severe MTHFR deficiency and neurological manifestations with particular attention to neurodevelopment and evolution of epileptic seizures. METHODS: Case study and review of literature. RESULTS: A 9 year old female infant born to Caucasian non-consanguineous parents presented with infantile spasms and developmental regression in the first year. The biochemical profile of low plasma methionine (below detectable limits), and slightly elevated homocystine (3  $\mu\text{mol/L}$  (0-trace) and homocystinuria (234  $\mu\text{mol/gm creatinine}$ ) (0-trace amounts) was suggestive of a disturbance in homocysteine metabolism. Plasma homocysteine measurements (30.7  $\mu\text{mol/L}$ , normal <13.5  $\mu\text{mol/L}$ ) confirmed hyperhomocysteinemia. Enzyme assay in skin fibroblasts confirmed severe MTHFR deficiency (patient 0.92, control 13.3+/-4.6  $\text{nmol/mg/h}$ ). Molecular genetic studies identified compound heterozygosity for 2 variant polymorphisms (c.677C>T, and c.1298A>C) and a splicing mutation (c.1348+1G>A). This is a novel mutation that removes a splice site at the end of exon 7 resulting in a premature stop codon that truncates the protein, losing exons 8-11. CSF neurotransmitter analysis showed an extremely low level of 5-methyl tetrahydrofolate of <5 (40-128  $\text{nmol/L}$ ). The course of epilepsy has been characterized by progression to severe epileptic encephalopathy. Periventricular white matter change consistent with demyelination is seen on MR imaging. Treatment protocols include; oral betaine, supplementation with methionine, folic acid, and 5-methyltetrahydrofolate with questionable benefit. Epileptic seizures remain pharmaco-resistant to antiepileptic medications singly and in combinations. Frequent bouts of status epilepticus have led to multiple hospitalizations, and neurosurgical interventions (corpus callosotomy, vagal nerve stimulation). At age 9 years, the patient remains severely impaired by vertebral compressive and limb fractures secondary to severe osteoporosis. CONCLUSION: Severe MTHFR deficiency is an important diagnostic consideration in infantile epileptic encephalopathies. Early diagnosis and specific treatment interventions are possible. Further research is needed into effective treatment of epilepsy and prevention of complications in this disorder. Genotype and phenotype correlations will be explored in the light of available biochemical and molecular genetic data.

4. **Shigeto H. [An adult neurologist's update on epilepsy therapy]. *Rinsho Shinkeigaku.* 2011;51(11):997-9. Japanese.**

<http://www.ncbi.nlm.nih.gov/pubmed/22277455>

**Abstract** Adult neurologists routinely encounter cases of epilepsy. Appropriate therapy based on a correct diagnosis is very important, and is aided by knowledge of seizure semiology and the correct reading of EEG findings. Many factors need to be considered when deciding upon a treatment regime for adult epilepsy patients, such as employment, marriage, child bearing status, and co-existent disease in elderly patients. Four new antiepileptic drugs (AEDs), which have been used in other countries for more than 10 years, have been authorized for use over the past few years in Japan. Because new AEDs also have interactions and side effects, administration to patients must be carried out based on an understanding of drug actions and interaction mechanisms. Surgical treatment should be considered for drug resistant patients, especially for those suffering from temporal lobe epilepsy with hippocampal sclerosis. For drug resistant patients who are not candidates for resection therapy, we can undertake vagus nerve stimulation therapy, which has recently been authorized for use in Japan. Other electrical stimulation therapies, targeting the anterior nucleus of thalamus, hippocampus and epileptic neo-cortex, have been investigated and are now under study in the USA. Neurologists should be aware of such newly introduced therapies in giving a better quality of life for epilepsy patients.

5. **Noe KH. Seizures: diagnosis and management in the outpatient setting. *Semin Neurol.* 2011;31(1):54-64. <http://www.ncbi.nlm.nih.gov/pubmed/21321833>**  
**Abstract** Epilepsy and seizures are common, and can significantly affect quality of life. A careful history and guided evaluation is necessary to avoid misdiagnosis, to establish causation, and to determine prognosis. Medical therapy is effective in controlling seizures in two thirds of people with epilepsy. In choosing which antiepileptic drug to use, it is important to consider epilepsy type, side effect profile, and cost. Even when seizures are controlled, dose-related side effects from antiepileptic medication, such as fatigue and imbalance, can negatively impact health-related quality of life. Teratogenic side effects are also of concern for women of childbearing age. Monotherapy is generally preferred, and with dose titration, a successful balance between efficacy and tolerability can be reached in the majority of patients. Epilepsy that is medically refractory may respond to epilepsy surgery or vagus nerve stimulation.
  
6. **Smith BJ, Cole AJ. Management of epilepsy in drug-resistant patients. *CNS Spectr.* 2010;15(1 Suppl 2):1, 3-7; quiz 7-8. <http://www.ncbi.nlm.nih.gov/pubmed/20394187>**  
**Abstract** Epilepsy affects > 2 million people in the United States, making it one of the most common neurobiological conditions. Typically, epilepsy is treated with one of several available antiepileptic drugs and patients are able to experience freedom from seizures with minimal side effects. However, there are some patients who do not respond to treatment and require the use of multiple drug combinations or surgical intervention. Although there are few studies supporting its use, multi-drug regimens have been known to be helpful for patients, although clinicians should monitor patients for adverse side effects. Vagus nerve stimulation is the only US Food and Drug Administration-approved surgical neurostimulation therapy for epilepsy, and patients' conditions often progress for many years before epilepsy surgery options are considered. Lastly, due to the chronic nature of epilepsy, clinicians should be aware of the presence of comorbid psychiatric conditions as well. This supplement is Part One in the "Case in Point: Evidence-Based Insights for Epilepsy Management" series. In this Expert Review Supplement, Andrew J. Cole, MD, FRCPC, outlines a case of a patient with drug resistant epilepsy, and Brien J. Smith, MD, outlines the best practices for the case patient including discussion on defining drug resistance in patients as well as the benefits and risks of available and emerging drug and surgical treatments.
  
7. **Quach MM, Mazin A, Riviello JJ, Jr. Newer anticonvulsant medications in pediatric neurology. *Curr Treat Options Neurol.* 2010;12(6):518-28. <http://www.ncbi.nlm.nih.gov/pubmed/20848327> <http://link.springer.com/article/10.1007%2Fs11940-010-0094-5>**  
**Abstract** OPINION STATEMENT: Antiepileptic drugs (AEDs) are the mainstay of treatment for recurrent seizures. Uncontrolled seizures may cause medical, developmental, and psychological disturbances. The medical practitioner should thus strive to eliminate or minimize seizures. Treatment advances in epilepsy include 1) identification of the basic mechanisms of epilepsy and action of AEDs, 2) the introduction of new AEDs, and 3) the use of neurostimulation, including vagus nerve stimulation. Treatment with AEDs involves balancing each AED's efficacy against its side effects. In some patients, effective AEDs must be discontinued because of intolerable side effects. Although all AEDs have a proven efficacy, the choice of AEDs should be based on better efficacy for individual seizure types or epilepsy syndromes. Side effects also differ from drug to drug and must be taken into account. This article focuses on studies and expert opinion consensus to guide the choice of AEDs.

8. **Treiman DM. Management of refractory complex partial seizures: current state of the art.**

*Neuropsychiatr Dis Treat.* 2010;6:297-308.

<http://www.ncbi.nlm.nih.gov/pubmed/20628630>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2898168/pdf/ndt-6-297.pdf>

**Abstract** Diagnosis of complex partial epilepsy is based on the clinical history, and laboratory tests, including EEG and neuroimaging studies, corroborate the diagnosis. The goal of epilepsy management is to make the patient completely seizure-free without drug-induced side effects, even in the patient with refractory complex partial seizures. Frequently this can be accomplished by choice of the optimal antiepileptic drug (AED) or a combination of drugs, the use of strategies to maximize the effectiveness of drug treatment, or by surgical removal of the seizure focus. Currently there are five "classical" first-line AEDs and 11 new AEDs available in the US and in many other countries for the treatment of localization-related epilepsy. The current state of the evidence is that no AED is clearly superior to other AEDs in the management of refractory complex partial seizures. Therefore the choice of which drug to use in an individual patient has to be based on other considerations, including the potential adverse reactions that may occur in that patient. There are a number of strategies for optimal use of AEDs in the management of refractory complex partial seizures. These include verification of the diagnosis of epilepsy and classification of specific seizure types, use of monotherapy if possible but polytherapy if necessary, starting with a low dose and raising it slowly but, until complete seizure control is achieved, pushing to the maximum tolerated dose, changing timing of dosing to reduce toxicity, using pharmacokinetic principles to fine-tune AED doses, adjusting dose for drug-drug interactions, and never giving up in the pursuit of better seizure control. Resection of the seizure focus can be curative in the majority of patients with seizures localized to one mesial temporal lobe. Success rates for resection of extratemporal seizure foci are lower. Vagus nerve stimulation (VNS) devices result in a significant reduction of seizure frequency in many patients, but patients rarely become completely seizure-free as a result of VNS device implantation. Management of refractory complex partial seizures continues to improve with the identification of new drugs and the development of new approaches to their control and cure.

9. **Elger CE, Schmidt D. Modern management of epilepsy: a practical approach. *Epilepsy Behav.***

2008;12(4):501-39.

<http://www.ncbi.nlm.nih.gov/pubmed/18314396>

**Abstract** The epilepsies are among the most common serious brain disorders, can occur at all ages, and are characterized by a variety of presentations and causes. Diagnosis of epilepsy remains clinical, and neurophysiological investigations support the diagnosis of the syndrome. Brain imaging is able to identify many of the structural causes of the epilepsies. Current antiepileptic drugs (AEDs) block seizures without influencing the underlying tendency to generate seizures, and are effective in 60-70% of individuals. Several modern drugs are as efficacious as the older medications, but have important advantages including the absence of adverse drug interactions and hypersensitivity reactions. Epilepsy is associated with an increased prevalence of mental health disorders including anxiety, depression, and suicidal thoughts. An understanding of the psychiatric correlates of epilepsy is important to the adequate management of people with epilepsy. Anticipation of common errors in the diagnosis and management of epilepsy is important. Frequent early diagnostic errors include nonepileptic psychogenic seizures, syncope with myoclonus, restless legs syndrome, and REM behavioral disorders, the last mostly in elderly men. Overtreatment with too rapid titration and too high doses or too many AEDs should be avoided. For people with refractory focal epilepsy, vagus nerve stimulation offers palliative treatment with possible mood improvement and neurosurgical resection offers the possibility of a life-changing cure. Potential advances in the management of epilepsy are briefly discussed. This short review summarizes the authors' how-to-do approach to the modern management of people with epilepsy.

10. **Malphrus AD, Wilfong AA. Use of the newer antiepileptic drugs in pediatric epilepsies. *Curr Treat Options Neurol.* 2007;9(4):256-67.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17580006>  
**Abstract** Children with epilepsy, particularly infants, differ from adults not only in the clinical manifestations of their seizures but also in the presence of unique electroencephalographic patterns, etiologies, and response to antiepileptic drugs (AEDs). There is a growing list of newer AEDs and nonpharmacologic therapies available to manage childhood epilepsy. These newer AEDs may not be overall more efficacious than the older drugs, but they do appear to be safer, better tolerated, and to have fewer drug-drug interactions. Selection of the AED for initial therapy must be based upon clinical judgment and patient-specific circumstances, such as the specific epilepsy syndrome being treated, anticipated duration of treatment, presence of comorbidities, ability to use certain formulations, and overall cost effectiveness. In some cases, seizures may be aggravated by the use of certain AEDs. Overall, oxcarbazepine is the first-line treatment for localization-related epilepsy with partial-onset seizures. For generalized epilepsies, the AED choice is highly dependent upon which specific syndrome is being treated. For generalized epilepsies with primarily absence seizures, lamotrigine is the AED of first choice. For mixed generalized epilepsies such as Lennox-Gastaut syndrome or juvenile myoclonic epilepsy, zonisamide or topiramate are the first-line agents. For infants with West syndrome, treatment is based upon the underlying etiology: vigabatrin for tuberous sclerosis; adrenocorticotrophic hormone for children with no specific etiology uncovered (cryptogenic); and zonisamide for those with a severe symptomatic etiology other than tuberous sclerosis. Single drug therapy (monotherapy) is the goal of epilepsy treatment because this is associated with better compliance, fewer adverse effects, and lower cost. If the seizures prove intractable or adverse effects are encountered with the first AED, then a second monotherapy trial is undertaken. Once three appropriate medications at therapeutic doses have failed, other modalities should be considered, including epilepsy surgery, vagus nerve stimulation, and the ketogenic diet.
11. **Abdul M, Riviello JJ. Update on the newer antiepileptic drugs in child neurology: advances in treatment of pediatric epilepsy. *Curr Treat Options Neurol.* 2007;9(6):395-403.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18173939>  
**Abstract** The goal of epilepsy treatment is the prevention of recurrent seizures, and antiepileptic drugs (AEDs) are the mainstay. Uncontrolled seizures may cause medical, developmental, and psychologic disturbances. Treatment advances include 1) identification of the basic mechanisms of epilepsy and action of AEDs, 2) the introduction of many new AEDs, and 3) the use of neurostimulation, starting with vagus nerve stimulation. We must balance the efficacy of an AED versus its side effects, which if persistent, lead to patient discontinuation of the AED. Although all AEDs have a proven efficacy, they are differentiated by their efficacy for a given seizure type or epilepsy syndrome versus the side effects or tolerability. The many new AEDs give us a larger armamentarium for epilepsy treatment. We refer to studies and expert opinion consensus.

12. **Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Perucca E, Tomson T. Progress report on new antiepileptic drugs: a summary of the Eighth Eilat Conference (EILAT VIII). *Epilepsy Res.* 2007;73(1):1-52.** <http://www.ncbi.nlm.nih.gov/pubmed/17158031>  
**Abstract** The Eighth Eilat Conference on New Antiepileptic Drugs (AEDs)-EILAT VII, took place in Sitges, Barcelona from the 10th to 14th September, 2006. Basic scientists, clinical pharmacologists and neurologists from 24 countries attended the conference, whose main themes included a focus on status epilepticus (epidemiology, current and future treatments), evidence-based treatment guidelines and the potential of neurostimulation in refractory epilepsy. Consistent with previous formats of this conference, the central part of the conference was devoted to a review of AEDs in development, as well as updates on marketed AEDs introduced since 1989. This article summarizes the information presented on drugs in development, including brivaracetam, eslicarbazepine acetate (BIA-2-093), fluorofelbamate, ganaxolone, huperzine, lacosamide, retigabine, rufinamide, seletracetam, stiripentol, talampanel, valroceamide, JZP-4, NS1209, PID and RWJ-333369. Updates on felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine and new extended release oxcarbazepine formulations, pregabalin, tiagabine, topiramate, vigabatrin, zonisamide and new extended release valproic acid formulations, and the antiepileptic vagal stimulator device are also presented.
13. **Bauer J. [Treatment of epilepsy in adults. Options and strategies]. *Nervenarzt.* 2007;78 Suppl 1:27-35; quiz 36. German.** <http://www.ncbi.nlm.nih.gov/pubmed/17628766>  
<http://rd.springer.com/article/10.1007%2Fs00115-007-2328-7>  
**Abstract** Currently, epilepsy can be treated with antiepileptic drugs and, in patients with focal and/or secondarily generalized seizures (focal epilepsy), by means of surgery and vagus nerve stimulation. In the choice of monotherapy possible negative drug related effects on cognitive, endocrine, and psychic symptoms must be considered. Newly developed antiepileptic drugs help to establish an individualized strategy, especially in antiepileptic drug monotherapy. Additionally these antiepileptic drugs have proven to be effective and well tolerated when combined with other antiepileptic drugs. Surgery of focal epilepsy offers the chance of complete cure. Vagus nerve stimulation is a nonmedical treatment option used in addition to antiepileptic drugs in patients with focal epilepsy. Tolerability and safety data should be considered to establish a long-term medical treatment tolerated and accepted by the patient.
14. **Salinsky MC. The efficacy of vagus nerve stimulation relative to other medical and surgical treatments. In: Miller JW, Silbergeld DL, Eds. *Epilepsy Surgery: Principles and Controversies.* New York, NY: Taylor & Francis; 2006:608-13.**
15. **Brodtkorb E, Mula M. Optimizing therapy of seizures in adult patients with psychiatric comorbidity. *Neurology.* 2006;67(12 Suppl 4):S39-44.** <http://www.ncbi.nlm.nih.gov/pubmed/17190921>  
**Abstract** This article provides an overview of appropriate antiepileptic treatment in adult patients with chronic epilepsy and concomitant psychiatric disorders. It highlights the influence of various treatment options for epilepsy on psychiatric symptoms. Six specific topics are discussed: psychosocial aspects and treatment compliance; positive and negative psychotropic effects of antiepileptic drugs (AEDs); pharmacokinetic and pharmacodynamic interactions between AEDs and psychoactive drugs; risks and benefits of resective surgery; the effect of vagal nerve stimulation; and recommended strategies for optimizing epilepsy therapy in patients with psychiatric disorders. Given the multitude of epilepsy treatment options with various CNS effects, it is crucial to select treatments according to the clinical profile of each individual patient.

16. **Nadkarni S, LaJoie J, Devinsky O. Current treatments of epilepsy. *Neurology*. 2005;64(12 Suppl 3):S2-11.** <http://www.ncbi.nlm.nih.gov/pubmed/15994220>  
**Abstract** Medical therapy is the mainstay for epilepsy, with most patients well controlled on a single antiepileptic drug (AED). In this non-refractory group, many patients have medication side effects and occasional seizures. Approximately 30% of patients with partial epilepsy and 25% of patients with generalized epilepsy are not well controlled on medications. These patients are often receiving multiple AEDs, with disabling seizures and side effects. Although second-generation AEDs are safer and better tolerated than the older AEDs, there are scant data to support significant advantages in efficacy. In VA studies with older AEDs, therapy with two AEDs improved seizure control in 40% of patients but seizure freedom was achieved in only 9%. A meta-analysis of the second-generation AEDs used as adjunctive therapies shows that 12% to 29% of patients had a 50% or greater reduction in seizure frequency. Surgery and the vagus nerve stimulator provide important therapeutic options in patients whose seizures are not controlled by AEDs. Special considerations about epilepsy care must be made in pediatric populations, those with developmental delays, women, and the elderly.
17. **Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Perucca E, Tomson T. Progress report on new antiepileptic drugs: a summary of the Seventh Eilat Conference (EILAT VII). *Epilepsy Res*. 2004;61(1-3):1-48.** <http://www.ncbi.nlm.nih.gov/pubmed/15570674>  
**Abstract** The Seventh Eilat Conference on New Antiepileptic Drugs (AEDs) (EILAT VII) took place in Villasimius, Sardinia, Italy from the 9th to 13th May 2004. Basic scientists, clinical pharmacologists and neurologists from 24 countries attended the conference, whose main themes included advances in pathophysiology of drug resistance, new AEDs in pediatric epilepsy syndromes, modes of AED action and spectrum of adverse effects and a re-appraisal of comparative responses to AED combinations. Consistent with previous formats of this conference, the central part of the conference was devoted to a review of AEDs in development, as well as updates on second-generation AEDs. This article summarizes the information presented on drugs in development, including atipamezole, BIA-2-093, fluorofelbamate, NPS 1776, pregabalin, retigabine, safinamide, SPM 927, stiripentol, talampanel, ucb 34714 and valroceamide (TV 1901). Updates on felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide, new oral and parenteral formulations of valproic acid and SPM 927 and the antiepileptic vagal stimulator device are also presented.
18. **Gil-Nagel A. [News treatments in epilepsy]. *Neurologia*. 2004;19 Suppl 2:22-7.**  
**Spanish.** <http://www.ncbi.nlm.nih.gov/pubmed/16184498>  
**Abstract** The epilepsies are common neurological disorders with different pathogenic mechanisms. Over the last fifteen years there has been an enormous advance in the therapeutic options for these disorders. These treatments, originally developed for the management of medically refractory patients, include ten new antiepileptic drugs with novel mechanisms of action, a better selection of surgical candidates, vagus nerve stimulation, treatment with gamma-knife, and electrical stimulation of the brain. There is not enough information yet to determine what will be the final role of some of these therapies, while others have advanced to the first lines of treatment in cases of new onset epilepsy.
19. **Nguyen DK, Spencer SS. Recent advances in the treatment of epilepsy. *Arch Neurol*. 2003;60(7):929-35.** <http://www.ncbi.nlm.nih.gov/pubmed/12873848> <http://archneur.jamanetwork.com/data/Journals/NEUR/13527/NNT30002.pdf>  
**Notes** This article does a good job of outlining the pros and cons of different epilepsy therapies in the context of their respective clinical trials. Initiation and choice of therapies for different types of seizures as well as for pharmacoresponsive and pharmacoresistant epilepsies are reviewed. A brief discussion of the inherent difficulties associated with clinical trial designs and epilepsy therapies also is discussed.

20. **Sirven JI. The current treatment of epilepsy: a challenge of choices. *Curr Neurol Neurosci Rep.* 2003;3(4):349-56.**

<http://www.ncbi.nlm.nih.gov/pubmed/12930706>

**Notes** Current epilepsy treatments AEDs, surgery, VNS, and ketogenic diet are reviewed in an effort to help physicians navigate through the increasing epilepsy management choices. This article is a good overview of the current epilepsy treatments, particularly the new AEDs. VNS therapy is discussed briefly and positioned between AEDs and surgery for those patients who are not surgical candidates or who prefer not to have surgery. The author does not present a clear view of how the stimulation is administered, however. Otherwise, the article is a good treatment overview source.

**Abstract** There are now several distinct choices for seizure and epilepsy treatment. These include 16 antiepileptic medications, surgery, vagus nerve stimulation, and ketogenic diet. However, not every option is appropriate for all individuals with epilepsy. This article reviews the commonly employed treatments for chronic seizures, with the goal of trying to assess when certain treatments should be considered. An approach to seizure management is presented to help navigate the challenge of epilepsy treatment choices.

21. **Albensi BC. A comparison of drug treatment versus electrical stimulation for suppressing seizure activity. *Drug News Perspect.* 2003;16(6):347-52.**

<http://www.ncbi.nlm.nih.gov/pubmed/12973445>

**Abstract** Currently, the management of seizure activity by using pharmacological approaches is in many cases successful. However, it is also known that some patients (up to 30%) do not respond to conventional treatment and are considered drug resistant. For this group other approaches are sometimes attempted, such as surgical resection (not reviewed here) or use of the ketogenic diet (also not reviewed here). More recently, though, procedures that utilize chronic electrical stimulation as a means for suppressing seizure events are being tried. Experiments based on electrical stimulation are being conducted in both animal models and in some limited human trials, but so far it has not been determined if chronic electrical stimulation is more or less effective than conventional drug therapy. This article reviews basic mechanisms of seizure activity, standard antiepileptic drugs (AEDs), and compares conventional AEDs to alternative approaches such as vagal nerve and deep brain stimulation.

22. **Cramer JA, Ben Menachem E, French J. Review of treatment options for refractory epilepsy: new medications and vagal nerve stimulation. *Epilepsy Res.* 2001;47(1-2):17-25.**

<http://www.ncbi.nlm.nih.gov/pubmed/11673017>

**Abstract** PURPOSE: the choices available for patients whose partial seizures are poorly controlled include seven new antiepileptic drugs (AEDs) or vagal nerve stimulation (VNS) as add-on therapy. Comparisons are needed to help physicians and patients select among the options for treatment. METHODS: we compared efficacy and adverse events of new treatments from controlled clinical trials of patients with uncontrolled partial seizures. Response rates (> or =50% decrease in partial seizures) at doses recommended in product labeling for adjunct therapy were tabulated for overall success (placebo response rate subtracted from AED response rate). Adverse events listed in product labeling were tabulated as complaint rates (placebo events subtracted from AED events). VNS trials used low dose stimulation as a pseudo-placebo. RESULTS: overall success rates fell into two general groups with ranges of 12-20% for gabapentin (GBP), lamotrigine (LTG), tiagabine (TGB), zonisamide and 27-29% for levetiracetam, oxcarbazepine, and topiramate (TPM). Summary Complaint Scores also fell into two general groups with ranges of -27 to -82 for GBP, levetiracetam, TGB, zonisamide and -113 to -205 for LTG, oxcarbazepine and TPM. VNS scores were in the lower or higher success and summary complaint categories depending on whether scores from the pseudo-placebo group were subtracted from the high dose group. CONCLUSIONS: these data allow comparisons among AEDs and VNS using similar data from standard types of clinical trials.

23. **Schachter SC. Epilepsy. *Neurol Clin.* 2001;19(1):57-78.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11471768>  
**Abstract** The successful management of epilepsy requires a thorough and individualized approach that accurately establishes the patient's seizure type(s) and, when appropriate, epilepsy syndrome. Selection of pharmacologic and nonpharmacologic therapy should be rational and tailored to each patient. In this manner, clinicians are able to take advantage of new treatments to minimize the impact of seizures, treatment side effects, and epilepsy-related psychosocial difficulties on their patients, thereby enabling them to function in society at the highest possible level.
24. **Ben-Menachem E. New antiepileptic drugs and non-pharmacological treatments. *Curr Opin Neurol.* 2000;13(2):165-70.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10987574>  
**Abstract** Many new drugs and therapies can now be offered to patients with epilepsy. The problem is that we do not know just how much better these new and more expensive therapies are compared with the old ones, nor do we know the full range of side-effects. This review focuses on the major clinical studies that have been published in the past year with emphasis on information as to tolerability and efficacy, especially when there is some information comparing different drugs or therapies. The topics include vigabatrin, lamotrigine, gabapentin, felbamate, topiramate, tiagabine, oxcarbazepine, levetiracetam, vagus nerve stimulation and the ketogenic diet. It is encouraging that some of the newly published double-blinded placebo-controlled studies now include children and the elderly, patient groups that have previously been neglected.
25. **Aiken SP, Brown WM. Treatment of epilepsy: existing therapies and future developments. *Front Biosci.* 2000;5:E124-52.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11056076>  
**Abstract** Epilepsy is a major public health issue, not least because of the aging population in many developed nations and the known increase in the frequency of epilepsy and seizures in later life. Despite the massive scale of the problem and much research, epilepsy remains poorly understood. Despite more than 20 approved drugs in the developed nations and several non-pharmacological options, up to 30% of patients are still refractory to treatment. Despite over a century of pharmacotherapy and neuroscience research, rational design of anti-epileptic drugs (AEDs) is only now starting to yield results, because of the heterogeneity of the disease and our still limited understanding of it. Discovery and development of AEDs has been especially difficult, because of the regulatory issues of satisfactorily proving safety and efficacy, ethical constraints on placebo-controlled trial designs, the fact that seizures are typically widely spaced in time, and the fact that the person undergoing the seizure is typically in no state to remember, let alone assess, what happened. Several non-pharmacological therapies have been developed: brain surgery was first used more than a century ago; the ketogenic diet was first developed 80 years ago; and the vagus nerve stimulator was introduced recently. Pharmacotherapy remains the mainstay of treatment and is effective in most patients. AEDs can be roughly divided according to their time on the market. The first generation extends from the bromides and the barbiturates (the first of which was phenobarbital), to sodium valproate and carbamazepine. The second generation begins with felbamate and includes drugs approved from 1993 to 2000. "Next generation" drugs are still in clinical development and may reach the marketplace in the near future. Intensive research is being conducted both by pharmaceutical and biotech companies and by academic scientists and clinicians; our understanding of the condition is advancing rapidly but many challenges remain in discovering and developing better AEDs.

26. **Privitera MD. Evidence-based medicine and antiepileptic drugs. *Epilepsia*. 1999;40 Suppl 5:S47-56.** <http://www.ncbi.nlm.nih.gov/pubmed/10530694>  
**Abstract** Evidence based health care uses systematic literature reviews with statistical strategies like meta-analysis to aid decision-making. This information can help clinicians by organizing data and providing up-to-date quantitative summaries of efficacy and adverse effects of treatments. Limitations of meta-analysis include problems inherent in combining data from trials of somewhat different design, choice of appropriate dosages, and summarizing complex questions as a single odds ratios. I summarize the results of a meta-analysis of the following antiepileptic treatments for partial seizures in adults: gabapentin, lamotrigine, topiramate, tiagabine, valproate and the vagal nerve stimulator. Each treatment was significantly more efficacious than placebo, and there were nonsignificant trends toward differences among the treatments in efficacy and tolerability. Quantitative analysis of adverse effects is presented. Absent the availability of a comprehensive randomized controlled trial for comparison, a rigorously conducted meta-analysis provides some useful information.
27. **Marks WJ, Jr., Garcia PA. Management of seizures and epilepsy. *Am Fam Physician*. 1998;57(7):1589-600, 1603-4.** <http://www.ncbi.nlm.nih.gov/pubmed/9556647>  
**Abstract** While the evaluation and treatment of patients with seizures or epilepsy is often challenging, modern therapy provides many patients with complete seizure control. After a first seizure, evaluation should focus on excluding an underlying neurologic or medical condition, assessing the relative risk of seizure recurrence and determining whether treatment is indicated. Successful management of patients with recurrent seizures begins with the establishment of an accurate diagnosis of epilepsy syndrome followed by treatment using an appropriate medication in a manner that optimizes efficacy. The goal of therapy is to completely control seizures without producing unacceptable medication side effects. Patients who do not achieve complete seizure control should be referred to an epilepsy specialist, since new medications and surgical treatments offer patients unprecedented options in seizure control.
28. **Sander JW. New drugs for epilepsy. *Curr Opin Neurol*. 1998;11(2):141-8.** <http://www.ncbi.nlm.nih.gov/pubmed/9551295>  
**Abstract** Seizure freedom with no side-effects is the aim of treatment, and new antiepileptic drugs have not lived up to expectations; only a few patients with chronic epilepsy have been rendered seizure-free. These treatments have side-effects but their safety profile may be better than older alternatives, although chronic effects have not yet been established. This article reviews newly marketed antiepileptic drugs. It concentrates on shortcomings of current antiepileptic treatment and on the way drugs are developed. A new approach to treatment is long overdue. The development of rational antiepileptic treatments should be strongly encouraged. More clinically relevant paradigms need to be developed and incorporated into clinical trial programmes as these are presently biased in their designs towards regulatory issues.
29. **Herman ST, Pedley TA. New options for the treatment of epilepsy. *JAMA*. 1998;280(8):693-4.** <http://www.ncbi.nlm.nih.gov/pubmed/9728627>
30. **Phillips P. Current view of advances in epilepsy. *JAMA*. 1997;278(11):883-6.** <http://www.ncbi.nlm.nih.gov/pubmed/9302225> [http://jama.jamanetwork.com/da ta/Journals/JAMA/9967/jama\\_278\\_11\\_008.pdf](http://jama.jamanetwork.com/da ta/Journals/JAMA/9967/jama_278_11_008.pdf)

31. **Neufeld MY, Korczyn AD. New drugs and vagal stimulation for treatment of epilepsy--the Israeli experience. *Neurol Neurochir Pol.* 1996;30 Suppl 2:113-20.**

<http://www.ncbi.nlm.nih.gov/pubmed/9100249>

**Abstract** Epilepsy is a common condition with a prevalence of just 1% in a given population. Many patients respond poorly to monotherapy and are treated with combinations of anticonvulsants that often cause disabling side-effects. The last few years have been exciting times for epileptologist. There has been a rush of new antiepileptic drugs into clinical development. These new promising drugs along with the development of new surgical treatment such as cortical ablation, callosotomy and lately vagal stimulation are providing formidable challenges to the clinician and hope for the epileptic patients. VNS is a novel method in its early phases of efficacy and safety studies in human subjects with intractable epilepsy. Additional controlled clinical trials with large patient population and long follow up periods are necessary to confirm its efficacy and define the indications.

**Review Articles - Epilepsy, Neurostimulation**

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1. **Bergey GK. Neurostimulation in the Treatment of Epilepsy. *Exp Neurol.* 2013. <http://www.ncbi.nlm.nih.gov/pubmed/23583414>**  
**Abstract** There is increased interest in neurostimulation as a treatment for drugresistant epilepsy. Two large pivotal trials have recently been completed, one using bilateral anterior thalamic stimulation and another employing closed loop responsive therapy of the brain. These are potential additions to the therapeutic options for neurostimulation in addition to already approved vagus nerve stimulation. This review will address the principles of the various types of neurostimulation, the results of the pivotal trials and the important considerations for interpreting the results of these trials which differ from trials of antiepileptic drugs.
  
2. **Schulze-Bonhage A, Coenen V. [Treatment of epilepsy : Peripheral and central stimulation techniques]. *Nervenarzt.* 2013;84(4):517-29. German. <http://www.ncbi.nlm.nih.gov/pubmed/23525589> <http://rd.springer.com/article/10.1007%2Fs00115-013-3749-0>**  
**Abstract** The efficacy of electrical stimulation in the treatment of epileptic seizures was demonstrated experimentally even in the 1970s. Clinical studies have proven the efficacy of vagus nerve stimulation and in recent years also of stimulation of the trigeminal nerve, the anterior nucleus of the thalamus and of the epileptic focus in treating focal epilepsy. Mechanisms of action depend on the stimulation site and parameters and include activation of endogenous antiepileptic nuclei, modulation of propagation of epileptic activity and suppression of ictal activity at the site of generation. Based on available data the tolerability of peripheral and central brain stimulation appears to be good but experiences from wider clinical use are still lacking.
  
3. **Ben-Menachem E. Neurostimulation-past, present, and beyond. *Epilepsy Curr.* 2012;12(5):188-91. <http://www.ncbi.nlm.nih.gov/pubmed/23118604> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3482717/pdf/j1535-7511-12-5-188.pdf>**  
**Abstract** Neurostimulation as a treatment for epilepsy has been around for almost 20 years in the form of vagus nerve stimulation. Newer types of neurostimulation are being developed and stand on the brink of approval for use. The two newest therapies, not yet approved in the United States, are deep brain stimulation and the Responsive Neurostimulator System . In fact, in Europe, approval has already been given for deep brain stimulation and newer forms of vagus nerve stimulation. Efficacy is similar between these therapies, and side effects are moderate, so what will be the future? The challenge will be to learn how to use these therapies correctly and offer the right treatment for the right patient.
  
4. **Vonck K, de Herdt V, Sprengers M, Ben-Menachem E. Neurostimulation for epilepsy. *Handb Clin Neurol.* 2012;108:955-70. <http://www.ncbi.nlm.nih.gov/pubmed/22939078>**
  
5. **Thompson A, Morishita T, Okun MS. DBS and electrical neuro-network modulation to treat neurological disorders. *Int Rev Neurobiol.* 2012;107:253-82. <http://www.ncbi.nlm.nih.gov/pubmed/23206686>**  
**Abstract** The use of neuromodulatory techniques in the treatment of neurological disorders is expanding and now includes devices targeting the motor cortex, basal ganglia, spinal cord, peripheral nervous system, and autonomic nervous system. In this chapter, we review and discuss the current and past literature as well as review indications for each of these devices in the ongoing management of many common neurological diseases including chronic pain, Parkinson's disease, tremor, dystonia, and epilepsy. We also discuss and update mechanisms of deep brain stimulation and electrical neuro-network modulation.

6. **Moddel G, Coenen VA, Elger CE. [Invasive neurostimulation as adjunct treatment for epilepsy]. *Nervenarzt*. 2012;83(8):1001-5. German.**

<http://www.ncbi.nlm.nih.gov/pubmed/22801665>

<http://rd.springer.com/article/10.1007%2Fs00115-012-3572-z>

**Abstract** Neurostimulation techniques are applied to reduce the frequency and severity of epileptic seizures. Class I evidence showed that vagus nerve stimulation (VNS) reduces seizure burden by 25-28% compared to 6-15% in placebo controls. Open-label studies, however, reported much greater efficacy. Since 2010 deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) is CE approved for epilepsy therapy in Europe. A multicenter randomized controlled trial reported seizure frequency reduction by 40.4% compared to 14.5% in controls. A significant effect was only found in patients with temporal seizure onset. 13% of stimulated patients became seizure-free for at least 6 months. Possible side-effects include depression (14.8%) and memory impairment (13%). Responsive neurostimulation (RNS) combines an automated seizure detection device with on-demand triggered stimulation of the epileptogenic zone. A randomized controlled trial reported seizure frequency reduction by 37.9% compared to 17.3% in controls. There were no relevant neuropsychological or psychiatric side-effects noted.

7. **Fridley J, Thomas JG, Navarro JC, Yoshor D. Brain stimulation for the treatment of epilepsy. *Neurosurg Focus*. 2012;32(3):E13.**

<http://www.ncbi.nlm.nih.gov/pubmed/22380854>

**Abstract** The treatment of patients with refractory epilepsy has always been challenging. Despite the availability of multiple antiepileptic medications and surgical procedures with which to resect seizure foci, there is a subset of epilepsy patients for whom little can be done. Currently available treatment options for these unfortunate patients include vagus nerve stimulation, the ketogenic diet, and electric stimulation, both direct and indirect, of brain nuclei thought to be involved in epileptogenesis. Studies of electrical stimulation of the brain in epilepsy treatment date back to the early 20th century, beginning with research on cerebellar stimulation. The number of potential targets has increased over the years to include the hippocampus, subthalamic nucleus, caudate nucleus, centromedian nucleus, and anterior nucleus of the thalamus (ANT). Recently the results of a large randomized controlled trial, the electrical Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial, were published, demonstrating a significant reduction in mean seizure frequency with ANT stimulation. Soon after, in 2011, the results of a second randomized, controlled trial-the NeuroPace RNS trial-were published. The RNS trial examined closed-loop, responsive cortical stimulation of seizure foci in patients with refractory partial epilepsy, again finding significant reduction in seizure frequency. In the present review, the authors examine the modern history of electrical stimulation of the brain for the treatment of epilepsy and discuss the results of 2 important, recently published trials, the SANTE and RNS trials.

8. **Bagary M. Epilepsy, consciousness and neurostimulation. *Behav Neurol.* 2011;24(1):75-81. <http://www.ncbi.nlm.nih.gov/pubmed/21447901>**

**Abstract** Consciousness is often disrupted in epilepsy. This may involve altered responsiveness or changes in awareness of self and subjective experiences. Subcortical arousal systems and paralimbic fronto-parietal association cortices are thought to underpin current concepts of consciousness. The Network Inhibition Hypothesis proposes a common neuroanatomical substrate for impaired consciousness during absence, complex partial and tonic-clonic seizures. Neurostimulation in epilepsy remains in its infancy with vagal nerve stimulation (VNS) as the only firmly established technique and a series of other methods under investigation including deep brain stimulation (DBS), intracranial cortical stimulation and repetitive transcranial magnetic stimulation (rTMS). Many of these systems impact on the neural systems thought to be involved in consciousness as a continuous duty cycle although some adaptive (seizure triggered) techniques have been developed. Theoretically, fixed duty cycle neurostimulation could have profound effects on responsiveness, awareness of self and subjective experience. Animal studies suggest vagal nerve stimulation positively influences hippocampal long term potentiation. In humans, a chronic effect of increased alertness in VNS implanted subjects and acute effect on memory consolidation have been reported but convincing data on either improvements or deterioration in attention and memory is lacking. Thalamic deep brain stimulation (DBS) is perhaps the most interesting neurostimulation technique in the context of consciousness. Neither bilateral anterior or centromedian thalamic nucleus DBS seem to affect cognition. Unilateral globus pallidus internus DBS caused transient wakefulness in an anaesthetised individual. As intracranial neurostimulation, particularly thalamic DBS, becomes more established as a clinical intervention, the effects on consciousness and cognition with variations in stimulus parameters will need to be studied to understand whether these secondary effects of neurostimulation make a significant positive (or adverse) contribution to quality of life.

9. **Steinberg H. Electrotherapeutic disputes: the 'Frankfurt Council' of 1891. *Brain*. 2011;134(Pt 4):1229-43.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21429866>  
<http://brain.oxfordjournals.org/content/134/4/1229.full.pdf>

**Abstract** Since the 1980s and 1990s, vagus nerve and deep brain stimulation, transcranial magnetic stimulation and cranial electrotherapy stimulation have found their way into neurology as therapeutic approaches to epilepsy, Morbus Parkinson and other central nervous symptoms. Moreover, these methods have proven useful and provided hope in the therapy of other diseases, most of all in psychiatry. From a historic perspective, this new emphasis on somatic therapies in the case of transcranial magnetic stimulation and cranial electrotherapy stimulation represents the return of therapeutic methods widely used in the 19th century and based on very similar techniques. Against the background of a general rise in the importance of neurobiological concepts in the neurosciences, we are now in a new situation of change. Yet, as in the 1880s and 1990s, many epistemic questions remain unresolved, the methods not yet having been standardized. In particular, the inability to explain which way and precisely how electricity induces healing processes in the body continues to put the neurosciences, which have always regarded themselves as exact and scientific in nature, in a rather uncomfortable position. There was a similar situation in the 1880s and 1990s, when positivist scientific dogmas prevailed. For ideological and professional reasons, neurologists strongly rejected the notion pioneered by Leipzig neuropsychiatrist Paul Julius Mobius that curative effects of electrotherapy were based on suggestion. One should see, however, that Mobius's actual concern was not to raise opposition towards or question electrotherapy as such, but rather to sensitize his colleagues in view of the prevailing solely materialistic-somatic approach in order that they should not neglect the psychological component of all illness, both in clinical practice and in research. A singular and very special event illustrates the heated debate among German-speaking neurologists on the psychological/suggestive effects of electrotherapy in the last decade of the 19th century-namely the 'Frankfurt Council' of 1891. The statements made at the Frankfurt convention of 35 leading electrotherapists in opposition to Mobius's criticism very much resemble present-day arguments and attitudes. Yet neuroscientists of earlier generations also found very individual answers to fundamental questions in their field that might help both to understand problems from a long-term perspective and enrich present-day discussion as a beneficial corrective.

10. **Tellez-Zenteno JF, Wiebe S. Hippocampal stimulation in the treatment of epilepsy. *Neurosurg Clin N Am*. 2011;22(4):465-75, vi.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21939845>

**Abstract** Neuromodulation is one of the fastest growing fields in neurosurgery, as reflected by the growing interest in the use of electrical brain stimulation (EBS) to treat drug-resistant epilepsy, pain, and movement disorders. Hippocampal stimulation should be regarded as an experimental therapy for epilepsy, and patients considered for this intervention should do so in the context of a well-designed randomized controlled trial. Only well-conducted, blinded, randomized trials, followed by long-term systematic observation will yield a clear picture of the effect of this promising therapy, and will help guide its future use. This article provides a critical review of the best available evidence on hippocampal stimulation for epilepsy.

11. **Kotagal P. Neurostimulation: vagus nerve stimulation and beyond. *Semin Pediatr Neurol.* 2011;18(3):186-94.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22062943>  
**Abstract** Patients with medically intractable epilepsy who are not candidates for epilepsy surgery could benefit from neurostimulation. At this time, vagus nerve stimulation (VNS) therapy is the only Food and Drug Administration-approved neurostimulation modality; it has been shown to be efficacious and just as well tolerated in children and adolescents as in adults. Notwithstanding the initial cost of the device and implantation, VNS therapy has been shown to be a cost-effective treatment, reducing direct medical costs and improving health-related quality of life measures. Deep brain stimulation of various brain regions, especially the anterior nucleus of the thalamus and responsive neurostimulation, also appear effective but are not yet approved for clinical use. Repetitive transcranial magnetic stimulation, which is also in early clinical development, is promising and could become available in the not too distant future.
  
12. **George MS. From the Editor-in-Chief's desk. Brain Stimulation enters a new decade with Volume 3. *Brain Stimul.* 2010;3(1):1.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20633425>
  
13. **Jobst BC. Electrical stimulation in epilepsy: vagus nerve and brain stimulation. *Curr Treat Options Neurol.* 2010;12(5):443-53.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20842599>  
<http://link.springer.com/article/10.1007%2Fs11940-010-0087-4>  
**Abstract** OPINION STATEMENT: Vagus nerve stimulation (VNS) for epilepsy is a well established and effective treatment for medically intractable epilepsy. VNS is indicated if resective epilepsy surgery is unsuccessful or is not an option. About 50% of patients with VNS have a seizure reduction greater than 50%, but less than 10% become seizure-free. VNS also has an alerting effect on patients and may allow a reduction in sedating medications. The major adverse event is hoarseness, but treatment is generally well tolerated. The therapeutic effect can be delayed: patients may improve several months after VNS implantation. Direct brain stimulation (DBS) is an emerging treatment for epilepsy. Scheduled stimulation is similar to brain stimulation in Parkinson's disease. Only the anterior thalamic nucleus has been studied in a larger randomized, controlled trial, in which patients with the stimulator turned on had a significantly reduced seizure frequency. Responsive stimulation applies an electrical stimulus at the site of seizure onset to terminate the seizure if one occurs. The seizure-onset zone must be well defined before implantation. Responsive stimulation requires seizure detection and application of a stimulus online. A large pivotal trial showed a significant reduction in seizure frequency. Both DBS and responsive neurostimulation are well tolerated, but there has been some concern about depression with DBS. Infection, hemorrhage, and lead breakage are adverse events possible with any type of stimulator. None of the brain stimulation devices have been approved by the US Food and Drug Administration, but final approval is expected soon. These devices are indicated for patients with bilateral seizure onset or seizure onset in eloquent areas. Although the initial trials of brain stimulation do not show overwhelming improvement in seizure frequency, the technology will improve with time as we continue to learn about the use of brain stimulation for epilepsy. Optimization of VNS has been going on for 10 years, and we need to ensure that brain stimulation is similarly developed further. In addition, sophisticated devices such as responsive neurostimulators can greatly enhance our understanding of the pathophysiology of epilepsy.

14. **George MS, Aston-Jones G. Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology*. 2010;35(1):301-16.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19693003>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3055429/pdf/npp200987a.pdf>  
**Abstract** Although the preceding chapters discuss much of the new knowledge of neurocircuitry of neuropsychiatric diseases, and an invasive approach to treatment, this chapter describes and reviews the noninvasive methods of testing circuit-based theories and treating neuropsychiatric diseases that do not involve implanting electrodes into the brain or on its surface. These techniques are transcranial magnetic stimulation, vagus nerve stimulation, and transcranial direct current stimulation. Two of these approaches have FDA approval as therapies.
  
15. **Boon P, Raedt R, de Herdt V, Wyckhuys T, Vonck K. Electrical stimulation for the treatment of epilepsy. *Neurotherapeutics*. 2009;6(2):218-27.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19332313>  
**Abstract** Despite the advent of new pharmacological treatments and the high success rate of many surgical treatments for epilepsy, a substantial number of patients either do not become seizure-free or they experience major adverse events (or both). Neurostimulation-based treatments have gained considerable interest in the last decade. Vagus nerve stimulation (VNS) is an alternative treatment for patients with medically refractory epilepsy, who are unsuitable candidates for conventional epilepsy surgery, or who have had such surgery without optimal outcome. Although responder identification studies are lacking, long-term VNS studies show response rates between 40% and 50% and long-term seizure freedom in 5% to 10% of patients. Surgical complications and perioperative morbidity are low. Research into the mechanism of action of VNS has revealed a crucial role for the thalamus and cortical areas that are important in the epileptogenic process. Acute deep brain stimulation (DBS) in various thalamic nuclei and medial temporal lobe structures has recently been shown to be efficacious in small pilot studies. There is little evidence-based information on rational targets and stimulation parameters. Amygdalohippocampal DBS has yielded a significant decrease of seizure counts and interictal EEG abnormalities during long-term follow-up. Data from pilot studies suggest that chronic DBS for epilepsy may be a feasible, effective, and safe procedure. Further trials with larger patient populations and with controlled, randomized, and closed-loop designs should now be initiated. Further progress in understanding the mechanism of action of DBS for epilepsy is a necessary step to making this therapy more efficacious and established.
  
16. **Implantable nerve stimulators. *Clin Privil White Pap*. 2008(417):1-20.** <http://www.ncbi.nlm.nih.gov/pubmed/19023911>
  
17. **Janicak PG. An interview with Philip G. Janicak, MD: Neuromodulation by Norman Sussman, MD. *CNS Spectr*. 2008;13(5):370-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18543409>

18. **Karceski S. Electrical stimulation devices in the treatment of epilepsy. *Acta Neurochir Suppl.* 2007;97(Pt 2):247-59.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17691311>  
**Abstract** Over the last ten years there has been a progressively increasing interest in the research and clinical application of implantable electrical brain stimulation devices in the treatment of drug-resistant epilepsy. The concept is not new, but the efforts were strengthened and accelerated after the efficacy of vagus nerve stimulation in controlling epilepsy was first demonstrated in the early 1990s and gained subsequently the approval of the USA Food and Drug Administration in 1997. This chapter reviews the progress made in this field. Special emphasis is given to the most important available evidence from animal and human studies, the neuroanatomical pathways and the role of the relevant neurotransmitters, the stimulation devices and the significance of correct programming of the stimulation parameters. The chapter also examines the antiepileptic efficacy of stimulation in all the known targets including vagus nerve, cerebellum, thalamus, subthalamic nucleus, locus ceruleus, and epileptogenic cortex. On the basis of the current evidence, the future directions of this exciting field are described.
19. **Theodore WH, Fisher R. Brain stimulation for epilepsy. *Acta Neurochir Suppl.* 2007;97(Pt 2):261-72.** <http://www.ncbi.nlm.nih.gov/pubmed/17691312>  
**Abstract** Brain stimulation has been receiving increasing attention as an alternative therapy for epilepsy that cannot be treated by either antiepileptic medication or surgical resection of the epileptogenic focus. The stimulation methods include transcranial magnetic stimulation (TMS) or electrical stimulation by implanted devices of the vagus nerve (VNS), deep brain structures (DBS) (thalamic or hippocampal), cerebellar or cortical areas. TMS is the simplest and least invasive approach. However, the most common epileptogenic areas (mesial temporal structures) probably lie too deep beneath the surface of the skull for effective TMS. The efficacy of VNS in reducing the frequency or severity of seizures is quite variable and depends on many factors which are currently investigated. VNS is well-tolerated and approved in many countries. DBS is much more invasive than either TMS or VNS. Currently, a number of targets for DBS are investigated including caudate, centromedian or anterior thalamic nuclei, and subthalamic nucleus. Direct stimulation of the epileptic cortical focus is another approach to the neuromodulation in epilepsy. Finally, another line of research investigates the usefulness of implantable seizure detection devices. The current chapter presents the most important evidence on the above methods. Furthermore, other important issues are reviewed such as the selection criteria of patients for brain stimulation and the potential role of brain stimulation in the treatment of depression in epileptic patients.
20. **Boon P, De Herdt V, Vonck K, Van Roost D. Clinical experience with vagus nerve stimulation and deep brain stimulation in epilepsy. *Acta Neurochir Suppl.* 2007;97(Pt 2):273-80.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17691313>  
**Abstract** Patients with refractory epilepsy present a particular challenge to new therapies. Vagus nerve stimulation (VNS) for the control of intractable seizures has become available since 1989. VNS is a relatively noninvasive treatment. It reduces seizure frequency by > or =50% in 1/3 of patients; an additional 1/3 of patients experience a worthwhile reduction of seizure frequency between 30 and 50%. In the remaining 1/3 of the patients there is little or no effect. Efficacy has a tendency to improve with longer duration of treatment up to 18 months postoperatively. Deep brain stimulation (DBS) or direct electrical stimulation of brain areas is an alternative neurostimulation modality. The cerebellum, various thalamic nuclei, the pallidum, and, more recently, medial temporal lobe structures have been chosen as targets. DBS for epilepsy is beyond the stage of proof-of-concept but still needs thorough evaluation in confirmatory pilot studies before it can be offered to larger patient populations. Analysis of larger patient groups and insight in the mode of action may help to identify patients with epileptic seizures or syndromes that respond better either to VNS or to DBS. Randomized and controlled studies in larger patient series are mandatory to identify the potential treatment population and optimal stimulation paradigms. Further improvements of clinical efficacy may result from these studies.

21. **Blum AS, Morvarid B. Neurostimulation for epilepsy. *Med Health R I.* 2006;89(4):127-9. <http://www.ncbi.nlm.nih.gov/pubmed/16676907>**
22. **Hajnsek S, Sporis D, Poljakovic Z, Basic S, Bielen I. [Minimally invasive neurosurgical methods in treatment of pharmacoresistant epilepsy]. *Acta Med Croatica.* 2005;59(1):51-4. Croatian. <http://www.ncbi.nlm.nih.gov/pubmed/15813355>**  
**Abstract** The first clinical attempts at neuromodulation in the form of applying functional electrostimulations started some thirty years ago. Nowadays, it is obvious that the approach to neuromodulation and functional electrostimulation has changed significantly. Neuromodulation tends to affect the disturbed function either by the modulation of neuronal signals or by abolition of dysfunction, preserving the intact central nervous system. The mechanism of activity is connected through direct afferent projections, neurotransmitter modulation and neuronal network regulation. NeuroCybernetic Prosthesis (NCP; Cyberonics) is a vagal nerve stimulator consisting of a pulse generator, bipolar VNS lead, programming wand with accompanying software for IBM-compatible computer, a tunneling tool and handheld magnets. NCP is placed on the left vagal nerve (middle cervical part). In 1988, Penry JK et al. inserted the first human implant. The Food and Drug Association indicated VNS as add-on therapy for diminishing the number of seizures in the adults and adolescents over 12 years of age with partial seizures, who are resistant to pharmacological therapy.
23. **Oommen J, Morrell M, Fisher RS. Experimental Electrical Stimulation Therapy for Epilepsy. *Curr Treat Options Neurol.* 2005;7(4):261-271. <http://www.ncbi.nlm.nih.gov/pubmed/15967089>**  
**Abstract** Electrical stimulation of the nervous system is an attractive possible therapy for intractable epilepsy, but only stimulation of the vagus nerve has been subjected to large, controlled, and completed clinical trials. Controlled trials are in progress for intermittent cycling stimulation of the anterior nuclei of the thalamus, and for cortical stimulation at a seizure focus, responsive to detection of seizure onset. Anecdotal experience has been gathered with stimulation of cerebellum, centromedian thalamus, subthalamus, caudate, hippocampus, and brainstem. All stimulation of the central nervous system for epilepsy must be considered experimental.
24. **Akamatsu N. [Newer treatment of epilepsy--brain pacemakers and transcranial magnetic stimulation]. *Rinsho Shinkeigaku.* 2005;45(11):928-30. Japanese. <http://www.ncbi.nlm.nih.gov/pubmed/16447765>**  
**Abstract** The antiepileptic medication and surgical treatment had brought many patients with epilepsy to be seizure free, however, one third of the patients continue to experience seizures. There has recently been an explosion of research into brain stimulation for treating these intractable epilepsy patients. This is largely due to the success of deep brain stimulation of movement disorders. The intelligent cardiac pacemakers also stimulated the neurosurgeons to utilize the implantable devices. In this paper, brain stimulations with vagus nerve stimulator (VNS), depth electrodes, subdural electrodes, external responsive neuro-stimulator, implantable brain stimulator and transcranial magnetic stimulator are reviewed. The VNS had been approved in Europe and United States for clinical use. The efficacy of the VNS has already proven by the controlled trials. Stimulation of the thalamus, subthalamic nucleus and hippocampus showed some efficacy in a small number of patients, however, large scale trials remains to be undertaken. External responsive neurostimulator has shown efficacy and safety to justify further studies with implantable brain stimulators. The multi-center cooperative study is ongoing in the US to examine the usefulness of the implantable stimulator. Animal studies showed efficacy of the transcranial magnetic stimulation for the treatment and prevention of the seizures and status epilepticus.

25. **Goodman JH. Brain stimulation as a therapy for epilepsy. *Adv Exp Med Biol.* 2004;548:239-47.** <http://www.ncbi.nlm.nih.gov/pubmed/15250598>  
**Abstract** The failure of current antiepileptic therapies to adequately treat a significant number of epileptic patients highlights the need for the development of new treatments for the disorder. A new strategy that is currently being developed is to deliver electrical stimulation directly to the brain to decrease or prevent seizure activity. Clinical evidence that electrical stimulation could interfere with seizure activity was initially reported in the 1930's. However, many of these early studies consisted of case reports or were poorly controlled. In addition, there were a number of studies that failed to observe any beneficial effect of brain stimulation on seizures. More recently, deep brain stimulation has been used successfully to treat patients with movement disorders and vagus nerve stimulation has been shown to effectively decrease seizure activity in a select population of epilepsy patients. These advances have led to a reexamination of the potential therapeutic benefits of deep brain stimulation for the treatment of epilepsy. There is now experimental and clinical evidence that direct electrical stimulation of the brain can prevent or decrease seizure activity. However, several fundamental questions remain to be resolved. They include where in the brain the stimulus should be delivered and what type of stimulation would be most effective. One goal of this research is to combine the beneficial aspects of electrical stimulation with seizure detection technology in an implantable responsive stimulator. The device will detect the onset of a seizure and deliver an electrical stimulus that will safely block seizure activity without interfering with normal brain function.
26. **Polkey CE. Brain stimulation in the treatment of epilepsy. *Expert Rev Neurother.* 2004;4(6):965-72.** <http://www.ncbi.nlm.nih.gov/pubmed/15853523> <http://www.expert-reviews.com/doi/pdfplus/10.1586/14737175.4.6.965>  
**Abstract** Stimulation of the brain for the treatment of epilepsy, indirectly via the vagus nerve and directly through intracranial targets, is feasible and has increased in use and complexity over the past 10 years. Vagus nerve stimulation is widely applied and the present indications and outcomes together with possible ways in which the treatment could be refined are reviewed. The application of stimulation to deep-brain targets is also reviewed along with present practice and results. Possible developments in the use of direct intracranial stimulation are also considered.
27. **Theodore WH, Fisher RS. Brain stimulation for epilepsy. *Lancet Neurol.* 2004;3(2):111-8.** <http://www.ncbi.nlm.nih.gov/pubmed/14747003>  
**Abstract** Neural stimulation is a promising new technology for the treatment of medically-intractable seizures. Vagus-nerve stimulation (VNS) is licensed in several countries as an adjunctive therapy. VNS is as effective as antiepileptic drug therapy, and serious complications are rare. Transcranial magnetic stimulation is simple, non-invasive, and widely used in neurophysiology. Therapeutic results in a few studies are equivocal at best. Deep brain stimulation, although experimental, has been applied to the cerebellum, caudate nucleus, centromedian thalamus, anterior thalamus, subthalamus, hippocampus, and neocortical seizure foci. Preliminary results are encouraging, but not conclusive. Electrode implantation in the brain for indications other than seizures has been associated with a 5% risk for intracranial haemorrhage and 5% for infection. A controlled study of anterior thalamic stimulation in patients with intractable partial and secondarily generalised seizures has been started. Future investigations are likely to study extrathalamic sites of stimulation, and effects of stimulation contingent upon detection of or prediction of EEG patterns of epileptiform activity.

28. **Vonck K, Boon P, Goossens L, Dedeurwaerdere S, Claeys P, Gossiaux F, et al. Neurostimulation for refractory epilepsy. *Acta Neurol Belg.* 2003;103(4):213-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/15008506>

**Abstract** Neurostimulation is an emerging treatment for refractory epilepsy. To date the precise mechanism of action remains to be elucidated. Better insight in the mechanism of action may identify seizure types or syndromes that respond to such a treatment and may guide the search for optimal stimulation parameters and finally improve clinical efficacy. In the past ten years some progress has been made through neurophysiological, neuroanatomical, neurochemical and cerebral blood flow studies in patients and animals undergoing vagus nerve stimulation (VNS). Interesting results have been found in VNS-treated patients that underwent evoked potential measurements, cerebrospinal fluid investigation, neuropsychological testing and PET, SPECT and fMRI testing. Desynchronisation of abnormal synchronous epileptic activity is one of the hypotheses on the mode of action that might primarily be responsible for an anti-seizure effect. There is however increasing evidence from research and clinical observation that VNS might establish a true and long-term anti-epileptic effect. It has been shown that VNS influences neurotransmission in the brain and provokes long-term changes in cerebral blood flow in areas crucial for epileptogenesis such as the thalamus and medial temporal lobe structures. Deep brain stimulation (DBS) for epilepsy has regained interest. Central nervous system structures known to play a key role in the epileptogenic network such as the thalamus and subthalamic nucleus have been targeted. Another approach is to target the ictal onset zone such as the medial temporal lobe. At Ghent University Hospital 10 patients have been treated with long-term amygdalohippocampal DBS. Several hypotheses have been raised for the mechanism of action of DBS for refractory seizures. Seizure reduction may be due to a microlesion caused by electrode insertion or by provoking a reversible functional lesion due to the effect of electrical current on hyperexcitable tissue. Neurophysiological techniques such as evoked potentials monitoring and intraoperative single unit potential recordings may guide correct electrode placement, individual DBS titration and elucidation of the mechanisms of action of DBS for epilepsy.

29. **Andrews RJ. Neuroprotection trek--the next generation: neuromodulation I. Techniques--deep brain stimulation, vagus nerve stimulation, and transcranial magnetic stimulation. *Ann N Y Acad Sci.* 2003;993:1-13; discussion 48-53.**

<http://www.ncbi.nlm.nih.gov/pubmed/12853290>

<http://onlinelibrary.wiley.com/doi/10.1111/j.1749-6632.2003.tb07506.x/abstract>

**Notes** This article provides very detailed reviews of DBS, VNS, and TMS for the treatment of depression, including diagrams and a Q & A section after the article.

**Abstract** Neuromodulation denotes controlled electrical stimulation of the central or peripheral nervous system. The three forms of neuromodulation described in this paper--deep brain stimulation, vagus nerve stimulation, and transcranial magnetic stimulation--were chosen primarily for their demonstrated or potential clinical usefulness. Deep brain stimulation is a completely implanted technique for improving movement disorders, such as Parkinson's disease, by very focal electrical stimulation of the brain--a technique that employs well-established hardware (electrode and pulse generator/battery). Vagus nerve stimulation is similar to deep brain stimulation in being well-established (for the treatment of refractory epilepsy), completely implanted, and having hardware that can be considered standard at the present time. Vagus nerve stimulation differs from deep brain stimulation, however, in that afferent stimulation of the vagus nerve results in diffuse effects on many regions throughout the brain. Although use of deep brain stimulation for applications beyond movement disorders will no doubt involve placing the stimulating electrode(s) in regions other than the thalamus, subthalamus, or globus pallidus, the use of vagus nerve stimulation for applications beyond epilepsy--for example, depression and eating disorders--is unlikely to require altering the hardware significantly (although stimulation protocols may differ). Transcranial magnetic stimulation is an example of an external or non-implanted, intermittent (at least given the current state of the hardware) stimulation technique, the clinical value of which for neuromodulation and neuroprotection remains to be determined.

**30. Murphy JV, Patil A. Stimulation of the nervous system for the management of seizures: current and future developments. *CNS Drugs*. 2003;17(2):101-15.**

<http://www.ncbi.nlm.nih.gov/pubmed/12521358>

**Abstract** Vagal nerve stimulation (VNS) for the treatment of refractory epilepsy appears to have started from the theory that since VNS can alter the EEG, it may influence epilepsy. It proved effective in several models of epilepsy and was then tried in short-term, open-label and double-blind trials, leading to approval in Canada, Europe and the US. Follow-up observations in these patients demonstrated continued improvement in seizure control for up to 2 years. Close to 50% of treated patients have achieved at least a 50% reduction in seizure frequency. This therapy was also useful as rescue therapy for ongoing seizures in some patients; many patients are more alert. The initial trials were completed in patients  $\geq 12$  years of age with refractory partial seizures. Subsequently, similar benefits were shown in patients with tuberous sclerosis complex, Lennox-Gastaut syndrome, hypothalamic hamartomas and primary generalised seizures. Implanting the generator and leads is technically easy, and complications are few. The method of action is largely unknown, although VNS appears to alter metabolic activity in specific brain nuclei. Considering that improvement in mood is frequently found in patients using VNS, it has undergone trials in patients with depression. Other illnesses deserving exploration with this unusual therapy are Alzheimer's disease and autism. Some aspects of VNS have proven disappointing. Although patients have fewer seizures, the number of antiepileptic drugs they take is not significantly reduced. In addition, there is no way to accurately predict the end of life of the generator. Optimal stimulation parameters, if they exist, are unknown. Deep brain stimulation is a new method for controlling medically refractory seizures. It is based on the observation that thalamic stimulation can influence the EEG over a wide area. Several thalamic nuclei have been the object of stimulation in different groups of patients. Intraoperative brain imaging is essential for electrode placement. The procedure is done under local anaesthesia. Experience with this therapy is currently limited, but growing.

**31. Cohen-Gadol AA, Britton JW, Wetjen NM, Marsh WR, Meyer FB, Raffel C. Neurostimulation therapy for epilepsy: current modalities and future directions. *Mayo Clin Proc*. 2003;78(2):238-48.**

<http://www.ncbi.nlm.nih.gov/pubmed/12583536>

**Abstract** Neurostimulation is a recent development in the treatment of epilepsy. Vagus nerve stimulation (VNS), the only approved neurostimulation therapy for epilepsy to date, has proved to be a viable adjunctive treatment option. The exact mechanism of action of VNS is not fully understood. In 2 randomized double-blind trials, seizure frequency declined approximately 30% after 3 months of treatment. Long-term follow-up studies suggest that response improves over time, with approximately 35% of patients experiencing a 50% reduction and 20% experiencing a 75% reduction in seizure frequency after 18 months of treatment. Unfortunately, the number of patients rendered medication-free and seizure-free with VNS is low. Vagus nerve stimulation is best viewed as an option for patients who are not surgical candidates or who hesitate to take the risk of surgery yet continue to have seizures despite maximal medical therapy. Stimulation of other regions of the central nervous system for treating epilepsy, including the anterior and centromedian nuclei of the thalamus, the hippocampus, the subthalamic nucleus, and the cerebral neocortex, is currently under investigation. We review the history, proposed mechanisms of action, clinical trials, adverse effects, and future direction of VNS and other modalities of neurostimulation therapy for epilepsy.

32. **Kellinghaus C, Loddenkemper T, Moddel G, Tergau F, Luders J, Ludemann P, et al. [Electric brain stimulation for epilepsy therapy]. *Nervenarzt*. 2003;74(8):664-76. German.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12904868>  
<http://rd.springer.com/article/10.1007%2Fs00115-003-1541-2>  
**Abstract** Attempts to control epileptic seizures by electrical brain stimulation have been performed for 50 years. Many different stimulation targets and methods have been investigated. Vagal nerve stimulation (VNS) is now approved for the treatment of refractory epilepsies by several governmental authorities in Europe and North America. However, it is mainly used as a palliative method when patients do not respond to medical treatment and epilepsy surgery is not possible. Numerous studies of the effect of deep brain stimulation (DBS) on epileptic seizures have been performed and almost invariably report remarkable success. However, a limited number of controlled studies failed to show a significant effect. Repetitive transcranial magnetic stimulation (rTMS) also was effective in open studies, and controlled studies are now being carried out. In addition, several uncontrolled reports describe successful treatment of refractory status epilepticus with electroconvulsive therapy (ECT). In summary, with the targets and stimulation parameters investigated so far, the effects of electrical brain stimulation on seizure frequency have been moderate at best. In the animal laboratory, we are now testing high-intensity, low-frequency stimulation of white matter tracts directly connected to the epileptogenic zone (e.g., fornix, corpus callosum) as a new methodology to increase the efficacy of DBS ("overdrive method").
33. **Labar D, Dean A. Neurostimulation therapy for epilepsy. *Curr Neurol Neurosci Rep*. 2002;2(4):357-64.** <http://www.ncbi.nlm.nih.gov/pubmed/12044255>  
**Abstract** Neurostimulation therapy for epilepsy is growing in popularity. By appropriate targeting of applied electrical activation at selected nervous system sites, antiseizure effects may be achieved without the common sedative side effects of antiepileptic medications. Risks of neurostimulation therapy are those associated with the device implantation surgical procedures. Vagus nerve stimulation (VNS) reduces seizures by 45% and has been employed in over 13,000 patients worldwide. New reports suggest VNS is particularly beneficial for patients with Lennox-Gastaut syndrome. VNS also reduces sudden unexpected death in epilepsy. New publications describing small, uncontrolled case series also suggest deep brain stimulation and transcranial magnetic stimulation may develop into effective antiepileptic therapies in the future.
34. **Lanska DJ. J.L. Corning and vagal nerve stimulation for seizures in the 1880s. *Neurology*. 2002;58(3):452-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11839848>  
<http://www.neurology.org/content/58/3/452.full.pdf>  
**Abstract** Beginning in the late 18th century, facial flushing and bounding carotid artery pulses during seizures were seen as evidence that seizures resulted from "venous hyperaemia" of the CNS. Consequently, physicians used digital compression of the carotid artery, and later carotid ligation, to abort seizures. In the early 1880s, New York neurologist James Leonard Corning (1855--1923) developed several instruments for carotid artery compression in the treatment of seizures. These devices included a two-pronged, fork-like instrument (the "carotid fork") for temporary compression as an abortive treatment and an adjustable belt-like instrument to encircle the neck (the "carotid truss") for chronic compression as a prophylactic treatment. Corning's uncontrolled observations suggested that the abortive treatment decreased the duration of seizures and that the prophylactic treatment decreased the frequency of seizures. Corning later combined instrumented carotid artery compression with other devices to decrease cerebral blood flow, including transcutaneous electrical vagal nerve and cervical sympathetic stimulation. Observed side effects of treatment included bradycardia, dizziness, and syncope. Corning's use of instrumented carotid compression and his precocious application of transcutaneous electrical vagal nerve stimulation were not widely adopted by neurologists, and these techniques and devices ultimately were abandoned in the late 19th century.

35. **Karczeski S. Devices in the treatment of epilepsy. *Semin Neurol.***

**2002;22(3):259-68.** <http://www.ncbi.nlm.nih.gov/pubmed/12528051>

**Abstract** The goal of the treatment of epilepsy is to eliminate seizures while causing no side effects. For persons whose seizures are refractory, epilepsy surgery may be an option. In addition, these patients may benefit from the vagus nerve stimulator (VNS), the first device approved for the treatment of refractory epilepsy. Although VNS was the first to be approved, investigators have been interested in the effectiveness of stimulating other brain regions: the cerebellum, thalamus, subthalamic nucleus, and locus coeruleus are a few examples. These studies have produced mixed results. As our understanding of the underlying mechanisms of epilepsy grows, it is likely that we will design better and more effective devices for the treatment of epilepsy.

**Review Articles - Epilepsy, Nonpharmacological Treatment**

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- 1. Saxena VS, Nadkarni VV. Nonpharmacological treatment of epilepsy. *Ann Indian Acad Neurol.* 2011;14(3):148-52.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22028523>  
<http://www.annalsofian.org/article.asp?issn=0972-2327;year=2011;volume=14;issue=3;page=148;epage=152;aulast=Saxena>

**Abstract** Nonpharmacological treatment of epilepsy includes surgery, vagal nerve stimulation, ketogenic diet, and other alternative/complementary therapies, e.g., yoga, Ayurveda, electroencephalography (EEG) biofeedback technique, aerobic exercise, music therapy, transcranial magnetic stimulation, acupuncture, and herbal remedies (traditional Chinese medicine). Alternative therapies, despite the term, should not be considered as an alternative to antiepileptic medication; they complement accepted drug treatment. Alternative therapies like yoga, through techniques that relax the body and mind, reduce stress, improve seizure control, and also improve quality of life. Ketogenic diet is a safe and effective treatment for intractable epilepsies; it has been recommended since 1921. The diet induces ketosis, which may control seizures. The most successful treatment of epilepsy is with modern antiepileptic drugs, which can achieve control of seizures in 70-80% cases. Patients opt for alternative therapies because they may be dissatisfied with antiepileptic drugs due to their unpleasant side effects, the long duration of treatment, failure to achieve control of seizures, cultural beliefs and, in the case of women, because they wish to get pregnant. Surgical treatment may lead to physical and psychological sequelae and is an option only for a minority of patients. This article presents supportive evidence from randomized controlled trials done to assess the benefit of non-pharmacological treatment.
  
- 2. Alexopoulos AV, Gonugunta V, Yang J, Boulis NM. Electrical stimulation and gene-based neuromodulation for control of medically-refractory epilepsy. *Acta Neurochir Suppl.* 2007;97(Pt 2):293-309.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17691316>

**Abstract** The failure of available antiepileptic medications to adequately control seizures in a substantial number of patients underscores the need to develop novel epilepsy therapies. Recent advancements in technology and the success of neuromodulation in treating a variety of neurological disorders have spurred interest in exploring promising therapeutic alternatives, such as electrical stimulation and gene-based synaptic control. A variety of different stimulation approaches to seizure control targeting structures in the central or peripheral nervous system have been investigated. Most studies have been based on uncontrolled observations and empirical stimulation protocols. Today the vagus nerve stimulator is the only FDA approved adjunctive treatment for epilepsy that utilizes electrical stimulation. Other potential strategies including direct stimulation of the epileptogenic cortex and deep brain stimulation of various targets are currently under investigation. Chronically implanted devices for electrical stimulation have a variety of limitations. First, they are susceptible to malfunction and infection. Second, most systems require battery replacement. Finally, electrical stimulation is incapable of manipulating neuronal function in a transmitter specific fashion. Gene delivery to epileptogenic targets or targets implicated in regulating seizure threshold has been investigated as an alternative means of neuromodulation in animal models. In summary, positive preliminary results and the lack of alternative treatment options provide the impetus for further exploration of electrical stimulation and gene-based therapies in pharmacoresistant epilepsy. Various specific targets and approaches to modulating their activity have been investigated in human studies.

3. **Sheth RD, Stafstrom CE, Hsu D. Nonpharmacological treatment options for epilepsy. *Semin Pediatr Neurol.* 2005;12(2):106-13.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16114176>  
**Abstract** Approximately one third of children with epilepsy have persistent seizures despite trials of multiple antiepileptic medications. For some of these patients, epilepsy surgery may provide freedom from seizures. However, in many cases, epilepsy surgery is not a viable treatment option. Nonpharmacological approaches are a useful adjunct to help manage seizures in these children. This review examines the role of vagus nerve stimulation, the ketogenic diet, and various forms of EEG biofeedback therapy in children with intractable epilepsy. Although the mechanism of action is not known precisely for any of these adjunctive therapies, they add an important and evolving dimension to the management of difficult to control epilepsy in children. In addition, pyridoxine-dependent seizures are discussed as an example of an etiology of refractory seizures that responds well to replacement therapy.
4. **Cohen-Gadol AA, Stoffman MR, Spencer DD. Emerging surgical and radiotherapeutic techniques for treating epilepsy. *Curr Opin Neurol.* 2003;16(2):213-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12644751>  
**Notes** Advances in both presurgical screening and surgical techniques have allowed the earlier use of more invasive treatments for patients with intractable epilepsy. This review presents the role of some of the newer surgical techniques being used to treat refractory epilepsy, including VNS therapy, deep brain stimulation, hemispherectomy, multiple subpial transection, radiotherapy, and radiosurgery. A succinct description of the procedures and effectiveness of each treatment is provided. The article is particularly useful for its discussion of the results from stimulation of specific areas of the brain and its substantial annotated bibliography.  
**Abstract** PURPOSE OF REVIEW: Recent advances in epilepsy surgery have developed a resurgence of interest in the use of surgical techniques for the treatment of intractable epilepsy. RECENT FINDINGS: More invasive procedures such as hemispherectomy and multiple subpial transection have become more popular. Disconnective techniques such as multiple subpial transection have provided a surgical option for patients whose epileptogenic zone resides in the eloquent cortex. Alternatively, new minimally invasive neurostimulation therapies have been introduced to preserve maximal cerebral tissue. Radiosurgery has been recently utilized in the treatment of epilepsy with preliminary promising results. SUMMARY: In this analysis, the authors will attempt to review the more recent surgical approaches and their indications for the treatment of medically intractable epilepsy. For patients with the epileptogenic zone in the noneloquent cortex, seizure focus resection remains the most reasonable approach to therapy.
5. **Forcadas-Berdusan MI. [Indications and results of nonpharmacological treatments of epilepsies: vagal stimulation, ketogenic diet and gamma rays]. *Rev Neurol.* 2002;35 Suppl 1:S144-50. Spanish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12373666>  
**Abstract** OBJECTIVES: In this paper we review alternative non pharmacological treatments for patients with epilepsy, both focal and generalized, which are resistant to the pharmacological treatment normally used. DEVELOPMENT: Vagal nerve stimulation (VNS) is a recently used palliative technique whose mechanism is not clearly understood. We analyze the clinical trials reported to date and the main indications and contra indications. Although the ketogenic diet (KD) has been used since the 1920s, recently there has been renewed interest in using it. Several papers have been published describing its use in children with epilepsy which was difficult to control. The complex metabolic and endocrine aspects of this type of diet make it difficult to select patients who may benefit from it. Gamma knife surgery is a new technique which has been discussed in this paper since it has been recently used in cases of refractory epilepsy, especially temporal medial epilepsy and hypothalamic hamartomas. CONCLUSIONS: VNS and KD are alternative treatments which may be used in patients whose condition cannot be satisfactorily controlled by pharmacological treatment and are not candidates for the surgery of epilepsy. Gamma knife surgery is a surgical technique which has recently been introduced for the treatment of these patients.

6. **Benbadis SR, Tatum WO, Vale FL. When drugs don't work: an algorithmic approach to medically intractable epilepsy. *Neurology*. 2000;55(12):1780-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11188984>

**Review Articles - Epilepsy, Overview**

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1. **Rudzinski LA, Meador KJ. Epilepsy: five new things. *Neurology*. 2011;76(7 Suppl 2):S20-5. <http://www.ncbi.nlm.nih.gov/pubmed/21321347>**
  
2. **Pati S, Alexopoulos AV. Pharmacoresistant epilepsy: from pathogenesis to current and emerging therapies. *Cleve Clin J Med*. 2010;77(7):457-67. <http://www.ncbi.nlm.nih.gov/pubmed/20601619> <http://www.ccjm.org/content/77/7/457.full.pdf>**  
**Abstract** Almost one-third of people with epilepsy continue to have seizures despite appropriate antiepileptic drug treatment, placing them at considerable risk of cognitive and psychosocial dysfunction and death. We recommend early referral to an epilepsy center when seizures are difficult to control.
  
3. **Shuper A. [Epilepsy in Israel--2008]. *Harefuah*. 2008;147(2):134-5, 182. Hebrew. <http://www.ncbi.nlm.nih.gov/pubmed/18357670>**  
**Abstract** The relatively high percentages of patients with epilepsy, in whom seizures are uncontrolled in spite of optimal antiepileptic drug use, lead to continuous struggles to improve the treatment of epilepsy. The advances in defining the genetic basis of epilepsy can potentially lead to better understanding of the disorder as well as to more effective treatment. An example is the finding of SCN1A gene mutations in association with a large spectrum of neurological diseases, from generalized epilepsy with febrile seizures plus (GEFS +) to severe myoclonic epilepsy of infancy and to vaccine-induced encephalopathy and Rasmussen encephalitis, Panayiotopoulos syndrome and familial hemiplegic migraine. In parallel, throughout the world, imaging modalities of very high technology are being used to define the epileptogenic focus. A description from The Hospital for Sick Children in Toronto, of a topographic movie of high frequency oscillations on the brain surface, which allows visualization of the dynamic ictal changes, is remarkable. The ketogenic diet is a significant treatment option. The John Freeman Epilepsy Center in Johns Hopkins Hospital leads the way in using the diet in very young infants, including West syndrome. The vagus nerve stimulation is being used as another relatively safe and effective treatment, while epilepsy surgery continues to be applied. Better matching of patients to each modality can be expected with increased success in seizure control.

4. **Wolf P. From precipitation to inhibition of seizures: rationale of a therapeutic paradigm. *Epilepsia*. 2005;46 Suppl 1:15-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15816972>  
<http://onlinelibrary.wiley.com/store/10.1111/j.0013-9580.2005.40904.x/asset/j.0013-9580.2005.40904.x.pdf?v=1&t=he943ddt&s=43659fe042619990d7476e7b6a7a96b6f0b2be4b>  
**Abstract** Epileptic seizures can be triggered by both nonspecific facilitating factors such as sleep withdrawal, fever, or excessive alcohol intake, and specific reflex epileptic mechanisms. These consist of sensory or cognitive inputs activating circumscribed cortical areas or functional anatomic systems that, due to some functional instability, respond with an epileptic discharge. Interruption of seizure activity at the stage of the aura (i.e., locally restricted discharge) also can be achieved by nonspecific (e.g., relaxation or concentration techniques or vagal nerve stimulation) or by specific focus-targeted sensory or cognitive inputs. The latter, again, activate circumscribed cortical areas. Intriguingly, in some patients, the same stimulus can either precipitate or abort a seizure. The response depends on the state of cortical activation: seizure precipitation occurs in the resting condition, and seizure interruption occurs when the epileptic discharge has begun close to the activated area. These relations can be understood on the background of experimental data showing that an intermediate state of neuronal activation is a precondition for the generation of paroxysmal depolarization shifts, whereas a hyperpolarized neuron will remain subthreshold, and a depolarized neuron that already produces action potentials is not recruitable for other activity. Sensory input meeting an intermediately activated pool of potentially epileptic neurons is adequate to produce a seizure. In another condition, the same stimulus can depolarize a neuron pool in the same area sufficiently to block the further propagation of nearby epileptic activity. Understanding these interactions facilitates the development of successful nonpharmaceutical therapeutic interventions for epilepsy.
5. **Ryvlin P. The modern challenges of drug resistant epilepsy. Introduction. *Epileptic Disord*. 2005;7 Suppl 1:S1-2.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16120486>
6. **Kelso AR, Cock HR. Advances in epilepsy. *Br Med Bull*. 2004;72:135-48.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15845748>  
<http://bmb.oxfordjournals.org/content/72/1/135.full.pdf>  
**Abstract** Advances in understanding of both the causes and consequences of epilepsy have been paralleled by a number of recent reports and clinical guidelines highlighting the complexities involved in both diagnosing and treating epilepsy. We review recent developments, including comments on the evolution of clinical guidelines, anti-epileptic drugs, epilepsy surgery and new treatment approaches in development. Epilepsy genetics and emerging evidence on mechanisms of drug resistance in epilepsy will also be discussed. Issues with respect to pregnancy and epilepsy are considered, together with more recently identified dilemmas including bone health in epilepsy and whether seizures themselves cause brain damage. Imaging in epilepsy has recently been reviewed elsewhere, and will not be discussed.

