Search Criteria for the VNS Therapy Reference List by Topic

The VNS Therapy reference lists contained on this CD were collected from searches on PubMed through December 2009.

The search terms used include VNS, vagus nerve stimulation, epilepsy, and depression. All articles related to VNS Therapy and the physiology of the vagus nerve as it relates to the possible mechanism of action were collected in a reference database and assigned to a category/topic. Each reference is included on this CD only once. For articles that would fit into multiple topics, the articles were assigned to the most prevalent topic covered by the article. When available, the abstracts provided in PubMed were included with each reference along with a link back to PubMed so that customers can order the full article if interested.

Articles that discuss epilepsy and mood or depression or that discuss the potential mechanism of action as it relates to both indications were included on this CD. VNS Therapy articles related solely to safety and effectiveness in treatment-resistant depression are not included on this CD. In addition, meeting abstracts published in supplements were not included.

For more information about how the literature search was conducted, please contact the Marketing Department at Cyberonics, Inc. at 281-228-7519.

Angelman Syndrome

1. **Thibert RL, Conant KD, Braun EK, et al. Epilepsy in Angelman syndrome: a questionnaire-based assessment of the natural history and current treatment options. *Epilepsia.* 2009;50:2369-76.**
Abstract: PURPOSE: Angelman syndrome (AS) commonly presents with epilepsy (>80%). The goal of this study was to examine the natural history and various treatments of epilepsy in AS in a large population. METHODS: A detailed electronic survey containing comprehensive questions regarding epilepsy in AS was conducted through the Angelman Syndrome Foundation. RESULTS: There were responses from 461 family members of individuals with AS, of whom 86% had epilepsy (60% with multiple seizure types), the most common being atonic, generalized tonic-clonic, absence, and complex partial. Partial-onset seizures only were reported in 11% of those with epilepsy. Epilepsy was most common among those with maternal deletions and unknown subtypes, with catastrophic epilepsies present in only these two subtypes. These epilepsies were refractory to medication, with only 15% responding to the first antiepileptic drug (AED). The most commonly prescribed AED were valproic acid and clonazepam, but lamotrigine and levetiracetam appeared to have similar efficacy and tolerability. DISCUSSION: This is the largest study to date assessing epilepsy in AS. Although epilepsy in AS is considered a generalized epilepsy, there was a high prevalence of partial seizures. There are few previous data regarding the use of newer AED in AS, and the results of this study suggest that these newer agents, specifically levetiracetam and lamotrigine, may have efficacy similar to that of valproic acid and clonazepam, and that they appear to have similar or better side-effect profiles. Nonpharmacologic therapies such as dietary therapy and vagus nerve stimulation (VNS) also suggest favorable efficacy and tolerability, although further studies are needed. Epilepsy in Angelman syndrome: a questionnaire-based assessment of the natural history and current treatment options.

Asperger Syndrome

1. **Warwick TC, Griffith J, Reyes B, Legesse B, Evans M. Effects of vagus nerve stimulation in a patient with temporal lobe epilepsy and Asperger syndrome: case report and review of the literature. *Epilepsy Behav.* 2007;10:344-7.**
Abstract: Seizures are a common comorbidity of autism and occur in as many as 30% of patients. This case report describes a 23-year-old man diagnosed with both Asperger syndrome and bitemporal epilepsy. The patient had behavioral regression that correlated with worsening of his intractable seizures. He subsequently underwent implantation of a vagus nerve stimulation therapy device for his refractory epilepsy. Both his seizures and his behavior were monitored for 6 months. We describe the efficacy of vagus nerve stimulation therapy in reducing seizure severity as well as improving the behavioral components of his Asperger syndrome. We also review the current literature regarding epilepsy in autistic spectrum disorders. Effects of vagus nerve stimulation in a patient with temporal lobe epilepsy and Asperger syndrome: case report and review of the literature.

Autism and Landau-Kleffner Syndrome

1. **Danielsson S, Viggedal G, Gillberg C, Olsson I. Lack of effects of vagus nerve stimulation on drug-resistant epilepsy in eight pediatric patients with autism spectrum disorders: A prospective 2-year follow-up study. *Epilepsy Behav.* 2008;12:298-304.**
   Abstract: Vagus nerve stimulation (VNS) therapy has been reported to reduce seizure frequency in some children with drug-resistant epilepsy who are not suitable candidates for epilepsy surgery. It has been suggested that there may be positive cognitive and/or behavioral effects independent of seizure control. We describe the effects of VNS with respect to seizure frequency, cognition, and autistic symptoms and behavior in eight children and adolescents with medically intractable epilepsy and autism. In comparison to baseline, seizure frequency had not decreased in anyone in our series at the 2-year follow-up. In three cases, minor improvements in general functioning were noted, but there were no positive cognitive effects. This open prospective pilot study highlights the need for more prospective studies to prevent false expectations of improvement in this severely disabled group. Lack of effects of vagus nerve stimulation on drug-resistant epilepsy in eight pediatric patients with autism spectrum disorders: a prospective 2-year follow-up study.

2. **Mikati MA, Shamseddine AN. Management of landau-kleffner syndrome. *Paediatr Drugs.* 2005;7:377-389.**
   Abstract: Landau-Kleffner syndrome (LKS) is an acquired epileptic aphasia disorder in which children, usually 3-8 years of age who have developed age-appropriate speech, experience language regression with verbal auditory agnosia, abnormal epileptiform activity, behavioral disturbances, and sometimes overt seizures. There are no controlled clinical trials investigating the therapeutic options for LKS. Only open-label data are available. Early diagnosis and initiation of prompt medical treatment appear to be important to achieving better long-term prognosis. Several antiepileptic drugs have been reported to be beneficial in treating this syndrome. These include valproic acid (valproate sodium), diazepam, ethosuximide, clobazam, and clonazepam. Reports on the efficacy of lamotrigine, sultiame, felbamate, nicardipine, vigabatrin, levetiracetam, vagal nerve stimulation, and a ketogenic diet are few and more experience is needed. Carbamazepine and possibly phenobarbital and phenytoin have been reported to occasionally exacerbate the syndrome. As initial therapy, valproic acid or diazepam is often empirically chosen. Subsequently, other antiepileptic drugs, corticosteroids, or intravenous immunoglobulin (IVIG) therapy are often used. Corticosteroid therapy should probably not be delayed more than 1-2 months after the initial diagnosis. Various corticosteroid regimens including oral prednisone and, recently, high doses of intravenous pulse corticosteroids, as well as corticotropin (adrenocorticotropic hormone) have been reported to be effective in LKS. Oral corticosteroids are used more often and usually need to be maintained for a long period of time to prevent relapses. The use of IVIG has been associated with an initial dramatic response in only a few patients. In our experience, a long-term worthwhile improvement has been noted in only 2 of 11 patients. These two patients had an immediate response to IVIG initially and after relapses before eventually achieving a long-term sustained remission. Surgical treatment by multiple subpial transection, which is reserved for patients who have not responded to multiple medical therapies, has been followed in

selected cases by a marked improvement in language skills and behavior. However, a widely accepted consensus about suitable candidates for this surgery and about its efficacy is still lacking.Speech therapy, including sign language, and a number of classroom and behavioral interventions are helpful in managing LKS, and should be used in all patients. Management of Landau-Kleffner syndrome.

3. **Park YD. The effects of vagus nerve stimulation therapy on patients with intractable seizures and either Landau-Kleffner syndrome or autism. *Epilepsy Behav.* 2003;4:286-290.**
Abstract: Acquired and developmental comorbid conditions, including language and behavioral disorders, are often associated with epilepsy. Although the relationship between these disorders is not fully understood, their close association may indicate that they share common features, suggesting that these conditions may respond to the same therapies. Not only has vagus nerve stimulation (VNS) therapy been proven to reduce the frequency of pharmacoresistant seizures in epilepsy patients, but preliminary studies also indicate that VNS therapy may improve neurocognitive performance. On the basis of these findings, we hypothesized that VNS therapy would improve the quality of life of patients with either Landau-Kleffner syndrome (LKS) or autism, independent of its effects on seizures. Data were retrospectively queried from the VNS therapy patient outcome registry (Cyberonics, Inc; Houston, TX, USA). A constant cohort of 6 LKS patients and 59 autistic patients were identified. Among the LKS patients, 3 patients at 6 months experienced at least a 50% reduction in seizure frequency as compared with baseline. Physicians reported quality-of-life improvements in all areas assessed for at least 3 of the 6 children. More than half of the patients with autism (58%) experienced at least a 50% reduction in seizure frequency at 12 months. Improvements in all areas of quality of life monitored were reported for most patients, particularly for alertness (76% at 12 months). Although these preliminary findings are encouraging, a prospective study using standardized measurement tools specific to these disorders and a longer-term follow-up are necessary to better gauge the efficacy of VNS therapy among these patient populations. The effects of vagus nerve stimulation therapy on patients with intractable seizures and either Landau-Kleffner syndrome or autism.

4. **Murphy JV, Wheless JW, Schmoll CM. Left vagal nerve stimulation in six patients with hypothalamic hamartomas. *Pediatr Neurol.* 2000;23:167-168.**
Abstract: Six patients with medically refractory epilepsy secondary to hypothalamic hamartomas were treated with intermittent stimulation of the left vagal nerve. Three of the patients had remarkable improvements in seizure control. Four of these six patients had severe autistic behaviors. Striking improvements in these behaviors were observed in all four during treatment with intermittent stimulation. This finding suggests that vagal nerve stimulation can control seizures and autistic behaviors in patients with hypothalamic hamartomas. Left vagal nerve stimulation in six patients with hypothalamic hamartomas.

Bitemporal Epilepsy

1. **Kuba R, Brazdil M, Novak Z, Chrastina J, Rektor I. Effect of vagal nerve stimulation on patients with bitemporal epilepsy. Eur J Neurol 2003:10: 91-4.**
Abstract: Patients with bitemporal epilepsy are characterized by the existence of independent bitemporal seizure onset zones. The aim of this study was to evaluate the effect of chronic vagal nerve stimulation (VNS) on eight patients with bitemporal epilepsy. We demonstrated the gradually increased effect of VNS on the reduction of seizures as compared with baseline seizure frequency in patients with bitemporal epilepsy. The average seizure reduction increased from 4.2% at the 3-month follow-up visit to 18.2, 34.4 and 42.2% at the 6, 12 and 18-month follow-up visits. Similarly, a >or=50% reduction of complex partial seizures was reported at the 3-month follow-up visit in no patients (0%); at the 6-month follow-up visit in one patient (12.5%); at the 12-month follow-up visit in three patients (37.5%); and at the 18-month follow-up visit in five patients (62.5%). These data demonstrate the positive and long-lasting effect of VNS on seizure reduction in patients with intractable bitemporal epilepsy. The main mechanism of this chronic effect is not fully understood. Effect of vagal nerve stimulation on patients with bitemporal epilepsy.

Catastrophic Childhood Epilepsies

1. **Zamponi N, Rychlicki F, Corpaci L, Cesaroni E, Trignani R. Vagus nerve stimulation (VNS) is effective in treating catastrophic 1 epilepsy in very young children. *Neurosurg Rev.* 2008;31:291-7.**
Abstract: The objective of this study is to evaluate the safety and efficacy of vagus nerve stimulation (VNS) in very young children suffering from catastrophic epilepsy and status epilepticus. We reviewed files of 60 VNS-implanted children at our institution and we selected six very young patients, less than 3 years old (mean age at implant 1.6 years). All patients suffered from severe cognitive impairment and catastrophic epilepsy with underlying diagnosis of hemimegalencephaly (1), hypoxic-ischemic encephalopathy (1), tuberous sclerosis complex (1), and malignant migrating partial epilepsy of infancy (3). Three patients were VNS-implanted during admission at intensive care unit (ICU) after developing life-threatening status epilepticus. The mean follow-up time was 41.6 months. The VNS was implanted using a single cervical incision. No surgery-related complications were observed. Four of six children have shown a significant, persistent improvement in seizure control (range, 60-90%). In patients with status, insertion of the vagal nerve stimulator allowed early cessation of status and discharge from ICU. Quality of life and parental satisfaction improved and for three children there was some milestone evolution. Catastrophic epilepsy in infancy can be devastating and difficult to treat with drugs and surgery. If resective surgery is inappropriate or refused, VNS can be considered as a well-tolerated and effective procedure even in toddlers affected by severe epilepsy and multiple developmental disabilities. Vagus nerve stimulation (VNS) is effective in treating catastrophic 1 epilepsy in very young children.

2. **Wheless JW. Nonpharmacologic treatment of the catastrophic epilepsies of childhood. *Epilepsia.* 2004;45(suppl 5):17-22.**
Abstract: Summary: The catastrophic epilepsy syndromes of childhood are initially treated with a pharmacologic intervention in most cases. However, due to the poor response patients often have to pharmacologic interventions, nonpharmacologic treatment options are an important part of a comprehensive treatment plan for this group of children. Additionally, nonpharmacologic therapy may offer a method to minimize associated morbidity and mortality. This article discusses the use of epilepsy surgery, the ketogenic diet, and vagus nerve stimulation in the treatment of patients with infantile spasms, Lennox-Gastaut syndrome, and progressive myoclonic epilepsy. Efficacy of the nonpharmacologic treatment options, as measured by reduction in seizure frequency, as well as by developmental progress or behavioral improvement, varies according to the specific catastrophic epilepsy disorder and the treatment option. Nonpharmacologic treatment of the catastrophic epilepsies of childhood.

Cerebral Palsy

1. **Jaseja H. Vagal nerve stimulation: exploring its efficacy and success for an improved prognosis and quality of life in cerebral palsy patients. *Clin Neurol Neurosurg.* 2008;110:755-62.**

Abstract: Cerebral palsy (CP) continues to pose a cause for major socioeconomic concern and medical challenge worldwide. It is associated with a multi-faceted symptomatology warranting a multi-dimensional management-approach. Recent recognition of neurocognitive impairment and its hopefully possible treatment has opened up a new dimension in its management to the neurologists. Vagal nerve stimulation (VNS) technique is presently emerging as an effective alternative anti-epileptic therapeutic measure in intractable epilepsy. VNS has recently been shown to possess a suppressive effect also on interictal epileptiform discharges (IEDs) that are now being widely accepted as established associates of neurocognitive impairment. In this paper, the author proposes VNS technique implantation in CP patients on account of its dual therapeutic effectiveness, i.e. anti-epileptic and IED-suppression. These two effects are likely to control seizures that are quite often drug-resistant and also improve neurocognition in CP patients, thus hoping for a better overall prognostic outcome and an improved quality of life of the CP patients by VNS. Vagal nerve stimulation: exploring its efficacy and success for an improved prognosis and quality of life in cerebral palsy patients.

Cranial Surgery

1. **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;44:196-8.**
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. Effect of vagus nerve stimulation in post-traumatic epilepsy and failed epilepsy surgery : preliminary report.

2. **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.* 2008;62 Suppl 2:506-13.**
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. Vagus nerve stimulation therapy after failed cranial surgery for intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry.

3. **Wong TT, Kwan SY, Chang KP, et al. Corpus callosotomy in children. *Childs Nerv Syst.* 2006;22:999-1011.**
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. Corpus callosotomy in children.

4. **Hamberger MJ, Drake EB. Cognitive functioning following epilepsy surgery. *Curr Neurol Neurosci Rep.* 2006;6:319-26.**
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. Cognitive functioning following epilepsy surgery.

5. **Schmidt D. Should VNS be considered before corpus callosotomy? In: Miller JW, Silbergeld DL, eds. *Epilepsy Surgery: Principles and Controversies*. New York: Taylor & Francis; 2006:614-619.**

Book chapter

http://www.amazon.com/Epilepsy-Surgery-Principles-Controversies-Neurological/dp/0824725913

6. **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;55:1086-93.**
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. Vagus nerve stimulation therapy after failed cranial surgery for intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry.

7. **Polkey CE. Clinical outcome of epilepsy surgery. *Curr Opin Neurol.* 2004;17:173-178.**
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. Clinical outcome of epilepsy surgery.

9. **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;44:673-676.**

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. A prospective study of the requirement for and the provision of epilepsy surgery in the United Kingdom.

10. **Koutroumanidis M, Binnie CD, Hennessy MJ, et al. VNS in patients with previous unsuccessful resective epilepsy surgery: antiepileptic and psychotropic effects. *Acta Neurol Scand.* 2003;107:117-21.**
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. VNS in patients with previous unsuccessful resective epilepsy surgery: antiepileptic and psychotropic effects.

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

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

13. **Kemeny AA. Surgery for epilepsy. *Seizure.* 2001;10:461-465.**
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. Surgery for epilepsy.

14. **Williamson PD, Jobst BC. Epilepsy surgery in developing countries. *Epilepsia.* 2000;41 Suppl 4:S45-S50.**
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. Epilepsy surgery in developing countries.

Early Use of VNS Therapy

1. **Helmers SL, Griesemer DA, Dean JC, 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;9:160-4.**
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. Observations on the use of vagus nerve stimulation earlier in the course of pharmacoresistant epilepsy: patients with seizures for six years or less.

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

VNS Therapy End of Service

1. **Vonck K, Dedeurwaerdere S, De Groote L, et al. Generator replacement in epilepsy patients treated with vagus nerve stimulation. *Seizure.* 2005;14:89-99.**
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 preceeded 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. Generator replacement in epilepsy patients treated with vagus nerve stimulation.

2. **Wennberg RA. Seizure frequency after battery depletion of the VNS device - a reply to Tarver. *J Neurol Neurosurg Psychiatry.* 2004.**
Abstract: electronic letter in response to Tarver's electronic letter in response to the original Wennberg letter published in JNNP 2004;75:939.

3. **Tatum IV WO, Benbadis SR. Vagus nerve stimulation end of service. *Epilepsy Behav.* 2004;5:613-615.** Vagus nerve stimulation for pharmacoresistant epilepsy: clinical symptoms with end of service.

4. **Andrade DM, Velazquez JL, Wennberg R. On the need for battery replacement before end of service in vagus nerve stimulation for epilepsy. *Epilepsy Behav.* 2004;5:612-613.** On the need for battery replacement before end of service in vagus nerve stimulation for epilepsy.

5. **Tarver WB. Response to letter to the editor Wenneberg R. *J Neurol Neurosurg Psychiatry.* 2004.**
Abstract: electronic letter published on the journals web site in response to the Wennberg letter published in JNNP 2004;75:939.

6. **Wennberg R. Short term benefit of battery depletion in vagus nerve stimulation for epilepsy. *J Neurol Neurosurg Psychiatry.* 2004;75:939.**
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.

7. Tatum WO 4th, Ferreira JA, Benbadis SR, et al. Vagus nerve stimulation for pharmacoresistant epilepsy: clinical symptoms with end of service. *Epilepsy Behav.* 2004;5:128-32.
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 pharmacoresistent 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 pharmacoresistent 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 (chi2=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. Vagus nerve stimulation for pharmacoresistant epilepsy: clinical symptoms with end of service.

Epilepsy Monitoring

1. **Casazza M, Avanzini G, Ferroli P, Villani F, Broggi G. Vagal nerve stimulation: relationship between outcome and electroclinical seizure pattern. Seizure 2006:15: 198-207.**
   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. Vagal nerve stimulation: relationship between outcome and electroclinical seizure pattern.

2. **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: 384-9.**
   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. Vagus nerve stimulation: predictors of seizure freedom.

3. **Benbadis SR, O'Neill E, Tatum WO, Heriaud L . Outcome of prolonged video-EEG monitoring at a typical referral epilepsy center. Epilepsia 2004:45: 1150-1153.**
Abstract: Summary: 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 (>/=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%). Outcome of prolonged video-EEG monitoring at a typical referral epilepsy center.

4. **Attarian H, Dowling J, Carter J, Gilliam F . Video EEG monitoring prior to vagal nerve stimulator implantation. Neurology 2003:61: 402-3.**
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. Video EEG monitoring prior to vagal nerve stimulator implantation.

5. **Jaseja H. Intractable epilepsy management: an EEG-oriented approach. Med Hypotheses 2003:61: 231-4.**
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 minimizing the intervention of invasive techniques like VNS and epilepsy brain surgery. Intractable epilepsy management: an EEG-oriented approach.

6. **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: 247-255.**
Abstract: PURPOSE: The purpose of this paper is to demonstrate the diagnostic efficacy and therapeutic relevance of video-EEG monitoring in an 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. Interictal and ictal video-EEG monitoring.

7. **Salinsky MC, Burchiel KJ. Vagus nerve stimulation has no effect on awake EEG rhythms in humans. Epilepsia 1993:34: 299-304.**
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. Vagus nerve stimulation has no effect on awake EEG rhythms in humans.

Epileptic Encephalopathies

1. **Tharp BR. Epileptic encephalopathies and their relationship to developmental disorders: Do spikes cause autism? Ment Retard Dev Disabil Res Rev 2004:10: 132-134.**
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. MRDD Research Reviews 2004;10:132-134.
 Epileptic encephalopathies and their relationship to developmental disorders: do spikes cause autism?

2. **Parker AP, Polkey CE, Robinson RO. Vagal nerve stimulation in the epileptic encephalopathies: 3-year follow-up. Pediatrics 2001:108: 221.** Vagal nerve stimulation in the epileptic encephalopathies: 3-year follow-up.

3. **Parker AP, Polkey CE, Binnie CD, Madigan C, Ferrie CD, Robinson RO. Vagal nerve stimulation in epileptic encephalopathies. Pediatrics 1999:103: 778-782.**
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. Vagal nerve stimulation in epileptic encephalopathies.

4. **Aicardi J. Vagal nerve stimulation in epileptic encephalopathies. Pediatrics 1999:103: 821-822.** Vagal nerve stimulation in epileptic encephalopathies.

Evaluations of VNS Therapy

1. **Privitera MD, Welty TE, Ficker DM, Welge J. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev 2002: CD002896.**
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. Vagus nerve stimulation for partial seizures.

2. **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: 666-669.** Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

3. **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: 293-297.**
Assessment of vagus nerve stimulation for epilepsy: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

Focal Motor Seizures

1. **Bokkala-Pinninti S , Pinninti N, Jenssen S. Vagus nerve stimulation effective for focal motor seizures and focal interictal parkinsonian symptoms. A case report. *J Neurol.* 2008;255:301-2.** Vagus nerve stimulation effective for focal motor seizures and focal interictal parkinsonian symptoms. A case report.

Generalized Seizures

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;19:197-9.**
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. Effect of vagal nerve stimulation in Dyke-Davidoff-Masson syndrome with refractory generalized seizures - case report.

2. **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;58:345-50.**
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. Vagus nerve stimulation suppresses generalized seizure activity and seizure-triggered postictal cardiac rhythm changes in rats.

3. **Kanner AM. Vagus nerve stimulation for generalized epilepsy?...Show me the evidence! *Epilepsy Curr* . 2008;8:35-6.** Vagus nerve stimulation for generalized epilepsy?...Show me the evidence!

4. **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.**
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. Is vagus nerve stimulation a treatment option for patients with drug-resistant idiopathic generalized epilepsy?

5. **Nei M, O'Connor M, Liporace J, Sperling MR. Refractory generalized seizures: response to corpus callosotomy and vagal nerve stimulation. *Epilepsia.* 2006;47:115-22.**
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 >or=50% decrease in the frequency of generalized tonic-clonic seizures, and 60% had >or=80% seizure reduction. For those with a VNS and generalized tonic-clonic seizures (n = 21), 50% had >or=50% seizure reduction, and 33% had >or=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. Refractory generalized seizures: response to corpus callosotomy and vagal nerve stimulation.

6. **Holmes MD. Is vagus nerve stimulation therapy effective for generalized epilepsy? In: Miller JW, Silbergeld DL, eds. *Epilepsy Surgery: Principles and Controversies*. New York: Taylor & Francis; 2006:620-623.**

Book chapter – book available via Amazon.com
http://www.amazon.com/Epilepsy-Surgery-Principles-Controversies-Neurological/dp/0824725913#

7. **Holmes MD, Silbergeld DL, Drouhard D, Wilensky AJ, Ojemann LM. Effect of vagus nerve stimulation on adults with pharmacoresistant generalized epilepsy syndromes. *Seizure.* 2004;13:340-5.**
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 pharmacoresistant 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 pharmacoresistant generalized seizure syndromes. Effect of vagus nerve stimulation on adults with pharmacoresistant generalized epilepsy syndromes.

8. **Ng M, Devinsky O. Vagus nerve stimulation for refractory idiopathic generalised epilepsy. *Seizure.* 2004;13:176-8.**
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. Vagus nerve stimulation for refractory idiopathic generalised epilepsy.

9. **Faught E. Treatment of refractory primary generalized epilepsy. *Rev Neurol Dis.* 2004;1(suppl 1): S34-S43.**
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. Treatment of refractory primary generalized epilepsy.

10. **Rafael H, Moromizato P. Vagus nerve stimulation (VNS) may be useful in treating patients with symptomatic generalized epilepsy. *Epilepsia.* 1998;39:1018.** Vagus nerve stimulation (VNS) may be useful in treating patients with symptomatic generalized epilepsy.