7. **Leonard EC, Jr. Did some 18th and 19th century treatments for mental disorders act on the brain? *Med Hypotheses*. 2004;62(2):219-21.**  
<http://www.ncbi.nlm.nih.gov/pubmed/14962630>  
**Notes** This historical overview of early psychiatric therapies reviews the effects and potential mechanisms of action of early treatments as a foundation for current treatments being studied for affective disorders today. Included in the review are early treatments using external (through the skin) stimulation of the vagus nerve.  
**Abstract** Review of 18th and 19th century psychiatric therapies raises the possibility that several may have altered the activity of vasopressin or Na-K-ATPase. Bleeding, whirling, nausea created by medicines, and vagus nerve stimulation by application of electricity through the skin all perturb the hypothalamic hormone, arginine vasopressin, while helleborus and digitalis inhibit the sodium pump enzyme, Na-K-ATPase. These approaches were used with reported benefit many years ago, acting on the brain in ways ongoing research suggests may play a role in affective disorders. Study of long-abandoned treatments may clarify their mechanisms of action and the characteristics of responsive patients.
8. **Refractory epilepsy. *Epilepsia*. 2003;44(suppl s6):81-2.**  
<http://onlinelibrary.wiley.com/doi/10.1046/j.1528-1157.44.s6.33.x/abstract>  
**Notes** This article addresses the difficulty of assessing what constitutes refractory epilepsy. The difficulties of treating refractory epilepsy, including patient noncompliance and AED side effects, also are discussed. VNS therapy and the ketogenic diet are discussed as alternative treatment modalities for patients with refractory epilepsy. The authors conclude with the following recommendation: "Refractory epilepsy is a significant problem. Recent advances in diagnostic techniques and increased treatment options have improved the situation, but further developments are needed."
9. **Devinsky O. Patients with refractory seizures. *N Engl J Med*. 1999;340(20):1565-70.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10332020>
10. **Spatz J, Pelzl G, Mamoli B, Zartl M. [Current problems in epilepsy]. *Wien Klin Wochenschr*. 1999;111(17):705-12. German.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10526394>  
**Abstract** Three new aspects of epilepsy are discussed: the mesiotemporal syndrome, vagus nerve stimulation, and epilepsy and driving fitness. In recent years mesiotemporal epilepsy has been recognised as the most frequent epileptic syndrome in adults. The main clinical features are febrile convulsions during childhood, followed by characteristic focal seizures in the second decade of life. The typical seizure is characterised by an aura, followed by loss of consciousness, with motor phenomena and automatisms followed by longer periods of postictal confusion. Atrophy of the hippocampus and sclerosis are observed in MRI. The syndrome is frequently drug resistant, however, 80% of the patients are free of seizure after surgical treatment. Vagus nerve stimulation is a new option in the treatment of patients with drug resistant epilepsy (partial seizures with or without secondary generalization, Lennox-Gastaut syndrome), especially when surgical intervention is not indicated. Worldwide a total of more than 4000 patients have been treated. More than 50% reduction in the frequency of seizures can be obtained in 35-40% of drug resistant patients. Complications are rare. Finally, the issue of driving fitness and epilepsy as well as provoked seizures are discussed. The current regulations and laws are taken into consideration and revised regulations for Austria are suggested.

**Review Articles - Epilepsy, Surgical Interventions**

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- 1. Wu C, Sharan AD. Neurostimulation for the treatment of epilepsy: a review of current surgical interventions. *Neuromodulation*. 2013;16(1):10-24; discussion 24.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22947069>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1525-1403.2012.00501.x/asset/ner501.pdf?v=1&t=hekioz z5&s=17ad4b02a9be09a28fcae2666a1426c55b102728>

**Abstract** OBJECTIVES: Epilepsy continues to provide challenges to clinicians, as a significant proportion of patients continue to suffer from seizures despite medical and surgical treatments. Neurostimulation has emerged as a new treatment modality that has the potential to improve quality of life and occasionally be curative for patients with medically refractory epilepsy who are not surgical candidates. In order to continue to advance the frontier of this field, it is imperative to have a firm grasp of the current body of knowledge. METHODS: We performed a thorough review of the current literature regarding the three main modalities of vagus nerve stimulation, deep brain stimulation, and closed-loop stimulation (responsive neurostimulator [RNS]) for the treatment of refractory epilepsy. For each of these forms of treatment, we discuss the current understanding of the underlying mechanism of action, patient selection, outcomes to date, and associated side effects or adverse reactions. We also provide an overview of related ongoing clinical trials. RESULTS: A total of 189 sources from 1938 to 2012 pertaining to neuromodulation for the treatment of epilepsy were reviewed. Sources included review articles, clinical trials, case reports, conference proceedings, animal studies, and government data bases. CONCLUSIONS: This review shows us how neurostimulation provides us with yet another tool with which to treat the complex disease of medically refractory epilepsy.
  
- 2. Fauser S, Zentner J. Critical review of palliative surgical techniques for intractable epilepsy. *Adv Tech Stand Neurosurg*. 2012;39:165-94.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23250841>  
[http://link.springer.com/chapter/10.1007%2F978-3-7091-1360-8\\_7](http://link.springer.com/chapter/10.1007%2F978-3-7091-1360-8_7)

**Abstract** Approximately one third of epilepsy patients are not adequately treatable by antiepileptic medication. Curative resective epilepsy surgery can be performed in only a subgroup of these pharmaco-resistant patients in whom the epileptogenic focus is localizable and does not overlap with eloquent brain areas. To the remaining patients (with bilateral or multiple epileptogenic foci, with epilepsy onset in eloquent areas, or with no identifiable epileptogenic focus) palliative epilepsy surgery can be offered if they suffer from disabling seizures. Standard palliative procedures currently comprise corpus callosotomy, multiple subpial transections, and vagus nerve stimulation. New approaches such as focus distant deep brain stimulation or direct stimulation of the hippocampus have gained the most interest. Feasibility studies, small pilot studies, and, recently, larger multicenter trials showed that direct brain stimulation shall be considered a potential helpful procedure in the field of palliative surgery. Moreover, with the increasing use of stereo-EEG in invasive video-EEG monitoring, stereo-EEG-guided thermocoagulation has the potential for a promising new treatment option in patients not amenable to resective epilepsy surgery. There is no general consensus on which palliative procedure is most effective in patients with difficult-to-treat epilepsy syndromes. The decision must be based on individual factors of a given patient. This review summarizes experience with palliative approaches collected in adult and pediatric patient series over the past decades and may help to thoroughly balance beneficial effects and risks of each procedure.

3. **Kunieda T, Kikuchi T, Miyamoto S. Epilepsy surgery: surgical aspects. *Curr Opin Anaesthesiol.* 2012;25(5):533-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22895124>  
**Abstract** PURPOSE OF REVIEW: This review highlights recent advances in epilepsy surgery specifically awake surgery technique, and introduces the clinical application of neuromodulation concept in this field. RECENT FINDINGS: Surgical success, improving quality-of-life in epilepsy patients, relies upon complete resection of epileptogenic areas and perfect protection of functional areas. As there is no single way to define these areas directly, invasive evaluations will be necessary in addition to conventional noninvasive ones. The optimal anesthetic management with awake surgery technique should provide favorable working conditions for the surgeons and the neurologists without compromising the safety and comfort of the patient. New methods of controlling epilepsy, based on the concept of neuromodulation, have been recently introduced. Some positive results of these new techniques, such as DBS and RNS, might lay the foundation for expansion of implantation surgery. SUMMARY: Although the final goal of epilepsy surgery is the same in most cases, -that is, maximizing normal neurological function while minimizing adverse effects, the clinical approach differs for each patient. Therefore, advancement of a new approach to identify the epileptogenic areas and new surgical treatment option would be greatly beneficial for patients with intractable epilepsy.
  
4. **Jadhav T, Cross JH. Surgical approaches to treating epilepsy in children. *Curr Treat Options Neurol.* 2012;14(6):620-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23054582>  
<http://link.springer.com/article/10.1007%2Fs11940-012-0203-8>  
**Abstract** OPINION STATEMENT: Surgery for refractory epilepsy in appropriately selected children is effective. The key factors influencing a good outcome are careful selection of candidates, early referral to pediatric epilepsy surgical unit, underlying neuropathology and the completeness of surgical resection of the seizure focus. Although the primary aim of a surgery is seizure freedom, benefits are also seen in cognitive development. Early prompt referral is therefore desired to optimise outcome. Focal resections involving the temporal and frontal lobes are the common resective procedures in children, with cortical malformations the most common underlying pathology. Hemispherectomy or multilobar procedures are more commonly performed in children younger than four years. Seizure free rates reach 60-80 %. The availability of newer techniques for presurgical evaluation, along with invasive intracranial electroencephalographic (EEG) recording, has facilitated surgical consideration. Resective surgery may also be beneficial for children who may appear to have bilateral or generalised clinical or EEG features associated with focal lesions on MRI. Vagal Nerve Stimulation (VNS) and corpus callosotomy are employed for selected candidates not suitable for resective surgery with good results.
  
5. **Romanelli P, Striano P, Barbarisi M, Coppola G, Anselmi DJ. Non-resective surgery and radiosurgery for treatment of drug-resistant epilepsy. *Epilepsy Res.* 2012;99(3):193-201.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22245137>  
**Abstract** Epilepsy surgery is an effective treatment for properly selected patients with intractable seizures. However, many patients with medically intractable epilepsy are not excellent candidates for surgical resection of the epileptogenic zone. Due to recent advances in computer technology and bioengineering, several novel techniques are receiving increasing interest for their role in the care of people with epilepsy. Neuromodulation is an emerging surgical option to be used when conventional resective surgery is not indicated. We review the indications and expected outcomes of neuromodulatory treatments currently available for the treatment of refractory epilepsy, i.e., vagus nerve stimulation, deep brain stimulation, stereotactic radiosurgery, and multiple subpial transections.

6. **Noachtar S, Remi J. [Epilepsy surgery]. *Nervenarzt*. 2012;83(2):209-12. German.** <http://www.ncbi.nlm.nih.gov/pubmed/22237649> <http://rd.springer.com/article/10.1007%2Fs00115-011-3341-4>  
**Abstract** Epilepsy surgery is an important therapeutic option for patients with epilepsy since one third of all epilepsy patients will still not be become seizure free despite newly developed antiepileptic drugs. Anterior temporal lobe resection is the most common procedure. Extratemporal resections require more complex diagnostics and often invasive evaluation which is not the case in most temporal epilepsy patients due to improved imaging (MRI, PET, SPECT). Electrical stimulation of the anterior thalamus has been available as a treatment option since last year.
  
7. **Al-Otaibi F, Al-Khairallah T. Functional neurosurgery. The modulation of neural and mind circuits. *Neurosciences (Riyadh)*. 2012;17(1):16-31.** <http://www.ncbi.nlm.nih.gov/pubmed/22246006>  
**Abstract** Different complex neuroanatomical and neurochemical circuits regulate a variety of neuronal behaviors and brain functions. Any disturbance in these circuits can generate functional disorders such as movement disorders, epilepsy, pain, memory disorders, and psychiatric disorders. Functional neurosurgery aims to restore these functions, either by removing or isolating the abnormally behaving neurons or by modulating the disturbed circuits. Neuromodulation is a fast-growing field, powered by the recent advances in neuroimaging and technology. Here, we discuss recent advances and new horizons in functional neurosurgery.
  
8. **Gigante PR, Goodman RR. Alternative surgical approaches in epilepsy. *Curr Neurol Neurosci Rep*. 2011;11(4):404-8.** <http://www.ncbi.nlm.nih.gov/pubmed/21584657> <http://link.springer.com/article/10.1007%2Fs11910-011-0209-8>  
**Abstract** The mainstay of epilepsy surgery is the resection of a presumed seizure focus or disruption of seizure propagation pathways. These approaches cannot be applied to all patients with medically refractory epilepsy (MRE). Since 1997, vagus nerve stimulation has been a palliative adjunct to the care of MRE patients. Deep brain stimulation (DBS) in select locations has been reported to reduce seizure frequency in small studies over the past three decades. Recently published results from the SANTE (Stimulation of the Anterior Nuclei of Thalamus for Epilepsy) trial-the first large-scale, randomized, double-blind trial of bilateral anterior thalamus DBS for MRE-demonstrate a significant reduction in seizure frequency with programmed stimulation. Another surgical alternative is the RNS System (NeuroPace, Mountain View, CA), which uses a closed-loop system termed responsive neurostimulation to both detect apparent seizure onsets and deliver stimulation. Recently presented results from the RNS pivotal trial demonstrate a sustained reduction in seizure frequency with stimulation, although comprehensive trial results are pending.

9. **Kelly KM, Chung SS. Surgical treatment for refractory epilepsy: review of patient evaluation and surgical options. *Epilepsy Res Treat.* 2011;2011:303624.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22937231>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3420605/pdf/ERT2011-303624.pdf>  
**Abstract** Treatment of epilepsy often imposes an exposure to various antiepileptic drugs and requires long-term commitment and compliance from the patient. Although many new medications are now available for the treatment of epilepsy, approximately 30% of epilepsy patients still experience recurrent seizures and many experience undesirable side effects. Treatment of epilepsy requires a multidisciplinary approach. For those patients with medically refractory seizures, surgical treatment has increased in prevalence as techniques and devices improve. With increased utilization, proper patient selection has become crucial in evaluating appropriateness of surgical intervention. Epilepsy syndromes in which surgery has shown to be effective include mesial temporal sclerosis, cortical dysplasia, many pediatric epilepsy syndromes, and vascular malformations. Monitoring in an epilepsy monitoring unit with continuous scalp or intracranial EEG is an important step in localization of seizure focus. MRI is the standard imaging technique for evaluation of anatomy. However, other imaging studies including SPECT and PET have become more widespread, often offering increased diagnostic value in select situations. In addition, as an alternative or adjunct to surgical resection, implantable devices such as vagus nerve stimulators, deep brain stimulators, and direct brain stimulators could be useful in seizure treatment.
10. **Bodensteiner JB, Ng YT. Ethical considerations in paediatric neurology: neuromuscular disease and epilepsy. *J Paediatr Child Health.* 2011;47(9):599-602.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21951440>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1754.2011.02159.x/abstract>  
**Abstract** The pace of developing technology with respect to many diagnostic tests, as well as available treatments including artificial ventilation, may have progressed at a faster rate than our ethical, humane ability to decide on the optimal choices for our patients. In fact, who should make these choices; physicians or patients and families? Certain ethical aspects of neuromuscular disorders and epilepsy are reviewed. For neuromuscular disease, the example of Duchenne muscular dystrophy (DMD) with regards to genetic testing, relatively early wheelchair placement and individualised invasive ventilation is discussed. In epilepsy, performing neurosurgery in severely impaired children is probably appropriate in some cases if desired by the family. Financial and human costs restrict therapies and testing for epilepsy as well as other neurological and medical diseases. Whether it is ethical to consider costs in medical treatment or not, it is certainly a reality.
11. **Chang EF, Barbaro NM. Epilepsy surgery: the emerging field of neuromodulation. *Neurosurg Clin N Am.* 2011;22(4):ix-x.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21939840>

- 12. Obeid M, Wyllie E, Rahi AC, Mikati MA. Approach to pediatric epilepsy surgery: State of the art, Part II: Approach to specific epilepsy syndromes and etiologies. *Eur J Paediatr Neurol.* 2009;13(2):115-27.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18590975>  
**Abstract** The second of this 2-part review depicts the specific approach to the common causes of pediatric refractory epilepsy amenable to surgery. These include tumors, malformations due to abnormal cortical development, vascular abnormalities and certain epileptic syndromes. Seizure freedom rates are high (usually 60-80%) following tailored focal resection, lesionectomy, and hemispherectomy. However, in patients in whom the epileptogenic zone overlaps with unresectable eloquent cortex, and in certain epileptic syndromes, seizure freedom may not be achievable. In such cases, palliative procedures such as callosotomy, multiple subpial transections and vagus nerve stimulation can achieve reduction in seizure severity but rarely seizure freedom. Integration of the new imaging techniques and the concepts of neuronal plasticity, the epileptogenic lesion, the ictal onset, symptomatogenic, irritative, and epileptogenic zones is an expanding and dynamic process that will allow us, in the future, to better decide on the surgical approach of choice and its timing.
- 13. O'Brien DF. Epilepsy surgery: a proven neurosurgical treatment and a multi-disciplinary team practice. *Ir Med J.* 2008;101(9):266-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19051612>
- 14. Schomer DL, Black PM. A 24-year-old woman with intractable seizures: review of surgery for epilepsy. *JAMA.* 2008;300(21):2527-38.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18984876>  
[http://jama.jamanetwork.com/data/Journals/JAMA/4442/jxr80010\\_2527\\_2538.pdf](http://jama.jamanetwork.com/data/Journals/JAMA/4442/jxr80010_2527_2538.pdf)  
**Abstract** Epilepsy, a recurrent seizure disorder affecting 1% of the population, can be genetic in origin and thereby affect multiple members in a family, or it can be sporadic. Many sporadic seizures come from a specific "focus" in the cortex. Focal-onset seizures account for 60% of all cases of epilepsy. Among patients with partial seizures, 35% respond poorly to available medication and may benefit from neurosurgical excisional surgery. In cases in which epilepsy is localized through different modes (electroencephalogram, magnetic resonance imaging, etc) to a specific area of the brain where there is an associated lesion, more than half of patients can expect a successful surgical outcome. In patients with consistent seizure-associated behavior but without a lesion, surgical treatment is less successful. Ms H, a young woman with a history of medically intractable partial epilepsy, does not have an anatomical lesion but wants to know if a surgical approach is a good option for her.
- 15. Balabanov A, Rossi MA. Epilepsy surgery and vagal nerve stimulation: what all neurologists should know. *Semin Neurol.* 2008;28(3):355-63.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18777482>  
**Abstract** Epilepsy surgery treatment should be considered as standard of care for all patients with medically intractable partial-onset epilepsy who are found to be good surgical candidates based on their presurgical evaluation. Delaying surgical treatment continues to be a problem among neurologists. The early recognition of pharmacoresistance and patients' referral for presurgical evaluation can shorten the time to identify potential surgical candidates. A successful early surgery can be expected to significantly improve these patients' quality of life, not only because of a seizure-free state but also by improving psychiatric comorbidities. Vagal nerve stimulation (VNS) is currently the only FDA-approved neurostimulation treatment strategy for patients who are not considered candidates for epilepsy surgery. VNS has been shown to decrease seizure frequency by approximately 50% in 30 to 40% of implanted patients. The future of epilepsy surgery and neurostimulation for those individuals with medically intractable partial-onset epilepsy shows great promise.

16. **Kawai K. [Less invasive treatment of intractable epilepsy--vagus nerve stimulation and stereotactic radiosurgery]. *Brain Nerve*. 2007;59(4):299-311. Japanese.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17447516>  
**Abstract** Vagus nerve stimulation (VNS) and stereotactic radiosurgery (SRS) represent novel and less invasive therapeutics for medically intractable epilepsy. VNS ushered in the recent advancement in clinical application of electrical stimulation therapy for epilepsy. Chronic stimulation of the left vagus nerve with implanted generator and electrodes inhibits seizure susceptibility of the cerebral cortices. Its efficacy and safety have been established by randomized clinical trials in 1990s in the Western countries and it has been widely accepted as a treatment option for patients with medically intractable epilepsy for whom brain surgery is not indicated or failed. Although the effect on seizures is not so dramatic, the less invasiveness and a wide range of indication have made VNS indispensable for comprehensive care of epilepsy. Since the devices are not approved for clinical use in Japan, there exist barriers to provide VNS to patients at present. Use of SRS for intractable epilepsy started in mid 90s as gamma knife surgery for mesial temporal lobe epilepsy. The marginal dose of 25 Gy to the medial temporal structures has been confirmed to be effective for seizure control, but there seems to be an unignorable risk of brain edema and radiation necrosis. It is still controversial whether the therapy is more effective and less invasive than brain surgery. A randomized clinical trial using the dose of 20 or 24 Gy is ongoing in the United States. SRS for intractable epilepsy associated with hypothalamic hamartoma has been advocated because of a high surgical morbidity, but further study is needed for standardization of the treatment. Substitute use of SRS for other surgical technique like callosotomy or disconnection of epileptic focus seems to be another direction worth pursuing.
17. **Hamberger MJ, Drake EB. Cognitive functioning following epilepsy surgery. *Curr Neurol Neurosci Rep*. 2006;6(4):319-26.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16822353>  
**Abstract** Temporal lobe resection is the most common surgery for intractable epilepsy because of its proven efficacy in seizure control. However, patients who may benefit from the procedure might be deterred from surgical evaluation due to concerns of postoperative cognitive decline. Recent reports on long-term follow-up indicate that, similar to findings within the year after surgery, cognition remains relatively stable in the years following right temporal resection. The verbal memory decline often observed 1 year after left temporal resection persists over time, yet is mitigated to some extent by good seizure outcome. Although memory decline observed on testing is not typically accompanied by functional decline, a small proportion of patients do experience reductions in occupational or academic status. Recent advances in functional imaging and refinements in preoperative mapping promise better prediction and protection of cognitive functioning. Additionally, results from studies comparing cognitive outcome among different surgical techniques suggest that more restricted resections benefit some patients, whereas more extended resections might be appropriate in a select group of well-defined patients. Preliminary reports on alternate treatments such as vagal nerve stimulation suggest no direct influence on cognition, although improvement in quality of life has been reported. The decision to pursue surgical treatment must balance the potential benefit of seizure control with the potential impact and probability of cognitive decline.

18. **Polkey CE. Clinical outcome of epilepsy surgery. *Curr Opin Neurol.* 2004;17(2):173-8. <http://www.ncbi.nlm.nih.gov/pubmed/15021245>**  
**Abstract** PURPOSE OF REVIEW: The outcome from current surgical methods of treating drug-resistant epilepsy will be considered, looking at changes in classical resective surgery and new methodology being introduced in the functional treatment of these patients. RECENT FINDINGS: There is now class I evidence that temporal lobe surgery is effective. Sophisticated and appropriate magnetic resonance imaging sequences, together with an assessment of the electroclinical syndrome, allow patients to be assessed for resective surgery. The concept of 'surgically remediable syndromes' determines the type of procedure that is effective for particular patients. Technical advances such as neuronavigation techniques and intra-operative magnetic resonance imaging have improved the effectiveness of these procedures. Other techniques of disconnection, such as multiple subpial transection, and stimulation both indirectly using the vagus nerve and directly using various intracranial targets, are currently effective and have potential for future development. SUMMARY: This review will demonstrate that current surgical techniques are safe and effective in relieving drug-resistant epilepsy.
19. **Halasz P, Vajda J, Czirjak S. [Surgical treatment of epilepsy]. *Ideggyogy Sz.* 2004;57(5-6):189-205. Hungarian. <http://www.ncbi.nlm.nih.gov/pubmed/15264694>**  
**Abstract** In this article the possibilities, indications, methods and results of surgery in epilepsy are summarized in general with the Hungarian experience emphasized. Surgery may provide effective treatment in about 5-10% of the epileptic population. Surgical solution nowadays became an essential treatment in medial temporal epilepsy, if hippocampal sclerosis or other lesion is present, in therapy resistant lesional extratemporal epilepsies and in catastrophic childhood epilepsies if the epileptic disorder is restricted to one hemisphere (Rasmussen syndrome, hemimegalencephaly, Sturge-Weber disease and posttraumatic or postencephalitic hemispherical epilepsies). The algorithms of the presurgical evaluation and the current methods for study the pacemaker area, forbidden zones, and hemispherical functions are treated. The currently used type and techniques of surgery, such as lesionectomy, temporal lobe resections, hemispherotomy, callosotomy, multiple subpial transections and their indications are described. The newest surgical approaches, as deep brain stimulation, vagal nerve stimulation, and irradiation techniques are also briefly touched. Lastly, we deal with prognostical factors of the surgical outcome, reasons of surgical failures and complications. In a brief chapter the importance of postsurgical rehabilitation is emphasized.
20. **Hudgins RJ, Gilreath CL. Managing epilepsy II: surgical treatment of epilepsy in children. *Nepal J Neurosci.* 2004;1(2):83-91. <http://www.neuroscience.org.np/tableofcontent2.html>**  
**Abstract** 10-20% of all epilepsy is intractable, that is, poorly controlled despite treatment with antiepileptic medications to therapeutic levels both singly and in combinations. Most intractable epilepsy begins during childhood. It has long been established that poorly controlled seizures have an adverse effect on cognitive and psychosocial development. In many cases when medications are not effective, surgery is a viable option. The preoperative evaluation involves video-EEG monitoring, high-resolution MRI, and detailed neuropsychological testing. Resection surgery is performed when the area of seizure onset is focal. Disconnection surgery such as corpus callosotomy is used if the seizures are generalized. Vagal nerve stimulation (VNS) is the procedure of choice if the area of seizure onset can not be localized or in many types of generalized seizures. Children have favorable outcomes from epilepsy surgery similar to those in adults.

21. **Polkey CE. Alternative surgical procedures to help drug-resistant epilepsy - a review. *Epileptic Disord.* 2003;5(2):63-75.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12875950>  
**Abstract** The concepts of pathophysiology of epilepsy which underly the non-resective surgical treatment of epilepsy are reviewed. The available techniques, lesioning, disconnection and stimulation are described and reviewed critically. Stereotactic lesioning, popular in the 1950's has been largely abandoned but stereotactic radiosurgery emerges as a useful technique, especially in the treatment of mesial temporal sclerosis. Disconnection by callosotomy has fewer applications than previously and multiple subpial transection (MST) has limited applications. Stimulation is a technique with increasing usefulness. Vagus nerve stimulation(VNS) is an accepted method of treatment with low morbidity and mortality, which improves seizure control in at least 30% of patients, together with concomitant improvements in QOL and economic advantages. Stimulation of deep brain targets in the thalamus, subthalamus and mesial temporal structures is practical. There are indications that this improves seizure control in groups of patients previously un helped by surgery, and this methodology has enormous potential.
22. **McKhann GM, 2nd, Bourgeois BF, Goodman RR. Epilepsy surgery: indications, approaches, and results. *Semin Neurol.* 2002;22(3):269-78.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12528052>  
**Abstract** The surgical treatment of epilepsy is divided into procedures with curative or palliative goals. Curative procedures are highly effective in rendering the majority of patients seizure free, and palliative procedures often result in marked improvement in seizure frequency, quality of life, or both. This brief overview of epilepsy surgery outlines the goals of surgery, criteria used to determine patient eligibility, the various types of epilepsy surgery, and anticipated outcomes of these approaches. Newer surgical techniques including vagus nerve and deep brain stimulation and gamma knife radiosurgery are also discussed.
23. **Devaux B, Chassoux F, Landre E, Turak B, Merlaud B, Oswald AM, et al. [Functional neurosurgery for epilepsy]. *Ann Fr Anesth Reanim.* 2001;20(2):137-44. French.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11270235>  
**Abstract** Introduced at the end of the last century, epilepsy surgery is indicated in patients with intractable partial seizures and based on the resection of the epileptogenic cerebral tissue from which ictal discharges originate. Palliative procedures include seizure spread pathways interruption (callosotomy, multiple subpial transections) and chronic stimulation of the vagus nerve. Complete preoperative investigations including seizure observation, clinical tests, video-EEG, MRI and functional MRI, and PET-scan are performed in order to identify the epileptogenic zone. In difficult cases, invasive seizure monitoring through depth electrode implantation (SEEG) is performed. Resections for temporal lobe seizures are associated with favorable outcome: 60 to 90% of patients will be seizure-free after surgery. A less favorable outcome is observed after extra-temporal resections: 40 to 60% seizure-free patients. A better outcome is observed after surgery for epilepsy associated with an image-defined lesion, most often a tumor, rather than for cryptogenic epilepsy. Tumors associated with chronic partial epilepsy are indolent, most of them are dysembryoplastic neuroepithelial tumors (DNET). Outcome after palliative procedures are more variable, depending on the etiology of epilepsy.

24. **Kemeny AA. Surgery for epilepsy. *Seizure*. 2001;10(6):461-5.** <http://www.ncbi.nlm.nih.gov/pubmed/11701004>  
[http://ac.els-cdn.com/S1059131101906302/1-s2.0-S1059131101906302-main.pdf?\\_tid=6e2d917a-8cc4-11e2-a19f-00000aab0f01&acdnat=1363278786\\_6c784b10a131d585b958d3152fd32554](http://ac.els-cdn.com/S1059131101906302/1-s2.0-S1059131101906302-main.pdf?_tid=6e2d917a-8cc4-11e2-a19f-00000aab0f01&acdnat=1363278786_6c784b10a131d585b958d3152fd32554)  
**Abstract** While medical treatment remains the first line of treatment for epilepsy, surgery provides effective long-term control in suitable patients. Detailed investigations are necessary to prove suitability and in order to choose the appropriate procedure. This article gives an outline of the investigative programme and the various operative approaches. Novel methods and those under investigation are also discussed.
25. **Gates JR, Dunn ME. Presurgical assessment and surgical treatment for epilepsy. *Acta Neurol Belg*. 1999;99(4):281-94.** <http://www.ncbi.nlm.nih.gov/pubmed/10674146>  
**Abstract** In the last ten years, dramatic advances in surgical treatment options and techniques have allowed surgical intervention for patients who would otherwise not have been considered as surgical candidates. In this article, a multidisciplinary, logical decision algorithm for a rational approach to surgical treatments is outlined. A carefully considered hierarchy is presented that provides for maximized seizure improvement outcomes. Topics presented include temporal lobectomy, detailed discussion of dominant temporal lobectomy and speech-sparing techniques, neocortical resection, the use of subdural electrode array, depth electrodes, and strip electrodes, multiple subpinal transection, vagus nerve stimulation, and corpus callosotomy. The application of these various techniques to maximize surgical outcome are discussed.

**Review Articles - Neurostimulation**

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1. **Steinberg H. A pioneer work on electric brain stimulation in psychotic patients. Rudolph Gottfried Arndt and his 1870s studies. *Brain Stimul.* 2012.**

<http://www.ncbi.nlm.nih.gov/pubmed/23266132>

**Abstract** BACKGROUND: Today's brain stimulation methods are commonly traced back historically to surgical brain operations. With this one-sided historical approach it is easy to overlook the fact that non-surgical electrical brain-stimulating applications preceded present-day therapies. OBJECTIVE/HYPOTHESIS: The first study on transcranial electrical brain stimulation for the treatment of severe mental diseases in a larger group of patients was carried out in the 1870s. METHODS: Between 1870 and 1878 German psychiatrist Rudolph Gottfried Arndt published the results of his studies in three reports. These are contextualized with contemporary developments of the time, focusing in particular on the (neuro-) sciences. As was common practice at the time, Arndt basically reported individual cases in which electricity was applied to treat severe psychoses with depressive symptoms or even catatonia, hypochondriac delusion and melancholia. Despite their lengthiness, there is frequently a lack of precise physical data on the application of psychological-psychopathological details. Only his 1878 report includes general rules for electrical brain stimulation. RESULTS: Despite their methodological shortcomings and lack of precise treatment data impeding exact understanding, Arndt's studies are pioneering works in the field of electric brain stimulation with psychoses and its positive impacts. Today's transcranial direct current stimulation, and partly vagus nerve stimulation, can be compared with Arndt's methods. Although Arndt's only tangible results were indications for the application of faradic electricity (for inactivity, stupor, weakness and manic depressions) and galvanic current (for affective disorders and psychoses), a historiography of present-day brain stimulation therapies should no longer neglect studies on electrotherapy published in German and international psychiatric and neurological journals and monographs in the 1870s and 1880s.

2. **Bystritsky A, Korb AS, Douglas PK, Cohen MS, Melega WP, Mulgaonkar AP, et al. A review of low-intensity focused ultrasound pulsation. *Brain Stimul.* 2011;4(3):125-36.**

<http://www.ncbi.nlm.nih.gov/pubmed/21777872>

**Abstract** With the recent approval by the Food and Drug Administration (FDA) of Deep Brain Stimulation (DBS) for Parkinson's Disease, dystonia and obsessive compulsive disorder (OCD), vagus nerve stimulation (VNS) for epilepsy and depression, and repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression, neuromodulation has become increasingly relevant to clinical research. However, these techniques have significant drawbacks (eg, lack of special specificity and depth for the rTMS, and invasiveness and cumbersome maintenance for DBS). This article reviews the background, rationale, and pilot studies to date, using a new brain stimulation method-low-intensity focused ultrasound pulsation (LIFUP). The ability of ultrasound to be focused noninvasively through the skull anywhere within the brain, together with concurrent imaging (ie, functional magnetic resonance imaging [fMRI]) techniques, may create a role for research and clinical use of LIFUP. This technique is still in preclinical testing and needs to be assessed thoroughly before being advanced to clinical trials. In this study, we review over 50 years of research data on the use of focused ultrasound (FUS) in neuronal tissue and live brain, and propose novel applications of this noninvasive neuromodulation method.

3. **Oluigbo CO, Rezai AR. Addressing neurological disorders with neuromodulation. *IEEE Trans Biomed Eng.* 2011;58(7):1907-17.**

<http://www.ncbi.nlm.nih.gov/pubmed/21193369>

<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=5678632>

**Abstract** Neurological disorders are becoming increasingly common in developed countries as a result of the aging population. In spite of medications, these disorders can result in progressive loss of function as well as chronic physical, cognitive, and emotional disability that ultimately places enormous emotional and economic on the patient, caretakers, and the society in general. Neuromodulation is emerging as a therapeutic option in these patients. Neuromodulation is a field, which involves implantable devices that allow for the reversible adjustable application of electrical, chemical, or biological agents to the central or peripheral nervous system with the objective of altering its functioning with the objective of achieving a therapeutic or clinically beneficial effect. It is a rapidly evolving field that brings together many different specialties in the fields of medicine, materials science, computer science and technology, biomedical, and neural engineering as well as the surgical or interventional specialties. It has multiple current and emerging indications, and an enormous potential for growth. The main challenges before it are in the need for effective collaboration between engineers, basic scientists, and clinicians to develop innovations that address specific problems resulting in new devices and clinical applications.

**Review Articles - Vagus Nerve**

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1. **Ruffoli R, Giorgi FS, Pizzanelli C, Murri L, Paparelli A, Fornai F. The chemical neuroanatomy of vagus nerve stimulation. *J Chem Neuroanat.* 2011;42(4):288-96.**

<http://www.ncbi.nlm.nih.gov/pubmed/21167932>

**Abstract** In this short overview a reappraisal of the anatomical connections of vagal afferents is reported. The manuscript moves from classic neuroanatomy to review details of vagus nerve anatomy which are now becoming more and more relevant for clinical outcomes (i.e. the therapeutic use of vagus nerve stimulation). In drawing such an updated odology of central vagal connections the anatomical basis subserving the neurochemical effects of vagal stimulation are addressed. In detail, apart from the thalamic projection of central vagal afferents, the monoaminergic systems appear to play a pivotal role. Stemming from the chemical neuroanatomy of monoamines such as serotonin and norepinephrine the widespread effects of vagal stimulation on cerebral cortical activity are better elucidated. This refers both to the antiepileptic effects and most recently to the beneficial effects of vagal stimulation in mood and cognitive disorders.

2. **Cullingford T. The vagus nerve--a common route for epilepsy therapies? *Lancet Neurol.* 2004;3(9):518; discussion 518.**

<http://www.ncbi.nlm.nih.gov/pubmed/15324719>

**Review Articles - VNS in Epilepsy**

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1. **Kawai K. [Vagus nerve stimulation therapy for epilepsy]. *Brain Nerve.* 2011;63(4):331-46. <http://www.ncbi.nlm.nih.gov/pubmed/21441636>**  
**Abstract** Vagus nerve stimulation is a palliative treatment for medically intractable epilepsy. This treatment reduces the frequency and severity of seizures refractory to antiepileptic drugs. Implanted generator and helical electrodes electrically stimulate the left vagus nerve at the neck chronically and intermittently. This was the first electrostimulation therapy clinically introduced for epilepsy. This treatment approach is supported by randomized double-blind trials even though the anti-seizure effect of vagus nerve stimulation is palliative and not curative. In Western countries, particularly the United States, this therapy has become an important alternative treatment for a subpopulation of patients with drug-resistant seizures who are not good candidates for craniotomy. In Japan, vagus nerve stimulation therapy was finally approved in January 2010 and has been covered by public health insurance since July 2010. Here, the author reviews the history, efficacy, and safety of this treatment, surgical anatomy and physiology of the vagus nerve, and the putative mechanisms underlying inhibition of epileptic seizures and accompanying effect on the central nervous system. Further experimental and clinical studies regarding this treatment approach are required to elucidate the detailed mechanism of action, to clarify the predicting factors of favorable outcome, and to scientifically confirm the anti-seizure effect in children and in generalized seizures and the efficacy in improvement of cognitive function, development, and quality of life.
  
2. **Poukas VS, Pollard JR, Anderson CT. Rescue therapies for seizures. *Curr Neurol Neurosci Rep.* 2011;11(4):418-22. <http://www.ncbi.nlm.nih.gov/pubmed/21509498>  
<http://link.springer.com/article/10.1007%2Fs11910-011-0207-x>**  
**Abstract** Most medical therapies for epilepsy consist of daily (or multiple-daily) dose, fixed-schedule, pharmacologic oral agents. Despite adherence, many patients continue to experience seizures. Various products have been discovered, designed, and marketed to serve as seizure-abortant therapies. These agents can be administered rapidly, as a "rescue" therapy, once a clinical seizure or cluster of seizures starts. Rescue medications are given as needed in an attempt to disrupt progression of a given seizure, and forestall what would otherwise be a more prolonged or more severe clinical event. Seizure-abortants also serve to aid in the management of seizure emergencies, such as prolonged, repetitive seizures, or status epilepticus. These compounds are not appropriate for all patients. Nevertheless, they do provide therapeutic benefit to several groups of patients: 1) those who perceive the onset of their seizures and have time to perform a self-intervention, 2) patients' caregivers who administer the therapy when they witness the onset of an ictal event, and 3) patients who are in the midst of an out-of-the-hospital seizure emergency (a seizure cluster or status epilepticus). In this article we will review currently available and future rescue therapies for seizures: US Food and Drug Administration (FDA) approved and FDA nonapproved drugs, nonpharmacologic behavioral treatments, the vagus nerve stimulator and the NeuroPace RNS(R) System (Mountain View, CA).

3. **Kawai K, Usami K, Saito N. [Vagus nerve stimulation for epilepsy]. *Rinsho Shinkeigaku*. 2011;51(11):990-2. Japanese.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22277453>  
**Abstract** Vagus nerve stimulation is the first electrical stimulation therapy for epilepsy. While its clinical use was approved by the European Union in 1994 and by the United States in 1997, it was approved last year and coverage by public insurance started last July in Japan. Owing to less invasiveness and broad indication, it is expected that vagus nerve stimulation will be increasingly used in Japan as well. Its efficacy for refractory partial seizures in patients older than 13 years was validated by two randomized control trials. Although it has been used for children and generalized seizures broadly, the efficacy for these subpopulations of patients has not been validated by randomized control trials, necessitating those studies in the near future. Afferent neural impulses generated by vagus nerve stimulation transmit to the solitary tract nucleus, then via multiple pathways including the monoamine system, vagus nerve stimulation affects the excitability of the cortical neurons. It likely exerts the anti-epileptic and anti-seizure effects using these pathways, but the detailed mechanisms underlying the effect remains to be elucidated further in future.
  
4. **Vagus nerve stimulation for epilepsy. *Drug Ther Bull*. 2010;48(4):42-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20392780>  
<http://dtb.bmj.com/content/48/4/42.long>  
**Abstract** In the UK, around 0.5-1% of the population have epilepsy,<sup>1</sup> and seizures remain uncontrolled in up to 50% of all people with the condition,<sup>2</sup> which can have a significant impact on work, family and social life.<sup>2</sup> Vagus nerve stimulation is now being used in both adults and children for epilepsy that is refractory to medical treatment.<sup>3-7</sup> Worldwide, over 52,000 patients have been treated with such a device. Here we examine the place of vagus nerve stimulation therapy in the management of people with epilepsy.
  
5. **Hansen CP, Sidenius P, Gyllenborg J, Uldall P, Erdal J, Hansen LK. [Epilepsy treatment by vagus nerve stimulation]. *Ugeskr Laeger*. 2010;172(45):3110-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21055380>  
**Abstract** Epilepsy is a common neurological disorder, and between one fourth and one third of the patients do not obtain seizure freedom after treatment with antiepileptic drugs. If the epileptic seizures in such patients have severe consequences, the patients should be assessed for epilepsy surgery. In case epilepsy surgery is not feasible, vagus nerve stimulation (VNS) should be offered. VNS seems to have an effect in all epilepsy syndromes and seizure types. VNS is generally well-tolerated, and may even improve mood and quality of life. Many more epilepsy patients in Denmark should be offered VNS.
  
6. **Vonck K, De Herdt V, Boon P. Vagal nerve stimulation--a 15-year survey of an established treatment modality in epilepsy surgery. *Adv Tech Stand Neurosurg*. 2009;34:111-46.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19368083>  
**Abstract** Neurostimulation is an emerging treatment for neurological diseases. Electrical stimulation of the tenth cranial nerve or vagus nerve stimulation (VNS) has become a valuable option in the therapeutic armamentarium for patients with refractory epilepsy. It is indicated in patients with refractory epilepsy who are unsuitable candidates for epilepsy surgery or who have had insufficient benefit from such a treatment. Vagus nerve stimulation reduces seizure frequency with > 50% in 1/3 of patients and has a mild side effects profile. Research to elucidate the mechanism of action of vagus nerve stimulation has shown that effective stimulation in humans is primarily mediated by afferent vagal A- and B-fibers. Crucial brainstem and intracranial structures include the locus coeruleus, the nucleus of the solitary tract, the thalamus and limbic structures. Neurotransmitters playing a role may involve the major inhibitory neurotransmitter GABA but also serotonergic and adrenergic systems. This manuscript reviews the clinical studies investigating efficacy and side effects in patients and the experimental studies aiming to elucidate the mechanisms of action.

- 7. Ramani R. Vagus nerve stimulation therapy for seizures. *J Neurosurg Anesthesiol.* 2008;20(1):29-35. <http://www.ncbi.nlm.nih.gov/pubmed/18157022>**  
**Abstract** Of the 3 million patients with seizures in North America approximately 70% have effective seizure control with medications. In the group refractory to medical treatment only a minority fit the criteria for surgical therapy. Vagus nerve stimulation therapy seems to be a suitable nonpharmacologic therapy for reducing seizure frequency in these cases. It is a simple device with 2 electrodes and an anchor loop implanted on the midcervical portion of left vagus nerve and the impulse generator is implanted subcutaneously in the left infraclavicular region. The left vagus is the preferred site as the right vagus innervates the sinoatrial node and influences the heart rate. Data from laboratory studies suggest that it most probably works by increasing the release of norepinephrine in the locus ceruleus, which in turn increases the seizure threshold. More than 32,000 devices have been implanted since it was approved in 1997. There is class I evidence that vagus nerve stimulator reduces the frequency of seizures. In addition it also elevates the patients' mood-independent of seizure control. In one of the studies 50% reduction in seizure frequency was 37% in the first year and 44% in the second and third year. The side effects commonly reported are constriction in the throat, change in voice, and throat pain which most patients are able to tolerate and continue the use of the device. In conclusion VNS seems to be an effective nonpharmacologic therapy for medically refractory partial onset seizures.
- 8. Garcia-March G, Sanchez-Ledesma MJ, Broseta J. [Vagus nerve stimulation for the treatment of refractory epilepsy. State of the art]. *Neurocirugia (Astur).* 2008;19(5):416-26. Spanish. <http://www.ncbi.nlm.nih.gov/pubmed/18936858>**  
**Abstract** The vagus nerve stimulation (VNS) therapy is a new neurostimulation technique used for treating pharmacoresistant epilepsy. It can be considered an effective and safe alternative for the treatment of refractory epilepsy patients. In the present review, we describe the surgical implantation technique, its indications and results achieved until now. We will also summarize the possible mechanisms of action of VNS therapy. Finally, we will comment on the difficulties and inconveniences that did not allow this antiepileptic surgical technique to become more widely used.
- 9. Atkinson PB, Labiner DM. Shocking the wandering nerve: Vagus nerve stimulation after a decade of widespread use. *Eur Neurol Rev.* 2007;1:14-16. <http://www.touchneurology.com/articles/shocking-wandering-nerve-vagus-nerve-stimulation-after-decade-widespread-use-0>**
- 10. Amar AP. Vagus nerve stimulation for the treatment of intractable epilepsy. *Expert Rev Neurother.* 2007;7(12):1763-73. <http://www.ncbi.nlm.nih.gov/pubmed/18052768>**  
**Abstract** Vagus nerve stimulation is a safe and reliable treatment adjunct for patients with medically intractable epilepsy. It is both a preventive and abortive form of therapy, potentially effective against both partial and generalized seizures in adults and children. Vagus nerve stimulation also has a number of serendipitous effects on mood, memory and attention, and has been approved for the treatment of refractory depression. Owing to its pleiotropic effects, it also holds promise for several other diseases. Its principal limitations are its unknown mechanism of action, the low likelihood of complete cure and the inability to predict which patients will derive substantial benefit. This article reviews the theoretical rationale, practical background and clinical applications of vagus nerve stimulation therapy.

11. **Tecoma ES, Iragui VJ. Vagus nerve stimulation use and effect in epilepsy: what have we learned? *Epilepsy Behav.* 2006;8(1):127-36.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16376157>  
**Abstract** Vagus nerve stimulation (VNS) for epilepsy has been available in the United States for 8 years. Pivotal randomized, blinded clinical trials leading to FDA approval in patients age 12 and older with refractory partial seizures have not been performed for other age groups or epilepsy syndromes. This practical review takes stock of the current information about VNS use and efficacy in various types of epilepsy. We review the evidence for commonly used stimulation parameters, end of battery life, predictors of response including duration of epilepsy, seizure type/epilepsy syndrome, bihemispheric seizures, age at implant, and prior cranial surgery. We review adverse events and VNS effects on respiratory patterns, cardiac function, and mood and behavior. With the recent U.S. approval of VNS for treatment-resistant depression, we anticipate that lessons learned from treating patients with epilepsy will be useful to physicians using VNS to treat patients with depression and possibly other conditions.
12. **Helmers SL, Holmes MD. Vagus nerve stimulation: History and overview. In: Miller JW, Silbergeld DL, Eds. *Epilepsy Surgery: Principles and Controversies*. New York, NY: Taylor & Francis; 2006:597-607.**
13. **Murphy JV, Patil AA. Improving the lives of patients with medically refractory epilepsy by electrical stimulation of the nervous system. *Expert Rev Med Devices.* 2005;2(2):175-89.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16293054>  
<http://www.expert-reviews.com/doi/pdfplus/10.1586/17434440.2.2.175>  
**Abstract** Vagal nerve stimulation proved effective in animal models of epilepsy, and in open and double-blinded trials, in over 450 patients. Seizure reduction improved for at least 2 years. Almost 50% of treated patients achieve at least a 50% reduction in seizure frequency. Other advantages include termination of a seizure and improved alertness. Benefits were demonstrated in children, partial and generalized epilepsies, and in specific neurologic syndromes.
14. **Biraben A, Stefani C. [Vagal nerve stimulation as a treatment of epilepsy]. *Rev Neurol (Paris)*. 2005;161(1):128-32. French.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15678011>  
**Abstract** INTRODUCTION: Vagus nerve stimulation (VNS) is a non-pharmacological treatment for drug resistant epilepsy. STATE OF ART: The good efficacy and tolerability of this device is now well established after several controlled studies, and more than 17000 people operated on in different countries. The physiology of VNS is not yet well known, and the potential mechanisms of action are reviewed. VNS seems to be as efficient as a new medication without some of the disadvantages (in case of pregnancy for example). SNV may have a beneficial effect for all kinds of drug-resistant epilepsy. PERSPECTIVES: Better knowledge of the underlying anti-epileptic mechanisms may help to select the better responders to this expensive anti-epileptic tool.
15. **Guberman A. Vagus nerve stimulation in the treatment of epilepsy. *CMAJ.* 2004;171(10):1165-6.** <http://www.ncbi.nlm.nih.gov/pubmed/15534307>

16. **Wheless JW, Baumgartner J. Vagus nerve stimulation therapy. *Drugs Today (Barc)*. 2004;40(6):501-15. <http://www.ncbi.nlm.nih.gov/pubmed/15349130>**  
**Abstract** Until recently, antiepileptic drugs and traditional epilepsy surgery were the two primary treatment options available to patients with epilepsy. Drug therapy, however, does not always control seizures and can be associated with negative side effects. Additionally, only a minority of patients are candidates for epilepsy surgery. Vagus nerve stimulation (VNS) therapy, approved by the US FDA in 1997, is now a treatment option that is effective in reducing seizure frequency and severity as well as improving patient quality of life without the pharmacological side effects associated with traditional antiepileptic drugs. Provided here is an overview of VNS therapy and the VNS therapy system, including the history of vagal nerve stimulation, patient selection guidelines and new indications currently under investigation for this novel therapy.
17. **Kernich CA. Patient and family fact sheet. Vagus nerve stimulation. *Neurologist*. 2004;10(1):57-8. <http://www.ncbi.nlm.nih.gov/pubmed/14720316>**  
**Notes** This short letter is directed towards epilepsy patients and their families and outlines the basics of VNS therapy. A brief history of the treatment, the indication, the costs, and a general outline of how the device is implanted are provided. General details of the therapy, including common side effects and response rates, also are listed.
18. **Salinsky MC. Vagus nerve stimulation as treatment for epileptic seizures. *Curr Treat Options Neurol*. 2003;5(2):111-20. <http://www.ncbi.nlm.nih.gov/pubmed/12628060>**  
**Notes** Salinsky reviews the efficacy and side effects of VNS Therapy for the treatment of epilepsy in the context of the Class I and Class III evidence. Clinical trials, special populations, long-term use, stimulus parameters, and cost effectiveness of the treatment are all discussed.  
**Abstract** Vagus nerve stimulation is a unique therapy for epileptic seizures. Two randomized controlled trials in patients with medically refractory partial seizures have demonstrated efficacy, leading to US Food and Drug Administration approval of vagus nerve stimulation therapy in 1997. Extensive safety testing has not revealed significant effects on cardiac, respiratory, or gastrointestinal function, though recent reports of intraoperative asystole and sleep-related airway obstruction have raised concerns. Vagus nerve stimulation is indicated for adjunctive therapy of partial-onset seizures in children and individuals older than 12 years (Class I evidence). Based on controlled, randomized trials, approximately 30% of these patients can be expected to have at least a 50% decrease in overall seizure frequency. Vagus nerve stimulation efficacy is similar to that of several newer antiepileptic drugs when used in similar populations in controlled, randomized trials. Long-term follow-up studies suggest continued efficacy over more than 1 year (Class III evidence). Case series suggest similar or greater efficacy in younger children, and in patients with refractory generalized seizures, including those associated with the Lennox-Gastaut syndrome (Class III evidence). Vagus nerve stimulation is appropriate therapy for patients with medically refractory epileptic seizures who are not optimal candidates for resective epilepsy surgery.
19. **Romano CJ. Another option for seizure control. *Neurol Rev*. 2003;9.**
20. **Upton A. Vagal stimulation for intractable seizures. *Adv Exp Med Biol*. 2002;497:233-9. <http://www.ncbi.nlm.nih.gov/pubmed/11993736>**  
**Abstract** Vagal stimulation has recently been approved for use in North America. Dr. Upton discusses the findings of a study conducted at the McMaster Medical Centre.

21. **Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet Neurol.* 2002;1(8):477-82.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12849332>  
**Abstract** Vagus-nerve stimulation (VNS) is now an accepted treatment for patients with refractory epilepsy. There have been many studies suggesting that VNS affects the brain in such areas as the thalamus and other limbic structures. In addition, there is some evidence that norepinephrine is important in the prophylactic antiseizure effects of VNS. The efficacy of VNS has been established for partial seizure types, even in refractory patients who did not respond to surgical treatment for epilepsy. There are also data, from open-label studies, that suggest efficacy in other seizure types. Therefore, VNS seems to be a broad-spectrum treatment for epilepsy. Improvement is not immediate but increases over 18-24 months of treatment. Most studies report subjective improvements in various quality-of-life measurements during treatment with VNS--objective trials have confirmed this observation. Side-effects are mainly stimulation related and reversible and they tend to decrease over time. They are generally mild to moderate and seldom necessitate the removal of the device. No idiosyncratic side-effects have been reported in 12 years of experience, and VNS does not interact with antiepileptic drugs. Most adverse events are predictable and related to the specific stimulation regimen. VNS does not have cognitive and systemic side-effects and can, therefore, be a valuable treatment approach even for patients who have poor tolerance of antiepileptic drugs.
22. **Schachter SC. Vagus nerve stimulation therapy summary: five years after FDA approval. *Neurology.* 2002;59(6 Suppl 4):S15-20.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12270963>  
**Abstract** With more than 16,000 patients implanted with the vagus nerve stimulation (VNS) therapy system (Cyberonics, Inc., Houston, Texas), VNS therapy has assumed an increasingly important role in the treatment of medically refractory seizures since its approval 5 years ago by the United States FDA. This review discusses the clinical trials that provided evidence for the approval, long-term efficacy, efficacy in special populations and co-morbid conditions, and safety and tolerability. Additional studies are suggested to further explore the capabilities of VNS therapy.
23. **Iriarte J, Urrestarazu E, D Lz, Schlumberger E. [Vagal stimulation in the treatment of epilepsy]. *Rev Neurol.* 2002;34(6):511-8. Spanish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12040494>  
**Abstract** INTRODUCTION: The vagal nerve stimulation is a new technique for the treatment of drug resistant epilepsies. DEVELOPMENT: In 1997, it was approved in United States by the FDA to be used in adults with refractory focal epilepsies not candidates for epilepsy surgery. Its mechanism of action is unknown. The results in the controlled studies indicated a decrease of 30 50% in the seizure frequency in around 50% of the patients. Although more experience is needed to corroborate these results, it seems reasonable as a treatment for patients with difficult epilepsies, especially when the response to the antiepileptic drugs is poor or they are producing secondary effects, and the resection of the focus is not possible.

24. **Schmidt D. Vagus nerve stimulation for the treatment of epilepsy. *Epilepsy Behav.* 2001;2(3 Suppl):S1-S5.**  
<http://www.sciencedirect.com/science/article/pii/S1525505001902148>  
**Abstract** Vagus nerve stimulation (VNS) is a neurostimulation procedure similar in efficacy to the newer antiepileptic drugs (AEDs) for patients with partial seizures whose seizures cannot be treated effectively with existing AEDs or resective epilepsy surgery. VNS refers to stimulation of the left vagus nerve with the NeuroCybernetic Prosthesis (NCP, Cyberonics, Inc.). It involves surgical implantation of the generator and subcutaneous lead, and connection of the lead to the cervical vagus nerve. The anticonvulsant mechanism of VNS remains elusive. In patients with refractory partial epilepsy enrolled in clinical trials, VNS facilitated 50% seizure reduction in approximately 50% of patients. In some patients, VNS appears to lessen seizure severity, abort seizures with on-demand stimulation, and improve mood and alertness. VNS is safe and well tolerated. During stimulation, mild to moderate voice changes and exertional dyspnea may occur.
25. **Boon PA. Vagus nerve stimulation for refractory epilepsy. *J Clin Neurophysiol.* 2001;18(5):393.** <http://www.ncbi.nlm.nih.gov/pubmed/11709642>
26. **Chadwick D. Vagal-nerve stimulation for epilepsy. *Lancet.* 2001;357(9270):1726-7.** <http://www.ncbi.nlm.nih.gov/pubmed/11403805>
27. **Chayasirisobhon S, Koulouris S, Parker E. Vagus nerve stimulation for refractory epilepsy. *The Permanente Journal.* 2001;5(4):21-26.**  
<http://xnet.kp.org/permanentejournal/Fall01/vagus.html>  
**Abstract** Context: Vagus nerve stimulation (VNS) is a relatively new treatment for epilepsy. Past studies have proposed that the antiepileptic action is related to the effect on the brainstem reticular activating system, and is mediated largely by the widespread release of two inhibitory agents (gamma aminobutyric acid [GABA] and glycine). Objective: To confirm the safety and efficacy of vagus nerve stimulation in postmarketing clinical practice. Design: Prospective case series. Intervention: Implantation of a device for vagus nerve stimulation (the NeuroCybernetic Prosthesis (NCP) system) in 24 patients with refractory epilepsy and monitoring their condition for six months. Main outcome measures: Frequency and type of postoperative seizures. Methods: Under general anesthesia, the Neurocybernetic Prosthesis was implanted in subcutaneous tissue on the upper left side of the chest by a neurosurgeon. Antiepileptic drug dosages were stable before patients entered the study and were not changed or adjusted during the six-month study period. The patients were evaluated with the Quality of Life in Epilepsy Inventory (QOLIE-10). Results: During the six-month study period, 14 patients had partial seizures with and without generalized seizures; 10 patients had multiple types of generalized seizures. Of the 24 patients, 15 (62.5%) had > 50% reduction in seizure frequency after NCP implantation; eight of those 15 patients had > 90% reduction in seizure frequency. Nine (37.5%) of the original 24 patients showed no clinically significant benefit. The seizure types that responded best to VNS were atonic, tonic, and generalized tonic-clonic. Partial seizure showed moderate response. Partial complex seizure showed the least response to VNS. No patients were completely without seizures at the six-month follow-up period. In general, the patients were more alert, in a better mood, and better able to concentrate. Two patients had vocal cord paralysis during NCP implantation but gradually recovered vocal function within a few months. Conclusion: This study in a large HMO, with an integrated delivery system, supports the safety and demonstrates significant efficacy of vagus nerve stimulation for treatment of medically refractory epilepsy.

28. **Sadzot B, Martin D. [How I treat ... refractory epilepsy by vagal nerve stimulation]. *Rev Med Liege.* 2001;56(6):407-10. French.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11496718>  
**Abstract** Intermittent left vagus nerve stimulation is a novel therapeutic modality that can be proposed to patients with a refractory epilepsy and for whom resective surgery is not an option. Its precise mechanism of action is not known. Controlled studies have shown that its efficacy is similar to that of antiepileptic drugs: 50% decrease in seizure frequency in 40% patients after two years. Side effects which are generally mild to moderate are the result of a diffusion of the stimulation to the larynx. No CNS side effect has been reported.
29. **Boon P, Vonck K, De Reuck J, Caemaert J. Vagus nerve stimulation for refractory epilepsy. *Seizure.* 2001;10(6):448-55.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11701002>  
[http://ac.els-cdn.com/S1059131101906260/1-s2.0-S1059131101906260-main.pdf?\\_tid=7d2c52dc-8d9c-11e2-8194-00000aab0f01&acdnat=1363371582\\_6c8c6f10de4f28b9573e85df4e539ff2](http://ac.els-cdn.com/S1059131101906260/1-s2.0-S1059131101906260-main.pdf?_tid=7d2c52dc-8d9c-11e2-8194-00000aab0f01&acdnat=1363371582_6c8c6f10de4f28b9573e85df4e539ff2)  
**Abstract** Vagus nerve stimulation (VNS) is a neurophysiological treatment for patients with medically or surgically refractory epilepsy. Since the first human implant in 1989, more than 10 000 patients have been treated with VNS. Two randomized controlled studies have shown a statistically significant decrease in seizure frequency during a 12-week treatment period versus a baseline period when 'high stimulation' mode was compared with 'low stimulation' mode. The efficacy appears to increase over time. In general, one third of the patients show a >50% reduction of seizure frequency; one third show a 30-50% seizure reduction, and one third of patients show no response. Few patients become seizure-free. Side effects during stimulation are mainly voice alteration, coughing, throat paraesthesia and discomfort. When studied on a long-term basis, VNS is an efficacious, safe and cost-effective treatment not only in adults but also in children and the elderly. The precise mechanism of action remains to be elucidated. In recent years much progress has been made through neurophysiological, neuroanatomical, neurochemical and cerebral blood flow studies in animals and patients treated with VNS. Further elucidation of the mechanism of action of VNS may increase its clinical efficacy and our general understanding of some physiopathological aspects of epilepsy. Finally, VNS may become an alternative treatment for other conditions such as depression and pain.
30. **Wheless JW. Vagus nerve stimulation. In: Wyllie E, Ed. *Treatment of Epilepsy. Principles and Practice.* Philadelphia, PA: Lippincott Williams & Wilkins; 2001:1007-15.**

31. **Uthman BM. Vagus nerve stimulation for seizures. *Arch Med Res.* 2000;31(3):300-3. <http://www.ncbi.nlm.nih.gov/pubmed/11036181>**  
**Abstract** It is agreed that 1% of the general population is afflicted with epilepsy and close to 30% of epilepsy patients are intractable to medications. In spite of a recent increase in the number of new medications that are available on the market, many patients continue to have seizures or their seizures are controlled at the expense of intolerable side effects. Resection epilepsy surgery is an alternative; however, not every intractable patient is a good candidate for this surgery. Additionally, it is only offered to a small fraction of these patients due to the lack of an adequate number of comprehensive epilepsy programs and financial support for such surgeries. Vagus nerve stimulation (VNS) is a novel adjunctive therapy that has recently become commercially available for intractable epilepsy. It is indicated as an add-on treatment for seizures of partial onset with or without secondary generalization in patients 12 years of age or older. The VNS system is comprised of a battery generator that delivers regular intermittent electrical stimuli programmed via menu-driven software and an interrogating wand. The generator is implanted in the left upper chest and connected to the left cervical vagus nerve via a pair of semi-circular helical electrodes wound around the vagus nerve and wires tunneled under the skin. Surgery is normally completed within 2 h under general anesthesia and the patient can go home within a few hours postoperatively. Experiments in humans began in 1988 with two single-blind pilot studies that demonstrated the feasibility and safety of this unconventional therapy. Following these studies, two multicenter, active-control, parallel, double-blind protocols showed a statistically significant reduction in partial onset seizures with reasonable and well-tolerated side effects. Adverse events related to VNS included voice alteration and a tingling sensation in the throat during stimulation only and a decrease in intensity over several weeks. Coughing during stimulation occurred normally when therapy was initiated and shortness of breath occurred mainly during exertion. Long-term follow-up suggests that reduction in seizure frequency and intensity is maintained over time. VNS is a novel adjunctive anti-epilepsy therapy that offers patients a better-tolerated option than medications in general and that is less invasive and extensive than resection surgery. Its efficacy may compare to novel potent anti-epilepsy drugs; however, VNS does not replace resection epilepsy surgery in selected patients in whom chances of seizure-free results are high (70-90%).
32. **Vagus nerve stimulation for epilepsy. *Clin Privil White Pap.* 2000(31):1-8. <http://www.ncbi.nlm.nih.gov/pubmed/11067712>**

33. **Binnie CD. Vagus nerve stimulation for epilepsy: a review. *Seizure*. 2000;9(3):161-9. <http://www.ncbi.nlm.nih.gov/pubmed/10775511>**  
**Abstract** Vagus nerve stimulation is an empirically based method for treatment of epilepsy by repeated stimulation of the left vagus nerve through implanted electrodes. Despite studies in animals and man, which show changes in brain electrophysiology, metabolism and neurochemistry, the mode of action remains unknown. Clinical testing has presented methodological challenges, as it is difficult to assess under double blind conditions a treatment which requires surgery and produces a sensation every time the stimulator comes on. This has nevertheless been successfully addressed in parallel design, controlled trials comparing high and low stimulation schedules. These have been performed in adults with medically intractable partial seizures, and demonstrated efficacy, safety and good tolerability. Efficacy, both in the controlled trials and in numerous reports arising from the considerable post-marketing experience is modest. Some 30% of patients achieve a 50% seizure reduction after 3 months of treatment, but this proportion progressively increases to about 50% after 18 months. Side-effects comprise: discomfort in the face or neck when the stimulator is activated, coughing, breathlessness on exertion and hoarseness of voice. All are related to intensity of stimulation and rapidly habituate in most subjects. In those patients who respond, a stimulus level can therefore generally be found which is acceptable to the subject. No indication other than refractory partial seizures in adults has been the subject of controlled trials, but post-marketing experience and uncontrolled reports indicate comparable efficacy and safety in a wide range of epilepsies, partial and generalized, idiopathic, cryptogenic, or symptomatic, in patients of all ages.
34. **Nerve stimulator useful in treating epilepsy. *Mayo Clin Health Lett*. 1999;17(8):4. <http://www.ncbi.nlm.nih.gov/pubmed/10487156>**
35. **Amar AP, Heck CN, DeGiorgio CM, Apuzzo ML. Experience with vagus nerve stimulation for intractable epilepsy: some questions and answers. *Neurol Med Chir (Tokyo)*. 1999;39(7):489-95. <http://www.ncbi.nlm.nih.gov/pubmed/10437376>**  
**Abstract** Vagus nerve stimulation (VNS) is gaining increasing popularity and credibility as a treatment option for patients with intractable epilepsy. VNS is a relatively recent innovation, however, and like many other incipient developments, it has engendered a number of unresolved controversies and perplexities. Limitations in our current understanding of how VNS works lie at the crux of these uncertainties. In this article, we present our clinical experience with VNS and review the fundamental issue which remain unsettled, such as the mechanism of VNS action, the factors underlying variability in patient outcome, and the selection of ideal candidates for VNS therapy. Although many enigmas persist, VNS has proven to be a safe, feasible, and potentially effective method of reducing seizures in select patient populations. It offers several advantages over extant treatments and, as a result, holds much promise for future therapy of medically refractory epilepsy.

36. **Alvarez LA, Dean P, Jayakar P, Duchowny M, Resnick T, Dunoyer C, et al. [Epilepsy treatment by vagal stimulation]. *Rev Neurol.* 1999;29(4):385-7. Spanish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10797931>  
**Abstract** INTRODUCTION: Vagal nerve stimulation is the latest therapeutic modality for the treatment of epilepsy. It consists of a lead implanted in the left vagal nerve which is connected to a subcutaneous stimulator implanted in the left axillary or pectoral region. DEVELOPMENT: The stimulator is programmed to intermittently stimulate the vagal nerve throughout the day and a magnet also allows the patient to control the stimulation from the outside. This treatment has been used in patients with intractable partial seizures who are not candidates for epilepsy surgery. The results reported have varied but in general the procedure appears promising with at least 50% of the implanted having over 50% improvement in their seizure frequency and many having complete control without significant side effects. CONCLUSION: Further review of the results are still needed to fully determine the true value of this treatment and to identify the subgroups of patients which will benefit the most.
37. **Ben-Menachem E. Vagus nerve stimulation for treatment of seizures? *Arch Neurol.* 1998;55(2):231-2; comment 234.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9482365>  
<http://archneur.jamanetwork.com/article.aspx?articleid=773559>
38. **McLachlan RS. Vagus nerve stimulation for treatment of seizures? *Arch Neurol.* 1998;55(2):232-3; comment 234.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9482366>  
<http://archneur.jamanetwork.com/article.aspx?articleid=773560>
39. **Schachter SC, Saper CB. Vagus nerve stimulation. *Epilepsia.* 1998;39(7):677-86.** <http://www.ncbi.nlm.nih.gov/pubmed/9670894>  
**Notes** Most comprehensive and accurate summary of VNS therapy when published and concludes that adjunctive VNS is safe, effective, and FDA approved for adults and adolescents with partial seizures. He notes that encouraging results also are seen among pediatric patients and patients with generalized seizures. Also notes that side effects are generally of mild to moderate severity and almost always disappear after the stimulation settings are adjusted. Therapeutic benefits last over time. This is the first paper to support MRI and mentions that MRI testing is safe.  
**Abstract** Left vagus nerve stimulation (VNS) is a promising new treatment for epilepsy. In 1997, VNS was approved in the United States as an adjunctive treatment for medically refractory partial-onset seizures in adults and adolescents. For some patients with partial-onset seizures, the adverse effects of antiepileptic drugs (AEDs) are intolerable; for others, no single AED or combination of anticonvulsant agents is effective. Cerebral resective surgery is an option to pharmacotherapy in some cases, but many patients with partial-onset seizures are not optimal candidates for intracranial surgery. VNS entails implantation of a programmable signal generator--the Neuro-cybernetic Prosthesis (NCP)--in the chest cavity. The stimulating electrodes of the NCP carry electrical signals from the generator to the left vagus nerve. Although the mechanism of action of VNS is not known, controlled studies have shown that it is safe and well-tolerated by patients with long-standing partial-onset epilepsy. Side effects, which are generally of mild to moderate severity, almost always disappear after the stimulation settings are adjusted. Encouraging results have also been reported in pediatric patients.

40. **Snively C, Counsell C, Lilly D. Vagus nerve stimulator as a treatment for intractable epilepsy. *J Neurosci Nurs.* 1998;30(5):286-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9816559>  
**Abstract** Vagus nerve stimulation was recently approved for control of medically intractable seizures. This therapy provides some relief of seizures for selective patients, however seizure freedom using this device is uncommon. Vagus nerve stimulation appears to work by calming "hyperexcited" nerve cells and reverting brain activity to its normal patterns. Many people do have significant relief in the intensity and duration of their seizures and report improved quality of life using this device.
41. **Henry TR. 10 most commonly asked questions about vagus nerve stimulation for epilepsy. *Neurologist.* 1998;4(5):284-90.**  
[http://journals.lww.com/theneurologist/Citation/1998/09000/10\\_Most\\_Commonly\\_Asked\\_Questions\\_About\\_Vagus\\_Nerve.5.aspx](http://journals.lww.com/theneurologist/Citation/1998/09000/10_Most_Commonly_Asked_Questions_About_Vagus_Nerve.5.aspx)
42. **Schachter SC. Vagus nerve stimulation: current status and clinical applications. *Expert Opin Investig Drugs.* 1997;6(10):1327-35.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15989504>  
<http://www.ingentaconnect.com/content/apl/eid/1997/00000006/00000010/art00002?token=004412f0dc41333c4a2f7a3f6a4d572b4652233f3b444f6d6222346b626876305021>  
**Abstract** Despite the recent introduction of new anti-epileptic drugs (AEDs), many patients with epilepsy, especially those with partial-onset seizures, continue to have seizures that are refractory to pharmacotherapy. Other patients are unable to tolerate the side-effects of AEDs given singly or in combination. Cerebral resective surgery may be an option for a sub-group of these patients; however, many patients with refractory partial epilepsy are not optimal candidates for epilepsy surgery. Consequently, the introduction of left vagus nerve stimulation (VNS) for those patients who have been afflicted by seizures or medication side-effects has opened up a new, non-pharmacological approach to epilepsy treatment. The mechanism of action of VNS is uncertain. VNS exerts an anticonvulsant effect in a variety of animal seizure models; has no effect on hepatic metabolic processes, serum concentrations of AEDS, or laboratory values; and has no clinically significant effect on vagally-mediated physiological processes. VNS is safe and well-tolerated in patients with long-standing, medically-refractory, partial-onset epilepsy. Adverse effects are usually mild to moderate in severity and related to stimulation, and almost always resolve with adjustment in stimulation settings. Controlled studies of patients on AED therapy show that adjunctive VNS is effective for partial-onset seizures when given every 5 min for 30 s intervals. Results of studies in paediatric patients are encouraging.
43. **McLachlan RS. Vagus nerve stimulation for intractable epilepsy: a review. *J Clin Neurophysiol.* 1997;14(5):358-68.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9415383>  
**Abstract** Electrical stimulation of the vagus nerve in the neck by using a programmable stimulator similar to a cardiac pacemaker is being explored as a treatment for epilepsy. There is sound rationale based on studies of animal seizure models for pursuing this treatment modality, and early clinical trials provide support for efficacy in patients with intractable epilepsy at least equivalent to that of some of the new antiepileptic drugs. Safety and tolerability have been demonstrated in >800 patients worldwide since the first implant in 1988. Most of these had partial seizures for which resective epilepsy surgery was not feasible or had failed, but efficacy of vagal stimulation appears to be the same for both partial and generalized epilepsy. Specific selection criteria for this procedure have yet to be established, and further studies are warranted to determine whether vagal stimulation becomes an accepted procedure for epilepsy management.

44. **Ben-Menachem E. Modern management of epilepsy: Vagus nerve stimulation. *Baillieres Clin Neurol.* 1996;5(4):841-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9068884>  
**Abstract** Vagus nerve stimulation (VNS) was first tried as a treatment for seizure patients in 1988. The idea to stimulate the vagus nerve and disrupt or prevent seizures was proposed by Jacob Zabarra. He observed a consistent finding among several animal studies which indicated that stimulation of the vagus nerve could alter the brain wave patterns of the animals under study. His hypothesis formed the basis for the development of the vagus nerve stimulator, an implantable device similar to a pacemaker, which is implanted in the left chest and attached to the left vagus nerve via a stimulating lead. Once implanted, the stimulator is programmed by a physician to deliver regular stimulation 24 hours a day regardless of seizure activity. Patients can also activate extra 'on-demand' stimulation with a handheld magnet. Clinical studies have demonstrated VNS therapy to be a safe and effective mode of treatment when added to the existing regimen of severe, refractory patients with epilepsy. Efficacy ranges from seizure free to no response with the majority of patients (> 50%) reporting at least a 50% improvement in number of seizures after 1.5 years of treatment. The side-effect profile is unique and mostly includes stimulation-related sensations in the neck and throat. The mechanism of action for VNS is not clearly understood although two theories have emerged. First, the direct connection theory hypothesizes that the anticonvulsant action of VNS is caused by a threshold raising effect of the connections to the nucleus of the solitary tract and on to other structures. The second is the concept that chronic stimulation of the vagus nerve increases the amount of inhibitory neurotransmitters and decreases the amount of excitatory neurotransmitters. Additional research into the optimal use of VNS is ongoing. Animal and clinical research have produced some interesting new data suggesting there are numerous ways to improve the clinical performance of vagus nerve stimulation as a treatment for refractory patients.
45. **Shimizu H, Ishijima B, Nakamura K, Asakura T, Ohtsuki T, Yoshimoto T, et al. Effect of vagal stimulation on intractable epilepsy. *Psychiatry Clin Neurosci.* 1995;49(3):S254-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/8612162>
46. **Tarver WB, George RE, Maschino SE, Holder LK, Wernicke JF. Clinical experience with a helical bipolar stimulating lead. *Pacing Clin Electrophysiol.* 1992;15(10 Pt 2):1545-56.**  
<http://www.ncbi.nlm.nih.gov/pubmed/1383969>  
**Abstract** Over 100 patients have been treated for partial epilepsy using a NeuroCybernetic Prosthesis System (NCP). The NCP System is comprised of an implantable pulse generator, an implantable bipolar stimulating lead, and an external communication system. The lead delivers electrical impulses from the NCP Generator to the vagus nerve, and includes a connector end that plugs into the generator, a silicone insulated lead body, and the helical electrode array that attaches to the nerve. The surgical implantation technique has a significant impact on lead reliability and performance. The lead electrode has performed well to date. Modifications to further improve reliability have been implemented. Clinical experience, case history examples, and voltage measurements are examined. The lead electrode is an important component of the overall system and plays a significant part in the success of vagus nerve stimulation therapy.

47. **Terry RS, Tarver WB, Zabara J. The implantable neurocybernetic prosthesis system. *Pacing Clin Electrophysiol.* 1991;14(1):86-93.**  
<http://www.ncbi.nlm.nih.gov/pubmed/1705341>  
**Abstract** The neurocybernetic prosthesis system (NCP) is an implantable, multiprogrammable pulse generator that delivers constant current electrical signals to the vagus nerve for the purpose of reducing the frequency and severity of epileptic seizures. The signals are delivered on a predetermined schedule, or may be initiated by the patient with an external magnet. The device is implanted in a subcutaneous pocket in the chest just below the clavicle, similar to pacemaker placement. The stimulation signal is transmitted from the prosthesis to the vagus nerve through a lead connected to an electrode which is a multi-turn silicone helix, with a platinum band on the inner turn of one helix. The prosthesis can be programmed with any IBM-compatible personal computer using NCP software and a programming wand.
48. **Vagus nerve stimulation for the control of epilepsy. Proceedings of a symposium held in conjunction with the American Epilepsy Society annual meeting. Boston, Massachusetts, December 2, 1989. *Epilepsia.* 1990;31 Suppl 2:S1-60.**  
<http://www.ncbi.nlm.nih.gov/pubmed/2226361>
49. **Terry R, Tarver WB, Zabara J. An implantable neurocybernetic prosthesis system. *Epilepsia.* 1990;31 Suppl 2:S33-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/2226364>  
**Abstract** The neurocybernetic prosthesis (Cyberonics, Inc.) is an implantable, multiprogrammable pulse generator that delivers constant current electrical signals to the vagus nerve for the purpose of reducing the frequency and/or severity of epileptic seizures. The device is implanted in a subcutaneous chest pocket just below the clavicle, similar to cardiac pacemaker placement. The stimulation signal is transmitted from the prosthesis to the vagus nerve through a stimulation lead. The prosthesis can be programmed using any IBM-compatible personal computer with programming software and a programming wand. The electrodes used in the first group of patients were found to break at an unacceptable rate. Design modifications appear to have resolved this problem.

**Review Articles - VNS Overview**

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- 1. Clancy JA, Deuchars SA, Deuchars J. The wonders of the Wanderer. *Exp Physiol.* 2013;98(1):38-45.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22848084>

**Abstract** Vagus is Latin for wandering, and the vagus nerve fully deserves this name due to its extensive distribution through the body. Indeed, one of the lines of the song that accompanied the 2012 G. L. Brown Prize Lecture exaggerates this diversity, 'My function's almost anythin', and vagus is my name'. Alteration of vagal activity was first investigated in the 1880s as a treatment for epilepsy, and vagus nerve stimulation is now an approved treatment for refractory epilepsy and depression in the USA, despite an incomplete understanding of the mechanisms involved. Vagus nerve stimulation could be beneficial in many other conditions, including heart failure, tinnitus, chronic hiccups, Alzheimer's disease and inflammatory diseases. Inhibition of vagal activity could also be beneficial in some conditions, e.g. reducing activation of vagal respiratory afferents to treat chronic cough. This review discusses evidence underlying some current and potential therapeutic applications of vagal modulation, illustrating the wonders of the Wanderer.
  
- 2. Bonaz B, Picq C, Sinniger V, Mayol JF, Clarencon D. Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway. *Neurogastroenterol Motil.* 2013;25(3):208-21.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23360102>  
<http://onlinelibrary.wiley.com/doi/10.1111/nmo.12076/abstract>

**Abstract** Background The brain and the gut communicate bidirectionally through the autonomic nervous system (ANS). The vagus nerve (VN), a major component of the ANS, plays a key role in the neuro-endocrine-immune axis to maintain homeostasis through its afferents (through the activation of the hypothalamic pituitary adrenal axis and the central ANS) and through its efferents (i.e. the cholinergic anti-inflammatory pathway; CAP). The CAP has an anti-TNF effect both through the release of acetylcholine at the distal VN acting on macrophages and through the connection of the VN with the spleen through the splenic sympathetic nerve. Vagus nerve stimulation (VNS) of vagal afferents at high frequency (20-30 Hz) is used for the treatment of drug-resistant epilepsy and depression. Low-frequency (5 Hz) VNS of vagal efferents activates the CAP for an anti-inflammatory effect that is as an anti-TNF therapy in inflammatory diseases where TNF is a key cytokine as represented by experimental sepsis, postoperative ileus, burn-induced intestinal barrier injury, colitis. However, both vagal afferents and efferents are activated by VNS. Purpose The objective of this review was to explore the following: (i) the supporting evidence for the importance of VNS in epilepsy (and depression) and its mechanisms of action, (ii) the anti-inflammatory characteristics of the VN, (iii) the experimental evidence that VNS impact on inflammatory disorders focusing on the digestive tract, and (iv) how VNS could potentially be harnessed therapeutically in human inflammatory disorders such as inflammatory bowel diseases, irritable bowel syndrome, postoperative ileus, rheumatoid arthritis as an anti-inflammatory therapy.

3. **De Ferrari GM, Schwartz PJ. Vagus nerve stimulation: from pre-clinical to clinical application: challenges and future directions. *Heart Fail Rev.* 2011;16(2):195-203.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21165697>  
<http://link.springer.com/article/10.1007%2Fs10741-010-9216-0>  
**Abstract** Vagus nerve stimulation was performed experimentally for the first time more than 150 years ago. In the 1980s and 1990s, vagus nerve stimulation was shown, both in the anesthetized and in the conscious animal, to exert marked antiarrhythmic effects, particularly during acute myocardial ischemia. There is a strong rationale for a beneficial effect of augmented vagal activity in the setting of chronic heart failure. Studies in experimental models of heart failure showed that chronic vagus nerve stimulation exerts beneficial effects on left ventricular function and on survival. Vagus nerve stimulation is approved in man for refractory epilepsy and depression. The first-in-man study performed in 32 patients with chronic heart failure suggests that vagus nerve stimulation was safe and well tolerated. Six months of open-label treatment was associated with significant improvements ( $P < 0.001$ ) in NYHA class, quality of life, 6-min walk test, LV ejection fraction (from 22 +/- 7 to 29 +/- 8%), and LV systolic volumes ( $P = 0.02$ ). These improvements were maintained at 1 year. Mechanisms of action may include the following: heart rate, anti-adrenergic, anti-apoptotic, and anti-inflammatory effects as well as an increase in nitric oxide. Controlled clinical trials will start soon to assess whether vagus nerve stimulation can indeed represent a new non-pharmacological approach for the treatment of symptomatic heart failure.
4. **Beekwilder JP, Beems T. Overview of the clinical applications of vagus nerve stimulation. *J Clin Neurophysiol.* 2010;27(2):130-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20505378>  
**Abstract** Vagus nerve stimulation (VNS) has become an established therapy for difficult-to-treat epilepsy during the past 20 years. The vagus nerve provides a unique entrance to the brain. Electrical stimulation of this structure in the cervical region allows direct modulative access to subcortical brain areas, requiring only minimally invasive surgery with low risks involved. VNS therapy has shown to reduce epileptic seizures both in number and severity in a group of patients not responding to antiepileptic drugs. The effects are accompanied by an atypical set of central side effects. After the success of the VNS therapy with epilepsy, the technique has been applied to a wide variety of disorders, ranging from major depressive disorder to Alzheimer's disease. The results of several of these are promising. In this review, the results as well as the rationale for the different applications of VNS are discussed.
5. **Lulic D, Ahmadian A, Baaj AA, Benbadis SR, Vale FL. Vagus nerve stimulation. *Neurosurg Focus.* 2009;27(3):E5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19722820>  
**Abstract** Vagus nerve stimulation (VNS) is a key tool in the treatment of patients with medically refractory epilepsy. Although the mechanism of action of VNS remains poorly understood, this modality is now the most widely used nonpharmacological treatment for drug-resistant epilepsy. The goal of this work is to review the history of VNS and provide information on recent advances and applications of this technology.
6. **Mapstone TB. Vagus nerve stimulation: current concepts. *Neurosurg Focus.* 2008;25(3):E9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18759633>  
**Abstract** Vagus nerve stimulation (VNS) has become an accepted treatment option for pharmacologically resistant epilepsy. Although initially approved for adults, it increasingly has gained acceptance in children. In this article the author reviews the current state of knowledge of VNS therapy and discusses its potential utility.

7. **Milby AH, Halpern CH, Baltuch GH. Vagus nerve stimulation for epilepsy and depression. *Neurotherapeutics*. 2008;5(1):75-85.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18164486>  
[http://download.springer.com/static/pdf/616/art%253A10.1016%252Fj.nurt.2007.10.071.pdf?auth66=1364573193\\_3ace10120c838fe6d3ed8e383b196a59&ext=.pdf](http://download.springer.com/static/pdf/616/art%253A10.1016%252Fj.nurt.2007.10.071.pdf?auth66=1364573193_3ace10120c838fe6d3ed8e383b196a59&ext=.pdf)  
**Abstract** Many patients with epilepsy suffer from persistent seizures despite maximal antiepileptic drug (AED) therapy. Chronic, intermittent vagus nerve stimulation (VNS) has proven to be a safe, effective option for patients suffering from refractory seizures who are not candidates for surgical resection. Although only a small minority of patients will be entirely seizure-free, VNS as an adjunct to medical therapy does appear to provide a significant amount of improvement in quality of life. Reports of antidepressant effects independent of seizure control, along with the use of multiple AEDs in the treatment of depression, has led to the investigation of VNS as a potential adjunctive treatment for major depressive disorder. Both the number of severely depressed patients refractory to available pharmacologic options and the need for repeated treatments and significant side effects associated with electroconvulsive therapy have heightened the interest in VNS for this patient population. Pilot studies of VNS for depression have shown impressive response rates; however, the effect appears to be gradual in onset, as demonstrated by the lack of a favorable response in a short-term, randomized controlled study. Investigation is thus needed to establish the potential role of VNS as an adjunctive treatment for severe depression.
8. **Ansari S, Chaudhri K, Al Moutaery KA. Vagus nerve stimulation: indications and limitations. *Acta Neurochir Suppl*. 2007;97(Pt 2):281-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17691314>  
**Abstract** Vagus nerve stimulation (VNS) is an established treatment for selected patients with medically refractory seizures. Recent studies suggest that VNS could be potentially useful in the treatment of resistant depressive disorder. Although a surgical procedure is required in order to implant the VNS device, the possibility of a long-term benefit largely free of severe side effects could give VNS a privileged place in the management of resistant depression. In addition, VNS appears to affect pain perception in depressed adults; a possible role of VNS in the treatment of severe refractory headache, intractable chronic migraine and cluster headache has also been suggested. VNS is currently investigated in clinical studies, as a potential treatment for essential tremor, cognitive deficits in Alzheimer's disease, anxiety disorders, and bulimia. Finally, other studies explore the potential use of VNS in the treatment of resistant obesity, addictions, sleep disorders, narcolepsy, coma and memory and learning deficits.
9. **Gross M, Goyal M. Central therapeutic effects of peripheral vagus nerve stimulation. *Am J Electroneurodiagnostic Technol*. 2007;47(1):47-52.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17503610>  
**Abstract** Despite the recent addition of more than ten new antiepileptic drugs on the market, epilepsy remains poorly controlled in almost 30% of patients. For this subgroup of patients with pharmacoresistant epilepsy, vagus nerve stimulation (VNS) has become a viable option. More recently, it has also shown promise in treatment-resistant depression. This article discusses VNS's history, current applications, and potential to treat chronic neurologic and psychiatric disorders.
10. **Howland RH. What is vagus nerve stimulation? *J Psychosoc Nurs Ment Health Serv*. 2006;44(8):11-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16937769>

11. **Shafique S, Dalsing MC. Vagus nerve stimulation therapy for treatment of drug-resistant epilepsy and depression. *Perspect Vasc Surg Endovasc Ther.* 2006;18(4):323-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17351201>  
<http://pvs.sagepub.com/content/18/4/323>  
**Abstract** Vagal nerve stimulation therapy is a new adjunctive treatment for drug-resistant epilepsy and depression. It consists of a pulse generator that transmits impulses to the left vagus nerve via an implantable electrode and can be performed by surgeons familiar with the anatomy of the cervical vagus nerve. The minimum age for vagal nerve stimulation therapy for epilepsy is 12 years, and for depression, 18 years. Hoarseness and cough are the most common side effects. Response rates to vagal nerve stimulation therapy vary and depend on several other factors. If used as adjunctive therapy, vagal nerve stimulation has shown better control of seizures or depression at smaller doses of antiepileptic or antidepressive medications and also results in decreased dose-dependent side effects. Vagal nerve stimulation therapy appears safe as an adjunctive treatment for drug-resistant epilepsy and depression. Long-term data are needed to better define its ultimate role in various subsets of patients.
12. **Groves DA, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. *Neurosci Biobehav Rev.* 2005;29(3):493-500.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15820552>  
**Abstract** Vagal nerve stimulation (VNS) is an approved treatment for epilepsy and is currently under investigation as a therapy for other disorders, including depression, anxiety and Alzheimer's disease. This review examines the pre-clinical and clinical literature relating to VNS. A brief historical perspective is given, followed by consideration of the efficacy of the various clinical applications of VNS. Finally, what is known about the mechanism by which VNS exerts clinical benefit is considered. It is concluded that although the precise mechanism of action of VNS is still unknown, the search for the mechanism has the potential to lend new insight into the neuropathology of depression. It is important that prior assumptions about the influence of VNS on particular aspects of brain function do not constrain the investigations.
13. **George MS, Nahas Z, Bohning DE, Mu Q, Kozel FA, Borckhardt J, et al. Mechanisms of action of vagus nerve stimulation (VNS). *Clin Neurosci Res.* 2004;4(1-2):71-79.**  
<http://www.sciencedirect.com/science/article/pii/S1566277204000325>  
**Abstract** In 1992, Dr Jake Zabara discovered in a canine model that repeated stimulation of the vagus nerve in the neck could stop seizures. Since that time, repeated stimulation of the vagus nerve has been FDA approved as an anticonvulsant. Zabara's work is built on a 50-year-old theme in the literature where scientists had sought to exploit the fact that the vagus nerve is composed of 80% afferent fibers. Thus vagus stimulation might potentially provide a 'window' into the brain. This manuscript reviews the basic science and brain imaging work done to date with VNS, attempting to understand how VNS affects the brain. This research is crucial to perfecting VNS as an anticonvulsant, and for determining other neuropsychiatric conditions that might be helped by VNS.
14. **Jellinger KA. Vagus nerve stimulation. *Eur J Neurol.* 2004;11(10):721.**  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1468-1331.2004.00852.x/abstract>

15. **Schachter SC. Vagus nerve stimulation: where are we? *Curr Opin Neurol.* 2002;15(2):201-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11923636>  
**Abstract** Now nearly 5 years post-approval, vagus nerve stimulation has emerged as a major non-pharmacological treatment for epilepsy. The place of vagus nerve stimulation among antiepileptic drugs and other surgical therapies is still evolving. This review evaluates the role of vagus nerve stimulation in light of recently published research of its mechanism(s) of action, long-term efficacy, safety and tolerability, and application to other disorders besides epilepsy.
16. **Kosel M, Schlaepfer TE. Mechanisms and state of the art of vagus nerve stimulation. *J ECT.* 2002;18(4):189-92.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12468993>  
**Abstract** Vagus nerve stimulation (VNS) is an established treatment of medically refractory partial-onset seizures. Recent data from an open-label multicenter pilot study also suggest a potential clinical usefulness in the acute and maintenance treatment of drug-resistant depressive disorder. Despite the fact that surgery is needed to implant the stimulating device, the option of long-term use largely devoid of severe side effects would give this treatment modality a privileged place in the management of drug-resistant depression. However, definite therapeutic effects of clinical significance remain to be confirmed in large, placebo-controlled trials. Besides the potential clinical usefulness, VNS can be used as a research tool in epilepsy patients implanted for clinical reasons, allowing neurophysiologic investigations of the parasympathetic system and its interactions with other parts of the central nervous system.
17. **Schachter SC, Wheless JW. The evolving place of vagus nerve stimulation therapy. *Neurology.* 2002;59(6 Suppl 4):S1-2.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12270961>  
**Abstract** Approximately 40% of patients with epilepsy have seizures that do not adequately respond to medical therapy. Vagus nerve stimulation (VNS) therapy, approved 5 years ago by the Food and Drug Administration, offers a therapeutic option for patients with pharmacoresistant seizures. This supplement updates developments with VNS therapy since its approval and suggests future directions for this still-evolving treatment.
18. **George MS, Nahas Z, Bohning DE, Kozel FA, Anderson B, Chae JH, et al. Vagus nerve stimulation therapy: a research update. *Neurology.* 2002;59(6 Suppl 4):S56-61.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12270970>  
**Abstract** Over the past 5 years, and especially within the last year, there has been a rapid expansion of vagus nerve stimulation (VNS)-related preclinical research, as well as clinical studies in indications other than epilepsy. The research advances in understanding VNS are occurring in the midst of a blossoming of other forms of therapeutic brain stimulation, such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS). In general, improved understanding of the neurobiological effects of VNS therapy as a function of the different use parameters (frequency, intensity, pulse width, duration, dose) is beginning to guide clinical use and help determine which diseases, in addition to epilepsy, VNS might treat.

**Right-Sided VNS Therapy (in Epilepsy)**

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1. **Navas M, Navarrete EG, Pascual JM, Carrasco R, Nunez JA, Shakur SF, et al. Treatment of refractory epilepsy in adult patients with right-sided vagus nerve stimulation. *Epilepsy Res.* 2010;90(1-2):1-7. <http://www.ncbi.nlm.nih.gov/pubmed/20488666>**

**Abstract** Vagus nerve stimulation (VNS) was introduced as a novel method for the treatment of patients with medically and/or surgically refractory epilepsy. VNS typically involves placement of the electrode on the left vagus nerve. However, there are some patients who cannot be implanted on this side because of complications related to the surgical procedure or side effects or infections forcing the left side VNS (L-VNS) explant. Because right side VNS (R-VNS) implants have shown similar effectiveness compared to L-VNS in reducing the frequency of seizures in animal models, treatment with R-VNS should be considered in patients who may not tolerate L-VNS. We present two adult patients who underwent R-VNS. One of the patients improved dramatically after L-VNS, but the device had to be removed because of mechanical malfunction. This patient was thought to be at high risk for nerve injury if L-VNS reimplantation was done, thus R-VNS was chosen. In the other patient, L-VNS was first attempted, but the operation had to be stopped due to significant bleeding caused by the accidental tearing of an ectopic vein. Both patients had a marked reduction in their seizure activity and none of them had cardiac side effects from therapeutic R-VNS. We conclude that R-VNS therapy is an alternative, promising therapy for reducing seizure activity in those patients who cannot undergo L-VNS implantation. Close follow-up and frequent ECG monitoring is required to detect the presence of cardiac side effects.

2. **Spuck S, Nowak G, Renneberg A, Tronnier V, Sperner J. Right-sided vagus nerve stimulation in humans: an effective therapy? *Epilepsy Res.* 2008;82(2-3):232-4. <http://www.ncbi.nlm.nih.gov/pubmed/18801642>**

**Abstract** Vagus nerve stimulation (VNS) is an additive treatment option for refractory epilepsy. The electrode is placed on the cervical trunk of the left vagus nerve. In patients who are not suitable for left-sided vagus nerve stimulation (L-VNS) right-sided vagus nerve stimulation (R-VNS) may be as effective. In animal models epilepsy is sufficiently suppressed by R-VNS. In a 16 years old boy suffering from medically refractory psychomotoric seizures with secondary generalisation, L-VNS reduced the frequency of generalized seizures. A deep wound infection required the removal of the system eight weeks later. Cicatrisation did not allow preparation of the left vagus nerve, therefore we implanted R-VNS with sufficient seizure suppression. However, compared to L-VNS, the effect occurred months later and cardiac symptoms were induced by stimulation of the right vagus nerve. R-VNS seems to be an effective and alternative therapy in selected patients responding to L-VNS where a left-sided reimplantation is not possible. Placement and adjustment of the device should be performed under ECG control. Further studies are necessary to compare the efficacy of L-VNS and R-VNS.

3. **Tubbs RS, Salter EG, Killingsworth C, Rollins DL, Smith WM, Ideker RE, et al. Right-sided vagus nerve stimulation inhibits induced spinal cord seizures. *Clin Anat.* 2007;20(1):23-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16302248>  
<http://onlinelibrary.wiley.com/doi/10.1002/ca.20253/abstract>  
**Abstract** We have previously shown that left-sided vagus nerve stimulation results in cessation of induced spinal cord seizures. To test our hypothesis that right-sided vagus nerve stimulation will also abort seizure activity, we have initiated seizures in the spinal cord and then performed right-sided vagus nerve stimulation in an animal model. Four pigs were anesthetized and placed in the lateral position and a small laminectomy performed in the lumbar region. Topical penicillin, a known epileptogenic drug to the cerebral cortex and spinal cord, was next applied to the dorsal surface of the exposed cord. With the exception of the control animal, once seizure activity was discernible via motor convulsion or increased electrical activity, the right vagus nerve previously isolated in the neck was stimulated. Following multiple stimulations of the vagus nerve and with seizure activity confirmed, the cord was transected in the midthoracic region and vagus nerve stimulation performed. Right-sided vagus nerve stimulation resulted in cessation of spinal cord seizure activity in all animals. Transection of the spinal cord superior to the site of seizure induction resulted in the ineffectiveness of vagus nerve stimulation in causing cessation of seizure activity in all study animals. As with left-sided vagus nerve stimulation, right-sided vagus nerve stimulation results in cessation of induced spinal cord seizures. Additionally, the effects of right-sided vagus nerve stimulation on induced spinal cord seizures involve descending spinal pathways. These data may aid in the development of alternative mechanisms for electrical stimulation for patients with medically intractable seizures and add to our knowledge regarding the mechanism for seizure cessation following peripheral nerve stimulation.
4. **McGregor A, Wheless J, Baumgartner J, Bettis D. Right-sided vagus nerve stimulation as a treatment for refractory epilepsy in humans. *Epilepsia.* 2005;46(1):91-6; comment *Epilepsia.* 2005;46(7):1152; author reply *Epilepsia.* 2005;46(7):1152-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15660773>  
<http://onlinelibrary.wiley.com/store/10.1111/j.0013-9580.2005.16404.x/asset/j.0013-9580.2005.16404.x.pdf?v=1&t=he941u9h&s=b7117ba37577326ecc816b46df3d47e5f140f2bc>  
**Abstract** PURPOSE: We present three children who underwent right-sided vagus nerve stimulation (R-VNS). This treatment option for people with refractory epilepsy has not been described in children. METHODS: We reviewed our database of >350 patients implanted with vagus nerve stimulators and now describe our experience in three patients with R-VNS for the treatment of intractable seizures. All three patients improved dramatically with left-sided vagus nerve stimulation (L-VNS), but the devices had to be removed because of infection. The patients were thought to be at high risk for nerve injury if they were reapproached for L-VNSs; therefore R-VNSs were implanted. RESULTS: All three patients with an R-VNS had a reduction in seizures. Our first patient has had an R-VNS for 5 years; he has been seizure free for >2 years on R-VNS monotherapy. The second patient had an R-VNS for 8 months. His seizure control improved slightly, but not as dramatically as with L-VNS. The third child has had an R-VNS for >7 months and has cessation of his most disabling seizure type (generalized tonic-clonic seizures). None of the patients had cardiac side effects from therapeutic R-VNS. However, two of the three patients had respiratory events with R-VNS. CONCLUSIONS: VNS is known to be an effective treatment in pharmacoresistant epilepsy. R-VNS should be considered if a patient has significant benefit from L-VNS but is unable to continue with L-VNS. R-VNS appears also to have antiepilepsy effects. Additionally, our case report suggests that in some patients, a differential response is found regarding seizure control with R-VNS or L-VNS, raising the question whether L-VNS failures should pursue a trial of R-VNS. Patients should be cautioned and monitored for reactive airway disease if they undergo R-VNS. More research is needed to compare the effects of right- and left-sided VNS on cardiac and pulmonary function in humans and to determine which has the best antiseizure effect.

5. **McGregor A, Wheless J. Response: Right-sided vagus nerve stimulation. *Epilepsia*. 2005;46(7):1152-3.** [http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.09205\\_2.x/abstract](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.09205_2.x/abstract)

6. **Krahl SE, Senanayake SS, Handforth A. Right-sided vagus nerve stimulation reduces generalized seizure severity in rats as effectively as left-sided. *Epilepsy Res*. 2003;56(1):1-4.** <http://www.ncbi.nlm.nih.gov/pubmed/14529948>

**Abstract** As currently utilized, vagus nerve stimulation (VNS) is applied to the cervical trunk of the left vagus nerve to suppress seizures clinically. Demonstration that VNS can also reduce seizure severity when electrodes are placed on the right cervical vagus nerve in rats would provide empirical evidence that the antiepileptic effects of VNS are not an exclusive property of the left vagus nerve. Rats were implanted with a custom cuff electrode on either the left or right cervical vagus nerve. Two days later, continuous VNS was begun in half the rats with left-sided and half with right-sided electrodes. The remaining rats were connected to the stimulator, but did not receive VNS. After 30s, pentylenetetrazole (PTZ) was administered systemically and seizures were rated by a blinded observer. The PTZ test was repeated two days later, with VNS administered to the previously unstimulated rats, while the others received no stimulation. VNS significantly reduced the severity of PTZ-induced seizures in rats regardless of the side of stimulation as compared to their no-VNS (control condition) seizure severity. No significant differences in efficacy existed based on the side of stimulation. These results indicate that right-sided VNS in rats is just as effective as left-sided VNS, suggesting that fibers necessary for seizure suppression are not unique to the left vagus nerve.

**Ring Chromosome 20 Syndrome (Epilepsy/VNS in...)**

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1. **Herrgard E, Mononen T, Mervaaala E, Kuusela L, Aikia M, Stenback U, et al. More severe epilepsy and cognitive impairment in the offspring of a mother with mosaicism for the ring 20 chromosome. *Epilepsy Res.* 2007;73(1):122-8.**

<http://www.ncbi.nlm.nih.gov/pubmed/17079116>

**Abstract** PURPOSE: Ring chromosome 20 [r(20)] syndrome is a rare chromosomal disorder. Cases tend to be sporadic. We elucidate the characteristics of an inherited r(20) mosaicism by describing the clinical features of three family members: a mother and her two children. RESULTS: The mosaicism rate of the mother was 10% and that of the children 40%. The mother experienced her first epileptic seizures at 24 years of age. Epilepsy was diagnosed two years later. After an unstable period lasting 3 years, she has been seizure-free for 13 years on a combination of valproate and lamotrigine. She has normal intelligence with full working capacity. The daughter exhibited her first epileptic seizures at the age of 7 years and she continues to have seizures weekly. The first epileptic seizures in the son were observed at 5 years of age. The son's epilepsy has been drug resistant from the onset, and a vagal nerve stimulator (VNS) has been ineffective. Psychomotor development was normal in both children up to the onset of epilepsy. Learning difficulties increased throughout school age and both children needed special educational programs. Neuropsychological evaluations have shown deterioration of cognitive levels. Both children had behavioural problems during school age but no longer in adolescence. All three subjects are nondysmorphic, normocephalic and of normal growth. CONCLUSION: In this family the phenotype of r(20) mosaicism seems to be more severe in the successive generation along with a greater level of mosaicism. The aggravated clinical picture in inherited r(20) mosaicism concerned the onset of epilepsy, drug responsiveness, the cognitive level and behavioural features.

2. **Alpman A, Serdaroglu G, Cogulu O, Tekgul H, Gokben S, Ozkinay F. Ring chromosome 20 syndrome with intractable epilepsy. *Dev Med Child Neurol.* 2005;47(5):343-6; comment *Dev Med Child Neurol.* 2006;48(1):80; author reply *Dev Med Child Neurol.* 2006;48(1):80.**

<http://www.ncbi.nlm.nih.gov/pubmed/15892377>

**Abstract** Ring chromosome 20 [r(20)] syndrome is characterized by mild to moderate learning disability\*, behavioural disorders, epilepsy, and various dysmorphic features. Although still considered rare, r (20) syndrome is being increasingly diagnosed. More than 30 cases have been described in the literature since 1976. Here we report an additional case of a 14-year-old male with r (20). He had moderate to severe learning disability and epileptic seizures manifesting at about 18 months of age. During the 13 years' follow-up period he showed intractable epileptic seizures, behavioural disorders, and mild dysmorphological features including microcephaly, strabismus, micrognathia, down-slanting eyelids, and ear abnormalities. Frequent episodes of atypical absence or non-convulsive status associated with electroencephalogram changes were seen in follow-up. He was treated with several classical and new antiepileptic drugs, including intravenous immunoglobulin, corticotropin, and vagal nerve stimulation, with unsuccessful control of seizures. Finally, surgical treatment (corpus callosotomy) was performed at the age of 13 years; severity of tonic seizures was diminished, but frequency was unchanged. Although his behavioural problems, e.g. hyperactivity, were mild in early childhood they became more severe when he was 11 years old. Aggressiveness, compulsiveness with self-injury, and panic attacks developed at the age of 13 years, and were more pronounced after callosotomy. This case report provides the first description of deterioration in psychological situation in patients with r(20) intractable epilepsy. The patient was diagnosed with r(20) syndrome after 13 years of clinical follow-up. Karyotype analysis should, therefore, be performed in every patient with intractable epilepsy of unknown aetiology.

3. **Chawla J, Sucholeiki R, Jones C, Silver K. Intractable epilepsy with ring chromosome 20 syndrome treated with vagal nerve stimulation: case report and review of the literature. *J Child Neurol.* 2002;17(10):778-80.**

<http://www.ncbi.nlm.nih.gov/pubmed/12546436>

**Abstract** We report a case of a 6-year old girl with ring chromosome 20 syndrome whose medically intractable seizures were successfully treated with vagal nerve stimulation therapy. Medically intractable seizures are an expected part of this rare syndrome, and the dramatic improvement in seizure control with vagal nerve stimulation is emphasized. Earlier use of vagal nerve stimulation in similar cases should be considered.

**Safety Information - Anaesthesia (VNS/Epilepsy and...)**

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1. **Koh JL, Egan B, McGraw T. Pediatric epilepsy surgery: anesthetic considerations. *Anesthesiol Clin.* 2012;30(2):191-206.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22901606>  
**Abstract** Despite advances in antiepileptic medication therapy, a significant number of pediatric patients with epilepsy have seizures that are not well controlled. This article provides anesthesiologists with an overview of seizures in the pediatric population, including evaluation, medical treatment, surgical options, and the anesthetic implications of caring for this special population.
2. **Maranhao MV, Gomes EA, de Carvalho PE. Epilepsy and anesthesia. *Rev Bras Anesthesiol.* 2011;61(2):232-41, 242-54, 124-36.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21474031>  
**Abstract** BACKGROUND AND OBJECTIVES: Epilepsy is one of the most frequent chronic neurological diseases. Although anesthesia for epilepsy patients is more common in neurosurgery, this group of patients needs, just as the general population, anesthesia for different diagnostic and therapeutic procedures. This article aims to address the issues of greatest interest to the anesthesiologist in the perioperative management of epileptic patients undergoing anesthesia for non-neurosurgical procedures. CONTENT: We discuss relevant aspects of pathophysiology, classification and diagnosis of epilepsy; anticonvulsant therapy and interactions with anesthetic drugs; surgery and the ketogenic diet; pro- and anticonvulsant effects of drugs used in anesthesia; preoperative evaluation, intra- and postoperative conduct in epileptic patients, as well as the diagnosis and treatment of perioperative seizures. CONCLUSIONS: In the perioperative management of epileptic patients is important for anesthesiologists to identify the type of epilepsy, the frequency, severity and the factors triggering the epileptogenic crises; the use of anticonvulsant drugs and possible interactions with drugs used in anesthesia; the presence of ketogenic diet and stimulatory of the vagus nerve, and its implications in anesthetic techniques. It is essential the understanding of pro- and anticonvulsant properties of drugs used in anesthesia, minimizing the risk of seizure activity in the intra- and postoperative. Finally, it is important to outline the diagnosis and initiate treatment of seizures, perioperative, which offers lower both morbidity and mortality.
3. **Raft J, Schaff JL, Rangeard O, Verhaeghe JL, Longrois D, Meistelman C, et al. [Perioperative anaesthetic management of an epileptic patient treated with a vagus nerve stimulation]. *Ann Fr Anesth Reanim.* 2010;29(12):913-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21112732>  
**Abstract** The vagal nerve stimulation is approved for medically refractory epilepsy and major depression. We report the perioperative management of an epileptic patient with this indwelling device. This observation summarizes the physiologic implications and the specific anaesthetic considerations for procedures with this pre-existing device.

4. **Hatton KW, McLarney JT, Pittman T, Fahy BG. Vagal nerve stimulation: overview and implications for anesthesiologists. *Anesth Analg*. 2006;103(5):1241-9; comment *Anesth Analg* 2007;105(3):884-5; author reply *Anesth Analg*. 2007;105(3):885.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17056962>  
<http://www.anesthesia-analgesia.org/content/103/5/1241.full.pdf>  
**Abstract** Vagal nerve stimulation is an important adjunctive therapy for medically refractory epilepsy and major depression. Additionally, it may prove effective in treating obesity, Alzheimer's disease, and some neuropsychiatric disorders. As the number of approved indications increases, more patients are becoming eligible for surgical placement of a commercial vagal nerve stimulator (VNS). Initial VNS placement typically requires general anesthesia, and patients with previously implanted devices may present for other surgical procedures requiring anesthetic management. In this review, we will focus on the indications for vagal nerve stimulation (both approved and experimental), proposed therapeutic mechanisms for vagal nerve stimulation, and potential perioperative complications during initial VNS placement. Anesthetic considerations during initial device placement, as well as anesthetic management issues for patients with a preexisting VNS, are reviewed.
  
5. **Chang KH, Hanaoka K. [Intraoperative coronary spasm in non-cardiac surgery]. *Masui*. 2004;53(1):2-9. Japanese.**  
<http://www.ncbi.nlm.nih.gov/pubmed/14968595>  
**Notes** Because this article is in Japanese, it is difficult to determine whether the vagal stimulation mentioned in the article as a potential cause for cardiovascular events during a non-cardiac surgery is referring to VNS therapy. However, the article is a review of the literature from Medline, so the article does appear to be citing VNS as a potential cause of cardiovascular events.  
**Abstract** BACKGROUND: Cardiovascular events are one of the most critical perioperative complications. The purpose of this study is to investigate the clinical characteristics, effective treatments, and clinical outcome of intraoperative coronary spasm through a review of the published literature. METHODS: Reports of intraoperative coronary spasm were identified using the Medline database (1977-2000) or by manually searching the Journal of Anesthesia (1987-2000). The clinical characteristics of intraoperative coronary spasm were analyzed in the 56 patients who had developed coronary spasm during non-cardiac surgery. RESULTS: The mean patient's age was 58 +/- 13 years. The majority of patients were men (75%), Japanese (78%), and had no history of chest pain (75%). Regional anesthesia, vasopressors, alkalosis, hypotension, inadequate depth of anesthesia, and vagal stimulation were noted as major contributing factors. More than half of the patients showed severe hypotension and 30% developed cardiovascular collapse. However, coronary dilators, and nitrates in particular, were very effective for the treatment, and the clinical outcome was relatively good (one death and three cases of myocardial infarction). CONCLUSIONS: Intraoperative coronary spasm may develop in patients with no history of chest pain. Some of the intraoperative conditions themselves are potent vasoconstricting factors. Once coronary spasm occurs, immediate administration of a full dose of coronary dilators is recommended.
  
6. **Tovey G, Griffiths R. Vagal nerve stimulators and anaesthesia. *Anaesthesia*. 2001;56(7):703-4; comment *Anaesthesia*. 2001;56(12):1209-10.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11437779>

**Safety Information - Bronchoconstriction/Cough (VNS and...)**

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1. **Corboz MR, Rivelli MA, Fernandez X, Greenfeder S. Neuromodulation mediated by the tachykinin NK3-receptor agonist [MePhe7]-neurokinin B in the isolated perfused lung of nonsensitized nonchallenged and ovalbumin-sensitized and -challenged guinea pig. *Exp Lung Res.* 2012;38(5):233-49. <http://www.ncbi.nlm.nih.gov/pubmed/22536826> <http://informahealthcare.com/doi/abs/10.3109/01902148.2012.673050>**

**Abstract** The neuromodulatory action of the tachykinin NK(3)-receptor agonist [MePhe(7)]-neurokinin B ([MePhe(7)]-NKB) was evaluated on vagal stimulation-induced bronchoconstriction in nonsensitized nonchallenged and ovalbumin (OVA)-sensitized and -challenged guinea pig using the isolated perfused lung preparation. Lungs were placed inside a warmed (37 degrees C) glass chamber and suspended from a force displacement transducer (Grass FT-03) with both vagi connected to a stimulating electrode. Isolated lungs were stimulated at a constant voltage (20 V) and pulse duration (5 ms) with electrical stimulation frequencies ranging from 1 to 128 Hz. The authors demonstrated that vagal stimulation produced frequency-dependent bronchoconstriction and [MePhe(7)]-NKB, at a dose (0.1  $\mu$ M) that does not produce bronchoconstriction by itself, potentiated the vagally induced bronchoconstriction at all frequencies in nonsensitized nonchallenged animals and to a greater extent in OVA-sensitized and -challenged guinea pigs; the potentiations were totally inhibited by the tachykinin NK(3)-receptor antagonist SR 142801 (1  $\mu$ M). In a second set of experiments, [MePhe(7)]-NKB produced bronchoconstriction in a dose-dependent (1 to 300  $\mu$ g/mL) manner with similar potencies and maximum responses in nonsensitized nonchallenged (EC(50) = 8.6 +/- 1.1  $\mu$ M; E(Max) = 61.1 +/- 3.5 mm Hg) and OVA-sensitized and -challenged (EC(50) = 8.5 +/- 1.3  $\mu$ M; E(Max) = 63.5 +/- 3.7 mm Hg) animals. In conclusion, these results demonstrated that [MePhe(7)]-NKB potentiated vagal stimulation-induced bronchoconstriction via the tachykinin NK(3)-receptors and OVA sensitization caused development of airway hyperresponsiveness in these potentiations. However, OVA sensitization had no effect on airway responsiveness of vagal stimulation-and [MePhe(7)]-NKB-induced bronchoconstrictions.

2. **ten Berge RE, Roffel AF, Zaagsma J. Conditional involvement of muscarinic M1 receptors in vagally mediated contraction of guinea-pig bronchi. *Naunyn Schmiedebergs Arch Pharmacol.* 1995;352(2):173-8. <http://www.ncbi.nlm.nih.gov/pubmed/7477440>**

**Abstract** The involvement of ganglionic muscarinic M1 receptors in vagally induced bronchoconstriction in guinea-pig airways is controversial. Therefore, we studied the effects of the M1-selective muscarinic receptor antagonist pirenzepine on vagus nerve (VNS, preganglionic) and electrical field stimulation (EFS, postganglionic)-induced contractions of the guinea-pig main bronchus under various experimental conditions. Using identical stimulation parameters for VNS and EFS (8V, 30 Hz, 0.5 ms, 5s every min), the amplitude of the VNS-induced twitch contractions was 30.4% of the EFS-induced responses, and pirenzepine showed 2.3-fold selectivity (pIC50-values 6.45 and 6.09, respectively) to inhibit vagally induced contractions. With the stimulation frequency for EFS lowered to match contraction levels obtained using VNS, pirenzepine was equipotent to inhibit both types of response at M3 receptor-selective concentrations, suggesting that M1 receptors are not involved. By contrast, when the stimulation episode was prolonged until plateau contraction (10-20 s), in the presence of the nicotinic antagonist hexamethonium (5  $\mu$ M), the M2 receptor antagonist AQ-RA 741 (0.1  $\mu$ M) and the beta-adrenoceptor antagonist timolol (1  $\mu$ M), and again using matched VNS- and EFS-induced contraction levels, pirenzepine inhibited nerve stimulation-evoked responses in a biphasic manner, yielding pIC50-values of 8.12 (indicative of M1 receptor blockade) and 6.43 (indicative of M3 receptor blockade) for the first and second phase, respectively, while postganglionic stimulation showed a purely monophasic inhibition (pIC50 = 6.32). These results show that facilitatory muscarinic M1 receptors are involved in vagally mediated contraction of guinea-pig bronchi, under conditions of elevated neurotransmission and partial nicotinic receptor blockade.

3. **Shirai M, Ninomiya I, Sada K. Thromboxane A2/endoperoxide receptors mediate cholinergic constriction of rabbit lung microvessels. *J Appl Physiol.* 1992;72(3):1179-85.**

<http://www.ncbi.nlm.nih.gov/pubmed/1533210>

**Abstract** Using an X-ray television system, we directly measured the internal diameter (ID; 100-1,000 microns) of small pulmonary arteries and analyzed the effects of cyclooxygenase inhibition and thromboxane A2/prostaglandin endoperoxide (TP) receptor blockade on the ID reductions in response to vagal nerve stimulation (VNS; 16 Hz) and injection of acetylcholine (ACh; 0.3 micrograms) in anesthetized rabbits. The ID reductions of the small arteries in response to VNS and ACh were completely abolished by pretreatment with cyclooxygenase inhibitors indomethacin and meclofenamate. Those reductions were also eliminated by pretreatment with TP receptor antagonists AA-2414 and Ono 3708. Both TP receptor antagonists abolished the ID reduction to thromboxane A2 mimetic U-46619 but did not affect the reduction to norepinephrine. The ID reductions in response to VNS and ACh were eliminated by atropine. The reduction in response to VNS was abolished by hexamethonium bromide, whereas the reduction in response to ACh was not altered by hexamethonium bromide. The results indicate that vasoconstrictions of the rabbit small pulmonary arteries in response to VNS and exogenous ACh are mediated by TP receptors as well as muscarinic receptors. The data suggest that during VNS endogenous ACh acts on muscarinic receptors to constrict the small arteries mainly by generating thromboxane A2 or prostaglandin endoperoxide.

4. **Myers AC, Udem BJ. Analysis of preganglionic nerve evoked cholinergic contractions of the guinea pig bronchus. *J Auton Nerv Syst.* 1991;35(3):175-84.**

<http://www.ncbi.nlm.nih.gov/pubmed/1744377>

**Abstract** We compared cholinergic bronchial muscle contractions induced by vagus nerve (preganglionic) stimulation (VNS) with those induced by electrical field (postganglionic) stimulation (EFS). When normalized to their respective maximum response, the frequency-response curves (10 s trains) between 4 and 16 Hz were similar between VNS and EFS; however, at frequencies of 0.1-2 Hz, and at frequencies greater than 32 Hz, the VNS contractions were significantly less than EFS. When contractions elicited by 100 pulses were examined, it was found that the responses to VNS were maximal at 10-30 Hz then declined significantly to 82-35% of maximal between 40 and 200 Hz, whereas the response to EFS was essentially unchanged at frequencies up to 60 Hz and declined only to 72% of maximal up to 200 Hz. At frequencies as low as 20 Hz, the contractions evoked by VNS faded to 45 +/- 9% of the peak contraction during 60 sec of continuous stimulation, whereas those evoked by 60 sec continuous EFS remained constant. This fade observed during prolonged VNS was not blocked by the antagonists, pirenzepine and AFDX-116, at concentrations selective for M1 and M2 muscarinic receptors, respectively; nor was the fade blocked by pre-treatment with indomethacin, propranolol, phentolamine, or choline. At frequencies greater than 10 Hz, the amplitude of the preganglionic compound action potential also faded during repetitive stimulation. The results support the hypothesis that the airway ganglion neurons innervating guinea pig bronchial smooth muscle effectively filter preganglionic stimuli, especially at low and relatively high frequencies. During continuous vagus nerve stimulation, preganglionic mechanisms may also play a role in limiting the ultimate output of airway ganglia.

**Safety Information - Dentistry (VNS in...)**

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1. **Lisowska P, Daly B. Vagus nerve stimulation therapy (VNST) in epilepsy - implications for dental practice. *Br Dent J.* 2012;212(2):69-72; comment *Br Dent J.* 2012(9):408.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22281628>  
**Abstract** Epilepsy is a chronic condition which affects about 1% of the population. It is important that the dental team is aware of the management of epileptic seizures and epileptic syndromes including recent advances in seizure management. As people with epilepsy often get a warning aura before seizures begin, the management of the condition has increasingly involved measures to prevent the seizure, once the aura has begun. Vagus nerve stimulation therapy (VNST) in epilepsy involves the use of an implantable electronic device and is being increasingly used in the UK to control severe treatment resistant epilepsy. As a result, more patients will be presented to clinicians in the primary healthcare setting and hospital services with these devices in place. Members of the dental team need to understand the principles of epilepsy control, how VNST is used in the management of intractable epilepsy, how the VNST system operates and the implications of VNST use for dental practice including medical devices, interactions and safety features.
  
2. **Turner MD, Glickman RS. Epilepsy in the oral and maxillofacial patient: current therapy. *J Oral Maxillofac Surg.* 2005;63(7):996-1005.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16003629>

**Safety Information - Electrical Interference (including MRI with VNS)**

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1. **Kakisaka Y, Mosher JC, Wang ZI, Jin K, Dubarry AS, Alexopoulos AV, et al. Utility of temporally-extended signal space separation algorithm for magnetic noise from vagal nerve stimulators. *Clin Neurophysiol.* 2012.**

<http://www.ncbi.nlm.nih.gov/pubmed/22727713>

**Abstract** OBJECTIVE: To evaluate the utility of a temporally-extended signal space separation algorithm (tSSS) for patients with vagal nerve stimulator (VNS). METHODS: We evaluated median nerve somatosensory evoked responses (SER) of magnetoencephalography (MEG) in 27 VNS patients (48 sides) with/without tSSS processing. We classified SER dipoles as 'acceptable' if: (A) the location of the dipole was in the expected location in the central sulcus, and (B) the goodness of fit value (GOF) was greater than 80%. We evaluated (1) the number of sides which produced acceptable dipoles in each dataset (i.e. with/without tSSS processing), and in cases where the both data produced reliable dipoles, (2) compared their GOFs and the 95% confidence volumes (CV) (mm<sup>3</sup>). Statistical differences in the GOF and CV between with/without tSSS conditions were determined by paired t test. RESULTS: Only 11 (23%) responses had reliable dipoles without tSSS processing, while all 48 (100%) had acceptable dipoles under tSSS processing. Additionally, the latter group had significantly higher GOF (increased by 7% on average) and lower CV (mean decrease of 200mm<sup>3</sup>) than the former (p<0.01). CONCLUSIONS: Processing with tSSS quantitatively improves dipole fitting of known sources in VNS patients. SIGNIFICANCE: This algorithm permits satisfactory MEG testing in the relatively commonly encountered epilepsy patient with VNS.

2. **Gossman MS, Ketkar A, Liu AK, Olin B. Vagus nerve stimulator stability and interference on radiation oncology x-ray beams. *Phys Med Biol.* 2012;57(20):N365-76.**

<http://www.ncbi.nlm.nih.gov/pubmed/23032351>

<http://iopscience.iop.org/0031-9155/57/20/N365/>

**Abstract** Five different models of Cyberonics, Inc. vagus nerve stimulation (VNS) therapy pulse generators were investigated for their stability under radiation and their ability to change the absorbed dose from incident radiation. X-ray beams of 6 MV and 18 MV were used to quantify these results up to clinical doses of 68-78 Gy delivered in a single fraction. In the first part, the effect on electronic stimulation signaling of each pulse generator was monitored during and immediately afterwards with computer interrogation. In the second part, the effects of having the pulse generators scatter or attenuate the x-ray beam was also characterized from dose calculations on a treatment planning system as well as from actual radiation measurements. Some device models were found to be susceptible to radiation interference when placed directly in the beam of high energy therapeutic x-ray radiation. While some models exhibited no effect at all, others showed an apparent loss of stimulation output immediately after radiation was experienced. Still, other models were observed to have a cumulative dose effect with a reduced output signal, followed by battery depletion above 49 Gy. Absorbed dose changes on computer underestimated attenuation by nearly half for both energies amongst all pulse generators, although the computer did depict the proper shape of the changed distribution of dose around the device. Measured attenuation ranged from 7.0% to 11.0% at 6 MV and 4.2% to 5.2% at 18 MV for x-rays. Processes of back-scatter and side-scatter were deemed negligible although recorded. Identical results from 6 MV and 18 MV x-ray beams conclude no neutron effect was induced for the 18 MV beam. As there were documented effects identified in this research regarding pulse generation, it emphasizes the importance of caution when considering radiation therapy on patients with implanted VNS devices with observed malfunctions consequential.

- 3. Carrette E, De Tiege X, Op De Beeck M, De Herdt V, Meurs A, Legros B, et al. Magnetoencephalography in epilepsy patients carrying a vagus nerve stimulator. *Epilepsy Res.* 2011;93(1):44-52.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21129918>  
**Abstract** Due to technical constraints, magnetoencephalography (MEG) is challenging in vagus nerve stimulation (VNS) patients. This study evaluates (1) the feasibility of MEG in VNS patients and (2) the added value of MEG in their presurgical evaluation (PE). Ten VNS patients were studied by MEG using the spatiotemporal signal space separation (tSSS) method. Equivalent current dipoles (ECD) were classified "clustered"/"scattered". It was evaluated whether MEG (1) confirmed localisation of the hypothesized epileptogenic zone (HEZ), (2) improved delineation of the HEZ, or (3) identified 1 out of multiple HEZs. Finally it was evaluated whether adding MEG to the PE improved patient management by changing or supporting the hypothesis. In 7/10 patients, tSSS allowed to obtain interpretable MEG data, with interictal epileptiform discharges in 6/7. ECD clustered within 1 lobe in 4/6; confirming the localisation of the HEZ in 2/4 and improving delineation of the HEZ in 2/4. When ECD clustered within 2 lobes (1/6) or were scattered (1/6), MEG could not identify 1 out of multiple HEZs. In 2 patients, MEG changed management to invasive video-EEG monitoring (IVEM) and resective surgery (RS). In 4 patients, MEG further supported the management; IVEM in 2/4 and unsuitability for RS in 2/4. So far IVEM, performed in 2, resulted into RS. This study demonstrates the feasibility of MEG in VNS patients. MEG changed management in 20% and further supported the proposed management in 40% illustrating the clinical value of MEG in the PE of VNS patients.
- 4. Gorny KR, Bernstein MA, Watson RE, Jr. 3 Tesla MRI of patients with a vagus nerve stimulator: initial experience using a T/R head coil under controlled conditions. *J Magn Reson Imaging.* 2010;31(2):475-81.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20099360>  
<http://onlinelibrary.wiley.com/doi/10.1002/jmri.22037/abstract>  
**Abstract** PURPOSE: To assess safety of clinical MRI of the head in patients with implanted model 100, 102, and 103 vagus nerve stimulation (VNS) Therapy Systems (Cyberonics, Inc., Houston, TX) in 3.0 Tesla MRI (GE Healthcare, Milwaukee, WI). MATERIALS AND METHODS: The distributions of the radiofrequency B(1) (+)-field produced by the clinically used transmit/receive (T/R) head coil (Advanced Imaging Research Incorporated, Cleveland, OH) and body coil were measured in a head and shoulders phantom. These measurements were supplemented by temperature measurements on the lead tips and the implantable pulse generator (IPG) of the VNS devices in a head and torso phantom with the same two coils. Clinical 3T MRI head scans were then acquired under highly controlled conditions in a series of 17 patients implanted with VNS. RESULTS: Phantom studies showed only weak B(1) (+) fields at the location of the VNS IPG and leads for MRI scans using the T/R head coil. The MRI-related heating on a VNS scanned in vitro at 3T was also found to be minimal (0.4-0.8 degrees C at the leads, negligible at the IPG). The patient MRI examinations were completed successfully without any adverse incidents. No patient reported any heating, discomfort, or any other unusual sensation. CONCLUSION: Safe clinical MRI head scanning of patients with implanted VNS is shown to be feasible on a GE Signa Excite 3T MRI system using one specific T/R head coil. These results apply to this particular MRI system configuration. Extrapolation or generalization of these results to more general or less controlled imaging situations without supporting data of safety is highly discouraged.
- 5. Roebing R, Huch K, Kassubek J, Lerche H, Weber Y. Cervical spinal MRI in a patient with a vagus nerve stimulator (VNS). *Epilepsy Res.* 2009;84(2-3):273-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19269790>  
**Abstract** Cranial MRI has been shown to be a safe procedure in patients with a vagus nerve stimulator (VNS), but body MRI may cause overheating of the stimulator lead. Here we report a case of a patient with an implanted vagus nerve stimulator who required a cervical spinal MRI due to a rapidly progressive paraparesis. The spinal MRI was performed in a 1.5T scanner without complications showing a nearly complete compression of the spinal cord.

- 6. Shellock FG, Begnaud J, Inman DM. Vagus nerve stimulation therapy system: in vitro evaluation of magnetic resonance imaging-related heating and function at 1.5 and 3 tesla. *Neuromodulation*. 2006;9(3):204-13.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22151708>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1525-1403.2006.00061.x/abstract>  
**Abstract** Objectives. To evaluate magnetic resonance imaging-related (MRI-related) heating for the VNS Therapy System at 1.5 and 3 tesla (T) using various device configurations and MRI conditions and to assess device function before and after MRI. Methods. The VNS Therapy System (pulse generator, Model 102; leads Models 300 and 302; Cyberonics, Inc., Houston, Tex, USA) underwent assessment of MRI-related heating at 1.5 and 3 T using different positioning configurations, leads, transmit radiofrequency (RF) coils (body and head), RF power levels, and scans on different body regions. The function of the VNS Therapy System was evaluated before and after scanning. Results. At 1.5 T using a transmit RF body coil, excessive temperature changes were associated with scans of the C-spine/shoulder (+11.5 degrees C, complete system; +29.5 degrees C, lead without pulse generator). The lowest temperature change occurred for the scan of the L-spine. At 1.5 T using a transmit/receive RF head coil, temperature changes did not exceed +0.2 degrees C under the conditions studied. At 3 T using a transmit RF body coil, the highest temperature change occurred with the scan of the C-spine/shoulder (+14.5 degrees C) with the lead configured with no strain relief loops at the vagus nerve. MRI performed using various conditions at 1.5 and 3 T produced no significant alterations in the function of the VNS Therapy System. Conclusions. MRI-related heating was characterized for a variety of scenarios, identifying unsafe as well as safe conditions. Device function was unaffected by MRI procedures at 1.5 and 3 T. By following specific conditions, safety guidelines for the VNS Therapy System may be expanded beyond those currently indicated by the manufacturer.
- 7. Schrader LM, Stern JM, Fields TA, Nuwer MR, Wilson CL. A lack of effect from transcranial magnetic stimulation (TMS) on the vagus nerve stimulator (VNS). *Clin Neurophysiol*. 2005;116(10):2501-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16122980>  
**Abstract** OBJECTIVE: The effects of transcranial magnetic stimulation (TMS) on vagus nerve stimulation (VNS) are unknown. Understanding these effects is important before exposing individuals with an implanted VNS to TMS, as could occur in epilepsy or depression TMS research. To explore this issue, the TMS-induced current in VNS leads and whether TMS has an effect on the VNS pulse generator was assessed. METHODS: Ex vivo measurement of current in VNS leads during single-pulse TMS and pulse generator function before, during, and after single-pulse TMS was assessed. RESULTS: At the highest intensity and with the TMS coil held approximately 5 mm from the VNS wires, a 200 nA, 1.0 ms current was induced by TMS. This translates to an induced charge density of 3.3 nC/cm<sup>2</sup>/phase. The function of the pulse generator was unaffected by single-pulse TMS, even when its case was directly stimulated by the coil. CONCLUSIONS: TMS-induced current in VNS electrodes was not only well outside of the range known to be injurious to peripheral nerve, but also below the activation threshold of nerve fibers. SIGNIFICANCE: Using single-pulse TMS in individuals with VNS should not result in nerve stimulation or damage. Furthermore, single-pulse TMS does not affect the VNS pulse generator's function.
- 8. Bejanishvili S, Osborne LE, Messenger K, Olejniczak P, Gutierrez A. EMG vagus nerve stimulator artifact. *Neurol Clin Neurophysiol*. 2005;2005:1.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17139390>  
**Abstract** EMG artifact produced by a VNS stimulator is described. A patient with a VNS stimulator underwent an EMG study for suspected ALS. Artifacts that appeared similar to positive sharp waves or fibrillations were noted that could produce a false clinical diagnosis. These VNS-EMG artifacts matched well with the VNS generator's set parameters. We conclude that EMG findings must be interpreted with caution in patients with VNS implants and also that EMG may have a possible monitoring value for VNS activity.

9. **Grant H, Heirman D, Kuriger G, Ravindran MM. In vitro study of the electromagnetic interaction between wireless phones and an implantable neural stimulator. *Bioelectromagnetics*. 2004;25(5):356-61.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15197759>  
<http://onlinelibrary.wiley.com/doi/10.1002/bem.10204/abstract>  
**Abstract** Several clinical and laboratory studies have demonstrated electromagnetic interaction between implantable medical devices like pacemakers and cell phones being operated in close proximity. Those devices are largely now immune to phone interaction or procedures have been established to limit their interaction. The use of cell phones near people with implanted neural stimulators has not been studied. This research was initiated to investigate electromagnetic interaction between current cell phone technology and specific models of Cyberonics neural stimulators. Out of 1080 test runs conducted for this study, no interactions were observed, and it was concluded that the phone technologies examined in this study did not adversely affect the Cyberonics NeuroStar (Model 102) NeuroCybernetic Prosthesis (NCP) System. This article provides details on the experimental procedure that was used, which can also be used to test other neural stimulators and test technologies, and the results obtained.
10. **Jandial R, Aryan HE, Hughes SA, Levy ML. Effect of vagus nerve stimulator magnet on programmable shunt settings. *Neurosurgery*. 2004;55(3):627-9; discussion 629-30.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15335429>  
**Abstract** OBJECTIVE: Vagus nerve stimulators and programmable shunt valves are used in the operative care of epilepsy and hydrocephalus, respectively. Both devices use magnetic fields to activate and program their various settings and functions. The authors conducted several ex vivo trials to better elucidate any interplay between the two systems. METHODS: A pulse generator controller (Cyberonics Corp., Houston, TX) was brought to within 4 cm of Strata programmable shunt valves (Medtronic Neurosurgery, Goleta, CA). Each of five valves was preset to either a low- or high-pressure setting and then challenged with the vagus nerve stimulator generator. Each valve was challenged 20 times, for a total of 100 trials. RESULTS: In 100 trials, 78 inadvertent pressure setting adjustments were recorded. In 46 attempts, the valve pressure was increased, and in 34 attempts, the pressure was decreased. CONCLUSION: This study provides some support to the anecdotal reports of inadvertent adjustments of programmable shunt valves by the external magnetic field created by vagus nerve stimulator pulse generator controllers. Further trials and a double-blind study are necessary to illustrate more clearly the possible relationship of these magnetically controlled neurosurgical devices.
11. **Sucholeiki R, Alsaadi TM, Morris GL, 3rd, Ulmer JL, Biswal B, Mueller WM. fMRI in patients implanted with a vagal nerve stimulator. *Seizure*. 2002;11(3):157-62.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12018958>  
[http://ac.els-cdn.com/S1059131101906016/1-s2.0-S1059131101906016-main.pdf?\\_tid=093a7a62-8cc4-11e2-9d2e-00000aab0f26&acdnat=1363278617\\_0766c34b975ac60c91fd29f1ef1120e1](http://ac.els-cdn.com/S1059131101906016/1-s2.0-S1059131101906016-main.pdf?_tid=093a7a62-8cc4-11e2-9d2e-00000aab0f26&acdnat=1363278617_0766c34b975ac60c91fd29f1ef1120e1)  
**Abstract** OBJECTIVE: To demonstrate the feasibility and safety of using functional magnetic resonance imaging (fMRI) to determine the blood oxygen level dependent changes (BOLD) in patients undergoing vagal nerve stimulation (VNS) for the treatment of epilepsy. METHODS: Four patients with an implanted vagus nerve stimulator had fMRI images acquired during several cycles of intermittent VNS. Blood oxygen level dependent changes were detected. These regions were then superimposed upon the patients' structural MR images. RESULTS: Patients undergoing VNS tolerated fMRI without difficulty. No complications with the implanted stimulators were encountered. Areas of activation were noted in several cortical regions, including frontal, temporal, parietal, and occipital cortices. CONCLUSION: Our study in four patients shows fMRI can be performed safely in patients with an implanted vagal nerve stimulator. The successful use of fMRI during VNS offers potential advantages over PET imaging by allowing rapid image acquisition and the ability to repeatedly study patients over time. Our preliminary results differ from previous PET or SPECT studies in failing to detect changes in subcortical areas. This finding could be due to the smaller n in this study compared with the other studies.

12. **Benbadis SR, Nyhenhuis J, Tatum WO, Murtagh FR, Gieron M, Vale FL. MRI of the brain is safe in patients implanted with the vagus nerve stimulator. *Seizure*. 2001;10(7):512-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/11749109>

**Abstract** Metallic devices generally represent a contra-indication for MRI scanning. Based on laboratory testing, the neuro cybernetic prosthesis (NCP) is labelled MRI compatible when used with a send and receive head coil. However, there are no published clinical data to support the safety of brain MRI in patients with the NCP. Our objective was to report clinical experience with such a population. We questioned 40 centres that had implanted the NCP system as of 10/1/99. If MRI had been performed on any vagus nerve stimulator patients, we collected information on these patients, the MRI technique used, any events noted during the scan, including both subjective reports (by the patient), and observable (objective) changes noted by the staff. Twelve centres (30%) responded. Over a time period of 3 years, there were a total of 27 MRI scans performed in 25 patients. All scanners were 1.5 T. A head coil was used in 26 scans, and a body coil in one. The indications for the scans were diverse. Seven were related to the epilepsy, including aetiology or pre-surgical evaluation. Others were unrelated, including brain tumours, cerebral haematoma, vasculitis, headaches, and head trauma. Three scans were performed with the stimulator on, while 24 were performed with the stimulator off. One patient had a mild objective voice change for several minutes. No other objective changes were noted in any of the patients. One 11-year old reported chest pain while experiencing severe claustrophobia. Twenty-five patients denied any discomfort around the lead or the generator. We conclude that this clinical series supports the safety of routine brain MRI using a send and receive head coil in patients implanted with the NCP System.

**Safety Information - Laryngeal Function (VNS effects on...)**

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- 1. El Tahry R, Mollet L, Raedt R, Delbeke J, De Herdt V, Wyckhuys T, et al. Repeated assessment of larynx compound muscle action potentials using a self-sizing cuff electrode around the vagus nerve in experimental rats. *J Neurosci Methods*. 2011;198(2):287-93.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21513735>

**Abstract** RATIONALE: Vagus nerve stimulation (VNS) is an adjunctive treatment for patients with refractory epilepsy. In more than 30% of the patients VNS has no therapeutic effect. The goal of this study was to find an objective parameter that can be used as an indicator of effective stimulation of the vagus nerve. METHODS: The electrophysiological response to VNS was recorded from the vagus nerve, recurrent laryngeal nerve and larynx muscles. Nerve lesions and muscle relaxing agent were used to find the source of the electrophysiological response. A cuff-electrode for chronic stimulation and recording was implanted for chronic recording of the VNS-induced electrophysiological response after implantation. Dose-response curves were determined daily during a follow-up period of 2 months. RESULTS: VNS induced an electrophysiological response around 3 ms after start of the stimulation. This response was identified as a larynx compound action potential (LCMAP) LCMAP could be recorded immediately after surgery in 11/21 rats, while in the other 10/21 rats, a recovery period with an average of 25 days was required. Once the LCAMP could be recorded, the latency and overall characteristics of the doses response curves of the LCMAP remained stable during the entire follow-up period. CONCLUSIONS: In this study, we provide an objective electrophysiological parameter for vagus nerve activation. LCAMP may indicate recovery of the vagus nerve after implantation, which may help to determine when up-titration of VNS therapy can be initiated. LCAMP could be of value in future experiments for objectification of VNS in animal models for epilepsy.
  
- 2. Ardesch JJ, Sikken JR, Veltink PH, van der Aa HE, Hageman G, Buschman HP. Vagus nerve stimulation for epilepsy activates the vocal folds maximally at therapeutic levels. *Epilepsy Res*. 2010;89(2-3):227-31.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20129758>

**Abstract** PURPOSE: Vagus nerve stimulation (VNS) for medically refractory epilepsy can give hoarseness due to stimulation of the recurrent laryngeal nerve. For a group of VNS-therapy users this side-effect interferes severely with their daily activities. Our goal was to investigate the severity of intra-operative VNS-related vocal fold contraction at different pulse widths and current output parameters. We investigated electromyographic and morphometric alterations on the vocal folds during VNS. METHODS: Vocal fold EMG experiments were conducted intra-operatively during the implantation of a VNS system. During surgery the VNS pulse generator was programmed to stimulate at different pulse durations. At each pulse width the EMG-threshold current was determined by electrical stimulation of the vagus nerve with increasing stimulation currents. Laryngostroboscopic examination was performed after surgery to analyze the effects of spontaneous stimulation on the larynx. RESULTS: The vocal fold EMG and morphodynamic changes in the larynx have been analyzed in eight patients. In all patients left vocal fold EMG-threshold was between 0.25 and 0.50 mA. Pulse duration had little influence on the EMG-threshold level. Vocal fold EMG saturation levels were reached between 0.75 and 1.00 mA. Video stroboscopic monitoring showed that stimulation induced an adductory spasm of either the ipsilateral vocal fold or the vestibular fold, and was present remarkably irrespective of the presence of hoarseness. CONCLUSIONS: VNS causes pronounced effects on the vocal folds even at low stimulation amplitudes. At therapeutic levels even at the lowest stimulation pulse durations, the vocal fold contract, however, this does not necessarily give hoarseness.

- 3. Shaw GY, Sechtem P, Searl J, Dowdy ES. Predictors of laryngeal complications in patients implanted with the Cyberonics vagal nerve stimulator. *Ann Otol Rhinol Laryngol.* 2006;115(4):260-7. <http://www.ncbi.nlm.nih.gov/pubmed/16676822>**

**Abstract** OBJECTIVES: Since its approval by the US Food and Drug Administration in 1997 for management of medically refractory seizures, more than 35,000 patients have been implanted with the Cyberonics vagal nerve stimulator. Preliminary reports described transient vocal changes in the majority of subjects, which were thought to be short-term. However, these reports were for the most part based upon perceptual evaluations by the subjects themselves. Later reports described possibly more permanent recurrent laryngeal nerve injury and recommended measuring the nerve diameter to use the safest spiral cuff electrode. To date, no study has systematically evaluated vocal fold mobility in subjects before and after implantation. The objectives of this study were to determine the true incidence of both short- and long-term recurrent laryngeal nerve injuries and determine whether there are any potential indicators to predict in which patients long-term nerve deficits may develop. METHODS: Thirteen subjects underwent preimplantation laryngeal electromyography, videolaryngoscopy, measurement of the maximum phonation time, Voice Handicap Index determination, and Consensus Auditory-Perceptual Evaluation of Voice. Two weeks after implantation, all subjects underwent videolaryngoscopy. Three months after implantation and activation of the device, all subjects were reevaluated. RESULTS: Six of the 13 subjects had significant vocal fold mobility abnormalities at 2 weeks. Significant electromyographic abnormalities were detected before implantation in 5 subjects. All 5 of these subjects, at 3 months after implantation, had prolonged left vocal fold paresis. CONCLUSIONS: The authors conclude that perioperative vocal fold paresis occurs in approximately 50% of subjects. Further, laryngeal electromyography performed before implantation of the vagal nerve stimulator is a statistically significant predictor ( $p < .05$ ) of which patients may be at risk for extended vocal fold abnormalities. Possible explanations for this phenomenon are offered. Surgical modifications to limit vagal nerve injury are offered.
  
- 4. Shaffer MJ, Jackson CE, Szabo CA, Simpson CB. Vagal nerve stimulation: clinical and electrophysiological effects on vocal fold function. *Ann Otol Rhinol Laryngol.* 2005;114(1 Pt 1):7-14. <http://www.ncbi.nlm.nih.gov/pubmed/15697156>**

**Abstract** More than 16,000 vagal nerve stimulators (VNSs) have been implanted for refractory epileptic seizures. The most commonly reported side effect is hoarseness. This study examines the effects of VNS placement on vocal fold function. Eleven patients who had undergone VNS placement at our institution were recruited. Subjective evaluation by a panel of speech and language pathologists of both connected speech and videolaryngoscopy recordings were used both at rest and during VNS activation. Additional subjective evaluation included use of the Voice Handicap Index for the study group. These results were compared to data from age- and sex-matched controls. Objective data included maximum phonation time in the study and control groups, as well as laryngeal electromyography performed on the VNS-implanted patients only. Motor unit potential morphology and recruitment, as well as spontaneous activity, were analyzed bilaterally for the cricothyroid and thyroarytenoid muscles. Significant differences were found between the study and control groups subjectively for vocal quality and videolaryngoscopy parameters. Vocal fold tension, supraglottic muscular hyperfunction, and reduced vocal fold mobility were the most common findings during VNS activation. Two of 10 patients had immobile left vocal folds in the absence of active stimulation. The maximum phonation time was generally reduced in the subject group, but this reduction did not reach statistical significance. Finally, 6 of 10 patients had abnormal electromyographic results, including large-amplitude polyphasic motor unit potentials and decreased recruitment. We conclude that implantation of a VNS can affect vocal fold function. The effects are magnified during periods of active stimulation. There is the potential for nerve degeneration after prolonged repetitive stimulation, and there may be a trend toward greater vocal fold dysfunction with higher stimulation parameters.

5. **Yelmen NK, Sahin G, Oruc T. The effects of vagal stimulation on laryngeal vascular resistance and intraluminal pressure in the dog. *Tohoku J Exp Med.* 2004;202(4):283-94.**

<http://www.ncbi.nlm.nih.gov/pubmed/15109126>

[https://www.jstage.jst.go.jp/article/tjem/202/4/202\\_4\\_283/\\_pdf](https://www.jstage.jst.go.jp/article/tjem/202/4/202_4_283/_pdf)

**Abstract** In anaesthetized dogs (sodium pentobarbitone 30 mg/kg, i.v.) laryngeal vascular resistance was measured by unilateral perfusion at constant flow of the branch of the cranial superior thyroid artery that supplies the larynx. Arterial perfusion was at constant flow and inflow pressure was divided by flow to give laryngeal vascular resistance (R(LV)). Intraluminal laryngeal pressure (P(L)) and systemic arterial blood pressure (BP) were also measured. Stimulation (20 V, 20 Hz, 0.2 milliseconds) of the central end of cervical vagus caused an increase in R(LV) (+22.9+/-6.1%) and a decrease in P(L) (-12.1+/-4.4%). Stimulation (10 V, 10 Hz, 0.2 milliseconds) of the central end of the recurrent laryngeal nerve (RLN) reduced RLV (-3.4+/-0.8%) and P(L) (-7.5+/-4.1%). Stimulation of the peripheral end of the RLN decreased R(LV) (-7.1+/-1.9%) and increased PL (+21.6+/-7.7%). Stimulation of the central end of the superior laryngeal nerve (SLN) increased R(LV) (+17.9+/-3.2%) and P(L) (+59.8+/-2.7%), whereas stimulation of the peripheral end of the SLN decreased R(LV) (-4.8+/-1.6%) and P(L) (-4.1+/-2.4%). After treatment with alpha-adrenoreceptor antagonist phentolamine (0.5 mg/kg, i.v.), stimulation of the central end of cervical vagus nerve reduced R(LV) by 25% and decreased BP. Phentolamine caused a decrease in BP and reduced the magnitude of increase in R(LV) in response to stimulation of central end of SLN. After atropine sulphate (0.5-2.0 mg/kg, i.v.), the stimulation of both central and peripheral ends of RLN reduced R(LV). The decrease in R(LV) during stimulation of peripheral end of SLN was reduced by atropine. Thereafter, pancuronium bromide (0.06-0.1 mg/kg, i.v.) was given and dogs were artificially ventilated. After paralyzed, stimulation of the central end of the SLN decreased R(LV) (+26.0+/-4.5%) but produced no change in P(L). It is concluded that parasympathetic motor fibers in the RLN and SLN are effective for the laryngeal vascularity and non-adrenergic system may be responsible for laryngeal vasoconstriction. laryngeal vasculature; vagal stimulation; phentolamine; atropine

6. **Santos PM. Evaluation of laryngeal function after implantation of the vagus nerve stimulation device. *Otolaryngol Head Neck Surg.* 2003;129(3):269-73.**

<http://www.ncbi.nlm.nih.gov/pubmed/12958579>

**Abstract** OBJECTIVES: The vagus nerve stimulation device (VNS) is used for the management of seizures. This study evaluated what effect the diameter of the vagus nerve helical electrode might have on true vocal cord (TVC) mobility. The study was prompted after 2 cases of TVC immobility. Electrode nerve compression was suspect. METHODS: Eighteen patients underwent intraoperative vagus nerve measurement and electrode placement with subsequent voice and TVC evaluation. Electrode selection was based on vagus nerve measurements. RESULTS: Seven patients had vagus nerves measuring less than 2 mm diameter and received the 2-mm inner diameter electrode. Eleven patients had vagus nerves measuring more than 2 mm in diameter and received the 3-mm inner diameter electrode. No patients experienced transient or permanent hoarseness or paresis/paralysis. CONCLUSION: Precise vagus nerve measurements and electrode selection appear to decrease the incidence of nerve compression injury and TVC immobility.

7. **Charous SJ, Kempster G, Manders E, Ristanovic R. The effect of vagal nerve stimulation on voice.**

*Laryngoscope*. 2001;111(11 Pt 1):2028-31.

<http://www.ncbi.nlm.nih.gov/pubmed/11801991>

<http://onlinelibrary.wiley.com/doi/10.1097/00005537-200111000-00030/abstract>

**Abstract** OBJECTIVE: Vagal nerve stimulation therapy through implanted vagal nerve stimulators is an accepted therapy for refractory seizure disorders. One significant side effect of vagal nerve stimulation is voice change. This study evaluates the impact that these voice changes have on patients' lives, and the physiological effects that vagal nerve stimulation has on the larynx. METHODS: Patients were selected from the pool of patients at Rush-Presbyterian-St. Luke's Medical Center who underwent implantation of vagal nerve stimulator devices. Three methods were used to evaluate the impact the devices had on patients and on their vocal cords. First, a questionnaire was sent to the patients to ascertain the degree of vocal and social impairment that occurs as a result of the implant. Second, videostroboscopy was used to analyze the effect that vagal nerve stimulation had on the larynx. Third, computerized voice analysis objectively analyzed the patients' voices both during and in between vagal nerve stimulations. RESULTS: Although patients noted significant voice changes during stimulation of the implant, the impairment is well tolerated and less debilitating than the underlying seizure disorder. Hyperstimulation of the affected vocal cord was observed during vagal stimulation with paramedian positioning, vocal fold tensing, and loss of mucosal wave. Increase in jitter and shimmer was consistent. CONCLUSION: Vagal nerve implantation devices create significant but well-tolerated vocal side effects. Investigation of these devices increases our understanding of laryngeal physiology and may give insight into future laryngeal pacing. Preimplantation laryngeal examination should be performed routinely to rule out laryngeal pathology that could lead to significant complications.

8. **Lundy DS, Casiano RR, Landy HJ, Gallo J, Gallo B, Ramsey RE. Effects of vagal nerve stimulation on laryngeal function. *J Voice*. 1993;7(4):359-64.**

<http://www.ncbi.nlm.nih.gov/pubmed/8293068>

**Abstract** Functional electrical stimulation is a developing methodology that shows significant potential in the management of peripheral neuromuscular deficits. Potential applications in the head and neck area, including control of bilateral vocal fold paralysis and spasmodic dysphonia, have recently been explored. Despite promising early results, very little is known about the mechanisms of action or the long-term effects of electrical stimulation on human laryngeal function. Recent development of implantable vagal nerve stimulators as a method to control intractable seizures in individuals who have not responded to medication provides a unique opportunity to study its effect on the normal human larynx. Laryngeal and vocal function testing was studied on five individuals who had undergone vagal nerve stimulator implants for intractable seizures. Consistent abduction/adduction of the left vocal fold was achieved at 20 and 40 Hz, respectively. Higher levels of electrical stimulation produced hemispasm of the larynx. Results were consistent with studies in the literature of recurrent laryngeal nerve stimulation in animal and human models. The vagus nerve provides relatively easy access for implantation of electrodes to provide electrical stimulation to the muscles of the larynx. Vagal nerve stimulation may prove efficacious in the treatment of movement disorders of the larynx; further study is needed.

**Safety Information - Other (VNS effects on...)**

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1. **Cohen ML, Georgievskaya Z. Histopathology of the stimulated Vagus nerve: primum non nocere. *Heart Fail Rev.* 2011;16(2):163-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20623184>  
<http://link.springer.com/article/10.1007%2Fs10741-010-9182-6>  
**Abstract** A primary concern in the utilization of implantable neural interfaces for the treatment of medical diseases is to follow the Hippocratic dictum: First, do no harm. If we are to avoid harm to the Vagus nerve in our use of stimulatory electrodes in the treatment of heart failure, we must understand the structural and functional elements that comprise peripheral nerves, their susceptibility to various types of injury that might be expected to occur secondary to functional electrical stimulation and how to separate the various components of the response of peripheral nervous system elements to stresses that may occur in the complex interactions that take place between electrode and nerve. To this end, we review the functional histology of peripheral nerve, followed by a consideration of salient types of nerve injuries, which have been elucidated through the combination of careful observations of human disease and well-constructed experimental models. We then examine the extant literature on stimulation-induced nerve injury in light of recent developments in the understanding of electropermeabilization of biological membranes. Finally, we briefly discuss our experience using the CardioFit electrode on the canine Vagus nerve.
  
2. **Rauchenzauner M, Haberlandt E, Ortler M, Tatarczyk T, Laimer M, Trinkka E, et al. N-terminal pro-brain natriuretic peptide (NT-proBNP) release in children with vagus nerve stimulation. A prospective case series. *J Neurol.* 2008;255(7):980-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18581038>  
<http://link.springer.com/article/10.1007%2Fs00415-008-0804-z>  
**Abstract** Brain natriuretic peptide(BNP) and the N-terminal pro-brain natriuretic peptide (NTproBNP)are important cardiac biomarkers secreted by the heart in response to increased ventricular wall stress associated with heart failure. The aim of our case series was to prospectively evaluate the influence of vagus nerve stimulation (VNS) on the release of NTproBNP.Three children with medically refractory epilepsy and scheduled for implantation of the VNS device were included. Pre-implantation,NT-proBNP measurements were taken at two different occasions after seizure-free periods of at least three days. After implantation,NT-proBNP measurements were taken every 2 to 4 weeks, immediately before and immediately after up-regulation of the VNS. After VNS implantation, the pattern of NT-proBNP increase was consistent for all children. In a 12 year-old girl, NT-proBNP concentrations reached a maximum of an almost 10-fold increase. Thereafter, NTproBNP concentrations returned continuously to baseline. In a three year-old boy, NT-proBNP concentrations reached a maximum of an almost 7-fold increase, accompanied by manifestation of side effects(voice alterations, snoring).Thereafter, NT-proBNP concentrations decreased to almost 4-fold those at baseline. In an 8 year-old girl, NT-proBNP concentrations increased slightly without yet reaching a plateau. This case series suggests that NT-proBNP concentrations increase in response to VNS-induced autonomic influences involving endocrinological stress-response mechanisms typically associated with cardiac injury.Especially in patients with pre-existing cardiovascular dysfunction,measurement of NT-proBNP concentrations may help to identify patients with high baseline concentrations and possibly at greater risk for cardiac side effects.

3. **Diaz-Guemes Martin-Portugues I, Sanchez Margallo FM, Pascual Sanchez-Gijon S, Crisostomo Ayala V, Uson Gargallo J. Histopathologic features of the vagus nerve after electrical stimulation in swine. *Histol Histopathol.* 2005;20(3):851-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15944935>  
**Abstract** This paper describes the histological features of the vagus nerve after its stimulation with an electrostimulation system that is being developed for morbid obesity treatment. An electrostimulation system was implanted laparoscopically around the ventral vagal trunk of five Large White female pigs (49.63±1.94 kg.). Vagal nerve stimulation was performed by continuous constant voltage current pulses. Thoracic samples of both ventral and dorsal vagal trunks were obtained thoracoscopically one month after implantation. Animals were sacrificed one month after thoracoscopic vaguectomy. Tissue samples were then harvested from the vagal nerve at the implantation site, 1cm cranial to it, thoracic portion of ventral and dorsal vagal trunks, sub-diaphragmatic dorsal vagal trunk, left and right vagus nerves. Specimens were analysed with light microscope. The severity of the lesions was graded from 0 to 4 (0: no lesion, 1: mild, 2: moderate, 3: severe and 4: extremely severe), taking into account fibrosis, vascularization, necrosis, fiber degeneration and inflammation. Electrode implantation resulted in thickened epineurium and endoneural connective tissue. The greatest lesion score was evidenced at the leads implantation site in the ventral vagal trunk, followed by, in order of decreasing lesion severity, left vagus nerve, thoracic portion of ventral vagal trunk, subdiaphragmatic dorsal vagal trunk, thoracic portion of dorsal vagal trunk and right vagus nerve. The stimulation device used in this study caused connective tissue growth, greatest in the samples located closer to the implantation site. However, there was no sign of altered vascularization in any studied specimen.
4. **Tubbs RS, Patwardhan R, Palmer CA, Kelly DR, Elton S, Blount JP, et al. Histological appearance of a chronically stimulated vagus nerve in a pediatric patient. *Pediatr Neurosurg.* 2001;35(2):99-102.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11549921>  
<http://www.karger.com/Article/FullText/50398>  
**Abstract** Histological analysis of chronically stimulated human vagus nerves is lacking in the literature. In this study, we describe the first microscopic findings in a chronically stimulated left vagus nerve from a pediatric patient. Our results show many histological changes in and around the stimulated nerve with severe demyelination. Further long-term clinical and postmortem examinations of chronically stimulated vagus nerves in both children and adults are needed to ascertain whether prolonged exposure to electrical current can cause clinical dysfunction of this nerve.
5. **Schallert G, Foster J, Lindquist N, Murphy JV. Chronic stimulation of the left vagal nerve in children: effect on swallowing. *Epilepsia.* 1998;39(10):1113-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9776333>  
**Abstract** PURPOSE: To learn whether stimulation of the left vagal nerve would influence swallowing. METHODS: Eight children receiving intermittent left vagal nerve stimulation (VNS) for their pharmaco-resistant epilepsy underwent barium swallow studies with their generators off, on, and at maximally tolerated settings. RESULTS: Laryngeal penetration of barium was present in three patients without stimulation, and was caused by VNS in one other patient. Aspiration never occurred. CONCLUSIONS: Stimulation of the left vagal nerve under conditions used to treat epilepsy does not cause aspiration.

6. **Tougas G, Fitzpatrick D, Hudoba P, Talalla A, Shine G, Hunt RH, et al. Effects of chronic left vagal stimulation on visceral vagal function in man. *Pacing Clin Electrophysiol.* 1992;15(10 Pt 2):1588-96. <http://www.ncbi.nlm.nih.gov/pubmed/1383974>**

**Abstract** We examined the effects of chronic left vagal electrostimulation on afferent and efferent gastrointestinal vagal function in eight patients. Afferent function was assessed using cortical evoked responses to electrical stimulation of the esophagus and to direct vagal stimulation using the implanted left vagal electrode. Efferent gastrointestinal vagal function was measured by examining the basal, maximal, and sham fed stimulated gastric acid output prior to and with chronic left vagal electrostimulation. Esophageal electrostimulation produced a cortical evoked response consisting of three negative and three positive peaks within 400 msec after stimulation. Prior to vagal electrostimulation the mean conduction velocity of the afferent signal was measured at 8.72 +/- 3.39 m/sec, compatible with A-delta fibers involvement. Basal, maximal, and sham fed acid output were 1.11, 21.87, and 9.37 mmol/hour, respectively. The evoked response to esophageal electrical stimulation was not changed with chronic left vagal electrostimulation. Direct vagal stimulation also produced evoked potentials that were comparable to those obtained with esophageal stimulation. The mean conduction velocity was 6.26 +/- 2.72 m/sec (NS) so that there was no evidence of loss of myelinated fibers with chronic stimulation. No differences were detected in basal (1.29 mmol/h), maximal (21.64 mmol/h), or sham fed stimulated (8.03 mmol/h) acid output, showing that vagal electrostimulation has no effect on either total or vagally mediated acid output, an efferent vagal function. In conclusion, chronic left vagal electrostimulation has no significant adverse effect on gastrointestinal vagal function.

**Safety Information - Preganancy (VNS in...)**

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- 1. Houser MV, Hennessy MD, Howard BC. Vagal nerve stimulator use during pregnancy for treatment of refractory seizure disorder. *Obstet Gynecol.* 2010;115(2 Pt 2):417-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20093864>

**Abstract** BACKGROUND: In patients with medically refractory seizures, vagal nerve stimulation is becoming an increasingly common adjunctive therapy. Although its safety and efficacy have been proven in the general population, little is known about its use during pregnancy. CASE: A 19-year-old primigravid woman presented during the first trimester for routine prenatal care. She had a past medical history significant for generalized tonic-clonic seizure disorder since childhood. Multiple medical regimens had failed, and a vagal nerve stimulator was implanted approximately 2 months before conception. The patient continued to take phenytoin, with improved seizure control. She had a term spontaneous delivery complicated by mild preeclampsia. CONCLUSION: Adjunctive treatment of medically refractory seizures with a vagal nerve stimulator is a viable option during pregnancy.
  
- 2. Danielsson I, Lister L. A pilot study of the teratogenicity of vagus nerve stimulation in a rabbit model. *Brain Stimul.* 2009;2(1):41-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20633402>

**Notes** ALTHOUGH NOT PART OF OUR SEARCH WINDOW, WE CAME ACROSS THIS ARTICLE WHILE UPDATING THE LIST.

**Abstract** BACKGROUND: Vagus nerve stimulation (VNS) is approved for the adjunctive treatment of both refractory epilepsy and treatment-resistant depression. This study assessed the effect of VNS on fertility, teratogenicity, and neonatal morbidity in rabbits. METHODS: Ten female New Zealand white rabbits (test animals) were implanted with the VNS device. Ten additional female rabbits (surgical controls) received nonfunctional devices. Four additional female rabbits served as untreated controls and 10 male rabbits served for siring purposes. Test rabbits received VNS at 1 mA, 30 Hz, 500 microseconds, 30 seconds ON, 5 minutes OFF. Rabbits mated and were randomly assigned into 2 groups: those killed on day 28 and those proceeding through parturition. Groups were compared by using a 1-way analysis of variance with a Newman-Keuls Multiple Comparison post-hoc test. Differences between control and test animals were considered statistically significant if  $P \leq .05$ . RESULTS: No statistically significant differences were noted for weight, matings required for successful copulation, food or water consumption, hematology, clinical chemistry, organ weights, uterine contents, kit weights and survival, or clinical observations. No changes or abnormalities could be attributed to the VNS device at necropsy or histopathologic assessment. No skeletal or soft tissue abnormalities were noted in any of the fetuses. CONCLUSIONS: In this very small sample of rabbits treated with VNS, we failed to find any conclusive teratogenic effects of VNS. The sample was too small, however, to support definitive conclusions regarding this issue. Brain stimulation devices in general and VNS in particular are potentially attractive in managing brain disorders such as epilepsy and depression during pregnancy and lactation as they do not have the systemic effects characteristic of medications and do not directly affect the fetus. Further studies are needed to address this issue.

3. **Husain MM, Stegman D, Trevino K. Pregnancy and delivery while receiving vagus nerve stimulation for the treatment of major depression: a case report. *Ann Gen Psychiatry*. 2005;4:16.**

<http://www.ncbi.nlm.nih.gov/pubmed/16168055>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1242217/pdf/1744-859X-4-16.pdf>

**Abstract** BACKGROUND: Depression during pregnancy can have significant health consequences for the mother and her infant. Antidepressant medications, which pass through the placenta, may increase the risk of low birth weight and preterm delivery. The use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy may induce serotonergic symptoms in the infant after delivery. Antidepressant medications in breast milk may also be passed to an infant. Vagus nerve stimulation (VNS) therapy is an effective non-pharmacologic treatment for treatment-resistant depression (TRD), but little information exists regarding the use of VNS therapy during pregnancy. CASE PRESENTATION: The patient began receiving VNS therapy for TRD in March 1999. The therapy was effective, producing substantial reductions in depressive symptoms and improvement of function. In 2002, the patient reported that she was pregnant. She continued receiving VNS therapy throughout her pregnancy, labor, and delivery, which enabled the sustained remission of her depression. The pregnancy was uneventful; a healthy daughter was delivered at full term. CONCLUSION: In this case, VNS therapy provided effective treatment for TRD during pregnancy and delivery. VNS was safe for the patient and her child.

**Safety Information - Review Articles**

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- 1. Higgins D, Dix D, Gold ME. Vagal nerve stimulation: a case report. *AANA J.* 2010;78(2):146-50. <http://www.ncbi.nlm.nih.gov/pubmed/20583461>**  
**Abstract** Despite numerous medications designed to eliminate or decrease seizures, an estimated 20% of epileptic patients in the United States remain refractory to these agents. Vagal nerve stimulation can decrease the number of seizure episodes. In 1997, the US Food and Drug Administration approved the first implantable stimulation device for the treatment of medically refractory epilepsy. This case report describes the anesthetic management of a patient for placement of a vagal nerve stimulator. A review is presented of the current literature regarding long-term antiepileptic drug therapy and its effect on anesthetic management, pathophysiology of epilepsy and seizure propagation, and the effects of commonly used anesthetic agents on the seizure threshold. Also discussed are the physiology of vagal nerve stimulation, benefits and potential complications that may occur with its implantation, and device mechanics as it relates to future surgical procedures. As the use of vagal nerve stimulators increases, knowledge of these processes is important to ensure safe and effective anesthetic management.
- 2. Wilong AA. Complications and consequences of epilepsy surgery, ketogenic diet, and vagus nerve stimulation. *Semin Pediatr Neurol.* 2007;14(4):201-3. <http://www.ncbi.nlm.nih.gov/pubmed/18070677>**  
**Abstract** Children with medically intractable epilepsy may be candidates for nonpharmacologic therapies such as resective and disconnection epilepsy surgery, the ketogenic diet and its variants, and vagus nerve stimulation. Each of these therapies offers unique advantages and disadvantages, and careful consideration of the risk-benefit analysis must be tailored to each child. The hopeful outcome from each of these therapies is seizure freedom or at least a very significant improvement in seizure control, with few or no adverse effects. However, unfortunate adverse consequences can and do occur. These may be serious and irreversible or more commonly mild and transient. An appreciation of these complications and consequences is necessary for the comprehensive management of these complex patients.
- 3. Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. *J Clin Neurophysiol.* 2001;18(5):415-8. <http://www.ncbi.nlm.nih.gov/pubmed/11709646>**  
**Abstract** Vagus nerve stimulation (VNS) is an accepted therapy for the treatment of refractory epilepsy and now even depression. More than 10,000 people have had the device implanted over a period of 12 years. Initial side effects in the early years such as lower facial weakness and electrode lead breaks have now been resolved. Postoperative infections occur in approximately 3% of patients but can be treated with oral antibiotics. Side effects during the use of VNS are usually related to the "on" phase of stimulation. Common side effects are cough, hoarseness, voice alteration, and paresthesias. These side effects tend to diminish with time. Cognitive side effects often seen with antiepileptic drug use are not reported. The side effect profile of VNS is positive, and this treatment option offers patients with refractory epilepsy prospects of good efficacy with only minor and often resolvable side effects.
- 4. Agnew WF, McCreery DB. Considerations for safety with chronically implanted nerve electrodes. *Epilepsia.* 1990;31 Suppl 2:S27-32. <http://www.ncbi.nlm.nih.gov/pubmed/2226363>**  
**Abstract** Electrical stimulation of cranial and peripheral nerves has been used to ameliorate a variety of neurologic disease states and neural injuries over the past 20 years. In this review, clinical applications and the histopathologic results of chronic implants in animals and humans are discussed, and the results of neural damage models developed at Huntington Medical Research Institutes are summarized. Chronically implanted electrode arrays may produce neural injury by either mechanical factors or by continuous, high-frequency electrical stimulation. The margin of safety to avoid electrically induced injury may be increased by minimizing the frequency or total stimulation time, and by the use of an intermittent duty cycle. The protocols presently being used for the stimulation of the vagus nerve to effect inhibition of seizures appear to have an adequate margin of safety.