11. **Labar D, Nikolov B, Tarver B, Fraser R. Vagus nerve stimulation for symptomatic generalized epilepsy: a pilot study. *Epilepsia.* 1998;39:201-5.**
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. Vagus nerve stimulation for medication-resistant generalized epilepsy. E04 VNS Study Group.

Geriatric Population

1. **Gallo BV. Epilepsy, surgery, and the elderly. Epilepsy Res 2006:68(suppl 1): 83-86.**
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. Epilepsy, surgery, and the elderly.

2. **LaRoche SM, Helmers SL. Epilepsy in the elderly. Neurologist 2003:9: 241-249.**
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. Epilepsy in the elderly.

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: 1179-82.**
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. Vagus nerve stimulation therapy for epilepsy in older adults.

Healthcare Utilization/Cost

1. **Forbes R. Cost-utility of vagus nerve stimulation (VNS) therapy for medically refractory epilepsy--an update. *Seizure.* 2008;17:387-88.** Cost-utility of vagus nerve stimulation (VNS) therapy for medically refractory epilepsy--an update.

2. **Bernstein AL, Barkan H, Hess T. Vagus nerve stimulation therapy for pharmacoresistant epilepsy: Effect on health care utilization. *Epilepsy Behav.* 2007;10:134-7.**
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 pharmacoresistant epilepsy. Vagus nerve stimulation therapy for pharmacoresistant epilepsy: effect on health care utilization.

3. **Forbes RB, Macdonald S, Eljamel S, Roberts RC. Cost-utility analysis of vagus nerve stimulators for adults with medically refractory epilepsy. *Seizure.* 2003;12:249-56.**
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. Cost-utility analysis of vagus nerve stimulators for adults with medically refractory epilepsy.

4. **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-S47.**
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. Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients.

5. **Boon P, D'Have M, Van Walleghem P, et al. Direct medical costs of refractory epilepsy incurred by three different treatment modalities: a prospective assessment. *Epilepsia*. 2002;43:96-102.**
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. Direct medical costs of refractory epilepsy incurred by three different treatment modalities: a prospective assessment.

6. **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;99:275-280.**

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. Cost-benefit of vagus nerve stimulation for refractory epilepsy.

7. **Boon P, Vonck K, Vandekerckhove T, et al. Vagus nerve stimulation for medically refractory epilepsy; efficacy and cost-benefit analysis. *Acta Neurochir (Wien).* 1999;141:447-453.**

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 > 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 > 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. Vagus nerve stimulation for medically refractory epilepsy; efficacy and cost-benefit analysis.

VNS Therapy and Ketogenic Diet

1. **Kossoff EH, Pyzik PL, Rubenstein JE, et al. Combined ketogenic diet and vagus nerve stimulation: rational polytherapy? *Epilepsia.* 2007;48:77-81.**
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. Combined ketogenic diet and vagus nerve stimulation: rational polytherapy?

2. **Marsh EB, Freeman JM, Kossoff EH, 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;47:425-30.**
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. 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.

3. **Stafstrom CE. Dietary approaches to epilepsy treatment: old and new options on the menu. *Epilepsy Curr.* 2004;4:215-222.**
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. Dietary approaches to epilepsy treatment: old and new options on the menu.

4. **Sheth RD, Stafstrom CE. Intractable pediatric epilepsy: vagal nerve stimulation and the ketogenic diet. *Neurol Clin.* 2002;20:1183-1194.**
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. Intractable pediatric epilepsy: vagal nerve stimulation and the ketogenic diet.

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

Lennox-Gastaut Syndrome

1. **Koenig SA, Longin E, Bell N, Reinhard J, Gerstner T. Vagus nerve stimulation improves severely impaired heart rate variability in a patient with Lennox-Gastaut-Syndrome. *Seizure.* 2008;17:469-72.**
   Abstract: Vagus nerve stimulation (VNS) is a new therapeutic option for refractory epilepsy. We report a patient with Lennox-Gastaut-Syndrome (LGS) and a severe impairment of heart rate variability (HRV), we could demonstrate in our patient that HRV was improved by VNS. Vagus nerve stimulation improves severely impaired heart rate variability in a patient with Lennox-Gastaut-Syndrome.

2. **You SJ, Kang HC, Ko TS, et al. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. *Brain Dev.* 2007.**
   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. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome.

3. **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;15:483-90.**
   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. Vagus nerve stimulation: clinical experience in drug-resistant pediatric epileptic patients.

4. **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;14:10-8.**
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. Vagus nerve stimulation in patients with catastrophic childhood epilepsy, a 2-year follow-up study.

5. **Buoni S, Zannolli R, Macucci F, et al. Delayed response of seizures with vagus nerve stimulation in Lennox-Gastaut syndrome. *Neurology.* 2004;63:1539-1540.** Delayed response of seizures with vagus nerve stimulation in Lennox-Gastaut syndrome.

6. **Aldenkamp AP, Majoie HJ, Berfelo MW, et al. Long-term effects of 24-month treatment with vagus nerve stimulation on behaviour in children with Lennox-Gastaut syndrome. *Epilepsy Behav.* 2002;3:475-479.**
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: 500&mgr;s; 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. Long-term effects of 24-month treatment with vagus nerve stimulation on behaviour in children with Lennox-Gastaut syndrome.

7. **Trevathan E. Infantile spasms and Lennox-Gastaut syndrome. *J Child Neurol.* 2002;17(suppl 2):2S9-2S22.**
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. Infantile spasms and Lennox-Gastaut syndrome.

8. **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;18:419-28.**
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. 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.

9. **Karceski S. Vagus nerve stimulation and Lennox-Gastaut syndrome: a review of the literature and data from the VNS patient registry. *CNS Spectr.* 2001;6:766-70.**
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 factor 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. Vagus nerve stimulation and Lennox-Gastaut syndrome: a review of the literature and data from the VNS patient registry.

10. **Frost M, Gates J, Helmers SL, et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. *Epilepsia.* 2001;42:1148-1152.**
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. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome.

11. **Aldenkamp AP, Van de Veerdonk SHA, Majoie HJM, 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;2:343-350.**
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, 112 to 2 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. 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.

12. **Hosain S, Nikalov B, Harden C, Li M, Fraser R, Labar D. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. *J Child Neurol.* 2000;15:509-512.**
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. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome.

MOA

1. **Zhang Y, Popovic ZB, Bibevski S, et al. Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. *Circ Heart Fail.* 2009;2:692-9.**
Abstract: BACKGROUND: Autonomic dysfunction, characterized by sympathetic activation and vagal withdrawal, contributes to the progression of heart failure (HF). Although the therapeutic benefits of sympathetic inhibition with beta-blockers in HF are clear, the role of increased vagal tone in this setting has been less studied. We have investigated the impact of enhancing vagal tone (achieved through chronic cervical vagus nerve stimulation, [VNS]) on HF development in a canine high-rate ventricular pacing model. METHODS AND RESULTS: Fifteen dogs were randomized into control (n=7) and VNS (n=8) groups. All dogs underwent 8 weeks of high-rate ventricular pacing (at 220 bpm for the first 4 weeks to develop HF and another 4 weeks at 180 bpm to maintain HF). Concomitant VNS, at an intensity reducing sinus rate approximately 20 bpm, was delivered together with the ventricular pacing in the VNS group. At 4 and 8 weeks of ventricular pacing, both left ventricular end-diastolic and -systolic volumes were lower and left ventricular ejection fraction was higher in the VNS group than in the control group. Heart rate variability and baroreflex sensitivity improved in the VNS dogs. Rises in plasma norepinephrine, angiotensin II, and C-reactive protein levels, ordinarily expected in this model, were markedly attenuated with VNS treatment. CONCLUSIONS: Chronic VNS improves cardiac autonomic control and significantly attenuates HF development in the canine high-rate ventricular pacing model. The therapeutic benefit of VNS is associated with pronounced anti-inflammatory effects. VNS is a novel and potentially useful therapy for treating HF. Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model.

2. **Wang H, Chen X, Lin Z, et al. Long-term effect of vagus nerve stimulation on interictal epileptiform discharges in refractory epilepsy. *J Neurol Sci.* 2009;284:96-102.**
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 > or = 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. Long-term effect of vagus nerve stimulation on interictal epileptiform discharges in refractory epilepsy.

3. **Lyubashina O, Panteleev S. Effects of cervical vagus nerve stimulation on amygdala-evoked responses of the medial prefrontal cortex neurons in rat. *Neurosci Res.* 2009;65:122-5.**
Abstract: In experiments on urethane-anaesthetized rats, the effects of repetitive vagus nerve stimulation (VNS) on responses of medial prefrontal cortex (mPFC) neurons to electrical stimulation of the basal nucleus of the amygdala were examined before and after intracerebroventricular administration of the neuronal nitric oxide synthase inhibitor 7-nitroindasole (7-NI). It was shown that the amygdala-evoked responses of cortical neurons were inhibited by repetitive VNS (pulses 50-150 microA, 0.5 ms, frequency 10 Hz). 7-NI administration did not change the amygdala-evoked neuronal reactions but reversed the effect of VNS on them. The present results suggest that the inhibitory action of VNS on amygdala-mPFC neurotransmission may involve a cortical NO-dependent mechanism. Effects of cervical vagus nerve stimulation on amygdala-evoked responses of the medial prefrontal cortex neurons in rat.

4. **De Herdt V, Puimege L, De Waele J, et al. Increased rat serum corticosterone suggests immunomodulation by stimulation of the vagal nerve. *J Neuroimmunol.* 2009;212:102-5.**
Abstract: The role of the vagal nerve within the immune system has not been fully elucidated. Vagal afferents connect to several central nervous system structures, including the hypothalamus. We investigated the effect of vagal nerve stimulation (VNS) on serum corticosterone levels in rats. Corticosterone levels were measured following 1 h of high frequency (30 Hz) or low frequency (1 Hz) VNS in awake animals. There was a significant increase ($p < 0.05$) in serum corticosterone levels following 30 Hz VNS compared to 1 Hz VNS or sham stimulation. These results suggest an immediate effect of VNS on the hypothalamic pituitary-adrenal (HPA) axis and support the role of the vagal nerve in immunomodulation. Increased rat serum corticosterone suggests immunomodulation by stimulation of the vagal nerve.

5. **Manta S, Dong J, Debonnel G, Blier P. Enhancement of the function of rat serotonin and norepinephrine neurons by sustained vagus nerve stimulation. *J Psychiatry Neurosci.* 2009;34:272-80.**
Abstract: BACKGROUND: Vagus nerve stimulation (VNS) is a recent intervention for treatment-resistant depression. Electrophysiological recordings in the rat brain showed that VNS increases the firing rate of norepinephrine (NE) neurons after 1 day of stimulation and that of serotonin (5-HT) neurons after 14 days. This study was conducted to further characterize these effects. METHODS: We implanted rats with a VNS electrode and

stimulator. We used the selective noradrenergic toxin DSP-4 to lesion NE neurons of the locus coeruleus. We recorded dorsal raphe 5-HT neurons under chloral hydrate anesthesia. We recorded hippocampus CA(3) pyramidal neurons using 5-barreled iontophoretic pipettes. RESULTS: Analysis of a previously published data set revealed that VNS increased not only the spontaneous firing rates of NE neurons, but also the percentage of neurons firing in bursts. The enhancement of the 5-HT neuron firing rate by VNS was abolished by lesioning NE neurons. We found that VNS increased the degree of activation of postsynaptic alpha(1)-adrenoceptors on 5-HT neurons, probably through an increased release of endogenous NE. The tonic activation of postsynaptic 5-HT(1A) receptors in the hippocampus was enhanced after 14 days of VNS, as with other antidepressant treatments. LIMITATIONS: Our study limitations include the fact that we turned off the stimulator during the electrophysiological recordings, which likely decreased the vagal tone to the brain. Also, we obtained the data while the animals were under anesthesia, therefore studies need to be carried out in unanesthetized rats to ascertain whether the anesthetic agent influenced the changes observed between control rats and those treated with VNS. CONCLUSION: Vagus nerve stimulation initially increases the firing activity and pattern of NE neurons and subsequently those of 5-HT neurons, presumably as a cascade effect via alpha(1)-postsynaptic adrenoceptors. To date, VNS appears to be a unique antidepressant treatment increasing 5-HT transmission and enhancing the firing activity of NE neurons. These effects could contribute to the effectiveness of VNS in treatment-resistant depression. Enhancement of the function of rat serotonin and norepinephrine neurons by sustained vagus nerve stimulation.

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

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. VEP indices of cortical lateral interactions in epilepsy treatment.

7. **Furukawa T, Hirao K, Horikawa-Tanami T, Hachiya H, Isobe M. Influence of autonomic stimulation on the genesis of atrial fibrillation in remodeled canine atria not the same as in normal atria. *Circ J.* 2009;73:468-75.**
Abstract: BACKGROUND: The role of autonomic effects in the occurrence and maintenance of atrial fibrillation (AF) has undergone little investigation in the remodeling heart. METHODS AND RESULTS: In the present study, 2 groups were studied: those with complete atrioventricular block (AVB) produced by radiofrequency current application (AVB dogs, n=17) and those not undergoing AVB (sham dogs, n=5). Eight weeks after creation of AVB, electrophysiologic study, including pulmonary vein (PV) pacing for AF induction, was performed under vagal nerve stimulation (VNS) and sympathetic stimulation (SS) in both groups. After 8 weeks, atrial dimensions and the percentage of fibrosis in the atria were significantly greater in the AVB dogs. In AVB dogs, atrial and PV effective refractory periods were shorter (P<0.01), and atrial conduction velocity increased (P=0.01) during SS, but not during VNS. Inducibility of AF increased only during SS in the AVB dogs (sustained AF: control 7%, SS 60%; P=0.005), whereas it increased only during VNS in the sham dogs. CONCLUSIONS: In the remodeled atria, sympathetic stimulation was crucial for the genesis of AF, which is completely different from the condition in normal atria. Influence of autonomic stimulation on the genesis of atrial fibrillation in remodeled canine atria not the same as in normal atria.

8. **Liu P, Guo JH, Zhang HC, et al. Vagal effects on the occurrence of focal atrial fibrillation originating from the pulmonary veins. *Circ J.* 2009;73:48-54.**
Abstract: BACKGROUND: There is evidence that the autonomic nervous system may be involved in the mechanism of focal atrial fibrillation (AF), so the present study investigated the effects of the parasympathetic nervous system on the occurrence of focal AF originating from the pulmonary veins (PVs). METHODS AND RESULTS: In 10 mongrel dogs, programmed stimulation and local burst stimulation (12.5 Hz, impulse duration 0.5 ms) were performed at each of the PVs. Pacing thresholds at different sites were determined and shown as a terraced distribution. The closer to the ostium of the PV, the lower was the pacing threshold (P<0.05-0.001). The local effective refractory period (ERP), AF induction and AF threshold were measured at baseline and during bilateral vagal nerve stimulation (VNS). VNS led to local ERP shortening at each of the PV sites (P<0.05-0.001), increased the inducibility of AF at all sites in the 4 PVs (P<0.05-0.001), and decreased the AF threshold at most sites, especially in the distal portions of the 4 PVs (P<0.05-0.01). CONCLUSIONS: VNS changes the electrophysiological characteristics of the PVs and facilitates the induction of AF. Interaction between the autonomic nervous system and local cardiac autonomic nerve system may be a potential mechanism. Vagal effects on the occurrence of focal atrial fibrillation originating from the pulmonary veins

9. **Zaaimi B, Grebe R, Wallois F. Animal model of the short-term cardiorespiratory effects of intermittent vagus nerve stimulation. *Auton Neurosci.* 2008;143:20-6.**
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. Animal model of the short-term cardiorespiratory effects of intermittent vagus nerve stimulation.

10. **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;17:699-706.**
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. Thalamic and limbic involvement in the mechanism of action of vagus nerve stimulation, a SPECT study.

11. **Revesz D, Tjernstrom M, Ben-Menachem E, Thorlin T. Effects of vagus nerve stimulation on rat hippocampal progenitor proliferation. *Exp Neurol.* 2008;214:259-65.**
Abstract: Vagus nerve stimulation (VNS), used in the treatment of epilepsy, was approved recently for treatment-resistant depression. The mechanisms of action of the VNS anti-depressive effects are not yet fully elucidated. Modulation of hippocampal neurogenesis has been proposed as an important factor in depression pathogenesis. We evaluated the effects of VNS on hippocampal progenitor turnover in the adult rat brain. Rats receiving VNS at the output current of 0.75 mA VNS for 2 days showed a significant 50% increase in dentate gyrus BrdU-incorporation consistent with an increase in progenitor proliferation.

Output currents of 0.5 or 1.5 mA yielded non-significant trends for increased BrdU-labeling indicating an inverted U-shaped proliferative dose response to VNS as previously reported for other VNS-induced effects. Specific analysis for progenitor survival revealed no effects by VNS on dentate gyrus BrdU-labeling. These results suggest that VNS induced an increase in the number of available progenitor cells in the adult rat dentate gyrus by a mechanism presumably involving increased progenitor proliferation. Effects of vagus nerve stimulation on rat hippocampal progenitor proliferation.

12. **Ohad DG, Sinai Y, Zaretsky A, Shofti R. Ventricular rate control using a novel vagus nerve stimulating system in a dog with chronic atrial fibrillation. *J Vet Cardiol.* 2008;10:147-54.**
Abstract: A 4-year-old, intact male Dogue de Bordeaux dog with congenital valvular pulmonic stenosis, tricuspid valve dysplasia, and chronic atrial fibrillation underwent ultrasound-guided balloon valvuloplasty in addition to pharmacological treatment. Owner compliance to prescribed pharmacotherapy proved very poor, and concerns developed regarding the ability to successfully control heart rate and symptoms using drug therapy alone. These concerns were addressed by the implantation of a novel vagal stimulation system that was programmed to prevent a ventricular rate of >145 bpm. Consequently, post-operative ventricular response rate decreased from up to 250 to 140 bpm. Successful ventricular rate control was maintained for 291 days post-operatively, following which euthanasia was elected by the owner due to persistent right-sided congestive heart failure. To the authors' knowledge, this is the first report of successful continuous rate control using a vagal stimulating system in a closed-chest, client-owned dog with chronic atrial fibrillation secondary to spontaneously occurring organic heart disease. Ventricular rate control using a novel vagus nerve stimulating system in a dog with chronic atrial fibrillation.

13. **Hydman J, Mattsson P. Collateral reinnervation by the superior laryngeal nerve after recurrent laryngeal nerve injury. *Muscle Nerve.* 2008;38:1280-9.**
Abstract: This study investigates the role of the intact superior laryngeal nerve (SLN) in the reinnervation process of one of the laryngeal muscles, the posterior cricoarytenoid muscle (PCA), following recurrent laryngeal nerve (RLN) injury. Using a chronic RLN injury model in the adult rat, PCA reinnervation was assessed by retrograde double-tracing techniques in combination with electrophysiology and immunohistochemistry of muscle sections. The results demonstrate that the PCA receives dual innervation from both laryngeal nerves even in the uninjured system. Functionally significant collateral reinnervation originates from intact SLN fibers following RLN injury, mainly due to intramuscular sprouting rather than by recruitment of more motor neurons. This may be important when choosing surgical and/or medical treatment for patients with RLN injury. Collateral reinnervation by the superior laryngeal nerve after recurrent laryngeal nerve injury.

14. **Zhang JL, Zhang SP, Zhang HQ. Antiepileptic effect of electroacupuncture vs. vagus nerve stimulation in the rat thalamus. *Neurosci Lett.* 2008;441:183-7.**
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. Antiepileptic effect of electroacupuncture vs. vagus nerve stimulation in the rat thalamus.

15. **Olshansky B, Sabbah HN, Hauptman PJ, Colucci WS. Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy. *Circulation.* 2008;118:863-71.** Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy.

16. **Pardo JV, Sheikh SA, Schwindt GC, et al. Chronic vagus nerve stimulation for treatment-resistant depression decreases resting ventromedial prefrontal glucose metabolism. *Neuroimage.* 2008;42:879-89.**
Abstract: Vagus nerve stimulation (VNS) is used as an adjunctive therapy for treatment-resistant depression (TRD). Its mechanism of action is not fully understood. Longitudinal measurement of changes in brain metabolism associated with VNS can provide insights into this new treatment modality. Eight severely depressed outpatients who were highly treatment-resistant underwent electrical stimulation of the left vagus nerve for approximately one year. The main outcome measures were resting regional brain glucose uptake measured with positron emission tomography (PET) and the 24-item Hamilton Depression Scale. The most significant and extensive change over one year of chronic VNS localized to the ventromedial prefrontal cortex extending from the subgenual cingulate to the frontal pole. This region continued to decline in metabolism even toward the end of the study. Clinically, this cohort showed a trend for improvement. No correlations surfaced between change in glucose uptake and depression scores. However, the sample size was small; none remitted; and the range of depression scores was limited. Chronic VNS as adjunctive therapy in patients with severe TRD produces protracted and robust declines in resting brain activity within the ventromedial prefrontal cortex, a network with dense connectivity to the amygdala and structures monitoring the internal milieu. Chronic vagus nerve stimulation for treatment-resistant depression decreases resting ventromedial prefrontal glucose metabolism.

17. **Del Rio CL, Dawson TA, Clymer BD, Paterson DJ, Billman GE. Effects of acute vagal nerve stimulation on the early passive electrical changes induced by myocardial ischaemia in dogs: heart rate-mediated attenuation. *Exp Physiol.* 2008;93:931-44.**
Abstract: Parasympathetic activity during acute coronary artery occlusion (CAO) can protect against ischaemia-induced malignant arrhythmias; nonetheless, the mechanism mediating this protection remains unclear. During CAO, myocardial electrotonic uncoupling is associated with autonomically mediated immediate (i.e. type 1A) arrhythmias and can modulate pro-arrhythmic dispersion of repolarization. Therefore, the effects of acutely enhanced or decreased cardiac parasympathetic activity on early

electrotonic coupling during CAO, as measured by myocardial electrical impedance (MEI), were investigated. Anaesthetized dogs were instrumented for MEI measurements, and left circumflex coronary arterial occlusions were performed in intact (CTRL) and vagotomized (VAG) animals. The CAO was followed by either vagotomy (CTRL) or vagal nerve stimulation (VNS, 10 Hz, 10 V) in the VAG dogs. Vagal nerve stimulation was studied in two additional sets of animals. In one set heart rate (HR) was maintained by pacing (220 beats min(-1)), while in the other set bilateral stellectomy preceded CAO. The MEI increased after CAO in all animals. A larger MEI increase was observed in vagotomized animals (+85 +/- 9 Omega, from 611 +/- 24 Omega, n = 16) when compared with intact control dogs (+43 +/- 5 Omega, from 620 +/- 20 Omega, n = 7). Acute vagotomy during ischaemia abruptly increased HR (from 155 +/- 11 to 193 +/- 15 beats min(-1)) and MEI (+12 +/- 1.1 Omega, from 663 +/- 18 Omega). In contrast, VNS during ischaemia (n = 11) abruptly reduced HR (from 206 +/- 6 to 73 +/- 9 beats min(-1)) and MEI (-16 +/- 2 Omega, from 700 +/- 44 Omega). These effects of VNS were eliminated by pacing but not by bilateral stellectomy. Vagal nerve stimulation during CAO also attenuated ECG-derived indices of ischaemia (e.g. ST segment, 0.22 +/- 0.03 versus 0.15 +/- 0.03 mV) and of rate-corrected repolarization dispersion [terminal portion of T wave (TPEc), 84.5 +/- 4.2 versus 65.8 +/- 5.9 ms; QTc, 340 +/- 8 versus 254 +/- 16 ms]. Vagal nerve stimulation during myocardial ischaemia exerts negative chronotropic effects, limiting early ischaemic electrotonic uncoupling and dispersion of repolarization, possibly via a decreased myocardial metabolic demand. Effects of acute vagal nerve stimulation on the early passive electrical changes induced by myocardial ischaemia in dogs: heart rate-mediated attenuation.

18. **Zhang JL, Zhang SP, Zhang HQ. Antiepileptic effects of electroacupuncture vs vagus nerve stimulation on cortical epileptiform activities. *J Neurol Sci.* 2008;270:114-21.**
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. Antiepileptic effects of electroacupuncture vs vagus nerve stimulation on cortical epileptiform activities.

19. **Gibson EL, Mohiyeddini C. Vagus nerve stimulation confuses appetite: comment on Bodenlos et al. (2007). *Appetite.* 2008; 51:223-5; discussion 226-30.**
Abstract: In a recent research report, [Bodenlos et al. 2007. Vagus nerve stimulation (VNS) acutely alters food craving in adults with depression. Appetite, 48, 145-153] concluded

that, in depressed patients, acute activation of a device for VNS caused a significant change in cravings specifically for sweet foods. We argue that there is no evidence for any effect on food cravings. Rather, the findings indicate that VNS confuses the patient's appetite for sweet foods: this might result from contextually unexpected internal afferent signals generated by the vagal stimulation. Unfortunately, their multiple regression of potential predictive variables cannot be interpreted reliably. The concept is interesting, but the design, analysis and interpretation should be reconsidered. Vagus nerve stimulation confuses appetite: comment on Bodenlos et al. (2007).