**Safety Information - Sleep Apnea**

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- 1. Linz D, Schotten U, Neuberger HR, Bohm M, Wirth K. Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation. *Heart Rhythm*. 2011;8(9):1436-43. <http://www.ncbi.nlm.nih.gov/pubmed/21457790>**

**Abstract** BACKGROUND: Obstructive sleep apnea (OSA) causes negative tracheal pressure (NTP) and is associated with atrial fibrillation (AF). OBJECTIVE: This study aimed to determine the mechanism of atrial electrophysiological changes during tracheal occlusion with or without applied NTP and to evaluate the role of vagal activation, Na(+)/H(+)exchanger (NHE), and ATP-dependent potassium channels (K(ATP)). METHODS: Seventeen closed-chest pigs were anesthetized with urethane, and an endotracheal tube was placed to apply NTP (up to -100 mbar), comparable to clinically observed OSA in patients by a negative pressure device for a time period of 2 minutes. Right atrial refractory periods (AERP) and AF inducibility were measured transvenously by a monophasic action potential recording and stimulation catheter. RESULTS: All tracheal occlusions with and without applied NTP resulted in comparable increases in blood pressure and hypoxemia. NTP shortened AERP (157.0 +/- 2.8 to 102.1 +/- 6.2 ms; P <.0001) and enhanced AF inducibility during AERP measurements from 0% at baseline to 90% (P <.00001) during NTP. Release of NTP resulted in a prompt restoration of sinus rhythm, and AERP returned to normal. NTP-induced AERP shortening and AF inducibility were prevented by atropine or vagotomy. Neither the NHE blocker cariporide nor the K(ATP) channel blocker glibenclamide abolished NTP-induced AERP shortening. By contrast, tracheal occlusion without applied NTP caused comparable changes in blood gases but did not induce AERP shortening or AF inducibility. CONCLUSION: NTP during obstructive events is a strong trigger for AF compared with changes in blood gases alone. NTP caused AERP shortening and increased susceptibility to AF mainly by enhanced vagal activation. AERP shortening was not prevented by K(ATP) channel blockade or NHE blockade.
- 2. Linz D, Schotten U, Neuberger HR, Bohm M, Wirth K. Combined blockade of early and late activated atrial potassium currents suppresses atrial fibrillation in a pig model of obstructive apnea. *Heart Rhythm*. 2011;8(12):1933-9. <http://www.ncbi.nlm.nih.gov/pubmed/21767520>**

**Abstract** BACKGROUND: Negative tracheal pressure (NTP) during tracheal obstruction in obstructive apnea increases vagal tone and causes pronounced shortening of the atrial effective refractory period (AERP), thereby perpetuating atrial fibrillation (AF). The role of different atrial potassium channels under those conditions has not been investigated. OBJECTIVE: The purpose of this study was to evaluate the atrial effects of blockade of the late activated potassium current (I(Kr)) by sotalol, of blockade of the early activated potassium currents (I(Kur)/I(to)) by AVE0118, and of the multichannel blocker amiodarone during tracheal occlusions with applied NTP. METHODS: Twenty-one pigs were anesthetized, and an endotracheal tube was placed to apply NTP (up to -100 mbar) comparable to clinically observed obstructive sleep apnea for 2 minutes. Right AERP and AF inducibility were measured transvenously by a monophasic action potential recording and stimulation catheter. RESULTS: Tracheal occlusion with applied NTP caused pronounced AERP shortening. AF was inducible during all NTP maneuvers. Blockade of I(Kr) by sotalol, blockade of I(Kur)/I(to) by AVE0118, and amiodarone did not affect NTP-induced AERP shortening, although they prolonged the AERP during normal breathing. Atropine given after amiodarone completely inhibited NTP-induced AERP shortening. The combined blockade of I(Kr) and I(Kur)/I(to) by sotalol plus AVE0118, however, attenuated NTP-induced AERP shortening and AF inducibility independent of the order of administration. CONCLUSION: The atrial proarrhythmic effect of NTP simulating obstructive apneas is difficult to inhibit by class III antiarrhythmic drugs. Neither amiodarone nor blockade of I(Kr) or I(Kur)/I(to) attenuated NTP-induced AERP shortening. However, the combined blockade of I(Kur)/I(to) and I(Kr) suppressed NTP-induced AERP shortening.

- 3. Parhizgar F, Nugent K, Raj R. Obstructive sleep apnea and respiratory complications associated with vagus nerve stimulators. *J Clin Sleep Med.* 2011;7(4):401-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21897779>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3161774/pdf/jcsm.7.4.401.pdf>

**Abstract** Intermittent vagus nerve stimulation can reduce the frequency of seizures in patients with refractory epilepsy. Stimulation of vagus nerve afferent fibers can also cause vocal cord dysfunction, laryngeal spasm, cough, dyspnea, nausea, and vomiting. Vagus nerve stimulation causes an increase in respiratory rate, decrease in respiratory amplitude, decrease in tidal volume, and decrease in oxygen saturation during periods of device activation. It usually does not cause an arousal, or a change in heart rate or blood pressure. Most patients have an increase in their apnea-hypopnea index (AHI). Patients with VNS can have central apneas, obstructive hypopneas, and obstructive apneas. These respiratory events can be reduced with changes in the vagus nerve stimulator operational parameters or with the use of CPAP. In summary, there are complex relationships between epilepsy and obstructive sleep apneas. In particular, patients with refractory epilepsy need assessment for undiagnosed and untreated obstructive sleep apnea before implantation of vagus nerve stimulator devices. Patients with vagus nerve stimulators often have an increase in apneic events after implantation, and these patients need screening for sleep apnea both before and after implantation.
  
- 4. Zaaimi B, Grebe R, Berquin P, Wallois F. Vagus nerve stimulation induces changes in respiratory sinus arrhythmia of epileptic children during sleep. *Epilepsia.* 2009;50(11):2473-80.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19682028>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2009.02190.x/asset/j.1528-1167.2009.02190.x.pdf?v=1&t=he943mwi&s=ee86c4d295fbd47398bd8b472cd415716b06787d>

**Abstract** PURPOSE: This study analyzed the direct short-term effect of vagus nerve stimulation (VNS) on respiratory sinus arrhythmia (RSA) in children with pharmaco-resistant epilepsy. METHODS: RSA magnitude is calculated as the ratio between maximum and minimum heart rate for each respiratory cycle-before, during, and after the actual VNS period. In 10 children, changes in RSA magnitude were evaluated on polysomnographic recordings, including electrocardiography (ECG), electroencephalography (EEG), thoracoabdominal distension, nasal airflow, and VNS artifacts. Measurements during stimulation were compared with those at baseline, immediately preceding the VNS periods and individually for each patient. RESULT: During VNS, respiratory frequency increased and respiratory amplitude decreased with a variable effect on cardiac activity. The coupling between heart rate and respiratory rate was disturbed and RSA magnitude decreased significantly in 6 of 10 children during VNS. These changes in RSA magnitude varied from one child to another. The observed changes for respiratory and cardiac activity were concomitant with changes in RSA but were not correlated. CONCLUSION: Together with disorders of respiration, cardiac activity, and oxygen saturation (SaO<sub>2</sub>) described previously. VNS also modifies synchronization between cardiac and respiratory activity, resulting in poor optimization of oxygen delivery to tissues that can be regarded as an additive side effect, which should be considered in patients with already altered brain function. This interaction between the effects of VNS and potential autonomic nervous system (ANS) dysfunction already reported in epileptic patients should be considered to be potentially life-threatening. In addition, evaluation of changes in respiratory parameters can also provide reliable markers for further evaluation of the effectiveness of VNS.

5. **Gschliesser V, Hogl B, Frauscher B, Brandauer E, Poewe W, Luef G. Mode of vagus nerve stimulation differentially affects sleep related breathing in patients with epilepsy. *Seizure*. 2009;18(5):339-42.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19136281>  
[http://ac.els-cdn.com/S1059131108002690/1-s2.0-S1059131108002690-main.pdf?\\_tid=4c8d1536-8cc4-11e2-90c0-00000aacb35e&acdnat=1363278730\\_534a5a02d0adab93b7c2de74a9d74720](http://ac.els-cdn.com/S1059131108002690/1-s2.0-S1059131108002690-main.pdf?_tid=4c8d1536-8cc4-11e2-90c0-00000aacb35e&acdnat=1363278730_534a5a02d0adab93b7c2de74a9d74720)  
**Abstract** PURPOSE: We describe the influence of vagus nerve stimulation (VNS) with standard mode and rapid cycling mode on sleep related breathing in two patients with epilepsy. METHODS: Two VNS treated patients underwent digital video-polysomnography for three nights (night 1: rapid cycling mode; night 2: standard mode; night 3: off mode). RESULTS: In patient 1, on off mode, apnea-hypopnea index (AHI) was 11.1/h, respiratory effort-related arousal index (RERAI) 0.9/h, flow limitation index (FLI) 0.9/h and oxygen desaturation index (ODI) 10.2/h. On standard mode, AHI was 5.5/h, RERAI 1.7/h, FLI 4.1/h and ODI 5.5/h. On rapid cycling mode, AHI was 10.4/h, RERAI 7.9/h, FLI 17.3/h and ODI 10.3/h. In patient 2, on off mode, AHI was 1.6/h, RERAI 0.8/h, FLI 2.2/h and ODI 0/h. On standard mode, AHI was 2.9/h, RERAI 2.4/h, FLI 2.6/h and ODI 2.9/h. On rapid cycling mode, AHI was 0.7/h, RERAI increased to 15.4/h, FLI to 52.0/h and ODI was 0.7/h. CONCLUSIONS: The number of RERAs as well as the number of flow limitations were higher with the rapid cycling mode compared to standard mode and stimulation off and might be related to the higher impulse frequency.
6. **Zaaimi B, Grebe R, Wallois F. Animal model of the short-term cardiorespiratory effects of intermittent vagus nerve stimulation. *Auton Neurosci*. 2008;143(1-2):20-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18757249>  
**Abstract** PURPOSE: To develop an animal model of the effects of vagus nerve stimulation (VNS) on heart rate and respiration in studies of seizure treatment. METHODS: Nine rats implanted with ECG, EMG, and VNS electrodes and pulse generator were stimulated with 81 different sets of parameters while they slept in a plethysmographic box. RESULT: From cardiorespiratory effects of VNS, an index (alpha) was found to distinguish between weak and strong VNS doses. Weak VNS dose induced an increase in respiratory frequency and no significant change in heart rate. The effect of VNS on respiration, similar to that observed in children, can be divided into 3 phases. Strong VNS dose induced a decrease in respiratory frequency concomitant with a decrease in heart rate. Increasing the intensity of the VNS induced a proportional increase in the maximal inspiratory strength. CONCLUSION: Various VNS parameter settings induce different and concomitant cardiorespiratory variations in conscious sleeping rats. These effects correlate with the intensity of the VNS parameters. Understanding the effects of the intensity of VNS parameters may allow for further optimization of VNS parameters in patients receiving VNS.

7. **Ebben MR, Sethi NK, Conte M, Pollak CP, Labar D. Vagus nerve stimulation, sleep apnea, and CPAP titration. *J Clin Sleep Med.* 2008;4(5):471-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18853706>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2576315/pdf/jcsm.4.5.471.pdf>  
**Abstract** Epilepsy and obstructive sleep apnea (OSA) are two relatively common disorders known to coexist and potentially exacerbate each other. Vagus nerve stimulation (VNS) is a currently used, adjunctive treatment for partial epilepsy and is generally well tolerated with few associated side effects. Some of the more common side effects include hoarseness of voice, laryngeal irritation and cough, especially after VNS current increases and the first few weeks of treatment. VNS therapy also affects respiration during sleep and has been shown to worsen preexisting obstructive sleep apnea/hypopnea syndrome (OSAHS) by increasing the number of apneas and hypopneas. Consistent sleep related decreases in airflow and effort coinciding with VNS activation have been documented, with apneas and hypopneas found to be more frequent during VNS activation than during nonactivation. VNS may also interfere with effective CPAP titration. The purpose of this case study was to examine the effects of VNS cycling on CPAP titration for OSA in a patient with medically intractable epilepsy. We found that adequate CPAP titration could not be achieved in the presence of the patient's standard VNS on/off cycling mode. However, when the patient was restudied with his VNS device turned off, a nasal CPAP pressure of 13 cm H<sub>2</sub>O resulted in effective treatment of his severe OSAHS. We suggest that polysomnography before VNS implantation should be considered in order to identify patients with OSA.
8. **Hsieh T, Chen M, McAfee A, Kifle Y. Sleep-related breathing disorder in children with vagal nerve stimulators. *Pediatr Neurol.* 2008;38(2):99-103; comment *Pediatr Neurol.* 2008;39(2):142; author reply *Pediatr Neurol.* 2008;39(2):142.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18206790>  
**Abstract** The effects of vagal nerve stimulation on sleep-related breathing have not been well-described in children. Vagal nerve stimulation was reported to cause decreases in airflow during sleep, although most studies reported this condition to be clinically insignificant. We present a retrospective case series of nine children who underwent polysomnography after vagal nerve-stimulator placement. All children, except for one, had sleep-disordered breathing after stimulator implantation. We describe in further detail a child who manifested severe, obstructive sleep apnea postimplantation, with apneas occurring regularly and consistently with stimulator activity, resulting in an elevated apnea-hypopnea index of 37 per hour. Polysomnography was repeated with the stimulator turned off, and revealed complete resolution of the stimulator-related sleep apnea. With the vagal nerve stimulator back on, continuous positive airway pressure treatment was effective in normalizing the apnea-hypopnea index. This study demonstrates that severe and clinically significant disturbances in sleep-related breathing may occur with vagal nerve stimulators. Obstructive apneas of this severity, related to vagal nerve stimulators, were not previously described in pediatric patients. This effect on sleep-related breathing warrants further investigation and care in managing pediatric patients.
9. **Kotagal P, Yardi N. The relationship between sleep and epilepsy. *Semin Pediatr Neurol.* 2008;15(2):42-9.** <http://www.ncbi.nlm.nih.gov/pubmed/18555190>  
**Abstract** The occurrence of seizures in the sleep state is observed in nearly one third of patients. This is caused by an intimate relationship between the physiological state of sleep and the pathological process underlying epileptic seizures. Both sleep and sleep deprivation influence the frequency of epileptiform discharges on electroencephalograms as well as the occurrence of clinical seizures, typically during nonrapid eye movement sleep. The relationship of epileptiform activity to nonrapid eye movement sleep is vividly shown in the syndrome of continuous spikes in slow-wave sleep and the Landau-Kleffner syndrome. Seizure semiology can also be influenced by sleep and sleep deprivation. Sleep disorders may influence seizure control, and effective treatment of sleep disorders can improve seizure control. Seizures, antiepileptic drugs, ketogenic diet, and vagus nerve stimulation all influence sleep quality, daytime alertness, and neurocognitive function.

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<http://www.ncbi.nlm.nih.gov/pubmed/17509001>  
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**Abstract** PURPOSE: This study analyzed changes in the heart rates of children receiving vagus nerve stimulation (VNS) therapy for pharmaco-resistant epilepsy. METHODS: Changes in the heart rates of ten children receiving VNS therapy for pharmaco-resistant epilepsy were evaluated with polysomnographic recordings, including electrocardiogram (ECG), EEG, thoraco-abdominal distension, nasal airflow, and VNS artifacts. Measurements during stimulation were compared with those at baseline for each patient. RESULT: While the VNS therapy pulse generator was delivering stimulation, the heart rates of four children increased significantly ( $p < 0.01$ ), decreased for one child, and increased at the end of the stimulation for one child. The heart rates of four children did not change. Changes in heart rate varied during VNS, within stimulation cycles for individual children and from one child to another. Changes in heart rate differed between rapid eye movement (REM) and non-REM (NREM) sleep states. Respiratory changes (increases in frequency and decreases in amplitude) were concomitant with the changes in heart rate. CONCLUSION: In this case series of children with pharmaco-resistant epilepsy, cardiorespiratory variations occurred while the VNS therapy pulse generator was delivering stimulation. Understanding these variations may allow further optimization of VNS parameters.
11. **Budzinska K, Ilasz R. Short-term depression of inspiratory activity following tonic vagal stimulation. *J Physiol Pharmacol*. 2006;57 Suppl 4:55-61.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17072030>  
**Abstract** This study tested the role of inhibitory neurotransmission in the glutaminergic control of short-term depression (STD) of the inspiratory activity initiated by sustained stimulation of the vagus nerve in anesthetized and vagotomized cats. STD, calculated from the integrated phrenic nerve signal, lasted longer when glutaminergic neurotransmission was inhibited by ketamine, a NMDA receptor antagonist. Application of picrotoxin, a GABAA receptor antagonist, reversed the effect of ketamine and shortened the STD duration below that present in the control condition. The results showed that alternation of the neural excitability by antagonists of excitatory and inhibitory neurotransmission modulates the STD of inspiratory activity, evoked by vagal stimulation. The STD depends on the state of neural excitability and is easier accomplished when the excitability is on the high side.
12. **Zaaimi B, Heberle C, Berquin P, Pruvost M, Grebe R, Wallois F. Vagus nerve stimulation induces concomitant respiratory alterations and a decrease in SaO<sub>2</sub> in children. *Epilepsia*. 2005;46(11):1802-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16302861>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2005.00283.x/asset/j.1528-1167.2005.00283.x.pdf?v=1&t=he943y7k&s=646e4691eec45b460b834dc104b8335b5c87df69>  
**Abstract** PURPOSE: To analyze respiratory alterations and effects on SaO<sub>2</sub> caused by vagus nerve stimulation (VNS) in children with epilepsy. METHODS: Polysomnographic recordings, including electroencephalography, thoracoabdominal distention, nasal airflow, SaO<sub>2</sub>, and VNS artifact were evaluated in 10 children with pharmaco-resistant epilepsy treated with VNS. RESULTS: Each VNS caused a significant increase in respiratory frequency ( $p < 0.05$ ) throughout the stimulation period and a decrease in thoracoabdominal-distention amplitude ( $p < 0.05$ ), especially at the beginning of the stimulation. These respiratory alterations induced a decrease in SaO<sub>2</sub> from 1 to 5%. The effects of VNS on respiration differed significantly between rapid-eye-movement (REM) and non-REM (NREM) sleep states. CONCLUSIONS: VNS caused a pronounced change in respiration in children with epilepsy, and this induced a decrease in SaO<sub>2</sub>. It is possible that VNS has a neuroprotective effect, and this possibility calls for further investigation.

13. **Nagarajan L, Walsh P, Gregory P, Stick S, Maul J, Ghosh S. Respiratory pattern changes in sleep in children on vagal nerve stimulation for refractory epilepsy. *Can J Neurol Sci.* 2003;30(3):224-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12945946>  
**Abstract** BACKGROUND: An altered breathing pattern in sleep, over two to three weeks, reported by the parents of a child on Vagal Nerve Stimulation (VNS) therapy for refractory epilepsy, prompted a sleep study in him. His polysomnography (PSG) revealed respiratory irregularity concordant with VNS activation. Dyspnoea is a well recognised and reported side effect of the VNS. However there are only a few studies looking at respiration in sleep with VNS. We therefore undertook PSGs in seven other children on VNS. METHODS: Sleep studies were undertaken, in accordance with standard clinical practice. Sleep and apnoeas and hypopneas were scored in accordance with conventional criteria. Respiratory pattern changes in sleep (RPCS) with VNS were looked for. RESULTS: Respiratory pattern changes in sleep were seen during PSG in seven of eight children on VNS for refractory epilepsy. Decreased effort and tidal volume occurred in seven children, concordant with VNS activation. In one child, this was associated with a fall in respiratory rate, in the other six children with an increase. No study showed an apnoea/hypopnoea index in the abnormal range. The RPCS were not associated with significant hypoxia or hypercapnoea. CONCLUSION: Our results suggest that RPCS occur in most children with VNS. This is not surprising in view of the significant influence vagal afferents have on respiratory control centres. The RPCS did not appear to have a clinical impact in our group. However further investigations are suggested to explore this phenomenon, especially in patients with sleep apnoea syndromes or compromised respiratory function.
14. **Marzec M, Edwards J, Sagher O, Fromes G, Malow BA. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. *Epilepsia.* 2003;44(7):930-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12823576>  
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**Abstract** PURPOSE: To describe the effects of vagus nerve stimulation (VNS) on sleep-related breathing in a sample of 16 epilepsy patients. METHODS: Sixteen adults with medically refractory epilepsy (nine men, seven women, ages 21-58 years) underwent baseline polysomnograms (PSGs). Three months after VNS therapy was initiated, PSGs were repeated. In addition, patient 7 had a study with esophageal pressure monitoring, and patient 1 had a continuous positive airway pressure (CPAP) trial. RESULTS: Baseline PSGs: One of 16 patients had an apnea-hypopnea index (AHI) >5 (6.8). Treatment PSGs: Five of 16 patients had treatment AHIs >5. Respiratory events were more frequent during periods with VNS activation (on-time) than without VNS activation (off-time;  $p = 0.016$ ). Follow-up studies: Esophageal pressure monitoring in patient 7 showed crescendos in esophageal pressure during VNS activation, supporting an obstructive pattern. The CPAP trial of patient 1 showed that all respiratory events were associated with VNS stimulation at low CPAP levels. They were resolved at higher CPAP levels. CONCLUSIONS: Treatment with VNS affects respiration during sleep and should be used with care, particularly in patients with preexisting obstructive sleep apnea. The AHI after VNS treatment remained <5 in the majority of patients and was only mildly elevated (<12) in five patients. In one patient, CPAP resolved VNS-related respiratory events.

15. **Malow BA, Edwards J, Marzec M, Sagher O, Fromes G. Effects of vagus nerve stimulation on respiration during sleep: a pilot study. *Neurology*. 2000;55(10):1450-4; comment *Neurology*. 2001;57(8):1523-4. <http://www.ncbi.nlm.nih.gov/pubmed/11094096>**

**Abstract** BACKGROUND: Vagus nerve stimulation (VNS) is associated with respiratory effects such as hoarseness, dyspnea, and laryngeal irritation. The effects of VNS on sleep-related breathing in humans have not been reported previously. METHODS: Four epilepsy patients underwent polysomnography (PSG) before and after 3 months of treatment with VNS. Two of the four patients also underwent follow-up PSG to assess the effects of changing stimulus parameters on sleep-related breathing. RESULTS: All patients showed consistent sleep-related decreases in airflow and effort coinciding with VNS activation, although most events did not meet laboratory criteria for apneas or hypopneas. Apneas and hypopneas were more frequent during VNS activation than during nonactivation. Apnea-hypopnea index (AHI) for three subjects during VNS treatment PSG was <5 apneas and hypopneas/hour. In one patient with obstructive sleep apnea (OSA) before VNS treatment, AHI rose from 4 (pretreatment) to 11.3 (treatment). In this patient and in another patient without clinically significant OSA, lowering stimulus frequency, but not stimulus intensity, pulse width, or on-time, ameliorated VNS-related apneas and hypopneas. CONCLUSIONS: VNS is associated with adverse changes in respiration during sleep. In patients without preexisting OSA, this VNS effect is probably not clinically significant. In patients with preexisting OSA, VNS should be administered with care. Lowering VNS stimulus frequency or prolonging off-time may prevent exacerbation of OSA.

**Safety Information - Vagal Bradycardia**

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1. **Herring N, Cranley J, Lokale MN, Li D, Shanks J, Alston EN, et al. The cardiac sympathetic co-transmitter galanin reduces acetylcholine release and vagal bradycardia: implications for neural control of cardiac excitability. *J Mol Cell Cardiol.* 2012;52(3):667-76.**

<http://www.ncbi.nlm.nih.gov/pubmed/22172449>

**Abstract** The autonomic phenotype of congestive cardiac failure is characterised by high sympathetic drive and impaired vagal tone, which are independent predictors of mortality. We hypothesize that impaired bradycardia to peripheral vagal stimulation following high-level sympathetic drive is due to sympatho-vagal crosstalk by the adrenergic co-transmitters galanin and neuropeptide-Y (NPY). Moreover we hypothesize that galanin acts similarly to NPY by reducing vagal acetylcholine release via a receptor mediated, protein kinase-dependent pathway. Prolonged right stellate ganglion stimulation (10 Hz, 2 min, in the presence of 10 µM metoprolol) in an isolated guinea pig atrial preparation with dual autonomic innervation leads to a significant ( $p < 0.05$ ) reduction in the magnitude of vagal bradycardia (5 Hz) maintained over the subsequent 20 min ( $n=6$ ). Immunohistochemistry demonstrated the presence of galanin in a small number of tyrosine hydroxylase positive neurons from freshly dissected stellate ganglion tissue sections. Following 3 days of tissue culture however, most stellate neurons expressed galanin. Stellate stimulation caused the release of low levels of galanin and significantly higher levels of NPY into the surrounding perfusate ( $n=6$ , using ELISA). The reduction in vagal bradycardia post sympathetic stimulation was partially reversed by the galanin receptor antagonist M40 after 10 min (1 µM,  $n=5$ ), and completely reversed with the NPY Y(2) receptor antagonist BIIE 0246 at all time points (1 µM,  $n=6$ ). Exogenous galanin ( $n=6$ , 50-500 nM) also reduced the heart rate response to vagal stimulation but had no effect on the response to carbamylcholine that produced similar degrees of bradycardia ( $n=6$ ). Galanin (500 nM) also significantly attenuated the release of (3)H-acetylcholine from isolated atria during field stimulation (5 Hz,  $n=5$ ). The effect of galanin on vagal bradycardia could be abolished by the galanin receptor antagonist M40 ( $n=5$ ). Importantly the GalR(1) receptor was immunofluorescently co-localised with choline acetyl-transferase containing neurons at the sinoatrial node. The protein kinase C inhibitor calphostin (100 nM,  $n=6$ ) abolished the effect of galanin on vagal bradycardia whilst the protein kinase A inhibitor H89 (500 nM,  $n=6$ ) had no effect. These results demonstrate that prolonged sympathetic activation releases the slowly diffusing adrenergic co-transmitter galanin in addition to NPY, and that this contributes to the attenuation in vagal bradycardia via a reduction in acetylcholine release. This effect is mediated by GalR(1) receptors on vagal neurons coupled to protein kinase C dependent signalling pathways. The role of galanin may become more important following an acute injury response where galanin expression is increased.

2. **Han SY, Bolter CP. The muscarinic-activated potassium channel always participates in vagal slowing of the guinea-pig sinoatrial pacemaker. *Auton Neurosci.* 2011;164(1-2):96-100.**

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**Abstract** Controversy persists regarding participation of the muscarinic-activated potassium current (c(KACh)) in small and moderate vagal bradycardia. We investigated this by (i) critical examination of earlier experimental data for mechanisms proposed to operate in modest vagal bradycardia (modulation of I(f) and inhibition of a junctional Na(+) current) and (ii) experiments performed on isolated vagally-innervated guinea-pig atria. In 8 superfused preparations, 10-s trains of vagal stimulation (1 to 20Hz) produced a bradycardia that ranged from 1 to 80%. Hyperpolarisation of sinoatrial cells accompanied bradycardia in 65/67 observations (linear correlation between bradycardia and increase in maximum diastolic potential (mV)=0.076x%; R(2)=0.57; P<0.001). In bath-mounted preparations single supramaximal stimuli to the vagus immediately and briefly increased pacemaker cycle length in 7 of 18 preparations. This response was eliminated by 300nM tertiapin-Q. Trains of 10 single supramaximal vagal stimuli applied at 1-s intervals caused progressive increase in overall cycle length during the train; immediate and brief increases in cycle length occurred following some stimuli. Immediate brief responses and part of the slower response to the stimulus train were removed by 300nM tertiapin-Q. Summary: experimental data shows that small and modest vagal bradycardia is accompanied by hyperpolarisation of the pacemaker cell which is severely attenuated by tertiapin-Q. These observations support the idea that activation of I(KACh) occurs at all levels of vagal bradycardia. Contradictory conclusions from earlier studies may be attributed to the nature of experimental models and experimental design.

3. **Jat KR, Lodha R, Kabra SK. Arrhythmias in children. *Indian J Pediatr.***

2011;78(2):211-8. <http://www.ncbi.nlm.nih.gov/pubmed/20978872> <http://rd.springer.com/article/10.1007%2Fs12098-010-0276-x>

**Abstract** Arrhythmias in children can be classified according to their effect on central pulse: Fast pulse rate - tachyarrhythmia; Slow pulse rate - bradyarrhythmia; and Absent pulse is pulseless arrest (cardiac arrest). Tachyarrhythmia may be narrow complex tachycardia (QRS duration  $\leq$  0.08 s): sinus tachycardia (ST), supraventricular tachycardia (SVT), atrial flutter or Wide-complex tachycardia (QRS duration  $>$ 0.08 s): ventricular tachycardia (VT), SVT with aberrant intraventricular conduction. The choice of therapy depends on the patient's degree of hemodynamic instability. Attempt vagal stimulation, if patient is stable and if it does not unduly delay chemical or electrical cardioversion. Bradyarrhythmias include: sinus bradycardia, sinus node arrest with atrial, junctional and idioventricular escape rhythms and AV block. The emergency treatment of bradycardia depends on its hemodynamic consequences. If heart rate is  $<$ 60 beats per minute with poor perfusion despite effective ventilation with oxygen, it may be treated with chest compressions, epinephrine through IV or endotracheal tube. If bradycardia persists or responds only transiently, consider a continuous infusion of epinephrine or isoproterenol and plan for emergency transcutaneous pacing. If bradycardia is due to vagal stimulation or primary A-V block, giving atropine may be beneficial.

4. **Choate JK, Danson EJ, Morris JF, Paterson DJ. Peripheral vagal control of heart rate is impaired in neuronal NOS knockout mice. *Am J Physiol Heart Circ Physiol.* 2001;281(6):H2310-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/11709397>

**Abstract** The role of nitric oxide (NO) in the vagal control of heart rate (HR) is controversial. We investigated the cholinergic regulation of HR in isolated atrial preparations with an intact right vagus nerve from wild-type (nNOS<sup>+/+</sup>, n = 81) and neuronal NO synthase (nNOS) knockout (nNOS<sup>-/-</sup>, n = 43) mice. nNOS was immunofluorescently colocalized within choline-acetyltransferase-positive neurons in nNOS<sup>+/+</sup> atria. The rate of decline in HR during vagal nerve stimulation (VNS, 3 and 5 Hz) was slower in nNOS<sup>-/-</sup> compared with nNOS<sup>+/+</sup> atria in vitro ( $P < 0.01$ ). There was no difference between the HR responses to carbamylcholine in nNOS<sup>+/+</sup> and nNOS<sup>-/-</sup> atria. Selective nNOS inhibitors, vinyl-L-nitrohydrochloride or 1-2-trifluoromethylphenyl imidazole, or the guanylyl cyclase inhibitor, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one significantly ( $P < 0.05$ ) attenuated the decrease in HR with VNS at 3 Hz in nNOS<sup>+/+</sup> atria. NOS inhibition had no effect in nNOS<sup>-/-</sup> atria during VNS. In all atria, the NO donor sodium nitroprusside significantly enhanced the magnitude of the vagal-induced bradycardia, showing the downstream intracellular pathways activated by NO were intact. These results suggest that neuronal NO facilitates vagally induced bradycardia via a presynaptic modulation of neurotransmission.

5. **Garcia Perez M, Jordan D. Effect of stimulating non-myelinated vagal axons on atrio-ventricular conduction and left ventricular function in anaesthetized rabbits. *Auton Neurosci.* 2001;86(3):183-91.**

<http://www.ncbi.nlm.nih.gov/pubmed/11270096>

**Abstract** It has previously been demonstrated in several species that stimulation of myelinated vagal efferent fibres evokes slowing of heart rate and atrio-ventricular (A-V) conduction and a decreased ventricular contractility but recruitment of non-myelinated fibres did not further increase the response. Only in rabbits was a significant bradycardia evoked on recruiting non-myelinated fibres. However, if stimulating myelinated fibres produced a near maximal response, then effects of further activation of non-myelinated fibres may have been missed. Indeed, selective stimulation of non-myelinated fibres alone now has been shown to evoke a slowing of heart rate independent of the effects of myelinated fibres. In the present study we tested in rabbits whether selective stimuli are also capable of slowing A-V conduction and changing ventricular contractility. In rabbits pretreated with the beta 1-adrenoceptor antagonist atenolol, ECG, arterial blood pressure, left ventricular pressure and dP/dt were recorded before and during stimulation of non-myelinated vagal efferent fibres using an anodal block technique (*J. Physiol.* 273 (1977) 539). R-R interval and A-V conduction times were computed off-line. Stimulation of non-myelinated vagal fibres increased R-R interval by 97.7 +/- 18.8 ms from a baseline of 315.3 +/- 7.7 ms, increased A-V conduction time by 9.9 +/- 1.1 ms from a baseline of 81.9 +/- 3.1 ms and decreased left ventricular dP/dtmax by 2486 +/- 362 mmHg s<sup>-1</sup> from a baseline of 11,186 +/- 795 mmHg s<sup>-1</sup>. When hearts were paced at a rate about 10% higher than normal, A-V conduction time still increased by 13.3 +/- 1.9 ms from a baseline of 104.2 +/- 3.6 ms and dP/dtmax still fell by 2300 +/- 188 mmHg s<sup>-1</sup> from a baseline of 11,200 +/- 777 mmHg s<sup>-1</sup>. Ganglionic blockade with hexamethonium (15-20 mg kg<sup>-1</sup>) always abolished the evoked increases in A-V conduction time, whilst there was still an increase in R-R interval in seven of the 12 animals tested. The data demonstrate that non-myelinated vagal efferent fibres can modulate chronotropic, dromotropic and inotropic actions on the heart.

6. **Almond SC, Paterson DJ. Sulphonylurea-sensitive channels and NO-cGMP pathway modulate the heart rate response to vagal nerve stimulation in vitro. *J Mol Cell Cardiol.* 2000;32(11):2065-73.**

<http://www.ncbi.nlm.nih.gov/pubmed/11040109>

**Abstract** Sulphonylurea-sensitive K(+)channels (K(ATP)) have been implicated in the release of acetylcholine (ACh) from the vagus nerve in the heart. Our aim was to establish the functional significance of this and to test whether this modulation could interact with stimulation of the NO-cGMP pathway that facilitates the decrease in heart rate (HR) in response to vagal nerve stimulation (VNS). We studied the effect of activation (diazoxide, 100 microM) and inhibition (glibenclamide 30 microM or tolbutamide 5 microM) of K(ATP)channels, and activation of the NO-cGMP pathway with the NO donor, sodium nitroprusside (SNP, 20 microM) or the cGMP analogue, 8-Br-cGMP (0.5 m M) on the HR response to VNS in the isolated guinea pig (*Cavia porcellus*) double atrial/right vagus preparation (n=40). Tolbutamide increased the bradycardia in response to vagal stimulation at 3 and 5 Hz (P<0.05); effects that were reversed by diazoxide. Glibenclamide also significantly increased the HR response to VNS at 1 and 3 Hz (P<0.05). Diazoxide alone significantly attenuated the HR response to VNS at 5 Hz (P<0.05). Neither glibenclamide nor diazoxide affected the HR response to carbamylcholine (CCh, 50-200 n M). In the presence of a maximal dose of tolbutamide, SNP or 8-Br-cGMP further increased the HR response to VNS at 5 Hz (P<0.05). These results are consistent with the hypothesis that inhibition of sulphonylurea-sensitive channels can increase the HR response to VNS by a pre-synaptic mechanism, and that this modulation may be independent of activation of the NO-cGMP pathway.

**Safety Reports - Case Reports**

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1. **Shankar R, Olotu VO, Cole N, Sullivan H, Jory C. Case report: Vagal nerve stimulation and late onset asystole. *Seizure*. 2013;22(4):312-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23290579>
  
2. **Clark AJ, Kuperman RA, Auguste KI, Sun PP. Intractable episodic bradycardia resulting from progressive lead traction in an epileptic child with a vagus nerve stimulator: a delayed complication. *J Neurosurg Pediatr*. 2012;9(4):389-93.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22462703>  
**Abstract** Vagus nerve stimulation (VNS) is used as palliation for adult and pediatric patients with intractable epilepsy who are not candidates for curative resection. Although the treatment is generally safe, complications can occur intraoperatively, perioperatively, and in a delayed time frame. In the literature, there are 2 reports of pediatric patients with implanted VNS units who had refractory bradycardia that resolved after the stimulation was turned off. The authors report the case of a 13-year-old boy with a history of vagus nerve stimulator placement at 2 years of age, who developed intractable episodic bradycardia that persisted despite the cessation of VNS and whose imaging results suggested vagus nerve tethering by the leads. He was subsequently taken to the operating room for exploration, where it was confirmed that the stimulator lead was exerting traction on the vagus nerve, which was displaced from the carotid sheath. After the vagus nerve was untethered and the leads were replaced, the bradycardia eventually resolved with continual effective VNS therapy. When placing a VNS unit in a very young child, accommodations must be made for years of expected growth. Delayed intractable bradycardia can result from a vagus nerve under traction by tethered stimulator leads.
  
3. **Aron M, Vlachos-Mayer H, Dorion D. Vocal cord adduction causing obstructive sleep apnea from vagal nerve stimulation: case report. *J Pediatr*. 2012;160(5):868-70.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22364850>  
**Abstract** A recognized complication of vagal nerve stimulation is new or worsening sleep apnea. Its pathophysiology is not clearly understood. We report a patient with obstructive sleep apnea that was directly associated with vagal nerve stimulation causing recurring vocal cord adduction. Adjusting the stimulator settings resolved the problem.
  
4. **Ford R, Haigh F, Hargreaves M. An unusual cause of stridor. *Anaesthesia*. 2011;66(11):1057.** <http://www.ncbi.nlm.nih.gov/pubmed/22004212>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1365-2044.2011.06905.x/asset/j.1365-2044.2011.06905.x.pdf?v=1&t=hfzqwt dg&s=88341a6e1db852403cfb1e38a80cd979d4970a79>
  
5. **Sheck L, Meyer HD. Episodic monocular vision loss after implantation of a vagal nerve stimulator. *Ann Intern Med*. 2011;155(9):648-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22041961>  
<http://annals.org/article.aspx?articleid=1033147>

6. **Gerson R, Murray E, Price B, Frankel M, Douglass LM, Cunningham M. Mania following vagus nerve stimulation: a case report and review of the literature. *Epilepsy Behav.* 2011;20(1):138-40.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21167787>  
**Abstract** Vagus nerve stimulation (VNS) is an increasingly used therapy for patients with treatment-refractory epilepsy and depression. Hypomanic and manic symptoms are a rare but recognized adverse effect of VNS treatment. Here we describe a case in which VNS treatment in a patient with epilepsy and unipolar depression was associated with the rapid development of manic symptoms. The patient's manic symptoms resolved with temporary discontinuation of the VNS current, and the patient was eventually able to resume VNS treatment with good effect and without further manic symptoms. Mania is a rare but serious side effect of VNS; however, in this case and in the majority of reported cases of VNS-associated mania, symptoms resolve and VNS can be safely administered.
7. **Murr NI, Azar NJ. Severe new seizures after initiation of vagus nerve stimulation therapy. *Epilepsy Behav.* 2011;22(2):398-400.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21820359>  
**Abstract** Vagus nerve stimulation is considered to be a safe and effective adjunctive therapy for patients with drug-resistant epilepsy. Contrary to some antiepileptic drugs, vagus nerve stimulation is not known to precipitate or aggravate new or preexisting seizures. We describe the emergence of a new type of disabling, recurrent partial seizure immediately after initiation of vagus nerve stimulation in a 51-year-old man with a known history of refractory partial epilepsy. Discontinuation of vagus nerve stimulation therapy and multiple antiepileptic drug interventions were required to abort these unexpected new seizures. We conclude that vagus nerve stimulation may induce paradoxical seizures, similarly to some antiepileptic drugs.
8. **Tran Y, Shah AK, Mittal S. Lead breakage and vocal cord paralysis following blunt neck trauma in a patient with vagal nerve stimulator. *J Neurol Sci.* 2011;304(1-2):132-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21397256>  
**Abstract** Patients with medically intractable seizures who are not candidates for epilepsy surgery are left with few options. Vagal nerve stimulation therapy is often a viable alternative for these patients and can have a positive impact on quality of life. Rarely complications may occur. We report a case of mild blunt neck trauma resulting in VNS malfunction and delayed vocal cord paralysis. A systematic review of the literature on VNS malfunction, self-inflicted injuries, vagal nerve injury, and common side effects including voice changes was performed. Only a handful of relevant publications were found. Symptoms following VNS dysfunction include pain, dyspnea, and dysphonia. These symptoms are usually nonspecific, and in many cases, do not help differentiate from vagal nerve traction, lead breakage, or pulse generator malfunction. In our case, lead fracture and visible traction injury to the left vagus nerve were seen during surgical exploration. The vocal cord function completely recovered after revision of the leads. Prompt medical attention including appropriate diagnostic studies and early surgical exploration is necessary in cases of delayed vocal cord dysfunction and can help prevent long-term complications such as neuroma formation. The authors present a unique case of reversible vocal cord injury from blunt neck trauma leading to left vagus nerve damage.

9. **Beal JC, Sogawa Y, Ceresnak SR, Mahgerefteh J, Moshe SL. Late onset ictal asystole in refractory epilepsy. *Pediatr Neurol.* 2011;45(4):253-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21907888>  
**Abstract** Ictal asystole is a cardiac phenomenon associated with epileptic seizures, and may play a role in sudden unexplained death in epilepsy. We present a 17-year-old boy with chronic intractable epilepsy and a vagus nerve stimulator who developed ictal asystole many years after the onset of epilepsy. The asystole was not linked to the vagus nerve stimulator, and ultimately necessitated the placement of a cardiac pacemaker. A cardiac pacemaker and vagus nerve stimulator can be safely used simultaneously after careful testing during placement. The onset of asystolic events many years after the onset of epilepsy suggests that repeated seizures may exert long-term effects on cardiac function.
10. **Terry GE, Conry JA, Taranto E, Yaun A. Failure of a vagus nerve stimulator following a nearby lightning strike. *Pediatr Neurosurg.* 2011;47(1):72-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21546762>  
**Abstract** We recently reported our experience with implanted vagus nerve stimulators (VNS) in 62 children over a 7-year period. Here, we present a case of a VNS that successfully reduced the number and severity of seizures in a patient with an unusual seizure pattern, and failed to function shortly after a lightning storm. To our knowledge, the failure of VNS or any implantable electrical devices by lightning has not been reported in the literature. This mechanism of electrical interference, while unusual, may require more attention as these devices are expected to be used more frequently.
11. **St Louis EK, Faber K. Reversible sleep-related stridor during vagus nerve stimulation. *Epileptic Disord.* 2010;12(1):76-80.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20189905>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2958706/pdf/nihms237719.pdf>  
**Abstract** A 23-year-old woman without history of antecedent vocal, respiratory, or sleep disorders received vagus nerve stimulation (VNS) therapy for refractory partial epilepsy and developed sleep-related stridor during the course of parameter titration. Reduction of VNS current during polysomnography completely eliminated stridor. We conclude that VNS may cause sleep-related stridor in rare cases, expanding the spectrum of known sleep-disordered breathing disorders associated with VNS therapy. Parameter adjustment during polysomnography may resolve nocturnal stridor caused by VNS.
12. **Bhatt YM, Hans PS, Belloso A. Airway compromise secondary to vagus nerve stimulator: case report and implications for otolaryngologists. *J Laryngol Otol.* 2010;124(5):557-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19796439>  
<http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=7637528>  
**Abstract** INTRODUCTION: Vagus nerve stimulators are devices used in the management of patients with drug-refractory epilepsy unsuitable for resective or disconnective surgery. Implanted usually by neurosurgeons, these devices are infrequently encountered by otolaryngologists. Despite significant anti-seizure efficacy, side effects related to laryngopharyngeal stimulation are not uncommon. CASE REPORT: A 28-year-old man with a history of effective vagus nerve stimulator use presented with a cluster of seizures and respiratory distress associated with intermittent stridor. The duration of stridor corresponded to the period of vagus nerve stimulation. Endoscopy revealed forced adduction of the left vocal fold against a medialised right vocal fold. The device was switched off and the stridor immediately resolved. CONCLUSION: Airway compromise is an under-recognised side effect of vagus nerve stimulation. We describe the first known case of stridor and contralateral vocal fold palsy in a vagus nerve stimulator user. We highlight the need for better understanding amongst otolaryngologists of the laryngopharyngeal side effects of this technology.

13. **Spitz MC, Winston KR, Maa EH, Ojemann SG. Insulation discontinuity in a vagus nerve stimulator lead: a treatable cause of intolerable stimulation-related symptoms. *J Neurosurg.* 2010;112(4):829-31.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19558306>  
**Abstract** Discontinuity in the silicone insulation over an electrode of a left vagus nerve stimulator (VNS) allowed the aberrant leak of current to the phrenic nerve and other structures. This resulted in ipsilateral diaphragmatic dysfunction, inability to vocalize, and severe radiating pain into the jaw and upper incisor for the duration of each stimulation. The device was explanted and a new device was implanted. All stimulation-related symptoms ceased immediately. A similar discontinuity in the silicone insulation is the likely explanation for several prior reports of poorly understood pains and phrenic nerve stimulation in patients with VNSs. The findings and analysis of this case establish a rationale for consideration of replacement of the VNS lead in all similarly symptomatic patients.
14. **Santermans L, Vanderbruggen N, Baeken C. Acute relapse after successful vagus nerve stimulation therapy: a case report of last-resort ECT treatment. *Prim Care Companion J Clin Psychiatry.* 2010;12(3):PCC.09100840.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20944785>
15. **Muller H, Seifert F, Weigel D, Garlichs C, Asemann R, Fluh G, et al. Vagus-nerve stimulation is tolerated in a patient with cardiac AV-Blocks. *Prog Neuropsychopharmacol Biol Psychiatry.* 2010;34(6):1150.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20677368>
16. **Santermans L, Vanderbruggen N, Zeeuws D, Baeken C. Successful ECT treatment after relapse during VNS therapy. *Psychiatr Danub.* 2010;22 Suppl 1:S166.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21057435>  
**Abstract** We present a case of a patient with severe treatment resistant depression who relapsed while being treated with vagus nerve stimulation. We describe that he was safely treated with unilateral ECT concomitantly with the VNS.
17. **Caceres R, Richter J, Safstrom K, Landtblom AM. Application of a vagal nerve stimulator in an epilepsy patient with cardiac pacemaker after post-ictal cardiac arrest. *Acta Neurol Scand.* 2009;120(2):139-42; comment *Acta Neurol Scand.* 2010;121(4):285-6; author reply *Acta Nuerol Scand.* 2010;121(4):287-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19053951>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0404.2008.01123.x/abstract>  
**Abstract** In this case report we present a patient with temporal lobe epilepsy (TLE) showing partial complex seizures and secondary generalization, and treated with several antiepileptic drugs. After two consecutive seizures she had an episode of cardiac arrest followed by AV-block III which led to the implantation of a cardiac pacemaker. She subsequently received a vagal nerve stimulator because of poor response to epilepsy treatment. Combined treatment with two different electromagnetic stimulators raises the question of safety during surgery which is discussed.
18. **Srinivasan SP, Hall JM, Leo RJ. Vocal cord dysfunction arising from vagal nerve stimulator removal. *Am J Psychiatry.* 2009;166(12):1412-3; comment *Am J Psychiatry.* 2010;167(6):719-20.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19952086>  
<http://psychiatryonline.org/data/Journals/AJP/3908/09aj1412.PDF>

19. **Iriarte J, Urrestarazu E, Alegre M, Macias A, Gomez A, Amaro P, et al. Late-onset periodic asystolia during vagus nerve stimulation. *Epilepsia*. 2009;50(4):928-32.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19055490>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2008.01918.x/asset/j.1528-1167.2008.01918.x.pdf?v=1&t=he940zs5&s=41b55487adf4176040e7bdbf38010bc97a71a954>  
**Abstract** Cardiac changes may occasionally occur during vagus nerve stimulation (VNS) used in epileptic patients. As they can be potentially life-threatening, it is important to detect them, and this is why an intraoperative test is performed during the implantation. Few cases of asystole during this test have been described. Only one patient with late-onset bradyarrhythmia caused by VNS has been reported. This patient had been implanted 2 years and 4 months before the episode. We present another case of late asystole in a patient whose VNS had been implanted 9 years before the arrhythmia onset. In our patient, each run of stimulation produced bradyarrhythmias and very often severe asystolia due to atrium-ventricular block.
20. **Singleton AH, Rosenquist PB, Kimball J, McCall WV. Cardiac rhythm disturbance in a depressed patient after implantation with a vagus nerve stimulator. *J ECT*. 2009;25(3):195-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19384253>  
**Abstract** A 52-year-old woman with a long-standing history of treatment-resistant depression failed multiple courses of electroconvulsive therapy and various trials of antidepressant medications. As a result, the patient was deemed a good candidate for vagus nerve stimulation (VNS) therapy and underwent VNS insertion in May 2006. However, in December 2007, she began to experience recurrent falls and was referred to a cardiologist for a syncope evaluation. During a portable 30-day cardiac event recording, she was noted to have intermittent second- and third-degree heart block with ventricular standstill, which was felt by her cardiologist to be associated with VNS stimulation. We believe this to be the first reported case of heart block related to VNS in a depressed patient.
21. **Rijkers K, Berfelo MW, Cornips EM, Majoie HJ. Hardware failure in vagus nerve stimulation therapy. *Acta Neurochir (Wien)*. 2008;150(4):403-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18278574>  
<http://link.springer.com/article/10.1007%2Fs00701-007-1492-7>  
**Abstract** A 20 year old male patient who had been successfully treated for epilepsy with vagus nerve stimulation (VNS) for 7 years (50% seizure frequency reduction), had experienced multiple episodes of severe hoarseness, throat pain and impaired breathing during physical exercise. As malfunctioning of the pulse generator was suspected, it was decided to replace the device. During surgery, the pulse generator was found to have broken in two, due to an unstable connection between the battery subunit and the connector subunit. With a new pulse generator seizure frequency reduction was restored. No side effects occurred.
22. **Abnoosian A, Maguire G. Case report of an interaction of a vagal nerve stimulation system with a microwave current from a body fat analyzer. *Ann Clin Psychiatry*. 2008;20(4):229-30.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19034756>
23. **Keller S, Lichtenberg P. Psychotic exacerbation in a patient with seizure disorder treated with vagus nerve stimulation. *Isr Med Assoc J*. 2008;10(7):550-1.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18751641>

24. **Hoerth M, Drazkowski J, Sirven J, Hinni M, Smith B, Labiner D. Vocal cord paralysis after vagus nerve stimulator battery replacement successfully treated with medialization thyroplasty. *Clin Neurol Neurosurg.* 2007;109(9):788-90.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17697747>  
**Abstract** The vagus nerve stimulator (VNS) has been used effectively for partial seizure disorders, however many patients suffer from side effects of alterations in voice. This case describes a new remediable adverse effect of the VNS. A patient with medically intractable epilepsy had improvement of his seizure control with VNS therapy after titrating him to a high output and rapid cycling paradigm with essentially no side effects. After a battery replacement, he was restarted on his previous settings and subsequently developed a hoarse voice. He was found to have complete left vocal cord paralysis, an adverse effect attributed to a rapid titration to his previous high output and rapid cycling paradigm. This side effect has not been previously described in the literature. The patient subsequently had a medialization thyroplasty with resolution of his hoarse voice.
25. **Papacostas SS, Myriantopoulou P, Dietis A, Papathanasiou ES. Induction of central-type sleep apnea by vagus nerve stimulation. *Electromyogr Clin Neurophysiol.* 2007;47(1):61-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17375884>  
**Abstract** Vagus nerve stimulation (VNS) is an acceptable and effective adjunctive therapy for pharmaco-resistant epilepsy. It is generally well tolerated and the most frequent side effects reported include respiratory dysfunction. We report the case of a female patient with intractable epilepsy who was implanted with the device and achieved a significant reduction in the number of her seizures. However, she developed central-type sleep apnea documented polysomnographically. Upon reduction of her VNS parameters, the apnea resolved and her sleep study reverted to normal. To our knowledge, this is the first case reported with polysomnographic evidence of VNS induction of central-type sleep apnea.
26. **Rauchenzauner M, Haberlandt E, Hogler W, Luef G. Brain-type natriuretic peptide release and seizure activity during vagal nerve stimulation. *Epilepsia.* 2007;48(2):397-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17295638>  
**Abstract** Vagus nerve stimulation (VNS) has emerged as an effective adjunctive therapy for medically refractory epilepsy when surgery is inadvisable. N-terminal brain-type natriuretic peptide (NT-proBNP) is a potent natriuretic, diuretic, and vasodilative compound first discovered in the human brain but mainly synthesized in the myocardium. The monitoring of VNS effectiveness in reducing seizure frequency or the detection of possible cardiac adverse effects would be helped by a reliable biochemical marker, which has not been available thus far. We report a four-year-old boy with drug-resistant idiopathic generalized epilepsy whose NT-proBNP levels increased during VNS and seizures.
27. **Amark P, Stodberg T, Wallstedt L. Late onset bradyarrhythmia during vagus nerve stimulation. *Epilepsia.* 2007;48(5):1023-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17381444>  
**Abstract** Vagus nerve stimulation (VNS) is widely used to treat refractory epilepsy. It is usually safe and has few side effects. Cardiac arrhythmia has been reported during lead tests performed during implantation of the device, but never during regular treatment. We report here a case where vagally induced bradyarrhythmia, perfectly correlated with the stimulation periods, suddenly occurred two years and four months after the VNS implantation. The diagnosis was based on the appearance of syncope-like episodes. No specific cause could be found to explain the appearance of the episodes. To our knowledge, this is the first report on this severe and life-threatening side effect of VNS and should alert clinicians to its possibility. However, considering the large number of VNS implantations performed worldwide, it must be regarded as an extremely rare complication.

28. **Liechty PG, Tubbs RS, Blount JP. The use of a sump antibiotic irrigation system to save infected hardware in a patient with a vagal nerve stimulator: technical note. *Surg Neurol.* 2006;65(1):48-9; discussion 49-50.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16378855>  
**Abstract** The authors describe the use of a sump irrigation system that was used to successfully treat the battery implantation site of a vagal nerve stimulator (VNS). Irrigation was composed of a dilution of vancomycin in lactated Ringer's solution. At long-term follow up, the patient has not returned with signs or symptoms of wound infection. She continues to effectively combat her epilepsy with VNS. The authors believe this to be the first description of this technique for salvaging an implanted VNS.
29. **Bijwadia JS, Hoch RC, Dexter DD. Identification and treatment of bronchoconstriction induced by a vagus nerve stimulator employed for management of seizure disorder. *Chest.* 2005;127(1):401-2.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15654007>  
**Abstract** We evaluated a 63-year-old woman who developed dyspnea with a sensation of chest tightness that was temporally associated with discharges from a vagus nerve stimulator that had been implanted for the control of intractable seizures. Spirometry demonstrated the development of significant airflow obstruction associated with the firing of the stimulator. Adjustment of the stimulator settings resolved the discharge-associated bronchoconstrictive phenomenon. These findings highlight an important association between vagus nerve stimulators and dyspnea that should be considered in the differential diagnosis of patients with these devices who present with dyspnea and/or chest tightness. The relative importance of vagal stimulation to bronchoconstriction is suggested by the findings.
30. **Srinivasan B, Awasthi A. Transient atrial fibrillation after the implantation of a vagus nerve stimulator. *Epilepsia.* 2004;45(12):1645.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15571525>  
<http://onlinelibrary.wiley.com/store/10.1111/j.0013-9580.2004.31004.x/asset/j.0013-9580.2004.31004.x.pdf?v=1&t=he942wpy&s=e8745f6ed7c5478dd2aedecf483ca6620e99d445>
31. **Vassilyadi M, Strawsburg RH. Delayed onset of vocal cord paralysis after explantation of a vagus nerve stimulator in a child. *Childs Nerv Syst.* 2003;19(4):261-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12715196>  
<http://link.springer.com/article/10.1007%2Fs00381-003-0722-4>  
**Abstract** INTRODUCTION: Vagus nerve stimulation for the management of intractable seizure disorders is increasingly being used, especially in younger children. Although complications such as infection or vocal cord paralysis are uncommon, some may be unreported. CLINICAL PRESENTATION: A 3.5-year-old boy with intractable complex partial and generalized seizures had a left vagus nerve stimulator (VNS) successfully implanted. Two weeks later, the cervical incision showed signs of infection, antibiotics were started, and the VNS generator and leads were explanted. Three weeks later the child's mother noted a change in the voice of her son, as well as increased coughing and gagging. Flexible laryngoscopy identified a left vocal cord paralysis, which eventually resolved after 6 months. CONCLUSION: Infection requiring explantation of a VNS is uncommon. The risk is higher in younger children, especially in those who are developmentally delayed. These children may continuously drool, with saliva or food soiling the fresh incision, or even pick at the incision to the point of twisting or even pulling out the electrodes. Less common is a vocal cord paralysis, especially occurring in a delayed fashion.

32. **Akman C, Riviello JJ, Madsen JR, Bergin AM. Pharyngeal dysesthesia in refractory complex partial epilepsy: new seizure or adverse effect of vagal nerve stimulation? *Epilepsia*. 2003;44(6):855-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12790902>  
**Notes** This is a case report on a 21-year-old man who began receiving VNS Therapy at age 19 years and received some decrease in seizure frequency but continued to have daily seizures. What turned out to be side effects with VNS--a tightness and tingling sensations in his throat--were initially diagnosed as seizures. Video-EEG monitoring was used to clarify the true natures of his symptoms. Once reassured that his symptoms were not due to seizures, the patient was less troubled by them and continued with VNS Therapy. This case illustrates some of the difficulties in clarifying sensory symptoms in cases of intractable epilepsy.  
**Abstract** Sensory symptoms are commonly seen in association with focal epilepsy, but viscerosensory auras, such as pharyngeal dysesthesias, are rarely the main clinical manifestation. With the introduction of vagal nerve stimulation (VNS) for medically refractory epilepsy, viscerosensory symptoms commonly occur as an adverse effect of VNS. Voice alterations (hoarseness or tremulousness), local neck or throat pain, and cough are the most common adverse effects seen during active stimulation (on-time). Numbness of the throat, neck, or chin, as well as a tingling sensation of the neck and throat is directly related to stimulation intensity. We present a case in which recurrent pharyngeal sensations caused a diagnostic dilemma and in which monitoring the VNS artifact during video/EEG and correlating this with clinical symptoms helped determine the etiology of the recurrent sensory symptoms.
33. **Klein JP, Jean-Baptiste M, Thompson JL, Bowers MB, Jr. A case report of hypomania following vagus nerve stimulation for refractory epilepsy. *J Clin Psychiatry*. 2003;64(4):485.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12716259>  
**Notes** This is a case report of hypomania believed to be the result of the mood-elevating properties of VNS Therapy. The female patient had a history of epilepsy (seizure onset at age 12 years) with coexisting mood disorders. The hypomania followed 2 months following a stimulus parameter change and remitted upon another parameter change. The authors speculate that the hypomania was a result of the VNS Therapy and that her underlying psychiatric conditions increased her susceptibility to this side effect. VNS stimulation parameter adjustments or the addition of mood-stabilizing agents may be indicated if manic symptoms develop following activation of the VNS device. Abstract: No abstract available.
34. **Holmes MD, Chang M, Kapur V. Sleep apnea and excessive daytime somnolence induced by vagal nerve stimulation. *Neurology*. 2003;61(8):1126-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/14581678>  
<http://www.neurology.org/content/61/8/1126.full.pdf>  
**Abstract** Vagal nerve stimulation (VNS) therapy affects respiration during sleep and can interrupt sleep. VNS has also been noted to improve excessive daytime sleepiness. The authors present a patient who developed excessive daytime sleepiness after VNS placement, as a consequence of apneas and arousals associated with intermittent electrical stimulation of the left vagus nerve.
35. **Shih JJ, Devier D, Behr A. Late onset laryngeal and facial pain in previously asymptomatic vagus nerve stimulation patients. *Neurology*. 2003;60(7):1214.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12682343>  
**Notes** This clinical/scientific note reports on late-onset side effects seen among two patients being treated with VNS Therapy at well-tolerated parameter settings. One patient (8-year-old girl) demonstrated pain in her left cheek after 2 months of treatment requiring a decrease in output current to 1.0 mA from 1.25 mA. A second patient (18-year-old man) experienced paroxysmal throat pain and coughing requiring a reduction in output current after 10 months of treatment.

36. Heberle C, Berquin P, Larnicol N, Wallois F. Vagus nerve stimulation in a case of epilepsy with CSWSS: respiratory side effects during sleep. *Epilepsia*. 2002;43(10):1268-70. <http://www.ncbi.nlm.nih.gov/pubmed/12366745>
37. Kalkanis JG, Krishna P, Espinosa JA, Naritoku DK. Self-inflicted vocal cord paralysis in patients with vagus nerve stimulators. Report of two cases. *J Neurosurg*. 2002;96(5):949-51. <http://www.ncbi.nlm.nih.gov/pubmed/12005405>  
**Abstract** Vagus nerve stimulation for treatment of epilepsy is considered safe; reports of severe complications are rare. The authors report on two developmentally disabled patients who experienced vocal cord paralysis weeks after placement of a vagus nerve stimulator. In both cases, traction injury to the vagus nerve resulting in vocal cord paralysis was caused by rotation of the pulse generator at the subclavicular pocket by the patient. Traumatic vagus nerve injury caused by patients tampering with their device has never been reported and may be analogous to a similar phenomenon reported for cardiac pacemakers in the literature. As the use of vagus nerve stimulation becomes widespread it is important to consider the potential for this adverse event.
38. Sanossian N, Haut S. Chronic diarrhea associated with vagal nerve stimulation. *Neurology*. 2002;58(2):330. <http://www.ncbi.nlm.nih.gov/pubmed/11805274>
39. Kim W, Clancy RR, Liu GT. Horner syndrome associated with implantation of a vagus nerve stimulator. *Am J Ophthalmol*. 2001;131(3):383-4. <http://www.ncbi.nlm.nih.gov/pubmed/11239877>  
**Abstract** PURPOSE: To report a case of Horner syndrome that occurred after implantation of a vagus nerve stimulator. METHODS: Case report. RESULTS: A 6-year-old female with cerebral dysgenesis and intractable partial seizures presented with Horner syndrome after vagus nerve stimulator implantation. CONCLUSION: Horner syndrome can occur as a result of the vagus nerve stimulator implant procedure and should be included as one of its possible surgical complications.
40. Prater JF. Recurrent depression with vagus nerve stimulation. *Am J Psychiatry*. 2001;158(5):816-7. <http://www.ncbi.nlm.nih.gov/pubmed/11329411> <http://psychiatryonline.org/data/Journals/AJP/3724/816.pdf>

41. **Ortler M, Luef G, Kofler A, Bauer G, Twerdy K. Deep wound infection after vagus nerve stimulator implantation: treatment without removal of the device. *Epilepsia*. 2001;42(1):133-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11207797>  
<http://onlinelibrary.wiley.com/store/10.1046/j.1528-1157.2001.23800.x/asset/j.1528-1157.2001.23800.x.pdf?v=1&t=he8vgnlw&s=4a603c712bf20506bc4b3dd8115a29fe97f4d77e>  
**Abstract** Effective treatment of deep wound infection without removal of a previously implanted foreign body is difficult. The Neurocybernetic Prosthesis (NCP) System (Cyberonics Inc., Webster, TX, U.S.A.), implanted for vagus nerve stimulation in patients with medically refractory epilepsy, uses coil-like electrodes placed around the left vagus nerve after exposure of the nerve in the carotid sheath. Infection within this compartment endangers the contained structures and makes removal of the system hazardous. We report the case of one patient implanted with the NCP who underwent successful open wound treatment without removal of the system. A 35-year-old man had local signs of wound infection 5 weeks after implantation of a vagus nerve stimulator. Systemic signs of infection were absent. C-reactive protein was slightly elevated, but all other laboratory values were normal. After open wound debridement and thorough rinsing with bacitracin-containing solution, the wound was packed with 3% iodoformized gauze. The NCP was left in place. Systemic antibiotic therapy with fosfomycin and cefmenoxim was started. Cultures confirmed an infection with *Staphylococcus aureus*. The wound was rinsed daily with 3% hydrogen peroxide solution and 5% saline until cultures were sterile and granulation tissue started to fill the wound. Delayed primary closure was performed 2 weeks later. Wound healing was accomplished without removal of the device. No signs of recurrent infection were observed during a follow-up of 1 year. Open wound treatment without removal of the implanted vagus nerve stimulator is feasible in cases of deep cervical wound infection and can be an alternative if removal of the device appears hazardous.
42. **Iriarte J, Artieda J, Alegre M, Schlumberger E, Urrestarazu E, Pastor MA, et al. Spasm of the sternocleidomastoid muscle induced by vagal nerve stimulation. *Neurology*. 2001;57(12):2319-20.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11756622>
43. **Duhaime AC, Melamed S, Clancy RR. Tonsillar pain mimicking glossopharyngeal neuralgia as a complication of vagus nerve stimulation: case report. *Epilepsia*. 2000;41(7):903-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10897165>  
**Notes** This is a case report of delayed stimulation-related severe tonsillar pain that stopped with an alternation in stimulus parameters. Seizure control also improved with the stimulus modification. The authors conclude that "this case would suggest that even when sensory symptoms are atypical, severe, and have delayed onset, individualized adjustment of stimulation parameters may result in melioration of pain symptoms as well as improved seizure control."  
**Abstract** An adolescent girl presented with severe, lancinating tonsillar pain exacerbated by swallowing 6 weeks after initiation of left vagus nerve stimulation for intractable epilepsy. Her symptoms mimicked those seen in glossopharyngeal neuralgia and were relieved by temporary cessation of stimulation. Gradual reinstatement of therapy with alteration in stimulus parameters resulted in improved seizure control as well as cessation of pain symptoms. Direct stimulation of the vagus nerve may result in vagoglossopharyngeal neuralgia, which, in this case, was amenable to stimulus modification.
44. **Gatzonis SD, Stamboulis E, Siafakas, Angelopoulos E, Georgaculias N, Sigounas E, et al. Acute psychosis and EEG normalisation after vagus nerve stimulation. *J Neurol Neurosurg Psychiatry*. 2000;69(2):278-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10960292>
45. **Koutroumanidis M, Hennessy MJ, Binnie CD, Polkey CE. Aggravation of partial epilepsy and emergence of new seizure type during treatment with VNS. *Neurology*. 2000;55(6):892-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10994021>

46. **Zumsteg D, Jenny D, Wieser HG. Vocal cord adduction during vagus nerve stimulation for treatment of epilepsy. *Neurology*. 2000;54(6):1388-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10746619>  
<http://www.neurology.org/content/54/6/1388.full.pdf>
47. **Asconape JJ, Moore DD, Zipes DP, Hartman LM, Duffell WH, Jr. Bradycardia and asystole with the use of vagus nerve stimulation for the treatment of epilepsy: a rare complication of intraoperative device testing. *Epilepsia*. 1999;40(10):1452-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10528943>  
**Abstract** PURPOSES: A 56-year-old man with mild mental retardation, right congenital hemiparesis, and refractory partial seizures was referred for vagus nerve stimulation (VNS). METHODS: Routine lead diagnostic testing during the surgical procedure (1.0 mA, 20 Hz, and 500 micros, for approximately 17 s) resulted, during the initial two stimulations, in a bradycardia of approximately 30 beats/min. A third attempt led to transient asystole that required atropine and brief cardiopulmonary resuscitation. RESULTS: The procedure was immediately terminated, the device removed, and the patient recovered completely. A postoperative cardiologic evaluation, including an ECG, 24-h Holter monitor, echocardiogram, and a tilt-table test, was normal. CONCLUSIONS: Possible mechanisms for the bradycardia/asystole include stimulation of cervical cardiac branches of the vagus nerve either by collateral current spread or directly by inadvertent placement of the electrodes on one of these branches; improper plugging of the electrodes into the pulse generator, resulting in erratic varying intensity of stimulation; reverse polarity; and idiosyncratic-type reaction in a hypersusceptible individual. The manufacturer reports the occurrence rate in approximately 3,500 implants for this intraoperative event to be approximately one in 875 cases or 0.1%.
48. **Leijten FS, Van Rijen PC. Stimulation of the phrenic nerve as a complication of vagus nerve pacing in a patient with epilepsy. *Neurology*. 1998;51(4):1224-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9781571>

**Safety Reports - Case Series**

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- 1. Carius A, Schulze-Bonhage A. Trigeminal pain under vagus nerve stimulation. *Pain*. 2005;118(1-2):271-3. <http://www.ncbi.nlm.nih.gov/pubmed/16202528>**  
**Abstract** Three epilepsy patients treated by cyclic continuous vagus nerve stimulation (VNS) experienced trigeminal pain during the periods of stimulation, which was reported as toothache in the left lower jaw, ipsilateral to the side of stimulation. The symptom occurred with a latency of days to weeks following an increase in stimulation current intensity (SCI). Trigeminal pain was reversible with decrease in SCI, or subsided due to habituation. These findings show that clinically relevant effects of VNS on nociception may occur. Because of the late onset and variable form of this side effect, trigeminal pain may not be regarded as VNS-related which may result in unnecessary diagnostic and therapeutic procedures.
- 2. Ali II, Pirzada NA, Kanjwal Y, Wannamaker B, Medhkour A, Koltz MT, et al. Complete heart block with ventricular asystole during left vagus nerve stimulation for epilepsy. *Epilepsy Behav*. 2004;5(5):768-71. <http://www.ncbi.nlm.nih.gov/pubmed/15380133>**  
**Abstract** Vagus nerve stimulation (VNS) is an important therapeutic option for individuals with refractory epilepsy who have failed multiple antiepileptic drugs (AEDs). The intricate relationship of the vagus nerve to cardiac function raises concern that vagal stimulation may affect cardiac rhythm and function. Previous pre- and postmarketing studies have not shown this to be a significant problem, with the incidence of bradyarrhythmias reported to be about 0.1%. We review three cases of ventricular asystole with complete heart block that occurred during intraoperative lead tests. The purpose of these case reports is to identify the specific type of cardiac abnormality associated with vagus nerve stimulation and to identify individuals at risk.
- 3. Patel NC, Edwards MS. Vagal nerve stimulator pocket infections. *Pediatr Infect Dis J*. 2004;23(7):681-3. <http://www.ncbi.nlm.nih.gov/pubmed/15247613>**  
**Abstract** Vagal nerve stimulator pocket infections are uncommon but can cause considerable morbidity. We describe 3 children from our institution and 8 others previously reported with infection after vagal nerve stimulator implantation for seizure control. Infection was suppressed but recurred despite appropriate antimicrobial therapy when the device remained in situ. Device removal was required in all patients to achieve cure.
- 4. De Herdt V, Boon P, Vonck K, Goossens L, Nieuwenhuis L, Paemeleire K, et al. Are psychotic symptoms related to vagus nerve stimulation in epilepsy patients? *Acta Neurol Belg*. 2003;103(3):170-5. <http://www.ncbi.nlm.nih.gov/pubmed/14626698>**  
**Abstract** Four patients with refractory epilepsy presented with psychotic symptoms following treatment with vagus nerve stimulation (VNS) to control seizures. Besides its anti-epileptic effect VNS has been shown to have an effect on various cognitive and behavioural functions. VNS is known to increase alertness and reduce sedation, which is independent from seizure control. VNS has also been shown to positively affect cognition and to exert strong antidepressant effects. Co-morbidity in epilepsy often comprises psychiatric illnesses. Increased psychiatric symptoms have mainly been described in association with successful outcome following epilepsy surgery as a result of 'forced normalisation'. Different hypotheses on the underlying aetiology of VNS-induced psychotic symptoms other than the previously described 'forced normalisation' are discussed.

5. **Zalvan C, Sulica L, Wolf S, Cohen J, Gonzalez-Yanes O, Blitzer A. Laryngopharyngeal dysfunction from the implant vagal nerve stimulator. *Laryngoscope*. 2003;113(2):221-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/12567072>

<http://onlinelibrary.wiley.com/doi/10.1097/00005537-200302000-00005/abstract>

**Notes** This is a small case series of four patients with implantation-related vocal fold paresis, three of whom also appear to have side effects from device activation. The article distinguishes between surgical and stimulation side effects and acknowledges that significant complications with VNS therapy are rare. All of the patients remained on VNS Therapy despite the laryngeal dysfunction and three were responding to the treatment.

**Abstract** OBJECTIVES/HYPOTHESIS: The objective of the study was to examine the side-effect profile of the vagal nerve stimulator. Vagal nerve stimulators have been used to treat intractable seizures in all age groups. They provide relief to the patient with a seizure disorder by decreasing the overall number and severity of seizure activities. Although significant complications are rare, many patients have some complaint, usually of their voice. STUDY DESIGN: A retrospective evaluation of four patients with intractable epilepsy. METHODS: Evaluation of charts and medical records and endoscopic examination of the larynx. RESULTS: In this small series, all four patients had implantation-related paresis. Three of the four appear to have side effects from device activation. CONCLUSIONS: Patients in whom a vagal nerve stimulator is placed can have adverse side effects. These can be related to the surgical manipulation of the vagus nerve, resulting in a temporary paresis of the vocal folds. A second set of side effects is related to the actual electrical stimulation of the device, and these side effects can directly affect the laryngeal musculature.

6. **Gatzonis SD, Korres S, Balatsouras DG, Stabulis E, Georgakulias N, Singunas E, et al. Influence of vagus nerve stimulation on vestibulo-ocular reflex. *ORL J Otorhinolaryngol Relat Spec*. 2003;65(4):223-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/14564098>

<http://www.karger.com/Article/FullText/73120>

**Notes** This article out of Greece looks at the affects of VNS on the vestibulo-ocular reflex (VOR) of five patients in an effort to determine whether VNS (as it is used for the treatment of epilepsy) has any influence on vestibular function. The study did not show any significant clinical alterations of the VOR during VNS. In addition, no worsening of autonomic control was seen after stimulation. The authors conclude that VNS "does not alter the vestibular influence on reflex ocular reactions" and that "the lack of such an influence indicates a pertinent safety of VNS as far as the patient's activities are concerned which demand vestibular integrity."

**Abstract** Vagus nerve stimulation (VNS), as used for the treatment of intractable epilepsy, may interfere with signals from viscera and modify the integration of autonomic afferent fibers in the brainstem. In order to detect an influence of VNS on vestibular function, the vestibulo-ocular reflex (VOR) of 5 patients was examined before and during VNS. Nonsignificant alterations of the maximum slow-phase velocity of the VOR were found. A significant clinical alteration of the VOR during VNS was not observed.

7. **Kersing W, Dejonckere PH, van der Aa HE, Buschman HP. Laryngeal and vocal changes during vagus nerve stimulation in epileptic patients. *J Voice*. 2002;16(2):251-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12150377>  
**Abstract** Left vagus nerve stimulation (VNS) by means of an implanted electrode has proven to reduce seizure frequency in epileptic patients with medically refractory seizures. This technique is now widely applied over the world. Voice changes appear to be one of the major side effects. The morphodynamic changes in the larynx and the acoustic impacts have been analyzed in detail in 7 implanted patients. Basic vagus stimulation is well tolerated. Extra stimulation induces an adductory spasm of either the ipsilateral vocal fold or the vestibular fold. The result, when the patient phonates, consists of a slight increase of F0 as well as a moderate increase of random period perturbation, but there is no evidence for the occurrence of "bifurcations." Further, as the glottic closure remains sufficient, there is no increase in turbulent noise. The lack of increase in turbulent noise and the lack of "bifurcations" appears to clearly differentiate a spasmodic contraction of the vocal cord from a unilateral vocal fold paralysis.
8. **Frei MG, Osorio I. Left vagus nerve stimulation with the neurocybernetic prosthesis has complex effects on heart rate and on its variability in humans. *Epilepsia*. 2001;42(8):1007-16.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11554886>  
<http://onlinelibrary.wiley.com/store/10.1046/j.1528-1157.2001.0420081007.x/asset/j.1528-1157.2001.0420081007.x.pdf?v=1&t=he940cam&s=b53f62ce360579d2ebd0692663d12feb7da55c4d>  
**Abstract** PURPOSE: The purpose of this study was to determine if stimulation of the left vagus nerve (LVNS) with the neurocybernetic prosthesis (NCP) in humans is, as claimed in the literature, without cardiac chronotropic actions. METHODS: We analyzed 228 h of ECG recorded from five subjects with intractable epilepsy who had not benefited from LVNS, for effects on instantaneous heart rate (IHR) and heart rate variability (HRV). RESULTS: There were two main cardiac responses: (a) bradycardia, and (b) tachycardia during the first half, followed by bradycardia during the second half of stimulation (biphasic response). Multiphasic responses characterized by alternating bradycardia and tachycardia were rarely observed. HRV was either increased or decreased depending on the subject and on the stimulation parameters. HRV as a function of HR also showed high interindividual variability, and interestingly, in one case behaved paradoxically, increasing at higher and decreasing at lower heart rates. CONCLUSIONS: LVNS at high intensities has complex effects on IHR and HRV, which show large interindividual variability. These spectra of cardiac responses reflect the interplay of autonomic, visceral, and somatic sensory afferences and the role of central structures in their integration. These findings also point to the need for more comprehensive studies of cardiac function in humans implanted with the NCP, using sensitive methods for data processing and analysis such as those developed for this study.
9. **Tatum WO, Moore DB, Stecker MM, Baltuch GH, French JA, Ferreira JA, et al. Ventricular asystole during vagus nerve stimulation for epilepsy in humans. *Neurology*. 1999;52(6):1267-9; comment *Neurology* 1999;52(6):1117-8; comment *Neurology*. 2000;54(3):775; author reply *Neurology*. 2000;54(3):776.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10214755>  
**Notes** Brief communication of asystole intraoperatively among four patients at four centers. VNS has shown no adverse cardiac effects during the clinical studies. In the history of VNS, only 4/3,000 patients experienced asystole during the surgical testing procedure, a rate of about 0.1%. All patients recovered without complications in the OR. One patient was still implanted after the asystole in the same case and has done fine for 9 months.  
**Abstract** Electrical stimulation of the vagus nerve, a recently available option for patients with refractory epilepsy, has demonstrated safety and efficacy. We report four patients with refractory epilepsy who experienced ventricular asystole intraoperatively during initial testing for implantation of the vagus nerve stimulator. Acute intraoperative vagus nerve stimulation may create ventricular asystole in humans. Extracorporeal cervical vagus nerve stimulation testing with continuous EKG monitoring intraoperatively before generator implantation is warranted.

10. **Lundgren J, Ekberg O, Olsson R. Aspiration: a potential complication to vagus nerve stimulation. *Epilepsia*. 1998;39(9):998-1000.**  
<http://www.ncbi.nlm.nih.gov/pubmed/9738680>  
**Abstract** PURPOSE: Vagus nerve stimulation (VNS) is reported to reduce the frequency of seizures in children and adults without causing serious side effects. However, clinical observation of swallowing difficulties in 2 children treated with VNS made further investigation necessary. METHODS: Seven patients aged 4-18 years and treated with VNS for 6-14 months were investigated with videoradiography during barium swallow. The children performed 5-30 barium swallow investigations with the VNS device turned off, running as programmed, or set at continuous stimulations. The degree of aspiration was scored from 0 to 3. RESULTS: In 5 of 7 children, of whom reported transient swallowing difficulties, no change in the degree of aspiration was noted. The 2 children with swallowing difficulties, however, showed increased aspiration score when the stimulator was set at continuous stimulations. In 1 the score also appeared to increase with the VNS running as programmed ( $p > 0.05$ ). Both children had severe mental and motor disabilities. CONCLUSIONS: Before and during VNS treatment patients should be evaluated with regard to swallowing problems. There needs to be an easy way to turn the device on and off to avoid aspirations, a hazardous and potentially life-threatening complication of VNS.
11. **Lotvall J, Lunde H, Augustinson LE, Hedner T, Svedmyr N, Ben-Menachem E. Airway effects of direct left-sided cervical vagal stimulation in patients with complex partial seizures. *Epilepsy Res*. 1994;18(2):149-54.**  
<http://www.ncbi.nlm.nih.gov/pubmed/7957037>  
**Abstract** Airway nerves have been implied in obstructive lung diseases for many years. In experimental animals, vagal stimulation produces several features of asthma, including airflow obstruction and airway plasma exudation. Vagal stimulation is a novel and effective therapy in patients with refractory epilepsy. We evaluated the airway response to left-sided cervical electrical stimulation using 1 Hz (low stimulation: 30 s, once every 90 min) and 30 Hz (high stimulation: 30 s, every 5 min) in a randomized double-blinded fashion for 3 months in epileptic patients participating in a phase two efficacy study. In eight patients with high stimulation and six with low stimulation, no effect on FEV1 (forced expiratory volume in 1 s) was seen over 3 months chronic stimulation. In a follow-up, up to 9 months, no further deterioration of lung function was observed. Of five patients without concomitant lung disease who consented to more extended experiments, one patient produced a reduction of FEV1 with variable frequency and current stimulation (10-87 Hz and 0.5-2.5 mA respectively). In one patient with obstructive lung disease, however, increased frequency and current stimulation led to a stimulation-dependent decrease in FEV1. After the addition of inhaled ipratropium bromide (160 micrograms, dry powder) to this patient, there was a clear improvement of baseline FEV1, but only a slight improvement of the stimulation-induced deterioration of FEV1. We conclude that long-term vagal stimulation in patients without concomitant lung disease does not induce any significant changes in FEV1. However, in patients with obstructive lung disease, intense vagal stimulation can cause a deterioration of lung function.(ABSTRACT TRUNCATED AT 250 WORDS)

**Safety Reports - Chart Review**

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- 1. Wozniak SE, Thompson EM, Selden NR. Vagal nerve stimulator infection: a lead-salvage protocol. *J Neurosurg Pediatr.* 2011;7(6):671-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21631207>

**Abstract** OBJECT: Vagal nerve stimulator (VNS) hardware infections are fraught with difficult management decisions. As with most implanted medical device-related infections, standard practice traditionally involves complete hardware removal, systemic antibiotic therapy, and subsequent reimplantation of the device. To avoid the potential morbidity of 2 repeat left carotid sheath surgical dissections, the authors have implemented a clinical protocol for managing VNS infections that involves generator removal and antibiotic therapy without lead removal. METHODS: A prospective, single-surgeon database was compared with hospital billing records to identify patients who underwent primary implantation or reimplantation of a VNS lead, generator, or both, from January 2001 to May 2010, at Oregon Health & Science University. From these records, the authors identified patients with VNS hardware infections and characterized their management, using a lead salvage protocol. RESULTS: In their review, the authors found a matching cohort of 206 children (age 3 months-17 years) who met the inclusion criteria. These children underwent 258 operations (including, in some children, multiple operations for generator end of life and/or lead malfunction). Six children experienced a single postimplantation infection (2.3% of the 258 operative cases), and no child experienced repeated infection. A lead-salvage protocol was used in 4 of 6 infected patients and was successful in 3 (75%), with clinical follow-up ranging from 10 months to 7.5 years. The fourth patient subsequently underwent lead removal and later reimplantation in standard fashion, with no adverse sequelae. CONCLUSIONS: Vagal nerve stimulator lead salvage is a safe and potentially advantageous strategy in the management of VNS-related infection. Further study is necessary to validate appropriate patient selection, success rates, and risks of this approach.
  
- 2. Air EL, Ghomri YM, Tyagi R, Grande AW, Crone K, Mangano FT. Management of vagal nerve stimulator infections: do they need to be removed? *J Neurosurg Pediatr.* 2009;3(1):73-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19119910>

**Abstract** OBJECT: Vagal nerve stimulators (VNSs) have been used successfully to treat medically refractory epilepsy. Although their efficacy is well established, appropriate management of infections is less clearly defined. In the authors' experience, patients who have gained a benefit from VNS implantation have been reluctant to have the device removed. The authors therefore sought conservative management options to salvage infected VNS systems. METHODS: The authors performed a retrospective review of 191 (93 female and 98 male) consecutive patients in whom VNS systems were placed between 2000 and 2007. RESULTS: They identified 10 infections (5.2%). In 9 of 10 patients the cultured organism was *Staphylococcus aureus*. Three (30%) of 10 patients underwent early removal (within 1 month) of the VNS as the initial treatment. The remaining 7 patients were initially treated with antibiotics. Two (28.6%) of these patients were successfully treated using antibiotics without VNS removal. Patients in whom conservative treatment failed were given cephalexin as first-line antibiotic treatment. All patients recovered completely regardless of treatment regimen. CONCLUSIONS: This study confirms the low rate of infection associated with VNS placement and suggests that, in the case of infection, treatment without removal is a viable option. However, the authors' data suggest that oral antibiotics are not the best first-line therapy.