20. **Cunningham JT, Mifflin SW, Gould GG, Frazer A. Induction of c-Fos and DeltaFosB immunoreactivity in rat brain by Vagal nerve stimulation. *Neuropsychopharmacology.* 2008;33:1884-95.**
Abstract: Vagus nerve stimulation (VNS) is used as therapy for treatment-resistant depression or epilepsy. This study used immunohistochemistry for biomarkers of short-term (c-Fos) and long-term (DeltaFosB) neuronal activation to map regions in brain that are activated by acute (2 h) or chronic (3 weeks) VNS in conscious Sprague-Dawley rats. Electrodes (Cyberonics Inc.) were implanted on the left vagus nerve and 1 week after surgery, stimulation began using parameters employed clinically (one burst of 20 Hz, 250 micros pulse width, 0.25 mA stimulation for 30 s every 5 min). Radio telemetry transmitters were used for monitoring blood pressure, heart rate, activity, and respiratory rate during VNS; neither acute nor chronic VNS significantly affected these parameters. Acute VNS significantly increased c-Fos staining in the nucleus of the solitary tract, paraventricular nucleus of the hypothalamus, parabrachial nucleus, ventral bed nucleus of the stria terminalis, and locus coeruleus but not in the cingulate cortex or dorsal raphe nucleus (DRN). Acute VNS did not affect DeltaFosB staining in any region. Chronic VNS significantly increased DeltaFosB and c-Fos staining bilaterally in each region affected by acute VNS as well as in the cingulate cortex and DRN. Using these stimulation parameters, VNS was tested for antidepressant-like activity using the forced swim test (FST). Both VNS and desipramine significantly decreased immobility in the FST; whereas desipramine decreased immobility by increasing climbing behavior, VNS did so by increasing swimming behavior. This study, then, identified potential sites in brain where VNS may produce its clinical effects. Induction of c-Fos and DeltaFosB immunoreactivity in rat brain by Vagal nerve stimulation

21. **Schmidt H, Muller-Werdan U, Werdan K. Assessment of vagal activity during transcutaneous vagus nerve stimulation in mice. *Crit Care Med.* 2008;36:1990.**
Assessment of vagal activity during transcutaneous vagus nerve stimulation in mice.

22. **Berthoud HR. Vagal and hormonal gut-brain communication: from satiation to satisfaction. *Neurogastroenterol Motil.* 2008;20 Suppl 1:64-72.**
Abstract: Studying communication between the gut and the brain is as relevant and exciting as it has been since Pavlov's discoveries a century ago. Although the efferent limb of this communication has witnessed significant advances, it is the afferent, or sensory, limb that has recently made for exciting news. It is now clear that signals from the gut are crucial for the control of appetite and the regulation of energy balance, glucose homeostasis, and more. Ghrelin, discovered just a few years ago, is the first gut hormone that increases appetite, and it may be involved in eating disorders. The stable analogue of glucagon-like

peptide-1 has rapidly advanced to one of the most promising treatment options for type-2 diabetes. Changes in the signalling patterns of these and other gut hormones best explain the remarkable capacity of gastric bypass surgery to lower food intake and excess body weight. Given the enormous societal implications of the obesity epidemic, these are no small feats. Together with the older gut hormone cholecystokinin and abundant vagal mechanosensors, the gut continuously sends information to the brain regarding the quality and quantity of ingested nutrients, not only important for satiation and meal termination, but also for the appetitive phase of ingestive behaviour and the patterning of meals within given environmental constraints. By acting not only on brainstem and hypothalamus, this stream of sensory information from the gut to the brain is in a position to generate a feeling of satisfaction and happiness as observed after a satiating meal and exploited in vagal afferent stimulation for depression. Vagal and hormonal gut-brain communication: from satiation to satisfaction.

23. **Valdes-Cruz A, Magdaleno-Madrigal VM, Martinez-Vargas D, Fernandez-Mas R, Almazan-Alvarado S. Long-term changes in sleep and electroencephalographic activity by chronic vagus nerve stimulation in cats.** ***Prog Neuropsychopharmacol Biol Psychiatry.*** **2008;32:828-34.**
Abstract: We previously reported the effect of vagus nerve electrical stimulation (VNS) on sleep and behavior in cats. The aim of the present study is to analyze the long-term effects of VNS on the electroencephalographic (EEG) power spectrum and on the different stages of the sleep-wakefulness cycle in the freely moving cat. To achieve this, six male cats were implanted with electrodes on the left vagal nerve and submitted to 15 rounds of 23 h continuous sleep recordings in three categories: baseline (BL), VNS and post-stimulus recording (PSR). The following parameters were analyzed: EEG power spectrum, total time and number of sleep phases, ponto-geniculo-occipital (PGO) wave density of the rapid eye movement (REM) sleep, and the number of times the narcoleptic reflex was present (sudden transition from wakefulness to REM sleep). Significant changes were detected, such as an enhancement of slow-wave sleep (SWS) stage II; a power increase in the bands corresponding to sleep spindles (8-14 Hz) and delta waves (1-4 Hz) with VNS and PSR; an increase in the total time, number of stages, and density of PGO wave in REM sleep with VNS; a decrease of wakefulness in PSR, and the eventual appearance of the narcoleptic reflex with VNS. The results show that the effect of the VNS changes during different stages of the sleep-wakefulness cycle. In REM sleep, the effect was present only during VNS, while the SWS II was affected beyond VNS periods. This suggests that ponto-medullar and thalamic mechanisms of slow EEG activity may be due to plastic changes elicited by vagal stimulation. Long-term changes in sleep and electroencephalographic activity by chronic vagus nerve stimulation in cats.

24. **Tsutsumi T, Ide T, Yamato M, et al. Modulation of the myocardial redox state by vagal nerve stimulation after experimental myocardial infarction.** ***Cardiovasc Res.*** **2008;77:713-21.**
Abstract: AIMS: Redox alteration plays a major role in the pathogenesis of heart failure (HF). Since vagal nerve stimulation (VNS) is known to improve survival and attenuate cardiac remodelling, we hypothesized that VNS may modulate the myocardial redox state. METHODS AND RESULTS: Using a chronic HF mouse model, we applied VNS for 15 min and measured myocardial redox status using in vivo electron spin resonance

spectroscopy. Signal decay rate of the nitroxyl probe, an index of redox status, was enhanced in HF compared with sham (0.16 +/- 0.01 vs. 0.13 +/- 0.01 min(-1), P < 0.05; n = 6), and VNS normalized this enhancement (0.13 +/- 0.01 min(-1), P < 0.05). Atropine sulphate abolished the VNS effects, indicating that the VNS modulates myocardial redox state via muscarinic receptors. N(omega)-Nitro-L-arginine methyl ester treatment and fixed-rate atrial pacing showed a trend to suppress the VNS effects, suggesting the involvement of nitric oxide-based signalling and myocardial oxygen consumption. Moreover, VNS decreased the myocardial norepinephrine (NE) level (0.25 +/- 0.07 vs. 0.60 +/- 0.12 ng/mL, P < 0.05; n = 6). Reactive oxygen species production from cultured cardiomyocytes was enhanced by beta-adrenergic activation, which was partially antagonized by 10 micromol/L acetylcholine (ACh) (relative value compared with control: NE 3.7 +/- 0.5, NE + ACh 2.5 +/- 0.3, P < 0.05; n = 12). CONCLUSION: The present study suggests that VNS modulates the cardiac redox status and adrenergic drive, and thereby suppresses free radical generation in the failing heart. Modulation of the myocardial redox state by vagal nerve stimulation after experimental myocardial infarction.

25. **Carpenter LL, Bayat L, Moreno F, et al. Decreased cerebrospinal fluid concentrations of substance P in treatment-resistant depression and lack of alteration after acute adjunct vagus nerve stimulation therapy. *Psychiatry Res.* 2008;157:123-9.**
Abstract: Recent preclinical and clinical research has demonstrated that the neuropeptide substance P (SP) plays a role in the central nervous system (CNS) response to stress, and perhaps in the etiology of major depression and/or anxiety disorders. The nature of this role, however, is poorly understood. A limited body of evidence suggests that in medication-free depressed patients, cerebrospinal fluid (CSF) concentrations of SP may be elevated relative to healthy controls. Two studies have shown that antidepressant treatment does not significantly change CSF concentrations of SP. Using standard lumbar puncture techniques, baseline CSF samples were obtained from 19 medication-free healthy controls and 19 medicated patients with treatment-resistant depression (TRD). Mean CSF SP concentration was significantly lower in TRD patients on psychotropic medications than in the group of healthy subjects. After 10-12 weeks of treatment with adjunct vagus nerve stimulation (VNS), CSF SP concentrations were not significantly changed. Low CSF SP may reflect a biological marker of the subtype of severe and chronic depression that is resistant to standard therapies. Decreased cerebrospinal fluid concentrations of substance P in treatment-resistant depression and lack of alteration after acute adjunct vagus nerve stimulation therapy.

26. **Arora R, Ulphani JS, Villuendas R, et al. Neural substrate for atrial fibrillation: implications for targeted parasympathetic blockade in the posterior left atrium. *Am J Physiol Heart Circ Physiol.* 2008;294:H134-44.**
Abstract: The parasympathetic (P) nervous system is thought to contribute significantly to focal atrial fibrillation (AF). Thus we hypothesized that P nerve fibers [and related muscarinic (M(2)) receptors] are preferentially located in the posterior left atrium (PLA) and that selective cholinergic blockade in the PLA can be successfully performed to alter vagal AF substrate. The PLA, pulmonary veins (PVs), and left atrial appendage (LAA) from six dogs were immunostained for sympathetic (S) nerves, P nerves, and M(2) receptors. Epicardial electrophysiological mapping was performed in seven additional dogs. The PLA was the most richly innervated, with nerve bundles containing P and S

fibers (0.9 +/- 1, 3.2 +/- 2.5, and 0.17 +/- 0.3/cm(2) in the PV, PLA, and LAA, respectively, P < 0.001); nerve bundles were located in fibrofatty tissue as well as in surrounding myocardium. P fibers predominated over S fibers within bundles (P-to-S ratio = 4.4, 7.2, and 5.8 in PV, PLA, and LAA, respectively). M(2) distribution was also most pronounced in the PLA (17.8 +/- 8.3, 14.3 +/- 7.3, and 14.5 +/- 8 M(2)-stained cells/cm(2) in the PLA, PV, and LAA, respectively, P = 0.012). Left cervical vagal stimulation (VS) caused significant effective refractory period shortening in all regions, with easily inducible AF. Topical application of 1% tropicamide to the PLA significantly attenuated VS-induced effective refractory period shortening in the PLA, PV, and LAA and decreased AF inducibility by 92% (P < 0.001). We conclude that 1) P fibers and M(2) receptors are preferentially located in the PLA, suggesting an important role for this region in creation of vagal AF substrate and 2) targeted P blockade in the PLA is feasible and results in attenuation of vagal responses in the entire left atrium and, consequently, a change in AF substrate. Neural substrate for atrial fibrillation: implications for targeted parasympathetic blockade in the posterior left atrium.

27. **Kuncova J, Faitova S, Capouch J, Stengl M, Slavikova J. Chronic atropine administration diminishes the contribution of vasoactive intestinal polypeptide to heart rate regulation. *Physiol Res.* 2007.**
Abstract: Vasoactive intestinal polypeptide (VIP) is implicated in the modulation of vagal effects on the heart rate. In this study, the impact of acute and chronic atropine administration on VIP levels in rat heart atria was investigated in relation to heart rate in the course of vagus nerves stimulation. Anaesthetised control and atropinized (10 mg/kg/day for 10 days) rats pretreated with metipranolol and phentolamine that were either given or not a single dose of atropine were subjected to bilateral vagus nerve stimulation (30 min: 0.7 mA, 20 Hz, 0.2 ms). VIP concentrations in the atria were determined after each stimulation protocol. In control rats with or without single atropine administration, the heart rate upon vagal stimulation was higher than in atropinized animals with or without single atropine dose, respectively. VIP concentrations in the control atria were significantly decreased after the stimulation; the decrease was comparable both in absence and presence of a single dose of atropine. Compared to controls, VIP levels were significantly decreased after chronic atropine treatment and they were not further reduced by vagal stimulation and single atropine administration. Administration of VIP antagonist completely abolished the differences in the heart rate upon vagal stimulation between control and atropinized groups. In conclusion, the data indicate that chronic atropine administration affects VIP synthesis in rat heart atria and consequently it modifies the heart rate regulation. Chronic atropine administration diminishes the contribution of vasoactive intestinal polypeptide to heart rate regulation.

28. **Follesa P, Biggio F, Gorini G, et al. Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. *Brain Res.* 2007;1179:28-34.**
Abstract: Vagus nerve stimulation therapy, effective for treatment-resistant epilepsy, has recently been approved also for treatment-resistant depression; nevertheless, the molecular mechanism(s) underlying its therapeutic action remains unclear. Given that neurotrophic factors and monoamines could play a crucial role in the pathophysiology of depression, we tested whether vagus nerve stimulation increases the expression of brain-derived

neurotrophic factor, fibroblast growth factor, and nerve growth factor as well as the concentration of norepinephrine in the rat brain. Rats were implanted with a vagus nerve stimulator device and the effects of acute stimulation were evaluated on the growth factors mRNA levels and norepinephrine concentration by ribonuclease protection assay and microdialysis, respectively. We found that acute vagus nerve stimulation increased the expression of brain-derived neurotrophic factor and fibroblast growth factor in the hippocampus and cerebral cortex, decreased the abundance of nerve growth factor mRNA in the hippocampus, and, similar to the antidepressant drug venlafaxine, increased the norepinephrine concentration in the prefrontal cortex. This study demonstrates that acute vagus nerve stimulation triggers neurochemical and molecular changes in the rat brain involving neurotransmitters and growth factors known to play a crucial role in neuronal trophism. These new findings contribute to the elucidation of the molecular mechanisms underlying the therapeutic actions of vagus nerve stimulation in both treatment-resistant depression and epilepsy. Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain.

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

30. **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;114:1485-93.**
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. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation.

31. **Brack KE, Patel VH, Coote JH, Ng GA. Nitric oxide mediates the vagal protective effect on ventricular fibrillation via effects on action potential duration restitution in the rabbit heart. *J Physiol.* 2007;583:695-704.**
Abstract: We have previously shown that direct vagus nerve stimulation (VNS) reduces the slope of action potential duration (APD) restitution while simultaneously protecting the heart against induction of ventricular fibrillation (VF) in the absence of any sympathetic activity or tone. In the current study we have examined the role of nitric oxide (NO) in the effect of VNS. Monophasic action potentials were recorded from a left ventricular epicardial site on innervated, isolated rabbit hearts (n = 7). Standard restitution, effective refractory period (ERP) and VF threshold (VFT) were measured at baseline and during VNS in the presence of the NO synthase inhibitor N(G)-nitro-L-arginine (L-NA, 200 microm) and during reversing NO blockade with L-arginine (L-Arg, 1 mm). Data represent the mean +/- S.E.M. The restitution curve was shifted upwards and became less steep with VNS when compared to baseline. L-NA blocked the effect of VNS whereas L-Arg restored the effect of VNS. The maximum slope of restitution was reduced from 1.17 +/- 0.14 to 0.60 +/- 0.09 (50 +/- 5%, P < 0.0001) during control, from 0.98 +/- 0.14 to 0.93 +/- 0.12 (2 +/- 10%, P = NS) in the presence of L-NA and from 1.16 +/- 0.17 to 0.50 +/- 0.10 (41 +/- 9%, P = 0.003) with L-Arg plus L-NA. ERP was increased by VNS in control from 119 +/- 6 ms to 130 +/- 6 ms (10 +/- 5%, P = 0.045) and this increase was not affected by L-NA (120 +/- 4 to 133 +/- 4 ms, 11 +/- 3%, P = 0.0019) or L-Arg with L-NA (114 +/- 4 to 123 +/- 4 ms, 8 +/- 2%, P = 0.006). VFT was increased from 3.0 +/- 0.3 to 5.8 +/- 0.5 mA (98 +/- 12%, P = 0.0017) in control, 3.4 +/- 0.4 to 3.8 +/- 0.5 mA (13 +/- 12%, P = 0.6) during perfusion with L-NA and 2.5 +/- 0.4 to 6.0 +/- 0.7 mA (175 +/- 50%, P = 0.0017) during perfusion with L-Arg plus L-NA. Direct VNS increased VFT and flattened the slope of APD restitution curve in this isolated rabbit heart preparation with intact autonomic nerves. These effects were blocked using L-NA and reversed by replenishing the substrate for NO production with L-Arg. This is the first study to demonstrate that NO plays an important role in the anti-fibrillatory effect of VNS on the rabbit ventricle, possibly via effects on APD restitution. Nitric oxide mediates the vagal protective effect on ventricular fibrillation via effects on action potential duration restitution in the rabbit heart.

32. **Shannahoff-Khalsa DS. Selective unilateral autonomic activation: implications for psychiatry. *CNS Spectr.* 2007;12:625-34.**
Abstract: Research advances have led to three methods for selectively activating one half of the autonomic nervous system in humans. The first method is an ancient yogic technique called unilateral forced nostril breathing (UFNB) that employs forced breathing through

only one nostril while closing off the other. The second method works by stimulation of an autonomic reflex point on the fifth intercostal space near the axilla. The most recent method employs unilateral vagus nerve stimulation (VNS) via the mid-inferior cervical branch and requires surgical implantation of a wire and pacemaker. UFNB is non-invasive and seems to selectively activate the ipsilateral branch of the sympathetic nervous system with a possible compensation effect leading to contralateral VNS. UFNB and VNS have been employed to treat psychiatric disorders. While UFNB has been studied for its potential effects on the endogenous ultradian rhythms of the autonomic and central nervous system, and their tightly coupled correlates, VNS has yet to be studied in this regard. This article reviews these three methods and discusses their similarities, putative mechanisms, their studied effects on the endogenous autonomic nervous system and central nervous system rhythms, and their implications for the treatment of psychiatric disorders. Selective unilateral autonomic activation: implications for psychiatry.

33. **Nahas Z, Teneback C, Chae JH, et al. Serial vagus nerve stimulation functional MRI in treatment-resistant depression. *Neuropsychopharmacology.* 2007;32:1649-60.**
Abstract: Vagus nerve stimulation (VNS) therapy has shown antidepressant effects in open acute and long-term studies of treatment-resistant major depression. Mechanisms of action are not fully understood, although clinical data suggest slower onset therapeutic benefit than conventional psychotropic interventions. We set out to map brain systems activated by VNS and to identify serial brain functional correlates of antidepressant treatment and symptomatic response. Nine adults, satisfying DSM-IV criteria for unipolar or bipolar disorder, severe depressed type, were implanted with adjunctive VNS therapy (MRI-compatible technique) and enrolled in a 3-month, double-blind, placebo-controlled, serial-interleaved VNS/functional MRI (fMRI) study and open 20-month follow-up. A multiple regression mixed model with blood oxygenation level dependent (BOLD) signal as the dependent variable revealed that over time, VNS therapy was associated with ventro-medial prefrontal cortex deactivation. Controlling for other variables, acute VNS produced greater right insula activation among the participants with a greater degree of depression. These results suggest that similar to other antidepressant treatments, BOLD deactivation in the ventro-medial prefrontal cortex correlates with the antidepressant response to VNS therapy. The increased acute VNS insula effects among actively depressed participants may also account for the lower dosing observed in VNS clinical trials of depression compared with epilepsy. Future interleaved VNS/fMRI studies to confirm these findings and further clarify the regional neurobiological effects of VNS. Serial vagus nerve stimulation functional MRI in treatment-resistant depression.

34. **Neuhaus AH, Luborzewski A, Rentzsch J, et al. P300 is enhanced in responders to vagus nerve stimulation for treatment of major depressive disorder. *J Affect Disord.* 2007;100:123-8.**
Abstract: BACKGROUND: Vagus nerve stimulation (VNS) is a new therapy option for treatment of otherwise therapy-refractory major depressive disorder. However, the mechanism of central nervous action is poorly understood. Electroencephalographic (EEG) studies may be of interest since chronic peripheral current application to the vagus nerve may exert lasting neurophysiologically detectable effects on central electrical activity. In an exploratory study, we investigated the effects of VNS on auditory event-related potentials (ERP). METHODS: Thirteen depressive patients (mean Hamilton depression score

(HAMD) at baseline=24.2) receiving VNS were investigated prior to implantation and 10 weeks after standard cycling VNS. Stimulation intensity was 0.94+/-0.46 mA, pulse width 0.250 mus, and frequency 20 Hz. 1 h prior to follow-up investigation, VNS was turned off. Auditory ERP were elicited using a standard auditory oddball paradigm and were recorded with 29-channel EEG. RESULTS: Post VNS, grand averages of the auditory ERP did not show significant differences as compared to baseline recording. However, differential effects were found when separating ERP of responders (N=5, mean HAMD post VNS=8.8) and non-responders (N=8, mean HAMD post VNS=22.4). In VNS responders only, P300 at midline electrodes Fz and Cz was significantly increased and correlated with HAMD scores. CONCLUSION: Auditory ERP seem to provide a useful tool for investigating VNS-induced changes concerning information processing in major depressive disorder. In our sample, enhancement of P300 distinguished VNS responders from non-responders 10 weeks after therapy onset. Our findings may be relevant for the understanding of both neurophysiological mechanism of action of VNS and pathophysiology of depression. P300 is enhanced in responders to vagus nerve stimulation for treatment of major depressive disorder.

35. **Bajbouj M, Gallinat J, Lang UE, et al. Motor cortex excitability after vagus nerve stimulation in major depression. *J Clin Psychopharmacol.* 2007;27:156-9.**
Abstract: Recent data suggest that inhibitory pathways may be involved in the pathophysiology of depression and in the mode of action of some antidepressant interventions. The aim of the present study was to test whether vagus nerve stimulation (VNS) can affect motor cortex excitability. Measures of motor cortical excitability were probed by using single-pulse and paired-pulse transcranial magnetic stimulation at baseline, after 10 weeks of left VNS, and additionally, in an on-off paradigm in 10 patients with treatment-resistant unipolar depression. Ten weeks of VNS was associated with a selective and pronounced increase in intracortical inhibition, whereas no changes occurred in the on-off paradigm. These results suggest that VNS is capable of changing motor cortical excitability in patients with depression. Motor cortex excitability after vagus nerve stimulation in major depression.

36. **Zuo Y, Smith DC, Jensen RA. Vagus nerve stimulation potentiates hippocampal LTP in freely-moving rats. *Physiol Behav.* 2007;90:583-9.**
Abstract: Previous studies have demonstrated that electrical stimulation of the vagus nerve (VNS) delivered at a moderate intensity following a learning experience enhances memory in laboratory rats and human subjects, while VNS at lower or higher intensities has little or no effect. This finding suggests that VNS may affect memory processes by modulating neural plasticity in brain structures associated with memory storage such as the hippocampus. To test this hypothesis, the present study investigated the modulatory effect of VNS on the development of long-term potentiation (LTP) in the dentate gyrus of freely-moving rats. Rats receiving 0.4 mA VNS showed enhanced potentiation of the population spike amplitude for at least 24 h after tetanus relative to the sham-stimulation group. In contrast, no such effect was observed with 0.2 mA VNS. Stimulation at 0.8 mA had a short-term effect and tended to enhance early LTP, but to a lesser extent than did 0.4 mA. The 0.4 mA stimulation was the same intensity that was previously shown to enhance retention performance in an inhibitory avoidance task. These findings suggest that the neural mechanisms underlying the mnemonic effect of VNS may involve modulating

synaptic plasticity in the hippocampus. These data also suggest that neural activity in the vagus nerve, occurring as a result of changes in peripheral state, is an important mechanism by which emotional experiences and arousal can enhance the storage of memories of those experiences. Vagus nerve stimulation potentiates hippocampal LTP in freely-moving rats.