3. **Pearl PL, Conry JA, Yaun A, Taylor JL, Heffron AM, Sigman M, et al. Misidentification of vagus nerve stimulator for intravenous access and other major adverse events. *Pediatr Neurol.* 2008;38(4):248-51.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18358402>  
**Abstract** The vagus nerve stimulator has become a standard modality for intractable pediatric epilepsy. We reviewed our experience with major adverse events, after accidental puncture of a stimulator wire by an emergency room physician seeking intravenous access to treat status epilepticus. The Children's National Medical Center database was reviewed for patients undergoing vagus nerve stimulator placement between January 1988 and June 2006. Patient characteristics, duration of therapy, and treatment-limiting adverse events were noted. Of 62 patients implanted over 8 years, 22 (35%) had adverse events which led to a change in therapy. Adverse events included prominent drooling, coughing, throat discomfort, dysphagia, wound infection, difficulty breathing, vomiting, vocal-cord weakness, lead failure, and iatrogenic (piercing of wire; surgical clipping of wire during revision). Eight patients required nonroutine surgical intervention (13%). There were two unusual case presentations. In a 13-year-old boy with status epilepticus at an outlying emergency department, the stimulator line was pierced in search of intravenous access. In a 25-year-old housepainter, neck paresthesias upon right lateral neck turning were attributed to insufficient strain relief. Treatment-limiting adverse events occurred in approximately one-third of patients. Unanticipated adverse events included misidentification of the wire for intravenous access, clipping of the wire during surgical dissection, and cervical dysesthesias associated with head-turning.
  
4. **Khurana DS, Reumann M, Hobdell EF, Neff S, Valencia I, Legido A, et al. Vagus nerve stimulation in children with refractory epilepsy: unusual complications and relationship to sleep-disordered breathing. *Childs Nerv Syst.* 2007;23(11):1309-12.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17619887>  
<http://link.springer.com/article/10.1007%2Fs00381-007-0404-8>  
**Abstract** BACKGROUND: Vagus nerve stimulation (VNS) is approved for use in patients with refractory epilepsy over the age of 12 years. While this procedure is widely used, there is little data on adverse events in young children. MATERIALS AND METHODS: A retrospective chart review was conducted on 26 children who had VNS implantation for refractory epilepsy from 1998 to 2004. RESULTS: Ages ranged from 3 to 17 years (16 boys and 10 girls). Seventy-seven percent had moderate to severe mental retardation. Sixty-five percent had more than 30 seizures per month. Symptomatic-generalized epilepsy was the predominant epilepsy syndrome seen in 77% of children. The duration of VNS treatment ranged from 1 month to 8 years (mean = 3.5 years). Twenty of 26 patients (77%) were on rapid-cycling mode. More than 50% reduction in seizure frequency was noted in 54% with two patients achieving seizure freedom. Twenty-three percent had less than 50% seizure reduction. Four patients were able to terminate seizures with use of the magnet. VNS was removed from one patient because of intractable cough persisting in spite of stimulation being turned off for 1 month. Another patient had it removed twice for infection. Obstructive sleep apnea (OSA) was observed in four patients (15%) after placement of VNS. CONCLUSION: VNS appears to be an effective treatment for children with refractory epilepsy. Development of intractable cough in one patient in spite of device being turned off and recurrent infection-related removal in another are unusual complications. Polysomnography before implantation of VNS should be considered to identify patients with pre-existing OSA.

5. **Ardesch JJ, Buschman HP, van der Burgh PH, Wagener-Schimmel LJ, van der Aa HE, Hageman G. Cardiac responses of vagus nerve stimulation: intraoperative bradycardia and subsequent chronic stimulation. *Clin Neurol Neurosurg.* 2007;109(10):849-52.**

<http://www.ncbi.nlm.nih.gov/pubmed/17825483>

**Abstract** OBJECTIVES: Few adverse events on heart rate have been reported with vagus nerve stimulation (VNS) for refractory epilepsy. We describe three cases with intraoperative bradycardia during device testing. PATIENTS AND METHODS: At our hospital 111 patients have received a VNS system. Intraoperative device testing is performed under ECG-monitoring. We reviewed the patients and their VNS-therapy follow-up outcome who experienced a change in heart rate, during device testing (Lead Test). RESULTS: Three patients with medically refractory epilepsy showed a bradycardia during intraoperative Lead Test. Postoperative the VNS-therapy started under ECG-monitoring. No change in cardiac rhythm occurred. Subsequent chronic stimulation is uneventful. All three have reduced seizure frequency. Two already have had their second implant, without the occurrence of bradycardia. CONCLUSION: In case of intraoperative bradycardia VNS-therapy onset should be done under ECG-monitoring. Subsequent chronic stimulation is safe in respect to heart rate. Bradycardia during intraoperative device testing is no reason to abort the operation.

6. **Rychlicki F, Zamponi N, Cesaroni E, Corpaci L, Trignani R, Ducati A, et al. Complications of vagal nerve stimulation for epilepsy in children. *Neurosurg Rev.* 2006;29(2):103-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/16518639>

<http://link.springer.com/article/10.1007%2Fs10143-005-0005-5>

**Abstract** Vagal nerve stimulation (VNS) is a surgical option to treat drug-resistant epilepsy. A few side effects have been described, mainly as anecdotal reports. We analysed our material concerning a juvenile population to identify the most common and most important complications, discussing them with the literature. Thirty-six patients were studied (18 months-18 years old). The children were assessed before the VNS implant and 3, 6, 12, 24 and 36 months after surgery. The mean follow-up was 30 months. Four patients required a second surgery: two for changing the device 3 years after implant; one for revision of an imperfect implant; one for removing a non-functioning device. In one patient a transient vocal cord paralysis was observed. Hoarseness was the main complaint (38.8%). More infrequent was mild sleep apnoea (8.3%), sternocleidomastoid muscle spasm, drooling and snoring in one patient each. Skin scars were reported with a different frequency according to the surgical technique. At variance with the literature reports, we did not observe infections. Side effects of VNS can be minimised, but not avoided completely, with a correct technical procedure, which in turn depends upon a thorough knowledge of vagus nerve anatomy.

7. **Smyth MD, Tubbs RS, Bebin EM, Grabb PA, Blount JP. Complications of chronic vagus nerve stimulation for epilepsy in children. *J Neurosurg.* 2003;99(3):500-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12959437>  
**Abstract** OBJECT: The aim of this study was to define better the incidence of surgical complications and untoward side effects of chronic vagus nerve stimulation (VNS) in a population of children with medically refractory epilepsy. METHODS: The authors retrospectively reviewed the cases of 74 consecutive patients (41 male and 33 female) 18 years of age or younger (mean age 8.8 years, range 11 months-18 years) who had undergone implantation of a vagal stimulator between 1998 and 2001 with a minimum follow up of 1 year (mean 2.2 years). Of the 74 patients treated, seven (9.4%) had a complication ultimately resulting in removal of the stimulator. The rate of deep infections necessitating device removal was 3.5% (three of 74 patients who had undergone 85 implantation and/or revision procedures). An additional three superficial infections occurred in patients in whom the stimulators were not removed: one was treated with superficial operative debridement and antibiotic agents and the other two with oral antibiotics only. Another four stimulators (5.4%) were removed because of the absence of clinical benefit and device intolerance. Two devices were revised because of lead fracture (2.7%). Among the cohort, 11 battery changes have been performed thus far, although none less than 33 months after initial implantation. Several patients experienced stimulation-induced symptoms (hoarseness, cough, drooling, outbursts of laughter, shoulder abduction, dysphagia, or urinary retention) that did not require device removal. Ipsilateral vocal cord paralysis was identified in one patient. One patient died of aspiration pneumonia more than 30 days after device implantation. CONCLUSIONS: Vagus nerve stimulation remains a viable option for improving seizure control in difficult to treat pediatric patients with epilepsy. Surgical complications such as hardware failure (2.7%) or deep infection (3.5%) occurred, resulting in device removal or revision. Occasional stimulation-induced symptoms such as hoarseness, dysphagia, or torticollis may be expected (5.4%).
8. **Blumer D, Davies K, Alexander A, Morgan S. Major Psychiatric Disorders Subsequent to Treating Epilepsy by Vagus Nerve Stimulation. *Epilepsy Behav.* 2001;2(5):466-72.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12609285>  
**Abstract** Purpose. The goal of this work was documentation of incidence, phenomenology, pathogenesis, and treatment of psychiatric disorders occurring subsequent to treating epilepsy by vagus nerve stimulation (VNS).Methods. In a series of 81 patients treated by VNS, all patients who developed major psychiatric complications underwent systematic psychiatric evaluation and treatment with psychotropic medication; VNS was modified if necessary.Results. After the seizure frequency was reduced by at least 75%, 7 of 81 patients (9%) developed major psychiatric disorders: Six became severely dysphoric (5 with catastrophic rage and 4 with psychotic symptoms), and one became psychotic. All 7 patients had experienced dysphoric disorders and 2 had experienced psychotic episodes prior to the VNS treatment. Five patients had frequent daily seizures prior to treatment. Remission or satisfactory improvement was achieved with psychotropic medication in 6 patients, aided by decreasing or interrupting VNS in two patients. One patient was noncompliant and suffered a fatal outcome.Conclusion. Severe interictal dysphoric disorders associated with catastrophic rage and psychotic episodes may develop on suppressing seizures by VNS in patients with previous epilepsy-related psychiatric disorders. Patients with multiple daily seizures may be more vulnerable to this occurrence. The phenomenon corresponds to the common finding of interictal dysphoric and psychotic symptoms emerging when inhibitory mechanisms predominate (alternative psychiatric disorders in the absence of seizures, or forced normalization of the EEG). The dysphoric symptom of catastrophic rage appears to occur more often on seizure suppression by VNS than by antiepileptic drugs. Psychiatric intervention, primarily with antidepressant medication, must be available to secure a good outcome; decrease of VNS may occasionally be required.

9. **Sato K, Shamoto H, Yoshimoto T. Severe bradycardia during epilepsy surgery. *J Neurosurg Anesthesiol.* 2001;13(4):329-32.**

<http://www.ncbi.nlm.nih.gov/pubmed/11733666>

**Abstract** Several kinds of arrhythmia are known to occur during epileptic seizure, and bradycardia has been reported in patients with temporal lobe epilepsy. The authors review the anesthesia records of patients with intractable epilepsy. Forty-two consecutive patients with intractable epilepsy who underwent epilepsy surgery were examined. Anterior temporal lobectomy was performed on 29 patients, frontal lobectomy on 2 patients, and a subdural electrode was set on 11 patients. Anesthesia was induced with propofol, fentanyl, and vecuronium and maintained with sevoflurane-fentanyl, propofol-fentanyl, or fentanyl-droperidol. Severe bradycardia (13-39 beats/min) was seen in six patients. All six patients recovered within 1 minute of interrupting the surgical procedure and administering intravenous atropine, and the surgeries were completed with no complications. The authors believe the six events were sinus bradycardias. They all occurred during amygdalo-hippocampectomy in cases of temporal lobectomy. This type of hemodynamic change was not seen in any of the patients undergoing temporal lobectomy without hippocampectomy, in patients undergoing frontal lobectomy, or when setting subdural electrodes. Experimentally, it has been shown that stimulation of the limbic system, such as the hippocampus, amygdala, and insular cortex, induces bradycardia and hypotension resulting from increased parasympathetic flow via the vagus nerve. Severe bradycardia may thus occur during surgery for temporal lobe epilepsy, and hemodynamic changes should be watched carefully during amygdalo-hippocampectomy.

10. **Murphy JV, Hornig GW, Schallert GS, Tilton CL. Adverse events in children receiving intermittent left vagal nerve stimulation. *Pediatr Neurol.* 1998;19(1):42-4.**

<http://www.ncbi.nlm.nih.gov/pubmed/9682884>

**Abstract** The purpose of this study was to determine the frequency of unexpected events during intermittent vagal nerve stimulation in 24 patients stimulated for a total of 61 patient years. The charts of 24 children undergoing periodic stimulation of the left vagal nerve on research protocols were reviewed to determine the nature and frequency of adverse events and the total length of time they were stimulated. Fifteen adverse events were discovered in 12 patients. Thirteen were likely related to the device, and four other events might have been related. Two of these resulted in voluntary termination of vagal nerve stimulation, and the rest were treatable. Vagal nerve stimulation was tolerated in this series of patients. As opposed to the more standard drug therapies, adverse events during vagal nerve stimulation do not necessitate termination of therapy, but these events frequently lead to unforeseen surgery under general anesthesia.

**Seizure Detection (Other than Cardiac-Based)**

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- 1. Feltane A, Faye Boudreaux-Bartels G, Besio W. Automatic seizure detection in rats using laplacian EEG and verification with human seizure signals. *Ann Biomed Eng.* 2013;41(3):645-54.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23073989>  
<http://rd.springer.com/article/10.1007%2Fs10439-012-0675-4>

**Abstract** Automated detection of seizures is still a challenging problem. This study presents an approach to detect seizure segments in Laplacian electroencephalography (tEEG) recorded from rats using the tripolar concentric ring electrode (TCRE) configuration. Three features, namely, median absolute deviation, approximate entropy, and maximum singular value were calculated and used as inputs into two different classifiers: support vector machines and adaptive boosting. The relative performance of the extracted features on TCRE tEEG was examined. Results are obtained with an overall accuracy between 84.81 and 96.51%. In addition to using TCRE tEEG data, the seizure detection algorithm was also applied to the recorded EEG signals from Andrzejak et al. database to show the efficiency of the proposed method for seizure detection.
  
- 2. Beniczky S, Polster T, Kjaer TW, Hjalgrim H. Detection of generalized tonic-clonic seizures by a wireless wrist accelerometer: A prospective, multicenter study. *Epilepsia.* 2013;54(4):e58-61.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23398578>  
<http://onlinelibrary.wiley.com/store/10.1111/epi.12120/asset/epi12120.pdf?v=1&t=hfzqlku4&s=c12743cea9758fae8e9e0da17d01c9b1fd418835>

**Abstract** Our objective was to assess the clinical reliability of a wrist-worn, wireless accelerometer sensor for detecting generalized tonic-clonic seizures (GTCS). Seventy-three consecutive patients (age 6-68 years; median 37 years) at risk of having GTCS and who were admitted to the long-term video-electroencephalography (EEG) monitoring unit (LTM) were recruited in three centers. The reference standard was considered the seizure time points identified by experienced clinical neurophysiologists, based on the video-EEG recordings and blinded to the accelerometer sensor data. Seizure time points detected real-time by the sensor were compared with the reference standard. Patients were monitored for 17-171 h (mean 66.8; total 4,878). Thirty-nine GTCS were recorded in 20 patients. The device detected 35 seizures (89.7%). In 16 patients all seizures were detected. In three patients more than two thirds of the seizures were detected. The mean of the sensitivity calculated for each patient was 91%. The mean detection latency measured from the start of the focal seizure preceding the secondarily GTCS was 55 s (95% confidence interval [CI] 38-73 s). The rate of false alarms was 0.2/day. Our results suggest that the wireless wrist accelerometer sensor detects GTCS with high sensitivity and specificity. Patients with GTCS have an increased risk for injuries related to seizures and for sudden unexpected death in epilepsy (SUDEP), and many nocturnal seizures remain undetected in unattended patients. A portable automatic seizure detection device will be an important tool for helping these patients.

3. **Van de Vel A, Cuppens K, Bonroy B, Milosevic M, Van Huffel S, Vanrumste B, et al. Long-term home monitoring of hypermotor seizures by patient-worn accelerometers. *Epilepsy Behav.* 2013;26(1):118-25. <http://www.ncbi.nlm.nih.gov/pubmed/23219410>**  
**Abstract** Long-term home monitoring of epileptic seizures is not feasible with the gold standard of video/electro-encephalography (EEG) monitoring. The authors developed a system and algorithm for nocturnal hypermotor seizure detection in pediatric patients based on an accelerometer (ACM) attached to extremities. Seizure detection is done using normal movement data, meaning that the system can be installed in a new patient's room immediately as prior knowledge on the patient's seizures is not needed for the patient-specific model. In this study, the authors compared video/EEG-based seizure detection with ACM data in seven patients and found a sensitivity of 95.71% and a positive predictive value of 57.84%. The authors focused on hypermotor seizures given the availability of this seizure type in the data, the typical occurrence of these seizures during sleep, i.e., when the measurements were done, and the importance of detection of hypermotor seizures given their often refractory nature and the possible serious consequences. To our knowledge, it is the first detection system focusing on this type of seizure in pediatric patients.
4. **Binder DK, Haut SR. Toward new paradigms of seizure detection. *Epilepsy Behav.* 2013;26(3):247-52. <http://www.ncbi.nlm.nih.gov/pubmed/23246145>**  
**Abstract** Great effort has been made toward defining and characterizing the pre-ictal state. Many studies have pursued the idea that there are recognizable electrographic (EEG-based) features which occur before overt clinical seizure activity. However, development of reliable EEG-based seizure detection and prediction algorithms has been difficult. In this review, we discuss the concepts of seizure detection vs. prediction and the pre-ictal "clinical milieu" and "EEG milieu". We proceed to discuss novel concepts of seizure detection based on the pre-ictal "physiological milieu"; in particular, we indicate some early evidence for the hypothesis that pre-ictal cell swelling/extracellular space constriction can be detected with novel optical methods. Development and validation of optical seizure detection technology could provide an entirely new translational approach for the many patients with intractable epilepsy. This article is part of a Special Issue entitled "The Future of Translational Epilepsy Research".
5. **Niknazar M, Mousavi SR, Motaghi S, Dehghani A, Vosoughi Vahdat B, Shamsollahi MB, et al. A unified approach for detection of induced epileptic seizures in rats using ECoG signals. *Epilepsy Behav.* 2013;27(2):355-64. <http://www.ncbi.nlm.nih.gov/pubmed/23542539>**  
**Abstract** **OBJECTIVE:** Epileptic seizure detection is a key step for epilepsy assessment. In this work, using the pentylenetetrazole (PTZ) model, seizures were induced in rats, and ECoG signals in interictal, preictal, ictal, and postictal periods were recorded. The recorded ECoG signals were then analyzed to detect epileptic seizures in the epileptic rats. **METHODS:** Two different approaches were considered in this work: thresholding and classification. In the thresholding approach, a feature is calculated in consecutive windows, and the resulted index is tracked over time and compared with a threshold. The moment the index crosses the threshold is considered as the moment of seizure onset. In the classification approach, features are extracted from before, during, and after ictal periods and statistically analyzed. Statistical characteristics of some features have a significant difference among these periods, thus resulting in epileptic seizure detection. **RESULTS:** Several features were examined in the thresholding approach. Nonlinear energy and coastline features were successful in epileptic seizure detection. The best result was achieved by the coastline feature, which led to a mean of a 2-second delay in its correct detections. In the classification approach, the best result was achieved using the fuzzy similarity index that led to  $P$ value<0.001. **CONCLUSION:** This study showed that variance-based features were more appropriate for tracking abrupt changes in ECoG signals. Therefore, these features perform better in seizure onset estimation, whereas nonlinear features or indices, which are based on dynamical systems, can better track the transition of neural system to ictal period. **SIGNIFICANCE:** This paper presents examination of different features and indices for detection of induced epileptic seizures from rat's ECoG signals.

6. **Buteneers P, Verstraeten D, Nieuwenhuysse BV, Stroobandt D, Raedt R, Vonck K, et al. Real-time detection of epileptic seizures in animal models using reservoir computing. *Epilepsy Res.* 2013;103(2-3):124-34.**

<http://www.ncbi.nlm.nih.gov/pubmed/22854191>

**Abstract** In recent years, an increasing number of studies have investigated the effects of closed-loop anti-epileptic treatments. Most of the current research still is very labour intensive: real-time treatment is manually triggered and conclusions can only be drawn after multiple days of manual review and annotation of the electroencephalogram (EEG). In this paper we propose a technique based on reservoir computing (RC) to automatically and in real-time detect epileptic seizures in the intra-cranial EEG (iEEG) of epileptic rats in order to immediately trigger seizure treatment. The performance of the system is evaluated in two different seizure types: absence seizures from genetic absence epilepsy rats from Strasbourg (GAERS) and limbic seizures from post status epilepticus (PSE) rats. The dataset consists of 452 hours iEEG from 23 GAERS and 2083 hours iEEG from 22 PSE rats. In the default set-up the system detects 0.09 and 0.13 false positives per seizure and misses 0.07 and 0.005 events per seizure for GAERS and PSE rats respectively. It achieves an average detection delay below 1s in GAERS and less than 10s in the PSE data. This detection delay and the number of missed seizures can be further decreased when a higher false positive rate is allowed. Our method outperforms state-of-the-art detection techniques and only a few parameters require optimization on a limited training set. It is therefore suited for automatic seizure detection based on iEEG and may serve as a useful tool for epilepsy researchers. The technique avoids the time-consuming manual review and annotation of EEG and can be incorporated in a closed-loop treatment strategy.

7. **Becq G, Kahane P, Minotti L, Bonnet S, Guillemaud R. Classification of Epileptic Motor Manifestations and Detection of Tonic-Clonic Seizures with Acceleration Norm Entropy. *IEEE Trans Biomed Eng.* 2013.**

<http://www.ncbi.nlm.nih.gov/pubmed/23392333>

<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6449295>

**Abstract** In this article, three triaxis accelerometers positioned on the wrists and the head of epileptic patients submitted to long-term video electroencephalographic monitoring as part of presurgical investigation are evaluated to characterize the different classes of motor manifestations observed during seizures. Quadratic discriminant classifiers are trained on features extracted from 1 s or 4 s windows. It is shown that a simple rule applied to the acceleration norm entropy HnA produces the best performances compared to other classifiers trained on other feature sets. The simple rule is as follows with values given in bits: ( $0 < \text{HnA} < 1.34$ ), no movement; ( $1.34 < \text{HnA} < 3.87$ ), tonic manifestations; ( $3.87 < \text{HnA}$ ), tonic-clonic manifestations. For this classifier, features are extracted from 1 s windows and the misclassification rate is 11% evaluated on 5 607 s of epileptic motor manifestations obtained from 58 seizures in 30 patients. A quantile normalization can improve the results with features based on absolute power spectral density but performances are not as good as the ones obtained with HnA. Based on the classifier using only HnA, a simple tonic-clonic seizure detector is proposed and produces a 80% sensitivity with a 95% specificity.

- 8. Rasekhi J, Mollaei MR, Bandarabadi M, Teixeira CA, Dourado A. Preprocessing effects of 22 linear univariate features on the performance of seizure prediction methods. *J Neurosci Methods*. 2013. <http://www.ncbi.nlm.nih.gov/pubmed/23567810>**  
**Abstract** Combining multiple linear univariate features in one feature space and classifying this feature space using machine learning methods could predict epileptic seizures, in the patients suffering from refractory epilepsy. For each patient, a set of twenty-two linear univariate features are extracted from 6 electroencephalogram (EEG) signals, and make a 132 dimensional feature space. Preprocessing and normalization methods of the features, affect the outputs of the seizure prediction algorithm, and are studied in terms of alarm sensitivity and false prediction rate (FPR). The problem of approximately choosing an optimal preictal time was tackled using 4 distinct values; 10, 20, 30, and 40minutes Seizure prediction problem has traditionally been considered as a two-class classification problem, which is also exercised here. The studies have been done on the features obtained from 10 patients. For each patient, 48 different combinations of methods are compared to find the best configuration. Normalization through dividing by maximum and smoothing, are found as the best configuration in most of the patients. Results also indicate that applying machine learning methods on a multidimensional feature space resulting from 22 univariate features could predict seizure onsets with high performance. In average, the seizures were predicted in 73.9% of the cases (34 out of 46 in 737.9hours of test data), with a FPR of 0.15h-1.
- 9. Flamm C, Graef A, Pirker S, Baumgartner C, Deistler M. Influence analysis for high-dimensional time series with an application to epileptic seizure onset zone detection. *J Neurosci Methods*. 2013;214(1):80-90. <http://www.ncbi.nlm.nih.gov/pubmed/23354014>**  
**Abstract** Granger causality is a useful concept for studying causal relations in networks. However, numerical problems occur when applying the corresponding methodology to high-dimensional time series showing co-movement, e.g. EEG recordings or economic data. In order to deal with these shortcomings, we propose a novel method for the causal analysis of such multivariate time series based on Granger causality and factor models. We present the theoretical background, successfully assess our methodology with the help of simulated data and show a potential application in EEG analysis of epileptic seizures.
- 10. Xie S, Krishnan S. Wavelet-based sparse functional linear model with applications to EEGs seizure detection and epilepsy diagnosis. *Med Biol Eng Comput*. 2013;51(1-2):49-60. <http://www.ncbi.nlm.nih.gov/pubmed/23054383> <http://rd.springer.com/article/10.1007%2Fs11517-012-0967-8>**  
**Abstract** In epilepsy diagnosis or epileptic seizure detection, much effort has been focused on finding effective combination of feature extraction and classification methods. In this paper, we develop a wavelet-based sparse functional linear model for representation of EEG signals. The aim of this modeling approach is to capture discriminative random components of EEG signals using wavelet variances. To achieve this goal, a forward search algorithm is proposed for determination of an appropriate wavelet decomposition level. Two EEG databases from University of Bonn and University of Freiburg are used for illustration of applicability of the proposed method to both epilepsy diagnosis and epileptic seizure detection problems. For this data considered, we show that wavelet-based sparse functional linear model with a simple classifier such as 1-NN classification method leads to higher classification results than those obtained using other complicated methods such as support vector machine. This approach produces a 100% classification accuracy for various classification tasks using the EEG database from University of Bonn, and outperforms many other state-of-the-art techniques. The proposed classification scheme leads to 99% overall classification accuracy for the EEG data from University of Freiburg.

- 11. Ayoubian L, Lacombe H, Gotman J. Automatic seizure detection in SEEG using high frequency activities in wavelet domain. *Med Eng Phys.* 2013;35(3):319-28.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22647836>  
**Abstract** Existing automatic detection techniques show high sensitivity and moderate specificity, and detect seizures a relatively long time after onset. High frequency (80-500 Hz) activity has recently been shown to be prominent in the intracranial EEG of epileptic patients but has not been used in seizure detection. The purpose of this study is to investigate if these frequencies can contribute to seizure detection. The system was designed using 30 h of intracranial EEG, including 15 seizures in 15 patients. Wavelet decomposition, feature extraction, adaptive thresholding and artifact removal were employed in training data. An EMG removal algorithm was developed based on two features: Lack of correlation between frequency bands and energy-spread in frequency. Results based on the analysis of testing data (36 h of intracranial EEG, including 18 seizures) show a sensitivity of 72%, a false detection of 0.7/h and a median delay of 5.7 s. Missed seizures originated mainly from seizures with subtle or absent high frequencies or from EMG removal procedures. False detections were mainly due to weak EMG or interictal high frequency activities. The system performed sufficiently well to be considered for clinical use, despite the exclusive use of frequencies not usually considered in clinical interpretation. High frequencies have the potential to contribute significantly to the detection of epileptic seizures.
- 12. Eberle MM, Reynolds CL, Szu JI, Wang Y, Hansen AM, Hsu MS, et al. In vivo detection of cortical optical changes associated with seizure activity with optical coherence tomography. *Biomed Opt Express.* 2012;3(11):2700-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23162709>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3493229/pdf/2700.pdf>  
**Abstract** The most common technology for seizure detection is with electroencephalography (EEG), which has low spatial resolution and minimal depth discrimination. Optical techniques using near-infrared (NIR) light have been used to improve upon EEG technology and previous research has suggested that optical changes, specifically changes in near-infrared optical scattering, may precede EEG seizure onset in in vivo models. Optical coherence tomography (OCT) is a high resolution, minimally invasive imaging technique, which can produce depth resolved cross-sectional images. In this study, OCT was used to detect changes in optical properties of cortical tissue in vivo in mice before and during the induction of generalized seizure activity. We demonstrated that a significant decrease ( $P < 0.001$ ) in backscattered intensity during seizure progression can be detected before the onset of observable manifestations of generalized (stage-5) seizures. These results indicate the feasibility of minimally-invasive optical detection of seizures with OCT.

13. **Duun-Henriksen J, Kjaer TW, Madsen RE, Remvig LS, Thomsen CE, Sorensen HB. Channel selection for automatic seizure detection. *Clin Neurophysiol.* 2012;123(1):84-92.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21752709>  
**Abstract** OBJECTIVE: To investigate the performance of epileptic seizure detection using only a few of the recorded EEG channels and the ability of software to select these channels compared with a neurophysiologist. METHODS: Fifty-nine seizures and 1419 h of interictal EEG are used for training and testing of an automatic channel selection method. The characteristics of the seizures are extracted by the use of a wavelet analysis and classified by a support vector machine. The best channel selection method is based upon maximum variance during the seizure. RESULTS: Using only three channels, a seizure detection sensitivity of 96% and a false detection rate of 0.14/h were obtained. This corresponds to the performance obtained when channels are selected through visual inspection by a clinical neurophysiologist, and constitutes a 4% improvement in sensitivity compared to seizure detection using channels recorded directly on the epileptic focus. CONCLUSIONS: Based on our dataset, automatic seizure detection can be done using only three EEG channels without loss of performance. These channels should be selected based on maximum variance and not, as often done, using the focal channels. SIGNIFICANCE: With this simple automatic channel selection method, we have shown a computational efficient way of making automatic seizure detection.
14. **Jouny CC, Bergey GK. Characterization of early partial seizure onset: frequency, complexity and entropy. *Clin Neurophysiol.* 2012;123(4):658-69.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21872526>  
**Abstract** OBJECTIVE: A clear classification of partial seizures onset features is not yet established. Complexity and entropy have been very widely used to describe dynamical systems, but a systematic evaluation of these measures to characterize partial seizures has never been performed. METHODS: Eighteen different measures including power in frequency bands up to 300 Hz, Gabor atom density (GAD), Higuchi fractal dimension (HFD), Lempel-Ziv complexity, Shannon entropy, sample entropy, and permutation entropy, were selected to test sensitivity to partial seizure onset. Intracranial recordings from 45 patients with mesial temporal, neocortical temporal and neocortical extratemporal seizure foci were included (331 partial seizures). RESULTS: GAD, Lempel-Ziv complexity, HFD, high frequency activity, and sample entropy were the most reliable measures to assess early seizure onset. CONCLUSIONS: Increases in complexity and occurrence of high-frequency components appear to be commonly associated with early stages of partial seizure evolution from all regions. The type of measure (frequency-based, complexity or entropy) does not predict the efficiency of the method to detect seizure onset. SIGNIFICANCE: Differences between measures such as GAD and HFD highlight the multimodal nature of partial seizure onsets. Improved methods for early seizure detection may be achieved from a better understanding of these underlying dynamics.

15. **Aarabi A, He B. A rule-based seizure prediction method for focal neocortical epilepsy. *Clin Neurophysiol.* 2012;123(6):1111-22.**

<http://www.ncbi.nlm.nih.gov/pubmed/22361267>

**Abstract** OBJECTIVE: In the present study, we have developed a novel patient-specific rule-based seizure prediction system for focal neocortical epilepsy. METHODS: Five univariate measures including correlation dimension, correlation entropy, noise level, Lempel-Ziv complexity, and largest Lyapunov exponent as well as one bivariate measure, nonlinear interdependence, were extracted from non-overlapping 10-s segments of intracranial electroencephalogram (iEEG) data recorded using electrodes implanted deep in the brain and/or placed on the cortical surface. The spatio-temporal information was then integrated by using rules established based on patient-specific changes observed in the period prior to a seizure sample for each patient. The system was tested on 316 h of iEEG data containing 49 seizures recorded in 11 patients with medically intractable focal neocortical epilepsy. RESULTS: For seizure occurrence periods of 30 and 50 min our method showed an average sensitivity of 79.9% and 90.2% with an average false prediction rate of 0.17 and 0.11/h, respectively. In terms of sensitivity and false prediction rate, the system showed superiority to random and periodical predictors. CONCLUSIONS: The nonlinear analysis of iEEG in the period prior to seizures revealed patient-specific spatio-temporal changes that were significantly different from those observed within baselines in the majority of the seizures analyzed in this study. SIGNIFICANCE: The present results suggest that the patient specific rule-based approach may become a potentially useful approach for predicting seizures prior to onset.

16. **Khamis H, Mohamed A, Simpson S, McEwan A. Detection of temporal lobe seizures and identification of lateralisation from audified EEG. *Clin Neurophysiol.* 2012;123(9):1714-20.**

<http://www.ncbi.nlm.nih.gov/pubmed/22418593>

**Abstract** OBJECTIVE: To investigate the accuracy of human listeners in identifying epileptic seizures and seizure lateralisation from audified EEG signals. METHODS: EEG data from 17 temporal lobe epilepsy patients (9 male, 8 female; aged 23-55) was converted to audio format by 60x time compression. Using a subset of 19% of the data, five auditory participants (2 female, 3 male; aged 23-58) were trained to identify seizures and their lateralisation by listening to audified EEG signals from difference electrodes P3-T5 and P4-T6. Following training, seizure detection performance of the auditory participants was tested using the remaining data. RESULTS: Allowing a 5s auditory time margin for successful detection, the mean sensitivity of the five auditory participants was 89.6% (SD 8.3%) with a false detection rate of only 0.0068/h (SD 0.0077/h). The mean accuracy of seizure lateralisation identification was 77.6% (SD 7.1%). CONCLUSIONS: With a limited amount of training, humans can detect seizures and seizure lateralisation from audified EEG signals of electrodes P3-T5 and P4-T6 with accuracy comparable to visual assessment of full EEG traces (21 electrodes) by an expert encephalographer. SIGNIFICANCE: A more efficient and accurate clinical tool for assessing EEG data based on audification may be developed, which will improve diagnosis and treatment of epilepsy.

17. **Hunyadi B, Signoretto M, Van Paesschen W, Suykens JA, Van Huffel S, De Vos M. Incorporating structural information from the multichannel EEG improves patient-specific seizure detection. *Clin Neurophysiol.* 2012;123(12):2352-61.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22727715>  
**Abstract** OBJECTIVE: A novel patient-specific seizure detection algorithm is presented. As the spatial distribution of the ictal pattern is characteristic for a patient's seizures, this work incorporates such information into the data representation and provides a learning algorithm exploiting it. METHODS: The proposed training algorithm uses nuclear norm regularization to convey structural information of the channel-feature matrices extracted from the EEG. This method is compared to two existing approaches utilizing the same feature set, but integrating the multichannel information in a different manner. The performances of the detectors are demonstrated on a publicly available dataset containing 131 seizures recorded in 892 h of scalp EEG from 22 pediatric patients. RESULTS: The proposed algorithm performed significantly better compared to the reference approaches ( $p=0.0170$  and  $p=0.0002$ ). It reaches a median performance of 100% sensitivity, 0.11h(-1) false detection rate and 7.8s alarm delay, outperforming a method in the literature using the same dataset. CONCLUSION: The strength of our method lies within conveying structural information from the multichannel EEG. Such formulation automatically includes crucial spatial information and improves detection performance. SIGNIFICANCE: Our solution facilitates accurate classification performance for small training sets, therefore, it potentially reduces the time needed to train the detector before starting monitoring.
18. **Majumdar K. Differential operator in seizure detection. *Comput Biol Med.* 2012;42(1):70-4.** <http://www.ncbi.nlm.nih.gov/pubmed/22104594>  
**Abstract** Differential operators can detect significant changes in signals. This has been utilized to enhance the contrast of the seizure signatures in depth EEG or ECoG. We have actually taken normalized exponential of absolute value of single or double derivative of epileptic ECoG. This in short we call differential filtering. Windowed variance operation has been performed to automatically detect seizure onset on differentially filtered signal. A novel method for determining the duration of seizure has also been proposed. Since all operations take only linear time, the whole method is extremely fast. Seven empirical parameters have been introduced whose patient specific thresholding brings down the rate of false detection to a bare minimum. Results of implementation of the methods on the ECoG data of four epileptic patients have been reported with an ROC curve analysis. High value of the area under the ROC curve indicates excellent detection performance.
19. **Rabbi AF, Fazel-Rezai R. A fuzzy logic system for seizure onset detection in intracranial EEG. *Comput Intell Neurosci.* 2012;2012:705140.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22577370>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3346687/pdf/CIN2012-705140.pdf>  
**Abstract** We present a multistage fuzzy rule-based algorithm for epileptic seizure onset detection. Amplitude, frequency, and entropy-based features were extracted from intracranial electroencephalogram (iEEG) recordings and considered as the inputs for a fuzzy system. These features extracted from multichannel iEEG signals were combined using fuzzy algorithms both in feature domain and in spatial domain. Fuzzy rules were derived based on experts' knowledge and reasoning. An adaptive fuzzy subsystem was used for combining characteristics features extracted from iEEG. For the spatial combination, three channels from epileptogenic zone and one from remote zone were considered into another fuzzy subsystem. Finally, a threshold procedure was applied to the fuzzy output derived from the final fuzzy subsystem. The method was evaluated on iEEG datasets selected from Freiburg Seizure Prediction EEG (FSPEEG) database. A total of 112.45 hours of intracranial EEG recordings was selected from 20 patients having 56 seizures was used for the system performance evaluation. The overall sensitivity of 95.8% with false detection rate of 0.26 per hour and average detection latency of 15.8 seconds was achieved.

20. **Pediaditis M, Tsiknakis M, Leitgeb N. Vision-based motion detection, analysis and recognition of epileptic seizures--a systematic review. *Comput Methods Programs Biomed.* 2012;108(3):1133-48.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22954620>  
**Abstract** The analysis of human motion from video has been the object of interest for many application areas, these including surveillance, control, biomedical analysis, video annotation etc. This paper addresses the advances within this topic in relation to epilepsy, a domain where human motion is with no doubt one of the most important elements of a patient's clinical image. It describes recent achievements in vision-based detection, analysis and recognition of human motion in epilepsy for marker-based and marker-free systems. An overview of motion-characterizing features extracted so far is presented separately. The objective is to gain existing knowledge in this field and set the route marks for the future development of an integrated decision support system for epilepsy diagnosis and disease management based on automated video analysis. This review revealed that the quantification of motion patterns of selected epileptic seizures has been studied thoroughly while the recognition of seizures is currently in its beginnings, but however feasible. Moreover, only a limited set of seizure types have been analyzed so far, indicating that a holistic approach addressing all epileptic syndromes is still missing.
21. **Pediaditis M, Tsiknakis M, Koumakis L, Karachaliou M, Voutoufianakis S, Vorgia P. Vision-based absence seizure detection. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:65-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23365833>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6345872>  
**Abstract** In order to diagnose epilepsy, neurologists rely on their experience, performing an equal assessment of the electroencephalogram and the clinical image. Since misdiagnosis reaches a rate of 30% and more than one-third of all epilepsies are poorly understood, a need for leveraging diagnostic precision is obvious. With the aim at enhancing the clinical image assessment procedure, this paper evaluates the suitability of certain facial expression features for detecting and quantifying absence seizures. These features are extracted by means of time-varying signal analysis from signals that are gained by applying computer vision techniques, such as face detection, dense optical flow computation and averaging background subtraction. For the evaluation, video sequences of four patients with absence seizures are used. The classification performance of a C4.5 decision tree shows accuracies of up to 99.96% with a worst percentage of incorrectly classified instances of 0.14%.
22. **McLaughlin BL, Mariano LJ, Prakash SR, Kindle AL, Czarnecki A, Modarres MH, et al. An electroencephalographic recording platform for real-time seizure detection. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:875-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23366032>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6346071>  
**Abstract** There are currently no clinical devices that can be worn by epilepsy patients who suffer from intractable seizures to warn them of seizure onset. Here we summarize state-of-the-art therapies and devices, and present a second-generation hardware platform in which seizure detection algorithms may be programmed into the device. Bi-polar electrographic data is presented for a prototype device and future implementations are discussed.

23. **Furbass F, Hartmann M, Perko H, Skupch A, Dollfuss P, Gritsch G, et al. Combining time series and frequency domain analysis for a automatic seizure detection. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:1020-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23366068>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6346107>  
**Abstract** The detection of epileptic seizures in long-term electroencephalographic (EEG) recordings is a time-consuming and tedious task requiring specially trained medical experts. The EpiScan seizure detection algorithm developed by the Austrian Institute of Technology (AIT) has proven to achieve high detection performance with a robust false alarm rate in the clinical setting. This paper introduces a novel time domain method for detection of epileptic seizure patterns with focus on irregular and distorted rhythmic activity. The method scans the EEG for sequences of similar epileptiform discharges and uses a combination of duration and similarity measure to decide for a seizure. The resulting method was tested on an EEG database with 275 patients including over 22000h of unselected and uncut EEG recording and 623 seizures. Used in combination with the EpiScan algorithm we increased the overall sensitivity from 70% to 73% while reducing the false alarm rate from 0.33 to 0.30 alarms per hour.
24. **Ayinala M, Parhi KK. Low complexity algorithm for seizure prediction using Adaboost. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:1061-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23366078>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6346117>  
**Abstract** This paper presents a novel low-complexity patient-specific algorithm for seizure prediction. Adaboost algorithm is used in two stages of the algorithm: feature selection and classification. The algorithm extracts spectral power features in 9 different sub-bands from the electroencephalogram (EEG) recordings. We have proposed a new feature ranking method to rank the features. The key (top ranked) features are used to make a prediction on the seizure event. Further, to reduce the complexity of classification stage, a non-linear classifier is built based on the Adaboost algorithm using decision stumps (linear classifier) as the base classifier. The proposed algorithm achieves a sensitivity of 94.375% for a total of 71 seizure events with a low false alarm rate of 0.13 per hour and 6.5% of time spent in false alarms using an average of 5 features for the Freiburg database. The low computational complexity of the proposed algorithm makes it suitable for an implantable device.
25. **Logesparan L, Casson AJ, Rodriguez-Villegas E. Improving seizure detection performance reporting: analysing the duration needed for a detection. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:1069-72.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23366080>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6346119>  
**Abstract** Improving seizure detection performance relies not only on novel signal processing approaches but also on new accurate, reliable and comparable performance reporting to give researchers better and fairer tools for understanding the true algorithm operation. This paper investigates the sensitivity of current performance metrics to the duration of data that must be marked as candidate seizure activity before a seizure detection is made. The results demonstrate that not all metrics are insensitive to this high level choice in the algorithm design, and provide new approaches for comparing between reported algorithm performances in a robust and reliable manner.

26. **Nagaraj SB, Stevenson N, Marnane W, Boylan G, Lightbody G. A novel dictionary for neonatal EEG seizure detection using atomic decomposition. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:1073-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23366081>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6346120>  
**Abstract** The development of automated methods of electroencephalogram (EEG) seizure detection is an important problem in neonatology. This paper proposes improvements to a previously described method of seizure detection based on atomic decomposition by developing a new time-frequency (TF) dictionary that is highly coherent with the newborn EEG seizure. We compare the performance of the proposed dictionary on neonatal EEG signals with that achieved using Gabor, Fourier and wavelet dictionaries. Through the analysis of real newborn EEG data, we show first, that dictionary selection can influence the seizure detection accuracy and second, that the proposed dictionary outperforms other dictionaries by at least 10% in seizure detection accuracy and 5% improvement in the area under the Receiver Operator Characteristic curve.
27. **Gritsch G, Hartmann M, Perko H, Furbass F, Kluge T. Automatic seizure detection based on the activity of a set of current dipoles: first steps. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:2853-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23366519>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6346558>  
**Abstract** In this paper we show advantages of using an advanced montage scheme with respect to the performance of automatic seizure detection systems. The main goal is to find the best performing montage scheme for our automatic seizure detection system. The new virtual montage is a fix set of dipoles within the brain. The current density signals for these dipoles are derived from the scalp EEG signals based on a smart linear transformation. The reason for testing an alternative approach is that traditional montages (reference, bipolar) have some limitations, e.g. the detection performance depends on the choice of the reference electrode and an extraction of spatial information is often demanding. In this paper we explain the detailed setup of how to adapt a modern seizure detection system to use current density signals. Furthermore, we show results concerning the detection performance of different montage schemes and their combination.
28. **Graef A, Flamm C, Pirker S, Deistler M, Baumgartner C. A physiologically motivated ECoG segmentation method for epileptic seizure onset zone detection. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:3500-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23366681>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6346720>  
**Abstract** In this paper we propose a novel segmentation method based on the relative frequency contributions of ictal multichannel ECoG data. Segments with predominant [[see text]]-activity are classified as epileptic. The seizure onset zone is determined by the temporal delay of the epileptic [[see text]]-activity (4-9Hz) on the different channels. We apply this methodology to three seizures of one patient suffering from focal epilepsy. The resulting segments reflect the visual characteristics of the ictal ECoG well. The seizure onset zone identified by the proposed method is in very good accordance with the clinical findings.

29. **Park YS, Netoff TI, Yang X, Parhi KK. Seizure detection on/off system using rats' ECoG. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:4688-91.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23366974>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6347013>  
**Abstract** We present an enhanced algorithm for seizure onset and offset detection in rats' ECoG. Because a seizure in rats' ECoG evolves much more stereotypically than that in human, analyzing seizure evolution in rats' ECoG is advantageous to understanding the evolution process. The proposed algorithm outperforms a prior automatic seizure detection and termination system in in-vivo rats' ECoG. We improve the algorithm by using relevant frequency bands of 14-22 Hz to onsets and 7-45 Hz to offsets; by using spectral power rather than spectral amplitudes for its feature; and by replacing the 2-point moving-average filter for postprocessing with a 2(nd) order Kalman filter. Not only does the proposed algorithm provide better detection statistics, but it lowers the system's complexity by no longer requiring computation of a fast Fourier transform and by using a single structure with the two different spectral power features for onset and offset detection.
30. **Ahmed R, Temko A, Marnane W, Boylan G, Lighbody G. Dynamic time warping based neonatal seizure detection system. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:4919-22.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23367031>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6347097>  
**Abstract** Neonatal seizures patterns evolve with changing frequency, morphology and propagation. This study is an initial attempt to incorporate the characteristics of temporal evolution of neonatal seizures into our developed neonatal seizure detector. The previously designed SVM-based neonatal seizure detector is modified by substituting the Gaussian kernel with the Gaussian dynamic time warping kernel, to enable the SVM to classify variable length sequences of feature vectors of neonatal seizures. The preliminary results obtained compare favorably with the conventional SVM. The fusion of the two approaches is expected to improve the current state of the art neonatal seizure detection system.
31. **Chang NF, Chen TC, Chiang CY, Chen LG. Channel selection for epilepsy seizure prediction method based on machine learning. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:5162-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23367091>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6347156>  
**Abstract** The studies on seizure prediction problem have shown great improvement these years. Machine learning based seizure prediction method shows great performance by doing pattern recognition on high-dimensional bivariate synchronization features. However, the computation loading of the machine learning based method may be too high to meet wearable or implantable devices with the power and area constraints. In this work, channel selection is proposed to reduce the channel number from 22 to less than 6 channels and therefore more than 93.73% of the computation loading is saved through the method. The best result shows successful rate of 60.6% in 3-channel cases of ECoG database and successful rate of 70% in 3-channel cases of EEG database.

32. **Qi Y, Wang Y, Zheng X, Zhang J, Zhu J, Guo J. Efficient epileptic seizure detection by a combined IMF-VoE feature. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:5170-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23367093>  
**Abstract** Automatic seizure detection from the electroencephalogram (EEG) plays an important role in an on-demand closed-loop therapeutic system. A new feature, called IMF-VoE, is proposed to predict the occurrence of seizures. The IMF-VoE feature combines three intrinsic mode functions (IMFs) from the empirical mode decomposition of a EEG signal and the variance of the range between the upper and lower envelopes (VoE) of the signal. These multiple cues encode the intrinsic characteristics of seizure states, thus are able to distinguish them from the background. The feature is tested on 80.4 hours of EEG data with 10 seizures of 4 patients. The sensitivity of 100% is obtained with a low false detection rate of 0.16 per hour. Average time delays are 19.4s, 13.2s, and 10.7s at the false detection rates of 0.16 per hour, 0.27 per hour, and 0.41 per hour respectively, when different thresholds are used. The result is competitive among recent studies. In addition, since the IMF-VoE is compact, the detection system is of high computational efficiency and able to run in real time.
33. **Bandarabadi M, Teixeira CA, Direito B, Dourado A. Epileptic seizure prediction based on a bivariate spectral power methodology. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:5943-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23367282>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6347347>  
**Abstract** The spectral power of 5 frequently considered frequency bands (Alpha, Beta, Gamma, Theta and Delta) for 6 EEG channels is computed and then all the possible pairwise combinations among the 30 features set, are used to create a 435 dimensional feature space. Two new feature selection methods are introduced to choose the best candidate features among those and to reduce the dimensionality of this feature space. The selected features are then fed to Support Vector Machines (SVMs) that classify the cerebral state in preictal and non-preictal classes. The outputs of the SVM are regularized using a method that accounts for the classification dynamics of the preictal class, also known as "Firing Power" method. The results obtained using our feature selection approaches are compared with the ones obtained using minimum Redundancy Maximum Relevance (mRMR) feature selection method. The results in a group of 12 patients of the EPILEPSIAE database, containing 46 seizures and 787 hours multichannel recording for out-of-sample data, indicate the efficiency of the bivariate approach as well as the two new feature selection methods. The best results presented sensitivity of 76.09% (35 of 46 seizures predicted) and a false prediction rate of 0.15(-1).
34. **Klatt J, Feldwisch-Drentrup H, Ihle M, Navarro V, Neufang M, Teixeira C, et al. The EPILEPSIAE database: an extensive electroencephalography database of epilepsy patients. *Epilepsia.* 2012;53(9):1669-76.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22738131>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2012.03564.x/asset/j.1528-1167.2012.03564.x.pdf?v=1&t=heki9rz6&s=57dfc3b59bdb53d927c0879685a56591f912a4e9>  
**Abstract** From the very beginning the seizure prediction community faced problems concerning evaluation, standardization, and reproducibility of its studies. One of the main reasons for these shortcomings was the lack of access to high-quality long-term electroencephalography (EEG) data. In this article we present the EPILEPSIAE database, which was made publicly available in 2012. We illustrate its content and scope. The EPILEPSIAE database provides long-term EEG recordings of 275 patients as well as extensive metadata and standardized annotation of the data sets. It will adhere to the current standards in the field of prediction and facilitate reproducibility and comparison of those studies. Beyond seizure prediction, it may also be of considerable benefit for studies focusing on seizure detection, basic neurophysiology, and other fields.

35. **Poh MZ, Loddenkemper T, Reinsberger C, Swenson NC, Goyal S, Sabtala MC, et al. Convulsive seizure detection using a wrist-worn electrodermal activity and accelerometry biosensor. *Epilepsia*. 2012;53(5):e93-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22432935>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2012.03444.x/asset/j.1528-1167.2012.03444.x.pdf?v=1&t=hfzr4zej&s=4d8933262f301caa62b8df93fdc5094547b6ddeb>  
**Abstract** The special requirements for a seizure detector suitable for everyday use in terms of cost, comfort, and social acceptance call for alternatives to electroencephalography (EEG)-based methods. Therefore, we developed an algorithm for automatic detection of generalized tonic-clonic (GTC) seizures based on sympathetically mediated electrodermal activity (EDA) and accelerometry measured using a novel wrist-worn biosensor. The problem of GTC seizure detection was posed as a supervised learning task in which the goal was to classify 10-s epochs as a seizure or nonseizure event based on 19 extracted features from EDA and accelerometry recordings using a Support Vector Machine. Performance was evaluated using a double cross-validation method. The new seizure detection algorithm was tested on >4,213 h of recordings from 80 patients and detected 15 (94%) of 16 of the GTC seizures from seven patients with 130 false alarms (0.74 per 24 h). This algorithm can potentially provide a convulsive seizure alarm system for caregivers and objective quantification of seizure frequency.
36. **Williamson JR, Bliss DW, Browne DW, Narayanan JT. Seizure prediction using EEG spatiotemporal correlation structure. *Epilepsy Behav*. 2012;25(2):230-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23041171>  
**Abstract** A seizure prediction algorithm is proposed that combines novel multivariate EEG features with patient-specific machine learning. The algorithm computes the eigenspectra of space-delay correlation and covariance matrices from 15-s blocks of EEG data at multiple delay scales. The principal components of these features are used to classify the patient's preictal or interictal state. This is done using a support vector machine (SVM), whose outputs are averaged using a running 15-minute window to obtain a final prediction score. The algorithm was tested on 19 of 21 patients in the Freiburg EEG data set who had three or more seizures, predicting 71 of 83 seizures, with 15 false predictions and 13.8 h in seizure warning during 448.3 h of interictal data. The proposed algorithm scales with the number of available EEG signals by discovering the variations in correlation structure among any given set of signals that correlate with seizure risk.
37. **Yuan Q, Zhou W, Liu Y, Wang J. Epileptic seizure detection with linear and nonlinear features. *Epilepsy Behav*. 2012;24(4):415-21.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22687388>  
**Abstract** Automatic seizure detection is significant in both diagnosis of epilepsy and relieving the heavy workload of inspecting prolonged EEG. This paper presents a new seizure detection method for multi-channel long-term EEG. The fractal intercept derived from fractal geometry is extracted as a novel nonlinear feature of EEG signals, and the relative fluctuation index is calculated as a linear feature. The feature vector, consisting of the two EEG descriptors, is fed into a single-layer neural network for classification. Extreme learning machine (ELM) algorithm is adopted to train the neural network. Finally, post-processing including smoothing, channel fusion, and collar technique is employed to obtain more accurate and stable results. Both the segment-based and event-based assessments are used for the performance evaluation of this method on the 21-patient Freiburg dataset. The segment-based sensitivity of 91.72% and specificity of 94.89% were achieved. For the event-based assessment, this method yielded a sensitivity of 93.85% with a false detection rate of 0.35/h.

38. **Javidan M. Electroencephalography in mesial temporal lobe epilepsy: a review. *Epilepsy Res Treat.* 2012;2012:637430.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22957235>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3420622/pdf/ERT2012-637430.pdf>  
**Abstract** Electroencephalography (EEG) has an important role in the diagnosis and classification of epilepsy. It can provide information for predicting the response to antiseizure drugs and to identify the surgically remediable epilepsies. In temporal lobe epilepsy (TLE) seizures could originate in the medial or lateral neocortical temporal region, and many of these patients are refractory to medical treatment. However, majority of patients have had excellent results after surgery and this often relies on the EEG and magnetic resonance imaging (MRI) data in presurgical evaluation. If the scalp EEG data is insufficient or discordant, invasive EEG recording with placement of intracranial electrodes could identify the seizure focus prior to surgery. This paper highlights the general information regarding the use of EEG in epilepsy, EEG patterns resembling epileptiform discharges, and the interictal, ictal and postictal findings in mesial temporal lobe epilepsy using scalp and intracranial recordings prior to surgery. The utility of the automated seizure detection and computerized mathematical models for increasing yield of non-invasive localization is discussed. This paper also describes the sensitivity, specificity, and predictive value of EEG for seizure recurrence after withdrawal of medications following seizure freedom with medical and surgical therapy.
39. **Tang Y, Durand D. A tunable support vector machine assembly classifier for epileptic seizure detection. *Expert Syst Appl.* 2012;39(4):3925-3938.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22563146>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3341176/pdf/nihms334855.pdf>  
**Abstract** Automating the detection of epileptic seizures could reduce the significant human resources necessary for the care of patients suffering from intractable epilepsy and offer improved solutions for closed-loop therapeutic devices such as implantable electrical stimulation systems. While numerous detection algorithms have been published, an effective detector in the clinical setting remains elusive. There are significant challenges facing seizure detection algorithms. The epilepsy EEG morphology can vary widely among the patient population. EEG recordings from the same patient can change over time. EEG recordings can be contaminated with artifacts that often resemble epileptic seizure activity. In order for an epileptic seizure detector to be successful, it must be able to adapt to these different challenges. In this study, a novel detector is proposed based on a support vector machine assembly classifier (SVMA). The SVMA consists of a group of SVMs each trained with a different set of weights between the seizure and non-seizure data and the user can selectively control the output of the SVMA classifier. The algorithm can improve the detection performance compared to traditional methods by providing an effective tuning strategy for specific patients. The proposed algorithm also demonstrates a clear advantage over threshold tuning. When compared with the detection performances reported by other studies using the publicly available epilepsy dataset hosted by the University of BONN, the proposed SVMA detector achieved the best total accuracy of 98.72%. These results demonstrate the efficacy of the proposed SVMA detector and its potential in the clinical setting.

40. **Temko A, Lightbody G, Thomas EM, Boylan GB, Marnane W. Instantaneous measure of EEG channel importance for improved patient-adaptive neonatal seizure detection. *IEEE Trans Biomed Eng.* 2012;59(3):717-27.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22156948>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3428726/pdf/ukmss-49512.pdf>  
**Abstract** A measure of bipolar channel importance is proposed for EEG-based detection of neonatal seizures. The channel weights are computed based on the integrated synchrony of classifier probabilistic outputs for the channels which share a common electrode. These estimated time-varying weights are introduced within a Bayesian probabilistic framework to provide a channel specific and, thus, adaptive seizure classification scheme. Validation results on a clinical dataset of neonatal seizures confirm the utility of the proposed channel weighting for the two patient-independent seizure detectors recently developed by this research group: one based on support vector machines (SVMs) and the other on Gaussian mixture models (GMMs). By exploiting the channel weighting, the receiver operating characteristic (ROC) area can be significantly increased for the most difficult patients, with the average ROC area across 17 patients increased by 22% (relative) for the SVM and by 15% (relative) for the GMM-based detector, respectively. It is shown that the system developed here outperforms the recent published studies in this area.
41. **Rana P, Lipor J, Lee H, van Drongelen W, Kohrman MH, Van Veen B. Seizure detection using the phase-slope index and multichannel ECoG. *IEEE Trans Biomed Eng.* 2012;59(4):1125-34.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22271828>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3369624/pdf/nihms-374037.pdf>  
**Abstract** Detection and analysis of epileptic seizures is of clinical and research interest. We propose a novel seizure detection and analysis scheme based on the phase-slope index (PSI) of directed influence applied to multichannel electrocorticogram data. The PSI metric identifies increases in the spatio-temporal interactions between channels that clearly distinguish seizure from interictal activity. We form a global metric of interaction between channels and compare this metric to a threshold to detect the presence of seizures. The threshold is chosen based on a moving average of recent activity to accommodate differences between patients and slow changes within each patient over time. We evaluate detection performance over a challenging population of five patients with different types of epilepsy using a total of 47 seizures in nearly 258 h of recorded data. Using a common threshold procedure, we show that our approach detects all of the seizures in four of the five patients with a false detection rate less than two per hour. A variation on the global metric is proposed to identify which channels are strong drivers of activity in each patient. These metrics are computationally efficient and suitable for real-time application.

42. **Yadav R, Swamy MN, Agarwal R. Model-based seizure detection for intracranial EEG recordings. *IEEE Trans Biomed Eng.* 2012;59(5):1419-28.**

<http://www.ncbi.nlm.nih.gov/pubmed/22361656>

<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6156421>

**Abstract** This paper presents a novel model-based patient-specific method for automatic detection of seizures in the intracranial EEG recordings. The proposed method overcomes the complexities in the practical implementation of the patient-specific approach of seizure detection. The method builds a seizure model (set of basis functions) for a priori known seizure (the template seizure pattern), and uses the statistically optimal null filters as a building block for the detection of similar seizures. The process of modeling the template seizure is fully automatic. Overall, the detection method involves the segmentation of the template seizure pattern, rejection of the redundant and noisy segments, extraction of features from the segments to generate a set of models, selection of the best seizure model, and training of the classifier. The trained classifier is used to detect similar seizures in the remaining data. The resulting seizure detection method was evaluated on a total of 304 h of single-channel depth EEG recordings from 14 patients. The system performance is further compared to the Qu-Gotman patient-specific system using the same data. A significant improvement in the proposed system, in terms of specificity, is observed over the compared method.

43. **Ntonfo GM, Ferrari G, Raheli R, Pisani F. Low-complexity image processing for real-time detection of neonatal clonic seizures. *IEEE Trans Inf Technol Biomed.* 2012;16(3):375-82.**

<http://www.ncbi.nlm.nih.gov/pubmed/22318500>

<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6145680>

**Abstract** In this paper, we consider a novel low-complexity real-time image-processing-based approach to the detection of neonatal clonic seizures. Our approach is based on the extraction, from a video of a newborn, of an average luminance signal representative of the body movements. Since clonic seizures are characterized by periodic movements of parts of the body (e.g., the limbs), by evaluating the periodicity of the extracted average luminance signal it is possible to detect the presence of a clonic seizure. The periodicity is investigated, through a hybrid autocorrelation-Yin estimation technique, on a per-window basis, where a time window is defined as a sequence of consecutive video frames. While processing is first carried out on a single window basis, we extend our approach to interlaced windows. The performance of the proposed detection algorithm is investigated, in terms of sensitivity and specificity, through receiver operating characteristic curves, considering video recordings of newborns affected by neonatal seizures.

44. **Liu Y, Zhou W, Yuan Q, Chen S. Automatic seizure detection using wavelet transform and SVM in long-term intracranial EEG. *IEEE Trans Neural Syst Rehabil Eng.* 2012;20(6):749-55.**

<http://www.ncbi.nlm.nih.gov/pubmed/22868635>

<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6255792>

**Abstract** Automatic seizure detection is of great significance for epilepsy long-term monitoring, diagnosis, and rehabilitation, and it is the key to closed-loop brain stimulation. This paper presents a novel wavelet-based automatic seizure detection method with high sensitivity. The proposed method first conducts wavelet decomposition of multi-channel intracranial EEG (iEEG) with five scales, and selects three frequency bands of them for subsequent processing. Effective features are extracted, such as relative energy, relative amplitude, coefficient of variation and fluctuation index at the selected scales, and then these features are sent into the support vector machine for training and classification. Afterwards a postprocessing is applied on the raw classification results to obtain more accurate and stable results. Postprocessing includes smoothing, multi-channel decision fusion and collar technique. Its performance is evaluated on a large dataset of 509 h from 21 epileptic patients. Experiments show that the proposed method could achieve a sensitivity of 94.46% and a specificity of 95.26% with a false detection rate of 0.58/h for seizure detection in long-term iEEG.

45. **Martis RJ, Acharya UR, Tan JH, Petznick A, Yanti R, Chua CK, et al. Application of empirical mode decomposition (emd) for automated detection of epilepsy using EEG signals. *Int J Neural Syst.* 2012;22(6):1250027.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23186276>  
**Abstract** Epilepsy is a global disease with considerable incidence due to recurrent unprovoked seizures. These seizures can be noninvasively diagnosed using electroencephalogram (EEG), a measure of neuronal electrical activity in brain recorded along scalp. EEG is highly nonlinear, nonstationary and non-Gaussian in nature. Nonlinear adaptive models such as empirical mode decomposition (EMD) provide intuitive understanding of information present in these signals. In this study a novel methodology is proposed to automatically classify EEG of normal, inter-ictal and ictal subjects using EMD decomposition. EEG decomposition using EMD yields few intrinsic mode functions (IMF), which are amplitude and frequency modulated (AM and FM) waves. Hilbert transform of these IMF provides AM and FM frequencies. Features such as spectral peaks, spectral entropy and spectral energy in each IMF are extracted and fed to decision tree classifier for automated diagnosis. In this work, we have compared the performance of classification using two types of decision trees (i) classification and regression tree (CART) and (ii) C4.5. We have obtained the highest average accuracy of 95.33%, average sensitivity of 98%, and average specificity of 97% using C4.5 decision tree classifier. The developed methodology is ready for clinical validation on large databases and can be deployed for mass screening.
46. **Fulton S, Van Poppel K, McGregor A, Ellis M, Patters A, Wheless J. Prospective Study of 2 Bed Alarms for Detection of Nocturnal Seizures. *J Child Neurol.* 2012.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23076428>  
<http://jcn.sagepub.com/content/early/2012/10/17/0883073812462064>  
**Abstract** For parents of children with epilepsy, seizures occurring in sleep are a major concern. Risk factors for sudden unexplained death in epilepsy patients include being in bed and generalized tonic-clonic seizures. A device for detecting nocturnal seizure activity would be valuable. Children with various seizure types undergoing evaluation had standard video electroencephalography (EEG), cardiopulmonary and nursing monitoring, and 1 of 2 models (ST-2 and MP5) of a Medpage bed alarm. The video EEG record was reviewed to detect any seizures missed by the bed alarms or caregivers. The ability of the bed alarms to detect motor seizures in general and specific seizure types was tested. In 15 patients, 69 seizures were recorded by video EEG. The ST-2 did not detect any nocturnal seizures. The MP5 alarm detected 1 of 15 in sleeping patients: a generalized tonic-clonic seizure. The Medpage seizure alarms do not appear to adequately detect nocturnal seizures.
47. **Zandi AS, Dumont GA, Javidan M, Tafreshi R. Detection of epileptic seizures in scalp electroencephalogram: an automated real-time wavelet-based approach. *J Clin Neurophysiol.* 2012;29(1):1-16.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22353980>  
**Abstract** This study evaluates a new automated patient-specific method for epileptic seizure detection using scalp electroencephalogram (EEG). The method relies on a normalized wavelet-based index, named the combined seizure index (CSI), and requires a seizure example and a nonseizure EEG interval as reference. The CSI is derived for every epoch in each EEG channel and is sensitive to both the rhythmicity and relative energy of that epoch and the consistency of EEG patterns among different channels. Increasing significantly as seizures occur, the CSI is monitored using a one-sided cumulative sum test to generate appropriate alarms in each channel. A seizure alarm is finally generated according to channel-based information. The proposed method was evaluated using the scalp EEG test data of approximately 236 hours from 26 patients with a total of 79 focal seizures, achieving a high sensitivity of approximately 91% with a false detection rate of 0.33 per hour and a median detection latency of 7 seconds. In addition, statistical analysis revealed that the average CSI around the onset on the side of the focus in patients with temporal lobe epilepsy (TLE) is significantly greater than that of the opposite side ( $P < 0.001$ ), indicating the capability of this index in lateralizing the seizure focus in this type of epilepsy.

48. **Orhan U, Hekim M, Ozer M. Epileptic seizure detection using probability distribution based on equal frequency discretization. *J Med Syst.* 2012;36(4):2219-24.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21445675>  
<http://rd.springer.com/article/10.1007%2Fs10916-011-9689-y>  
**Abstract** In this study, we offered a new feature extraction approach called probability distribution based on equal frequency discretization (EFD) to be used in the detection of epileptic seizure from electroencephalogram (EEG) signals. Here, after EEG signals were discretized by using EFD method, the probability densities of the signals were computed according to the number of data points in each interval. Two different probability density functions were defined by means of the polynomial curve fitting for the subjects without epileptic seizure and the subjects with epileptic seizure, and then when using the mean square error criterion for these two functions, the success of epileptic seizure detection was 96.72%. In addition, when the probability densities of EEG segments were used as the inputs of a multilayer perceptron neural network (MLPNN) model, the success of epileptic seizure detection was 99.23%. This results show that non-linear classifiers can easily detect the epileptic seizures from EEG signals by means of probability distribution based on EFD.
49. **Song Y, Crowcroft J, Zhang J. Automatic epileptic seizure detection in EEGs based on optimized sample entropy and extreme learning machine. *J Neurosci Methods.* 2012;210(2):132-46.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22824535>  
**Abstract** Epilepsy is one of the most common neurological disorders - approximately one in every 100 people worldwide are suffering from it. The electroencephalogram (EEG) is the most common source of information used to monitor, diagnose and manage neurological disorders related to epilepsy. Large amounts of data are produced by EEG monitoring devices, and analysis by visual inspection of long recordings of EEG in order to find traces of epilepsy is not routinely possible. Therefore, automated detection of epilepsy has been a goal of many researchers for a long time. This paper presents a novel method for automatic epileptic seizure detection. An optimized sample entropy (O-SampEn) algorithm is proposed and combined with extreme learning machine (ELM) to identify the EEG signals regarding the existence of seizure or not. To the knowledge of the authors, there exists no similar work in the literature. A public dataset was utilized for evaluating the proposed method. Results show that the proposed epilepsy detection approach achieves not only high detection accuracy but also a very fast computation speed, which demonstrates its huge potential for the real-time detection of epileptic seizures.
50. **Salami P, Levesque M, Gotman J, Avoli M. A comparison between automated detection methods of high-frequency oscillations (80-500 Hz) during seizures. *J Neurosci Methods.* 2012;211(2):265-71.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22983173>  
**Abstract** High-frequency oscillations (HFOs, ripples: 80-200 Hz, fast ripples: 250-500 Hz) recorded from the epileptic brain are thought to reflect abnormal network-driven activity. They are also better markers of seizure onset zones compared to interictal spikes. There is thus an increasing number of studies analysing HFOs in vitro, in vivo and in the EEG of human patients with refractory epilepsy. However, most of these studies have focused on HFOs during interictal events or at seizure onset, and few have analysed HFOs during seizures. In this study, we are comparing three different automated methods of HFO detection to two methods of visual analysis, during the pre-ictal, ictal and post-ictal periods on multiple channels using the rat pilocarpine model of temporal lobe epilepsy. The first method (method 1) detected HFOs using the average of the normalised period, the second (method 2) detected HFOs using the average of the normalised period in 1s windows and the third (method 3) detected HFOs using the average of a reference period before seizure onset. Overall, methods 2 and 3 showed higher sensitivity compared to method 1. When dividing the analysed traces in pre-, ictal and post-ictal periods, method 3 showed the highest sensitivity during the ictal period compared to method 1, while method 2 was not significantly different from method 1. These findings suggest that method 3 could be used for automated and reliable detection of HFOs on large data sets containing multiple channels during the ictal period.

51. **Fernandez-Blanco E, Rivero D, Rabunal J, Dorado J, Pazos A, Munteanu CR. Automatic seizure detection based on star graph topological indices. *J Neurosci Methods*. 2012;209(2):410-9.**

<http://www.ncbi.nlm.nih.gov/pubmed/22814089>

**Abstract** The recognition of seizures is very important for the diagnosis of patients with epilepsy. The seizure is a process of rhythmic discharge in brain and occurs rarely and unpredictably. This behavior generates a need of an automatic detection of seizures by using the signals of long-term electroencephalographic (EEG) recordings. Due to the non-stationary character of EEG signals, the conventional methods of frequency analysis are not the best alternative to obtain good results in diagnostic purpose. The present work proposes a method of EEG signal analysis based on star graph topological indices (SGTIs) for the first time. The signal information, such as amplitude and time occurrence, is codified into invariant SGTIs which are the basis for the classification models that can discriminate the epileptic EEG records from the non-epileptic ones. The method with SGTIs and the simplest linear discriminant methods provide similar results to those previously published, which are based on the time-frequency analysis and artificial neural networks. Thus, this work proposes a simpler and faster alternative for automatic detection of seizures from the EEG recordings.

52. **Logesparan L, Casson AJ, Rodriguez-Villegas E. Optimal features for online seizure detection. *Med Biol Eng Comput*. 2012;50(7):659-69.**

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<http://rd.springer.com/article/10.1007%2Fs11517-012-0904-x>

**Abstract** This study identifies characteristic features in scalp EEG that simultaneously give the best discrimination between epileptic seizures and background EEG in minimally pre-processed scalp data; and have minimal computational complexity to be suitable for online, real-time analysis. The discriminative performance of 65 previously reported features has been evaluated in terms of sensitivity, specificity, area under the sensitivity-specificity curve (AUC), and relative computational complexity, on 47 seizures (split in 2,698 2 s sections) in over 172 h of scalp EEG from 24 adults. The best performing features are line length and relative power in the 12.5-25 Hz band. Relative power has a better seizure detection performance (AUC = 0.83; line length AUC = 0.77), but is calculated after the discrete wavelet transform and is thus more computationally complex. Hence, relative power achieves the best performance for offline detection, whilst line length would be preferable for online low complexity detection. These results, from the largest systematic study of seizure detection features, aid future researchers in selecting an optimal set of features when designing algorithms for both standard offline detection and new online low computational complexity detectors.

53. **Stevenson NJ, O'Toole JM, Rankine LJ, Boylan GB, Boashash B. A nonparametric feature for neonatal EEG seizure detection based on a representation of pseudo-periodicity. *Med Eng Phys.* 2012;34(4):437-46.**

<http://www.ncbi.nlm.nih.gov/pubmed/21925920>

**Abstract** Automated methods of neonatal EEG seizure detection attempt to highlight the evolving, stereotypical, pseudo-periodic, nature of EEG seizure while rejecting the nonstationary, modulated, coloured stochastic background in the presence of various EEG artefacts. An important aspect of neonatal seizure detection is, therefore, the accurate representation and detection of pseudo-periodicity in the neonatal EEG. This paper describes a method of detecting pseudo-periodic components associated with neonatal EEG seizure based on a novel signal representation; the nonstationary frequency marginal (NFM). The NFM can be considered as an alternative time-frequency distribution (TFD) frequency marginal. This method integrates the TFD along data-dependent, time-frequency paths that are automatically extracted from the TFD using an edge linking procedure and has the advantage of reducing the dimension of a TFD. The reduction in dimension simplifies the process of estimating a decision statistic designed for the detection of the pseudo-periodicity associated with neonatal EEG seizure. The use of the NFM resulted in a significant detection improvement compared to existing stationary and nonstationary methods. The decision statistic estimated using the NFM was then combined with a measurement of EEG amplitude and nominal pre- and post-processing stages to form a seizure detection algorithm. This algorithm was tested on a neonatal EEG database of 18 neonates, 826 h in length with 1389 seizures, and achieved comparable performance to existing second generation algorithms (a median receiver operating characteristic area of 0.902; IQR 0.835-0.943 across 18 neonates).

54. **Duun-Henriksen J, Madsen RE, Remvig LS, Thomsen CE, Sorensen HB, Kjaer TW. Automatic detection of childhood absence epilepsy seizures: toward a monitoring device. *Pediatr Neurol.* 2012;46(5):287-92.**

<http://www.ncbi.nlm.nih.gov/pubmed/22520349>

**Abstract** Automatic detections of paroxysms in patients with childhood absence epilepsy have been neglected for several years. We acquire reliable detections using only a single-channel brainwave monitor, allowing for unobtrusive monitoring of antiepileptic drug effects. Ultimately we seek to obtain optimal long-term prognoses, balancing antiepileptic effects and side effects. The electroencephalographic appearance of paroxysms in childhood absence epilepsy is fairly homogeneous, making it feasible to develop patient-independent automatic detection. We implemented a state-of-the-art algorithm to investigate the performance of paroxysm detection. Using only a single scalp electroencephalogram channel from 20 patients with a total of 125 paroxysms >2 seconds, 97.2% of paroxysms could be detected with no false detections. This result leads us to recommend further investigations of tiny, one-channel electroencephalogram systems in an ambulatory setting.

55. **Johnson AN, Sow D, Biem A. A discriminative approach to EEG seizure detection. *AMIA Annu Symp Proc.* 2011;2011:1309-17.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22195192>  
[http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243149/pdf/1309\\_amia\\_2011\\_proc.pdf](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243149/pdf/1309_amia_2011_proc.pdf)  
**Abstract** Seizures are abnormal sudden discharges in the brain with signatures represented in electroencephalograms (EEG). The efficacy of the application of speech processing techniques to discriminate between seizure and non-seizure states in EEGs is reported. The approach accounts for the challenges of unbalanced datasets (seizure and non-seizure), while also showing a system capable of real-time seizure detection. The Minimum Classification Error (MCE) algorithm, which is a discriminative learning algorithm with wide-use in speech processing, is applied and compared with conventional classification techniques that have already been applied to the discrimination between seizure and non-seizure states in the literature. The system is evaluated on 22 pediatric patients multi-channel EEG recordings. Experimental results show that the application of speech processing techniques and MCE compare favorably with conventional classification techniques in terms of classification performance, while requiring less computational overhead. The results strongly suggests the possibility of deploying the designed system at the bedside.
56. **Ray S. Question 1. Is cerebral function monitoring as accurate as conventional EEG in the detection of neonatal seizures? *Arch Dis Child.* 2011;96(3):314-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21317126>  
<http://adc.bmj.com/content/96/3/314.2.long>
57. **West CR, Harding JE, Williams CE, Nolan M, Battin MR. Cot-side electroencephalography for outcome prediction in preterm infants: observational study. *Arch Dis Child Fetal Neonatal Ed.* 2011;96(2):F108-13.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20870908>  
<http://fn.bmj.com/content/96/2/F108.long>  
**Abstract** OBJECTIVE: To assess the use of two-channel electroencephalographical (EEG) recordings for predicting adverse neurodevelopmental outcome (death or Bayley II mental developmental index/psychomotor developmental index < 70) in extremely preterm infants and to determine the relationship between quantitative continuity measures and a specialist neurophysiologist assessment of the same EEG segment for predicting outcome. DESIGN: Observational study. SETTING: The study was conducted in a neonatal intensive care unit. PATIENTS: Preterm infants born <29 weeks' gestation. INTERVENTIONS: Two-channel EEGs using the reBRM2 monitor (BrainZ Instruments, Auckland, New Zealand) within 48 h of delivery. One-hour segments were analysed, blinded to the clinical outcome, by off-line quantitative analysis of continuity and a review of the raw EEG by a neurophysiologist. MAIN OUTCOME MEASURES: Developmental assessment at a median of 15 months' corrected age. RESULTS: 76 infants had an EEG within 48 h of delivery and a developmental assessment. The analysed segment of the EEG was obtained at 24 (3-48) h of age (median (range)). The neurophysiologist's assessment was a better predictor of adverse outcome than the continuity measures (positive predictive value 95% CI 75 (54% to 96%) vs 41 (22% to 60) at 25-microV threshold, negative predictive value 88 (80% to 96%) vs 84 (74% to 94%) and positive likelihood ratio 9.0 (3.2 to 24.6) vs 2.0 (1.2 to 3.6)). All the infants with definite seizures identified by the neurophysiologist had poor outcomes. CONCLUSIONS: Modified cot-side EEG has potential to assist with identification of extremely preterm infants at risk for adverse neurodevelopmental outcomes. However, analysis by a neurophysiologist performed better than the currently available continuity analyses.

58. **Buteneers P, Verstraeten D, van Mierlo P, Wyckhuys T, Stroobandt D, Raedt R, et al. Automatic detection of epileptic seizures on the intra-cranial electroencephalogram of rats using reservoir computing. *Artif Intell Med.* 2011;53(3):215-23.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21955575>  
**Abstract** INTRODUCTION: In this paper we propose a technique based on reservoir computing (RC) to mark epileptic seizures on the intra-cranial electroencephalogram (EEG) of rats. RC is a recurrent neural networks training technique which has been shown to possess good generalization properties with limited training. MATERIALS: The system is evaluated on data containing two different seizure types: absence seizures from genetic absence epilepsy rats from Strasbourg (GAERS) and tonic-clonic seizures from kainate-induced temporal-lobe epilepsy rats. The dataset consists of 452hours from 23 GAERS and 982hours from 15 kainate-induced temporal-lobe epilepsy rats. METHODS: During the preprocessing stage, several features are extracted from the EEG. A feature selection algorithm selects the best features, which are then presented as input to the RC-based classification algorithm. To classify the output of this algorithm a two-threshold technique is used. This technique is compared with other state-of-the-art techniques. RESULTS: A balanced error rate (BER) of 3.7% and 3.5% was achieved on the data from GAERS and kainate rats, respectively. This resulted in a sensitivity of 96% and 94% and a specificity of 96% and 99% respectively. The state-of-the-art technique for GAERS achieved a BER of 4%, whereas the best technique to detect tonic-clonic seizures achieved a BER of 16%. CONCLUSION: Our method outperforms up-to-date techniques and only a few parameters need to be optimized on a limited training set. It is therefore suited as an automatic aid for epilepsy researchers and is able to eliminate the tedious manual review and annotation of EEG.
59. **Chiu AW, Derchansky M, Cotic M, Carlen PL, Turner SO, Bardakjian BL. Wavelet-based Gaussian-mixture hidden Markov model for the detection of multistage seizure dynamics: a proof-of-concept study. *Biomed Eng Online.* 2011;10:29.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21504608>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3094216/pdf/1475-925X-10-29.pdf>  
**Abstract** BACKGROUND: Epilepsy is a common neurological disorder characterized by recurrent electrophysiological activities, known as seizures. Without the appropriate detection strategies, these seizure episodes can dramatically affect the quality of life for those afflicted. The rationale of this study is to develop an unsupervised algorithm for the detection of seizure states so that it may be implemented along with potential intervention strategies. METHODS: Hidden Markov model (HMM) was developed to interpret the state transitions of the in vitro rat hippocampal slice local field potentials (LFPs) during seizure episodes. It can be used to estimate the probability of state transitions and the corresponding characteristics of each state. Wavelet features were clustered and used to differentiate the electrophysiological characteristics at each corresponding HMM states. Using unsupervised training method, the HMM and the clustering parameters were obtained simultaneously. The HMM states were then assigned to the electrophysiological data using expert guided technique. Minimum redundancy maximum relevance (mRMR) analysis and Akaike Information Criterion (AICc) were applied to reduce the effect of over-fitting. The sensitivity, specificity and optimality index of chronic seizure detection were compared for various HMM topologies. The ability of distinguishing early and late tonic firing patterns prior to chronic seizures were also evaluated. RESULTS: Significant improvement in state detection performance was achieved when additional wavelet coefficient rates of change information were used as features. The final HMM topology obtained using mRMR and AICc was able to detect non-ictal (interictal), early and late tonic firing, chronic seizures and postictal activities. A mean sensitivity of 95.7%, mean specificity of 98.9% and optimality index of 0.995 in the detection of chronic seizures was achieved. The detection of early and late tonic firing was validated with experimental intracellular electrical recordings of seizures. CONCLUSIONS: The HMM implementation of a seizure dynamics detector is an improvement over existing approaches using visual detection and complexity measures. The subjectivity involved in partitioning the observed data prior to training can be eliminated. It can also decipher the probabilities of seizure state transitions using the magnitude and rate of change wavelet information of the LFPs.

60. **Temko A, Thomas E, Marnane W, Lightbody G, Boylan G. EEG-based neonatal seizure detection with Support Vector Machines. *Clin Neurophysiol.* 2011;122(3):464-73.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20713314>  
**Abstract** OBJECTIVE: The study presents a multi-channel patient-independent neonatal seizure detection system based on the Support Vector Machine (SVM) classifier. METHODS: A machine learning algorithm (SVM) is used as a classifier to discriminate between seizure and non-seizure EEG epochs. Two post-processing steps are proposed to increase both the temporal precision and the robustness of the system. The resulting system is validated on a large clinical dataset of 267 h of EEG data from 17 full-term newborns with seizures. RESULTS: The performance of the system using event-based metrics is reported. The system showed the best up-to-date performance of a neonatal seizure detection system. The system was able to achieve an average good detection rate of ~89% with one false seizure detection per hour, ~96% with two false detections per hour, or ~100% with four false detections per hour. An analysis of errors revealed sources of misclassification in terms of both missed seizures and false detections. CONCLUSIONS: The results obtained with the proposed SVM-based seizure detection system allow for its practical application in neonatal intensive care units. SIGNIFICANCE: The proposed SVM-based seizure detection system can greatly assist clinical staff, in a neonatal intensive care unit, to interpret the EEG. The system allows control of the final decision by choosing different confidence levels which makes it flexible for clinical needs. The obtained results may provide a reference for future seizure detection systems.
61. **Wang L, Wang C, Fu F, Yu X, Guo H, Xu C, et al. Temporal lobe seizure prediction based on a complex Gaussian wavelet. *Clin Neurophysiol.* 2011;122(4):656-63.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20980197>  
**Abstract** OBJECTIVE: Abnormal synchronisation change is closely associated with the process of seizure generation. The immediate and accurate detection of the changes in synchronisation may offer advantages in seizure prediction. Thus, we develop a phase synchronisation detection method for this purpose. METHODS: An analysis of phase synchronisation based on the complex Gaussian wavelet transform (PSW) was conducted to detect synchronised phases of long-lasting scalp electroencephalograph (EEG) recordings from eight epilepsy patients with intractable temporal lobe epilepsy. Four assessment indicators, namely sensitivity, maximum false prediction rate, seizure occurrence period and seizure prediction horizon were used to assess and compare PSW with the analysis of phase synchronisation, based on the Hilbert transform (PSH) and a random predictor Poisson process. RESULTS: An obvious decrease was found upon phase synchronisation prior to visual detection of electroencephalograph seizure onset, which was consistent with the EEG mechanism in the ictal events. The results suggest that PSW is the most effective among the three prediction methods. CONCLUSIONS: The results confirm that the analysis of phase synchronisation based on the complex Gaussian wavelet transform can be used for seizure prediction. SIGNIFICANCE: Phase synchronisation analysis may be a useful algorithm for clinical application in epileptic prediction.