37. **Stocker SD, Toney GM. Vagal afferent input alters the discharge of osmotic and ANG II-responsive median preoptic neurons projecting to the hypothalamic paraventricular nucleus. *Brain Res.* 2007;1131:118-28.**
Abstract: The goal of the present study was to determine the effect of activating vagal afferent fibers on the discharge of median preoptic (MnPO) neurons responsive to peripheral angiotensin II (ANG II) and osmotic inputs. Vagal afferents were activated by electrical stimulation of the proximal end of the transected cervical vagus nerve (3 pulses, 100 Hz, 1 ms, 100-500 muA). Of 21 MnPO neurons, 19 were antidromically activated from the hypothalamic paraventricular nucleus (PVH) (latency: 10.3+/-1.3 ms, threshold: 278+/-25 muA). MnPO-PVH cells had an average spontaneous discharge of 2.1+/-0.4 Hz. Injection of ANG II (150 ng) and/or hypertonic NaCl (1.5 Osm/L, 100 mul) through the internal carotid artery significantly (P<0.01) increased the firing rate of most MnPO-PVH neurons (16/19, 84%). Vagus nerve stimulation significantly (P<0.01) decreased discharge (-73+/-9%) in 10 of 16 (63%) neurons with an average onset latency of 108+/-19 ms. Among the remaining 6 MnPO-PVH neurons vagal activation either increased discharge (177+/-100%) with a latency of 115+/-15 ms (n=2) or had no effect (n=4). Pharmacological activation of chemosensitive vagal afferents with phenyl biguanide produced an increase (n=3), decrease (n=2), or no change (n=6) in discharge. These observations indicate that a significant proportion of ANG II- and/or osmo-sensitive MnPO neurons receive convergent vagal input. Although the sensory modalities transmitted by the vagal afferents to MnPO-PVH neurons are not presently known, the presence of inhibitory and excitatory vagal-evoked responses indicates that synaptic processing by these cells integrates humoral and visceral information to subserve potentially important cardiovascular and body fluid homeostatic functions. Vagal afferent input alters the discharge of osmotic and ANG II-responsive median preoptic neurons projecting to the hypothalamic paraventricular nucleus.

38. **Rauchenzauner M, Haberlandt E, Hogler W, Luef G. Brain-type natriuretic peptide release and seizure activity during vagal nerve stimulation. *Epilepsia.* 2007;48:397-9.**
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 vasodilatative 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. Brain-type natriuretic peptide secretion following febrile and afebrile seizures - a new marker in childhood epilepsy?

39. **Critchley HD, Lewis PA, Orth M, et al. Vagus nerve stimulation for treatment-resistant depression: behavioral and neural effects on encoding negative material. *Psychosom Med.* 2007;69:17-22.**
Abstract: OBJECTIVES: Vagus nerve stimulation (VNS) can improve depression. Cognitive models of depression highlight an over-representation of negative thoughts and memories, with depressed individuals showing memory facilitation for negative material. We hypothesized that the antidepressant action of VNS may emerge through corrective influences on 'negativity bias' in memory. We therefore examined the impact of VNS on emotional memory and its underlying brain activity. METHODS: We tested a single patient undergoing VNS for treatment-resistant depression (TRD). Stimulation was set at a 30/66-second on/off cycle during three encoding blocks when the patient viewed randomly presented positive, negative, and neutral words. Following each block, VNS was switched off and the patient identified previously seen words from distractors in a subsequent recognition memory task. The patient was scanned using functional magnetic resonance imaging (fMRI) during the first encoding block. RESULTS: There was robust recall of negative material viewed during 'off' cycles of VNS but subsequent memory of negative words was attenuated during active VNS ('on' cycles). VNS did not influence memory for neutral and positive words. With neuroimaging, direct modulatory effects of VNS were observed in dorsomedial, dorsolateral, and orbital regions of the prefrontal cortex. Moreover, during encoding of negative words, compared with positive and neutral words, VNS also modulated activity within orbitofrontal, ventromedial and polar prefrontal cortices, midcingulate cortex, and brain stem. CONCLUSIONS: Our observations show that VNS can interfere with memory of negative information, an effect that may contribute to its antidepressant role. Neuroimaging implicated regions including the ventral and medial prefrontal cortex as an underlying neural substrate. Vagus nerve stimulation for treatment-resistant depression: behavioral and neural effects on encoding negative material.

40. **Nabutovsky Y, Florio J, Morgan K, Grill WM, Farazi TG. Lead design and initial applications of a new lead for long-term endovascular vagal stimulation. *Pacing Clin Electrophysiol.* 2007;30 Suppl 1:S215-8.**
Abstract: Background: Vagal nerve stimulation (VNS) has negative chronotropic and dromotropic effects. We developed and tested an endovascular spiral vagal stimulation lead (ESVL) designed to follow the projection of the cardiac branches of the vagus nerve around the superior vena cava (SVC) to optimize VNS. Methods: ESVL contained six 5-mm coil electrodes, spaced 5-mm apart with a spiral guidewire to provide shape. The tightness and diameter of the guidewire were changed before each placement to simulate different lead designs. Various 2-, 3-, and 4-electrode combinations were used and several lead positions were tested each time. Each VNS protocol included 2-12 V, 15-second pulse trains at 20 Hz, with 2 ms pulse duration. A basket catheter (BC) was used as control and to approximate the initial VNS location. The VNS protocol was performed at the optimal location, using first the BC and then several ESVL configurations. Results: VNS caused a voltage-dependent decrease in heart rate (HR). Using the optimal ESVL configuration at 7 V, HR decreased by 30.4% (37.2 bpm) in dog no. 1 and 12.4% (16.6 bpm) in dog no. 2, versus 15.5% (16.6 bpm) and 16.7% (19.5 bpm) with the BC. Conclusions: A new endovascular spiral lead that takes advantage of the anatomy of the cardiac branches of the vagus nerve in the SVC was developed. VNS using ESVL produced significant HR slowing at voltages slightly below the highest pulse generator output of 7.5 V, which may

be suitable for long-term implantation. (PACE 2007; 29:S215-S218). Lead design and initial applications of a new lead for long-term endovascular vagal stimulation.

41. **Vonck K, Boon P, Van Roost D. Anatomical and physiological basis and mechanism of action of neurostimulation for epilepsy. *Acta Neurochir Suppl.* 2007;97:321-8.**
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. Anatomical and physiological basis and mechanism of action of neurostimulation for epilepsy.

42. **Cakmak YO. Epilepsy, electroacupuncture and the nucleus of the solitary tract. *Acupunct Med.* 2006;24:164-8.**
Abstract: Vagal nerve stimulation and electroacupuncture have some promise as neuroprotective therapies for patients with poorly controlled epilepsy. It has been demonstrated that stimulation of acupuncture points on the extremities results in stimulation of the vagus nerve. It is possible that the antiepileptic effects of these two applications might be targeting the same centre in the brain. The nucleus of the solitary tract, which is a primary site at which vagal afferents terminate, is also the site for afferent pathways of facial, scalp and auricular acupuncture via trigeminal, cervical spinal and glossopharyngeal nerves. Taken together with laboratory findings, the neuroprotective pathways of electroacupuncture in epileptic models may stem from the collaboration of its anti-inflammatory and neurotrophic actions through the nucleus of the solitary tract via vagus nerve stimulation. Epilepsy, electroacupuncture and the nucleus of the solitary tract.

43. **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;1119:124-32.**
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. Increased extracellular concentrations of norepinephrine in cortex and hippocampus following vagus nerve stimulation in the rat.

44. **van Westerloo DJ, Giebelen IA, Meijers JC, et al. Vagus nerve stimulation inhibits activation of coagulation and fibrinolysis during endotoxemia in rats. *J Thromb Haemost.* 2006;4:1997-2002.**
Abstract: BACKGROUND: Sepsis and endotoxemia are associated with concurrent activation of inflammation and the hemostatic mechanism, which both contribute to organ dysfunction and death. Electrical vagus nerve stimulation (VNS) has been found to inhibit tumor necrosis factor (TNF)-alpha release during endotoxemia in rodents. OBJECTIVE: To determine the effect of VNS on activation of coagulation and fibrinolysis. METHODS: Rats received a sublethal i.v. dose of lipopolysaccharide (LPS) after electrical VNS or sham stimulation. Activation of coagulation and fibrinolysis, as well as cytokine release, was measured before LPS injection and 2, 4 and 6 h thereafter. Results: LPS induced activation of the coagulation system (increases in the plasma concentrations of thrombin-antithrombin complexes and D-dimer, and a decrease in antithrombin) and biphasic changes in the fibrinolytic system [early rises of plasminogen activator activity and tissue-type plasminogen activator, followed by a delayed increase in plasminogen activator inhibitor type 1 (PAI-1)]. VNS strongly inhibited all LPS-induced procoagulant responses and more modestly attenuated the fibrinolytic response. In addition, VNS attenuated the LPS-induced increases in plasma and splenic concentrations of the proinflammatory cytokines TNF-alpha and interleukin-6 (IL-6), while not influencing the release of the anti-inflammatory cytokine IL-10. CONCLUSION: These data illustrate a thus far unrecognized effect of VNS and suggest that the cholinergic anti-inflammatory pathway not only impacts on inflammation but also on the coagulant-anticoagulant balance. Vagus nerve stimulation inhibits activation of coagulation and fibrinolysis during endotoxemia in rats.

45. **Budzinska K, Ilasz R. Short-term depression of inspiratory activity following tonic vagal stimulation. *J Physiol Pharmacol.* 2006;57 Suppl 4:55-61.**
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. Short-term depression of inspiratory activity following tonic vagal stimulation.

46. **Howland RH. What is vagus nerve stimulation? *J Psychosoc Nurs Ment Health Serv.* 2006;44:11-4.** What is vagus nerve stimulation?

47. **Dorr AE, Debonnel G. Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. *J Pharmacol Exp Ther.* 2006;318:890-8.**
Abstract: Vagus nerve stimulation (VNS) is an antiepileptic treatment, which has recently shown promise as an antidepressant. Yet, its antidepressant mechanisms of action are unknown. Serotonergic [5-hydroxytryptamine (5-HT, serotonin)] and noradrenergic [norepinephrine (NE)] systems are involved in the pathophysiology of depression and in the mechanisms of action of antidepressants. The present study analyzes 5-HT and NE neuronal firing rates in their brainstem nuclei: the dorsal raphe nucleus (DRN) and locus coeruleus (LC), respectively. The basal firing rates in the DRN and LC were significantly increased after long-term treatments with VNS. After short-term VNS treatments, firing rates were significantly higher for LC (at 1 h and 3 days). As changes in their firing rate may have been due to altered autoreceptor sensitivities, the responses of autoreceptors to the acute administration of their respective agonists were assessed. However, no significant difference was seen in the DRN. No significant differences in dose response curves for 5-HT(1A) somatodendritic and alpha 2-adrenergic autoreceptors were noticed between long-term VNS and controls. VNS appears to have a novel mechanism of antidepressant action, enabling its effectiveness in treatment-resistant depression. LC firing rates significantly increase earlier than the DRN basal firing. As the LC has an excitatory influence on DRN, it is possible that the increased DRN firing rate is secondary to an initial increased LC firing rate from VNS. Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission.

48. **Mravec B. Possible involvement of the vagus nerve in monitoring plasma catecholamine levels. *Neurobiol Learn Mem.* 2006.**
Abstract: In their article Miyashita and Williams (Neurobiology of Learning and Memory 2006, 85, 116-124) describe the effect of peripheral administration of epinephrine on neural discharge in vagal afferent fibers. It seems that described data supports the hypothesis of the vagus nerve participation in monitoring plasma catecholamine levels and consequently modifying brain functions. However, do these results indicate indeed that afferent vagus nerve pathways are activated by circulating epinephrine? Catecholamines influence virtually all tissues and many functions. Vagus nerve participates significantly in monitoring of those effects. Therefore epinephrine-induced increases of afferent vagus nerve activity described by Miyashita and Williams may reflect not only exclusive activation of beta-adrenergic receptors but also an activation of other types of receptors on vagal sensory nerve endings, e.g., mechanosensors, chemoreceptors, and osmosensors. Discussion is focused on the possibility that the increase in afferent vagus nerve activity may reflect activation of mechanoreceptors of the vagus nerve endings in the epinephrine-activated heart. Possible involvement of the vagus nerve in monitoring plasma catecholamine levels.

49. **Garriock HA, Delgado P, Kling MA, et al. Number of risk genotypes is a risk factor for major depressive disorder: a case control study. *Behav Brain Funct.* 2006;2:24.**
Abstract: ABSTRACT: BACKGROUND: The objective of the study was to determine the genetic basis of Major Depressive Disorder, and the capacity to respond to antidepressant treatment. An association study of 21 candidate polymorphisms relevant to monoamine function and the mechanism of antidepressant response was conducted in 3 phenotypically distinct samples: a group with chronic or recurrent depression unable to respond to antidepressants (non-responders) (n=58), a group capable of symptomatic improvement with or without treatment (responders) (n=39), and volunteer controls (n=85). The responders and non-responders constituted a larger group of depressed subjects. METHODS: A candidate gene approach was employed to asses the genetics basis of Major Depressive Disorder. The genotypic frequencies of selected polymorphisms were compared between the controls and depressed subjects. To asses the genetics basis of the capacity to respond to antidepressant treatment, the responders were compared to the non-responders. Candidate genes were chosen based on functional studies and proximity to whole genome linkage findings in the literature. Risk genotypes were identified by previous functional studies and association studies. RESULTS: A statistically significant difference in genotype frequency for the SLC6A4 intron 2 VNTR was detected between the subjects with a history of depression and controls ($p = 0.004$). Surprisingly, a statistically significant difference was detected between responders and non-responders for the DRD4 exon III VNTR genotype frequencies ($p = 0.009$). Furthermore, a difference between the controls and depressed subjects as well as between the controls and non-responders was detected for the number and distribution of risk genotypes in each group. CONCLUSIONS: An association between several monoamine-related genes and Major Depressive Disorder is supported. The data suggest that the two depressive phenotypes are genetically different, inferring that the genetic basis for the capacity to respond to standard antidepressant treatment, and the genetic susceptibility to Major Depressive Disorder may be independent. In addition, a proof of concept is provided demonstrating that the number of risk genotypes may be an indication of susceptibility of major depressive disorder and the severity of the disorder. Number of risk genotypes is a risk factor for major depressive disorder: a case control study.

50. **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;9:204-213.**

51. **Lang UE, Bajbouj M, Gallinat J, Hellweg R. Brain-derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation. *Psychopharmacology (Berl).* 2006;187:56-59.**
Abstract: BACKGROUND: Vagus nerve stimulation (VNS) and repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex are brain stimulation techniques used as therapeutic interventions in major depression. METHODS: In this study, we report the impact of these stimulation techniques on serum concentrations of brain-derived neurotrophic factor (BDNF) in treatment-resistant patients with a diagnosis of major depression. RESULTS: We found no changes of BDNF serum concentrations and no association of neurotrophin concentrations in serum with clinical parameters in our sample. CONCLUSION: Our preliminary results suggest that brain stimulation techniques-

in contrast to several antidepressant medications-do not change BDNF serum concentrations. Brain-derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation.

52. **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.**
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 (intragastric 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. Autonomic response and Fos expression in the NTS following intermittent vagal stimulation: importance of pulse frequency.

53. **Dedeurwaerdere S, Vonck K, De Herdt V, et al. Neuromodulation with levetiracetam and vagus nerve stimulation in experimental animal models of epilepsy. *Acta Neurol Belg.* 2006;106:91-7.**
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. Neuromodulation with levetiracetam and vagus nerve stimulation in experimental animal models of epilepsy.

54. **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;140:1443-51.**
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. Vagus nerve stimulation does not affect spatial memory in fast rats, but has both anti-convulsive and pro-convulsive effects on amygdala-kindled seizures.

55. **Conway CR, Sheline YI, Chibnall JT, George MS, Fletcher JW, Mintun MA. Cerebral blood flow changes during vagus nerve stimulation for depression. *Psychiatry Res.* 2006;146:179-84.**
Abstract: Positron emission tomography (PET oxygen-15 labeled water or PET [15O]H2O) was used to identify changes in regional cerebral blood flow (rCBF) in response to acute vagus nerve stimulation (VNS) in four subjects with treatment-resistant major depression (TRMD). Four 90-s PET [15O]H2O scans were performed on each subject in an off-on sequence (2 VNS de-activated; 2 VNS activated). PET images were aligned, normalized for global uptake, and resampled to standard atlas space. Statistical t-images were used to evaluate change. VNS-induced increases in rCBF were found in the bilateral orbitofrontal cortex, bilateral anterior cingulate cortex, and right superior and medial frontal cortex. Decreases were found in the bilateral temporal cortex and right parietal area. Regions of change were consistent with brain structures associated with depression and the afferent

pathways of the vagus nerve. Cerebral blood flow changes during vagus nerve stimulation for depression.

56. **Ronkainen E, Korpelainen JT, Heikkinen E, Myllyla VV, Huikuri HV, Isojarvi JI. Cardiac autonomic control in patients with refractory epilepsy before and during vagus nerve stimulation treatment: a one-year follow-up study. *Epilepsia.* 2006;47:556-62.**
Abstract: PURPOSE: To elucidate possible effect of vagus nerve stimulation (VNS) therapy on interictal heart rate (HR) variability in patients with refractory epilepsy before and after 1-year VNS treatment. METHODS: A 24-hour electrocardiogram (ECG) was recorded at the baseline and after 12 months of VNS treatment in 14 patients with refractory epilepsy, and once in 28 healthy age- and sex-matched control subjects. Time and frequency domain measures, along with fractal and complexity measures of HR variability, were analyzed from the ECG recordings. RESULTS: The mean value of the RR interval ($p=0.008$), standard deviation of N-N intervals (SDNN) ($p<0.001$), very-low frequency (VLF) ($p<0.001$), low-frequency (LF) ($p=0.001$), and high-frequency (HF) ($p=0.002$) spectral components of HR variability, and the Poincare components SD(1) ($p=0.005$) and SD(2) ($p<0.001$) of the patients with refractory epilepsy were significantly lower than those of the control subjects before VNS implantation. The nocturnal increase in HR variability usually seen in the normal population was absent in patients with refractory epilepsy. VNS had no significant effects on any of the HR-variability indexes despite a significant reduction in the frequency of seizures. CONCLUSIONS: HR variability was reduced, and the nocturnal increase in HR variability was not present in patients with refractory epilepsy. One-year treatment with VNS did not have a marked effect on HR variability, suggesting that impaired cardiovascular autonomic regulation is associated with the epileptic process itself rather than with recurrent seizures. Cardiac autonomic control in patients with refractory epilepsy before and during vagus nerve stimulation treatment: a one-year follow-up study.

57. **Kuramoto H, Kadowaki M. Vagus nerve stimulation preferentially induces Fos expression in nitrergic neurons of rat esophagus. *Cell Tissue Res.* 2006;361-7.**
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. Vagus nerve stimulation preferentially induces Fos expression in nitrergic neurons of rat esophagus.

58. **Kawada T, Yamazaki T, Akiyama T, et al. Vagal stimulation suppresses ischemia-induced myocardial interstitial norepinephrine release. *Life Sci.* 2006;78:882-887.**
Abstract: Although electrical vagal stimulation exerts beneficial effects on the ischemic heart such as an antiarrhythmic effect, whether it modulates norepinephrine (NE) and acetylcholine (ACh) releases in the ischemic myocardium remains unknown. To clarify the neural modulation in the ischemic region during vagal stimulation, we examined ischemia-induced NE and ACh releases in anesthetized and vagotomized cats. In a control group (VX, n = 8), occlusion of the left anterior descending coronary artery increased myocardial interstitial NE level from 0.46+/-0.09 to 83.2+/-17.6 nM at 30-45 min of ischemia (mean+/-SE). Vagal stimulation at 5 Hz (VS, n = 8) decreased heart rate by approximately 80 beats/min during the ischemic period and suppressed the NE release to 24.4+/-10.6 nM ($P < 0.05$ from the VX group). Fixed-rate ventricular pacing (VSP, n=8) abolished this vagally mediated suppression of ischemia-induced NE release. The vagal stimulation augmented ischemia-induced ACh release at 0-15 min of ischemia (VX: 11.1+/-2.1 vs. VS: 20.7+/-3.9 nM, $P < 0.05$). In the VSP group, the ACh release was not augmented. In conclusion, vagal stimulation suppressed the ischemia-induced NE release and augmented the initial increase in the ACh level. These modulations of NE and ACh levels in the ischemic myocardium may contribute to the beneficial effects of vagal stimulation on the heart during acute myocardial ischemia. Vagal stimulation suppresses ischemia-induced myocardial interstitial norepinephrine release.

59. **Jaseja H. Mechanism of vagal nerve stimulation (VNS) anti-convulsant action. *Med Hypotheses.* 2006;66:680-1.** Mechanism of vagal nerve stimulation (VNS) anti-convulsant action.

60. **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: Taylor & Francis; 2006:624-629.**

61. **Dedeurwaerdere S, Cornelissen B, Van Laere K, et al. Small animal positron emission tomography during vagus nerve stimulation in rats: a pilot study. *Epilepsy Res.* 2005;67:133-41.**
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. Small animal positron emission tomography during vagus nerve stimulation in rats: a pilot study.

62. **Sugiura H, Chinushi M, Komura S, Hirono T, Aizawa Y. Heart rate variability is a useful parameter for evaluation of anticholinergic effect associated with inducibility of atrial fibrillation. *Pacing Clin Electrophysiol.* 2005;28:1208-14.**
Abstract: BACKGROUND: Disopyramide is thought to have an advantageous effect for atrial fibrillation (AF) associated with vagal activity because of its anticholinergic effect. METHOD: We used a canine vagal nerve stimulation (VNS) model. The monophasic action potential (MAP) duration at 90% repolarization (MAP(90)), the intraatrial conduction time, the induciblity of AF by electrical stimulation, and the amplitude of high-frequency component (HF-amp) of the heart rate variability (HRV) were evaluated before and after the administration of disopyramide (1 mg/kg) (group D, n = 8) or pilsicainide (1 mg/kg) (group P, n = 5). RESULTS: In group D, HF-amp decreased in the baseline condition from 1.1 +/- 0.6 to 0.6 +/- 0.4 ms and the degree of VNS-induced augmentation of HF-amp was attenuated from +492% to +127%. VNS-induced shortening of MAP(90) was also attenuated in the right atrium (from -30 +/- 15% to -10 +/- 6%) and in the left atrium (from -15 +/- 9% to -6 +/- 6%). In group P, little effect was shown in these parameters. The vagotonic AF became noninducible in all eight experiments in group D, while in only one of five in group P. CONCLUSION: The beneficial effect of disopyramide for vagotonic AF is based on the decrease of basal vagal tone and attenuation of the effect of vagal stimulation in the atrial myocardium. HRV is a useful parameter for evaluation of the effect of antiarrhythmic drugs on the autonomic nerve system, and the evaluation of variability may be useful for testing drug efficacy for arrhythmias. Heart rate variability is a useful parameter for evaluation of anticholinergic effect associated with inducibility of atrial fibrillation.

63. **Paton JF, Boscan P, Pickering AE, Nalivaiko E. The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited. *Brain Res Brain Res Rev.* 2005;49:555-65.**
Abstract: We review the pattern of activity in the parasympathetic and sympathetic nerves innervating the heart. Unlike the conventional textbook picture of reciprocal control of cardiac vagal and sympathetic nervous activity, as seen during a baroreceptor reflex, many

other reflexes involve simultaneous co-activation of both autonomic limbs. Indeed, even at 'rest', the heart receives tonic drives from both sympathetic and parasympathetic cardiac nerves. Autonomic co-activation occurs during peripheral chemoreceptor, diving, oculocardiac, somatic nociceptor reflex responses as well as being evoked from structures within the brain. It is suggested that simultaneous co-activation may lead to a more efficient cardiac function giving greater cardiac output than activation of the sympathetic limb alone; this permits both a longer time for ventricular filling and a stronger contraction of the myocardium. This may be important when pumping blood into a constricted vascular tree such as is the case during the diving response. We discuss that in some instances, high drive to the heart from both autonomic limbs may also be arrhythmogenic. The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited.

64. **Bajbouj M, Lang UE, Neu P, Heuser I. Therapeutic brain stimulation and cortical excitability in depressed patients. *Am J Psychiatry.* 2005;162:2192-2193.** Therapeutic brain stimulation and cortical excitability in depressed patients.

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

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

67. **de Jonge WJ, van der Zanden EP, The FO, et al. Erratum: Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. *Nat Immunol.* 2005;6:954.**

68. **Zobel A, Joe A, Freymann N, et al. Changes in regional cerebral blood flow by therapeutic vagus nerve stimulation in depression: an exploratory approach. *Psychiatry Res.* 2005;139:165-79.**
Abstract: Abnormalities in regional cerebral blood flow (rCBF) have been reported to characterize depressive episodes; they are at least partly reversed by antidepressant treatment. Treatment-specific as well as response-related changes in rCBF have been reported. We explored the changes in rCBF induced by vagus nerve stimulation (VNS), a recently proposed antidepressant strategy, by application of single photon emission-computed tomography with (99m)Tc-hexamethyl-propylene amine oxime in otherwise treatment-refractory patients. Both region-of-interest (ROI) and statistical parametric mapping (SPM) analytic approaches were used. Decreases of rCBF in the amygdala, left hippocampus, left subgenual cingulate cortex, left and right ventral anterior cingulum, right thalamus and brain stem were observed; the only increase of rCBF was found by SPM analysis in the middle frontal gyrus. This pattern shares features with changes of rCBF previously associated with the administration of selective serotonin reuptake inhibitors. Similarities to other brain-stimulation strategies in antidepressant treatment were less pronounced. Changes in regional cerebral blood flow by therapeutic vagus nerve stimulation in depression: an exploratory approach.