62. **Chua EC, Patel K, Fitzsimons M, Bleakley CJ. Improved patient specific seizure detection during pre-surgical evaluation. *Clin Neurophysiol.* 2011;122(4):672-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21130030>  
**Abstract** OBJECTIVE: There is considerable interest in improved off-line automated seizure detection methods that will decrease the workload of EEG monitoring units. Subject-specific approaches have been demonstrated to perform better than subject-independent ones. However, for pre-surgical diagnostics, the traditional method of obtaining a priori data to train subject-specific classifiers is not practical. We present an alternative method that works by adapting the threshold of a subject-independent to a specific subject based on feedback from the user. METHODS: A subject-independent quadratic discriminant classifier incorporating modified features based partially on the Gotman algorithm was first built. It was then used to derive subject-specific classifiers by determining subject-specific posterior probability thresholds via user interaction. The two schemes were tested on 529 h of intracranial EEG containing 63 seizures from 15 subjects undergoing pre-surgical evaluation. To provide comparison, the standard Gotman algorithm was implemented and optimised for this dataset by tuning the detection thresholds. RESULTS: Compared to the tuned Gotman algorithm, the subject-independent scheme reduced the false positive rate by 51% (0.23 to 0.11 h<sup>-1</sup>) while increasing sensitivity from 53% to 62%. The subject-specific scheme further improved sensitivity to 78%, but with a small increase in false positive rate to 0.18 h<sup>-1</sup>. CONCLUSIONS: The results suggest that a subject-independent classifier scheme with modified features is useful for reducing false positive rate, while subject adaptation further enhances performance by improving sensitivity. The results also suggest that the proposed subject-adapted classifier scheme approximates the performance of the subject-specific Gotman algorithm. SIGNIFICANCE: The proposed method could potentially increase the productivity of offline EEG analysis. The approach could also be generalised to enhance the performance of other subject independent algorithms.
63. **Alegre M, Urrestarazu E. Neonatal automated seizure detection: going ahead into clinical use. *Clin Neurophysiol.* 2011;122(8):1480-1.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21349762>

64. **Cherian PJ, Deburchgraeve W, Swarte RM, De Vos M, Govaert P, Van Huffel S, et al. Validation of a new automated neonatal seizure detection system: a clinician's perspective. *Clin Neurophysiol.* 2011;122(8):1490-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21396883>  
**Abstract** OBJECTIVE: To validate an improved automated electroencephalography (EEG)-based neonatal seizure detection algorithm (NeoGuard) in an independent data set. METHODS: EEG background was classified into eight grades based on the evolution of discontinuity and presence of sleep-wake cycles. Patients were further sub-classified into two groups; gpl: mild to moderate (grades 1-5) and gpII: severe (grades 6-8) EEG background abnormalities. Seizures were categorised as definite and dubious. Seizure characteristics were compared between gpl and gpII. The algorithm was tested on 756 h of EEG data from 24 consecutive neonates (median 25 h per patient) with encephalopathy and recorded seizures during continuous monitoring (cEEG). No selection was made regarding the quality of EEG or presence of artefacts. RESULTS: Seizure amplitudes significantly decreased with worsening EEG background. Seizures were detected with a total sensitivity of 61.9% (1285/2077). The detected seizure burden was 66,244/97,574 s (67.9%). Sensitivity per patient was 65.9%, with a mean positive predictive value (PPV) of 73.7%. After excluding four patients with severely abnormal EEG background, and predominantly having dubious seizures, the algorithm showed a median sensitivity per patient of 86.9%, PPV of 89.5% and false positive rate of 0.28 h(-1). Sensitivity tended to be better for patients in gpl. CONCLUSIONS: The algorithm detects neonatal seizures well, has a good PPV and is suited for cEEG monitoring. Changes in electrographic characteristics such as amplitude, duration and rhythmicity in relation to deteriorating EEG background tend to worsen the performance of automated seizure detection. SIGNIFICANCE: cEEG monitoring is important for detecting seizures in the neonatal intensive care unit (NICU). Our automated algorithm reliably detects neonatal seizures that are likely to be clinically most relevant, as reflected by the associated EEG background abnormality.
65. **De Vos M, Deburchgraeve W, Cherian PJ, Matic V, Swarte RM, Govaert P, et al. Automated artifact removal as preprocessing refines neonatal seizure detection. *Clin Neurophysiol.* 2011;122(12):2345-54.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21705269>  
**Abstract** OBJECTIVE: The description and evaluation of algorithms using Independent Component Analysis (ICA) for automatic removal of ECG, pulsation and respiration artifacts in neonatal EEG before automated seizure detection. METHODS: The developed algorithms decompose the EEG using ICA into its underlying sources. The artifact source was identified using the simultaneously recorded polygraphy signals after preprocessing. The EEG was reconstructed without the corrupting source, leading to a clean EEG. The impact of the artifact removal was measured by comparing the performance of a previously developed seizure detector before and after the artifact removal in 13 selected patients (9 having artifact-contaminated and 4 having artifact-free EEGs). RESULTS: A significant decrease in false alarms ( $p=0.01$ ) was found while the Good Detection Rate (GDR) for seizures was not altered ( $p=0.50$ ). CONCLUSIONS: The techniques reduced the number of false positive detections without lowering sensitivity and are beneficial in long term EEG seizure monitoring in the presence of disturbing biological artifacts. SIGNIFICANCE: The proposed algorithms improve neonatal seizure monitoring.

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<http://www.ncbi.nlm.nih.gov/pubmed/22254589>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090356>  
**Abstract** Signal normalization is an essential part of patient independent algorithms, for example to correct for variations in signal amplitude from different parts of the body, prior to applying a fixed threshold for event detection. Multiple methods for providing the required normalization are available. This paper presents a systematic investigation into the effects of five different methods using epileptic seizure detection from the EEG as an illustration case. It is found that, whilst normalization is essential, four of the considered methods actually decrease the ability to detect seizures, counteracting the algorithm aim. For optimal detection performance the effects of the signal normalization illustrated here should be incorporated into future algorithm designs.
67. Temko A, Lightbody G, Boylan G, Marnane W. Online EEG channel weighting for detection of seizures in the neonate. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:1447-50.  
<http://www.ncbi.nlm.nih.gov/pubmed/22254591>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090358>  
**Abstract** A framework for online dynamic channel weighting is developed for the task of EEG-based neonatal seizure detection. The channel weights are computed on-the-fly by combining the up-to-now patient-specific history and the clinically-derived prior channel importance. These estimated time-varying weights are introduced within a Bayesian probabilistic framework to provide a channel-specific and thus patient-adaptive seizure classification scheme. Validation results on one of the largest clinical datasets of neonatal seizures confirm the utility of the proposed channel weighting for the SVM-based detector recently developed by this research group. Exploiting the channel weighting, the precision-recall area can be drastically increased (up to 25%) for the most difficult patients, with the average increase from 81.0% to 84.42%. It is also shown that the increase in performance with channel weighting is proportional to the time the patient is observed.
68. Schelter B, Feldwisch-Drentrup H, Ihle M, Schulze-Bonhage A, Timmer J. Seizure prediction in epilepsy: from circadian concepts via probabilistic forecasting to statistical evaluation. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:1624-7.  
<http://www.ncbi.nlm.nih.gov/pubmed/22254634>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090469>  
**Abstract** Seizure prediction performance is hampered by high numbers of false predictions. Here we present an approach to reduce the number of false predictions based on circadian concepts. Based on eight representative patients we demonstrate that this approach increases the performance considerably. The fraction of patients for whom we found a significant seizure prediction performance was increased from 25% to 38% by accounting for circadian dependencies.

69. **Castellaro C, Favaro G, Salemi G, Sarto M, Rizzo N. Hardware for seizure prediction: towards wearable devices to support epileptic people. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:1628-31.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22254635>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090470>  
**Abstract** This paper presents the hardware developed for the EPILEPSIAE project ([www.epilepsiae.eu](http://www.epilepsiae.eu)), focused on epileptic seizure prediction. A portable low power acquisition system for EEG signals, called LTM-EU (Long Term Monitoring), with 64 channels and 2048 Hz sampling rate each and a safe (high isolation) PC interface on a PCIe bus specifically designed for this task, is described. The acquisition system, designed for a rapid commercialization, though used for research purposes, got the CE certification. The signal from the patient, on each channel, is amplified, converted in digital form and stored into a local flash memory (SD-MMC, 4 GB). Data are then formatted into a serial stream at 4 Mb/s and sent through a half-duplex RS485 link to the host where a specifically designed PCIe (BQPCle) interface receive them and release the information to the OS (Windows or Linux). The amplifier runs with a couple of AA battery for more than 15 hours (300 mW). If a wireless link is established (Bluetooth), a bandwidth limited stream of data (or a subset of channels) is sent for monitoring purposes. The mission is to support the researchers of the consortium with a suitable hardware to have a real time seizure prediction system for algorithms tests. In the experimental phase all algorithms run on a portable PC, wire or wireless connected to the acquisition system.
70. **Alvarado-Rojas C, Valderrama M, Witon A, Navarro V, Le Van Quyen M. Probing cortical excitability using cross-frequency coupling in intracranial EEG recordings: a new method for seizure prediction. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:1632-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22254636>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090471>  
**Abstract** The need of a reliable seizure prediction is motivated by the 50 million people in the world suffering from epilepsy, of whom 30% have no control on seizures with current pharmacological treatments. Seizure prediction research holds great promise for such patients, since an effective algorithm will enable the development of a closed-loop system that intervenes before the clinical onset of a seizure. As a step toward practical implementation of this technology, we present a new method based on a measure of brain excitability identified by couplings between low-frequency phases and high-frequency amplitudes of brain oscillations. The proposed method was applied to long-term intracranial recordings of 20 patients with partial epilepsy, for a total of 267 seizures and more than 3400-hour-long interictal activities. We found that our predictor was in 50% of cases better than chance, with an average sensitivity of 98.9% and false prediction rate of 1.84/hour. From these observations, we concluded that our method enables a new quantitative way to identify preictal states with a high risk of seizure generation.
71. **Direito B, Ventura F, Teixeira C, Dourado A. Optimized feature subsets for epileptic seizure prediction studies. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:1636-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22254637>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090472>  
**Abstract** The reduction of the number of EEG features to give as inputs to epilepsy seizure predictors is a needed step towards the development of a transportable device for real-time warning. This paper presents a comparative study of three feature selection methods, based on Support Vector Machines. Minimum-Redundancy Maximum-Relevance, Recursive Feature Elimination, Genetic Algorithms, show that, for three patients of the European Database on Epilepsy, the most important univariate features are related to spectral information and statistical moments.

72. **Brown MJ, Netoff T, Parhi KK. A low complexity seizure prediction algorithm. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:1640-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22254638>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090473>  
**Abstract** A new low complexity seizure prediction algorithm is proposed. The algorithm achieves high sensitivity and low false positive rates in 10 out of 18 epileptic patients from the Freiburg database. Its primary achievement is two orders of magnitude computational complexity reduction. The reduced complexity makes an implantable medical device application realizable. In the subset of ten highly predictable patients average sensitivity is 96%, average specificity is 0.25 false positives per hour, and 13.5% of time is spent in false alarms. For all eighteen patients tested, the average sensitivity is 83%, the average specificity is 0.38 false positives per hour, and the amount of time spent in false alarms is 21.1%. This result may be compared with sensitivity of 97.5%, specificity of 0.27 false positives per hour, and 13% of time is spent in false alarms of prior results without complexity reduction.
73. **Aarabi A, He B. Seizure prediction in intracranial EEG: a patient-specific rule-based approach. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:2566-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22254865>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090709>  
**Abstract** In this study, we report our development of a patient-specific rule-based seizure prediction system. Five univariate and one bivariate nonlinear measures were extracted from non-overlapping 10-second segments of intracranial EEG (iEEG) data recorded using both depth electrodes in the brain and subdural electrodes over the cortical surface. Nonlinear features representing the specific characteristic properties of EEG signal were then integrated spatio-temporally in a way to predict to predict seizure with high sensitivity. The present system was tested on 58 hours of iEEG data containing ten seizures recorded in two patients with medically intractable focal epilepsy. Within a prediction horizon of 30 and 60 minutes, our method showed an average sensitivity of 90% and 96.5% with an average false prediction rate of 0.06/h and 0.055/h, respectively. The present results suggest that such a rule-based system can become potentially a useful approach for predicting seizures prior to onset.
74. **Gritsch G, Hartmann MM, Perko H, Furbass F, Ossenblok P, Kluge T. Automatic detection of the seizure onset zone based on ictal EEG. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:3901-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22255192>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6090969>  
**Abstract** In this paper we show a proof of concept for novel automatic seizure onset zone detector. The proposed approach utilizes the Austrian Institute of Technology (AIT) seizure detection system EpiScan extended by a frequency domain source localization module. EpiScan was proven to detect rhythmic epileptiform seizure activity often seen during the early phase of epileptic seizures with reasonable high sensitivity and specificity. Additionally, the core module of EpiScan provides complex coefficients and fundamental frequencies representing the rhythmic activity of the ictal EEG signal. These parameters serve as input to a frequency domain version of the Minimum Variance Beamformer to estimate the most dominant source. The position of this source is the detected seizure onset zone. The results are compared to a state of the art wavelet transformation approach based on a manually chosen frequency band. Our first results are encouraging since they coincide with those obtained with the wavelet approach and furthermore show excellent accordance with the medical report for the majority of analyzed seizures. In contrast to the wavelet approach our method has the advantage that it does not rely on a manual selection of the frequency band.

75. **Petersen EB, Duun-Henriksen J, Mazzaretto A, Kjaer TW, Thomsen CE, Sorensen HB. Generic single-channel detection of absence seizures. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:4820-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22255417>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6091194>  
**Abstract** A long-term EEG-monitoring system, which automatically marks seizure events, is useful for diagnosing and treating epilepsy. A generic method utilizing the low inter-and intra-patient variabilities in EEG-characteristics during absence seizures is proposed. This paper investigates if the spike-and-wave behaviour during absence seizures is so distinct that a single-channel implementation is possible. 18 channels of scalp electroencephalography (EEG), from 19 patients suffering from childhood absence epilepsy, are analysed individually. The characteristics of the seizures are captured using the energy content of wavelet transform subbands and classified using a support vector machine. To ease the evaluation of the method, we present a new graphical visualization of the performance based on the topographical distribution on the scalp. The presented seizure detection method shows that the best result is obtained for the derivation F7-FP1. Using this channel a sensitivity of 99.1 %, positive predictive value of 94.8 %, mean detection latency of 3.7 s, and false detection rate value of 0.5/h was obtained. The topographical visualization of the results clearly shows that the frontal, midline, and parietal channels outperform detection based on the channels in the occipital region.
76. **Hartmann MM, Furbass F, Perko H, Skupch A, Lackmayer K, Baumgartner C, et al. EpiScan: online seizure detection for epilepsy monitoring units. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:6096-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22255730>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6091506>  
**Abstract** An online seizure detection algorithm for long-term EEG monitoring is presented, which is based on a periodic waveform analysis detecting rhythmic EEG patterns and an adaptation module automatically adjusting the algorithm to patient-specific EEG properties. The algorithm was evaluated using 4.300 hours of unselected EEG recordings from 48 patients with temporal lobe epilepsy. For 66% of the patients the algorithm detected 100% of the seizures. A mean sensitivity of 83% was achieved. An average of 7.2 false alarms within 24 hours for unselected EEG makes the algorithm attractive for epilepsy monitoring units.
77. **Li H, Jeremic A. Neonatal seizure detection using blind distributed detection with correlated decisions. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:6580-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22255847>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6091623>  
**Abstract** Seizure is the result of excessive electrical discharges of neurons, which usually develops synchronously and happens suddenly in the central nervous system. Clinically, it is difficult for physician to identify neonatal seizures visually, while EEG seizures can be recognized by the trained experts. By extending our previous results on multichannel information fusion, we propose an automated distributed detection system consisting of the existing detectors and a fusion centre to detect the seizure activities in the newborn EEG assuming that the decisions of local detectors are correlated. The advantage of this proposed technique is that it accounts for correlated decisions of the local detectors. It has been shown that correlation between local detectors can lead to severe performance degradation if not modelled properly. Therefore our proposed technique can potentially improve the performance of existing single and multichannel neonatal seizure detection algorithms.

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<http://www.ncbi.nlm.nih.gov/pubmed/22255895>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6091672>  
**Abstract** Treating epilepsy with deep brain stimulation (DBS) is attracting more and more attention these years, especially the close loop method that gives stimuli when needed so that the implanted device will work longer. People have tried to detect seizure with electrocorticogram (ECoG), but the extra implants put more risks to it. We plan to detect seizure with local field potential (LFP) that recorded with depth electrodes of traditional DBS. To prove the validation of this method, we recorded local field potential (LFP) of anterior thalamic (ANT) of rats who have been induced to acute temporal lobe epilepsy (TLE) by kainic acid injected in hippocampus, and succeeded in detecting electrographic onset (EO) in these data. A variation of generic Osorio-Frei algorithm (GOFA) was used as the detection method with some adjustments which mainly focus on increasing calculation speed and decreasing number of total calculations to meet the future need of transplanting to battery powered embedded medical device.
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<http://www.ncbi.nlm.nih.gov/pubmed/22255964>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6091784>  
**Abstract** Wepilet is a series of novel orthogonal wavelets optimized for Electroencephalogram (EEG) signals, specialized for epileptic seizure prediction. The main idea is to design a mother wavelet that when applied to EEG signal to create the feature space, should enable a better classification of the brain state. Wepilet is developed by an iterative optimization process, employing Genetic Algorithm (GA). Frequency sub-band features are first extracted using wepilet under design for the EEG signal captured by one single surface channel. These features are then fed to Support Vector Machines (SVMs) that classify the cerebral state in preictal and inter-ictal classes. The results of the classification are then used to compute the Probability of Error Rate (PER), which in turn is the GA objective function to be minimized. Results in a group of four patients, indicate the efficiency of optimized mother wavelet compared to the well-known Daubechies wavelet in EEG processing.
80. Zandi AS, Dumont GA, Javidan M, Tafreshi R. Epileptic seizure prediction using variational mixture of Gaussians. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:7549-52.  
<http://www.ncbi.nlm.nih.gov/pubmed/22256085>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6091861>  
**Abstract** We propose a novel patient-specific method for predicting epileptic seizures by analysis of positive zero-crossing intervals in scalp electroencephalogram (EEG). In real-time analysis, the histogram of these intervals for the current EEG epoch is computed, and the values which correspond to the bins discriminating between interictal and preictal references are selected as an observation. Then, the set of observations from the last 5 min is compared with two reference sets of data points (interictal and preictal) using a variational Gaussian mixture model (GMM) of the data, and a combined index is computed. Comparing this index with a patient-specific threshold, an alarm sequence is produced for each channel. Finally, a seizure prediction alarm is generated according to channel-based information. The proposed method was evaluated using ~40.3 h of scalp EEG recordings from 6 patients with total of 28 partial seizures. A high sensitivity of 95% was achieved with a false prediction rate of 0.134/h and an average prediction time of 22.8 min for the test dataset.

81. **Chiang CY, Chang NF, Chen TC, Chen HH, Chen LG. Seizure prediction based on classification of EEG synchronization patterns with on-line retraining and post-processing scheme. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:7564-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22256089>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6091865>  
**Abstract** Epilepsy is one of the most common brain disorders in the world. The spontaneous seizure onset influences the daily life of epilepsy patients. The studies on feature extraction and feature classification from Electroencephalography(EEG) signal in seizure prediction methods have shown great improvement these years. However, the variation issue of EEG signal (being awake, being asleep, severity of epilepsy, etc.) poses a fundamental difficulty in seizure prediction problem. The traditional off-line training method trains the model using a fixed training set, and expects the performance of the model to remain stable even after a long period of time, and thus suffers from variation issue. In this paper, we propose an on-line retraining method to leverage the recent input data by gradually enlarging the training set and retraining the model. Also, a simple post-processing scheme is incorporated to reduce false alarms. We develop our method based on the state of the art machine learning based classification of bivariate patterns method. The performance of the method is evaluated on Electrocorticogram(ECoG) recording from Freiburg database as well as long-term scalp EEG recording from CHB-MIT EEG Database and National Taiwan University Hospital. The proposed method achieves 74.2% sensitivity on ECoG database and 52.2% sensitivity on scalp EEG database, while improving the sensitivity of off-line training method by 29.0% and 17.4% in ECoG database and EEG database respectively. The experimental result suggests that on-line retraining can greatly improve the reliability and is promising for future seizure prediction method development.
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<http://www.ncbi.nlm.nih.gov/pubmed/22256266>  
<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6092042>  
**Abstract** Epilepsy affects approximately one percent of the world population. Antiepileptic drugs are ineffective in approximately 30% of patients and have side effects. We are developing a noninvasive, or minimally invasive, transcranial focal electrical stimulation (TFS) system through our novel concentric ring electrodes to control seizures. Here we report on the development of a seizure detecting algorithm to be used for automatic application of TFS. A cumulative sum (CUSUM) algorithm was evaluated that detected the electrographic seizure activity in all experiments well in advance of the behavioral seizure activity.

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<http://www.ncbi.nlm.nih.gov/pubmed/21692794>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2011.03138.x/asset/j.1528-1167.2011.03138.x.pdf?v=1&t=hfzr4dfd&s=1bdba4728dcd25961f0c360c4bc429c41c5ba08d>  
**Abstract** PURPOSE: We propose a patient-specific algorithm for seizure prediction using multiple features of spectral power from electroencephalogram (EEG) and support vector machine (SVM) classification. METHODS: The proposed patient-specific algorithm consists of preprocessing, feature extraction, SVM classification, and postprocessing. Preprocessing removes artifacts of intracranial EEG recordings and they are further preprocessed in bipolar and/or time-differential methods. Features of spectral power of raw, or bipolar and/or time-differential intracranial EEG (iEEG) recordings in nine bands are extracted from a sliding 20-s-long and half-overlapped window. Nine bands are selected based on standard EEG frequency bands, but the wide gamma bands are split into four. Cost-sensitive SVMs are used for classification of preictal and interictal samples, and double cross-validation is used to achieve in-sample optimization and out-of-sample testing. We postprocess SVM classification outputs using the Kalman Filter and it removes sporadic and isolated false alarms. The algorithm has been tested on iEEG of 18 patients of 20 available in the Freiburg EEG database who had three or more seizure events. To investigate the discriminability of the features between preictal and interictal, we use the Kernel Fisher Discriminant analysis. KEY FINDINGS: The proposed patient-specific algorithm for seizure prediction has achieved high sensitivity of 97.5% with total 80 seizure events and a low false alarm rate of 0.27 per hour and total false prediction times of 13.0% over a total of 433.2 interictal hours by bipolar preprocessing (92.5% sensitivity, a false positive rate of 0.20 per hour, and false prediction times of 9.5% by time-differential preprocessing). This high prediction rate demonstrates that seizures can be predicted by the patient-specific approach using linear features of spectral power and nonlinear classifiers. Bipolar and/or time-differential preprocessing significantly improves sensitivity and specificity. Spectral powers in high gamma bands are the most discriminating features between preictal and interictal. SIGNIFICANCE: High sensitivity and specificity are achieved by nonlinear classification of linear features of spectral power. Power changes in certain frequency bands already demonstrated their possibilities for seizure prediction indicators, but we have demonstrated that combining those spectral power features and classifying them in a multivariate approach led to much higher prediction rates. Employing only linear features is advantageous, especially when it comes to an implantable device, because they can be computed rapidly with low power consumption.
- 84. Lockman J, Fisher RS, Olson DM. Detection of seizure-like movements using a wrist accelerometer. *Epilepsy Behav*. 2011;20(4):638-41.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21450533>  
**Abstract** Caregivers of people with epilepsy are commonly concerned about unwitnessed seizures causing injury and even death. The goal of this study was to determine if a wrist-worn motion detector could detect tonic-clonic seizures. Individuals admitted for continuous video/EEG monitoring wore a wristwatch-size device that was programmed to detect rhythmic movements such as those that occur during tonic-clonic seizures. When such movement was detected, the device sent a Bluetooth signal to a computer that registered the time and duration of the movements. Recorded detections were compared with the routinely recorded video/EEG data. Six of 40 patients had a total of eight tonic-clonic seizures. Seven of the eight seizures were detected. Nonseizure movements were detected 204 times, with opportunity for canceling transmission by the patient. Only one false detection occurred during sleep. In principle, this device should allow caregivers of people with tonic-clonic seizures to be alerted when a seizure occurs.
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<http://www.ncbi.nlm.nih.gov/pubmed/22078509>

86. **Hogan RE. Automated EEG detection algorithms and clinical semiology in epilepsy: importance of correlations. *Epilepsy Behav.* 2011;22 Suppl 1:S4-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22078517>  
**Abstract** With advances in technological innovation, electroencephalography has remained the gold standard for classification and localization of epileptic seizures. Like other diagnostic modalities, technological advances have opened new avenues for assessment of data, and hold great promise to improve interpretive capabilities. However, proper overall interpretation and application of electroencephalographic findings relies on valid correlations of associated clinical semiology. This article addresses interpretation of clinical signs and symptoms in the context of the diagnostic predictive value of electroencephalographic, clinical, and electrographic definitions of seizures, and upcoming challenges of interpreting intracranial high-frequency electroencephalographic data. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.
87. **Osorio I, Lyubushin A, Sornette D. Automated seizure detection: unrecognized challenges, unexpected insights. *Epilepsy Behav.* 2011;22 Suppl 1:S7-17.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22078522>  
**Abstract** One of epileptology's fundamental aims is the formulation of a universal, internally consistent seizure definition. To assess this aim's feasibility three signal analysis methods were applied to a seizure time series and performance comparisons were undertaken among them and with respect to a validated algorithm. One of the methods uses a Fisher's matrix weighted measure of the rate of parameters change of a 2nd order auto-regressive model, another is based on the Wavelet Transform Maximum Modulus for quantification of changes in the logarithm of the standard deviation of ECoG power and yet another employs the ratio of short-to-long term averages computed from cortical signals. The central finding, fluctuating concordance among all methods' output as a function of seizure duration, uncovers unexpected hurdles in the path to a universal definition, while furnishing relevant knowledge in the dynamical (spectral non-stationarity/varying ictal signal complexity) and clinical (potential un-attainability of consensus) domains. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.
88. **Osorio I, Lyubushin A, Sornette D. Toward a probabilistic definition of seizures. *Epilepsy Behav.* 2011;22 Suppl 1:S18-28.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22078513>  
**Abstract** This writing (1) draws attention to the intricacies inherent to the pursuit of a universal seizure definition even when powerful, well-understood signal analysis methods are used to this end; (2) identifies this aim as a multi-objective optimization problem and discusses the advantages and disadvantages of adopting or rejecting a unitary seizure definition; and (3) introduces a probabilistic measure of seizure activity to manage this thorny issue. The challenges posed by the attempt to define seizures unitarily may be partly related to their fractal properties and understood through a simplistic analogy to the so-called "Richardson effect." A revision of the time-honored conceptualization of seizures may be warranted to further advance epileptology. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.

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<http://www.ncbi.nlm.nih.gov/pubmed/22078515>  
**Abstract** This article addresses the problem of real-time seizure detection from intracranial EEG (IEEG). One difficulty in creating an approach that can be used for many patients is the heterogeneity of seizure IEEG patterns across different patients and even within a patient. In addition, simultaneously maximizing sensitivity and minimizing latency and false detection rates has been challenging as these are competing objectives. Automated machine learning systems provide a mechanism for dealing with these hurdles. Here we present and evaluate an algorithm for real-time seizure onset detection from IEEG using a machine-learning approach that permits a patient-specific solution. We extract temporal and spectral features across all intracranial EEG channels. A pattern recognition component is trained using these feature vectors and tested against unseen continuous data from the same patient. When tested on more than 875 hours of IEEG data from 10 patients, the algorithm detected 97% of 67 test seizures of several types with a median detection delay of 5 seconds and a median false alarm rate of 0.6 false alarms per 24-hour period. The sensitivity was 100% for 8 of 10 patients. These results indicate that a sensitive, specific, and relatively short-latency detection system based on machine learning can be employed for seizure detection from EEG using a full set of intracranial electrodes to individual patients. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.
90. **Shoeb A, Kharbouch A, Soegaard J, Schachter S, Gutttag J. A machine-learning algorithm for detecting seizure termination in scalp EEG. *Epilepsy Behav.* 2011;22 Suppl 1:S36-43.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22078516>  
**Abstract** Efforts to develop algorithms that can robustly detect the cessation of seizure activity within scalp EEGs are now underway. Such algorithms can facilitate novel clinical applications such as the estimation of a seizure's duration; the delivery of therapies designed to mitigate postictal period symptoms; or detection of the presence of status epilepticus. In this article, we present and evaluate a novel, machine learning-based method for detecting the termination of electrographic seizure activity. When tested on 133 seizures from a public database, our method successfully detected the end of 132 seizures within 10.3 +/- 5.5 seconds of the time determined by an electroencephalographer to represent the electrographic end of seizure. Furthermore, by pairing our seizure end detector with a previously published seizure onset detector, we could automatically estimate the duration of 85% of test electrographic seizures within a 15-second error margin compared with electroencephalographer determinations. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.
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<http://www.ncbi.nlm.nih.gov/pubmed/22078518>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3233224/pdf/nihms322212.pdf>  
**Abstract** Over the last decade, the search for a method able to reliably predict seizures hours in advance has been largely replaced by the more realistic goal of very early detection of seizure onset, which would allow therapeutic or warning devices to be triggered prior to the onset of disabling clinical symptoms. We explore in this article the steps along the pathway from data acquisition to closed-loop applications that can and should be considered to design the most efficient early seizure detection. Microelectrodes, high-frequency oscillations, high sampling rate, high-density arrays, and modern analysis techniques are all elements of the recording and detection process that in combination with modeling studies can provide new insights into the dynamics of seizure onsets. Each of these steps needs to be considered if detection devices that will favorably impact the quality of life of patients are to be implemented. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.

92. **Santaniello S, Burns SP, Golby AJ, Singer JM, Anderson WS, Sarma SV. Quickest detection of drug-resistant seizures: an optimal control approach. *Epilepsy Behav.* 2011;22 Suppl 1:S49-60.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22078519>  
[http://ac.els-cdn.com/S1525505011005051/1-s2.0-S1525505011005051-main.pdf?\\_tid=9bd3d21e-9279-11e2-a9e8-00000aab0f02&acdnat=1363906357\\_5425e5a9cf4ede6d6c8478e9a18dc50b](http://ac.els-cdn.com/S1525505011005051/1-s2.0-S1525505011005051-main.pdf?_tid=9bd3d21e-9279-11e2-a9e8-00000aab0f02&acdnat=1363906357_5425e5a9cf4ede6d6c8478e9a18dc50b)  
**Abstract** Epilepsy affects 50 million people worldwide, and seizures in 30% of the cases remain drug resistant. This has increased interest in responsive neurostimulation, which is most effective when administered during seizure onset. We propose a novel framework for seizure onset detection that involves (i) constructing statistics from multichannel intracranial EEG (iEEG) to distinguish nonictal versus ictal states; (ii) modeling the dynamics of these statistics in each state and the state transitions; you can remove this word if there is no room. (iii) developing an optimal control-based "quickest detection" (QD) strategy to estimate the transition times from nonictal to ictal states from sequential iEEG measurements. The QD strategy minimizes a cost function of detection delay and false positive probability. The solution is a threshold that non-monotonically decreases over time and avoids responding to rare events that normally trigger false positives. We applied QD to four drug resistant epileptic patients (168 hour continuous recordings, 26-44 electrodes, 33 seizures) and achieved 100% sensitivity with low false positive rates (0.16 false positive/hour). This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.
93. **Raghunathan S, Jaitli A, Irazoqui PP. Multistage seizure detection techniques optimized for low-power hardware platforms. *Epilepsy Behav.* 2011;22 Suppl 1:S61-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22078520>  
**Abstract** Closed-loop neurostimulation devices that stimulate the brain to treat epileptic seizures have shown great promise in treating more than a third of the 2 million people with epilepsy in the United States alone whose seizures are currently nonresponsive to pharmaceutical treatment. Seizure detection algorithms facilitate responsive therapeutic intervention that is believed to increase the efficacy of neurostimulation by improving on its spatial and temporal specificity. Translating these signal processing algorithms into battery-powered, implantable devices poses a number of challenges that severely limit the computational power of the chosen algorithm. We propose a cascaded two-stage seizure detection algorithm that is computationally efficient (resulting in a low-power hardware implementation) without compromising on detection efficacy. Unlike traditional detection algorithms, the proposed technique does not explicitly require a "training" phase from individual to individual and, instead, relies on using features that result in distinct "patterns" at the electrographic seizure onset. We tested the algorithm on spontaneous clinical seizures recorded using depth electrodes from patients with focal intractable epilepsy and annotated by epileptologists at the University of Freiburg Medical Center, via the Freiburg database. The algorithm performs with a specificity and sensitivity of 99.82 and 87.5%, detecting seizures in less than 9.08% of their duration after onset. The proposed technique is also shown to be computationally efficient, facilitating low-power hardware implementation. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.

94. **Sackellares JC, Shiao DS, Halford JJ, LaRoche SM, Kelly KM. Quantitative EEG analysis for automated detection of nonconvulsive seizures in intensive care units. *Epilepsy Behav.* 2011;22 Suppl 1:S69-73. <http://www.ncbi.nlm.nih.gov/pubmed/22078521>**  
**Abstract** Because of increased awareness of the high prevalence of nonconvulsive seizures in critically ill patients, use of continuous EEG (cEEG) monitoring is rapidly increasing in ICUs. However, cEEG monitoring is labor intensive, and manual review and interpretation of the EEG are impractical in most ICUs. Effective methods to assist in rapid and accurate detection of nonconvulsive seizures would greatly reduce the cost of cEEG monitoring and enhance the quality of patient care. In this study, we report a preliminary investigation of a novel ICU EEG analysis and seizure detection algorithm. Twenty-four prolonged cEEG recordings were included in this study. Seizure detection sensitivity and specificity were assessed for the new algorithm and for the two commercial seizure detection software systems. The new algorithm performed with a mean sensitivity of 90.4% and a mean false detection rate of 0.066/hour. The two commercial detection products performed with low sensitivities (12.9 and 10.1%) and false detection rates of 1.036/hour and 0.013/hour, respectively. These findings suggest that the novel algorithm has potential to be the basis of clinically useful software that can assist ICU staff in timely identification of nonconvulsive seizures. This study also suggests that currently available seizure detection software does not perform sufficiently in detection of nonconvulsive seizures in critically ill patients. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.
95. **Osorio I, Schachter S. Extracerebral detection of seizures: a new era in epileptology? *Epilepsy Behav.* 2011;22 Suppl 1:S82-7. <http://www.ncbi.nlm.nih.gov/pubmed/22078524>**  
**Abstract** The medical and psycho-socio-economic burden imposed on patients, caregivers, and health systems by pharmaco-resistant epilepsies is enormous. Intracranial devices for automated detection, warning, and delivery of therapy, the presently preferred "line of attack" for an abundance of weighty reasons, would be insufficient to adequately address said burden on a global scale. Reliance on signals that, although extracerebral, are under cortical modulation or control and are altered by seizures, such as cardiac or motor signals, emerges as a viable research direction with potentially fruitful clinical applications. The greater ease of implementation and lower cost of automated real-time detection, warning, and therapy systems based on extracerebral signals, compared with those requiring intracranial placement, make them worthy of investigation. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.
96. **Schulze-Bonhage A, Feldwisch-Drentrup H, Ihle M. The role of high-quality EEG databases in the improvement and assessment of seizure prediction methods. *Epilepsy Behav.* 2011;22 Suppl 1:S88-93. <http://www.ncbi.nlm.nih.gov/pubmed/22078525>**  
**Abstract** Initially, seizure prediction was based on the analysis of brief EEG segments preceding clinically manifest seizures. Whereas such approaches suggested that the sensitivities of various EEG-derived features in predicting seizures were high, the inclusion of longer interictal periods and the combined assessment of sensitivity and specificity and the application of statistical validation methods have put into question the validity of such claims. We here show that the duration of EEG on which analyses are based and the number of seizures assessed negatively correlate with the reported sensitivities of prediction studies. Methodological aspects of seizure prediction are discussed in the framework of currently existing databases and of the newly established European Union database. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.

97. **Carney PR, Myers S, Geyer JD. Seizure prediction: methods. *Epilepsy Behav.* 2011;22 Suppl 1:S94-101.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22078526>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3233702/pdf/nihms-331345.pdf>  
**Abstract** Epilepsy, one of the most common neurological diseases, affects over 50 million people worldwide. Epilepsy can have a broad spectrum of debilitating medical and social consequences. Although antiepileptic drugs have helped treat millions of patients, roughly a third of all patients have seizures that are refractory to pharmacological intervention. The evolution of our understanding of this dynamic disease leads to new treatment possibilities. There is great interest in the development of devices that incorporate algorithms capable of detecting early onset of seizures or even predicting them hours before they occur. The lead time provided by these new technologies will allow for new types of interventional treatment. In the near future, seizures may be detected and aborted before physical manifestations begin. In this chapter we discuss the algorithms that make these devices possible and how they have been implemented to date. We also compare and contrast these measures, and review their individual strengths and weaknesses. Finally, we illustrate how these techniques can be combined in a closed-loop seizure prevention system. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.
98. **Kalitzin S, Koppert M, Petkov G, Velis D, da Silva FL. Computational model prospective on the observation of proictal states in epileptic neuronal systems. *Epilepsy Behav.* 2011;22 Suppl 1:S102-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22078510>  
**Abstract** Epilepsy is a pathological condition of the human central nervous system in which normal brain functions are impaired by unexpected transitions to states called seizures. We developed a lumped neuronal model that has the property of switching between two states as a result of intrinsic or extrinsic perturbations, such as noisy fluctuations. In one version of the model, seizure risk is controlled by a single connectivity parameter representing excitatory couplings between two model lumps. We show that this risk can be reconstructed from calculation of the cross-covariance between the activities of the two neural populations during the nonictal phase. In a second simulation sequence, we use a system of 10 interconnected lumps with randomly generated connectivity matrices. We show again that the tendency to develop seizures can be inferred from the cross-covariances calculated during the nonictal states. Our conclusion is that the risk of epileptic transitions in biological systems can be objectively quantified. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.
99. **Freestone DR, Kuhlmann L, Grayden DB, Burkitt AN, Lai A, Nelson TS, et al. Electrical probing of cortical excitability in patients with epilepsy. *Epilepsy Behav.* 2011;22 Suppl 1:S110-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22078511>  
**Abstract** Standard methods for seizure prediction involve passive monitoring of intracranial electroencephalography (iEEG) in order to track the 'state' of the brain. This paper introduces a new method for measuring cortical excitability using an electrical probing stimulus. Electrical probing enables feature extraction in a more robust and controlled manner compared to passively tracking features of iEEG signals. The probing stimuli consist of 100 bi-phasic pulses, delivered every 10 min. Features representing neural excitability are estimated from the iEEG responses to the stimuli. These features include the amplitude of the electrically evoked potential, the mean phase variance (univariate), and the phase-locking value (bivariate). In one patient, it is shown how the features vary over time in relation to the sleep-wake cycle and an epileptic seizure. For a second patient, it is demonstrated how the features vary with the rate of interictal discharges. In addition, the spatial pattern of increases and decreases in phase synchrony is explored when comparing periods of low and high interictal discharge rates, or sleep and awake states. The results demonstrate a proof-of-principle for the method to be applied in a seizure anticipation framework. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.

100. **Feldwisch-Drentrup H, Ihle M, Quyen Mle V, Teixeira C, Dourado A, Timmer J, et al. Anticipating the unobserved: prediction of subclinical seizures. *Epilepsy Behav.* 2011;22 Suppl 1:S119-26.**

<http://www.ncbi.nlm.nih.gov/pubmed/22078512>

**Abstract** Subclinical seizures (SCS) have rarely been considered in the diagnosis and therapy of epilepsy and have not been systematically analyzed in studies on seizure prediction. Here, we investigate whether predictions of subclinical seizures are feasible and how their occurrence may affect the performance of prediction algorithms. Using the European database of long-term recordings of surface and invasive electroencephalography data, we analyzed the data from 21 patients with SCS, including in total 413 clinically manifest seizures (CS) and 3341 SCS. Based on the mean phase coherence we investigated the predictive performance of CS and SCS. The two types of seizures had similar prediction sensitivities. Significant performance was found considerably more often for SCS than for CS, especially for patients with invasive recordings. When analyzing false alarms triggered by predicting CS, a significant number of these false predictions were followed by SCS for 9 of 21 patients. Although currently observed prediction performance may not be deemed sufficient for clinical applications for the majority of the patients, it can be concluded that the prediction of SCS is feasible on a similar level as for CS and allows a prediction of more of the seizures impairing patients, possibly also reducing the number of false alarms that were in fact correct predictions of CS. This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.

101. **Akman CI, Micic V, Thompson A, Riviello JJ, Jr. Seizure detection using digital trend analysis: Factors affecting utility. *Epilepsy Res.* 2011;93(1):66-72.**

<http://www.ncbi.nlm.nih.gov/pubmed/21146370>

**Abstract** BACKGROUND: EEG monitoring is important for the early detection of seizures during the course of critical illness. However, the logistics of real time EEG interpretation is challenging for the neurophysiology and critical care medicine teams. This study evaluated factors affecting the utility of digital trend analysis (DTA) for rapid seizure identification in children. METHODS: digital EEG files of seizures in critically ill children were retrieved for DTA. The envelop trend (ET) and compressed spectral array (CSA) were applied to the raw EEG data and presented to an experienced and inexperienced user for interpretation who were blinded to conventional EEG findings. The EEG findings with and without presence of seizures and features of seizures were analyzed. RESULTS: we found that a number of factors affected accurate seizure detection including factors related to interpreter's experiences, display size and type of DTA methods used for analysis in addition to baseline EEG findings. ET was more dependent on user experience, furthermore, display size and multimodal DTA application (CSA and ET combined) increased the sensitivity of seizure detection for the experienced user compared to inexperienced users. The artifacts were reported as seizures regardless of experience without presence of conventional EEG recording. The maximum spike amplitude, seizure duration, and seizure frequency were other important determinants for accuracy. Electrographic seizures with shorter duration were better detected by ET, and the maximum spike amplitude was important for both the ET and CSA. Repetitive seizures are readily detected by both digital trending methods. Artifacts may be reported as seizures regardless of experience if conventional EEG recording is not available for the interpretation. CONCLUSION: DTA applied to the raw EEG data does produce a graphic display that facilitates identification of seizures. The actual characteristics of the electrographic seizure may predict which DTA method is better and the overall accuracy of seizure detection may increase when multimodal trending is used simultaneously. Application of DTA alone with display of conventional EEG is beneficial for rapid interpretation of EEG findings regardless of experience.

102. **Schulc E, Unterberger I, Saboor S, Hilbe J, Ertl M, Ammenwerth E, et al. Measurement and quantification of generalized tonic-clonic seizures in epilepsy patients by means of accelerometry--an explorative study. *Epilepsy Res.* 2011;95(1-2):173-83.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21450442>  
**Abstract** Epilepsy is one of the most common neurological diseases, which has a cumulative lifetime incidence of 3%. Two to threefold increased morbidity and mortality rates are reported, especially if generalized tonic-clonic seizures (GTCS) occur. A wireless small and user-friendly detection system would be helpful in early identification of seizures. This could minimize the risk of seizure-related injuries and further allow complete seizure frequency documentation, especially in a non-clinical private setting. The aim of our study was to develop a design and to conduct an exploratory validation of an accelerometry (ACM)-based detection system for GTCS detection in real-time. Patients were recruited via the Epilepsy Monitoring Unit at the Department of Neurology, Medical University Innsbruck. In three out of 20 patients, four GTCS could be recorded. The ACM sensors recorded increased activities at the stated seizure time, which clearly differed from everyday movements. The temporary sensitivity (100%), specificity ( $\geq 88\%$ ) and the positive predictive value ( $\geq 75\%$ ) of the detection suggests a promising alarm/false alarm ratio. The validity of the detection device has to be evaluated with more data in order to be able to significantly confirm the positive results and to further develop a cut-off algorithm for automatic seizure detection.
103. **Schulze-Bonhage A, Haut S. Premonitory features and seizure self-prediction: artifact or real? *Epilepsy Res.* 2011;97(3):231-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22088481>  
**Abstract** Seizure prediction is currently largely investigated by means of EEG analyses. We here report on evidence available on the ability of epilepsy patients themselves to predict seizures either by means of subjective experiences ("prodromes"), apparent awareness of precipitants, or a feeling of impending seizure (self-prediction). These data have been collected prospectively by paper or electronic diaries. Whereas evidence for a predictive value of prodromes is missing, some patients nevertheless can foresee impending seizures above chance level. Relevant cues and practical implications are discussed.
104. **Temko A, Nadeu C, Marnane W, Boylan G, Lightbody G. EEG signal description with spectral-envelope-based speech recognition features for detection of neonatal seizures. *IEEE Trans Inf Technol Biomed.* 2011;15(6):839-47.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21690018>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3428725/pdf/ukmss-49511.pdf>  
**Abstract** In this paper, features which are usually employed in automatic speech recognition (ASR) are used for the detection of seizures in newborn EEG. In particular, spectral envelope-based features, composed of spectral powers and their spectral derivatives are compared to the established feature set which has been previously developed for EEG analysis. The results indicate that the ASR features which model the spectral derivatives, either full-band or localized in frequency, yielded a performance improvement, in comparison to spectral-power-based features. Indeed it is shown here that they perform reasonably well in comparison with the conventional EEG feature set. The contribution of the ASR features was analyzed here using the support vector machines (SVM) recursive feature elimination technique. It is shown that the spectral derivative features consistently appear among the top-rank features. The study shows that the ASR features should be given a high priority when dealing with the description of the EEG signal.

105. **Majumdar KK, Vardhan P. Automatic seizure detection in ECoG by differential operator and windowed variance. *IEEE Trans Neural Syst Rehabil Eng.* 2011;19(4):356-65.**

<http://www.ncbi.nlm.nih.gov/pubmed/21622080>

<http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=5773498>

**Abstract** Differential operator has long been used in image and signal processing with great success to detect significant changes. In this paper we show that differentiation can enhance certain features of brain electrophysiological signals, contaminated with noise, artifacts, and acquisition defects, leading to efficient detection of those changes. Windowed variance method has been very successful in detecting seizure onset in the brain electrophysiological signals. In this paper we have combined these two powerful methods under the name of differential windowed variance (DWV) algorithm to automatically detect seizure onsets in almost real time, in continuous ECoG (depth-EEG) signals of epileptic patients. The main advantages of the method are simplicity of implementation and speed. We have tested the algorithm on 369 h of nonseizure ECoG as well as 59 h of seizure ECoG of 15 epileptic patients. It detected all but six seizures (91.525% accuracy) with an average delay of 9.2 s after the onset with a maximum false detection of three in 24 h of nonseizure data. Eight novel empirical measures have been introduced to avoid false detections. To ascertain the reliability of the detection method a novel methodology, called quasi-ROC (qROC) curve analysis has been introduced. DWV has been compared with a difference filter based sharp transient (ST) detection algorithm.

106. **Acharya UR, Sree SV, Suri JS. Automatic detection of epileptic EEG signals using higher order cumulant features. *Int J Neural Syst.* 2011;21(5):403-14.**

<http://www.ncbi.nlm.nih.gov/pubmed/21956932>

**Abstract** The unpredictability of the occurrence of epileptic seizures makes it difficult to detect and treat this condition effectively. An automatic system that characterizes epileptic activities in EEG signals would allow patients or the people near them to take appropriate precautions, would allow clinicians to better manage the condition, and could provide more insight into these phenomena thereby revealing important clinical information. Various methods have been proposed to detect epileptic activity in EEG recordings. Because of the nonlinear and dynamic nature of EEG signals, the use of nonlinear Higher Order Spectra (HOS) features is a seemingly promising approach. This paper presents the methodology employed to extract HOS features (specifically, cumulants) from normal, interictal, and epileptic EEG segments and to use significant features in classifiers for the detection of these three classes. In this work, 300 sets of EEG data belonging to the three classes were used for feature extraction and classifier development and evaluation. The results show that the HOS based measures have unique ranges for the different classes with high confidence level ( $p$ -value  $< 0.0001$ ). On evaluating several classifiers with the significant features, it was observed that the Support Vector Machine (SVM) presented a high detection accuracy of 98.5% thereby establishing the possibility of effective EEG segment classification using the proposed technique.

107. **Kramer U, Kipervasser S, Shlitner A, Kuzniecky R. A novel portable seizure detection alarm system: preliminary results. *J Clin Neurophysiol.* 2011;28(1):36-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21221012>  
**Abstract** The unpredictable and random occurrence of seizures is of the most distressful issue affecting patients and their families. Unattended seizures can have serious consequences including injury or death. The objective of this study is to develop a small, portable, wearable device capable of detecting seizures and alerting patients and families on recognition of specific seizures' motor activity. Ictal data were prospectively obtained in consecutive patients admitted to two video-EEG units. This study included patients with a history of motor seizures, clonic or tonic, or tonic-clonic seizures or patients with complex partial seizures with frequent secondary generalization. A "Motion Sensor" unit mounted on a bracelet was attached to one wrist. The "Sensor" contains a three-axis accelerometer and a transmitter. The three-axis movements' data were transmitted to a portable computer. Algorithm specially developed for this purpose analyzed the recorded data. Seizures' alerts were compared with the video-EEG data. Ictal data were acquired in 15 of the 31 recruited patients. The algorithm correctly identified 20 of 22 (91%) captured seizures and generated an alarm within a median period of 17 seconds. All events lasting >30 seconds (i.e., 19 events) were identified. The system failed to identify 2 of 22 seizures (9%). There were eight false alarms during 1,692 hours of monitoring. Preliminary data suggest that this motion detection device/alarm system can identify most motor seizures with high sensitivity and with a low false alarm rate.
108. **Janati A. Interictal epileptiform discharges and epilepsy prediction. *J Clin Neurophysiol.* 2011;28(1):75; author reply 75.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21221009>
109. **Shayegh F, Fattahi RA, Sadri S, Ansari-Asl K. A Brief Survey of Computational Models of Normal and Epileptic EEG Signals: A Guideline to Model-based Seizure Prediction. *J Med Signals Sens.* 2011;1(1):62-72.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22606660>  
**Abstract** In recent decades, seizure prediction has caused a lot of research in both signal processing and the neuroscience field. The researches have tried to enhance the conventional seizure prediction algorithms such that the rate of the false alarms be appropriately small, so that seizures can be predicted according to clinical standards. To date, none of the proposed algorithms have been sufficiently adequate. In this article we show that in considering the mechanism of the generation of seizures, the prediction results may be improved. For this purpose, an algorithm based on the identification of the parameters of a physiological model of seizures is introduced. Some models of electroencephalographic (EEG) signals that can also be potentially considered as models of seizure and some developed seizure models are reviewed. As an example the model of depth-EEG signals, proposed by Wendling, is studied and is shown to be a suitable model.

110. **Teixeira CA, Direito B, Feldwisch-Drentrup H, Valderrama M, Costa RP, Alvarado-Rojas C, et al. EPILAB: a software package for studies on the prediction of epileptic seizures. *J Neurosci Methods*. 2011;200(2):257-71.**

<http://www.ncbi.nlm.nih.gov/pubmed/21763347>

**Abstract** A Matlab(R)-based software package, EPILAB, was developed for supporting researchers in performing studies on the prediction of epileptic seizures. It provides an intuitive and convenient graphical user interface. Fundamental concepts that are crucial for epileptic seizure prediction studies were implemented. This includes, for example, the development and statistical validation of prediction methodologies in long-term continuous recordings. Seizure prediction is usually based on electroencephalography (EEG) and electrocardiography (ECG) signals. EPILAB is able to process both EEG and ECG data stored in different formats. More than 35 time and frequency domain measures (features) can be extracted based on univariate and multivariate data analysis. These features can be post-processed and used for prediction purposes. The predictions may be conducted based on optimized thresholds or by applying classifications methods such as artificial neural networks, cellular neuronal networks, and support vector machines. EPILAB proved to be an efficient tool for seizure prediction, and aims to be a way to communicate, evaluate, and compare results and data among the seizure prediction community.

111. **Harreby KR, Sevcencu C, Struijk JJ. Early seizure detection in rats based on vagus nerve activity. *Med Biol Eng Comput*. 2011;49(2):143-51.**

<http://www.ncbi.nlm.nih.gov/pubmed/20890672>

<http://link.springer.com/article/10.1007%2Fs11517-010-0683-1>

**Abstract** Continuous, scheduled vagus nerve stimulation (VNS) is used for the treatment of refractory epilepsy. On-demand VNS, started prior to or at the onset of a seizure may improve the effect of the treatment, however, this requires seizures to be predicted or detected early. This study investigates the possibility of early seizure detection based on the cervical vagus electroneurogram (VENG). Fourteen anesthetized rats received an intravenous infusion (IV) of either saline (control, n = 6) or pentylentetrazol (PTZ) diluted in saline (PTZ-treated, n = 8). A cardiac-related VENG profile (CrVENG) was derived by using R-peak triggered averaging of the VENG energy. Following, changes in this profile were evaluated as a seizure predictor. Using left nerve VENG, seizures were detected in all PTZ-treated rats 103 +/- 51 s (mean +/- SD) before they developed tonic seizures. Control rats did not develop seizures and our method did also not detected seizures in these rats. Seizures can be early detecting based on left nerve VENG in anesthetized rats. Preictal CrVENG changes may reflect central-mediated changes and/or changes in the relation between the respiration and the cardiac cycle. Further research is needed to evaluate the method in awake and freely moving animals and eventually in humans.

- 112. Park S, Roederer A, Mani R, Schmitt S, LeRoux PD, Ungar LH, et al. Limitations of threshold-based brain oxygen monitoring for seizure detection. *Neurocrit Care*. 2011;15(3):469-76.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21523525>  
<http://rd.springer.com/article/10.1007%2Fs12028-011-9540-9>  
**Abstract** BACKGROUND: Brain tissue oxygen (PbtO(2)) monitors are utilized in a threshold-based fashion, triggering actions based on the presumption of tissue compromise when PbtO(2) is less than 20 mmHg. Some early published practice guidelines suggest that seizure is a potential culprit when PbtO(2) crosses this threshold; evidence for this is not well defined. METHODS: Data were collected manually as part of a prospective observational database. PbtO(2) monitors and continuous electroencephalogram (cEEG) were placed by clinical protocol in aneurysmal subarachnoid hemorrhage (aSAH) or traumatic brain injury (TBI) patients with a Glasgow Coma Scale (GCS)  $\leq$  8. Eight patients with discrete seizures during an overlapping monitored period were identified. Probability of seizure when PbtO(2) value was  $<$ 20 mmHg (and the inverse) were calculated. RESULTS: There were 343 distinct seizure episodes and 1797 PbtO(2) measurements. 8.9% of seizures were followed by a PbtO(2) value below 20 mmHg. Of all observed low PbtO(2) values, 3.8% were associated with seizure. Seizure length did not influence PbtO(2). Two patients with the highest number of seizures developed low PbtO(2) values post-seizure. CONCLUSIONS: Seizures were neither associated with a PbtO(2) value of  $<$ 20 mmHg nor associated with a drop in PbtO(2) value across a clinically significant threshold. However, we cannot rule out the existence of any relationship between PbtO(2) and seizure with this limited data set. Prospective research using electronically recorded data is required to more effectively examine the relationship between PbtO(2) and seizure.
- 113. Kosior RK, Lauzon ML, Federico P, Frayne R. Algebraic T2 estimation improves detection of right temporal lobe epilepsy by MR T2 relaxometry. *Neuroimage*. 2011;58(1):189-97.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21689766>  
**Abstract** Seizure related abnormalities may be detected with T2 relaxometry, which involves quantitative estimation of T2 values. Accounting for the partial-volume effect of cerebrospinal fluid (CSF) is important, especially for voxel-based relaxometry, VBR. With a mono-exponential decay model, this can be accomplished by including a baseline constant. An algebraic calculation, which accommodates this constant, offers improved T2 estimation speed over the commonly used non-linear fitting approach. Our objective was to compare the algebraic approach against three fitting approaches for the detection of seizure related abnormalities. We tested the performance of the four methods in the presence of noise using simulated data as well as real data acquired at 3 T with a Carr-Purcell-Meiboom-Gill sequence from 45 healthy subjects and 24 patients with confirmed right temporal lobe epilepsy. A quantitative analysis was performed on spatially normalized data by measuring T2 in various regions and with a whole brain tissue segmentation analysis. The detection rate of hippocampal T2 changes in patients was assessed by comparing the regional T2 measurements from each patient against the control data with a z-score threshold of 2.33. The algebraic method yielded high sensitivity for detection of hippocampal abnormalities in the epileptic patients in regional assessment and in follow-up single-subject VBR. This can be attributed to the relatively small variance across healthy subjects and improved precision in the presence of CSF and noise in simulation. In conclusion, the algebraic method is better than fitting based on faster calculation speed and better sensitivity for detecting seizure-related T2 changes.

114. **Iasemidis LD. Seizure prediction and its applications. *Neurosurg Clin N Am.* 2011;22(4):489-506, vi.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21939848>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3237404/pdf/nihms311166.pdf>  
**Abstract** Epilepsy is characterized by intermittent, paroxysmal, hypersynchronous electrical activity that may remain localized and/or spread and severely disrupt the brain's normal multitask and multiprocessing function. Epileptic seizures are the hallmarks of such activity. The ability to issue warnings in real time of impending seizures may lead to novel diagnostic tools and treatments for epilepsy. Applications may range from a warning to the patient to avert seizure-associated injuries, to automatic timely administration of an appropriate stimulus. Seizure prediction could become an integral part of the treatment of epilepsy through neuromodulation, especially in the new generation of closed-loop seizure control systems.
115. **Han Y, Hsin YL, Harnod T, Liu W. Features and futures: seizure detection in partial epilepsies. *Neurosurg Clin N Am.* 2011;22(4):507-18, vii.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21939849>  
**Abstract** Many factors underlying basic epileptic conditions determine the characteristics of epileptic seizures and the therapeutic outcome. Diagnosis and treatment rely on the clinical manifestations as well as electroencephalographic (EEG) epileptic activities. This article briefly reviews the fundamentals of the EEG, interictal, and ictal electrical activities of both extracranial and intracranial EEG of partial epilepsies, based on the information obtained from epilepsy patients who have undergone epilepsy surgery. The authors also present the status of their current research, focusing on decomposed seizure sources and the rendered spatial-temporal transitions in focal seizure.
116. **Guastello SJ, Boeh H, Lynn M. Long-range prediction of epileptic seizures with nonlinear dynamics. *Nonlinear Dynamics Psychol Life Sci.* 2011;15(3):377-88.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21645436>  
**Abstract** Patients with uncontrolled epilepsy have some significant problems with planning life routines, and thus one goal of the present study was to explore the viability of predicting seizures in time intervals of one week. The second goal was to utilize the principle of dynamic diseases and to assess the viability of a cusp catastrophe model for seizure onset that was proposed by Cerf (2006). A seizure history of 124 weeks from one adult male patient fit both the cusp and fold catastrophe models ( $R^2 = .92$  and  $.88$  respectively) reasonably well using the pdf method and more accurately than counterpart linear models. Prediction of future states was possible, but somewhat compromised because of the nonstationary nature of the data and uncertainties regarding the control variables in the catastrophe models. Analyses of lag functions, however, revealed some surprising elements, suggesting that the precursory conditions for a seizure could be building up over a period of several weeks and that a self-correcting effect within the nervous system could have been occurring.

117. **Zimbric MR, Sharpe CM, Albright KC, Nespeca MP. Three-channel electroencephalogram montage in neonatal seizure detection and quantification. *Pediatr Neurol.* 2011;44(1):31-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21147384>  
**Abstract** We compared three-channel montage with 21-channel neonatal minimal placement montage for the detection of neonatal seizures and quantification of seizure burden. Thirty-five neonatal electroencephalograms were retrospectively and blindly reviewed by two independent readers. Tracings were analyzed in the three-channel montage for seizure number, duration, and quantification of seizure burden before reanalysis with the full 21-channel neonatal minimal placement montage. Seizures were identified using standard definitions of electroencephalographic seizure. Sensitivity, specificity, and interrater reliability were calculated. The sensitivity and specificity of three-channel montage for detecting seizures > 10 seconds were 91% and 100% for reader 1, respectively, and 82% and 96% for reader 2, respectively. The interrater agreement for detection of seizures was excellent ( $\kappa = 0.86$ , 94% percent overall agreement). For quantification of seizure burden, strong, positive correlation existed between assessments by full montage and three-channel montage (for reader 1,  $r = 0.945$ ,  $n = 11$ ,  $P < 0.0001$ ; for reader 2,  $r = 0.902$ ,  $n = 11$ ,  $P < 0.0001$ ), and strong correlation existed between the readers for three-channel montage ( $r = 0.879$ ,  $n = 11$ ,  $P < 0.0001$ ). Despite its limitations, three-channel montage is useful in the detection of neonatal seizures and quantification of seizure burden.
118. **Feldwisch-Drentrup H, Schulze-Bonhage A, Timmer J, Schelter B. Statistical validation of event predictors: a comparative study based on the field of seizure prediction. *Phys Rev E Stat Nonlin Soft Matter Phys.* 2011;83(6 Pt 2):066704.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21797513>  
**Abstract** The prediction of events is of substantial interest in many research areas. To evaluate the performance of prediction methods, the statistical validation of these methods is of utmost importance. Here, we compare an analytical validation method to numerical approaches that are based on Monte Carlo simulations. The comparison is performed in the field of the prediction of epileptic seizures. In contrast to the analytical validation method, we found that for numerical validation methods insufficient but realistic sample sizes can lead to invalid high rates of false positive conclusions. Hence we outline necessary preconditions for sound statistical tests on above chance predictions.
119. **Navarro V, Le Van Quyen M, Clemenceau S, Adam C, Petitmengin C, Dubeau F, et al. [Seizure prediction: from myth to reality]. *Rev Neurol (Paris).* 2011;167(3):205-15. French.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20934733>  
**Abstract** INTRODUCTION: Clinical, metabolic and electrophysiologic studies suggest the existence of a preictal state, a transition between the interictal state and seizure. STATE OF THE ART: Analysis of the intracranial EEG by mathematical methods shows changes of the brain dynamics several minutes before the occurrence of partial seizures. These modifications can be widespread and not restricted to the epileptogenic focus, which would explain why they can also be detected from scalp EEG. Several scenarios could underlie the preictal state: a progressive recruitment of neurons or a facilitating state with a high probability of seizure occurrence. Because of the high rate of false predictions, no satisfactory method for seizure prediction has been currently proposed. PERSPECTIVES: A European multicenter study (Evolving platform for improving living expectation of patients suffering from Ictal events [EPILEPSIAE]) is currently evaluating a combination of 44 methods applied for EEG and ECG analysis on long-term recordings obtained from a large multicenter database ([www.epilepsiae.eu](http://www.epilepsiae.eu)). CONCLUSION: Combining analyses of multi-level signals including intracranial EEG and microelectrodes, scalp EEG and in vitro electrophysiological studies of post-operative tissues should help clarify brain dynamics during the pre-ictal state.

120. **Shoeb A, Pang T, Guttag J, Schachter S. Non-invasive computerized system for automatically initiating vagus nerve stimulation following patient-specific detection of seizures or epileptiform discharges. *Int J Neural Syst.* 2009;19(3):157-72.**

<http://www.ncbi.nlm.nih.gov/pubmed/19575506>

**Abstract** OBJECTIVE: To demonstrate the feasibility of using a computerized system to detect the onset of a seizure and, in response, initiate Vagus nerve stimulation (VNS) in patients with medically refractory epilepsy. METHODS: We designed and built a non-invasive, computerized system that automatically initiates VNS following the real-time detection of a pre-identified seizure or epileptiform discharge. The system detects these events through patient-specific analysis of the scalp electroencephalogram (EEG) and electrocardiogram (ECG) signals. RESULTS: We evaluated the performance of the system on 5 patients (A-E). For patients A and B the computerized system initiated VNS in response to seizures; for patients C and D the system initiated VNS in response to epileptiform discharges; and for patient E neither seizures nor epileptiform discharges were observed during the evaluation period. During the 81 hour clinical test of the system on patient A, the computerized system detected 5/5 seizures and initiated VNS within 5 seconds of the appearance of ictal discharges in the EEG; VNS did not seem to alter the electrographic or behavioral characteristics of the seizures in this case. During the same testing session the computerized system initiated false stimulations at the rate of 1 false stimulus every 2.5 hours while the subject was at rest and not ambulating. During the 26 hour clinical test of the system on patient B, the computerized system detected 1/1 seizures and initiated VNS within 16 seconds of the appearance of ictal discharges; VNS did not alter the electrographic duration of the seizure but decreased anxiety and increased awareness during the post-seizure recovery phase. During the same testing session the computerized system did not declare any false detections. SIGNIFICANCE: Initiating Vagus nerve stimulation soon after the onset of a seizure may abort or ameliorate seizure symptoms in some patients; unfortunately, a significant number of patients cannot initiate VNS by themselves following the start of a seizure. A system that automatically couples automated detection of seizure onset to initiation of VNS may be helpful for seizure treatment.

121. **Mader EC, Jr., Fisch BJ, Carey ME, Villemarette-Pittman NR. Ictal onset slow potential shifts recorded with hippocampal depth electrodes. *Neurol Clin Neurophysiol.* 2005;2005:4.**

<http://www.ncbi.nlm.nih.gov/pubmed/17139393>

**Abstract** PURPOSE: Reports of direct current shifts at the onset of scalp-recorded seizures prompted us to inspect depth-recorded seizures for the presence of similar slow potential shifts at the onset of the seizure to determine whether slow potential (SP) shifts actually occur at the onset of depth-recorded seizures and if these shifts can facilitate localization of the seizure focus. METHODS: With the low frequency filter "opened" (LLF=0.1 Hz, HLF=70 Hz, 3 dB/octave), 32 seizures recorded with hippocampal depth and subdural electrodes were visually inspected to identify an SP shift at the onset of the seizure. A seizure was considered as having an SP shift when the slow potential waveform was > 1.5 sec in duration and > 100 microV in amplitude. Seizures were obtained from 5 subjects; 4 underwent epilepsy surgery (3=Engel I, 1=Engel II) and one received VNS. SP shift duration, peak voltage and polarity were measured for each seizure. The ability to identify seizures based on SP shift configuration was also evaluated. RESULTS: In 84% of the seizures, ictal onset was associated with a localized SP shift. Shift duration ranged from 1.5 sec to 11.5 sec (96% > 2 sec, 62% > 5 sec). The maximum shift ranged from 139 microV to 2305 microV (mean = 1123 microV, SD = 660 microV). In all the seizures, polarity was positive at the point of maximum shift. By visually examining the SP shift, seizures could be identified as originating from the same focus or from different foci. CONCLUSIONS: The onset of depth-recorded seizures appears to be commonly associated with a localized positive SP shift. An SP shift at the onset of depth-recorded seizures is likely to be a useful visual aid for localizing electrographic seizure onset.

122. **Waterhouse E. New horizons in ambulatory electroencephalography. *IEEE Eng Med Biol Mag.* 2003;22(3):74-80.**

<http://www.ncbi.nlm.nih.gov/pubmed/12845822>

**Notes** Since its inception 30 years ago, ambulatory electroencephalography (AEEG) remains an important tool in epilepsy evaluation, with more sophisticated AEEGs under development. The authors are attempting to link future seizure prediction systems (improved AEEG) with therapeutic intervention to prevent the initiation of a seizure. VNS and deep brain stimulation are discussed as possible therapeutic interventions. The authors' hope is that patients with refractory epilepsy may gain control over their seizures and enjoy significantly improved quality of life.

**Abstract** Since its inception 30 years ago, AEEG has continued to evolve--from four-channel tape recorders to 32-channel digital recorders with sophisticated automatic spike and seizure detection algorithms. AEEG remains an important tool in epilepsy evaluation. In the near future, smaller, faster, and more sophisticated AEEGs will be developed. Seizure detection/anticipation systems will allow the wearer to be forewarned of a seizure so that appropriate safety measures can be taken. With further refinement in our understanding of nonlinear dynamic analysis to define the pre-ictal state, AEEG will be coupled with an accurate seizure anticipation device in a closed-loop system, providing a time window during which therapeutic intervention can occur, to prevent a seizure. The therapeutic intervention will most likely involve vagus nerve or deep brain stimulation. An alternative is that the patient may learn to recognize early symptoms of the pre-ictal state and use behavioral biofeedback interventions to avoid a clinical seizure. In order to achieve convenient ambulatory recording and seizure detection that could realistically improve the lives of patients with refractory epilepsy, the process of miniaturization of such a device to a convenient size must be accomplished. One of the aspects of epilepsy that patients find most frustrating, and that most limits activities, is the vulnerability to sudden unexpected incapacitation due to the occurrence of a seizure. With miniaturization of AEEG and seizure anticipation technology, and advancements in our ability to identify the transition from pre-ictal to ictal state, there is realistic hope that patients with refractory epilepsy may gain control over their seizures and enjoy significantly improved quality of life.

**Status Epilepticus (VNS efficacy in...)**

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- 1. Shorvon S, Ferlisi M. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain*. 2012;135(Pt 8):2314-28.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22577217>  
<http://brain.oxfordjournals.org/content/135/8/2314.long>

**Abstract** In a previous paper, we reviewed the range of therapies available for the treatment of super-refractory status epilepticus. Here we report a review of the outcome of therapies in refractory and super-refractory status epilepticus. Patients (n = 1168) are reported who had therapy with: thiopental, pentobarbital, midazolam, propofol, ketamine, inhalational anaesthetics (isoflurane, desflurane), antiepileptic drugs (topiramate, lacosamide, pregabalin, levetiracetam), hypothermia, magnesium, pyridoxine, immunotherapy, ketogenic diet, emergency neurosurgery, electroconvulsive therapy, cerebrospinal fluid drainage, vagal nerve stimulation and deep brain stimulation. The outcome parameters reported include control of status epilepticus, relapse on withdrawal, breakthrough seizures and mortality. Where reported (596 cases), the long-term outcome was found to be death (35%), severe neurological deficit (13%), mild neurological deficit (13%), undefined deficit (4%) and recovery to baseline (35%). The quality of reported outcome data is generally poor and the number of cases reported for all non-anaesthetic therapies is low. Outcome assessment is complicated by changes in co-medication, delay in response and publication bias. Given these deficits, only broad recommendations can be made regarding optimal therapy. An approach to therapy, divided into first-line, second-line and third-line therapy, is suggested on the basis of this outcome evaluation. The importance of treatments directed at the cause of the status epilepticus, and of supportive ITU care is also emphasized.
  
- 2. Fernandez A, Claassen J. Refractory status epilepticus. *Curr Opin Crit Care*. 2012;18(2):127-31.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22322261>

**Abstract** PURPOSE OF REVIEW: Refractory status epilepticus (RSE) has a high morbidity and mortality. There are currently no definitive data to guide both the optimal choice of therapy and treatment goals. This review focuses on RSE diagnosis and outcome and discusses both commonly used and anecdotal therapies for RSE. RECENT FINDINGS: The challenges in performing randomized controlled trials (RCTs) in neurocritical care and more specifically for the treatment of RSE are illustrated by the early termination of the first RCT of RSE due to low recruitment that compared propofol to barbiturates. Recent case series include the successful treatment of recurrent RSE with ketamine, intravenous lacosamide as an add-on treatment, the use of combination antiepileptics (phenytoin, levetiracetam, and pregabalin), and surgical treatments (vagal nerve and deep brain stimulation) for the control of RSE. SUMMARY: A number of different therapeutic options are available for the treatment of RSE but none have been shown to be superior to others at this point.

3. **Sierra-Marcos A, Maestro I, Rodriguez-Osorio X, Miro J, Donaire A, Aparicio J, et al. Successful outcome of episodes of status epilepticus after vagus nerve stimulation: a multicenter study. *Eur J Neurol.* 2012;19(9):1219-23.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22891774>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1468-1331.2012.03707.x/abstract>  
**Abstract** BACKGROUND AND PURPOSE: Vagus nerve stimulation (VNS) has been reported to be a safe and effective treatment for drug-resistant epilepsy. The aim of this study is to describe the effect of VNS in patients with a history of repeated episodes of status epilepticus (SE) before implantation. METHODS: From a total of 83 adult patients with drug-resistant epilepsy who had VNS implanted in four tertiary centers in Spain between 2000 and 2010, eight had a previous history of repeated episodes of SE. We performed a retrospective observational study analyzing the outcome of seizures and episodes of SE after implantation. Stimulation was started at the usual settings, and intensity increased according to clinical response and tolerability. RESULTS: Regarding the eight patients with a history of SE, the mean age at time of VNS implantation was 25.1 [14-40] years. Duration of epilepsy until the implantation was 21.7 [7-39.5] years, and they had been treated with a mean of 12 antiepileptic drugs [10-16]. Mean follow-up since implantation was 4.15 [2-7.5] years. Average seizure frequency decreased from 46 to 8.2 per month. Interestingly, four of the eight patients remained free of new episodes of SE after implantation, and in two additional patients, the frequency decreased by >75%. Adverse effects were mild or moderate in intensity and included mainly coughing and dysphonia. CONCLUSION: In those patients with refractory epilepsy and history of SE who are not surgical candidates, VNS is a safe and effective method to reduce seizure frequency and episodes of SE.
4. **Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain.* 2011;134(Pt 10):2802-18.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21914716>  
<http://brain.oxfordjournals.org/content/134/10/2802.full.pdf>  
**Abstract** Super-refractory status epilepticus is defined as status epilepticus that continues or recurs 24 h or more after the onset of anaesthetic therapy, including those cases where status epilepticus recurs on the reduction or withdrawal of anaesthesia. It is an uncommon but important clinical problem with high mortality and morbidity rates. This article reviews the treatment approaches. There are no controlled or randomized studies, and so therapy has to be based on clinical reports and opinion. The published world literature on the following treatments was critically evaluated: anaesthetic agents, anti-epileptic drugs, magnesium infusion, pyridoxine, steroids and immunotherapy, ketogenic diet, hypothermia, emergency resective neurosurgery and multiple subpial transection, transcranial magnetic stimulation, vagal nerve stimulation, deep brain stimulation, electroconvulsive therapy, drainage of the cerebrospinal fluid and other older drug therapies. The importance of treating the identifying cause is stressed. A protocol and flowchart for managing super-refractory status epilepticus is suggested. In view of the small number of published reports, there is an urgent need for the establishment of a database of outcomes of individual therapies.
5. **Walker MC. The potential of brain stimulation in status epilepticus. *Epilepsia.* 2011;52 Suppl 8:61-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21967366>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2011.03240.x/asset/j.1528-1167.2011.03240.x.pdf?v=1&t=hfzrb586&s=fa3a04abce772de46c4cb64c28410ad0ec5b88f4>  
**Abstract** There is a long history of the use of brain stimulation in the treatment of epilepsy but relatively little experience for its use in status epilepticus. Electroconvulsive therapy, transcranial magnetic stimulation, subcortical and cortical stimulation have all been tried with varying degrees of success in single cases or small case series. It remains unclear, however, which brain areas should be stimulated and the parameters that should be used. Moreover, the aim (stopping status epilepticus) is different from preventing seizures and so the brain areas and parameters that are useful in epilepsy may not directly translate to the treatment of status epilepticus.

6. **O'Neill BR, Valeriano J, Synowiec A, Thielmann D, Lane C, Wilberger J. Refractory status epilepticus treated with vagal nerve stimulation: case report. *Neurosurgery*. 2011;69(5):E1172-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21577172>  
**Abstract** BACKGROUND AND IMPORTANCE: Status epilepticus (SE) refractory to medical treatment has a high mortality rate and few effective treatments. CLINICAL PRESENTATION: We describe the implantation of a vagal nerve stimulator to help terminate a case of refractory SE. A 23-year-old man was in SE for 3 weeks without being able to be weaned from intravenous anesthetic agents. After implantation of a vagal nerve stimulator, SE soon terminated, and the patient could be weaned from sedative agents and made a full recovery. CONCLUSION: Vagal nerve stimulator should be considered in cases of refractory SE.
  
7. **Carreno M, Garcia-Alvarez D, Maestro I, Fernandez S, Donaie A, Boget T, et al. Malignant autosomal dominant frontal lobe epilepsy with repeated episodes of status epilepticus: successful treatment with vagal nerve stimulation. *Epileptic Disord*. 2010;12(2):155-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20478764>  
**Abstract** Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a familial partial epilepsy syndrome characterized by seizures suggesting a frontal lobe origin occurring predominantly during sleep. Up to a third of patients may have refractory seizures, with repeated episodes of status epilepticus, intellectual disability of variable degree and psychiatric disturbances. We report a patient with ADNFLE, refractory seizures and repeated episodes of life-threatening convulsive status epilepticus who underwent prolonged video-EEG monitoring and was implanted with a vagal nerve stimulator. At 3.5 years of follow-up, a decrease of more than 80% in seizure frequency was achieved, episodes of status were completely controlled and he displayed improved mood and alertness. Vagal nerve stimulation may be considered as therapy for patients with refractory epilepsies of genetic cause, as well as repeated status epilepticus.
  
8. **Garcia-Penas JJ. [Neurocognitive dysfunction in electrical status epilepticus during slow-wave sleep syndrome: Can the natural course of the syndrome be modified with early pharmacological treatment?]. *Rev Neurol*. 2010;50 Suppl 3:S37-47. Spanish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20200847>  
**Abstract** INTRODUCTION: Epileptic syndromes with continuous spike wave in slow-wave sleep (CSWS), including electrical status epilepticus in sleep (ESES) and Landau-Kleffner syndrome, are true epileptic encephalopathies where sustained epileptic activity is related to cognitive and behavioural decline. AIMS: To review the natural course of ESES, to define the general principles of treatment of epileptic syndromes with CSWS, to delineate the different options that are currently available for treating these epileptic encephalopathies, and to analyze the prognostic factors linked to pharmacological treatment of ESES. DEVELOPMENT: Epileptic syndromes with CSWS are initially treated with a pharmacologic intervention with polytherapy of antiepileptic drugs in most cases. However, due to the poor response that CSWS often have to antiepileptic drugs, non-pharmacologic treatment options are an important part of a comprehensive treatment plan for this group of children. This article discusses the use of corticosteroids, intravenous immunoglobulins, ketogenic diet, vagus nerve stimulation, and epilepsy surgery in the treatment of patients with epileptic syndromes with CSWS. CONCLUSIONS: Treatment of ESES extends beyond just control of the seizures; amelioration of the continuous epileptiform discharge must occur to improve neuropsychological outcome. There is a significant correlation between the length of the ESES period and the extent of residual intellectual deficit at follow-up. According to this knowledge, there is a well defined therapeutic interval where our different strategies of treatment may be useful, and the upper limits of this time frame to a critical period of 12-18 months.

9. **De Herdt V, Waterschoot L, Vonck K, Dermaut B, Verhelst H, Van Coster R, et al. Vagus nerve stimulation for refractory status epilepticus. *Eur J Paediatr Neurol.* 2009;13(3):286-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18585939>  
**Abstract** We report on the long-term follow-up of a patient with refractory non-convulsive SE who was successfully treated with VNS. A 7-year old girl with a medical history of thrombosis in the right internal cerebral vein and right thalamic bleeding 8 days after birth, developed epilepsy at the age of 13 months. At the age of 6 she presented with a refractory non-convulsive SE. A vagus nerve stimulator was placed after 11 days of thiopental-induced coma. Three days after VNS implantation, the thiopental-induced coma was successfully withdrawn and electroencephalography showed normalization one week after start of VNS. After a follow-up of 13 months she remains seizure-free and AEDs have been partially tapered. This case illustrates a potential acute abortive effect with sustained long-term seizure reduction of VNS in a 7-year old girl who presented with refractory non-convulsive SE.
10. **Robakis TK, Hirsch LJ. Literature review, case report, and expert discussion of prolonged refractory status epilepticus. *Neurocrit Care.* 2006;4(1):35-46.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16498194>  
<http://link.springer.com/article/10.1385%2FNCC%3A4%3A1%3A035>  
**Abstract** We report the case of a 30-year-old woman with severe, prolonged refractory status epilepticus requiring more than 6 months of iatrogenic coma. Opinions on prognosis and clinical management were solicited from a number of experienced neurointensivists and epileptologists at multiple time-points during the clinical course. The ensuing discussion, annotated with references, is presented here. Several experts commented on isolated cases of young patients with encephalitis requiring up to 2-3 months of iatrogenic coma, yet still having good outcomes. Treatments discussed include ketamine, gammaglobulin, plasmapheresis, steroids, adrenocorticotrophic hormone, very high-dose phenobarbital, isoflurane, lidocaine, electroconvulsive therapy, ketogenic diet, hypothermia, magnesium, transcranial magnetic stimulation, vagus nerve stimulation, deep brain stimulation, and neurosurgery. The patient eventually suffered a cardiac arrest but was resuscitated as requested by the family. Seizures then stopped, and the patient has remained in a persistent vegetative state since.
11. **Patwardhan RV, Dellabadia J, Jr., Rashidi M, Grier L, Nanda A. Control of refractory status epilepticus precipitated by anticonvulsant withdrawal using left vagal nerve stimulation: a case report. *Surg Neurol.* 2005;64(2):170-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16051017>  
**Abstract** OBJECTIVE: To describe a case of left vagal nerve stimulation (VNS) resulting in immediate cessation of status epilepticus (SE) with good neurological outcome. CASE DESCRIPTION: A 30-year-old man with medically intractable seizures including episodes of SE was successfully treated using left VNS. After requiring discontinuation of phenytoin, valproic acid, carbamazepine, and topiramate because of severe allergic reactions resembling Stevens-Johnson syndrome, the patient required pentobarbital coma along with phenobarbital, tiagabine, and levetiracetam for seizure frequency reduction. He underwent left vagal nerve stimulator placement after nearly 9 days of barbiturate-induced coma, with stimulation initiated in the operating room. On the following day, electroencephalography revealed resolution of previously observed periodic lateral epileptiform discharges and the patient was free of seizures. Prestimulation seizure frequency was recorded at 59 times a day, with some seizures enduring 45 minutes despite barbiturate coma. Poststimulation, the patient has been free of seizures for 19 days and is presently taking only levetiracetam and phenobarbital, from which he continues to be successfully weaned without seizures. He is awake, alert, and can recall events leading up to his seizures, with good long-term memory and residual left upper extremity and lower extremity weakness. CONCLUSION: This case illustrates the role of left vagal stimulation in the treatment of SE and otherwise medically intractable seizures caused by allergic reactions. To our knowledge, this is the first case in the world literature for adults reporting cessation of SE after VNS. Another case with a similar improvement has been reported in the pediatric population.

12. **Winston KR, Levisohn P, Miller BR, Freeman J. Vagal nerve stimulation for status epilepticus. *Pediatr Neurosurg.* 2001;34(4):190-2.**

<http://www.ncbi.nlm.nih.gov/pubmed/11359111>

<http://www.karger.com/Article/FullText/56018>

**Notes** This is a case report discussing the immediate cessation of generalized convulsive status epilepticus upon initiation of VNS Therapy in a 13-year-old boy. The patient had suffered from uncontrolled seizures since the age of 3 years despite multiple AED therapies, treatment with the ketogenic diet, and a 90% anterior corpus callosotomy. Upon admittance to the hospital, the patient was having nearly continuous, asymmetric, tonic seizures with clonic episodes occurring every 3-10 minutes and was in poor and deteriorating health. Withdrawal of supportive medical care was considered. VNS Therapy was tried as a last resort, with no reappearance of status epilepticus after implantation and activation of the stimulator. The patient steadily became more alert and interactive and the magnet was able to abort seizures. The patient experienced a significant improvement in quality of life. The authors conclude that VNS Therapy should be considered as part of the therapeutic armamentarium for treatment refractory status epilepticus, which is associated with approximately a 20% mortality rate.