69. **Wang GM, Song G, Zhang H. Phenomenon of non-associative learning in Hering-Breuer reflex simulated by electrical vagal stimulation in rabbits. *Sheng Li Xue Bao.* 2005;57:511-516.**
Abstract: The purpose of this study was to explore learning and memory in the Hering-Breuer (HB) reflex simulated by a 60-second-long electrical stimulation of vagus nerve. The responses of phrenic nerve discharge to electrical stimulation (10-100 Hz, 20-60 muA, pulse duration 0.3 ms, for 60 s) of the vagus nerve were observed in rabbits. The results showed that 60-second-long stimulation of vagus nerve produced classic HB reflex, which is composed of two components - lung inflation reflex that is the inhibition of inspiration, and lung deflation reflex that is the facilitation of inspiration. (1) High frequency stimulation (>/=40 Hz, 60 s) of the central end of vagus nerve induced shortening of the inspiratory phase and lengthening of expiratory duration. The inhibitory effect on phrenic discharge was released gradually during sustained vagal stimulation, indicating the habituation of the inhibition. At the cessation of stimulation, the phrenic discharge showed transient post-stimulus rebound. Low frequency stimulation (<40 Hz, 60 s) of the central end of vagus nerve caused an increase in respiratory frequency (f) and shortening of expiratory duration. The excitatory effect on phrenic discharge was also released gradually during the vagal stimulation. The phrenic discharge returned to control level gradually after

the removal of the vagal stimulus, indicating short-term potentiation (STP). (2) The habituation of HB reflex was inversely dependent on stimulus intensity and frequency. With an increase in the stimulus frequency or intensity, the degree of the habituation decreased. On the other hand, with the decrease of stimulation intensity and frequency, the degree of the habituation increased. These data indicate a phenomenon of non-associative learning in HB reflex simulated by vagal stimulation. Neural synaptic plasticity and accommodation may exist in the reflex control of respiration in rabbits. Phenomenon of non-associative learning in Hering-Breuer reflex simulated by electrical vagal stimulation in rabbits.

70. **de Jonge WJ, van der Zanden EP, The FO, et al. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. *Nat Immunol.* 2005;6:844-851.**
Abstract: Acetylcholine released by efferent vagus nerves inhibits macrophage activation. Here we show that the anti-inflammatory action of nicotinic receptor activation in peritoneal macrophages was associated with activation of the transcription factor STAT3. STAT3 was phosphorylated by the tyrosine kinase Jak2 that was recruited to the alpha7 subunit of the nicotinic acetylcholine receptor. The anti-inflammatory effect of nicotine required the ability of phosphorylated STAT3 to bind and transactivate its DNA response elements. In a mouse model of intestinal manipulation, stimulation of the vagus nerve ameliorated surgery-induced inflammation and postoperative ileus by activating STAT3 in intestinal macrophages. We conclude that the vagal anti-inflammatory pathway acts by alpha7 subunit-mediated Jak2-STAT3 activation. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway.

71. **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;20:851-856.**
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+/-1.94kg.). 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. Histopathologic features of the vagus nerve after electrical stimulation in swine.

72. **Groves DA, Bowman EM, Brown VJ. Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetised rat. *Neurosci Lett.* 2005;379:174-9.**
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. Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetised rat.

73. **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;43:365-74.**
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. Influence of variable nerve fibre geometry on the excitation and blocking threshold. A simulation study.

74. **Peitl B, Dobronte R, Nemeth J, et al. The prandial insulin sensitivity-modifying effect of vagal stimulation in rats. *Metabolism.* 2005;54:579-583.**
Abstract: 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. The prandial insulin sensitivity-modifying effect of vagal stimulation in rats.

75. **Tubbs RS, Killingsworth CR, Rollins DL, et al. Vagus nerve stimulation for induced spinal cord seizures: insights into seizure cessation. *J Neurosurg.* 2005;102(2 suppl):213-217.**
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. Vagus nerve stimulation for induced spinal cord seizures: insights into seizure cessation.

76. **Neu P, Heuser I, Bajbouj M. Cerebral blood flow during vagus nerve stimulation--a transcranial Doppler study. *Neuropsychobiology.* 2005;51:265-8.**
Abstract: BACKGROUND AND OBJECTIVES: Vagus nerve stimulation (VNS) is an approved treatment of partial onset seizures and has recently shown antidepressant effects in patients with treatment-resistant depression. This study was conducted to investigate whether acute VNS has an influence on cerebral blood flow (CBF) in humans. METHODS: This investigation was designed as an add-on study. In 10 patients with an implanted stimulator who participated in a multicenter clinical trial to evaluate the efficacy of VNS in depression, CBF was investigated by functional transcranial Doppler at baseline (before the stimulator was turned on for the first time) and during stimulation with three different stimulation intensities in a randomized order. RESULTS: Immediately after every increase of the current, CBF velocity showed a nonsignificant increase. Otherwise, no change of CBF above standard deviation could be registered. CONCLUSION: Acute VNS does not have an influence on CBF velocity in depressive patients. Cerebral blood flow during vagus nerve stimulation--a transcranial Doppler study.

77. **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.**
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. Ictal onset slow potential shifts recorded with hippocampal depth electrodes.

78. **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.**
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. The acute and chronic effect of vagus nerve stimulation in genetic absence epilepsy rats from Strasbourg (GAERS).

79. **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;12:307-9.**
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. The effects of vagus nerve stimulation on pro- and anti-inflammatory cytokines in humans: a preliminary report.

80. **Bejanishvili S, Osborne LE, Messenger K, Olejniczak P, Gutierrez A. EMG vagus nerve stimulator artifact. *Neurol Clin Neurophysiol.* 2005;2005:1.**
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. EMG vagus nerve stimulator artifact.

81. **Kirchner A, Landis BN, Haslbeck M, Stefan H, Renner B, Hummel T. Chemosensory function in patients with vagal nerve stimulators. *J Clin Neurophysiol.* 2004;21:418-25.**
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 H2S 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. Chemosensory function in patients with vagal nerve stimulators.

82. **Rozman J, Bunc M. Modulation of visceral function by selective stimulation of the left vagus nerve in dogs. *Exp Physiol.* 2004;89:717-25.**
Abstract: The superficial regions of the left vagus nerves of a dog were selectively stimulated with 39-electrode spiral cuffs having 13 circumferential groups of three electrodes (GTE) to modulate the function of the innervated internal organs and glands. Under general anaesthesia, the cuffs were chronically implanted around the nerve in the neck in two adult Beagle dogs and remained viable for 16 months. The regions were stimulated with biphasic, rectangular current pulses (2 mA, 200 micros, 20 Hz) delivered to

the group of GTE lying close to the region innervating the specific internal organs or glands. The results showed that specific electrode configurations had actions on the heart (GTE 9), lungs (GTE 4) and pressure in the urinary bladder (GTE 1). It was also shown that GTE no. 10 significantly modified the endocrine function of the pancreas. The results of this study clearly demonstrate that internal organs and glands can be selectively stimulated via the selective stimulation of innervating superficial regions of the autonomous peripheral nerve. Modulation of visceral function by selective stimulation of the left vagus nerve in dogs.

83. **Yusuf S, Nok AJ, Ameh DA, Adelaiye AB, Balogun EO. Quantitative changes in gastric mucosal glycoproteins: effect of cholinergic agonist and vagal nerve stimulation in the rat. *Neurogastroenterol Motil.* 2004;16:613-619.**
Abstract: Abstract The role of the vagus nerve and cholinergic mechanisms in the control of the rat gastric mucin and protein (PROT) release in vivo was investigated. Under urethane anaesthesia (1.25 g kg(-1)), the rats had their gastric lumen perfused with saline. Mucus secretion was measured as a function of adherent mucus on the mucosa surface and the luminal content of sialic acids (SIA), galactose (GAL), pyruvate and PROT. Electrical stimulation of the vagi significantly increased the levels of mucus (3.23 +/- 025 ÎĽg g(-1) tissue, $P < 0.05$), free sialic acid (FS) (0.18 +/- 0.04 mg mL(-1), $P < 0.05$) and PROT (0.25 +/- 0.003 mg mL(-1), $P < 0.05$) when compared with control animals. Bilateral cervical vagotomy had no significant effect on adherent mucus or basal levels of PROT, SIA and GAL ($P > 0.05$) with respect to the control. In both vagotomized and vagal intact animals, the cholinergic agonist (carbachol, 200 mg kg(-1)) significantly increased PROT, adherent mucus and FS ($P < 0.05$) and decreased bound sialic acid ($P > 0.05$). There were no visible haemorrhagic streaks on the gastric mucosa of vagotomized, vagal intact and carbachol-treated animals. The results suggest that vagus nerve does not exert a tonic control on gastric glycoprotein secretion in vivo and that cholinergic effect on the mucus secreting cells may be implemented via the intrinsic nerves of the enteric nervous system.
Quantitative changes in gastric mucosal glycoproteins: effect of cholinergic agonist and vagal nerve stimulation in the rat.

84. **Evans MS, Verma-Ahuja S, Naritoku DK, Espinosa JA. Intraoperative human vagus nerve compound action potentials. *Acta Neurol Scand.* 2004;110:232-8.**
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. Intraoperative human vagus nerve compound action potentials.

85. **Carpenter LL, Moreno FA, Kling MA, et al. Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. *Biol Psychiatry.* 2004;56:418-26.**
Abstract: BACKGROUND: Vagus nerve stimulation (VNS) has shown promising antidepressant effects in treatment-resistant depression, but the mechanisms of action are not known. Cerebrospinal fluid (CSF) studies in epilepsy patients show that VNS alters concentrations of monamines and gamma-aminobutyric acid (GABA), neurotransmitter systems possibly involved in the pathogenesis of depression. METHODS: Twenty-one adults with treatment-resistant, recurrent, or chronic major depression underwent standardized lumbar puncture for collection of 12 mL CSF on three separate but identical procedure days during participation in the VNS D-02 clinical trial. All subjects remained on stable regimens of mood medications. Collections were made at baseline (2 weeks after surgical implantation but before device activation), week 12 (end of the acute-phase study), and week 24. Cerebrospinal fluid concentrations of norepinephrine (NE), 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) were determined with high-performance liquid chromatography. Concentrations of GABA were assayed with mass spectrometry. RESULTS: Comparison of sham versus active VNS revealed a significant (mean 21%) VNS-associated increase in CSF HVA. Mean CSF concentrations of NE, 5-HIAA, MHPG, and GABA did not change significantly. Higher baseline HVA/5-HIAA ratio predicted worse clinical outcome. CONCLUSIONS: Although several of the CSF neurochemical effects we observed in this VNS study were similar to those described in the literature for antidepressants and electroconvulsive therapy, the results do not suggest a putative antidepressant mechanism of action for VNS. Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients.

86. **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;45:1064-70.**
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 [15O]H2O. 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. Brain blood-flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: II. prolonged effects at high and low levels of stimulation.

87. **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;28:507-524.**
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. The role of norepinephrine in epilepsy: from the bench to the bedside.

88. **Cullingford T. The vagus nerve-a common route for epilepsy therapies? *Lancet Neurol.* 2004;3:518.** The vagus nerve-a common route for epilepsy therapies?

89. **Osharina VV, Savenko YN, Dyuzhikova NA, et al. Vagal stimulation modifies parameters of heterochromatin in the nuclei of vagosolitary complex neurons of medulla oblongata in rats. *Bull Exp Biol Med.* 2004;138:113-115.**
Abstract: New data were obtained on modification of heterochromatin parameters in the nuclei of medulla oblongata neurons in Wistar rats after stimulation of the vagus nerve: decrease in the area of heterochromatin regions and redistribution of chromocenters within the neuronal nuclear system. It was concluded that realization of the viscero-visceral reflex is associated with rearrangement of chromatin in neurons involved in transmission of the corresponding information. Vagal stimulation modifies parameters of heterochromatin in the nuclei of vagosolitary complex neurons of medulla oblongata in rats.

90. **Di Lazzaro V, Oliviero A, Pilato F, et al. Effects of vagus nerve stimulation on cortical excitability in epileptic patients. *Neurology.* 2004;62:2310-2.**
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. Effects of vagus nerve stimulation on cortical excitability in epileptic patients.

91. **Zhang Y, McGuire M, White DP, Ling L. Serotonin receptor subtypes involved in vagus nerve stimulation-induced phrenic long-term facilitation in rats. *Neurosci Lett.* 2004;363:108-11.**
Abstract: Episodic vagus nerve stimulation (VNS) induces phrenic long-term facilitation (LTF, a persistent augmentation of phrenic nerve activity after the stimulation ends), sensitive to the serotonin 5-HT(1,2,5,6,7) receptor antagonist methysergide and similar to that elicited by episodic hypoxia or carotid sinus nerve stimulation. This study examined the effect of ketanserin (5-HT(2) antagonist) or clozapine (5-HT(2,6,7) antagonist) on VNS-induced LTF in anesthetized, vagotomized, paralyzed and ventilated rats to determine which receptor subtype(s) is involved. Three episodes of 5 min VNS (50 Hz, 0.1 ms, approximately 500 microA) with 5 min intervals elicited phrenic LTF in control (amplitude: 38% above baseline at 60 min post-VNS) and ketanserin (2 mg x kg(-1), i.p.) pre-treated rats (45%), but not clozapine (3 mg x kg(-1)) rats (8%). These data suggest that unlike hypoxia-induced LTF (5-HT(2) receptor-dependent), VNS-induced LTF requires non-5-HT(2) serotonin receptors, perhaps 5-HT(6) and/or 5-HT(7) subtype(s). Serotonin receptor subtypes involved in vagus nerve stimulation-induced phrenic long-term facilitation in rats.

92. **Tatum IV WO, Malek A, Recio M, Orlowski J, Murtagh R. Diffusion-weighted imaging and status epilepticus during vagus nerve stimulation. *Epilepsy Behav.* 2004;5:411-415.**
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 pharmacoresistant 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. Diffusion-weighted imaging and status epilepticus during vagus nerve stimulation.

93. **Krahl SE, Senanayake SS, Pekary AE, Sattin A. Vagus nerve stimulation (VNS) is effective in a rat model of antidepressant action. *J Psychiatr Res.* 2004;38:237-240.**
Abstract: Depression is a common but debilitating illness that afflicts a large population and costs the US economy a staggering $40 billion dollars per year. Clinical studies have demonstrated that vagus nerve stimulation (VNS) is an effective treatment for medication-resistant depression. Understanding VNS's antidepressant mechanisms is key to improving the therapy and selecting the best surgical candidates, and demonstration that VNS is effective in a validated test of antidepressant activity allows us to elucidate these mechanisms in a cost-effective manner. In the present study, Wistar Kyoto rats were implanted with a cuff electrode on the left cervical vagus nerve. The next day, they were placed into a water-filled Plexiglas cylinder for 15 min. After this forced-swim session, one of three treatment conditions were administered over 4 consecutive days: 30 min per day of continuous VNS, 10 mg/kg of desipramine twice per day, or three daily electroconvulsive shocks (ECS). Yoked controls underwent sham procedures, but received no treatment. On the fourth day, the rats were given a 5-min, videotaped swim test. A blinded observer used the videotape to calculate the percentage of time that the rats were immobile (an index of depression) during the swim test. VNS significantly reduced immobility time as compared to unstimulated controls, indicating good antidepressant efficacy. This reduction did not differ statistically from that obtained from rats treated with either desipramine or ECS, two standard antidepressant treatments. These results indicate that VNS is an effective antidepressant in the forced-swim test, allowing us to now investigate possible therapeutic mechanisms. Vagus nerve stimulation (VNS) is effective in a rat model of antidepressant action.

94. **Mu Q, Bohning DE, Nahas Z, et al. Acute vagus nerve stimulation using different pulse widths produces varying brain effects. *Biol Psychiatry.* 2004;55:816-25.**
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. Acute vagus nerve stimulation using different pulse widths produces varying brain effects.

95. **Dedeurwaerdere S, Vonck K, Claeys P, et al. Acute vagus nerve stimulation does not suppress spike and wave discharges in genetic absence epilepsy rats from Strasbourg. *Epilepsy Res* . 2004;59:191-8.**
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. Acute vagus nerve stimulation does not suppress spike and wave discharges in genetic absence epilepsy rats from Strasbourg.

96. **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;202:283-294.**
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 artifically 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. The effects of vagal stimulation on laryngeal vascular resistance and intraluminal pressure in the dog.

97. **Hassert DL, Miyashita T, Williams CL. The effects of peripheral vagal nerve stimulation at a memory-modulating intensity on norepinephrine output in the basolateral amygdala. *Behav Neurosci.* 2004;118:79-88.**
Abstract: Vagal nerve stimulation (VNS) is known to improve cognitive processing, presumably by affecting activity in central nervous system structures that process recently acquired information. It has long been assumed that these effects are related to stimulation-induced increases of norepinephrine (NE) release in limbic brain structures. The present study examined this hypothesis by administering VNS at an intensity and duration that improves memory and then measuring fluctuations in NE output in the basolateral amygdala (BLA) with in vivo microdialysis. In Experiment 1, VNS caused a 98% increase in NE output relative to baseline. In Experiment 2, methyl atropine was given 10 min before VNS to assess whether stimulation-induced increases in amygdala NE are mediated by afferent or efferent vagal branches. Methyl atropine did not alter NE release in the BLA in comparison with saline. The significance of these findings in understanding how peripheral neural activity modulates limbic structures to encode and store new information into memory is discussed. The effects of peripheral vagal nerve stimulation at a memory-modulating intensity on norepinephrine output in the basolateral amygdala.

98. **Brack KE, Coote JH, Ng GA. Interaction between direct sympathetic and vagus nerve stimulation on heart rate in the isolated rabbit heart. *Exp Physiol.* 2004;89:128-139.**
Abstract: The interaction between the effects of vagus nerve stimulation (VS) and sympathetic stimulation (SS) on intrinsic heart rate was studied in the novel innervated isolated rabbit heart preparation. The effects of background VS, at different frequencies--2 Hz (low), 5 Hz (medium), 7 Hz (high)--on the chronotropic effects of different frequencies of SS--2 Hz (low), 5 Hz (medium), 10 Hz (high)--were studied. The experiments were repeated in the reverse direction studying the effects of different levels of background SS on the chronotropic effects of different levels of VS. Background VS reduced the overall positive chronotropic effect of SS at steady state in a frequency dependent manner and the rate of increase in heart rate during low and medium SS (but not high SS) was slowed in the presence of background VS. These results suggest that pre- and postjunctional mechanisms may be involved in the sympatho-vagal interaction on heart rate. On the other hand, the chronotropic effect of VS was enhanced in the presence of background SS. Vagal stimulation appears to play a dominant role over sympathetic stimulation in chronotropic effects on the isolated heart. The innervated isolated heart preparation is a valuable model to study the complex mechanisms underlying the interaction between sympathetic and parasympathetic stimulation on cardiac function. Interaction between direct sympathetic and vagus nerve stimulation on heart rate in the isolated rabbit heart.

99. **Jaseja H. Vagal nerve stimulation technique: enhancing its efficacy and acceptability by augmentation with auto activation and deactivation mode of operation. *Med Hypotheses.* 2004;63:76-9.**
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. Vagal nerve stimulation technique: enhancing its efficacy and acceptability by augmentation with auto activation and deactivation mode of operation.

100. **George MS, Nahas Z, Bohning DE, et al. Mechanisms of action of vagus nerve stimulation (VNS). *Clin Neurosci Res.* 2004;4:71-79.** Mechanisms of action of vagus nerve stimulation (VNS)

101. **Labar D, Ponticello L. Persistent antiepileptic effects after vagus nerve stimulation ends? *Neurology.* 2003;61:1818.**
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." Persistent antiepileptic effects after vagus nerve stimulation ends?

102. **Holmes MD, Miller JW, Voipio J, Kaila K, Vanhatalo S. Vagal nerve stimulation induces intermittent hypocapnia. *Epilepsia.* 2003;44:1588-91.**
Abstract: PURPOSE: To study whether respiratory alteration caused by vagal nerve stimulation (VNS) can change end-tidal carbon dioxide (EtCO2) 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 EtCO2 during VNS. Three subjects showed occasional decreases in EtCO2 during VNS, and two showed no clearly detectable VNS-related EtCO2 changes. CONCLUSIONS: Our findings suggest that VNS may alter brain CO2 levels through changes in respiration. Because carbon dioxide (CO2) has potent effects on various brain functions, it is possible that these transient CO2 changes may have an effect on the state transitions between interictal and preictal states. Vagal nerve stimulation induces intermittent hypocapnia.

103. **Fallgatter AJ, Neuhauser B, Herrmann MJ, et al. Far field potentials from the brain stem after transcutaneous vagus nerve stimulation. *J Neural Transm.* 2003;110:1437-1443.**
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. Far field potentials from the brain stem after transcutaneous vagus nerve stimulation.

104. **Chae JH, Nahas Z, Lomarev M, et al. A review of functional neuroimaging studies of vagus nerve stimulation (VNS). *J Psychiatr Res.* 2003;37:443-55.**
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. A review of functional neuroimaging studies of vagus nerve stimulation (VNS).

105. **Miyamoto O, Pang J, Sumitani K, Negi T, Hayashida Y, Itano T. Mechanisms of the anti-ischemic effect of vagus nerve stimulation in the gerbil hippocampus.** ***Neuroreport.*** **2003;14:1971-4.**
Abstract: The neuroprotective mechanisms of cervical vagus nerve stimulation (VNS) in transient ischemia were investigated. Left VNS (0.4 mA, 40 Hz) was performed during 5 min ischemia in gerbils. About 50% of the hippocampal neurons were rescued from ischemic insult by VNS, and this effect was prevented by transection of the vagus nerve centrally to the site of cervical stimulation. VNS significantly attenuated both ischemia-induced glutamate release and transient increase of hippocampal blood flow during reperfusion. Hyperemia as well as excessive glutamate release after ischemia is regarded as an important factor in ischemic brain damage as it leads to generate considerable reactive oxygen species. Thus, VNS might protect neurons from ischemia-induced glutamate excitotoxicity and reperfusion injury via the afferent path-way of the vagus. Mechanisms of the anti-ischemic effect of vagus nerve stimulation in the gerbil hippocampus.

106. **Zhang X, Cui J, Tan Z, Jiang C, Fogel R. The central nucleus of the amygdala modulates gut-sensitive neurons in the dorsal vagal complex in rats.** ***J Physiol.*** **2003;1005-1018.**
Abstract: The central nucleus of the amygdala and the dorsal vagal complex play very important roles in integrating of emotion, motivation, learning, memory, and feeding behavior with gastrointestinal function. Using retrograde tract-tracing and electrophysiological methods, we characterized the anatomic and functional relationship between the central nucleus of the amygdala and the dorsal vagal complex. Retrograde tract-tracing techniques revealed that the central nucleus of the amygdala projected to the dorsal vagal complex with a topographic distribution. Following injection of retrograde tracer into the vagal complex, retrograde- labeled neurons in the central nucleus of the amygdala were clustered in the central portion at the rostral level and in the medial part at the middle level of the nucleus. Few labeled neurons were seen at the caudal level. Electrical stimulation of the central nucleus of the amygdala altered the basal firing rates of 65% of gut-related neurons in the nucleus of the solitary tract and in the dorsal motor nucleus of the vagus. Eighty-one percent of the neurons in the nucleus of the solitary tract and 47% of the neurons in the dorsal motor nucleus were inhibited. Electrical stimulation of the central nucleus of the amygdala also modulated the response of neurons in the dorsal vagal complex to gastrointestinal stimuli. The predominant effect on was opposite to that of gastrointestinal stimuli. These results suggest that the central nucleus of the amygdala influences gut- related neurons in the dorsal vagal complex and provides a neuronal circuitry to explain regulation of gastrointestinal activity by the amygdala. The central nucleus of the amygdala modulates gut-related neurons in the dorsal vagal complex in rats.

107. **Hashiba E, Hirota K, Suzuki K, Matsuki A. Effects of propofol on bronchoconstriction and bradycardia induced by vagal nerve stimulation.** ***Acta Anaesthesiol Scand.*** **2003;47:1059-63.**
Abstract: BACKGROUND: Vagolysis has been considered as a mechanism by which

propofol produces bronchodilation. However, it has also been suggested that propofol-induced bradycardia may result from increased vagal tone. In this study, we have determined whether propofol has vagolytic effects on both the airway and cardiovascular system. METHODS: Mongrel dogs were anesthetized with pentobarbital. Bronchoconstriction was assessed by measuring changes in a bronchial cross-sectional area (BCA) using a bronchoscopic method. Heart rate (HR) and direct arterial blood pressure were also monitored. Vagal nerve stimulation (VNS) was performed for 60 s to produce both bronchoconstriction and bradycardia. To determine the effect of propofol on VNS-induced bronchoconstriction and bradycardia (n = 7), 0 (saline), 2.0 and 20 mg/kg propofol were administered intravenously at 20-min intervals with VNS commenced 5 min later. In addition, to determine if propofol-induced bradycardia is due to a vagomimetic action, two groups of six dogs were given 20 mg/kg propofol with or without 0.2 mg/kg atropine pre-treatment. HR was measured before and 5 min after propofol. RESULTS: Propofol 20 mg/kg significantly inhibited VNS-induced bronchoconstriction. Although propofol per se significantly reduced HR (24%) and blood pressure (37%), the reduction in HR produced by VNS after 20 mg/kg propofol did not differ from that after saline or the lower dose of propofol (2 mg/kg). As atropine pre-treatment did not attenuate propofol-induced bradycardia, this response is unlikely to be simply due to vagomimetic actions. CONCLUSION: Propofol has vagolytic effects on the airway but does not worsen bradycardia produced by parasympathetic stimulation. Effects of propofol on bronchoconstriction and bradycardia induced by vagal nerve stimulation.