**Abstract** Refractory generalized convulsive status epilepticus in a 13-year-old boy was halted by left vagal nerve stimulation. Over the next 1.5 years, seizures have continued at a rate and severity which is significantly better than it had been in the year before insertion of the stimulator.

**SUDEP**

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- 1. Lamberts RJ, Laranjo S, Kalitzin SN, Velis DN, Rocha I, Sander JW, et al. Postictal generalized EEG suppression is not associated with periictal cardiac autonomic instability in people with convulsive seizures. *Epilepsia*. 2013;54(3):523-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23157655>  
<http://onlinelibrary.wiley.com/store/10.1111/epi.12021/asset/epi12021.pdf?v=1&t=hfzqa1o&s=c25056a8376bef6ea54edcb55ce4a279e57c3ecc>

**Abstract** PURPOSE: Postictal generalized EEG suppression (PGES) seems to be a pathophysiologic hallmark in ictal recordings of sudden unexpected death in epilepsy (SUDEP). It has recently been suggested that presence and duration of PGES might be a predictor of SUDEP risk. Little is known about the etiology of PGES. METHODS: We conducted a retrospective case-control study in 50 people with convulsive seizures (CS) recorded on digital video-electroencephalography (EEG). One CS per individual was reviewed for presence and duration of PGES by two independent observers: Preictal and postictal heart rate (HR) (1 min before seizure onset and 1, 3, 5, 15, and 30 min after seizure end) and frequency domain measures of heart rate variability (HRV), including the ratio of low frequency (LF) versus high frequency (HF) power, were analyzed. The relationship between PGES and periictal autonomic changes was evaluated, as well as its association with several clinical variables. KEY FINDINGS: Thirty-seven individuals (74%) exhibited PGES and 13 (26%) did not. CS resulted in a significant increase of periictal HR and the LF/HF ratio. PGES was associated with neither periictal HR (mean HR difference between PGES+ and PGES- seizures: -2 beats per minute [bpm], 95% confidence interval [CI] -10 to +6 bpm) nor HRV change. There was no association between the duration of PGES and periictal HR change. People with PGES were more likely to be asleep before seizure onset (odds ratio [OR] 4.7, 95% CI 1.2-18.3) and had a higher age of onset of epilepsy (median age 15 vs. 4 years). SIGNIFICANCE: PGES was not associated with substantial changes in measures of cardiac autonomic instability but was more prevalent in CS arising from sleep.
  
- 2. Spatola M, Jeannet PY, Pollo C, Wider C, Labrum R, Rossetti AO. Effect of vagus nerve stimulation in an adult patient with dravet syndrome: contribution to sudden unexpected death in epilepsy risk reduction? *Eur Neurol*. 2013;69(2):119-21.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23207687>  
<http://www.karger.com/Article/PDF/345132>

**Abstract** We report on a patient who developed, from 5 months of age, multiple seizure types, including myoclonic, associated with severe psychomotor delay, leading to the diagnosis of Dravet syndrome. Over the years, he developed refractory epilepsy and was implanted with a vagus nerve stimulator at the age of 19. After 3 months, he experienced a progressive improvement of partial and generalized seizures, with a >90% reduction, and better alertness. This meaningful clinical improvement is discussed in the light of the sudden unexpected death in epilepsy risk, which is high in this setting, and seems remarkably diminished in our patient in view of the reduction of generalized convulsions.

3. **Damasceno DD, Savergnini SQ, Gomes ER, Guatimosim S, Ferreira AJ, Doretto MC, et al. Cardiac dysfunction in rats prone to audiogenic epileptic seizures. *Seizure*. 2013;22(4):259-66.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23340275>  
**Abstract** PURPOSE: Cardiac dysfunction is one of the possible causes of sudden unexpected death in epilepsy (SUDEP). Therefore, the objective of this study was to evaluate cardiac and electrocardiographic parameters in rats with audiogenic epileptic seizures (WAR - Wistar audiogenic rats). METHODS: In vivo arterial pressure, heart rate (HR), autonomic tone and electrocardiography (ECG) were measured in awake animals in order to examine cardiac function and rhythm. Ex vivo, the Langendorff technique was used to analyze the cardiac function and the severity of reperfusion arrhythmias. In vitro, confocal microscopy was used to evaluate calcium transient parameters of isolated ventricular cardiomyocytes. RESULTS: In vivo autonomic tone evaluation revealed enhanced sympathetic activity, changes in cardiac function with increased systolic arterial pressure and higher basal HR in WAR. In addition, ECG analysis demonstrated electrical alterations with prolongation of the QT interval and QRS complex in these animals. Ex vivo, we observed a decrease in systolic tone and HR and an increase in the duration of ischemia/reperfusion arrhythmias in WAR. Moreover, intracellular Ca(2+) handling analysis revealed an increase in the peak of calcium and calcium transient decay in audiogenic rats. Treatment with atenolol (beta1-adrenergic antagonist) normalized the systolic tone, reduced cardiac hypertrophy and the associated increase in the susceptibility to reperfusion arrhythmias observed in WAR. CONCLUSION: We present evidence that chronic disturbances in sympathetic tone in WAR cause increases the risk to life-threatening arrhythmias. Our results support a relationship between seizures, cardiac dysfunction and cardiac arrhythmias, which may contribute to the occurrence of SUDEP.
4. **Sprimont P, Ossemann M, Blommaert D. Brain controls the heart: a case of ictal asystole. *Acta Cardiol*. 2012;67(5):589-92.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23252011>  
**Abstract** Ictal asystole is a rare complication of epileptic seizures and is frequently unrecognized by non-neurologists. We describe a case of ictal asystole as first clinical manifestation of unknown temporal lobe epilepsy and we discuss epidemiologic, pathophysiologic and therapeutic features.
5. **Terra VC, Nisyiama MA, Abrao J, Sakamoto AC, Machado HR, Arida RM, et al. Epileptologists probe vagus nerve stimulation in children with refractory epilepsy: a promise against sudden unexpected death in epilepsy. *Arq Neuropsiquiatr*. 2012;70(12):953-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23295425>  
<http://www.scielo.br/pdf/anp/v70n12/10.pdf>  
**Abstract** It is clear that sudden unexpected death in epilepsy (SUDEP) is mainly a problem for people with refractory epilepsy, but our understanding of the best way to its prevention is still incomplete. Although the pharmacological treatments available for epilepsies have expanded, some antiepileptic drugs are still limited in clinical efficacy. In the present paper, we described an experience with vagus nerve stimulation (VNS) treatment by opening space and providing the opportunity to implement effective preventative maps to reduce the incidence of SUDEP in children and adolescents with refractory epilepsy.

6. **Sieweke N, Allendorfer J, Franzen W, Feustel A, Reichenberger F, Pabst W, et al. Cardiac Troponin I elevation after epileptic seizure. *BMC Neurol.* 2012;12:58.**

<http://www.ncbi.nlm.nih.gov/pubmed/22804867>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3517409/pdf/1471-2377-12-58.pdf>

**Abstract** BACKGROUND: Cardiac troponin-I (cTNI) is highly specific biomarker to prove myocardial damage, e.g. in acute coronary syndrome (ACS). However, it occurs in other conditions as well. We therefore analysed cTNI increase in patients after generalized convulsive seizure. METHODS: Consecutive patients admitted with acute generalized convulsive seizure were included in case of cTNI measurement on admission. Among 898 selected cases, 53 patients were referred secondary to our department; in 845 cases cTNI measurements on admission were available. In case of multiple admissions (81 cases), only the first admission entered our analysis. In 17 patients elevated cTNI was determined due to ACS; in one patient a myocarditis was found. 5 patients suffered of relevant renal insufficiency. Finally 741 patients were included in the analysis. A cTNI cut-off level of  $\geq 0.1$  ng/ml was considered. Factors associated with a cTNI increase were analysed subsequently. RESULTS: The mean age of the study population (n = 741) was 47.8 years (SD  $\pm$  18.6), 40.9% were female. In 50 patients (6.7%) a cTNI elevation of unknown origin was found; no obvious cardiac involvement could be detected in these patients who all remained asymptomatic. A vascular risk profile (including at least hypertension, hypercholesterolemia or diabetes) (OR = 3.62; CI: 1.59 to 8.21; p = 0.001) and elevated creatine kinase on admission (OR = 2.36; CI: 1.26 to 4.39; p = 0.002) were independent factors associated with cTNI release. CONCLUSION: cTNI release occurs in patients with generalized convulsive seizure with predominance in patients with vascular risk profile.

7. **Agostini SD, Aniles E, Sirven J, Drazkowski JF. The importance of cardiac monitoring in the epilepsy monitoring unit: a case presentation of ictal asystole. *Neurodiagn J.* 2012;52(3):250-60.**

<http://www.ncbi.nlm.nih.gov/pubmed/23019762>

**Abstract** Ictal asystole may be a potent marker for epilepsy patients at high risk for sudden unexpected death in epilepsy (SUDEP). The use of inpatient long-term video-electroencephalographic (VEEG) monitoring coupled with simultaneous continuous cardiac telemetry is an important tool to detect ictal asystole as well as other significant ictal cardiac arrhythmias. In this paper a case of ictal asystole detected during VEEG is presented. Routine 12-lead EKG was normal upon admission. After antiepileptic medication was tapered, the patient had a typical complex partial seizure with oral automatisms at onset followed by secondary generalization. Ictal onset was noted in left temporal lobe with subsequent spread to the right temporal region. A 20 second period of asystole began just prior to the secondary generalization. During this admission the patient underwent a potentially life-saving pacemaker implantation. The use of cardiac telemetry and baseline EKG are suggested for patients admitted into epilepsy monitoring units as part of the standard epilepsy monitoring protocol.

8. **Velagapudi P, Turagam M, Laurence T, Kocheril A. Cardiac arrhythmias and sudden unexpected death in epilepsy (SUDEP). *Pacing Clin Electrophysiol.* 2012;35(3):363-70.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22126214>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1540-8159.2011.03276.x/abstract>  
**Abstract** Sudden unexpected death in epilepsy (SUDEP) is a major clinical problem in epilepsy patients in the United States, especially those with chronic, uncontrolled epilepsy. Several pathophysiological events contributing to SUDEP include cardiac arrhythmias, respiratory dysfunction, and dysregulation of systemic or cerebral circulation. There is a significant body of literature suggesting the prominent role of cardiac arrhythmias in the pathogenesis of SUDEP. There is evidence to say that long-standing epilepsy can cause physiological and anatomical autonomic instability resulting in life-threatening arrhythmias. Tachyarrhythmias, bradyarrhythmias, and asystole are commonly seen during ictal, interictal, and postictal phase in epilepsy patients. It is unclear if these rhythm disturbances need attention as some of them may be just benign findings. Evidence regarding prolonged cardiovascular monitoring or the benefit of pacemaker/defibrillator implantation for primary or secondary prevention in epilepsy patients is limited. Awareness regarding pathophysiology, cardiac effects, and management options of SUDEP will become useful in guiding more individualized treatment in the near future. (PACE 2011; 1-8).
9. **Stahli C, Muller F, Krause M. [Seizure by asystole or asystole by seizure?]. *Ther Umsch.* 2012;69(12):693-5. German.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23188781>  
**Abstract** A 75 years old man is suffering from recurrent seizures since several years. The seizures start with vegetative symptoms including tingling sensations, followed by a deep feeling of eternity and happiness. In one third of the cases he loses consciousness completely. Several workups have failed to reveal a diagnosis. An ECG loop recorder was implanted which finally revealed an asystole of 15 seconds duration. It was thought that this caused cerebral hypoxia which was triggering focal seizures. A pacemaker was inserted. The attacks of unconsciousness disappeared; however, the spells of vegetative sensations persisted. After antiepileptic treatment was initiated the symptoms improved, however it was not possible to achieve complete control. Is this patient primarily suffering from recurrent asystole or from epilepsy which causes complex seizures with disturbance of cardiac rhythm? The latter phenomenon in its most extreme presentation is better known as sudden unexplained death in epilepsy (SUDEP). The diagnostic approach and therapy of both diseases are discussed.
10. **Pinto KG, Scorza FA, Arida RM, Cavalheiro EA, Martins LD, Machado HR, et al. Sudden unexpected death in an adolescent with epilepsy: all roads lead to the heart? *Cardiol J.* 2011;18(2):194-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21432828>  
**Abstract** The incidence of sudden unexpected death in epilepsy (SUDEP) has been estimated from 0.5-1.4/1,000 person-years in people with treated epilepsy, and 9/1,000 person-years in candidates for epilepsy surgery. Potential risk factors for SUDEP include: age, early onset of epilepsy, duration of epilepsy, uncontrolled seizures, seizure type and winter temperatures. The arrhythmogenic side-effect of antiepileptic drugs and seizures may increase the risk of SUDEP. In this report, we describe a patient with prolonged post-ictal tachycardia in EEG video recordings with a typical case of SUDEP: a 16-year-old boy with medically intractable complex partial seizures. Magnetic resonance imaging revealed left mesial temporal sclerosis. During non-invasive video-EEG monitoring, the patient presented a post-ictal heart rate increased for five hours. Two months after video-EEG, he died from SUDEP during a tonic-clonic secondary generalized seizure. The possibility of cardiac involvement in the pathogenesis of SUDEP has been suggested by many studies. Evaluation of this patient with EEG-video monitoring, including measurement of heart rate, contributed to an identification of ictal tachycardia that may have played a role in the SUDEP. Premature mortality seems to be increased in patients with epilepsy, and cardiac abnormalities may be a possible cause of SUDEP.

11. **Burghaus L, Fink GR, Erdmann E, Muller-Ehmsen J. [Epileptic seizures: effects on cardiac function]. *Dtsch Med Wochenschr.* 2011;136(7):315-9. German.**

<http://www.ncbi.nlm.nih.gov/pubmed/21302206>

**Abstract** Sudden loss of consciousness can be caused by syncope or epileptic seizure, which therefore requires a diagnostic work-up including cardiological and neurological examinations. Thus, in clinical practice cooperation of these two medical specialties is common and of high relevance. Seizures may lead to cardiac arrhythmia or ictal asystole, and "sudden unexpected death in epilepsy" (SUDEP) is an important field of epilepsy research. Cardiac channelopathies such as long QT syndrome may be associated with seizures, suggesting a possible link between cardiac and cerebral channelopathy. We here review in detail cardiac effects due to epileptic seizures as well as possible pathogenetic correlations between cardiac and epileptic diseases.

12. **Seyal M, Pascual F, Lee CY, Li CS, Bateman LM. Seizure-related cardiac repolarization abnormalities are associated with ictal hypoxemia. *Epilepsia*. 2011;52(11):2105-11.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21906052>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2011.03262.x/asset/j.1528-1167.2011.03262.x.pdf?v=1&t=hekim2l6&s=1dfe617a09a7f7dc8699bc9f637b10825639f061>  
**Abstract** PURPOSE: Cardiac arrhythmias and respiratory disturbances have been proposed as likely causes for sudden unexpected death in epilepsy. Oxygen desaturation occurs in one-third of patients with localization-related epilepsy (LRE) undergoing inpatient video-electroencephalography (EEG) telemetry (VET) as part of their presurgical workup. Ictal-related oxygen desaturation is accompanied by hypercapnia. Both abnormal lengthening and shortening of the corrected QT interval (QTc) on electrocardiography (ECG) have been reported with seizures. QTc abnormalities are associated with increased risk of sudden cardiac death. We hypothesized that there may be an association between ictal hypoxemia and cardiac repolarization abnormalities. METHODS: VET data from patients with refractory LRE were analyzed. Consecutive patients having at least one seizure with accompanying oxygen desaturation below 90% and artifact-free ECG data were selected. ECG during the 1 min prior to seizure onset (PRE) and during the ictal/postictal period with accompanying oxygen desaturation below 90% (DESAT) was analyzed. Consecutive QT and RR intervals were measured. In the same patients, DESAT seizures were compared with seizures without accompanying oxygen desaturation below 90% (NODESAT). For NODESAT seizures, QT and RR intervals for 2 min after seizure onset were measured. KEY FINDINGS: Thirty-seven DESAT seizures were analyzed in 17 patients with localization-related epilepsy. A total of 2,448 QT and RR intervals were analyzed during PRE. During DESAT, 1,554 QT and RR intervals were analyzed. Twelve of the 17 patients had at least one NODESAT seizure. A total of 19 NODESAT seizures were analyzed, including 1,558 QT and RR intervals during PRE and 3,408 QT and RR intervals during NODESAT. The odds ratio for an abnormally prolonged (>457 ms) QTcH (Hodges correction method) during DESAT relative to PRE was 10.64 ( $p < 0.0001$ ). The odds ratio for an abnormally shortened (<372 ms) QTcH during DESAT relative to PRE was 1.65 ( $p < 0.0001$ ). Seizure-related shortening and prolongation of QTc during DESAT were also observed when Fridericia correction of the QT was applied. During DESAT seizures, the mean range of QT values (QTr) (61.14 ms) was significantly different from that during PRE (44.43 ms) ( $p = 0.01$ ). There was a significant association between DESAT QTr and oxygen saturation nadir ( $p = 0.025$ ) and between DESAT QTr and duration of oxygen desaturation ( $p < 0.0001$ ). Both QTcH prolongation and shortening also occurred with NODESAT seizures. A seizure-associated prolonged QTcH was more likely during DESAT than NODESAT, with an odds ratio of 4.30 ( $p < 0.0001$ ). A seizure-associated shortened QTcH was more likely during DESAT than NODESAT with an odds ratio of 2.13 ( $p < 0.0001$ ). SIGNIFICANCE: We have shown that the likelihood of abnormal QTcH prolongation is increased 4.3-fold with seizures that are associated with oxygen desaturation when compared with seizures that are not accompanied with oxygen desaturation. The likelihood of abnormally shortened QTcH increases with seizures that are accompanied by oxygen desaturation with an odds ratio of 2.13 compared with that in seizures without desaturations. There is a significant association between the depth and duration of oxygen desaturation and QTr increase. These findings may be related to the pathophysiology of SUDEP.
13. **Scorza FA, Cavalheiro EA, Arida RM, Cukiert A. Sudden unexpected death in epilepsy: uncovering the magic in hippocampal deep brain stimulation. *Epilepsy Behav*. 2011;21(4):492-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21700500>
14. **Kanner AM. Peri-Ictal Cardiac and Respiratory Disturbances in Epilepsy: Incidental Finding or Culprit of SUDEP. *Epilepsy Curr*. 2011;11(1):16-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21852861>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3063570/pdf/epcu-11-1-16.pdf>

15. **Suorsa E, Korpelainen JT, Ansakorpi H, Huikuri HV, Suorsa V, Myllyla VV, et al. Heart rate dynamics in temporal lobe epilepsy-A long-term follow-up study. *Epilepsy Res.* 2011;93(1):80-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21093218>  
**Abstract** The aim of the present study was to prospectively evaluate long-term changes in interictal heart rate variability (HRV) in patients with temporal lobe epilepsy (TLE). A 24-h ECG was recorded at baseline and after a mean follow-up of 6.1 years in 18 patients with refractory TLE and 18 patients with well-controlled TLE. After the follow-up, the Poincare components SD(1) ( $p=0.039$ ) and SD(2) ( $p=0.001$ ) were decreased in patients with refractory TLE compared to baseline, whereas in patients with well-controlled TLE no changes ( $p>0.05$ ) in HR variability were observed. The reduction in HRV seems to be progressive in patients with chronic refractory TLE with recurrent seizures.
16. **Irsel Tezer F, Saygi S. The association of cardiac asystole with partial seizures: does it result from ictal or interictal activity? *Epilepsy Res.* 2011;96(1-2):180-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21632212>  
**Abstract** Bradycardia or asystole that occur during some seizures may be life threatening as a leading cause of SUDEP. A patient with right and left temporal lobe onset seizures and preceding bradycardia or asystole is presented. He had bilateral hippocampal atrophy on MRI. The unreliability of ictal bradycardia or asystole as a lateralizing sign in patients with partial epilepsy and the role of interictal autonomic activity in heart rate changes during seizures are discussed.
17. **Bassareo PP, Bassareo V, Manca D, Fanos V, Mercurio G. An old drug for use in the prevention of sudden infant unexpected death due to vagal hypertonia. *Eur J Pediatr.* 2011;170(12):1569-75.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21814782>  
<http://link.springer.com/article/10.1007%2Fs00431-011-1544-0>  
**Abstract** Reflex vagal hypertonia (RVH) has been identified as a possible cause of sudden unexpected death in infants during the first year of life. Homatropine methylbromide (HM) is an anticholinergic drug known to inhibit muscarinic acetylcholine receptors, thus affecting the parasympathetic nervous system. The aim of the present study was to investigate the effects of HM on 24-h Holter electrocardiographic signs of RVH (pre-HM treatment vs post-HM treatment; post-HM treatment vs a control group of healthy infants). A total of 50 patients (mean age, 6.1 +/- 2.7 months; 28 males, 22 females; 12 born pre-term) affected by RVH were enrolled in the study. Pre-HM treatment vs post-HM treatment: statistically significant differences were detected for higher heart rate, lower heart rate, mean heart rate, longer sinusual pause, presence of advanced atrio-ventricular blocks, and systolic blood pressure ( $p < 0.001$ ,  $p < 0.00001$ ,  $p < 0.02$ ,  $p < 0.00001$ ,  $p < 0.05$ , and  $p < 0.04$ , respectively). A statistically significant correlation was revealed between HM-administered dose and both average heart rate and systolic blood pressure ( $r = 0.93$ ,  $p < 0.0001$ ;  $r = 0.94$ ,  $p < 0.0001$ , respectively). No significant differences were detected between post-HM treatment electrocardiographic data and those of the control group. By antagonizing action of the vagus nerve of the parasympathetic system on the heart, thus increasing cardiac frequency, HM treatment appears to feature a good safety profile and be highly effective in preventing transient infantile hypervagotonia, the potential cause of several cases of sudden unexpected death during the first year of life.

18. **Shorvon S, Tomson T. Sudden unexpected death in epilepsy. *Lancet*. 2011;378(9808):2028-38.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21737136>  
**Abstract** Sudden unexpected death in epilepsy (SUDEP) refers to the sudden death of a seemingly healthy individual with epilepsy, usually occurring during, or immediately after, a tonic-clonic seizure. The frequency of SUDEP varies depending on the severity of the epilepsy, but overall the risk of sudden death is more than 20 times higher than that in the general population. Several different mechanisms probably exist, and most research has focused on seizure-related respiratory depression, cardiac arrhythmia, cerebral depression, and autonomic dysfunction. Data from a pooled analysis of risk factors indicate that the higher the frequency of tonic-clonic seizures, the higher the risk of SUDEP; furthermore, risk of SUDEP is also elevated in male patients, patients with long-duration epilepsy, and those on antiepileptic polytherapy. SUDEP usually occurs when the seizures are not witnessed and often at night. In this Seminar, we provide advice to clinicians on ways to minimise the risk of SUDEP, information to pass on to patients, and medicolegal aspects of these deaths.
19. **Lanz M, Oehl B, Brandt A, Schulze-Bonhage A. Seizure induced cardiac asystole in epilepsy patients undergoing long term video-EEG monitoring. *Seizure*. 2011;20(2):167-72.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21183363>  
[http://ac.els-cdn.com/S1059131110003006/1-s2.0-S1059131110003006-main.pdf?\\_tid=c46daff2-9278-11e2-83d3-0000aacb35f&acdnat=1363905996\\_2e243e1a1618c3e89c8b9605c1169dbb](http://ac.els-cdn.com/S1059131110003006/1-s2.0-S1059131110003006-main.pdf?_tid=c46daff2-9278-11e2-83d3-0000aacb35f&acdnat=1363905996_2e243e1a1618c3e89c8b9605c1169dbb)  
**Abstract** Ictal-related cardiac asystole is supposed to be a risk factor for sudden unexpected death in epilepsy (SUDEP). We retrospectively analyzed the occurrence of ictal asystole in 2003 epilepsy patients undergoing long-term video EEG/ECG monitoring from 1/1999 to 6/2010 at the Freiburg epilepsy centre. Seven patients had cardiac arrest with a duration of at least 3s; 6 ictal, one postictal. In all patients, the temporal lobe was involved in ictal activity based on neurophysiological investigations or morphological lesion. Whereas asystole was self-limited in six cases, one patient with insular seizure origin had to undergo cardiopulmonary resuscitation. Interestingly, also patients with a short history of epilepsy, low seizure frequency and under treatment in monotherapy showed episodes of asystole. In all cases, even with brief cardiac arrest, asystole was associated with subsequent EEG flattening. In conclusion, ictal asystole is a rare event even in a population undergoing major changes in antiepileptic medication. Temporal lobe epilepsy was associated with a risk for asystole; cardiac arrest also occurred in patients who, based on their history, might have not been considered at elevated risk for SUDEP.
20. **Serafini A, Gelisse P, Reana V, Crespel A. Cardiac asystole during a cluster of right temporo-parietal seizures. *Seizure*. 2011;20(2):181-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21112225>  
**Abstract** Ictal bradycardia and asystole can appear during an epileptic seizure. They must be promptly recognized and treated due to their potential life threatening consequences. Indeed, they have been implicated in the pathogenesis of sudden unexpected death in epilepsy (SUDEP). We report the case of a 33 year-old woman with a right temporo-parietal lobe epilepsy who presented a 19 s asystole during a cluster of seizures. Careful interview revealed appearance of numerous episodes of fall in the previous years. The patient underwent cardiological investigations including echocardiography and His bundle electrography that resulted to be normal. A pacemaker was immediately implanted and, although she continued presenting seizures, no more episodes of falls occurred. In order to better preview ictal asystole several risk factors need to be searched. Attention should be paid to an accurate medical history (ask for episodes of falls) and a simultaneous ECG/EEG recording. The occurrence of bradycardia during a seizure should lead to further cardiological investigations. This could help preventing the occurrence of dramatic consequences such as traumatic falls or SUDEP.

21. **Surges R, Taggart P, Sander JW, Walker MC. Too long or too short? New insights into abnormal cardiac repolarization in people with chronic epilepsy and its potential role in sudden unexpected death. *Epilepsia*. 2010;51(5):738-44; comment *Epilepsia*. 2011;52(3):654-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20384763>  
**Abstract** SUMMARY: Sudden unexpected death in epilepsy (SUDEP) is probably caused by periictal cardiorespiratory alterations such as central apnea, bradyarrhythmia, and neurogenic pulmonary edema. These alterations may occur in people with epilepsy and vary in duration and severity. Seizure-related ventricular tachyarrhythmias have also been hypothesized to be involved in SUDEP, but compelling evidence of these, or of predisposition to these, is lacking. Ventricular tachyarrhythmias are facilitated by pathologic cardiac repolarization. Electrocardiography (ECG) indicators of pathologic cardiac repolarization, such as prolongation or shortening of QT intervals as well as increased QT dispersion, are established risk factors for life-threatening tachyarrhythmia and sudden cardiac death (SCD). Abnormalities in cardiac repolarization have recently been described in people with epilepsy. Importantly, periictal ventricular tachycardia and fibrillation have also been reported in the absence of any underlying cardiac disease. Therefore, pathologic cardiac repolarization could promote SCD in people with epilepsy and could be one plausible cause for SUDEP. Herein, we review abnormal cardiac repolarization in people with epilepsy, describe the putative contribution of antiepileptic drugs, and discuss the potential role of pathologic cardiac repolarization in SUDEP. Based on these, measures to reduce the risk of or prevent SUDEP may include antiarrhythmic medication and implantation of cardiac combined pacemaker-defibrillator devices.
22. **Schachter SC. Therapeutic effects of vagus nerve stimulation in epilepsy and implications for sudden unexpected death in epilepsy. *Clin Auton Res*. 2006;16(1):29-32.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16477492>  
<http://link.springer.com/article/10.1007%2Fs10286-006-0275-1>  
**Abstract** Vagus nerve stimulation (VNS) is a non-pharmacological therapy approved by the FDA for treatment of patients with partial-onset epilepsy. The most frequently encountered adverse effects typically occur during stimulation, are usually mild to moderate in severity, and resolve with reduction in current intensity or spontaneously over time. There are no apparent effects of VNS on vagally mediated visceral function. Though the precise mechanism of action of VNS remains unknown, available evidence suggests that central autonomic nervous system pathways are involved, which have also been implicated in sudden unexpected death in epilepsy (SUDEP). Studies to date of VNS and SUDEP are limited and do not conclusively show an association between VNS and SUDEP rates independent of other epilepsy-specific variables.

23. **Sanya EO. Increasing awareness about sudden unexplained death in epilepsy--a review. *Afr J Med Med Sci.* 2005;34(4):323-7.**

<http://www.ncbi.nlm.nih.gov/pubmed/16752659>

**Abstract** Sudden unexplained death in epilepsy (SUDEP) is the commonest cause of epilepsy-related death and most of the presumed risks factors associated with it are probably avoidable. In Nigeria most deaths in individuals with epilepsy occurred at home and so were never reported. Therefore, autopsies are usually not carried to determine the cause of death. This article hopes to reawaken the attention of clinicians to this important, yet not so well known phenomenon, with a view towards addressing problems highlighted. Literatures and research publications on SUDEP were systematically reviewed. Case definition, criteria for diagnosis, risk factors, pathophysiology and treatment options for SUDEP and possible methods towards decreasing its incidence was discussed. Incidence of SUDEP increases with the severity of seizure, early onset epilepsy, poor seizure control, generalised tonic-clonic seizure, multiple antiepileptic medications and frequent adjustment of antiepileptic drugs (AEDs). The pathophysiology of SUDEP is not yet clearly elucidated, but it seems to involve interplay of several factors. At the centre of this, is the impaired cardio-respiratory reflexes leading to central apnoea, hypoxia and oedema along with cardiac arrhythmias. Education of patients, relatives and caregivers is crucial to reducing the incidence of SUDEP. Optimal seizure management with an effective monotherapy where possible, should be the goal of the managing physician. In cases of intractable epilepsy, vagal nerve stimulation and neurosurgery should be considered early.

24. **Annegers JF, Coan SP, Hauser WA, Leestma J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. *Epilepsia.* 2000;41(5):549-53.**

<http://www.ncbi.nlm.nih.gov/pubmed/10802760>

**Notes** A very favorable update on SUDEP and VNS from Annegers' previous SUDEP paper, with the overall VNS SUDEP rate staying about the same at 4.1 per 1,000 person years vs 4.5 per 1,000 person years reported previously. The drop in SUDEP rates over time "may be a benefit of improved seizure control" and is considered low for this refractory group of patients.

**Abstract** **PURPOSE:** This report concerns the 2-year extension of the study of mortality and sudden, unexpected, unexplained death in epilepsy (SUDEP) in the cohort of patients receiving vagal nerve stimulation by the NCP System for the treatment of epilepsy. **METHODS:** A cohort of 1,819 individuals was followed 3,176.3 person-years from implantation. The 25 deaths that occurred during NCP System activation were reviewed for SUDEP by a panel. **RESULTS:** The mortality rates were lower [standardized mortality ratio (SMR = 3.6)] with the extended follow-up compared to the previous finding (SMR = 5.3). The SUDEP rates (4.1 vs. 4.5 per 1,000 person-years) were similar to those in the previous study of this cohort. When the vagal nerve stimulation experience is stratified by duration of use, the rate of SUDEP was 5.5 per 1,000 over the first 2 years, but only 1.7 per 1,000 thereafter. **CONCLUSIONS:** The mortality and SUDEP rates are similar to those reported from clinical trials of new drugs and cohorts of severe epilepsy. The lower SUDEP rates after 2 years of follow-up are intriguing, but require further investigation.

25. **Annegers JF, Coan SP, Hauser WA, Leestma J, Duffell W, Tarver B. Epilepsy, vagal nerve stimulation by the NCP system, mortality, and sudden, unexpected, unexplained death. *Epilepsia*. 1998;39(2):206-12. <http://www.ncbi.nlm.nih.gov/pubmed/9578002>**

**Notes** First stand-alone, peer-reviewed article on SUDEP. As of 8/14/1996, 15 deaths occurred during active treatment with VNS of 791 VNS patients (1,335 patients-years), of which 6 were definite or probable SUDEP for an incidence rate of 4.5 per 1,000 person years. Two deaths were possible SUDEP, with a rate of 6.0 per 1,000 person years for definite/probable/possible SUDEP. Good definitions of SUDEP are provided (p. 207). The mortality rates and standardized mortality ratios are comparable with studies of young adults with intractable epilepsy who were not treated with VNS. These SUDEP rates are not significantly different from those reported in the recent studies of lamotrigine (LTG), gabapentin (GBP), and tiagabine (TGB). The higher rates of SUDEP in the VNS cohort, as compared with recent drug trials, presumably is explained by the selection of relatively higher-risk patients for the VNS Therapy System.

**Abstract** PURPOSE: To determine rates of all-cause mortality and of sudden, unexpected, unexplained deaths in epilepsy (SUDEP) in a cohort of individuals treated with the Neuro Cybernetic Prosthesis (NCP) System for intractable epilepsy, and; to contrast the NCP experience with other epilepsy cohorts. METHODS: A cohort of 791 individuals were followed for 1,335 person-years from implantation. Of the total cohort, 120 individuals had their NCP System devices deactivated. The 15 deaths which occurred during NCP System activation were reviewed for SUDEP by a panel. There were three additional deaths and 242.5 person-years of monitoring after deactivation. RESULTS: The standardized mortality ratios for NCP System were 5.3, 95% confidence interval (CI) 3.0-8.7; and for the time period after device deactivation, 4.4, 95% CI 0.9-12.8. Six of the deaths during stimulation were considered definite or probable SUDEP and two as possible SUDEP. Seven were not considered to be SUDEP. The incidence of definite/probable SUDEP was 4.5 per 1,000 person-years and 6.0 per 1,000 person-years for definite/probable/possible SUDEP. CONCLUSIONS: The mortality rates and standardized mortality ratios are comparable with studies of young adults with intractable epilepsy who were not treated with NCP System. These SUDEP rates are not significantly different from those reported in the recent studies of lamotrigine (LTG), gabapentin (GBP), and tiagabine (TGB). The higher rates of SUDEP in the NCP System cohort, as compared with recent drug trials, presumably is explained by the selection of relatively higher-risk patients for the NCP System device.

**Temporal Lobe/Complex Partial Epilepsy (VNS efficacy in...)**

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- 1. Devinsky O. Diagnosis and treatment of temporal lobe epilepsy. *Rev Neurol Dis.* 2004;1(1):2-9. <http://www.ncbi.nlm.nih.gov/pubmed/16397445>**  
**Abstract** Of the 1,200,000 Americans with partial epilepsy, temporal lobe epilepsy (TLE) occurs in more than 400,000. Temporal lobe seizures are usually stereotypic in their symptoms and duration. A typical sequence is an aura followed by arrest of motor behavior, blank stare, and automatisms. Patients with TLE often show impairments in attention, memory, mental processing speed, executive functions, mood, personality, and drive-related behaviors. Interictal depression occurs in approximately one third of TLE patients. TLE is diagnosed by a history of characteristic partial seizure symptoms. The diagnosis is confirmed by the capture of a typical episode during an electroencephalogram (EEG) or video-EEG, with epileptiform activity over one or both temporal regions. Video-EEG monitoring has revolutionized diagnosis and should be considered in patients in whom diagnosis is uncertain. TLE is treated with medications, resective surgery, and vagus nerve stimulation. Epilepsy surgery should be considered in all patients with refractory partial epilepsy.
- 2. Alsaadi TM, Laxer KD, Barbaro NM, Marks WJ, Jr., Garcia PA. Vagus nerve stimulation for the treatment of bilateral independent temporal lobe epilepsy. *Epilepsia.* 2001;42(7):954-6. <http://www.ncbi.nlm.nih.gov/pubmed/11488900>**  
**Abstract** PURPOSE: We studied the effect of vagus nerve stimulation (VNS) on seizure reduction in patients with intractable epilepsy with bilateral independent temporal lobe foci. METHODS: Ten patients who met the criterion of the presence of two distinctive clinical and ictal EEG seizure patterns were identified and followed up for 1 year. RESULTS: Six patients had >50% reduction in their seizure frequency that persisted up to > or =1 year of follow-up, whereas four patients reported small or no reduction in their partial seizures. CONCLUSIONS: VNS is often effective and well tolerated in this select group of intractable epilepsy patients.
- 3. Landy HJ, Ramsay RE, Slater J, Casiano RR, Morgan R. Vagus nerve stimulation for complex partial seizures: surgical technique, safety, and efficacy. *J Neurosurg.* 1993;78(1):26-31; comment *J Neurosurg.* 1993;79(4):636-7. <http://www.ncbi.nlm.nih.gov/pubmed/8416238>**  
**Abstract** Electrical stimulation of the vagus nerve has shown efficacy in controlling seizures in experimental models, and early clinical trials have suggested possible benefit in humans. Eleven patients with complex partial seizures were subjected to implantation of vagus nerve stimulators. Electrode contacts embedded in silicone rubber spirals were placed on the left vagus nerve in the low cervical area. A transcutaneously programmable stimulator module was placed in an infraclavicular subcutaneous pocket and connected to the electrode. One patient required replacement of the system due to electrode fracture. Another patient developed delayed ipsilateral vocal-cord paralysis; the technique was then modified to allow more tolerance for postoperative nerve edema. A third patient showed asymptomatic vocal-cord paresis on immediate postoperative laryngoscopy. Vagus nerve stimulation produces transient vocal-cord dysfunction while the current is on. Nine patients were randomly assigned to receive either high- or low-current stimulation, and seizure frequency was recorded. The high-current stimulation group showed a median reduction in seizure frequency of 27.7% compared to the preimplantation baseline, while the low-current stimulation group showed a median increase of 6.3%. This difference approached statistical significance. The entire population then received maximally tolerable stimulation. The high-current stimulation group showed a further 14.3% reduction, while the low-current stimulation group showed a 25.4% reduction compared to the blinded period. The efficacy of vagus nerve stimulation seemed to depend on stimulus parameters, and a cumulative effect was evident. These results are encouraging, and further study of this modality as an adjunct treatment for epilepsy is warranted.

**Tourette Syndrome (VNS efficacy in...)**

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1. Sperling W, Reulbach U, Maihofner C, Kornhuber J, Bleich S. Vagus nerve stimulation in a patient with Gilles de la Tourette syndrome and major depression. *Pharmacopsychiatry*. 2008;41(3):117-8.  
<http://www.ncbi.nlm.nih.gov/pubmed/18484555>
2. Diamond A, Kenney C, Jankovic J. Effect of vagal nerve stimulation in a case of Tourette's syndrome and complex partial epilepsy. *Mov Disord*. 2006;21(8):1273-5.  
<http://www.ncbi.nlm.nih.gov/pubmed/16703589>  
<http://onlinelibrary.wiley.com/store/10.1002/mds.20949/asset/20949 ftp.pdf?v=1&t=hea2u1uv&s=474458b4e6bafbc2a87c349a6985b8c8ab9f3fca>

**Abstract** We report on a 30-year-old man with Tourette's syndrome (TS) and medication-refractory epilepsy whose tics improved after implantation of a vagal nerve stimulator (VNS). To verify the patient's observation, we performed a blinded video assessment using the modified Rush video-based tic rating scale. The patient underwent two separate video recordings (VNS on and VNS off). A rater, blinded to patient's VNS status, evaluated the videos with the modified Rush video-based tic rating scale. There were improvements in total tic score and motor and phonic tic frequency. If verified by controlled clinical trials, this observation may provide insights into the pathophysiology of tics and may lead to a novel therapy for patients with severe TS.

**Treatment Guidelines (Epilepsy)**

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1. **Cross JH, Jayakar P, Nordli D, Delalande O, Duchowny M, Wieser HG, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. *Epilepsia*. 2006;47(6):952-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16822241>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2006.00569.x/asset/j.1528-1167.2006.00569.x.pdf?v=1&t=he9441ob&s=5828fa2b35148a08a53a8f24e2574aa75fe8268c>  
**Abstract** The Commission on Neurosurgery of the International League Against Epilepsy (ILAE) formed the Pediatric Epilepsy Surgery Subcommission in 1998 and charged it with formulating guidelines and recommendations for epilepsy surgery in childhood. Also endorsed by the Commission on Paediatrics, the following document is the consensus agreement after a meeting of 32 individuals from 12 countries in 2003. The panel agreed that insufficient class 1 evidence exists to recommend practice guidelines at this time. Instead, the panel generated criteria concerning the unique features of pediatric epilepsy patients to justify dedicated resources for specialty pediatric surgical centers, suggested guidelines for physicians for when to refer children with refractory epilepsy, and recommendations on presurgical evaluation and postoperative assessments. The panel also outlined areas of agreement and disagreement on which future research and consensus meetings should focus attention to generate practice guidelines and criteria for pediatric epilepsy surgery centers.
  
2. **Sanchez-Alvarez JC, Altuzarra-Corral A, Mercade-Cerda JM, Casado-Chocan JL, Moreno-Alegre V, Rufo-Campos M, et al. [The Andalusia Epilepsy Society's Guide to Epilepsy Therapy 2005: IV. General principles of antiepileptic polytherapy and therapeutic strategies in refractory epilepsy]. *Rev Neurol*. 2005;40(12):743-50. Spanish.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15973642>  
**Notes** CORPORATE NAME: Sociedad Andaluza de Epilepsia.  
**Abstract** AIMS: The objective of this work was to produce a scientific evidence-based guide to clinical practice dealing with the basic questions concerning the treatment of epilepsy. DEVELOPMENT: A committee of 11 experts belonging to the Andalusia Epilepsy Society, made up of six neurologists, three neuropaediatricians, one neurosurgeon and a pharmacologist, all of whom were deeply involved and experienced in epilepsy, conducted a thorough review of the literature in search of all the evidence available on the proposed subject matter. The following databases were used: MEDLINE, Cochrane Library and the databases of several clinical practice guidelines (National Guideline Clearinghouse, National Institute of Clinical Excellence and the American Academy of Neurology's Clinical Guidelines). The Guide was set out in seven sections and was published in four parts. From a total number of 187 relevant documents, the committee found 63 examples of scientific evidence and 91 therapeutic recommendations. These were tabulated and classified according to the European Federation of Neurological Societies' criteria for producing Clinical Practice Guidelines. CONCLUSIONS: The results of this survey provide scientific evidence-based clinical guidelines that are useful, simple and applicable at different levels of health care.
  
3. **Karceski S, Morrell M, Carpenter D. The Expert Consensus Guideline Series\*: Treatment of Epilepsy. *Epilepsy Behav*. 2001;2(6):A1-50.**  
<http://www.sciencedirect.com/science/article/pii/S1525505001902835>

**Tuberous Sclerosis Complex (VNS efficacy in...)**

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- 1. Curatolo P, Jozwiak S, Nabbout R, SEGA TSCCMf, Epilepsy M. Management of epilepsy associated with tuberous sclerosis complex (TSC): clinical recommendations. *Eur J Paediatr Neurol.* 2012;16(6):582-6. <http://www.ncbi.nlm.nih.gov/pubmed/22695035>**

**Abstract** Tuberous sclerosis complex (TSC) is a leading genetic cause of epilepsy. TSC-associated epilepsy generally begins during the first year of life, and is associated with neurodevelopmental and cognitive problems. Management is challenging and seizures tend to persist in a large proportion of patients despite pharmacological and surgical treatment. This report summarizes the clinical recommendations for the management of TSC-associated epilepsy made by a panel of European experts in March 2012. Current treatment options and outstanding questions are outlined.
- 2. Dorofeeva M, Belousova ED. [The course and treatment of epilepsy in children with tuberose sclerosis]. *Zh Nevrol Psikhiatr Im S S Korsakova.* 2012;112(6 Pt 2):27-31. Russian. <http://www.ncbi.nlm.nih.gov/pubmed/22983234>**

**Abstract** Tuberous sclerosis complex is a multisystem genetic disorder. Epilepsy is very common in tuberous sclerosis and occurs in 75-92% of affected individuals during their life-time. Onset usually occurs during childhood and up to one third of children with tuberous sclerosis will develop infantile spasms. Of all the possible manifestations of this complex disorder the resistant epilepsy, the cognitive and behavioral problems represent the area of greatest concern to parents, caregivers and physicians. Treatment of epilepsy in tuberous sclerosis is similar to epilepsy resulting from other cases and includes anticonvulsant medications, the epilepsy surgery, the vagus nerve stimulation and the ketogenic diet. Vigabatrin has been shown to be particularly effective in treating infantile spasms in the setting of tuberous sclerosis.
- 3. Moavero R, Cerminara C, Curatolo P. Epilepsy secondary to tuberous sclerosis: lessons learned and current challenges. *Childs Nerv Syst.* 2010;26(11):1495-504. <http://www.ncbi.nlm.nih.gov/pubmed/20358377> <http://link.springer.com/article/10.1007%2Fs00381-010-1128-8>**

**Abstract** BACKGROUND: In tuberous sclerosis complex (TSC), a substantially increased risk of developing epilepsy is present as a result of a disruption of a TSC gene expression in the brain and secondary abnormal cellular differentiation, migration, and proliferation. Dysregulated excitation probably has its roots in the disruption of GABAergic interneuron development. There is an age-dependent electroclinical expression of seizures, and epilepsy is often quite severe and unremitting. DISCUSSION: The majority of patients (>60%) who are candidates for surgery remain seizure-free after tuberectomy. During the recent years technical advances in the localization of the epileptogenic zone during the recent years have lead to a 63% of Engel class I status after surgery compared with a previous 52%. In medically refractory patients not suitable for surgery, vagus nerve stimulation has proved efficacy in significantly reducing seizure frequency in more than 50% of cases. New evidence suggests that mTOR inhibitors may be helpful in the management of intractable epilepsy for individuals with TSC.

4. **Zamponi N, Petrelli C, Passamonti C, Moavero R, Curatolo P. Vagus nerve stimulation for refractory epilepsy in tuberous sclerosis. *Pediatr Neurol.* 2010;43(1):29-34.**

<http://www.ncbi.nlm.nih.gov/pubmed/20682200>

**Abstract** The goal of the study was to assess the long-term seizure and neuropsychologic outcomes of patients with tuberous sclerosis and refractory epilepsy who received vagus nerve stimulator implantation. Eleven patients with a follow-up period of at least 12 months were studied retrospectively. The mean age at the time of implantation was 14 years (range, 2-35). Seizure outcome was rated as class I (>80% seizure frequency reduction) in 1 (9%), class II (50-79% reduction) in 7 (63%), and class III (<50% reduction) in 3 (27%). No patient experienced permanent adverse effects after the procedure. A significant increase of adaptive behaviors and quality of life was observed. Patients who had implantation during childhood exhibited a greater improvement in cognitive and neuropsychologic functioning. Vagus nerve stimulation can be considered an effective and safe therapeutic option in patients with tuberous sclerosis and refractory epilepsy who are not candidates for epilepsy surgery.

5. **Elliott RE, Carlson C, Kalthorn SP, Moshel YA, Weiner HL, Devinsky O, et al. Refractory epilepsy in tuberous sclerosis: vagus nerve stimulation with or without subsequent resective surgery. *Epilepsy Behav.* 2009;16(3):454-60.**

<http://www.ncbi.nlm.nih.gov/pubmed/19767244>

**Abstract** **OBJECTIVE:** The goal of the work described here was to assess the efficacy and safety of vagus nerve stimulation in a cohort of patients with tuberous sclerosis complex with refractory epilepsy. Furthermore, we examined the impact of vagus nerve stimulation failure on the ultimate outcome following subsequent intracranial epilepsy surgery. **METHODS:** A retrospective review was performed on 19 patients with refractory epilepsy and TSC who underwent vagus nerve stimulator (VNS) implantation. There were 11 (58%) females and 8 (42%) males aged 2 to 44 years when the VNS was implanted (mean: 14.7+/-12 years). Twelve patients underwent primary VNS implantation after having failed a mean of 7.1 antiepileptic drugs. Two patients (17%) had generalized epilepsy, one had a single seizure focus, three (25%) had multifocal epilepsy, and six (50%) had multifocal and generalized epilepsy. Seven patients were referred for device removal and evaluation for intracranial procedures. One patient in the primary implantation group was lost to follow-up and excluded from outcome analysis. **RESULTS:** All implantations and removals were performed without permanent complications. The duration of treatment for primary VNS implants varied from 8.5 months to 9.6 years (mean: 4.9 years). Mean seizure frequency significantly improved following VNS implantation (mean reduction: 72%, P<0.002). Two patients had Engel Class I (18%), one had Class II (9%), seven had Class III (64%), and one had Class IV (9%) outcome. Three patients with poor response to vagus nerve stimulation therapy at our center underwent resection of one or more seizure foci (Engel Class I, two patients; Engel Class III, one patient). Seven patients referred to our center for VNS removal and craniotomy underwent seizure focus resection (6) or corpus callosotomy (1) (Engel Class II: 2, Engel III: 2; Engel IV: 3). In total, 8 of 10 (80%) patients experienced improved seizure control following intracranial surgery (mean reduction: 65%, range: 0-100%, P<0.05). **CONCLUSIONS:** VNS is a safe and effective treatment option for medically refractory epilepsy in patients with tuberous sclerosis complex. Nine of 11 patients (82%) experienced at least a 67% reduction in seizure burden. Lack of response to vagus nerve stimulation does not preclude subsequent improvement in seizure burden with intracranial epilepsy surgery.

- 6. Major P, Thiele EA. Vagus nerve stimulation for intractable epilepsy in tuberous sclerosis complex. *Epilepsy Behav.* 2008;13(2):357-60.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18468492>  
**Abstract** OBJECTIVES: The aim of the study described here was to characterize the efficacy and safety of vagus nerve stimulation in a population of patients with tuberous sclerosis complex (TSC) and intractable epilepsy. METHODS: This retrospective study comprised 16 patients with TSC who underwent implantation of a vagus nerve stimulator for treatment of intractable epilepsy. RESULTS: The average age at vagus nerve stimulator implantation was 15 years (range: 2-44, SD: 12.5) and the average duration of follow-up on VNS was 4 years (range: 0.5-8.6, SD: 2.3). Outcome was rated class I (>80% seizure frequency reduction) in 3 (19%), class II (50-79% reduction) in 5 (31%), class III (<50% reduction) in 2 (13%), class IV (magnet benefit only) in 1 (6%), and class V (no improvement) in 5 (31%) patients. Intermittent magnet use was effective in aborting seizures in 8 (50%). Five (31%) patients reported an improved level of functioning. CONCLUSION: The findings suggest that the vagus nerve stimulation can be an effective and safe therapy for patients with TSC with intractable epilepsy.
- 7. Connolly MB, Hendson G, Steinbok P. Tuberous sclerosis complex: a review of the management of epilepsy with emphasis on surgical aspects. *Childs Nerv Syst.* 2006;22(8):896-908.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16770618>  
<http://link.springer.com/article/10.1007%2Fs00381-006-0130-7>  
**Abstract** OBJECTIVE: To review the management of epilepsy in patients with tuberous sclerosis complex (TSC) with an emphasis on surgical aspects, neuropathology, and pathogenesis. METHODS: Review of the literature and presentation of the authors' experience of surgery for refractory epilepsy in patients with TSC. RESULTS: TSC is a multisystem genetic disorder with variable phenotypic expression. TSC results from a mutation in the TSC1 gene on chromosome 9, which codes for hamartin, or in the TSC 2 gene on chromosome 16 which codes for tuberin. The majority of the patients have TSC as a result of spontaneous genetic mutations while in one-third of the patients, the disorder is inherited in an autosomal dominant manner. Epilepsy is the most common neurological complication, and up to 80-90% of individuals with TSC develop epilepsy at some point in their lifetime. The onset of epilepsy is typically in early childhood. Infantile spasms are a very common early seizure type although partial seizures may occur. Developmental delay, intellectual impairment, autism, behavioral problems, and neuropsychiatric disorders occur commonly in individuals with TSC and may be associated with poorly controlled epilepsy. Antiepileptic drugs are the first-line management for epilepsy but the ketogenic diet, resection of one or more tubers, corpus callosotomy, and vagus nerve stimulation are other therapeutic options for individuals with poorly controlled epilepsy.
- 8. Thiele EA. Managing epilepsy in tuberous sclerosis complex. *J Child Neurol.* 2004;19(9):680-6.** <http://www.ncbi.nlm.nih.gov/pubmed/15563014>  
**Abstract** Epilepsy is very common in tuberous sclerosis complex and occurs in 80 to 90% of affected individuals during their lifetime. Onset usually occurs during childhood, and up to one third of children with tuberous sclerosis complex will develop infantile spasms. Although not completely understood, the incidence of epilepsy is thought to relate to the neuropathologic features of the disorder, including cortical tubers and other dysgenetic features. Individuals with tuberous sclerosis complex frequently have epileptiform features to their electroencephalograms. Treatment of epilepsy in tuberous sclerosis complex is similar to epilepsy resulting from other causes and includes anticonvulsant medications, the vagus nerve stimulator, and the ketogenic diet. Vigabatrin has been shown to be particularly effective in treating infantile spasms in the setting of tuberous sclerosis complex. Epilepsy surgery has a very important role in the management of children and adults with pharmacoresistant epilepsy in tuberous sclerosis complex.

9. **Parain D, Penniello MJ, Berquen P, Delangre T, Billard C, Murphy JV. Vagal nerve stimulation in tuberous sclerosis complex patients. *Pediatr Neurol.* 2001;25(3):213-6.**

<http://www.ncbi.nlm.nih.gov/pubmed/11587875>

**Abstract** This is an open-label, retrospective, multicenter study to determine the outcome of intermittent stimulation of the left vagal nerve in children with tuberous sclerosis complex and medically refractory epilepsy. The records of all children treated with vagal nerve stimulation were reviewed in five pediatric epilepsy centers to locate those with tuberous sclerosis complex who had been treated with vagal nerve stimulation for at least 6 months. These patients were compared with (1) a series of patients obtained from the literature, (2) 10 similar control patients with epilepsy obtained from a registry of patients receiving vagal nerve stimulation, and (3) four published series of tuberous sclerosis complex patients whose epilepsy was surgically managed. Ten tuberous sclerosis complex patients with medically refractory epilepsy treated with vagal nerve stimulation were found. Nine experienced at least a 50% reduction in seizure frequency, and half had a 90% or greater reduction in seizure frequency. No adverse events were encountered. Comparison with published and registry patients revealed improved seizure control in the tuberous sclerosis complex patients. Comparison with the group undergoing seizure surgery demonstrated improved outcomes after surgery. Vagal nerve stimulation appears to be an effective and well-tolerated adjunctive therapy in patients with tuberous sclerosis complex and seizures refractory to medical therapy. Resective surgery has a better prospect for improved seizure control.

#### tVNS

1. **Kraus T, Kiess O, Hosl K, Terekhin P, Kornhuber J, Forster C. CNS BOLD fMRI effects of sham-controlled transcutaneous electrical nerve stimulation in the left outer auditory canal - A pilot study. *Brain Stimul.* 2013.**

<http://www.ncbi.nlm.nih.gov/pubmed/23453934>

**Abstract** BACKGROUND: It has recently been shown that electrical stimulation of sensory afferents within the outer auditory canal may facilitate a transcutaneous form of central nervous system stimulation. Functional magnetic resonance imaging (fMRI) blood oxygenation level dependent (BOLD) effects in limbic and temporal structures have been detected in two independent studies. In the present study, we investigated BOLD fMRI effects in response to transcutaneous electrical stimulation of two different zones in the left outer auditory canal. It is hypothesized that different central nervous system (CNS) activation patterns might help to localize and specifically stimulate auricular cutaneous vagal afferents. METHODOLOGY: 16 healthy subjects aged between 20 and 37 years were divided into two groups. 8 subjects were stimulated in the anterior wall, the other 8 persons received transcutaneous vagus nervous stimulation (tVNS) at the posterior side of their left outer auditory canal. For sham control, both groups were also stimulated in an alternating manner on their corresponding ear lobe, which is generally known to be free of cutaneous vagal innervation. Functional MR data from the cortex and brain stem level were collected and a group analysis was performed. RESULTS: In most cortical areas, BOLD changes were in the opposite direction when comparing anterior vs. posterior stimulation of the left auditory canal. The only exception was in the insular cortex, where both stimulation types evoked positive BOLD changes. Prominent decreases of the BOLD signals were detected in the parahippocampal gyrus, posterior cingulate cortex and right thalamus (pulvinar) following anterior stimulation. In subcortical areas at brain stem level, a stronger BOLD decrease as compared with sham stimulation was found in the locus coeruleus and the solitary tract only during stimulation of the anterior part of the auditory canal. CONCLUSIONS: The results of the study are in line with previous fMRI studies showing robust BOLD signal decreases in limbic structures and the brain stem during electrical stimulation of the left anterior auditory canal. BOLD signal decreases in the area of the nuclei of the vagus nerve may indicate an effective stimulation of vagal afferences. In contrast, stimulation at the posterior wall seems to lead to unspecific changes of the BOLD signal within the solitary tract, which is a key relay station of vagal neurotransmission. The results of the study show promise for a specific novel method of cranial nerve stimulation and provide a basis for further developments and applications of non-invasive transcutaneous vagus stimulation in psychiatric patients.

2. **Busch V, Zeman F, Heckel A, Menne F, Ellrich J, Eichhammer P. The effect of transcutaneous vagus nerve stimulation on pain perception - An experimental study. *Brain Stimul.* 2013;6(2):202-9.**

<http://www.ncbi.nlm.nih.gov/pubmed/22621941>

**Abstract** BACKGROUND: Recent preclinical work strongly suggests that vagus nerve stimulation efficiently modulates nociception and pain processing in humans. Most recently, a medical device has offered a transcutaneous electrical stimulation of the auricular branch of the vagus nerve (t-VNS) without any surgery. OBJECTIVE: Our study investigates whether t-VNS may have the potential to alter pain processing using a controlled design. METHODS: Different submodalities of the somatosensory system were assessed with quantitative sensory testing (QST) including a tonic heat pain paradigm in 48 healthy volunteers. Each subject participated in two experimental sessions with active t-VNS (stimulation) or sham t-VNS (no stimulation) on different days in a randomized order (crossed-over). One session consisted of two QST measurements on the ipsi- and contralateral hand, each before and during 1 h of a continuous t-VNS on the left ear using rectangular pulses (250  $\mu$ S, 25 Hz). RESULTS: We found an increase of mechanical and pressure pain threshold and a reduction of mechanical pain sensitivity. Moreover, active t-VNS significantly reduced pain ratings during sustained application of painful heat for 5 min compared to sham condition. No relevant alterations of cardiac or breathing activity or clinical relevant side effects were observed during t-VNS. CONCLUSIONS: Our findings of a reduced sensitivity of mechanically evoked pain and an inhibition of temporal summation of noxious tonic heat in healthy volunteers may pave the way for future studies on patients with chronic pain addressing the potential analgesic effects of t-VNS under clinical conditions.

3. **Yu L, Scherlag BJ, Li S, Fan Y, Dyer J, Male S, et al. Low-level transcutaneous electrical stimulation of the auricular branch of the vagus nerve: A noninvasive approach to treat the initial phase of atrial fibrillation. *Heart Rhythm.* 2013;10(3):428-35.**

<http://www.ncbi.nlm.nih.gov/pubmed/23183191>

**Abstract** BACKGROUND: We studied the effects of transcutaneous electrical stimulation at the tragus, the anterior protuberance of the outer ear, for inhibiting atrial fibrillation (AF). OBJECTIVE: To develop a noninvasive transcutaneous approach to deliver low-level vagal nerve stimulation to the tragus in order to treat cardiac arrhythmias such as AF. METHODS: In 16 pentobarbital anesthetized dogs, multielectrode catheters were attached to pulmonary veins and atria. Three tungsten-coated microelectrodes were inserted into the anterior right ganglionated plexi to record neural activity. Tragus stimulation (20 Hz) in the right ear was accomplished by attaching 2 alligator clips onto the tragus. The voltage slowing the sinus rate or atrioventricular conduction was used as the threshold for setting the low-level tragus stimulation (LL-TS) at 80% below the threshold. At baseline, programmed stimulation determined the effective refractory period (ERP) and the window of vulnerability (WOV), a measure of AF inducibility. For hours 1-3, rapid atrial pacing (RAP) was applied alone, followed by concomitant RAP+LL-TS for hours 4-6 (N = 6). The same parameters were measured during sinus rhythm when RAP stopped after each hour. In 4 other animals, bivagal transection was performed before LL-TS. RESULTS: During hours 1-3 of RAP, there was a progressive and significant decrease in ERP, increase in WOVI, and increase in neural activity vs baseline (all  $P < .05$ ). With RAP+LL-TS during hours 4-6, there was a linear return of ERP, WOVI, and neural activity toward baseline levels (all  $P < .05$ , compared to the third-hour values). In 4 dogs, bivagal transection prevented the reversal of ERP and WOVI despite 3 hours of RAP+LL-TS. CONCLUSIONS: LL-TS can reverse RAP-induced atrial remodeling and inhibit AF inducibility, suggesting a potential noninvasive treatment of AF.

- 4. Lehtimaki J, Hyvarinen P, Ylikoski M, Bergholm M, Makela JP, Aarnisalo A, et al. Transcutaneous vagus nerve stimulation in tinnitus: a pilot study. *Acta Otolaryngol.* 2012.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23237096>  
<http://informahealthcare.com/doi/abs/10.3109/00016489.2012.750736>

**Abstract** Abstract Conclusions: This pilot study shows that transcutaneous vagus nerve stimulation (tVNS), if combined with sound therapy (ST), reduces the severity of tinnitus and tinnitus-associated distress. Our magnetoencephalography (MEG) results show that auditory cortical activation can be modulated by the application of tVNS. Thus, tVNS might offer a new avenue to treat tinnitus and tinnitus-associated distress. Objectives: Recent studies suggest that tinnitus can be improved by tailored ST or by VNS plus ST. Our aims were to study whether tVNS has therapeutic effects on patients with tinnitus and, additionally, if tVNS has effects on acoustically evoked neuronal activity of the auditory cortex. Methods: The clinical efficacy was studied by a short-term tVNS plus ST trial in 10 patients with tinnitus using disease-specific and general well-being questionnaires. tVNS was delivered to the left tragus. The acute effects of tVNS were evaluated in eight patients in the MEG study in which the N1m response was analyzed in terms of source level amplitude and latency in the presence or absence of tVNS. Results: The treatment with tVNS plus ST produced improved mood and decreased tinnitus handicap scores, indicating reduced tinnitus severity. The application of tVNS decreased the amplitude of auditory N1m responses in both hemispheres.
  
- 5. Rong PJ, Fang JL, Wang LP, Meng H, Liu J, Ma YG, et al. Transcutaneous vagus nerve stimulation for the treatment of depression: a study protocol for a double blinded randomized clinical trial. *BMC Complement Altern Med.* 2012;12:255.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23241431>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3537743/pdf/1472-6882-12-255.pdf>

**Abstract** BACKGROUND: Depressive disorders are the most common form of mental disorders in community and health care settings. Unfortunately, the treatment of Major Depressive Disorder (MDD) is far from satisfactory. Vagus nerve stimulation (VNS) is a relatively new and promising physical treatment for depressive disorders. One particularly appealing element of VNS is the long-term benefit in mood regulation. However, because this intervention involves surgery, perioperative risks, and potentially significant side effects, this treatment has been limited to those patients with treatment-resistant depression who have failed medication trials and exhausted established somatic treatments for major depression, due to intolerance or lack of response. This double-blinded randomized clinical trial aims to overcome these limitations by introducing a novel method of stimulating superficial branches of the vagus nerve on the ear to treat MDD. The rationale is that direct stimulation of the afferent nerve fibers on the ear area with afferent vagus nerve distribution should produce a similar effect as classic VNS in reducing depressive symptoms without the burden of surgical intervention. DESIGN: One hundred twenty cases (60 males) of volunteer patients with mild and moderate depression will be randomly divided into transcutaneous vagus nerve stimulation group (tVNS) and sham tVNS group. The treatment period lasts 4 months and all clinical and physiological measurements are acquired at the beginning and the end of the treatment period. DISCUSSION: This study has the potential to significantly extend the application of VNS treatment for MDD and other disorders (including epilepsy, bipolar disorder, and morbid obesity), resulting in direct benefit to the patients suffering from these highly prevalent disorders. In addition, the results of this double-blinded clinical trial will shed new light on our understanding of acupuncture point specificity, and development of methodologies in clinical trials of acupuncture treatment. TRIALS REGISTRATION: Clinical Trials. ChiCTR-TRC-11001201 <http://www.chictr.org/cn/>

6. **Stefan H, Kreiselmeyer G, Kerling F, Kurzbuch K, Rauch C, Heers M, et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmaco-resistant epilepsies: a proof of concept trial. *Epilepsia*. 2012;53(7):e115-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22554199>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2012.03492.x/asset/j.1528-1167.2012.03492.x.pdf?v=1&t=hekin2hv&s=d04f19ab15010d52bc5ed0e695426c0db4df683d>  
**Abstract** To elucidate, in a pilot-study, whether noninvasive transcutaneous vagus nerve stimulation (t-VNS) is a safe and tolerable alternative treatment option in pharmaco-resistant epilepsy. t-VNS was applied to 10 patients with pharmaco-resistant epilepsies. Stimulation via the auricular branch of the vagus nerve of the left tragus was delivered three times per day for 9 months. Subjective documentation of stimulation effects was obtained from patients' seizure diaries. For a more reliable assessment of seizure frequency, we carried out prolonged outpatient video-electroencephalography (EEG) monitoring. In addition, computerized testing of cognitive, affective, and emotional functions was performed. Three patients aborted the study. Of the remaining seven patients, an overall reduction of seizure frequency was observed in five patients after 9 months of t-VNS. The noninvasive t-VNS stimulation is a safe and well-tolerated method for relatively long periods, and might be an alternative treatment option for patients with epilepsy.
7. **Zhao YX, He W, Jing XH, Liu JL, Rong PJ, Ben H, et al. Transcutaneous auricular vagus nerve stimulation protects endotoxemic rat from lipopolysaccharide-induced inflammation. *Evid Based Complement Alternat Med*. 2012;2012:627023.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23346208>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3544369/pdf/ECAM2012-627023.pdf>  
**Abstract** Background. Transcutaneous auricular vagus nerve stimulation (ta-VNS) could evoke parasympathetic activities via activating the brainstem autonomic nuclei, similar to the effects that are produced after vagus nerve stimulation (VNS). VNS modulates immune function through activating the cholinergic anti-inflammatory pathway. Methods. VNS, ta-VNS, or transcutaneous electrical acupoint stimulation (TEAS) on ST36 was performed to modulate the inflammatory response. The concentration of serum proinflammatory cytokines and tissue NF-kappa B p65 (NF-kappaB p65) were detected in endotoxaemia affected anesthetized rats. Results. Similar to the effect of VNS, ta-VNS suppressed the serum proinflammatory cytokines levels, such as tumour necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1beta), and interleukin-6 (IL-6) as well as NF-kappa B p65 expressions of lung tissues. ST36 stimulation also decreases LPS-induced high TNF-alpha level and NF-kappaB signal, but it did not restrain proinflammatory cytokine IL-1beta and IL-6. Neither ta-VNS nor ST36 stimulation could suppress LPS-induced TNF-alpha and NF-kappaB after vagotomy or with alpha7nAChR antagonist injection. Conclusions. The present paper demonstrated that ta-VNS could be utilized to suppress LPS-induced inflammatory responses via alpha7nAChR-mediated cholinergic anti-inflammatory pathway.

8. **Kreuzer PM, Landgrebe M, Husser O, Resch M, Schecklmann M, Geisreiter F, et al. Transcutaneous vagus nerve stimulation: retrospective assessment of cardiac safety in a pilot study. *Front Psychiatry*. 2012;3:70.**

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<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3413045/pdf/fpsy-03-00070.pdf>

**Abstract** Background: Vagus nerve stimulation has been successfully used as a treatment strategy for epilepsy and affective disorders for years. Transcutaneous vagus nerve stimulation (tVNS) is a new non-invasive method to stimulate the vagus nerve, which has been shown to modulate neuronal activity in distinct brain areas. Objectives: Here we report effects of tVNS on cardiac function from a pilot study, which was conducted to evaluate the feasibility and safety of tVNS for the treatment of chronic tinnitus. Methods: Twenty-four patients with chronic tinnitus underwent treatment with tVNS over 3-10 weeks in an open single-armed pilot study. Safety criteria and practical usability of the neurostimulating device were to investigate by clinical examination and electrocardiography at baseline and at several visits during and after tVNS treatment (week 2, 4, 8, 16, and 24). Results: Two adverse cardiac events (one classified as a severe adverse event) were registered but considered very unlikely to have been caused by the tVNS device. Retrospective analyses of electrocardiographic parameters revealed a trend toward shortening of the QRS complex after tVNS. Conclusion: To our knowledge this is one of the first studies investigating feasibility and safety of tVNS in a clinical sample. In those subjects with no known pre-existing cardiac pathology, preliminary data do not indicate arrhythmic effects of tVNS.

9. **Yang AC, Zhang JG, Rong PJ, Liu HG, Chen N, Zhu B. A new choice for the treatment of epilepsy: electrical auricula-vagus-stimulation. *Med Hypotheses*. 2011;77(2):244-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/21601370>

**Abstract** Preliminary reports have suggested that chronic, intermittent electrical stimulation of the cervical vagus nerve (VNS) is an effective treatment for patients who suffered from medically refractory epilepsy. But the traditional VNS is an invasive and implantable procedure that will bring some injury to the patient. Anatomic studies have confirmed the existence of auricular branch of the vagus nerve-Arnold nerve. The Arnold nerve mainly consists of afferent fibers and the superficial sites of the Arnold nerve are optimal for electrical stimulation. We hypothesized that electrical auricula-vagus-stimulation could be a new choice for the treatment of epilepsy.

10. **Dietrich S, Smith J, Scherzinger C, Hofmann-Preiss K, Freitag T, Eisenkolb A, et al. [A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI]. *Biomed Tech (Berl)*. 2008;53(3):104-11. German.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18601618>  
**Abstract** BACKGROUND: Left cervical vagus nerve stimulation (VNS) using the implanted NeuroCybernetic Prosthesis (NCP) can reduce epileptic seizures and has recently been shown to give promising results for treating therapy-resistant depression. To address a disadvantage of this state-of-the-art VNS device, the use of an alternative transcutaneous electrical nerve stimulation technique, designed for muscular stimulation, was studied. Functional magnetic resonance imaging (MRI) has been used to test non-invasively access nerve structures associated with the vagus nerve system. The results and their impact are unsatisfying due to missing brainstem activations. These activations, however, are mandatory for reasoning, higher subcortical and cortical activations of vagus nerve structures. The objective of this study was to test a new parameter setting and a novel device for performing specific (well-controlled) transcutaneous VNS (tvNS) at the inner side of the tragus. This paper shows the feasibility of these and their potential for brainstem and cerebral activations as measured by blood oxygenation level dependent functional MRI (BOLD fMRI). MATERIALS AND METHODS: In total, four healthy male adults were scanned inside a 1.5-Tesla MR scanner while undergoing tvNS at the left tragus. We ensured that our newly developed tvNS stimulator was adapted to be an MR-safe stimulation device. In the experiment, cortical and brainstem representations during tvNS were compared to a baseline. RESULTS: A positive BOLD response was detected during stimulation in brain areas associated with higher order relay nuclei of vagal afferent pathways, respectively the left locus coeruleus, the thalamus (left >> right), the left prefrontal cortex, the right and the left postcentral gyrus, the left posterior cingulated gyrus and the left insula. Deactivations were found in the right nucleus accumbens and the right cerebellar hemisphere. CONCLUSION: The method and device are feasible and appropriate for accessing cerebral vagus nerve structures, respectively. As functional patterns share features with fMRI BOLD, the effects previously studied with the NCP are discussed and new possibilities of tvNS are hypothesised.
11. **Bauhofer A, Torossian A. Mechanical vagus nerve stimulation--A new adjunct in sepsis prophylaxis and treatment? *Crit Care Med*. 2007;35(12):2868-9; comment *Crit Care Med*. 2007;35(12):2762-8; comment *Crit Care Med*. 2008;36(6):1990.**  
<http://www.ncbi.nlm.nih.gov/pubmed/18043211>  
**Abstract** OBJECTIVE: Electrical vagus nerve stimulation inhibits proinflammatory cytokine production and prevents shock during lethal systemic inflammation through an alpha7 nicotinic acetylcholine receptor (alpha7nAChR)-dependent pathway to the spleen, termed the cholinergic anti-inflammatory pathway. Pharmacologic alpha7nAChR agonists inhibit production of the critical proinflammatory mediator high mobility group box 1 (HMGB1) and rescue mice from lethal polymicrobial sepsis. Here we developed a method of transcutaneous mechanical vagus nerve stimulation and then investigated whether this therapy can protect mice against sepsis lethality. DESIGN: Prospective, randomized study. SETTING: Institute-based research laboratory. SUBJECTS: Male BALB/c mice. INTERVENTIONS: Mice received lipopolysaccharide to induce lethal endotoxemia or underwent cecal ligation and puncture to induce polymicrobial sepsis. Mice were then randomized to receive electrical, transcutaneous, or sham vagus nerve stimulation and were followed for survival or euthanized at predetermined time points for cytokine analysis. MEASUREMENTS AND MAIN RESULTS: Transcutaneous vagus nerve stimulation dose-dependently reduced systemic tumor necrosis factor levels during lethal endotoxemia. Treatment with transcutaneous vagus nerve stimulation inhibited HMGB1 levels and improved survival in mice with polymicrobial sepsis, even when administered 24 hrs after the onset of disease. CONCLUSIONS: Transcutaneous vagus nerve stimulation is an efficacious treatment for mice with lethal endotoxemia or polymicrobial sepsis.

12. **Kraus T, Hosl K, Kiess O, Schanze A, Kornhuber J, Forster C. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. *J Neural Transm.* 2007;114(11):1485-93.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17564758>  
<http://link.springer.com/article/10.1007%2Fs00702-007-0755-z>  
**Abstract** Direct vagus nerve stimulation (VNS) has proved to be an effective treatment for seizure disorder and major depression. However, since this invasive technique implies surgery, with its side-effects and relatively high financial costs, a non-invasive method to stimulate vagal afferences would be a great step forward. We studied effects of non-invasive electrical stimulation of the nerves in the left outer auditory canal in healthy subjects (n = 22), aiming to activate vagal afferences transcutaneously (t-VNS). Short-term changes in brain activation and subjective well-being induced by t-VNS were investigated by functional magnetic resonance imaging (fMRI) and psychometric assessment using the Adjective Mood Scale (AMS), a self-rating scale for current subjective feeling. Stimulation of the ear lobe served as a sham control. fMRI showed that robust t-VNS induced BOLD-signal decreases in limbic brain areas, including the amygdala, hippocampus, parahippocampal gyrus and the middle and superior temporal gyrus. Increased activation was seen in the insula, precentral gyrus and the thalamus. Psychometric assessment revealed significant improvement of well-being after t-VNS. Ear lobe stimulation as a sham control intervention did not show similar effects in either fMRI or psychometric assessment. No significant effects on heart rate, blood pressure or peripheral microcirculation could be detected during the stimulation procedure. **CONCLUSIONS:** Our study shows the feasibility and beneficial effects of transcutaneous nerve stimulation in the left auditory canal of healthy subjects. Brain activation patterns clearly share features with changes observed during invasive vagus nerve stimulation.
13. **Fallgatter AJ, Neuhauser B, Herrmann MJ, Ehlis AC, Wagerer A, Scheuerpflug P, et al. Far field potentials from the brain stem after transcutaneous vagus nerve stimulation. *J Neural Transm.* 2003;110(12):1437-43.**  
<http://www.ncbi.nlm.nih.gov/pubmed/14666414>  
<http://link.springer.com/article/10.1007%2Fs00702-003-0087-6>  
**Abstract** Recently, the vagus nerve has gained particular interest in neuropsychiatry, as neurodegenerative diseases like Alzheimer's and Parkinson's disease are supposed to affect the brainstem nuclei of the vagus nerve early in their course. In addition, electric stimulation of the vagus nerve has therapeutic effects in otherwise therapy-refractory epilepsies and depressions. So far, no method is available to assess vagus nerve function in this context. On this background and based on the established techniques of early acoustic evoked potentials we investigated if a transcutaneous electric stimulation of the sensory auricular branch of the vagus nerve innervating parts of the outer ear is feasible in healthy subjects using this hypothesis-generated approach. We were able to record a clear, reproducible Vagus Sensory Evoked Potential (VSEP) measured as far field potential probably originating in vagus nuclei in the brainstem. Further studies are needed to test the interindividual stability and test-retest reliability of this new method before potential diagnostic and therapeutic applications might be evaluated.
14. **Parker AP, Polkey CE, Robinson RO. Vagal nerve stimulation in the epileptic encephalopathies: 3-year follow-up. *Pediatrics.* 2001;108(1):221.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11452969>

**Unverricht-Lundborg Type (VNS efficacy in...)**

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1. **Smith B, Shatz R, Elisevich K, Bepalova IN, Burmeister M. Effects of vagus nerve stimulation on progressive myoclonus epilepsy of Unverricht-Lundborg type. *Epilepsia*. 2000;41(8):1046-8. <http://www.ncbi.nlm.nih.gov/pubmed/10961635>**

**Abstract** PURPOSE: A 34-year-old woman with progressive myoclonus epilepsy of Unverricht-Lundborg type was considered for vagus nerve stimulation (VNS) therapy. METHODS: After demonstration of intractability to multiple antiepileptic regimens and progressive deterioration in cerebellar function, the patient was implanted with a vagus nerve stimulator and followed for 1 year. Neurological status, seizure frequency, and parameter changes were analyzed. RESULTS: VNS therapy resulted in reduction of seizures (more than 90%) and a significant improvement in cerebellar function demonstrated on neurological examination. The patient reported improved quality of life based in part on her ability to perform activities of daily living. CONCLUSIONS: VNS therapy may be considered a treatment option for progressive myoclonus epilepsy. The effects of VNS on seizure control and cerebellar dysfunction may provide clues to the underlying mechanism(s) of action.

**VNS Efficacy in Epilepsy, NOS/Other**

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1. Wang DD, Deans AE, Barkovich AJ, Tihan T, Barbaro NM, Garcia PA, et al. Transmantle sign in focal cortical dysplasia: a unique radiological entity with excellent prognosis for seizure control. *J Neurosurg.* 2013;118(2):337-44.  
<http://www.ncbi.nlm.nih.gov/pubmed/23216463>  
**Abstract** OBJECT: Focal cortical dysplasia (FCD) represents a spectrum of developmental cortical abnormalities and is one of the most common causes of intractable epilepsy in children and young adults. Outcomes after surgery for FCD are highly variable, and prognosticators of seizure freedom are unclear. In a subset of FCDs, a transmantle sign is observed on imaging that focally spans the entire cerebral mantle from the ventricle to the cortical surface. The aim of this study was to characterize seizure control outcomes and prognostic significance of the transmantle sign in FCD epilepsy. METHODS: Fourteen patients with the transmantle sign underwent epilepsy surgery for medically refractory epilepsy. Thirteen patients underwent resective surgery and 1 underwent multiple subpial transections with vagus nerve stimulator placement. Patient demographics, MRI, electroencephalography, intraoperative electrocorticography (ECoG), and pathology were reviewed. The results of this series were compared with those of 114 previously reported patients with FCD without the transmantle sign. RESULTS: All patients were found to have childhood seizure onset and concordant MRI and ECoG findings. The primary MRI findings associated with transmantle sign included gray-white junction blurring, appearance of cortical thickening, T2 or FLAIR abnormality, and bottom-of-the-sulcus dysplasia. The transmantle sign was usually a focal finding, typically confined to 1 or several gyri with well-circumscribed epileptic tissue. Correlation of the transmantle sign with FCD histopathological subtypes was highly variable. Patients who underwent complete resection of MRI and ECoG abnormalities (12 of 13 patients) became seizure free. When compared with 114 FCD patients without the transmantle sign, patients with the transmantle sign showed significantly improved seizure-free outcomes after complete resections ( $p = 0.04$ ). CONCLUSIONS: The presence of the transmantle sign in patients with medically refractory partial epilepsy is associated with highly favorable seizure control outcomes after surgical treatment.
  
2. Kalanithi PS, Arrigo RT, Tran P, Gephart MH, Shuer L, Fisher R, et al. Rehospitalization and Emergency Department Use Rates Before and After Vagus Nerve Stimulation for Epilepsy: Use of State Databases to Provide Longitudinal Data Across Multiple Clinical Settings. *Neuromodulation.* 2013;544-54.  
<http://www.ncbi.nlm.nih.gov/pubmed/23551457>  
<http://onlinelibrary.wiley.com/doi/10.1111/ner.12051/abstract>  
**Abstract** OBJECTIVES: Data regarding rehospitalization and emergency department (ED) visits following vagus nerve stimulation (VNS) present data analysis challenges. We present a method that uses California's multiple databases to more completely assay VNS efficacy. MATERIALS AND METHODS: The Healthcare Cost and Utilization Project's California Inpatient and Ambulatory Surgery databases were assayed for all VNS surgeries from 2005 to 2009. Patients were selected by epilepsy diagnosis codes and VNS procedure codes. Patients (total N = 629) were tracked across multiple databases using unique identifiers. Thirty-day and one-year post-implantation rates of VNS complication and healthcare visits were abstracted, along with one-year preoperative hospital and ED use. Statistics included correction for multiple comparisons. RESULTS: The one-year reoperation rate for adult patients (N = 536) was 3.9%; during the second year, an additional 3.2% of patients had reoperations. Within the first 30 days, <2% of patients experienced a complication. Four percent of patients were readmitted to a hospital, and 11.6% of patients visited an ED. The most common reason for rehospitalization or ED visit was seizure. In the first year after VNS, total seizure-related visits (hospitalization and ED) were 17% lower (2.12 visits per year to 1.71;  $p = 0.03$ ). In the second year following VNS, seizure-related visits were 42% lower (2.21 visits per year to 1.27,  $p = 0.01$ ). Pediatric patients (N = 93) had comparable results. CONCLUSIONS: VNS surgery has low rates of complications and reoperations and is associated with reduced incidence of seizure-related ED visits and hospital admissions in the first and second postoperative years.

3. **Hoppe C. Vagus nerve stimulation: urgent need for the critical reappraisal of clinical effectiveness. *Seizure*. 2013;22(1):83-4; response *Seizure*. 2013. [ePub ahead of print].**  
<http://www.ncbi.nlm.nih.gov/pubmed/23140994>
4. **Bremer A, Lossius MI, Nakken KO. Dravet syndrome--considerable delay in making the diagnosis. *Acta Neurol Scand*. 2012;125(5):359-62.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22050316>  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0404.2011.01609.x/abstract>  
**Abstract** OBJECTIVES: To assess delay in diagnosis and clinical characteristics of Dravet syndrome based on the Dravet register at The National Centre for Epilepsy in Norway. MATERIAL AND METHODS: Medical records of patients diagnosed with Dravet syndrome since 2007 were analysed. RESULTS: Twenty-two patients were identified. In 15, genetic screening disclosed mutations/deletions in the SCN1A gene. Average time from seizure onset to diagnosis was 7.4 years. Mean age at seizure onset was 6.7 months, nine had hemiconvulsions and 13 had generalized tonic-clonic seizures. The seizures were precipitated by fever in 17, by external heating in three. During second year of life, multiple seizure types and cognitive and motoric stagnation occurred. No patients became seizure-free with antiepileptic drugs. The effect of vagal nerve stimulation was disappointing. CONCLUSIONS: By making an early diagnosis, an extensive presurgical evaluation may be avoided, and the patient and their parents may be offered genetic guidance.
5. **Kaya M, Becker AJ, Gurses C. Blood-brain barrier, epileptogenesis, and treatment strategies in cortical dysplasia. *Epilepsia*. 2012;53 Suppl 6:31-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23134493>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2012.03700.x/asset/j.1528-1167.2012.03700.x.pdf?v=1&t=heki98rf&s=ca2e9517dd71e97d3e4b537978daf40365496ed7>  
**Abstract** Cortical dysplasia (CD) is one of the most important causes of intractable epilepsy. The precise mechanisms of epileptogenesis in CD are not known. Using CD animal models, we attempted to understand the mechanisms and efficacy of various antiepileptic drugs. In two separate studies, we assessed (1) the effects of levetiracetam (LEV) and vagus nerve stimulation (VNS) on pentylenetetrazol (PTZ)-kindled rats, and (2) the effects of LEV and topiramate (TPM) on rats with CD and hyperthermia (HT). In the HT-induced rats with CD study, LEV and TPM decreased both the intensity of seizures and the number of rats with seizure. In these studies, we used immunocytochemistry (occludin, glial fibrillary acidic protein [GFAP], and P-glycoprotein [Pgp antibodies] and electron microscopy (EM) (sodium fluorescein [NaFlu]) and horseradish peroxidase [HRP]) to assess blood-brain barrier (BBB) integrity. Both LEV and TPM protected BBB. In PTZ-kindled rats with CD, both LEV and VNS reduced the duration of seizures. Immunocytochemistry and EM revealed no BBB impairment in any of the treatment groups. In a second set of experiments, we assessed the relationship between disruption of vascular components and epileptogenesis. Astrocytic albumin uptake in focal epileptogenic lesions with vascular components suggested that dysfunction of the BBB contributes immediately to epileptogenesis, rather than simply resulting from seizure activity. Hemosiderin deposits were seen as potential epileptogenic triggers in vascular malformations (e.g., cavernomas [CA] or arteriovenous malformations [AVMs] with or without a dysplastic cortical component). However, we found strikingly high accumulation of astrocytic albumin deposits in surgically removed brain parenchyma in the vicinity of CAs and AVMs from patients with pharmaco-resistant epilepsy, which suggests different pathophysiologic dispersion pathways for hemosiderin and albumin in vascular lesions.
6. **Funnell M, Ranta A. Vagal nerve stimulation in New Zealand: improvement of seizure control following the implantation of a vagal nerve stimulator. *N Z Med J*. 2012;125(1361):109-11.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22960725>

7. **Connor DE, Jr., Nixon M, Nanda A, Guthikonda B. Vagal nerve stimulation for the treatment of medically refractory epilepsy: a review of the current literature. *Neurosurg Focus*. 2012;32(3):E12.**

<http://www.ncbi.nlm.nih.gov/pubmed/22380853>

**Abstract** OBJECT: The authors conducted a study to evaluate the published results of vagal nerve stimulation (VNS) for medically refractory seizures according to evidence-based criteria. METHODS: The authors performed a review of available literature published between 1980 and 2010. Inclusion criteria for articles included more than 10 patients evaluated, average follow-up of 1 or more years, inclusion of medically refractory epilepsy, and consistent preoperative surgical evaluation. Articles were divided into 4 classes of evidence according to criteria established by the American Academy of Neurology. RESULTS: A total of 70 publications were reviewed, of which 20 were selected for review based on inclusion and exclusion criteria. There were 2 articles that provided Class I evidence, 7 that met criteria for Class II evidence, and 11 that provided Class III evidence. The majority of evidence supports VNS usage in partial epilepsy with a seizure reduction of 50% or more in the majority of cases and freedom from seizure in 6%-27% of patients who responded to stimulation. High stimulation with a gradual increase in VNS stimulation over the first 6 weeks to 3 months postoperatively is well supported by Class I and II data. Predictors of positive response included absence of bilateral interictal epileptiform activity and cortical malformations. CONCLUSIONS: Vagal nerve stimulation is a safe and effective alternative for adult and pediatric populations with epilepsy refractory to medical and other surgical management.

8. **Rolston JD, Englot DJ, Wang DD, Shih T, Chang EF. Comparison of seizure control outcomes and the safety of vagus nerve, thalamic deep brain, and responsive neurostimulation: evidence from randomized controlled trials. *Neurosurg Focus*. 2012;32(3):E14.**

<http://www.ncbi.nlm.nih.gov/pubmed/22380855>

**Abstract** Epilepsy is a devastating disease, often refractory to medication and not amenable to resective surgery. For patients whose seizures continue despite the best medical and surgical therapy, 3 stimulation-based therapies have demonstrated positive results in prospective randomized trials: vagus nerve stimulation, deep brain stimulation of the thalamic anterior nucleus, and responsive neurostimulation. All 3 neuromodulatory therapies offer significant reductions in seizure frequency for patients with partial epilepsy. A direct comparison of trial results, however, reveals important differences among outcomes and surgical risk between devices. The authors review published results from these pivotal trials and highlight important differences between the trials and devices and their application in clinical use.

9. **Chrastina J, Novak Z, Riha I, Ghallab K, Martinek L, Brazdil M. [Pharmacoresistant epilepsy after craniocerebral injury]. *Rozhl Chir.* 2012;91(1):18-25. Czech.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22746074>  
**Abstract** INTRODUCTION: Posttraumatic epilepsy is one of the possible serious consequences of both closed and open head injury with clinical manifestation months or years after surgery. In pharmacoresistant patients, surgical therapy should be considered. MATERIAL AND METHODS: The study summarises the results of surgical treatment of pharmacoresistant posttraumatic epilepsy in a group of 13 patients (11 males and 2 females). Average age at the time of injury was 9.6 years in males and 8.8 years in females. The average number of seizures was 10.7-17 seizures/month preoperatively. Invasive EEG monitoring was required in 5 patients in whom non invasive or semiinvasive investigations failed to localize the epileptogenic zone adequately. Temporal lobe resections were performed in 4 patients, 4 patients underwent extratemporal resections and vagus nerve stimulation system was implanted in 5 patients. RESULTS: Three patients (75%) after temporal resections became seizure free (Engel I) and in the remaining patient significant reduction of seizures was achieved (Engel III). There were 2 seizure free patients after extratemporal resections (50%) and significant reduction of seizure rates was achieved (Engel III) in the remaining two. One patient after vagus nerve stimulation met the criteria for > 90% response and there was a 50-90% seizure rate reduction in the remaining 4 patients (vagus nerve stimulation responder). CONCLUSIONS: Although in limited group of patients the study confirms good results of surgical treatment of selected posttraumatic epilepsy patients--mainly temporal epilepsy patients and patients after vagus nerve stimulation. Meticulous presurgical evaluation including invasive encephalography in indicated patients is a precondition for surgical success.
10. **Kahlenberg CA, Fadul CE, Roberts DW, Thadani VM, Bujarski KA, Scott RC, et al. Seizure prognosis of patients with low-grade tumors. *Seizure.* 2012;21(7):540-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22726817>  
**Abstract** PURPOSE: Seizures frequently impact the quality of life of patients with low grade tumors. Management is often based on best clinical judgment. We examined factors that correlate with seizure outcome to optimize seizure management. METHODS: Patients with supratentorial low-grade tumors evaluated at a single institution were retrospectively reviewed. Using multiple regression analysis the patient characteristics and treatments were correlated with seizure outcome using Engel's classification. RESULTS: Of the 73 patients with low grade tumors and median follow up of 3.8 years (range 1-20 years), 54 (74%) patients had a seizure ever and 46 (63%) had at least one seizure before tumor surgery. The only factor significantly associated with pre-surgical seizures was tumor histology. Of the 54 patients with seizures ever, 25 (46.3%) had a class I outcome at last follow up. There was no difference in seizure outcome between grade II gliomas (astrocytoma grade II, oligodendroglioma grade II, mixed oligo-astrocytoma grade II) and other pathologies (pilocytic astrocytoma, ependymomas, DNET, gangliocytoma and ganglioglioma). Once seizures were established seizure prognosis was similar between different pathologies. Chemotherapy (p=0.03) and radiation therapy (p=0.02) had a positive effect on seizure outcome. No other parameter including significant tumor growth during the follow up period predicted seizure outcome. Only three patients developed new-onset seizures after tumor surgery that were non-perioperative. Anticonvulsant medication was tapered in 14 patients with seizures and 10 had no further seizures. Five patients underwent additional epilepsy surgery with a class I outcome in four. Two patients received a vagal nerve stimulator with >50% seizure reduction. DISCUSSION: Seizures at presentation are the most important factor associated with continued seizures after tumor surgery. Pathology does not influence seizure outcome. Use of long term prophylactic anticonvulsants is unwarranted. Chemotherapy and radiation therapy have a favorable impact on seizure outcome. Additional epilepsy surgery is effective.

11. **Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. *J Neurosurg.* 2011;115(6):1248-55.**

<http://www.ncbi.nlm.nih.gov/pubmed/21838505>

**Abstract** Vagus nerve stimulation (VNS) was approved by the US FDA in 1997 as an adjunctive treatment for medically refractory epilepsy. It is considered for use in patients who are poor candidates for resection or those in whom resection has failed. However, disagreement regarding the utility of VNS in epilepsy continues because of the variability in benefit reported across clinical studies. Moreover, although VNS was approved only for adults and adolescents with partial epilepsy, its efficacy in children and in patients with generalized epilepsy remains unclear. The authors performed the first meta-analysis of VNS efficacy in epilepsy, identifying 74 clinical studies with 3321 patients suffering from intractable epilepsy. These studies included 3 blinded, randomized controlled trials (Class I evidence); 2 nonblinded, randomized controlled trials (Class II evidence); 10 prospective studies (Class III evidence); and numerous retrospective studies. After VNS, seizure frequency was reduced by an average of 45%, with a 36% reduction in seizures at 3-12 months after surgery and a 51% reduction after > 1 year of therapy. At the last follow-up, seizures were reduced by 50% or more in approximately 50% of the patients, and VNS predicted a  $\geq 50\%$  reduction in seizures with a main effects OR of 1.83 (95% CI 1.80-1.86). Patients with generalized epilepsy and children benefited significantly from VNS despite their exclusion from initial approval of the device. Furthermore, posttraumatic epilepsy and tuberous sclerosis were positive predictors of a favorable outcome. In conclusion, VNS is an effective and relatively safe adjunctive therapy in patients with medically refractory epilepsy not amenable to resection. However, it is important to recognize that complete seizure freedom is rarely achieved using VNS and that a quarter of patients do not receive any benefit from therapy.

12. **Zamponi N, Passamonti C, Cesaroni E, Trignani R, Rychlicki F. Effectiveness of vagal nerve stimulation (VNS) in patients with drop-attacks and different epileptic syndromes. *Seizure.* 2011;20(6):468-74.**

<http://www.ncbi.nlm.nih.gov/pubmed/21396833>

[http://ac.els-cdn.com/S1059131111000677/1-s2.0-S1059131111000677-main.pdf?\\_tid=505c1214-927a-11e2-97ca-00000aacb35f&acdnat=1363906660\\_98d10bf91406f517da5267160311587f](http://ac.els-cdn.com/S1059131111000677/1-s2.0-S1059131111000677-main.pdf?_tid=505c1214-927a-11e2-97ca-00000aacb35f&acdnat=1363906660_98d10bf91406f517da5267160311587f)

**Abstract** PURPOSE: The effectiveness of VNS was evaluated in thirty-nine encephalopathic patients with drug-resistant epilepsy characterized by multiple seizures and drop attacks. Twenty-five patients were affected by severe epilepsy with multiple independent spike foci (SE-MISF) and fourteen patients by Lennox-Gastaut syndrome (LGS). METHOD: Changes in seizure frequency, cognition, adaptive behaviour and quality of life were assessed before and after VNS implant until three years. Outcome assessment for all seizure types included the number of seizures/month and the reduction in seizure frequency rate at each follow-up. Moreover, the effect of VNS on frequency, duration and intensity of drop attacks was separately addressed by a modification of McHugh scale. RESULTS: VNS produced a mean seizure rate reduction of 41% at six months, 50% at twelve months, and 54% at thirty-six months. After one year of stimulation, thirteen patients with SE-MISF (52%) and three patients with LGS (21%) showed a reduction above 50% in all seizures' frequency rate. As for drop attacks, eight patients (20%) gained a reduction above 50%, while seven patients (17%) showed a reduction only in intensity and duration. Cognitive level and adaptive behaviour were unchanged, while a better quality of life was reported in half out of the patients. CONCLUSIONS: VNS had a greater effect in reducing seizures frequency and drop attacks' intensity and duration in SE-MISF patients than LGS patients. An improved quality of life was observed also in those patients who only reduced the intensity and duration of drop attacks.

13. **Rose S, Tao JX. Seizure freedom with VNS monotherapy: a case report. *Seizure*. 2011;20(9):735-7.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21764334>  
[http://ac.els-cdn.com/S1059131111001750/1-s2.0-S1059131111001750-main.pdf?\\_tid=8978494c-9279-11e2-9b1f-00000aacb360&acdnat=1363906327\\_ef4898e1372a9d6b7f7acf33fd534326](http://ac.els-cdn.com/S1059131111001750/1-s2.0-S1059131111001750-main.pdf?_tid=8978494c-9279-11e2-9b1f-00000aacb360&acdnat=1363906327_ef4898e1372a9d6b7f7acf33fd534326)  
**Abstract** Vagus nerve stimulation (VNS) is generally considered as a palliative treatment for patients with drug-resistant partial onset epilepsy. Although seizure freedom can be occasionally achieved in patients with VNS, anti-epileptic medications (AEDs) are commonly required to maintain seizure freedom. We report a case that a patient became seizure free for 5 years with VNS monotherapy. To our knowledge, a similar case has not been reported previously.
14. **Cukiert A, Mariani PP, Burattini JA, Cukiert CM, Forster C, Baise C, et al. Vagus nerve stimulation might have a unique effect in reflex eating seizures. *Epilepsia*. 2010;51(2):301-3.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19780799>  
<http://onlinelibrary.wiley.com/store/10.1111/j.1528-1167.2009.02278.x/asset/j.1528-1167.2009.02278.x.pdf?v=1&t=he943q5y&s=f5ea9752caa16c27c943b34635282f0925b64dea>  
**Abstract** We studied the effects of vagus nerve stimulation (VNS) on eating seizures, which theoretically would be triggered by neural activity and signaling from organs innervated by the vagus nerve. Three adult patients with daily nonreflex and reflex eating seizures were studied; one patient also had hot-water seizures. One patient had bilateral polymicrogyria and two had normal magnetic resonance imaging (MRI) findings. All patients were submitted to VNS implantation and had at least 2 years of postimplantation follow-up. Final stimulation parameters were 2.0-2.5 mA, 500 micros, and 30 Hz. Eating seizures decreased 70-95% and nonreflex seizures decreased 0-40% after VNS. There was no improvement in hot-water seizures. VNS seems to be an especially useful treatment modality in patients with reflex eating seizures not amenable to resective surgery.
15. **Kamath MV, Thomson MS, Gaitonde S, Upton A. Longer-term effects of implanted vagal nerve stimulation. *J Long Term Eff Med Implants*. 2010;20(3):251-67.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21395521>  
**Abstract** Vagal nerve stimulation (VNS) is a non-pharmacologic therapeutic intervention approved in adults and children with neuropsychiatric disorders. Studies conducted over the past 20 years have demonstrated that VNS results in immediate and longer-term changes in brain regions implicated in neuropsychiatric disorders, such as the thalamus, cerebellum, orbitofrontal cortex, limbic system, hypothalamus, and medulla with vagus innervations. This review summarizes the effects of longer-term implanted VNS and how the incorporation of this non-pharmacologic therapeutic management in the treatment regime can be beneficial to address the needs of patients who are unable to tolerate medications and/or undergo surgery and do not respond to pharmacologic therapies. We also highlight the therapeutic efficacy of longer-term implanted VNS, safety, tolerability, patient acceptance, adherence, and adverse events, if any, in adults and children in this modality of treatment.

16. **Kuba R, Nesvadba D, Brazdil M, Oslejskova H, Rzyi M, Rektor I. Effect of chronic vagal nerve stimulation on interictal epileptiform discharges. *Seizure*. 2010;19(6):352-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20579909>  
[http://ac.els-cdn.com/S1059131110001135/1-s2.0-S1059131110001135-main.pdf?\\_tid=89ad43f0-8cc4-11e2-93fa-00000aab0f6c&acdnat=1363278832\\_1eb06b020def77b09e420c277035c07a](http://ac.els-cdn.com/S1059131110001135/1-s2.0-S1059131110001135-main.pdf?_tid=89ad43f0-8cc4-11e2-93fa-00000aab0f6c&acdnat=1363278832_1eb06b020def77b09e420c277035c07a)  
**Abstract** We evaluated the effect of vagus nerve stimulation (VNS) on interictal epileptiform discharges (IEDs) in 32 epileptic patients (18 females; 14 males) with an average age of 42.2+/-11.4 years, all of whom had been suffering from epilepsy for an average of 29.2+/-14.5 years. All of the patients had received VNS for 5 years. The first EEG was performed prior to the initiation of stimulation; the second EEG was performed at the 5-year follow-up visit. The duration of each EEG was 30 min. We compared these two EEGs in terms of the number of IEDs present in each patient and correlated them to other variables. The average total number of IEDs during EEG and the total number of seconds in which IEDs were present decreased significantly after 5 years of stimulation from 97.3+/-106.9 resp. 80.6+/-86.1 to 49.4+/-94.0 resp. 37.8+/-65.0. Although there was no positive correlation between the reduction of IEDs and the percent of seizure reduction, we found a greater decrease of IEDs in patients who responded to VNS in comparison to those who did not. The decrease of IEDs was more pronounced in patients suffering from temporal lobe epilepsy than in patients suffering from extratemporal epilepsy. No other significant correlations were found. VNS reduced IEDs in patients chronically simulated for epilepsy. The reduction of IEDs was greater in patients who responded to VNS and in patients suffering from temporal lobe epilepsy.
17. **Lee HO, Koh EJ, Oh YM, Park SS, Kwon KH, Choi HY. Effect of vagus nerve stimulation in post-traumatic epilepsy and failed epilepsy surgery : preliminary report. *J Korean Neurosurg Soc*. 2008;44(4):196-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19096676>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2588308/pdf/jkns-44-196.pdf>  
**Abstract** OBJECTIVE: Vagus nerve stimulation (VNS) has been used in epilepsy patients refractory to standard medical treatments and unsuitable candidates for resective or disconnective surgery. In this study, we investigated the efficacy of VNS to patients who had refractory result to epilepsy surgery and patients with post-traumatic epilepsy. METHODS: We analyzed the effect of VNS in 11 patients who had undergone previous epilepsy surgery and patients with intractable post-traumatic epilepsy associated with brain injury. All patients underwent VNS implantation between October 2005 and December 2006. RESULTS: We evaluated seizure frequency before and after implantation of VNS and maximum follow up period was 24 months. In the first 6 months, 11 patients showed an average of 74.3% seizure reduction. After 12 months, 10 patients showed 85.2% seizure reduction. Eighteen months after implantation, 9 patients showed 92.4% seizure reduction and 7 patients showed 97.2% seizure reduction after 24 months. Six patients were seizure-free at this time. CONCLUSION: We conclude that the VNS is a helpful treatment modality in patients with surgically refractory epilepsy and in patients with post-traumatic epilepsy due to severe brain injury.
18. **Krapohl BD, Deutinger M, Komurcu F. Vagus nerve stimulation: treatment modality for epilepsy. *Medsurg Nurs*. 2007;16(1):39-44; discussion 45, 54.**  
<http://www.ncbi.nlm.nih.gov/pubmed/17441630>  
**Abstract** Anticonvulsant medication is the golden standard for treatment of epilepsy. For patients who do not benefit sufficiently from anticonvulsants, vagal nerve stimulation using an implantable electrical nerve stimulator may be an option to reduce seizure frequency and intensity, thus improving patients' quality of life. The results of a series of vagus nerve stimulator implantations are described.

19. Hui AC, Lam JM, Wong KS, Kay R, Poon WS. Vagus nerve stimulation for refractory epilepsy: long term efficacy and side-effects. *Chin Med J (Engl)*. 2004;117(1):58-61. <http://www.ncbi.nlm.nih.gov/pubmed/14733774>  
**Abstract** BACKGROUND: In general vagus nerve stimulation (VNS) can serve as an adjunctive treatment for patients with refractory partial-onset seizures. And we evaluated the long-term efficacy and safety of VNS in a group of Chinese patients with refractory epilepsy. METHODS: Of 127 patients with refractory epilepsy, 13 patients who were not eligible for surgical intervention were implanted with the Cyberonics VNS system. Seizure frequency, physical examination and side effects profile were recorded at follow-up visits for a minimum of 18 months. RESULTS: Mean duration of treatment was 47.4 months, and the longest follow-up period was 71 months. Mean baseline seizure frequency was 26.6 seizures per month. The mean percentage reductions in convulsions were 33.2%, 47.1% and 40.0% at 6, 12 and 18 months, respectively. One patient became seizure free, and six (46%) had 50% or more reduction in seizure frequency. Response was poor (< 20% reduction) in five patients (39%). Side effects were uncommon. CONCLUSIONS: The effectiveness of VNS was sustained and was well tolerated but benefited only a sub-group of patients with intractable convulsions.
20. Fisher RS, Handforth A. Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 1999;53(4):666-9; comment *Neurology*. 2000;54(10):2027. <http://www.ncbi.nlm.nih.gov/pubmed/10489023>
21. Durm K. Vagal stimulator helps patients control seizures. *Nurs Spectr (Wash D C)*. 1998;8(8):7. <http://www.ncbi.nlm.nih.gov/pubmed/10542710>
22. Fisher RS, Krauss GL, Ramsay E, Laxer K, Gates J. Assessment of vagus nerve stimulation for epilepsy: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 1997;49(1):293-7; comment *Neurology*. 2000;54(10):2027. <http://www.ncbi.nlm.nih.gov/pubmed/9222210>
23. Salinsky MC, Burchiel KJ. Vagus nerve stimulation has no effect on awake EEG rhythms in humans. *Epilepsia*. 1993;34(2):299-304. <http://www.ncbi.nlm.nih.gov/pubmed/8453941>  
**Abstract** Vagus nerve stimulation (VNS) has been shown to have an anticonvulsant effect in several animal models, and clinical trials in patients were recently started. Experimental data have suggested that VNS may act by modulating EEG rhythmic activity. We studied the acute effects of VNS on EEG background rhythms in patients undergoing treatment for poorly controlled partial seizures. Six patients had recordings of satisfactory quality for quantitative EEG analysis. A significant effect of VNS on EEG total power, median frequency, or power in any of the conventional frequency bands, could not be demonstrated. Intraindividual analysis did not show a significant effect of VNS on total power for any patient, including those with apparent clinical response. We conclude that VNS at the parameters in current clinical use does not alter awake EEG background rhythms. The mechanism mediating acute antiepileptic effect remains unknown.

**VNS Mentioned**

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1. **Henze M, Tiniakov R, Samarel A, Holmes E, Scrogin K. Chronic fluoxetine reduces autonomic control of cardiac rhythms in rats with congestive heart failure. *Am J Physiol Heart Circ Physiol.* 2013;304(3):H444-54.**

<http://www.ncbi.nlm.nih.gov/pubmed/23220332>

<http://ajpheart.physiology.org/content/304/3/H444.long>

**Abstract** Up to 40% of patients with heart failure develop depression, and depression is an independent risk factor for cardiovascular mortality in this patient population. Consequently, increasing numbers of patients with heart failure are treated with antidepressants. Selective serotonin reuptake inhibitors are typically the antidepressant of choice since this drug class has limited cardiovascular toxicity. However, little is known about the effects of selective serotonin reuptake inhibitors on autonomic cardiac regulation in congestive heart failure (CHF). Here, indexes of cardiac autonomic control were evaluated before and during chronic fluoxetine (FLX) treatment (20 mg.kg<sup>-1</sup>.day<sup>-1</sup>, 5 wk) in rats that developed CHF after coronary artery ligation. FLX reduced the low-frequency (LF) component of heart rate variability (HRV;  $P < 0.01$ ) as well as the sympathetic contribution to LF HRV ( $P < 0.01$ ) in both CHF and sham-operated rats. Both FLX and CHF reduced high-frequency HRV ( $P < 0.01$ ). Spontaneous baroreflex gain was decreased in CHF rats 8 wk after ligation ( $P < 0.01$ ). Cross-spectral coherence between the interbeat interval and mean arterial pressure was reduced in the LF domain 3 wk after ligation in CHF rats ( $P < 0.01$ ) and was further reduced after chronic FLX treatment ( $P < 0.01$ ). Plasma catecholamines and LF blood pressure variability were not affected by FLX. Chronotropic responses to both efferent vagal nerve stimulation and isoproterenol administration were reduced in CHF rats and by FLX ( $P < 0.01$ ), whereas inotropic responses to isoproterenol were reduced only in CHF rats ( $P < 0.01$ ). These data indicate that chronic FLX reduces the responsiveness to autonomic output controlling cardiac rhythm and may further compromise autonomic regulation of cardiac function in CHF.

2. **Motohashi N. [Will electroconvulsive therapy disappear in the near future?]. *Seishin Shinkeigaku Zasshi.* 2012;114(10):1208-15. Japanese.**

<http://www.ncbi.nlm.nih.gov/pubmed/23234202>

**Abstract** Electroconvulsive therapy (ECT) has been widely used, with some modification of its methods, for the treatment of refractory mental disorders. In Japan, brief-pulse ECT was approved in 2002 under conditions that well-trained psychiatrists should administer ECT and that modified ECT is mandatory. However, unmodified ECT is still often performed in Japan. We have to improve safety of ECT further. Major indications for ECT are depression and catatonia. Mechanisms of ECT are still unknown, but the neurogenesis hypothesis is promising. Furthermore, several brain stimulation techniques without seizure induction, such as transcranial magnetic stimulation, vagus nerve stimulation, deep brain stimulation and transcranial direct current stimulation, have been introduced for the treatment of refractory mental disorders. Ethical criteria must be determined for further research and treatment with these techniques.

3. **Kalyani BG, Venkatasubramanian G, Arasappa R, Rao NP, Kalmady SV, Behere RV, et al. Neurohemodynamic correlates of 'OM' chanting: A pilot functional magnetic resonance imaging study. *Int J Yoga*. 2011;4(1):3-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21654968>  
<http://www.ijoy.org.in/article.asp?issn=0973-6131;year=2011;volume=4;issue=1;spage=3;epage=6;aulast=Kalyani>

**Abstract** BACKGROUND: A sensation of vibration is experienced during audible 'OM' chanting. This has the potential for vagus nerve stimulation through its auricular branches and the effects on the brain thereof. The neurohemodynamic correlates of 'OM' chanting are yet to be explored. MATERIALS AND METHODS: Using functional Magnetic Resonance Imaging (fMRI), the neurohemodynamic correlates of audible 'OM' chanting were examined in right-handed healthy volunteers (n=12; nine men). The 'OM' chanting condition was compared with pronunciation of "ssss" as well as a rest state. fMRI analysis was done using Statistical Parametric Mapping 5 (SPM5). RESULTS: In this study, significant deactivation was observed bilaterally during 'OM' chanting in comparison to the resting brain state in bilateral orbitofrontal, anterior cingulate, parahippocampal gyri, thalami and hippocampi. The right amygdala too demonstrated significant deactivation. No significant activation was observed during 'OM' chanting. In contrast, neither activation nor deactivation occurred in these brain regions during the comparative task - namely the 'ssss' pronunciation condition. CONCLUSION: The neurohemodynamic correlates of 'OM' chanting indicate limbic deactivation. As similar observations have been recorded with vagus nerve stimulation treatment used in depression and epilepsy, the study findings argue for a potential role of this 'OM' chanting in clinical practice.

4. **Al-Otaibi FA, Hamani C, Lozano AM. Neuromodulation in epilepsy. *Neurosurgery*. 2011;69(4):957-79; discussion 979.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21716154>

**Abstract** Neuromodulation strategies have been proposed to treat a variety of neurological disorders, including medication-resistant epilepsy. Electrical stimulation of both central and peripheral nervous systems has emerged as a possible alternative for patients who are not deemed to be good candidates for resective procedures. In addition to well-established treatments such as vagus nerve stimulation, epilepsy centers around the world are investigating the safety and efficacy of neurostimulation at different brain targets, including the hippocampus, thalamus, and subthalamic nucleus. Also promising are the preliminary results of responsive neuromodulation studies, which involve the delivery of stimulation to the brain in response to detected epileptiform or preepileptiform activity. In addition to electrical stimulation, novel therapeutic methods that may open new horizons in the management of epilepsy include transcranial magnetic stimulation, focal drug delivery, cellular transplantation, and gene therapy. We review the current strategies and future applications of neuromodulation in epilepsy.

5. **Howland RH. Serendipity and psychopharmacology. *J Psychosoc Nurs Ment Health Serv.* 2010;48(10):9-12.**

<http://www.ncbi.nlm.nih.gov/pubmed/20873698>

**Abstract** This article describes several examples where the development of drugs and devices for use in psychiatry followed from initial serendipitous observations. The potential psychotropic properties of chlorpromazine (Thorazine((R))) were first noted in surgical patients when the drug was being investigated as a potentiator of anesthesia. Similar findings were noted with iproniazid (Marsilid((R))), developed for the treatment of tuberculosis, and the drug was later released for clinical use as an antidepressant agent. The development of meprobamate (Miltown((R))), an approved treatment for anxiety, evolved from initial efforts to find a chemical that would inhibit the enzymatic destruction of the antibiotic drug penicillin. The psychiatric uses of lamotrigine (Lamictal((R))) and vagus nerve stimulation were prompted by initial observations that epilepsy patients receiving these treatments had positive mood effects. Nurses should be familiar with the concept of serendipity, as they often are in the best position to observe, record, and report on unexpected clinical effects in patients taking any kind of prescription or nonprescription medication.

6. **Li X, Fan M, Cao Y, Hong Z. Electrical stimulation of the olfactory mucosa: an alternative treatment for the temporal lobe epilepsy? *Med Hypotheses.* 2010;74(1):24-6.**

<http://www.ncbi.nlm.nih.gov/pubmed/19762161>

**Abstract** Epilepsy threatens the health of more than 50 million people all over the world. The temporal lobe epilepsy (TLE) is one of the most common forms of epilepsy and still is one of the commonest drug-resistant epilepsies (so called refractory epilepsy). Vagus nerve stimulation (VNS) was the first non-pharmaceutical therapy used for the treatment of medically refractory partial onset seizures in 1997, but its more extensive application was hampered by its high cost and side effects. It had been suggested that olfactory stimulation with chemical products was likely to lead to widespread de-synchronization, akin to VNS in exercising its seizure-reducing property. But it is hard to control the "dosage" of olfactory stimulation with chemical products and the awful feelings caused by chemicals made it difficult to clinic practice. Here we propose an alternative method, electric stimulation to the olfactory mucosa for the treatment of TLE. Different from VNS, a tiny electrode for the stimulation will be minimized into a dimension small enough to fix into nasal cavity and attached to the olfactory mucosa through a nostril in current proposal, so the side effects of VNS caused by operation will be totally avoided. Based on data from related researches, we believe that current therapy we propose here may be a safe and efficient treatment for TLE in the future.

7. **Arts WF, Geerts AT. When to start drug treatment for childhood epilepsy: the clinical-epidemiological evidence. *Eur J Paediatr Neurol.* 2009;13(2):93-101.**

<http://www.ncbi.nlm.nih.gov/pubmed/18567515>

**Abstract** INTRODUCTION: Many data on the course and prognosis after provoked and unprovoked single and multiple seizures in childhood have been collected in the past decennia by prospective, large-scale, long-term observational cohort studies. These data may serve to guide treatment decisions and help to design controlled trials investigating treatment strategies in childhood epilepsy. METHODS: The results of the Dutch study of epilepsy in childhood will be compared with those of other studies. We will also discuss the potential consequences of these results for the "why" and "when" of the decision to start treatment. RESULTS: Recurrence after a solitary unprovoked seizure in childhood is about 50%. Those with a recurrence have a similar outcome of their epilepsy compared to children presenting with multiple seizures, regardless whether they were treated after the first seizure or not. This argues in favour of postponing anti-epileptic drug (AED) treatment until at least a second seizure has occurred. After an unprovoked status epilepticus (SE), later outcome is not worse than after presentation with a short seizure. Therefore, long-term AED treatment after a single unprovoked SE may not be necessary either. The same holds true for children presenting with a short (less than one week) burst of unprovoked seizures. One quarter of them do not have recurrences and the final prognosis of children with recurrences does again not differ from the prognosis of the entire cohort. Findings in new-onset epilepsy further indicate that AED treatment can be safely omitted or at least postponed in about 15%, especially those with only a small number of seizures before presentation, those with benign partial epilepsy and those with sporadic generalised tonic-clonic seizures. On the reverse side, three considerations might lead to the decision to start early and aggressive treatment: the dangers of the seizures, the chance of intractability and the possibility of intellectual decline caused by recurrent seizures or epileptic activity. In idiopathic generalised absence epilepsy, the risks of accidents and learning problems indeed prompt early AED treatment. A self-propagating mechanism of seizures promoting the occurrence of more seizures, in the end causing intractable epilepsy (Gowers), occurs only rarely. Real intractability is seen in only 5-15% of the children with new-onset epilepsy. The chance of intractability is increased by variables like symptomatic aetiology, localisation-related epilepsy, and an early unfavourable course. Landau-Kleffner or continuous spikes and waves during sleep (CSWS) syndrome cause cognitive decline and syndromes like West, Lennox-Gastaut or Dravet's induce both psychomotor regression and intractability. In such cases, early aggressive treatment is indicated, including early consideration of the ketogenic diet, immunotherapy, vagus nerve stimulation and, if possible, referral for epilepsy surgery. CONCLUSIONS: Omitting or postponing treatment after a solitary seizure, an unprovoked SE, a single burst of seizures or multiple infrequent seizures usually does not worsen the prognosis. A poor prognosis and the consequent indication for early and aggressive treatment are dependent mainly upon the presence of variables like symptomatic aetiology, certain epilepsy types and syndromes, and the early evolution of the epilepsy in that particular child. Intellectual decline caused by seizures or epilepsy is rare and may be confined to certain specific and readily recognizable syndromes.

8. **Wong TT, Kwan SY, Chang KP, Hsiu-Mei W, Yang TF, Chen YS, et al. Corpus callosotomy in children. *Childs Nerv Syst.* 2006;22(8):999-1011.**

<http://www.ncbi.nlm.nih.gov/pubmed/16830167>

<http://link.springer.com/article/10.1007%2Fs00381-006-0133-4>

**Abstract** INTRODUCTION: For children of medical resistant epilepsy without resectable epileptogenic zone, corpus callosotomy and vagus nerve stimulation (VNS) therapy are the two commonly used palliative epilepsy surgeries that can be considered. Although their routes and mechanisms to control epilepsy are different, both surgeries have shown their efficacy in selected candidates. The most common candidates for palliative surgery are in infants and children with organic encephalopathic types of epilepsy including infantile spasms/West syndrome, Lennox-Gastaut syndrome (LGS), severe epilepsy with multiple independent spike foci (SE-MISF) and selected symptomatic partial epilepsy to relief seizures and to stabilize co morbidities (Hirsch and Arzimanoglou, *Revue Neurologique* [Hirsch E and Arzimanoglou A, *Rev Neurol (Paris)*. 160 Spec No 1:5S210-S219, (2004); Ohtahara S and Yamatogi Y, *J Clin Neurophysiol* 20(6):398-407, (2003); Wheless JW and *Epilepsia* 45(Suppl 5):17-22, (2004); Trevathan E, *J Child Neurol* 17 Suppl 2:2S9-2S22, (2002)]. DISCUSSION: Callosotomy is a major and destructive but affordable surgical procedure as compare to the relative simple but costly extracranial procedure of VNS therapy. However, callosotomy is a safe and effective palliative operation in neurosurgeons familiar with the surgical procedure. Equipments for callosotomy can be as simple as headlight and binocular loupes, self-retention brain retractor, bipolar cauterization, and simple microinstruments.

9. **Giorgi FS, Pizzanelli C, Biagioni F, Murri L, Fornai F. The role of norepinephrine in epilepsy: from the bench to the bedside. *Neurosci Biobehav Rev.* 2004;28(5):507-24.**

<http://www.ncbi.nlm.nih.gov/pubmed/15465138>

**Abstract** This article provides a brief review of the role of norepinephrine (NE) in epilepsy, starting from early studies reproducing the kindling model in NE-lesioned rats, through the use of specific ligands for adrenergic receptors in experimental models of epilepsy, up to recent advances obtained by using transgenic and knock-out mice for specific genes expressed in the NE system. Data obtained from multiple experimental models converge to demonstrate the antiepileptic role of endogenous NE. This effect predominantly consists in counteracting the development of an epileptic circuit (such as in the kindling model) rather than increasing the epileptic threshold. This suggests that NE activity is critical in modifying epilepsy-induced neuronal changes especially on the limbic system. These data encompass from experimental models to clinical applications as recently evidenced by the need of an intact NE innervation for the antiepileptic mechanisms of vagal nerve stimulation (VNS) in patients suffering from refractory epilepsy. Finally, recent data demonstrate that NE loss increases neuronal damage following focally induced limbic status epilepticus, confirming a protective effect of brain NE, which has already been shown in other neurological disorders.

**VNS Surgical Procedure - Implantation**

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1. **Horowitz G, Amit M, Fried I, Neufeld MY, Sharf L, Kramer U, et al. Vagal nerve stimulation for refractory epilepsy: the surgical procedure and complications in 100 implantations by a single medical center. *Eur Arch Otorhinolaryngol.* 2013;270(1):355-8.**

<http://www.ncbi.nlm.nih.gov/pubmed/22836871>

**Abstract** In 1997, the US Food and Drug Administration approved the use of intermittent stimulation of the left vagal nerve as adjunctive therapy for seizure control. Vagal nerve stimulation (VNS) has since been considered a safe and effective treatment for medically intractable seizures. The objective of this study is to present our experience with the surgical procedure and outcomes after VNS insertion in the first 100 consecutive patients treated at the Tel-Aviv "Sourasky" Medical Center (TASMC). All patients who underwent VNS device implantation by the authors at TASMC between 2005 and 2011 were studied. The collected data included age at onset of epilepsy, seizure type, duration of epilepsy, age at VNS device implantation, seizure reduction, surgical complications, and adverse effects of VNS over time. Fifty-three males and 47 females, age 21.2 +/- 11.1 years, underwent VNS implantation. Indications for surgery were medically refractory epilepsy. The most common seizure type was focal (55 patients, 55 %). Seizure duration until implantation was 14.4 +/- 9 years. Mean follow-up time after device insertion was 24.5 +/- 22 months. Complications were encountered in 12 patients. The most common complication was local infection (6 patients, 6 %). Six devices were removed-four due to infection and two due to loss of clinical effect. Currently, 63 patients remain in active long-term follow-up; of these, 35 patients have >50 % reduction in frequency of attacks. VNS is a well-tolerated and effective therapeutic alternative in the management of medically refractory epilepsy. The surgical procedure is safe and has a low complication rate.

2. **Duty BD, Wozniak SE, Selden NR. Vagal nerve stimulator placement for medically refractory seizures in a child treated with phrenic nerve pacing for congenital central hypoventilation syndrome. *J Neurosurg Pediatr.* 2011;7(4):413-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/21456915>

**Abstract** Congenital central hypoventilation syndrome (CCHS) is a rare, idiopathic disorder characterized by a failure of automatic respiration. Abnormalities such as seizure disorder, failure to thrive, and Hirschsprung disease have been associated with CCHS. In this report, the authors discuss the use of vagal nerve stimulation (VNS) to treat a medically refractory seizure disorder in a child who had previously undergone placement of bilateral phrenic nerve stimulators for treatment of CCHS. Concomitant use of phrenic and vagal nerve stimulators has not previously been reported in the literature. No adverse reactions were noted with both devices working. Diaphragmatic pacing (DP) was clinically unaffected by VNS. The patient experienced a marked reduction in seizure frequency and severity following vagal nerve stimulator placement. Based on this case, the authors conclude that VNS is a potentially safe and efficacious treatment option for seizure disorder associated with CCHS in patients undergoing DP.

3. **Spuck S, Tronnier V, Orosz I, Schonweiler R, Sepehrnia A, Nowak G, et al. Operative and technical complications of vagus nerve stimulator implantation. *Neurosurgery*. 2010;67(2 Suppl Operative):489-94.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21099577>  
**Abstract** BACKGROUND: The treatment of refractory epilepsy by vagus nerve stimulation (VNS) is a well-established therapy option for patients not suitable for epilepsy surgery and therapy refractory depressions. OBJECTIVE: To analyze surgical and technical complications after implantation of left-sided VNS in patients with therapy-refractory epilepsy and depression. METHODS: One hundred five patients receiving a VNS or VNS-related operations (n = 118) from 1999 to 2008 were investigated retrospectively. RESULTS: At the time of operation, 84 patients were younger than 18 years, with a mean age of 10.5 years. Twenty (19%) patients had technical problems or complications. In 6 (5.7%) patients these problems were caused by the operation. The device was removed in 8 cases. The range of surgically and technically induced complications included electrode fractures, early and late onset of deep wound infections, transient vocal cord palsy, cardiac arrhythmia under test stimulation, electrode malfunction, and posttraumatic dysfunction of the stimulator. CONCLUSION: VNS therapy is combined with a wide spread of possible complications. Technical problems are to be expected, including electrode fracture, dislocation, and generator malfunction. The major complication in younger patients is the electrode fracture, which might be induced by growth during adolescence. Surgically induced complications of VNS implantation are comparably low. Cardiac symptoms and recurrent nerve palsy need to be taken into consideration.
4. **Iturri Clavero F, Gonzalez Uriarte A, Tamayo Medel G, Pomposo Gaztelu IC, Cano Dorransoro M, Martinez Ruiz A. [Perioperative considerations in vagal nerve stimulator implantation]. *Rev Esp Anesthesiol Reanim*. 2010;57(7):431-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20857639>  
**Abstract** Vagal nerve stimulation has become an a important tool in the treatment of refractory epilepsy, which continues to be the main indication for this technique. Other therapeutic indications are emerging, however, and vagal nerve stimulation has now been approved for major depression. Additional possible uses under study include morbid obesity, Alzheimer disease, chronic pain syndromes, and certain neuropsychologic disorders. This review considers perioperative aspects relevant to using this therapeutic procedure with a view to facilitating better and more integrated management of its application.
5. **Pratap R, Farboud A, Patel H, Montgomery P. Vagal nerve stimulator implantation: the otolaryngologist's perspective. *Eur Arch Otorhinolaryngol*. 2009;266(9):1455-9.**  
<http://www.ncbi.nlm.nih.gov/pubmed/19083010>  
<http://link.springer.com/article/10.1007%2Fs00405-008-0887-2>  
**Abstract** Vagal nerve stimulation (VNS) is a recognised and effective measure in treating refractory epilepsy and depression. VNS implantation is a widely accepted surgical procedure, most commonly performed by neurosurgeons. Otolaryngologists, in particular those with an interest in head and neck surgery, are very familiar with the surgical anatomy and dissection of the vagus nerve in the carotid sheath. We present a retrospective analysis of the first 12 patients to be implanted in our department. Our series suggests that otolaryngologists can safely and effectively perform VNS implantation. Otolaryngologists can assess and treat the most common post-operative complication of dysphonia and help the neurologist set the correct level of stimulation in such a way as to minimise laryngeal complications.
6. **Gercek A, ozek MM. From the anesthesiologist's perspective: placement of vagal nerve stimulator. *Anesth Analg*. 2006;102(6):1910.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16717360>

7. **Tubbs RS, Loukas M, Shoja MM, Salter EG, Oakes WJ, Blount JP. Approach to the cervical portion of the vagus nerve via the posterior cervical triangle: a cadaveric feasibility study with potential use in vagus nerve stimulation procedures. *J Neurosurg Spine*. 2006;5(6):540-2.**

<http://www.ncbi.nlm.nih.gov/pubmed/17176019>

**Abstract** OBJECT: The authors describe a technique in which the cervical portion of the vagus nerve is exposed during procedures such as neuroma resection or, more commonly, during the placement of a vagus nerve stimulator. METHODS: To test their hypothesis that a posterolateral approach to the vagus nerve may be feasible and efficacious, the authors performed dissection of the left-sided vagus nerve in 13 adult cadavers. The carotid sheath was exposed via the posterior cervical triangle, and the vagus nerve was identified posterolaterally. Measurements were made of the length of available nerve, and the anatomical approach was documented. As part of a comparison study regarding the available length of nerve, the authors exposed the left vagus nerve in five additional adult cadavers via a standard anterior approach to the carotid sheath, and compared the results obtained with each technique. A mean length of 12 cm of the vagus nerve was isolated when using the posterior approach to the carotid sheath, whereas a mean length of 11 cm of the nerve was documented when using the anterior approach. With the aforementioned posterior approach, no obvious injury occurred to the vagus nerve or other local neurovascular structures such as the spinal accessory nerve. CONCLUSIONS: Evaluation of the findings obtained in the present cadaveric study showed that a posterior approach to the vagus nerve is feasible. The technique for posterior exposure of the carotid sheath may prove useful in surgical exposures of the vagus nerve when a standard anterior method is not possible.

8. **Bauman JA, Ridgway EB, Devinsky O, Doyle WK. Subpectoral implantation of the vagus nerve stimulator. *Neurosurgery*. 2006;58(4 Suppl 2):ONS-322-5; discussion ONS-325-6.**

<http://www.ncbi.nlm.nih.gov/pubmed/16582656>

**Abstract** OBJECTIVE: To report the technique of subpectoral (SP) implantation of the vagus nerve stimulator (VNS) generator. METHODS: We retrospectively reviewed and compared demographics and complications from patients receiving either subcutaneous (SQ; n = 107) or SP (n = 138) VNS implants, performed by one surgeon (WKD) between 1999 and 2003. Selection of implant location was made during the preoperative surgeon-patient consultation on the basis of surgeon recommendation and patient preference. RESULTS: The standard VNS generator implantation is performed within a SQ pocket in the left infraclavicular region of the chest. We have modified this technique by placing the generator into a deeper pocket SP, beneath the pectoralis major muscle, while tunneling the electrodes SQ in the usual fashion. The SP group was substantially younger (median age 19 yr) compared with the SQ group (median age 29 yr). At an average follow-up of 52 months for SQ implants and 28.4 months for SP implants, there were 2.9% infections per patient in the SQ group and 2.5% infections per patient in the SP group. There were three cases of excessive generator mobility in the SQ group; no cases occurred in the SP group. CONCLUSION: The SP implantation technique provides an attractive alternative to SQ VNS implantation. With increased soft tissue coverage, we provide improved cosmesis, increased wound durability to tampering and trauma, and a comparable infection rate with the SQ group.

9. **Ghanem T, Early SV. Vagal nerve stimulator implantation: an otolaryngologist's perspective. *Otolaryngol Head Neck Surg.* 2006;135(1):46-51.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16815181>  
<http://oto.sagepub.com/content/135/1/46>  
**Abstract** OBJECTIVE: This study was conducted to compare an otolaryngologist's experience with a cohort of epilepsy patients implanted with a vagal nerve stimulator (VNS) to previously published data. METHODS: Demographics, preoperative seizure frequency, medications, and complications were retrospectively collected from patients implanted by the senior author. Postoperative medications and seizure frequency were obtained from referring neurologists. RESULTS: Seventeen patients were implanted over a 24-month period. Average age was 28.3 years. Patients presented with petit mal (n = 3), tonic-clonic (n = 6), complex partial (n = 5), and grand mal (n = 8) seizures. Mean follow-up postimplantation was 13.5 months. Most patients had at least a 50% reduction of seizure frequency, with 3 patients being seizure free. There were no postoperative infections. One patient had left vocal cord immobility. The most common side effect was voice disturbance during device activation. CONCLUSION: Otolaryngologists are well equipped to perform VNS implantation and to diagnose and treat possible laryngeal side effects. EBM rating: C-4.
10. **Lobe TE, Wright SK, Irish MS. Novel uses of surgical robotics in head and neck surgery. *J Laparoendosc Adv Surg Tech A.* 2005;15(6):647-52.**  
<http://www.ncbi.nlm.nih.gov/pubmed/16366877>  
<http://online.liebertpub.com/doi/abs/10.1089/lap.2005.15.647>  
**Abstract** PURPOSE: To demonstrate the utility of robotically assisted approaches in head and neck surgery. MATERIALS AND METHODS: Two teenage patients, one with a solitary thyroid nodule who was scheduled for a right thyroid lobectomy and the other with intractable seizures who was scheduled for placement of a vagal nerve stimulator were offered the option of a robotically assisted technique using a transaxillary endoscopic approach. RESULTS: Both procedures were completed successfully using the da Vinci surgical system (Intuitive Surgical, Sunnyvale, California). A 12 mm telescope and 5 mm instruments were used. There was sufficient mobility of the robotic arms despite the small working space. There were no complications, minimal pain in the axillary incisions, and patient satisfaction was high. Operative times were 4.5 and 4.2 hours, respectively. CONCLUSION: Transaxillary, endoscopic, robotically assisted approaches to the head and neck are feasible. The addition of robotics improves surgical dexterity in a difficult-to-reach anatomic region. Patient satisfaction appears high because of the avoidance of a cervical incision.
11. **Santos PM. Surgical placement of the vagus nerve stimulator. *Operative Techniques in Otolaryngology-Head and Neck Surgery.* 2004;15(3):201-9.**  
<http://www.sciencedirect.com/science/article/pii/S1043181004000880>  
**Abstract** The vagus nerve stimulator has become increasingly more common as an adjunctive therapy for patients with antiepileptic medication resistance. The surgical procedure is performed within the left cervical portion of the vagus nerve with the combined pulse generator/battery placed in a preaxillary position. A growing number of otolaryngologists are performing this procedure. This article is presented to assist in the surgeon's understanding of the device parts, patient/guardian consent requirements, preoperative planning on the part of the surgeon as well as the operating room team, intraoperative surgical techniques to maximize the success of the surgery, and methods for decreasing the risk of complications.

12. Kirse DJ, Werle AH, Murphy JV, Eyen TP, Bruegger DE, Hornig GW, et al. Vagus nerve stimulator implantation in children. *Arch Otolaryngol Head Neck Surg.* 2002;128(11):1263-8.  
<http://www.ncbi.nlm.nih.gov/pubmed/12431167>  
<http://archotol.jamanetwork.com/data/Journals/OTOL/11881/OOA10241.pdf>  
**Abstract** BACKGROUND: Vagus nerve stimulation was approved in 1997 as an adjunctive treatment of partial-onset seizures refractory to medical therapy. Subsequent to the initial clinical trials, few studies have been published specifically addressing perioperative management issues. OBJECTIVES: To review the operative technique and perioperative management of patients undergoing vagus nerve stimulator implantation and to analyze complications and their management. DESIGN: Retrospective medical record review and survey of patients who underwent implantation. SETTING: A tertiary care pediatric hospital in Kansas City, Mo. PATIENTS: One hundred two patients aged 21 months to 40 years. INTERVENTION: Vagus nerve stimulator implantation and lead placement. MAIN OUTCOME MEASURES: The surgical technique of vagus nerve stimulator implantation is presented in detail. Perioperative complications are enumerated, and strategies for their management are described. A subjective patient survey addresses some quality-of-life issues and the effect on swallowing and voice. RESULTS: One hundred two patients successfully underwent vagus nerve stimulator implantation. Three patients experienced infection of the chest wound holding the generator and required explantation. These 3 patients underwent reimplantation within 2 months after the infection had cleared. Most patients experience some degree of hoarseness when the generator is activated, but this symptom usually does not significantly affect the ability to communicate. Responses to questions regarding quality of life are positive. CONCLUSIONS: Vagus nerve stimulator implantation has a low incidence of serious complications. Quality of life seems to be improved for most patients. Modifications to the surgical procedure must be considered when performing the implantation on a young patient.
13. Le H, Chico M, Hecox K, Frim D. Interscapular placement of a vagal nerve stimulator pulse generator for prevention of wound tampering. Technical note. *Pediatr Neurosurg.* 2002;36(3):164-6.  
<http://www.ncbi.nlm.nih.gov/pubmed/11919454>  
<http://www.karger.com/Article/FullText/48375>  
**Abstract** In some cognitively delayed children who require a vagal nerve stimulator for treatment of their seizures, there is a risk of wound breakdown and infection from obsessive tampering with the wound. We describe the interscapular placement of the vagal nerve stimulator pulse generator as a method to reduce this risk.

14. **Bernard EJ, Passannante AN, Mann B, Lannon S, Vaughn BV. Insertion of vagal nerve stimulator using local and regional anesthesia. *Surg Neurol.* 2002;57(2):94-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11904199>  
**Abstract** BACKGROUND: Vagal nerve stimulation (VNS) is a valuable therapy for patients with intractable epilepsy. Placement of a vagal nerve stimulator typically requires general anesthesia, which frequently interrupts anticonvulsant therapy. Insertion of the stimulator using regional/local anesthesia may offer the advantages of continuity of anticonvulsant therapy and implantation in the outpatient setting. METHODS: We retrospectively compared the first 10 consecutive patients undergoing VNS implantation under general anesthesia with the first 12 consecutive patients undergoing VNS implantation under regional/local anesthesia. Patients for the regional/local anesthesia were selected on the basis of their ability to cooperate and follow commands. Regional anesthesia for implantation of the VNS leads was achieved by performing superficial and deep cervical plexus blocks. A local anesthetic field block of a small area of the posterior chest provided anesthesia for insertion of the generator. RESULTS: All of the patients undergoing regional/local anesthesia completed the procedure without difficulty and on an outpatient basis. None complained of discomfort, sedation, nausea, or vomiting and none had seizures in the perioperative period. These results contrasted with the group that underwent general anesthesia (n = 10), who had an 80% incidence of nausea and vomiting and a 30% incidence of postoperative seizures. CONCLUSION: VNS implantation under regional/local anesthesia is proficiently performed as an outpatient procedure with minimal postoperative side effects.
15. **Vaughn BV, Bernard E, Lannon S, Mann B, D'Cruz OF, Shockley W, et al. Intraoperative methods for confirmation of correct placement of the vagus nerve stimulator. *Epileptic Disord.* 2001;3(2):75-8.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11431169>  
**Abstract** Vagus nerve stimulation is a progressive therapy for intractable epilepsy. Variations in cervical anatomy can complicate localization of the vagus nerve and may lead to inappropriate placement of the stimulator leads. We have developed two intraoperative techniques that improve correct identification of the vagus nerve. Both of these techniques utilize the co-localization of the recurrent laryngeal nerve with the vagus nerve. For patients undergoing stimulator placement with regional and local anesthesia, the stimulator current intensity is increased until alteration of voice can be confirmed with a voice test. Patients undergoing general anesthesia can also be tested by direct stimulation of the isolated vagus nerve. Utilizing visualization of the larynx and vocal cords via fiberoptic endoscopy, direct stimulation of the vagus nerve will produce a contraction of the left lateral wall of the larynx and tightening of the left vocal cord. Neither of these procedures produce any untoward effects for the patients. We have found these methods improve our ability to confirm correct placement of the stimulator with minimal increase in operative time (with Video).
16. **Patil A, Chand A, Andrews R. Single incision for implanting a vagal nerve stimulator system (VNSS): technical note. *Surg Neurol.* 2001;55(2):103-5.**  
<http://www.ncbi.nlm.nih.gov/pubmed/11301092>  
**Abstract** BACKGROUND: A technique for implanting the vagal nerve stimulator system through a single incision is described. METHOD: A transverse incision is made in the lower part of the neck. Subcutaneous (s.c.) dissection is then done over the clavicle into the infraclavicular area to create a pocket. The vagus nerve is exposed and the electrodes are wrapped around it through the neck incision. The distal ends of the lead are connected to the pulse generator, and latter is then placed in the infraclavicular pocket through the neck incision. RESULTS: Thirty-eight implants were conducted with this technique. The pulse generator could be implanted and anchored to the underlying tissue without any difficulty. Except for wound infections in two patients there was no other complication. CONCLUSION: A single incision is an alternate to the double incision procedure. This procedure can be performed safely.

17. **Williamson PD, Jobst BC. Epilepsy surgery in developing countries. *Epilepsia*. 2000;41 Suppl 4:S45-50. <http://www.ncbi.nlm.nih.gov/pubmed/10963478>**  
**Abstract** Epilepsy surgery (ES) is a well-accepted treatment for medically intractable epilepsy patients in developed countries, but it is highly technology dependent. Such technology is not usually available in developing countries. For presurgical evaluation, magnetic resonance imaging (MRI) and electroencephalogram recording while videotaping the patient have been important. High technology equipment will, in conjunction with MRI, identify approximately 70% of ES candidates. Introducing ES into developing countries will require determining the candidates that are appropriate for the existing medical infrastructure. This article reviews ES and its possible introduction into conditions existing in developing countries. The authors address (a) the types of patients to be considered for resective ES (some patients require a fairly standard series of noninvasive studies: others will require extensive invasive studies), (b) ways to determine which patients might be appropriate for the existing situation (unilateral mesial temporal lobe epilepsy detected with MRI, epilepsy with a circumscribed MRI lesion, hemispheric lesions, circumscribed MRI detected neuronal migration, and development disorders), (c) surgical procedures (local resection, functional hemispherectomy, multiple subpial transections, corpus callosotomy, and implantation of a vagal nerve stimulator), (d) special considerations for introducing ES into developing countries (medical infrastructure, technology, seizure monitoring systems, selective intracarotid/carotid Amytal testing, and surgical equipment), and (e) the limitations, realistic expectations, personnel requirements, and educational function for selected professionals. Delivery of the technology and expertise to perform ES in developing regions of the world is a realizable project, but it would be limited by available technology and existing medical infrastructure. It should be possible in most areas to train local personnel and thereby leave a lasting legacy.
18. **Carey ME, Kutz S. Modified malis bayonet forceps aids application of the cyberonics vagus nerve stimulator electrode: technical note. *Neurosurgery*. 2000;47(4):985-6; discussion 986-7. <http://www.ncbi.nlm.nih.gov/pubmed/11014443>**  
**Abstract** **OBJECTIVE:** To notify neurosurgeons about a modified bayonet forceps that aids application of the vagus nerve stimulating electrode. **METHODS:** The manufacturer (Codman & Shurtleff, Inc., Raynham, MA) extended the tips of an upward-angled Malis bayonet forceps from 2 mm to 6 mm. **RESULTS:** The modified bayonet tips, when placed under the vagus nerve, extend well beyond the edge of the usual vagus nerve to easily accept the electrode lead. **CONCLUSION:** The modified bayonet forceps and depicted wrapping sequence shorten electrode wrapping time.

19. **Maniker A, Liu WC, Marks D, Moser K, Kalnin A. Positioning of vagal nerve stimulators: technical note. *Surg Neurol.* 2000;53(2):178-81.**

<http://www.ncbi.nlm.nih.gov/pubmed/10713198>

**Abstract** BACKGROUND: Vagal nerve stimulation has become an important treatment for patients with intractable seizure disorders. Many of these patients will require magnetic resonance imaging (MRIs) of the brain after the stimulator has been implanted to monitor underlying neurologic conditions. Functional MRI (fMRI) is also being used in the evaluation of epilepsy. With the current recommended implant techniques the magnetic field of the MRI will deactivate the pulse generator while the patient is in the supine position for the scan. A simple change in positioning of the pulse generator will help to avoid deactivating the device during an MRI. This will avoid exposing the patient to lengthy time periods with a deactivated stimulator and also allow for the performance of fMRIs and any other MRI scans needed to monitor underlying neurologic conditions. METHODS: A working model of the NeuroCybernetic Prosthesis (NCP) pulse generator was assessed with an oscilloscope and LED light connected to it that related activation of the generator while in the MRI. This simulation was performed with the device alone, in multiple positions. Then patients with implanted devices who could personally confirm the activation of their stimulators were also studied. RESULTS: A pulse generator placed with the electrode inputs parallel to the long axis of the body was not deactivated by the magnetic field of the MRI when the patient was in the supine position. CONCLUSION: Changing the implant position of a vagal nerve stimulator pulse generator will help to prevent deactivation of the device while in the MRI, allowing for the performance of fMRIs while not exposing the patient to lengthy time periods with a deactivated vagal nerve stimulator.

20. **Cortese JJ. Vagus nerve stimulation: a new treatment for intractable epilepsy. *Surg Technol.* 1999;31(2):11-18.**

**Notes** This article presents a comprehensive summary of the surgical procedure, including the materials needed in the operating room to do a VNS implant, and would be good for the surgical and operating room staff. \*Seminal surgery article according to Andre

21. **Reid SA. Surgical technique for implantation of the neurocybernetic prosthesis. *Epilepsia.* 1990;31 Suppl 2:S38-9.**

<http://www.ncbi.nlm.nih.gov/pubmed/2226365>

**Abstract** The surgical technique for the implantation of the neurocybernetic prosthesis is described in detail. This procedure is straightforward and is easily carried out by surgeons familiar with carotid surgery.

**VNS Surgical Procedure - Lead Revision**

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1. **Dlouhy BJ, Viljoen SV, Kung DK, Vogel TW, Granner MA, Howard MA, 3rd, et al. Vagus nerve stimulation after lead revision. *Neurosurg Focus.* 2012;32(3):E11.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22380852>

**Abstract** OBJECT: Vagus nerve stimulation (VNS) has demonstrated benefit in patients with medically intractable partial epilepsy. As in other therapies with mechanical devices, hardware failure occurs, most notably within the VNS lead, requiring replacement. However, the spiral-designed lead electrodes wrapped around the vagus nerve are often encased in dense scar tissue hampering dissection and removal. The objective in this study was to characterize VNS lead failure and lead revision surgery and to examine VNS efficacy after placement of a new electrode on the previously used segment of vagus nerve. METHODS: The authors reviewed all VNS lead revisions performed between October 2001 and August 2011 at the University of Iowa Hospitals and Clinics. Twenty-four patients underwent 25 lead revisions. In all cases, the helical electrodes were removed, and a new lead was placed on the previously used segment of vagus nerve. All inpatient and outpatient records of the 25 lead revisions were retrospectively reviewed. RESULTS: Four cases were second lead revisions, and 21 cases were first lead revisions. The average time to any revision was 5 years (range 1.8-11.1 years), with essentially no difference between a first and second lead revision. The most common reason for a revision was intrinsic lead failure resulting in high impedance (64%), and the most common symptom was increased seizure frequency (72%). The average duration of surgery for the initial implantation in the 15 patients whose VNS system was initially implanted at the authors' institution was much shorter (94 minutes) than the average duration of lead revision surgery (173 minutes). However, there was a significant trend toward shorter surgical times as more revision surgeries were performed. Sixteen of the 25 cases of lead revision were followed up for more than 3 months. In 15 of these 16 cases, the revision was as effective as the previous VNS lead. In most of these cases, both the severity and frequency of seizures were decreased to levels similar to those following the previous implantation procedure. Only 1 complication occurred, and there were no postoperative infections. CONCLUSIONS: Lead revision surgery involving the placement of a new electrode at the previously used segment of vagus nerve is effective at decreasing the seizure burden to an extent similar to that obtained following the initial VNS implantation. Even with multiple lead revisions, patients can obtain VNS efficacy similar to that following the initial lead implantation. There is a learning curve with revision surgery, and overall the duration of surgery is longer than for the initial implantation. Note, however, that complications and infection are rare.
  
2. **Agarwal G, Wilfong AA, Edmonds JL, Jr. Surgical revision of vagus nerve stimulation electrodes in children. *Otolaryngol Head Neck Surg.* 2011;144(1):123-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/21493401>  
<http://oto.sagepub.com/content/144/1/123>

**Abstract** Use of vagus nerve stimulation (VNS) has increased in the past decade, resulting in frequent revision cases for device failure. The authors report their series of children who underwent reimplantation of the VNS device after removal of old electrodes and leads. Patients with medically refractory seizures who underwent revision of VNS electrodes were included (n = 23). Twenty patients had high lead impedance and underwent removal of the device and replacement of the VNS electrodes during the same procedure. In 3 patients, electrodes and the device had been removed previously at an outside institution because of infection. None of the patients experienced any major complications. Mean operative time was 2.3 +/- 0.9 hours. The reimplanted device worked well in all patients, and seizure control was similar to or better than that reported with the previous device. Thus, implantation of the VNS electrodes is reversible, and it appears that the electrodes can be removed or replaced safely if the device is not functioning properly.

- 3. Ng WH, Donner E, Go C, Abou-Hamden A, Rutka JT. Revision of vagal nerve stimulation (VNS) electrodes: review and report on use of ultra-sharp monopolar tip. *Childs Nerv Syst.* 2010;26(8):1081-4.**  
<http://www.ncbi.nlm.nih.gov/pubmed/20225085>  
<http://link.springer.com/article/10.1007%2Fs00381-010-1121-2>

**Abstract** PURPOSE: As a result of the increasingly popularity of vagal nerve stimulation (VNS) for intractable seizures, neurosurgeons not uncommonly encounter cases which require electrode revision. We examine our experience of VNS revision and reports the use of the ultra-sharp monopolar tip for safe dissection and removal of the electrode from the vagus nerve. METHODS: A retrospective review was performed from January 2000 to Dec 2009 reviewed eight cases of VNS revision. RESULTS: The indications for VNS revision were device malfunction manifesting with increased seizures or increased impedance of the device and infection. The time from initial VNS implantation to revision ranged from 6 to 108 months (mean: 38 months). The entire VNS electrode system, was removed in seven cases and the helical coils were left in-situ in one case who did not derive any benefit from VNS and it was deemed unnecessary to subject the patient to the additional risk of vagal nerve injury. One case had dislodgement of the lower two coils and three cases had dense scarring to the vagus nerve causing high impedance and malfunction. The other three cases demonstrated no fibrotic scar tissue between the helical coils and the vagus nerve. Four cases had replacement of new VNS system but the case of infected VNS stimulator was not replaced as there was no benefit from the device. CONCLUSION: VNS revision is normally performed in cases of device malfunction or infection and can be safely performed using a combination of ultra-sharp monopolar coagulation and sharp dissection.
  
- 4. MacDonald J, Couldwell WT. Revision of vagal nerve stimulator electrodes: technical approach. *Acta Neurochir (Wien).* 2004;146(6):567-70; discussion 570.**  
<http://www.ncbi.nlm.nih.gov/pubmed/15168224>  
<http://link.springer.com/article/10.1007%2Fs00701-004-0246-z>

**Abstract** BACKGROUND: As the number of implanted vagal nerve stimulators grows, the need for removal or revision of the devices will become more frequent. Our purpose was to demonstrate the feasibility of complete removal of the vagal nerve stimulator electrode using microsurgical technique. METHODS: . Operative databases at the University of Utah (1995 through 2002), Westchester Medical Center (1995 through 2001), and University of Arizona Health Sciences Center (1995 through 1999) were retrospectively reviewed. Patients who had undergone removal or revision of a previously placed vagal nerve stimulator electrode were identified. Patients who had a vagal nerve stimulator device removed but had the lead trimmed and incompletely removed were excluded. FINDINGS: Seven patients underwent complete removal of the lead. Microsurgical dissection allowed removal of the helical electrode from the vagus nerve without apparent physiological consequences. Four patients had a new electrode placed just proximal to the original lead site. The operative procedure required an additional 30 minutes to complete compared with initial device placement. The four patients who underwent replacement of the electrode demonstrated normal device function and lead resistance at the time of postoperative follow-up. Each experienced a return to prior stimulation response and seizure control. CONCLUSIONS: This series suggests that the electrode can be removed from the vagus nerve and repositioned without significant consequence in most cases.

5. **Espinosa J, Aiello MT, Naritoku DK. Revision and removal of stimulating electrodes following long-term therapy with the vagus nerve stimulator. *Surg Neurol.* 1999;51(6):659-64.**  
<http://www.ncbi.nlm.nih.gov/pubmed/10369236>

**Notes** This is the first paper on the technique and results of explanting or revising the VNS therapy system. The system was completely removed in 7 of 10 patients with no adverse events seen intraoperatively or postoperatively, indicating that the procedure could be reversed with little difficulty. After removal of the electrodes, the nerve showed no evidence of physical injury even after the electrodes have been implanted for several years. Explant is now a routine procedure and the reversibility of lead implantation may enhance the attractiveness of VNS Therapy.

**Abstract** BACKGROUND: A significant concern about vagus nerve stimulation therapy has been the disposition of the spiral stimulating electrodes once treatment is considered ineffective or is no longer desired. Because the electrodes are wrapped around the vagus nerve, there is the potential for nerve injury during their removal. METHODS: We attempted removal of the spiral stimulating electrodes from 10 patients who received long-term vagus nerve stimulation therapy for drug-resistant epilepsy. In some patients, replacement with electrodes was also performed for poorly functioning leads. RESULTS: The mean duration of electrode implantation was 3.7+/-2.2 years (range 1.1-7.3 years). In seven patients, the old electrodes were removed completely from the nerve. No adverse events occurred intraoperatively or postoperatively. CONCLUSIONS: Our results indicate that the spiral electrodes may be safely removed from the vagus nerve, even after the electrodes have been implanted for several years. The reversibility of lead implantation may enhance the attractiveness of vagus nerve stimulation therapy for patients with medically-intractable epilepsy.

**VNS Surgical Procedure - Usage Statistics**

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1. **Neligan A, Haliasos N, Pettorini B, Harkness WF, Solomon JK. A survey of adult and pediatric epilepsy surgery in the United Kingdom. *Epilepsia*. 2013.**  
<http://www.ncbi.nlm.nih.gov/pubmed/23551079>  
<http://onlinelibrary.wiley.com/store/10.1111/epi.12148/asset/epi12148.pdf?v=1&t=hfzrd09v&s=a392338ba43cfaf2576476146a60282c8a3faff8>

**Abstract** All consultant epilepsy neurosurgeons were asked to prospectively record all epilepsy surgery procedures carried out at their center between April 2010 and March 2011. Figures were compared to a previous survey completed in 2000. Of a total of 710 procedures, temporal lobe surgery was the most common resective surgery. Although extratemporal lesional surgery was less common, vagus nerve stimulator (VNS) implantation accounted for almost half the procedures. The numbers for all surgical procedures, with the exception of VNS implantations, had decreased. This decrease may represent a global rather than a regional phenomenon. Further longitudinal multinational data on epilepsy surgery is required to confirm or refute this theory.
  
2. **Morioka T, Sayama T, Shimogawa T, Hamamura T, Hashiguchi K, Kawai K, et al. [Frequency of the use of vagus nerve stimulation for the treatment of intractable epilepsy during the first year of public health insurance coverage with in Kyushu Rosai Hospital and other areas in Japan]. *Brain Nerve*. 2012;64(6):681-7. Japanese.**  
<http://www.ncbi.nlm.nih.gov/pubmed/22647476>

**Abstract** Vagus nerve stimulation (VNS) is a palliative treatment for medically intractable epilepsy and has been covered by public health insurance in Japan since July 1, 2010. The frequency of the use of VNS during the first year of insurance coverage was determined by assessing the number of cases for which VNS was performed in Kyushu Rosai Hospital, the number of registered cases, and the questionnaire survey filled by 68 surgeons who are board certified as both epileptologists and neurosurgeons. VNS devices were placed in 98 patients from July 2010 to June 2011. These devices were placed in an average of 4.4 patients per month from July 2010 to November 2010 and in an average of 10.9 patients from December 2010 to June 2011. However, we did not observe an increasing trend. Almost all of the surgeries were performed in the Kanto (56 patients in 8 institutes) and Tokai (24 patients in 2 institutes) areas. VNS was not performed in many institutes primarily because VNS was not indicated for any of the patients. The questionnaire survey indicated that the use of VNS was likely to increase with an increase in the number of neurologists who decide on performing VNS preoperatively and regulate the conditions of the vagus nerve stimulator postoperatively. In conclusion, VNS is currently being applied in a limited number of institutes in the Kanto and Tokai areas, and a close association between the epileptologists and neurologists during preoperative and postoperative periods will increase the use of VNS.

3. **Mikati MA, Ataya N, El-Ferezli J, Shamseddine A, Rahi A, Herlopian A, et al. Epilepsy surgery in a developing country (Lebanon): ten years experience and predictors of outcome. *Epileptic Disord.* 2012;14(3):267-74.**

<http://www.ncbi.nlm.nih.gov/pubmed/22951375>

**Abstract** We present our 10-year experience and preoperative predictors of outcome in 93 adults and children who underwent epilepsy surgery at the American University of Beirut. Presurgical evaluation included video-EEG monitoring, MRI, neuropsychological assessment with invasive monitoring, and other tests (PET, SPECT, Wada). Surgeries included temporal (54%), extratemporal (22%), and multilobar resections (13%), hemispherectomy (4%), vagal nerve stimulation (6%), and corpus callosotomy (1%). Mesial temporal sclerosis was the most common aetiology (37%). After resective surgery, 70% had Engel class I, 9% class II, 14% class III, and 7% class IV. The number of antiepileptic drugs before surgery was the only preoperative factor associated with Engel class I ( $p=0.005$ ). Despite the presence of financial and philanthropic aid, many patients could not be operated on for financial reasons. We conclude that advanced epilepsy presurgical workups, surgical procedures, and favourable outcomes, comparable to those of developed countries, are achievable in developing countries, but that issues of financial coverage remain to be addressed.

4. **Donadio M, D'Giano C, Moussalli M, Barrios L, Ugarnes G, Segalovich M, et al. Epilepsy surgery in Argentina: long-term results in a comprehensive epilepsy centre. *Seizure.* 2011;20(6):442-5.**

<http://www.ncbi.nlm.nih.gov/pubmed/21478034>

[http://ac.els-cdn.com/S105913111100046X/1-s2.0-S105913111100046X-main.pdf?\\_tid=e997e154-9277-11e2-8d97-0000aab0f02&acdnat=1363905629\\_b138cff59f5b1fed9c1b2f1611f97eb4](http://ac.els-cdn.com/S105913111100046X/1-s2.0-S105913111100046X-main.pdf?_tid=e997e154-9277-11e2-8d97-0000aab0f02&acdnat=1363905629_b138cff59f5b1fed9c1b2f1611f97eb4)

**Abstract** RATIONALE: Epilepsy surgery procedures started in Argentina more than 50 years ago. This is the first comprehensive and systematic survey of epilepsy surgery long-term outcome from our country. METHODS: A descriptive cohort study was conducted between 1998 and 2008 for drug-resistant epilepsy surgery with a minimum of 12 months follow-up ( $n=110$ ). In 84 cases (76.36%) resective surgery was performed, and outcome periodically assessed using the Engel score. Patients were stratified into groups: 12, 13-36, 37-60 and over than 60 months of follow-up. Video-EEG with and without intracranial electrode implants, intraoperative electrocorticograms, Wada tests, pathology reports, use of antiepileptic drugs (AEDs), and surgical complication rates were evaluated. RESULTS: Surgical techniques included: 69 lobectomies (62.7%), 15 lesionectomies (13.6%), 6 callosotomies (5.4%), 6 multiple subpial transection (5.4%), 11 vagus nerve stimulations (10%), 3 hemispherectomies (2.7%). Male: female ratio: 1/1.44. Mean age at time of surgery: 26.2 years. Mean duration of epilepsy: 14 years. Age at seizure onset: 11.5 years. Mean follow-up: 46 months. Pathology findings: mesial temporal sclerosis 32 (35.1%); dual pathology 17 (18.7%); cortical dysplasia 15 (16.4%); non-specific inflammatory changes 11 (12.1%); tumors 7 (7.7%); other 6 (6.8%). Engel scores at 12 months follow-up: 72.6% (61) class I, 16.6% (14) class II and 15.5% (13) class III-IV; 13-36 months after surgery: 68.1% of cases were class I, 15.9% class II and 15.5% class III-IV. After 37-60 months, 74% class I, 14% class II, 14% class III-IV. Over 60 months ( $n=45$ ) 78% class I, 13.5% class II and 8.1% class III-IV. CONCLUSION: Conducting a successful epilepsy surgery program in a developing country is challenging. These results should encourage specialists in these countries. Long-term outcome results comparable to centres in developed countries can be achieved.

5. **Bulteau C, Dorfmueller G, Fohlen M, Jalin C, Oliver MV, Delalande O. [Epilepsy surgery during infancy and early childhood in France]. *Neurochirurgie*. 2008;54(3):342-6.**

<http://www.ncbi.nlm.nih.gov/pubmed/18436266>

**Abstract** BACKGROUND AND PURPOSE: We present the epilepsy surgery activity in infants and children at the Fondation Rothschild Hospital, the main center dedicated to this activity in France. METHOD: A prospective study was conducted from 2003 to 2007 based on three populations: (1) children selected as candidates for surgery, (2) children undergoing presurgical evaluation and (3) children undergoing surgical procedures for epilepsy. RESULTS: Children selected as candidates for surgery: 304 children were referred and discussed by our multidisciplinary staff. They came from Paris and its suburbs (40%), the provinces (43%) or from other countries (14%). Sixty-one percent of them were included in our surgery program and 24% were excluded. Sixty-one percent of them were under 10 years of age. Children undergoing presurgical evaluation: 296 children were recorded: 140 EEG (47%), 46 with foramen ovale electrodes (16%) and 110 with invasive recording techniques (37%). Seventy percent of these children were under 10 years of age. Children undergoing surgical procedures: 316 children underwent surgery; 68% of them were under 10 years of age. The surgical procedures were focal resection (136 children), vertical parasagittal hemispherotomy (77 children), resection and or disconnection for hypothalamic hamartoma (69 children) and 34 had palliative surgery (callosotomy or vagal nerve stimulation). CONCLUSION: Eighty to 100 children undergo surgery each year in our department for drug-resistant partial epilepsy; 70% of them are less than 10 years of age. This activity is part of a network of pediatric neurologists who are deeply involved in treatment of severe epilepsy in children.

6. **Baaj AA, Benbadis SR, Tatum WO, Vale FL. Trends in the use of vagus nerve stimulation for epilepsy: analysis of a nationwide database. *Neurosurg Focus*. 2008;25(3):E10.**

<http://www.ncbi.nlm.nih.gov/pubmed/18759611>

**Abstract** OBJECT: Vagus nerve stimulation (VNS) plays a significant role in the treatment of intractable epilepsy. The goal of this study was to analyze trends in the use of VNS for epilepsy in the US by using a nationwide database. METHODS: Data for patients undergoing VNS were obtained from the nationwide inpatient sample for the years 1998-2005. Trends regarding number of procedures, length of stay (LOS), hospital charges, patient sex, and payer information were retrieved and analyzed. RESULTS: The number of VNS procedures for epilepsy increased between 1998 and 2003 but decreased in the subsequent 2 years. The LOS and hospital charges showed yearly increases. Female patients underwent VNS implantation more than males did, and most procedures were performed in the 18- to 64-year-old age group. The combination of Medicare and Medicaid provided most of the funding for VNS from 2002 through 2005. The VNS procedures were performed mostly in teaching hospitals. CONCLUSIONS: Trends from a national database reveal consistent use of VNS for intractable epilepsy. Greater use of the procedure appears to be reflected in the female population, and the procedure has been performed most often at tertiary care teaching hospitals, where a comprehensive evaluation for all forms of therapy is arguably best able to target appropriate patients for appropriate therapies. With the recent application of VNS to target populations without epilepsy, such as patients with refractory depression, the trend of continued use of this treatment for epilepsy appears likely.

7. **Lhatoo SD, Solomon JK, McEvoy AW, Kitchen ND, Shorvon SD, Sander JW. A prospective study of the requirement for and the provision of epilepsy surgery in the United Kingdom. *Epilepsia*. 2003;44(5):673-6.**  
<http://www.ncbi.nlm.nih.gov/pubmed/12752466>  
<http://onlinelibrary.wiley.com/store/10.1046/j.1528-1157.2003.46002.x/asset/j.1528-1157.2003.46002.x.pdf?v=1&t=he8vwxen&s=cf5a10219eaf1c1537b0ee009840f8a9dcc04f07>

**Notes** This study out of England sought to assess the total number and types of epilepsy procedures currently performed in the U.K. (adults and children). Temporal lobe resection for hippocampal sclerosis was the most common procedure. Implantation of the vagus nerve stimulator was the second most common procedure performed over a 6-month period, accounting for 27% of all procedures (156 procedures). With the large number of patients receiving surgery for VNS therapy, the authors do question the emphasis being placed on curative versus palliative procedures. But the authors also note that many patients with refractory epilepsy are not candidates for resective surgery and remain underinvestigated and, therefore, untreated.

**Abstract** **PURPOSE:** Of the 30,000 persons in whom epilepsy develops annually in the United Kingdom, in approximately 6000 (20%), intractability develops. Some of these patients will be appropriate for epilepsy surgery. We aimed to estimate the number of patients who should be considered surgical candidates, by extrapolation from a population-based study of prognosis and the number who are receiving epilepsy surgery, by a survey of U.K. neurosurgeons. **METHODS:** We identified the number of patients who may eventually require surgery from a prospective cohort of patients with newly diagnosed epilepsy. We identified all U.K. neurosurgeons who had performed any epilepsy surgery in the past year. Each identified surgeon prospectively recorded the number and types of operations carried out for 6 months. **RESULTS:** Of newly diagnosed patients each year, 450 (1.5%) may eventually require surgery. Thirty-two respondents (22% of all U.K. neurosurgeons) reported that they performed epilepsy surgery. The 211 operations were carried out in the 6 months surveyed (422 operations annually or 13 per surgeon per year). Temporal lobe resection (77%) was the most common procedure. **CONCLUSIONS:** Based on a prevalence of 5/1,000 persons with epilepsy, < or =4,500 patients in the U.K. require epilepsy surgery. Every year, 450 patients with newly diagnosed epilepsy who may eventually require surgery are added to this "surgical pool." At the current annual rate of operations, a large number of refractory patients remain untreated. This is probably partly because many patients are not referred for specialist care and therefore remain underinvestigated.

8. **van Veelen CW, van Rijen PC, Debets RM, van Wijk-Leenaars PW, van Emde Boas W. [Dutch Collaborative Epilepsy Surgery Program: reduction of seizures, operative complications and tapering of medication in 338 patients, 1973-1998]. *Ned Tijdschr Geneeskd.* 2001;145(46):2223-8. Dutch. <http://www.ncbi.nlm.nih.gov/pubmed/11757246>**

**Abstract** OBJECTIVE: To determine the results of surgical treatment in patients with drug-resistant epilepsy, referred to the Dutch Epilepsy Surgery Program, who were treated in the University Medical Centre Utrecht, the Netherlands, in the period January 1973-December 1998. DESIGN: Retrospective descriptive. METHOD: A total of 338 patients were operated on; 269 underwent temporal lobe resection, 41 extratemporal resection, 12 a functional hemispherectomy and 10 callosotomy. Six patients were treated with vagus nerve stimulation. For seven of the patients no follow-up data was available. RESULTS: After a minimum follow-up of 1 year class I or class II results (in accordance with the University of California in Los Angeles classification (UCLA) where class I = seizure-free and class II < or = 3 seizures per year) were obtained in 91% of patients who underwent temporal lobe resections, 67% of patients who underwent extratemporal resections, 81% of patients who underwent functional hemispherectomy and 10% of patients who underwent anterior callosotomy. In five of these patients an improvement in their behaviour occurred. Of the 6 patients who underwent vagus nerve stimulation only 1 experienced a beneficial seizure reduction (UCLA class III). Transient physical complications occurred in 4% of the patients treated and permanent damage in 1%. Postoperative psychiatric complications occurred almost exclusively following temporal resections; in 11% of which 7% de novo. After 4 postoperative years this had decreased to 5%. In a group of 143 patients who were seizure-free for 2 or more years, post-surgery medication was tapered in 75 cases, stopped in 33 cases and remained unchanged in 35 cases. The relapse rate following a tapering or stopping of the medication was 30% and with unchanged medication 17%. Although the majority of patients were once again seizure-free upon restarting the medication, a significant number continued to experience seizures. CONCLUSION: For a number of carefully selected epilepsy patients with intractable seizures, surgery is a successful treatment with few serious complications.