108. Zhang Y, McGuire M, White DP, Ling L. Episodic phrenic-inhibitory vagus nerve stimulation paradoxically induces phrenic long-term facilitation in rats. *J Physiol.* 2003;551:981-91.

Abstract: All respiratory long-term facilitation (LTF) is induced by inspiratory-excitatory stimulation, suggesting that LTF needs inspiratory augmentation and is the result of a Hebbian mechanism (coincident pre- and post-synaptic activity strengthens synapses). The present study examined the long-term effects of episodic inspiratory-inhibitory vagus nerve stimulation (VNS) on phrenic nerve activity. We hypothesized that episodic VNS would induce phrenic long-term depression. The results are compared with those obtained following serotonin receptor antagonism or episodic carotid sinus nerve stimulation (CSNS). Integrated phrenic neurograms were measured before, during and after three episodes of 5 min VNS (50 Hz, 0.1 ms), each separated by a 5 min interval, at a low (approximately 50 microA), medium (approximately 200 microA) or high (approximately 500 microA) stimulus intensity in anaesthetized, vagotomized, neuromuscularly blocked and artificially ventilated rats. Medium- and high-intensity VNS eliminated rhythmic phrenic activity during VNS, while low-intensity VNS only reduced phrenic burst frequency. At 60 min post-VNS, phrenic amplitude was higher than baseline (35 +/- 5% above baseline, mean +/- S.E.M., $P < 0.05$) in the high-intensity group but not in the low- (-4 +/- 4%) or medium-intensity groups (-10 +/- 15%), or in the high-intensity with methysergide group (4 mg kg(-1), i.p.) (-11 +/- 5%). These data, which are inconsistent with our hypothesis, indicate that phrenic-inhibitory VNS induces a serotonin-dependent phrenic LTF similar to that induced by phrenic-excitatory CSNS (33 +/- 7%) and may require activation of high-threshold afferent fibres. These data also suggest that the synapses on phrenic motoneurons do not use the Hebbian mechanism in this LTF, as these motoneurons were suppressed during VNS. Episodic phrenic-inhibitory vagus nerve

stimulation paradoxically induces phrenic long-term facilitation in rats.

109. **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;28:784-5.**
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. Thalamic hypometabolism in a patient undergoing vagal nerve stimulation seen on F-18 FDG PET imaging.

110. **Galli R, Limbruno U, Pizzanelli C, et al. Analysis of RR variability in drug-resistant epilepsy patients chronically treated with vagus nerve stimulation. *Auton Neurosci.* 2003;107:52-9.**
Abstract: Vagus nerve stimulation (VNS) has been suggested as an adjunctive treatment for drug-resistant epilepsy when surgery is inadvisable. The overall safety profile of VNS seems to be favorable as only minor adverse effects have been described. The purpose of this study was to determine if cardiac vagal tone is eventually modified by short- and long-term VNS. The effects of short- and long-term VNS were evaluated in seven subjects with intractable epilepsy. Autonomic cardiac function has been carried out by means of a 24-h analysis of RR variability at baseline (t(0)), 1 month (t(1), short-term VNS) and 36 months after VNS initiation (t(2), long-term VNS). Frequency- and time-domain parameters were calculated. Periodic cardiological and neurological evaluations were performed.Clinically relevant cardiac effects were not observed throughout the study. Despite the limited number of patients and the variety of data among them, for all the patients, a common trend towards a nocturnal decrease in the high-frequency (HF) component of the spectrum was observed after long-term VNS (mean+/-S.D.: 40+/-18 normalized units (nu) at t(0), 38+/-17 nu at t(1), 18+/-10 nu at t(2); $p<0.05$ of t(2) vs. either t(0) or t(1)). The day-to-night changes in the power of low-frequency (LF) and HF components were significantly blunted after long-term VNS (LF day-to-night change: +16+/-13 nu at t(0) and +15+/-8 nu at t(1) vs. +3+/-13 nu at t(2), $p<0.02$; HF day-to-night change: -18+/-13 nu at t(0) and -13+/-11 nu at t(1) vs. +3+/-12 nu at t(2), $p<0.003$). No significant changes were observed with regard to the time-domain parameters of the heart rate variability.Throughout the neurological follow-up, one subject became seizure-free, three experienced a seizure reduction of >50%, two patients of <50% and one had no changes in his seizure frequency.Our findings suggest that long-term VNS might slightly affect cardiac autonomic function with a reduction of the HF component of the spectrum during night and a flattening of sympathovagal circadian changes, not inducing, however, clinically relevant cardiac side effects. Analysis of RR variability in drug-resistant epilepsy patients chronically treated with vagus nerve stimulation.

111. **Gatzonis SD, Korres S, Balatsouras DG, et al. Influence of vagus nerve stimulation on vestibulo-ocular reflex. *ORL J Otorhinolaryngol Relat Spec.* 2003;65:223-5.**

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. Influence of vagus nerve stimulation on vestibulo-ocular reflex.

112. **Gorman JM. New methods of brain stimulation: what they tell us about the old methods and about the brain. *CNS Spectr.* 2003;8:475.**
Notes: This letter from the editor focuses primarily on the effectiveness of ECT. TMS, VNS, and DBS also are mentioned as newer methods of brain stimulation that have yet to be proven effective in relieving depression. The author briefly mentions that a true benefit of all of these new methods of brain stimulation is the ability these methods have for revealing more about brain function in general. New methods of brain stimulation: what they tell us about the old methods and about the brain.

113. **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;55:59-70.**
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 [123I]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. Correlation between GABA(A) receptor density and vagus nerve stimulation in individuals with drug-resistant partial epilepsy.

114. **Sitdikov FG, Gil'mutdinova RI, Minnakhmetov RR, Gizzatullin AR . Effect of electrical stimulation of vagus nerves on cardiac activity in sympathectomized rats during postnatal ontogeny. *Bull Exp Biol Med.* 2003;135:534-536.**
Abstract: In intact rats vagal stimulation reduced heart rate, but had no effect on stroke volume. In sympathectomized animals this treatment decreased both the heart rate and stroke volume. Sympathectomized rats displayed higher sensitivity to vagal nerve stimulation compared to intact animals of the same age (except for rats aging 21 and 56 days). Effect of electrical stimulation of vagus nerves on cardiac activity in sympathectomized rats during postnatal ontogeny.

115. **Liu WC, Mosier K, Kalnin AJ, Marks D. BOLD fMRI activation induced by vagus nerve stimulation in seizure patients. *J Neurol Neurosurg Psychiatry.* 2003;74:811-813.**
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 Echospeed 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. BOLD fMRI activation induced by vagus nerve stimulation in seizure patients.

116. **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;30:301-5.**
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. Investigation into the mechanisms of vagus nerve stimulation for the treatment of intractable epilepsy, using 99mTc-HMPAO SPET brain images.

117. **Murakawa Y, Yamashita T, Ajiki K, Hayami N, Omata M, Nagai R. Effect of cervical vagal nerve stimulation on defibrillation energy: a possible adjunct to efficient defibrillation. *Jpn Heart J.* 2003;44:91-100.**
Abstract: The efficacy of electrical defibrillation is considered to be related to the autonomic status. In search of a possible adjunct to enhance the therapeutic performance of an implantable cardioverter-defibrillator. we investigated whether parasympathetic manipulation by cervical vagal nerve stimulation (VNS) increases defibrillation efficacy. The effects of VNS on transcardiac defibrillation threshold (DFT) were assessed in 55 anesthetized dogs. In neurally intact dogs, right and left unilateral VNS at 10 mA for 7 seconds significantly decreased the DFT after 10 seconds of ventricular fibrillation (control: 3.1 +/- 0.9 J, right: 2.1 +/- 0.9 J [delta-35 +/- 12%, P < 0.0001], left: 2.2 +/- 0.8 J [delta-31 +/- 11%, P < 0.0005]), while bilateral VNS did not (2.8 +/- 1.0 J). In dogs with decentralized vagus nerves, both unilateral and bilateral VNS decreased the DFT. The extent of the VNS-induced decrease in DFT was dependent on the current and the duration of stimulation. We conclude that unilateral VNS decreases the DFT, while bilateral VNS paradoxically has no effect on the DFT unless the vagi are decentralized. Effect of cervical vagal nerve stimulation on defibrillation energy: a possible adjunct to efficient defibrillation.

118. **Mohan RM, Heaton DA, Danson EJ, et al. Neuronal nitric oxide synthase gene transfer promotes cardiac vagal gain of function. *Circ Res.* 2002;91:1089-91.**
Abstract: Nitric oxide (NO) generated from neuronal nitric oxide synthase (NOS-1) in intrinsic cardiac ganglia has been implicated in parasympathetic-induced bradycardia. We provide direct evidence that NOS-1 acts in a site-specific manner to promote cardiac vagal neurotransmission and bradycardia. NOS-1 gene transfer to the guinea pig right atrium increased protein expression and NOS-1 immunolocalization in cholinergic ganglia. It also increased the release of acetylcholine and enhanced the heart rate (HR) response to vagal nerve stimulation (VNS) in vitro and in vivo. NOS inhibition normalized the HR response to VNS in the NOS-1-treated group compared with the control groups (enhanced green fluorescent protein and sham) in vitro. In contrast, an acetylcholine analogue reduced HR to the same extent in all groups before and during NOS inhibition. These results demonstrate that NOS-1-derived NO acts presynaptically to facilitate vagally induced bradycardia and that upregulation of NOS-1 via gene transfer may provide a novel method

for increasing cardiac vagal function. Neuronal nitric oxide synthase gene transfer promotes cardiac vagal gain of function.

119. **Narayanan JT, Watts R, Haddad N, Labar DR, Li PM, Filippi CG. Cerebral activation during vagus nerve stimulation: a functional MR study. *Epilepsia.* 2002;43:1509-14.**
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. Cerebral activation during vagus nerve stimulation: a functional MR study.

120. **Kosel M, Schlaepfer TE. Mechanisms and state of the art of vagus nerve stimulation. *J ECT.* 2002;18:189-92.**
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. Mechanisms and state of the art of vagus nerve stimulation.

121. **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;43:1181-1188.**
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 >/=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. Effect of vagal nerve stimulation on interictal epileptiform discharges: a scalp EEG study

122. **Henry TR. Therapeutic mechanisms of vagus nerve stimulation. *Neurology*. 2002;59:S3-14.**
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. Therapeutic mechanisms of vagus nerve stimulation.

123. **Hosoi T, Okuma Y, Nomura Y. The mechanisms of immune-to-brain communication in inflammation as a drug target. *Curr Drug Targets Inflamm Allergy*. 2002;1:257-262.**
Abstract: There is considerable evidence that the peripheral immune system can signal the brain to elicit a sickness response during infection and inflammation. The induction of the sickness response involves the expression of proinflammatory cytokines such as interleukin (IL)-1beta, tumor necrosis factor-alpha (TNF-alpha), and IL-6, both in the periphery and in the brain. The mechanisms by which peripheral cytokines can affect brain function have been the subject of much debate. The precise mechanisms by which cytokines signal the central nervous system (CNS) are unknown, but possibilities include: 1) the direct entry of cytokine into the brain across the blood-brain barrier by a saturable transport mechanism: 2) the interaction of cytokine with circumventricular organs such as the orgnum vasculosum of the lamina terminalis [OVLT] and area postrema, which lack the blood-brain barrier; and 3) activation of afferent neurons of the vagus nerve. Increasing evidence has suggested that the afferent vagus nerve is an important pathway for immune-to-brain

communication. However, there are inconsistent findings for the involvement of the afferent vagus nerve in the mediation of transmitting inflammatory signals to the brain. Thus, we describe here the functional relevance of the vagal afferent nerve in mediating these effects. An understanding of the mechanisms involved in immune-to-brain communication should permit us to create new drugs as therapeutic targets to decrease sickness or promote recovery. This review focuses on recent discoveries of the multipathway mechanisms for the induction of sickness behavior mediated through neuroimmune interactions in the CNS. The mechanisms of immune-to-brain communication in inflammation as a drug target.

124. **Lomarev M, Denslow S, Nahas Z, Chae J, George M, Bohning D. Vagus nerve stimulation (VNS) synchronized BOLD fMRI suggests that VNS in depressed adults has frequency/dose dependent effects. *J Psychiatr Res.* 2002;36:219-227.**
Abstract: Stimulation of the vagus nerve in the neck can reduce seizures in epilepsy patients, and may be helpful in treating depression. PET studies have shown that vagus nerve stimulation (VNS) in epilepsy patients causes acute dose (intensity) dependent changes in regional cerebral blood flow. We sought to use the newly developed VNS synchronized fMRI technique to examine whether VNS BOLD signal changes depend on the frequency of stimulation. Six adults with recurrent depression were scanned inside a 1.5 T MR scanner. Data were acquired at rest, with the VNS device on for 7 s, and also, for comparison, while the patient listened to a tone for 7 s. In two separate back-to- back sessions, the VNS stimulation frequency was set to either 5 or 20 Hz. Data were transformed into Talairach space and then compared by condition. Compared to 5 Hz, 20 Hz VNS produced more acute activity changes from rest in regions similar to our initial VNS synchronized fMRI feasibility study in depression. Brain regions activated by hearing a tone were also greater when VNS was intermittently being applied at 20 Hz than at 5 Hz. In depressed adults, left cervical VNS causes regional brain activity changes that depend on the frequency of stimulation or total dose, or both. In addition to the acute immediate effects of VNS on regional brain activity, this study suggests further that VNS at different frequencies likely has frequency or dose dependent modulatory effects on other brain activities (e.g. hearing a tone). Vagus nerve stimulation (VNS) synchronized BOLD fMRI suggests that VNS in depressed adults has frequency/dose dependent effects.

125. **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;43:733-44.**
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, $P <$ 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. Perfusion SPECT changes after acute and chronic vagus nerve stimulation in relation to prestimulus condition and long-term clinical efficacy.

126. **Valdes-Cruz A, Magdaleno-Madrigal VM, Martinez-Vargas D, et al. Chronic stimulation of the cat vagus nerve: effect on sleep and behavior.** ***Prog Neuropsychopharmacol Biol Psychiatry*** **. 2002;26:113-8.**
Abstract: The effect of electrical vagus nerve stimulation (VNS) on sleep and behavior was analyzed in freely moving cats. Eight cats were prepared for 23-h sleep recordings. The left vagus nerve of four of them was stimulated during 1 min, five times at 1-h intervals, for 5 days. The VNS induces: ipsilateral myosis, blinking, licking, abdominal contractions, upward gaze, swallowing, and eventually yawning and compulsive eating, as well as an increase of ponto-geniculate-occipital (PGO) wave density and of the number of stages and total amount of rapid eye movement (REM) sleep. Besides, there was a sudden transition from waking stage to REM sleep. The present results suggest that VNS modifies sleep in the cat. This effect could be explained by an activation of the areas involved in the physiological mechanisms of sleep. Chronic stimulation of the cat vagus nerve: effect on sleep and behavior.

127. **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:H2310-7.**
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+/+, $n = 81$) and neuronal NO synthase (nNOS) knockout (nNOS-/-, $n = 43$) mice. nNOS was immunofluorescently colocalized within choline-acetyltransferase-positive neurons in nNOS+/+ atria. The rate of decline in HR during vagal nerve stimulation (VNS, 3 and 5 Hz) was slower in nNOS-/- compared with nNOS+/+ atria in vitro ($P < 0.01$). There was no difference between the HR responses to carbamylcholine in nNOS+/+ and nNOS-/- atria.

Selective nNOS inhibitors, vinyl-L-niohydrochloride 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+/+ atria. NOS inhibition had no effect in nNOS-/- 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. Peripheral vagal control of heart rate is impaired in neuronal NOS knockout mice.

128. **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;918:60-66.**
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. Vagal and sciatic nerve stimulation have complex, time-dependent effects on chemically-induced seizures: a controlled study.

129. **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;18:394-401.**
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. The mechanism of action of vagus nerve stimulation for refractory epilepsy: the current status.

130. **Koo B. EEG changes with vagus nerve stimulation. *J Clin Neurophysiol.* 2001;18:434-441.**
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. EEG changes with vagus nerve stimulation.

131. **Bohning DE, Lomarev MP, Denslow S, Nahas Z, Shastri A, George MS. Feasibility of vagus nerve stimulation-synchronized blood oxygenation level-dependent functional MRI. *Invest Radiol.* 2001;36:470-479.**
Abstract: RATIONALE AND OBJECTIVES: Left cervical vagus nerve stimulation (VNS) by use of an implanted neurocybernetic prosthesis (NCP) system is effective in treating epilepsy, with open data suggesting effectiveness in depression, yet the mechanisms of action are unknown. Our objective was to develop a methodology for performing VNS-synchronized functional magnetic resonance imaging (VNS-fMRI) and then to demonstrate its feasibility for studying VNS effects. METHODS: In nine patients implanted for treatment of intractable depression, a Macintosh computer was used to detect the signal from the implanted VNS stimulator and then to synchronize fMRI image acquisition with its regular firing. RESULTS: With our VNS-fMRI methodology, the blood oxygenation level- dependent response to VNS was shown in brain regions regulated by the vagus nerve: orbitofrontal and parieto-occipital cortex bilaterally, left temporal cortex, the hypothalamus, and the left amygdala. CONCLUSIONS: Vagus nerve stimulation pulses from an NCP system can be detected externally to determine its firing pattern, thus

allowing VNS- fMRI studies of VNS-induced brain activity. Feasibility of vagus nerve stimulation-synchronized blood oxygenation level-dependent functional MRI.

132. **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;42:586-589.**
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. Destruction of peripheral C-fibers does not alter subsequent vagus nerve stimulation-induced seizure suppression in rats.

133. **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;42:423-9.**
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. The effect of vagus nerve stimulation on epileptiform activity recorded from hippocampal depth electrodes.

134. **Benthem L, Mundinger TO, Taborsky GJ Jr. Parasympathetic inhibition of sympathetic neural activity to the pancreas. *Am J Physiol Endocrinol Metab.* 2001;280:E378-81.**
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, PNESO 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 PNESO 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 PNESO 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. Parasympathetic inhibition of sympathetic neural activity to the pancreas.

135. **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;86:183-91.**
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-1 from a baseline of 11,186 +/- 795 mmHg s-1. 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-1 from a baseline of 11,200 +/- 777 mmHg s-1. Ganglionic blockade with hexamethonium (15-20 mg kg-1) 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. Effect of stimulating non-myelinated vagal axons on atrio-ventricular conduction and left ventricular function in anaesthetized rabbits.

136. **Dasheiff RM, Sandberg T, Thompson J, Arrambide S. Vagal nerve stimulation does not unkindle seizures. *J Clin Neurophysiol.* 2001;18:68-74.**
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 antikindling 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. Vagal nerve stimulation does not unkindle seizures.

137. **Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. *Auton Neurosci.* 2000;85:1-17.**
Abstract: The results of neural tracing studies suggest that vagal afferent fibers in cervical and thoracic branches innervate the esophagus, lower airways, heart, aorta, and possibly the thymus, and via abdominal branches the entire gastrointestinal tract, liver, portal vein, billiary system, pancreas, but not the spleen. In addition, vagal afferents innervate numerous thoracic and abdominal paraganglia associated with the vagus nerves. Specific terminal structures such as flower basket terminals, intraganglionic laminar endings and intramuscular arrays have been identified in the various organs and organ compartments, suggesting functional specializations. Electrophysiological recording studies have identified mechano- and chemo-receptors, as well as temperature- and osmo-sensors. In the rat and several other species, mostly polymodal units, while in the cat more specialized units have been reported. Few details of the peripheral transduction cascades and the transmitters for signal propagation in the CNS are known. Glutamate and its various receptors are likely to play an important role at the level of primary afferent signaling to the solitary nucleus. The vagal afferent system is thus in an excellent position to detect immune-related events in the periphery and generate appropriate autonomic, endocrine, and behavioral responses via central reflex pathways. There is also good evidence for a role of vagal afferents in nociception, as manifested by affective-emotional responses such as increased blood pressure and tachycardia, typically associated with the perception of pain, and mediated via central reflex pathways involving the amygdala and other parts of the limbic system. The massive central projections are likely to be responsible for the antiepileptic properties of afferent vagal stimulation in humans. Furthermore, these functions are in line with a general defensive character ascribed to the vagal afferent,

paraventricular system in lower vertebrates. Functional and chemical anatomy of the afferent vagal system.

138. **Fanselow EE, Reid AP, Nicolelis MA. Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation. *J Neurosci.* 2000;20:8160-8168.**
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. Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation.

139. **Zagon A, Kemeny AA. Slow hyperpolarization in cortical neurons: a possible mechanism behind vagus nerve simulation therapy for refractory epilepsy? *Epilepsia.* 2000;41:1382-9.**
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. Slow hyperpolarization in cortical neurons: a possible mechanism behind vagus nerve simulation therapy for refractory epilepsy?

140. **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;32:2065-2073.**
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. Sulphonylurea-sensitive channels and NO-cGMP pathway modulate the heart rate response to vagal nerve stimulation in vitro.

141. **Ring HA, White S, Costa DC, et al. A SPECT study of the effect of vagal nerve stimulation on thalamic activity in patients with epilepsy. *Seizure.* 2000;9:380-4.**
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. A SPECT study of the effect of vagal nerve stimulation on thalamic activity in patients with epilepsy.

142. **Gatzonis SD, Stamboulis E, Siafakas, et al. Acute psychosis and EEG normalisation after vagus nerve stimulation. *J Neurol Neurosurg Psychiatry.* 2000;69:278-279.** Acute psychosis and EEG normalisation after vagus nerve stimulation.

143. **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;41:1145-54.**
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 cysteinate 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 H2(15)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. Vagus nerve stimulation in refractory epilepsy: SPECT activation study.

144. **Vonck K, Boon P, Van Laere K, et al. Acute single photon emission computed tomographic study of vagus nerve stimulation in refractory epilepsy. *Epilepsia.* 2000;41:601-9.**

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 99mTc-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. Acute single photon emission computed tomographic study of vagus nerve stimulation in refractory epilepsy.

145. **Henry TR. Functional imaging studies of epilepsy therapies. *Adv Neurol.* 2000;83:305-317.** Functional imaging studies of epilepsy therapies.

146. **Boon P, Michielsen G, Goossens L, et al. Interictal and ictal video-EEG monitoring. *Acta Neurol Belg.* 1999;99:247-255.**
Abstract: PURPOSE: The purpose of this paper is to demonstrate the diagnostic efficacy and therapeutic relevance of video-EEG monitoring in an 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. Interictal and ictal video-EEG monitoring.

147. **Sears CE, Noble P, Noble D, Paterson DJ. Vagal control of heart rate is modulated by extracellular potassium. *J Auton Nerv Syst.* 1999;77:164-71.**
Abstract: Heart rate (HR) recovery from heavy exercise is associated with a shift in cardiac sympatho-vagal balance and a transient hypokalaemia. Since changes in extracellular potassium ([K+]0) affect membrane currents in the sino-atrial node, in particular the acetylcholine-activated potassium current (I(K,ACh)), the hyperpolarization-activated current (I(f)) and the L-type calcium current (I(Ca,L)), we investigated whether mimicking [K+]0 concentrations seen during and immediately after exercise could directly modulate the HR response to vagal nerve stimulation (VNS) in the isolated guinea-pig atria preparation pre-stimulated with noradrenaline (NA, 1 microM). Lowering [K+]0 from 4 to 3 mM significantly enhanced the HR response to VNS (5 Hz, 5 V, 30 s, deltaHR 84.5 +/- 14.1 bpm and 119.3 +/- 18.2 bpm, respectively). Increasing [K+]0 to 8 or 10 mM significantly decreased the drop in HR with VNS in comparison to the response to 3 mM K+ Tyrode (deltaHR 56.4 +/- 9.1 bpm and 52.1 +/- 8.7 bpm, respectively). These results could be simulated using the OXSOFT heart sino-atrial node computer model by activating I(K,ACh) during changes in [K+]0. However, changing [K+]0 in the model had no significant effect on the decrease in beating frequency brought about by decreasing I(f) or I(Ca,L). We conclude that the magnitude of the decrease in HR with VNS is enhanced in low [K +]0 and reduced in high [K+]0. The increased efficacy of cardiac vagal activation in low [K+]0 might therefore facilitate the drop in HR after heavy exercise where there is a transient hypokalaemia. Modelling suggests this result may be explained by the effects of changes in [K+]0 on the current-voltage relationship for I(K,ACh). Vagal control of heart rate is modulated by extracellular potassium.

148. **Walker BR, Easton A, Gale K. Regulation of limbic motor seizures by GABA and glutamate transmission in nucleus tractus solitarius. *Epilepsia.* 1999;40:1051-1057.**
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. Regulation of limbic motor seizures by GABA and glutamate transmission in nucleus tractus solitarius.

149. 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;40:822-9.

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. Vagus nerve prolonged stimulation in cats: effects on epileptogenesis (amygdala electrical kindling): behavioral and electrographic changes.

150. **Gatzonis SD, Georgaculias N, Singounas E, Jenkins A, Stamboulis E, Siafakas A. Elimination of oxcarbazepine-induced oculogyric crisis following vagus nerve stimulation. *Neurology.* 1999;52:1918-1919.** Elimination of oxcarbazepine-induced oculogyric crisis following vagus nerve stimulation.

151. **Henry TR, Votaw JR, Pennell PB, et al. Acute blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy. *Neurology.* 1999;52:1166-1173.**
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 [O-15]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. Acute blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy.

152. **Sears CE, Choate JK, Paterson DJ. NO-cGMP pathway accentuates the decrease in heart rate caused by cardiac vagal nerve stimulation. *J Appl Physiol.* 1999;86:510-6.**
Abstract: The role of the cardiac muscarinic-receptor-coupled nitric oxide (NO) pathway in the cholinergic control of heart rate (HR) is controversial. We investigated whether

adding excessive NO or its intracellular messenger cGMP could significantly modulate the HR response to vagal nerve stimulation (VNS) in the anesthetized rabbit and isolated guinea pig atria. The NO donor molsidomine (0.2 mg/kg iv) significantly enhanced the decrease in HR seen with right VNS (5 Hz, 5 V, 30 s) in vivo. A qualitatively similar effect was seen with the NO donor sodium nitroprusside (SNP; 10 and 100 microM) during VNS in vitro. This effect was still present when the baseline shift in HR caused by SNP was eliminated by using the specific hyperpolarization-activated current antagonist 4-(N-ethyl-N-phenylamino)-1,2-dimethyl-6-(methylamino)-pyrimidinium chloride (ZD-7288, 1 microM). The accentuated decrease in HR with SNP during VNS was mimicked by the stable analog of cyclic GMP, 8-bromoguanosine 3',5'-cyclic monophosphate (0.5 mM). This, however, was not seen with bath application of the stable analog of acetylcholine, carbamylcholine chloride (100 nM). We conclude that excessive NO enhances the magnitude of the decrease in HR caused by VNS. This effect appears to involve a presynaptic action via a cGMP-dependent pathway because it was not mimicked by bath-applied carbamylcholine chloride. NO-cGMP pathway accentuates the decrease in heart rate caused by cardiac vagal nerve stimulation.

153. **Jobe PC, Dailey JW, Wernicke JF. A noradrenergic and serotonergic hypothesis of the linkage between epilepsy and affective disorders. *Crit Rev Neurobiol.* 1999;13:317-356.**
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. A noradrenergic and serotonergic hypothesis of the linkage between epilepsy and affective disorders.

154. **Clark KB, Smith DC, Hassert DL, Browning RA, Naritoku DK, Jensen RA. Posttraining electrical stimulation of vagal afferents with concomitant vagal efferent inactivation enhances memory storage processes in the rat. *Neurobiol Learn Mem.* 1998;70:364-373.**
Abstract: Peripherally administered or released substances that modulate memory storage, but do not freely enter the brain, may produce their effects on memory by activating peripheral receptors that send messages centrally through the vagus nerve. Indeed, vagus nerve stimulation enhances memory performance, although it is unclear whether this effect

is due to the activation of vagal afferents or efferents. To eliminate the possible influence of descending fibers on memory storage processes, rats were implanted with cuff electrode/catheter systems along the left cervical vagus. Forty-eight hours following surgery, each animal received a 3. 0-microliter infusion (1.0 microliter/min) of either lidocaine hydrochloride (75.0 mM) or isotonic saline below the point of stimulation. Animals were then trained 10 min later on an inhibitory-avoidance task with a 0.75-mA, 1.0-s foot shock. Sham stimulation or vagus nerve stimulation (0.5-ms biphasic pulses; 20.0 Hz; 30 s; 0.2, 0.4, or 0.8 mA) was administered immediately after training. Memory, tested 24 h later, was enhanced by stimulation whether descending vagus nerve fibers were inactivated or not. Both lidocaine- and saline-infused groups showed an intensity-dependent, inverted-U-shaped pattern of retention performance, with the greatest effect observed for 0.4 mA ($U = 9$, $p < .05$, and $U = 7$, $p < .01$, respectively). Additionally, animals that received lidocaine infusions, but no vagus nerve stimulation, showed impaired memory compared to the performance of saline-infused control animals ($U = 11$, $p < .05$). Together, these findings suggest that vagal afferents carry messages about peripheral states that lead to the modulation of memory storage and that the memory-enhancing effect produced by vagus nerve stimulation is not mediated via the activation of vagal efferents. Posttraining electrical stimulation of vagal afferents with concomitant vagal efferent inactivation enhances memory storage processes in the rat.

155. **Feliciano L, Henning RJ. Vagal nerve stimulation releases vasoactive intestinal peptide which significantly increases coronary artery blood flow. *Cardiovasc Res.* 1998;40:45-55.**
Abstract: OBJECTIVE: To determine the effects of vasoactive intestinal peptide (VIP), released endogenously from cardiac vagal nerves, on coronary artery blood flow (CBF). METHODS: We determined the effects of vagal nerve stimulation (VNS) at frequencies of 10, 15, 20, and 30 Hz on left circumflex coronary artery (LCx) blood flow. The increases in CBF during VNS were compared with the increases in CBF produced by exogenous VIP and also nitroglycerin (NTG). In 18 anesthetized open chest mongrel dogs, we blocked the muscarinic and beta-adrenergic receptors with atropine and propranolol. We controlled heart rate and aortic pressure by right atrial pacing and an arterial reservoir. CBF was measured in the LCx with a Doppler flow probe. A 25 gauge catheter was placed in the proximal LCx to inject the VIP receptor antagonist [4Cl-D-Phe6Leu17]VIP, VIP, NTG, or vehicle. CBF, aortic and ventricular pressures, ventricular contractility (+dp/dt(max)) and relaxation (-dp/dt(min)) and the EKG were measured. RESULTS: VNS (0.5 ms, 20 V, 5 min.) at 20 Hz maximally increased CBF by 62 +/- 14% at 5 min from 71 +/- 10 to 115 +/- 19 ml/min ($p < 0.01$). VNS at 10, 15, and 30 Hz increased CBF by 6 +/- 1%, 24 +/- 5%, and 24 +/- 7%, respectively (all $p < 0.05$ vs control). Following 20 Hz VNS, CBF returned toward the baseline over 30 min. Aortic and left ventricular (LV) pressures, LV +dp/dt(max) and LV-dp/dt(min) did not significantly change. After the direct administration of [4Cl-D-Phe6Leu17]VIP into the LCx, VNS increased CBF by only 10 +/- 4% ($p = NS$). Exogenous VIP, in doses of 9.0 x 10(-11) to 2.1 x 10(-9) mol, increased CBF by 106 +/- 17% to 169 +/- 17% (all $p < 0.01$ vs control). NTG, in doses of 2.2 x 10(-8) to 1.7 x 10(-7) mol, increased CBF by 101 +/- 15% to 169 +/- 20% (all $p < 0.01$ vs control). These increases in CBF persisted during the 1 to 2 min injection period and returned to the baseline within 5 min. Neither VIP nor NTG significantly changed the heart rate, aortic or LV pressures, LV +dp/dt(max) or LV -dp/dt(min). VNS at 20 Hz, exogenous VIP, 9.0 x

10(-11) mol, and exogenous NTG, 2.2 x 10(-8) to 4.4 x 10(-8) mol, produced equivalent increases in CBF by analysis of variance determination. CONCLUSION: The present experiments suggest that VNS releases VIP which directly dilates coronary arteries and significantly increases coronary artery blood flow. Vagal nerve stimulation releases vasoactive intestinal peptide which significantly increases coronary artery blood flow.

156. **Henry TR, Bakay RA, Votaw JR, 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;39:983-990.**
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 hypothalami, thalami, 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. Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: I. Acute effects at high and low levels of stimulation.

157. **Krahl SE, Clark KB, Smith DC, Browning RA. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia.* 1998;39:709-14.**
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. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation.

158. **Carter LP. Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H2(15)O blood flow imaging. *Neurosurgery.* 1998;42:1196.** Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H2(15)O blood flow imaging.

159. **Loomis CW, Yao D, Bieger D. Characterization of an esophagocardiovascular reflex in the rat. *Am J Physiol.* 1997;272:R1783-91.**
Abstract: A cardiovascular reflex evoked by esophageal distension (ECR) in urethan-anesthetized male Sprague-Dawley rats was studied to 1) determine whether the relevant sensory input from the esophagus is conveyed by vagal and/or spinal afferents and 2) evaluate the effects and sites of action of antinociceptive agents. Esophageal distension evoked a rise in arterial blood pressure and heart rate that increased linearly with the log of inflation pressure (25-150 mmHg). Distension (100 mmHg for 20 s) of the lower esophagus was a more effective stimulus than distension of the upper esophagus. The ECR was attenuated by unilateral and abolished by bilateral cervical vagotomy and dose dependently inhibited by morphine (1.0-4.0 mg/kg iv) or by intrathecal (T4-T5) administration of dexmedetomidine (DX, 0.05-0.5 microgram), but not by intrathecal (T4-T5) morphine (4-16 micrograms) or intrathecal (L1-L2) or intravenous DX (0.05-0.5 microgram). The ECR was also inhibited by capsaicin and by the topical administration of DX or morphine to the solitary complex. The pressor response persisted after intravenous pancuronium, scopolamine, and methscopolamine. The ECR circuit appears to consist of vagal afferents, efferent sympathetic preganglionic pathways originating in the thoracic spinal cord, and bulbospinal neurons yet to be identified. This reflex fulfills some criteria of a nociceptive event, but this interpretation requires further investigation.
Characterization of an esophagocardiovascular reflex in the rat.

160. **Uysal H, Inan LE, Kuli P. Vagal stimulation. *Neurology.* 1996;47:1355-1356.** Vagal stimulation.

161. **Takaya M, Terry WJ, Naritoku DK. Vagus nerve stimulation induces a sustained anticonvulsant effect. *Epilepsia.* 1996;37:1111-6.**

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. Vagus nerve stimulation induces a sustained anticonvulsant effect.

162. **Ko D, Heck C, Grafton S, et al. Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H2(15)O blood flow imaging.** ***Neurosurgery.*** **1996;39:426-30; discussion 430-1.**
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. Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H2(15)O blood flow imaging.

163. **Jones JF, Wang Y, Jordan D. Heart rate responses to selective stimulation of cardiac vagal C fibres in anaesthetized cats, rats and rabbits. *J Physiol.* 1995;489 (Pt 1):203-14.**

Abstract: 1. The contribution of cardiac vagal C fibres to vagal chronotropic control in anaesthetized cats, rats and rabbits was analysed using electrical stimulation of the vagus nerve with a selective anodal block technique. 2. After bilateral vagotomy and pretreatment with atenolol, 10 Hz continuous selective stimulation of unmyelinated fibres in the cut peripheral end of the cervical vagus evoked a bradycardia in anaesthetized rats, cats and rabbits. With this stimulation protocol the three species exhibited a similar lengthening of the heart period (R-R interval) when expressed as a percentage of their basal cardiac interval. 3. The mechanism of action of the selective blocking technique was analysed by recording eighty-nine single A- (n = 12), B- (n = 22) and C-fibre (n = 55) vagal-projecting neurones in the medulla of the rat. This demonstrated that the technique can selectively block conduction in myelinated fibres and that 'break excitation' is seen mainly in unmyelinated fibres. Although thirty C fibres showed break excitation sixteen did not and this difference could not be correlated with their axonal conduction velocity, chronaxie or initial segment frequency following. 4. Using the anodal block technique the vagal effects on heart rate were reanalysed in the cat by incorporating a collision technique. B fibres were activated orthodromically to evoke cardioinhibition and simultaneously antidromically to collide with errant B-fibre spikes activated at the electrode producing anodal block. With this protocol it was noted that the B- and C-fibre bradycardias were not additive. Using a double anodal block and collision technique, it was demonstrated that this phenomenon was likely to be due to occlusion of the effects of B and C fibres. 5. In conclusion, in addition to the well-defined effects of vagal B fibres on heart rate, selective stimulation of vagal C fibres also had a cardioinhibitory effect in all three species studied. However, since the effects of cardiac C fibres on heart rate was small, these neurones alone cannot account for the cardioinhibition of the pulmonary chemoreflex. It is likely that activation of both B- and C-fibre cardiac vagal preganglionic neurones accounts for this reflex cardioinhibition. Heart rate responses to selective stimulation of cardiac vagal C fibres in anaesthetized cats, rats and rabbits.

164. **Naritoku DK, Terry WJ, Helfert RH. Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. *Epilepsy Res.* 1995;22:53-62.**

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. Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve.

165. **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;352:173-8.**
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 microM), the M2 receptor antagonist AQ-RA 741 (0.1 microM) and the beta-adrenoceptor antagonist timolol (1 microM), 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. Conditional involvement of muscarinic M1 receptors in vagally mediated contraction of guinea-pig bronchi.

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

167. **Tougas G, Hudoba P, Fitzpatrick D, Hunt RH, Upton AR. Cerebral-evoked potential responses following direct vagal and esophageal electrical stimulation in humans. *Am J Physiol.* 1993;264:G486-G491.**
Abstract: Cerebral evoked responses following direct electrical stimulation of the vagus and esophagus were compared in 8 epileptic subjects and with those recorded after esophageal stimulation in 12 healthy nonepileptic controls. Direct vagal stimulation was performed using a left cervical vagal pacemaker, which is used in the treatment of epilepsy. Esophageal stimulation was obtained with the use of an esophageal assembly incorporating two electrodes positioned 5 and 20 cm orad to the lower esophageal sphincter. Evoked potential responses were recorded with the use of 20 scalp electrodes. The evoked potential responses consisted of three distinct negative peaks and were similar with the use of either vagal or esophageal stimulation. The measured conduction velocity of the afferent response was 7.5 m/s in epileptic subjects and 10 m/s in healthy controls, suggesting that afferent conduction is through A delta-fibers rather than slower C afferent fibers. We conclude that the cortical-evoked potential responses following esophageal electrical stimulation are comparable to direct electrical stimulation of the vagus nerve and involve mostly A delta-fibers. This approach provides a method for the assessment of vagal afferent gastrointestinal sensory pathways in health and disease. Cerebral-evoked potential responses following direct vagal and esophageal electrical stimulation in humans.

168. **Zabara J. Inhibition of experimental seizures in canines by repetitive vagal stimulation. *Epilepsia.* 1992;33:1005-1012.**
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. Inhibition of experimental seizures in canines by repetitive vagal stimulation.

169. **Hammond EJ, Uthman BM, Reid SA, Wilder BJ. Electrophysiological studies of cervical vagus nerve stimulation in humans: I. EEG effects. *Epilepsia.* 1992;33:1013-1020.**
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. Electrophysiological studies of cervical vagus nerve stimulation in humans: I. EEG effects.

170. **Hammond EJ, Uthman BM, Reid SA, Wilder BJ. Electrophysiologic studies of cervical vagus nerve stimulation in humans: II. Evoked potentials. *Epilepsia.* 1992;33:1021-1028.**
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. Electrophysiologic studies of cervical vagus nerve stimulation in humans: II. Evoked potentials.

171. **Tougas G, Fitzpatrick D, Hudoba P, et al. Effects of chronic left vagal stimulation on visceral vagal function in man. *Pacing Clin Electrophysiol.* 1992;15:1588-1596.**
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. Effects of chronic left vagal stimulation on visceral vagal function in man.

172. **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;15:1572-1578.**
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. Chronic vagus nerve stimulation increases the latency of the thalamocortical somatosensory evoked potential.

173. **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;15:1579-1580.** Regional cerebral blood flow in man manipulated by direct vagal stimulation.

174. **Hammond EJ, Uthman BM, Wilder BJ, et al. Neurochemical effects of vagus nerve stimulation in humans. *Brain Res.* 1992;583:300-303.**
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. Neurochemical effects of vagus nerve stimulation in humans.

175. **Shirai M, Ninomiya I, Sada K. Thromboxane A2/endoperoxide receptors mediate cholinergic constriction of rabbit lung microvessels. *J Appl Physiol.* 1992;72:1179-85.**
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. Thromboxane A2/endoperoxide receptors mediate cholinergic constriction of rabbit lung microvessels.

176. **Joyner MJ, Warner DO, Rehder K. Halothane changes the relationships between lung resistances and lung volume. *Anesthesiology.* 1992;76:229-35.**
Abstract: The authors hypothesized that relaxation of airway smooth muscle by halothane lessens the dependence of airway resistance on lung volume, and that halothane alters the relationship between pulmonary resistance and lung volume by changing both the airway and tissue components of pulmonary resistance. The relationship among airway resistance, tissue resistance, and lung volume was examined in mongrel dogs before and during the administration of halothane, both in airways with reduced smooth muscle tone (after vagotomy) and during moderate increases in smooth muscle tone caused by vagus nerve stimulation (VNS). Resistance were measured at several levels of positive end-expiratory pressure (PEEP, 4-15 cmH2O) using an alveolar capsule technique. Before halothane administration, airway resistance increased at low PEEP; VNS accentuated this increase. Tissue resistance increased at low PEEP only during VNS. Halothane had no significant effect on any resistance before VNS. During VNS, halothane markedly blunted increases in airway resistance and tissue resistance as PEEP decreased. The authors conclude that during stimulation of airway smooth muscle in dogs, halothane attenuates increases in airway resistance and tissue resistance with reductions in lung volume in dogs. Thus, moderate changes in lung volume have little effect on these resistances during halothane anesthesia under these conditions. Halothane changes the relationships between lung resistances and lung volume.

177. **Myers AC, Undem BJ. Analysis of preganglionic nerve evoked cholinergic contractions of the guinea pig bronchus. *J Auton Nerv Syst.* 1991;35:175-84.**
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. Analysis of preganglionic nerve evoked cholinergic contractions of the guinea pig bronchus.

178. **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;14:94-107.**
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 pentylenetetrazol (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. Vagal stimulation reduces the severity of maximal electroshock seizures in intact rats: use of a cuff electrode for stimulating and recording.

179. **Upton AR, Tougas G, Talalla A, et al. Neurophysiological effects of left vagal stimulation in man. *Pacing Clin Electrophysiol.* 1991;14:70-76.** Neurophysiological effects of left vagal stimulation in man.

180. **Habermeier-Muth A, Altes U, Forsyth KM, Muscholl E. A presynaptic excitatory M1 muscarine receptor at postganglionic cardiac noradrenergic nerve fibres that is activated by endogenous acetylcholine. *Naunyn Schmiedebergs Arch Pharmacol.* 1990;342:483-9.**
Abstract: Rabbit atria were isolated with the extrinsic right vagus and sympathetic nerves intact and perfused with Tyrode solution. Noradrenaline overflow evoked by sympathetic nerve stimulation (SNS) at 3 Hz for 3 min was determined before, during, and after vagus nerve stimulation (VNS), also at 3 Hz and for 3 min. The VNS pulses preceded the SNS pulses by 3, 100 and 233 ms. Acetylcholine overflow was determined after labelling of the transmitter stores with [14C]choline. Pirenzepine 80 nmol/l failed to alter the muscarinic inhibition of noradrenaline overflow when the vago-sympathetic impulse intervals were 3 and 233 ms. At an interval of 100 ms VNS did not significantly inhibit noradrenaline overflow in the absence of pirenzepine but produced an inhibition in the presence of the drug. When the pirenzepine concentration was varied (0.4-300 nmol/l) the largest inhibition of noradrenaline overflow was observed at 5.7 nmol/l whereas 300 nmol/l fully antagonized the inhibition. Acetylcholine overflow evoked by VNS was not altered by pirenzepine 0.4-300 nmol/l. AF-DX 116 (11-[(2[(diethylamino)methyl]-1-piperidinyl)-acetyl]-5, 11-dihydro-6H-pyrido-[2,3-b]-[1,4]benzodiazepine-6-one), an M2 receptor selective antagonist, concentration-dependently (100-800 nmol/l) inhibited the decrease of tension development elicited by VNS. At the 100 ms vago-sympathetic impulse interval noradrenaline overflow was enhanced in the presence of AF-DX 116 400 and 800 nmol/l. However, already 100 nmol/l of the drug caused a maximum (fourfold) increase of acetylcholine overflow. It is concluded that acetylcholine released onto noradrenergic nerve fibres causes a small facilitation of noradrenaline overflow at a vago-sympathetic impulse interval of 100 ms.(ABSTRACT TRUNCATED AT 250 WORDS) A presynaptic excitatory M1 muscarine receptor at postganglionic cardiac noradrenergic nerve fibres that is activated by endogenous acetylcholine.

181. **Wendt DJ, Martins JB. Autonomic neural regulation of intact Purkinje system of dogs. *Am J Physiol.* 1990;258:H1420-6.**
Abstract: To characterize autonomic influences on the Purkinje system in vivo, we measured Purkinje relative refractory period (PRRP) in response to sympathetic (SNS) and vagal nerve stimulation (VNS). Effects of SNS on PRRP were primarily mediated via beta-adrenergic mechanisms because shortening of PRRP during SNS [from 215 +/- 7 (SE) to 202 +/- 8 ms, P less than 0.01] was entirely blocked by metoprolol (1 mg/kg). Vagal influences in the ambient state did not prolong PRRP, even when effective refractory period of adjacent muscle did prolong. When VNS was augmented with physostigmine, PRRP prolonged from 205 +/- 12 to 212 +/- 13 ms, P less than 0.05. Similar provocation of parasympathetic effects on PRRP occurred when VNS was performed during SNS; PRRP prolonged from 188 +/- 9 to 193 +/- 9 ms, P less than 0.05. Also, when alpha-adrenergic stimulation was produced by phenylephrine infusion (25 micrograms.kg-1.min-1) in the presence of metoprolol (1 mg/kg), which prolonged PRRP from 242 +/- 8 to 246 +/- 9 ms, P less than 0.05, the addition of VNS further prolonged PRRP from 246 +/- 9 to 253 +/- 9 ms, P less than 0.05. Thus some refractory period responses in the Purkinje system were similar to adjacent muscle, because beta-adrenergic activation shortened refractory period and vagal stimulation antagonized the shortening. Findings unique to Purkinje tissue were refractory period prolongation by vagal stimulation when facilitated by concurrent

prolongation of refractory period during alpha-adrenergic stimulation. Autonomic neural regulation of intact Purkinje system of dogs.

182. **Woodbury DM, Woodbury JW. Effects of vagal stimulation on experimentally induced seizures in rats. *Epilepsia.* 1990;31(suppl 2):S7-S19.**
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/mm2 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. Effects of vagal stimulation on experimentally induced seizures in rats.

183. **Terry R, Tarver WB, Zabara J. An implantable neurocybernetic prosthesis system. *Epilepsia.* 1990;31(suppl 2):S33-S37.**
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. An implantable neurocybernetic prosthesis system.

184. **Rutecki P. Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. *Epilepsia.* 1990;31(suppl 2):S1-S6.**
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 desychronization 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- mercaptoproprionic 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. Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation.

185. **Lockard JS, Congdon WC, DuCharme LL. Feasibility and safety of vagal stimulation in monkey model. *Epilepsia.* 1990;31(suppl 2):S20-S26.**
Abstract: The feasibility, safety, and preliminary effects of chronic vagal stimulation were studied in an aluminagel 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. Feasibility and safety of vagal stimulation in monkey model.

186. **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-S59.**
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. Vagus nerve stimulation in humans: neurophysiological studies and electrophysiological monitoring.

187. **Sada K, Shirai M, Ninomiya I. Vagally and acetylcholine-mediated constriction in small pulmonary vessels of rabbits. *J Appl Physiol.* 1987;63:1601-9.**
Abstract: Using a new X-ray TV system, we analyzed effects of vagal nerve stimulation (VNS; 1-30 Hz) and intravenous injection of acetylcholine (Ach; 0.3-0.9 microgram) on the internal diameter (ID; 100-1,500 microns) of small pulmonary arteries and veins in anesthetized rabbits. In selective segments of the arteries, ID decreased abruptly and maximally by 50-70% in a specific stimulus frequency to the vagal nerve and a dose of ACh. The vasoconstrictor sites were distributed near the branching points of the arteries, particularly those downstream, and their numbers increased with an increase in the stimulus frequencies and ACh doses. The relative frequencies of occurrences were 15.3% with VNS (30 Hz) and 5.3% with ACh (0.9 microgram). In nonselective segments with VNS, ID decreased frequency dependently by 0, 4, 12, and 26% at 1, 4, 15, and 30 Hz, respectively, and with ACh, decreased dose dependently by 21 and 35% with 0.3 and 0.9 microgram, respectively. The vasoconstriction in response to VNS and ACh was attenuated by atropine, enhanced by eserine, and not affected by phentolamine. That vasoconstriction to VNS was abolished by hexamethonium. No selective constriction was found in veins and the ID was decreased uniformly by 1-2% with VNS and ACh. Vagally and acetylcholine-mediated constriction in small pulmonary vessels of rabbits.

188. **Kollai M, Koizumi K. Reciprocal and non-reciprocal action of the vagal and sympathetic nerves innervating the heart. *J Auton Nerv Syst.* 1979;1:33-52.**
Abstract: Simultaneous recordings were made from vagal and sympathetic fibers innervating the heart in dogs anesthetized with chloralose. Reciprocal relationship between the two autonomic nerves was clearly seen in the baroreceptor reflex. Stimulation of chemoreceptors, however, evoked non-reciprocal responses of the two nerves; at the onset of the chemoreceptor reflex cardiac vagal and sympathetic discharges both increased, then, as baroreceptors became excited due to a pressor response, sympathetic nerve activity suddenly decreased while vagal discharges remained high, indicating the appearance of the reciprocal action typifying the baroreceptor reflex. Decrease in ventilatory volume and a slight increase in end-expired CO2 level augmented greatly both vagal and sympathetic discharges. As the phrenic-locked activity of the two nerves (i.e. the activity in vagus nerve occurs only in the absence of phrenic bursts while sympathetic discharges increase with phrenic bursts) increased, the alternate discharges between the two nerves became more conspicuous and the heart rate fluctuated with the respiratory (phrenic) rhythm. Thus, strong reciprocity between vagus and sympathetic can result in an oscillatory heart rate. When ventilatory volume was increased, both nerve activities decreased below control level. Mild hypoxia had similar effects to hypercapnia though changes in nerve activity were greater. When coactivation of vagal and sympathetic nerve was produced in reflex

action, changes in vagal discharges occurred earlier and faster than in the sympathetic fibers. The magnitude of change in vagus activity was also far greater. The elimination of afferents in the vagi, the aortic and sinus nerves reduced cardiac vagal activity greatly. However, discharges were still present and occurred between phrenic bursts, indicating that the vagal "tone" is maintained centrally as well as peripherally by input from receptors in the cardiovascular system. The physiological significance of reciprocal and non-reciprocal control of vagal and sympathetic nerves innervating the heart was discussed. Reciprocal and non-reciprocal action of the vagal and sympathetic nerves innervating the heart.

189. Mei N. Vagal glucoreceptors in the small intestine of the cat. *J Physiol.* 1978;282:485-506.

Abstract: 1. In anaesthetized cats, the unitary activity of seventy-eight sensory vagal neurones was recorded in nodose ganglia by means of extracellular glass microelectrodes. 2. These neurones were stimulated by perfusion of the small intestine (duodenum and first part of jejunum) with glucose or other different carbohydrates at concentrations of 1--20 g/l. (i.e. 55--1100 m-osmole/l.). 3. The neurones were slowly adapting to stimulation and their discharge frequency was always low (1--30 Hz). 4. The activity of these neurones depended on the particular carbohydrate used and on its concentration: the discharge frequency generally increased when the concentration rose. 5. The neurones were of the C type (conduction velocities: 0.8--1.4 m/sec; mean, 1.1 m/sec). 6. In contrast with the known neurones connected to the gastro-intestinal tension receptors, they were not obviously activated by intestinal contractions or distensions. 7. In the same way, the stimuli which produced the response of other known endings, i.e. the mucosal receptors, were not effective; these stimuli included in particular stroking of the mucosa, over-distension of the bowel, intestinal perfusion with alkaline or acid solutions. On the other hand, the use of substances other than glucose (KCl and NaCl of the same osmolarity) showed that the osmotic pressure was not directly related to the receptor activation. 8. Therefore it is proposed to call the endings corresponding to these neurones 'glucoreceptors'. 9. The effect of glycaemia and intestinal motility were also studied. These variables acted presumably by changing the intestinal absorption rate. 10. The functional characteristics of the glucoreceptors (in particular the short latency of their response) strongly suggested that they were located close to the intestinal epithelium. 11. An ultrastructural study was performed in an attempt to identify the histological site of the receptors. Many non-medullated fibres were observed in the villi, especially beneath the epithelial layer. They gave complex branchings with abundant swellings. Some of them, at least, belonged to the vagal sensory component, because they were less numerous after unilateral selective sensory vagotomy. Therefore these complex endings could serve as the vagal glucoreceptors. 12. The roles of vagal intestinal glucoreceptors are discussed. Their functional characteristics as well as the clinical and experimental data suggest that they may be involved in the regulation of different types of alimentary behaviour (hunger, thirst, alliesthesia) and energy balance. Vagal glucoreceptors in the small intestine of the cat.

190. Kolman BS, Verrier RL, Lown B. Effect of vagus nerve stimulation upon excitability of the canine ventricle. Role of sympathetic-parasympathetic interactions. *Am J Cardiol.* 1976;37:1041-1045.

Abstract: The effect of vagus nerve stimulation on ventricular excitability was studied in 28 dogs under various conditions of adrenergic neural tone. Strength-interval curves were

delineated from the apex of the right ventricular endocardium with a transvenous bipolar catheter. Vagus nerve stimulation in both closed chest and open chest dogs shifted the strength-interval curve 6 to 8 msec later into electrical diastole (P less than 0.001). Left stellate ganglion stimulation shifted the strength-interval curve 9 to 11 msec earlier into diastole (P less than 0.001). The effect of simultaneous left stellate ganglion and vagus nerve stimulation was not significantly different from that of left stellate ganglion stimulation alone. The influence of vagus nerve stimulation on the strength-interval curve under basal conditions was abolished by acute beta adrenergic blockade with propranolol. It is concluded that vagus nerve stimulation affects ventricular excitability as well as vulnerability by opposing the effects of sympathetic neural tone. Effect of vagus nerve stimulation upon excitability of the canine ventricle. Role of sympathetic-parasympathetic interactions.

191. **Kolman BS, Verrier RL, Lown B. The effect of vagus nerve stimulation upon vulnerability of the canine ventricle: role of sympathetic-parasympathetic interactions. *Circulation.* 1975;52:578-85.**
Abstract: The effect of vagus nerve stimulation (VNS) upon ventricular vulnerability was studied in 30 mongrel dogs subjected to varying levels of adrenergic stimulation. Vulnerability was assessed both by determining the minimum current required to produce ventricular fibrillation (VF threshold) and by plotting VF threshold throughout the vulnerable period (VF zone). Chloralose-anesthetized animals were studied by means of sequential pulses applied to the apex of the right ventricular endocardium. Testing was carried out in closed-chest dogs, in open-chest dogs with and without left stellate ganglion stimulation (LSGS), and in open- and closed-chest dogs pretreated with propranolol. In the absence of adrenergic stimulation. VNS was without significant effect on either the VF threshold or the VF zone under closed- or open-chest conditions. During LSGS, however, VNS was associated with a 93 +/- 22% (mean +/- SE) increase in VF threshold (P less than 0.01) and constriction of the VF zone. Vagus nerve stimulation combined with LSGS raised VF threshold to the control value, but not beyond. After beta-adrenergic blockade with propranolol, VNS was without effect on VF threshold in either open- or closed-chest animals. It is concluded that augmented sympathetic tone is a precondition for a VNS-induced elevation in VF threshold. The vagal effect is indirect and is expressed by opposing the effects of heightened adrenergic tone on ventricular vulnerability. The effect of vagus nerve stimulation upon vulnerability of the canine ventricle: role of sympathetic-parasympathetic interactions.

192. **Foley JO, DuBOIS FS. Quantitative studies of the vagus nerve in the cat. *J Comp Neurol.* 1937;67:49-87.**

MR/DD Population

1. **Huber B, Seidel M. Update on treatment of epilepsy in people with intellectual disabilities. *Curr Opin Psychiatry.* 2006;19:492-496.**
   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. Update on treatment of epilepsy in people with intellectual disabilities

2. **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;6:417-23.**
   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. 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.

3. **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-S64.**
   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. Management of epilepsy in mentally retarded children using the newer antiepileptic drugs, vagus nerve stimulation, and surgery.

4. **Wilfong AA. Treatment considerations: role of vagus nerve stimulator. *Epilepsy Behav.* 2002;3:S41-S44.**
   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. Treatment considerations: role of vagus nerve stimulator.

5. **Devinsky O. What do you do when they grow up? Approaches to seizures in developmentally delayed adults. *Epilepsia.* 2002;43(suppl 3):71-79.**
   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 mediations are

worthwhile. Vagus nerve stimulation and epilepsy surgery for those with medically refractory epilepsy may be options after careful evaluation. What do you do when they grow up? Approaches to seizures in developmentally delayed adults.

6. **Gates J, Huf R, Frost M. Vagus Nerve Stimulation for Patients in Residential Treatment Facilities. *Epilepsy Behav.* 2001;2:563-567.**
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. Vagus Nerve Stimulation for Patients in Residential Treatment Facilities.

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

Myoclonic Seizures/Syndromes (Pediatric)

1. **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: 279-83.**
   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. Vagus nerve stimulation in children with mitochondrial electron transport chain deficiencies.

2. **Wheless JW, Sankar R. Treatment strategies for myoclonic seizures and epilepsy syndromes with myoclonic seizures. Epilepsia 2003:44(suppl 11): 27-37.**
   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. Treatment strategies for myoclonic seizures and epilepsy syndromes with myoclonic seizures.

Non-English Articles

1. **Simoni RF, Cangiani LM, Pereira AM, Abreu MP, Cangiani LH, Zemi G . [Efficacy of intraoperative methadone and clonidine in pain control in the immediate postoperative period after the use of remifentanil].** ***Rev Bras Anestesiol.*** **2009;59:421-30.** [Portuguese]
   Abstract: BACKGROUND AND OBJECTIVES: Due to its pharmacokinetic characteristics, remifentanil does not promote residual analgesia in the immediate postoperative period. The objective of this study was to compare the efficacy of methadone and clonidine in the control of postoperative pain of videolaparoscopic surgeries under total intravenous anesthesia with target-controlled remifentanil infusion. METHODS: One hundred and twenty-six patients, ages 18 to 65 years, ASA I and II, of both genders, scheduled for laparoscopic surgeries, participated in this randomized, double- blind, placebo-controlled study. After venipuncture, intravenous ketoprofen and dypirone were administered. Target-controlled infusion of remifentanil and propofol was used for induction and maintenance of anesthesia. Before beginning the procedure, an intravenous solution containing 0.1 mg.kg-1 of methadone (methadone group), 2.0 (1/4)g.kg-1 of clonidine (clonidine group), or NS (placebo group) was administered. In the post-anesthetic care unit, postoperative pain was evaluated by the Verbal Numeric Scale (VNS). Absence of pain was defined as a score < 2, and pain as a score of > 3. RESULTS: The incidence of pain in the methadone group was significantly lower than in the clonidine and placebo groups (11, 21, and 23, respectively; $p < 0.02$). Significant differences in the incidence of pain in the placebo and clonidine groups were not observed. CONCLUSIONS: Methadone was more effective than clonidine in the control of postoperative pain in videolaparoscopic surgeries under total intravenous anesthesia with remifentanil; and using clonidine was not better than not using it. Efficacy of intraoperative methadone and clonidine in pain control in the immediate postoperative period after the use of remifentanil.

2. **Aliev RR. [Computer simulation of the sinoatrial node pacemaker synchronization in response to periodic stimulation of the vagus nerve].** ***Biofizika.*** **2008;53:1125-8.** [Russian]
   Abstract: The effect of periodic stimulation of the vagus nerve on the activity of the central cell of the sinoatrial node has been simulated. The regions of synchronization and desynchronization have been revealed, and the phase shift at different stimulation frequencies has been estimated. The positive chronotropic effect has been shown to occur at some frequencies of stimulation. Computer simulation of the sinoatrial node pacemaker synchronization in response to periodic stimulation of the vagus nerve.

3. **Kawai K. [Vagus nerve stimulation for intractable epilepsy: implantation of vagus nerve stimulator].** ***No Shinkei Geka.*** **2008;36:979-89.** [Japanese]

4. **Garcia-March G, Sanchez-Ledesma MJ, Broseta J. [Vagus nerve stimulation for the treatment of refractory epilepsy. State of the art].** ***Neurocirugia (Astur).*** **2008;19:416-26.** [Spanish]
   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. Vagus nerve stimulation for the treatment of refractory epilepsy. State of the art.

5. **Roux FX, Turak B, Landre E. [Vagus nerve stimulation for the treatment of refractory epilepsy].** ***Neurochirurgie.*** **2008;54:332-9.** [French]
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. Vagus nerve stimulation for the treatment of refractory epilepsy.

6. **Bottai T. [Non-drug treatment for depression].** ***Presse Med.*** **2008;37:877-82.** [French]
Abstract: The principal alternatives to pharmacological treatment of major depressive disorder (besides electroconvulsive therapy) are different forms of psychotherapy, frequently used in combination with antidepressant drugs. The types of psychotherapy that have proven efficacy are mainly cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT). The efficacy of psychoanalytic therapy has not been proven in methodologically sound studies, despite its frequent use. Repetitive transcranial magnetic stimulation appears promising for some subtypes of depression. Vagal nerve stimulation is most often combined with antidepressant drugs for treatment-resistant depression. Light therapy, also called phototherapy, is frequently combined with sleep deprivation. It appears effective in some subtypes of depression. It is often prescribed together with antidepressants. Non-drug treatment for depression.

7. **Huang J, Zhang NC, Zhou J, Yang ZH. [Effects of stimulation of intact vagus nerve on systemic inflammatory response in rats].** ***Zhonghua Shao Shang Za Zhi.*** **2008;24:99-101.** [Chinese]
Abstract: OBJECTIVE: To observe the effects of stimulation of intact vagus nerve (IVNS) on systemic inflammatory response in rats. METHODS: The model of systemic inflammatory response was reproduced by lipopolysaccharide (LPS). One hundred Sprague Dawley rats were randomly divided into A group (with intravenous injection of LPS), B group (with stimulation of efferent nerve trunk of vagus nerve after intravenous injection of lipopolysaccharide and vagotomy), C group (with stimulation of intact vagus nerve after intravenous injection of LPS), D group (with vagus nerve stimulation after injection of equivalent isotonic saline), E group (with intravenous injection of equivalent isotonic saline), with 20 rats in each group. Five rats of each group were used to determine mean

aortic pressure (MAP) before injection and l0 min, 0.5 h, 1 h, 2 h, 4 h and 6 h after injection. The serum levels of tumor necrosis factor (TNF) alpha and interleukin (IL) 10 were determined with enzyme linked immunosorbent assay before injection and 2, 4 and 6 hour after injection. RESULTS: The level of MAP rose in A, B, C groups at 10 min after injection, especially in A group (134.40 +/- 7.3 mm Hg, l mm Hg = 0.033 kPa, $P < 0.05$), but it dropped in above groups at 30 min after injection. The level of MAP in A group was obviously lower than that in B, C groups during 10 min -6 h after injection. The serum level of TNF-alpha in A group was significantly higher than that in B, C groups at 2, 4, 6 hours after injection ($P < 0.05$). Compared with that in C group, the serum level of IL-10 in A, B groups lowered markedly at 4, 6 hours after injection ($P < 0.05$). CONCLUSION: IVNS can stabilize hemodynamics and exert have anti-inflammatory effects at early stage of systemic inflammatory response. Effects of stimulation of intact vagus nerve on systemic inflammatory response in rats.

8. **Shuper A. [Epilepsy in Israel--2008]. *Harefuah.* 2008;147:134-5, 182.** [Hebrew]
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. Epilepsy in Israel--2008.

9. **Heyman E, Lahat E, Lotan G. [Vagal nerve stimulation for refractory epilepsy in children]. *Harefuah.* 2008;147:136-8, 182.** [Hebrew]
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. Vagal nerve stimulation for refractory epilepsy in children.

10. **Dietrich S, Smith J, Scherzinger C, et al. [A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI]. *Biomed Tech (Berl).* 2008;53:104-11.** [German]
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. A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI.

11. **Schlapfer TE. [Brain stimulation methods for resistance to therapy]. *Nervenarzt.* 2007;78 Suppl 3:575-81; quiz 582-3.** [German]
Abstract: In psychiatry there is growing awareness of the urgent need for treatment of patients with severe depression who are refractory to treatment. While highly efficacious over its nearly 70-year history, electroconvulsive treatment is tainted with two basic disadvantages: high relapse quotas and sometimes extensive cognitive side effects. Therefore novel methods of brain stimulation are being employed: transcranial magnetic stimulation, magnetic seizure stimulation, vagus nerve stimulation, and deep brain stimulation. These four techniques are used in individual cases but still outside the framework of scientific research studies. Their clinical effects and effectivity require further definition. This paper reports the current status of brain stimulation methods and describes possible further developments. Brain stimulation methods for resistance to therapy.

12. **Braga RJ, Petrides G. [Somatic therapies for treatment-resistant psychiatric disorders]. *Rev Bras Psiquiatr.* 2007;29 Suppl 2:S77-84.** [Portuguese]
Abstract: OBJECTIVE: This paper reviews the current knowledge of somatic treatment in psychiatry, with a focus on treatment-resistant psychiatric disorders. METHOD: A computerized search of the literature was conducted on Medline using the words "electroconvulsive therapy", "transcranial magnetic stimulation", "vagus nerve stimulation", "deep brain stimulation" and "magnetic seizure therapy". References from each paper were also screened. RESULTS: The development of new non-pharmacological psychiatric interventions in the past decades has renewed the clinical and research interest in somatic therapies. Although electroconvulsive therapy remains the only somatic treatment with undisputed efficacy, transcranial magnetic stimulation, magnetic seizure therapy, vagus nerve stimulation and deep brain stimulation all offer potential as novel means of psychiatric treatment. CONCLUSIONS: New treatment modalities still have an insufficient body of data. Notwithstanding, biological strategies continue to hold promise as a safer and more effective approach to psychiatric treatment. Somatic therapies for treatment-resistant psychiatric disorders.

13. **Tamaoki T, Motohashi N. [Other treatments for depressive patients]. *Nippon Rinsho.* 2007;65:1655-9.** [Japanese]
Abstract: Electroconvulsive therapy (ECT) is one of the most important methods in treating depressive patients especially who can not be improved with medication. Meta analysis shows that ECT is superior to pharmacotherapy as acute treatment for depression. ECT was invented in 1938, and it took some improvement afterwards such as development of modified ECT and introduction of brief-pulse stimulation for the purpose of reducing adverse effects. However, adverse effects such as cognitive impairment are not completely solved, and some patients do not respond to ECT. Transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS) are under investigation to get over the shortcomings of ECT. Other treatments for depressive patients.

14. **Bauer J. [Treatment of epilepsy in adults. Options and strategies]. *Nervenarzt.* 2007;78 Suppl 1:27-35; quiz 36.** [German]
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. Treatment of epilepsy in adults. Options and strategies.

15. **Kawai K. [Less invasive treatment of intractable epilepsy--vagus nerve stimulation and stereotactic radiosurgery]. *Brain Nerve.* 2007;59:299-311.** [Japanese]
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. Less invasive treatment of intractable epilepsy--vagus nerve stimulation and stereotactic radiosurgery.

16. **Gorczyca I, Zwolinski P, Roszkowsk M, Niemcewicz S. [Vagus nerve stimulation in severe, treatment-resistent depression]. *Psychiatr Pol.* 2006;40:1137-42.** [Polish]
Abstract: Since a few years, attempts are taken at the application of vagus nerve stimulation in the treatment of severe depression. It appears that the vagus nerve exerts a direct influence on areas of the brain associated with the regulation of mood and increases the level of biogenic amines. What is more, studies have confirmed an increased activity of fronto-orbital and prefrontal cortex, hypothalamus, cingulum and an increased concentration of serotonin and noradrenalin in the CNS and in the cerebro-spinal fluid. Preliminary clinical trials have confirmed the efficacy, good tolerance and safety of this treatment modality, although some objections have been raised whether these promising results were not partly due to the placebo effect. Therefore new, multicenter clinical studies have been designed, enabling an unbiased evaluation of usefulness of this method in the treatment of depression. Vagus nerve stimulation in severe, treatment-resistent depression.

17. **Engelsen BA. [Vagus nerve stimulation]. *Tidsskr Nor Laegeforen.* 2006;126:895 .** [Norwegian] [Vagus nerve stimulation]. Tidsskr Nor Laegeforen.

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

19. **Liu P, Guo JH, Zhang HC, Sun JL, Yi Z, Liu G. [Vagal effects on inducibility of atrial fibrillation at different sites of pulmonary veins after autonomic denervation].** ***Zhonghua Yi Xue Za Zhi.*** **2006;86:317-20.** [Chinese]
Abstract: OBJECTIVE: To investigate the vagal effects on the inducibility of atrial fibrillation (AF) at different sites of pulmonary vein after autonomic denervation. METHODS: The bilateral cervical vagal trunks of 10 male mongrel dogs were isolated and decentralized. The ansae subclaviae were exposed, ligated, and cut. Needle electrodes were inserted into the subcutaneous tissue of the 4 extremities to record the myocardiogram. Right ventricle electrode was introduced via femoral vein and an electrode with 4 poles was sutured with the right appendage (RAA), left appendage (LAA), left atrium (LA), left superior pulmonary vein (LSPV), right superior pulmonary vein (RSPV), left inferior pulmonary vein (LIPV), and right inferior pulmonary vein (RIPV) respectively. Local burst stimulation (S1S1 = 80 ms, impulse duration = 0.5 ms) was performed on these sites to record the baseline AF inducibility. When sinus cardiac arrest for 2 s or complete atrio-ventricular block occurred programmed bilateral vagal nerves stimulation (VNS) was performed with the frequency of 12.5 Hz, impulse duration of 0.5 ms, and voltage of 5-8 V. Atropine 0.04 mg/kg was dripped intravenously. The changes of AV inducibility were observed. RESULTS: In the baseline state, S1S1 programmed stimulation on all the sites evoked single or multiple atrial premature beats and short runs of atrial tachycardia, only a few sites induced AF. However, S1S1 programmed stimulation combined with VNS significantly increased the frequencies of induced AV at the sites of 4 PVs ($P < 0.05$, $P < 0.01$). When atropine was dripped the AV induction rates at all sites did not changed significantly (all $P > 0.05$). CONCLUSION: Vagal nerve may play an important role in the initiation of AF originating from pulmonary veins. Vagal effects on inducibility of atrial fibrillation at different sites of pulmonary veins after autonomic denervation.

20. **Akamatsu N. [Newer treatment of epilepsy--brain pacemakers and transcranial magnetic stimulation]. *Rinsho Shinkeigaku.* 2005;45:928-930.** [Japanese]
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 traials 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. Newer treatment of epilepsy--brain pacemakers and transcranial magnetic stimulation.

21. **Berney A, Vingerhoets F. [Novel brain stimulation techniques: therapeutic perspectives in psychiatry] . *Rev Med Suisse.* 2005;1:2162-4, 2166.** [French]
Abstract: Recent advances have allowed the development of new physical techniques in neurology and psychiatry, such as Transcranial Magnetic Stimulation (TMS), Vagus Nerve Stimulation (VNS), and Deep Brain Stimulation (DBS). These techniques are already recognized as therapeutic approaches in several late stage refractory neurological disorders (Parkinson's disease, tremor, epilepsy), and currently investigated in psychiatric conditions, refractory to medical treatment (obsessive-compulsive disorder, resistant major depression). In Paralell, these new techniques offer a new window to understand the neurobiology of human behavior. Novel brain stimulation techniques: therapeutic perspectives in psychiatry.

22. **Sanchez-Alvarez JC, Altuzarra-Corral A, Mercade-Cerda JM, 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;40:743-750.** [Spanish]
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. The Andalusia Epilepsy Society's Guide to Epilepsy Therapy 2005: IV. General principles of antiepileptic polytherapy and therapeutic strategies in refractory epilepsy.

23. **[Therapies for Lennox-Gastaut syndrome].** ***Srp Arh Celok Lek.*** **2005;133:283-287.** [Serbian]
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. Therapies for Lennox-Gastaut syndrome.

24. **Adan J, Escosa M, Ayuso-Mateos JL. [Vagus nerve stimulation and psychosis. A single case report].** ***Actas Esp Psiquiatr.*** **2005;33:130-4.** [Spanish]
Abstract: The appearance of behavioral disorders in the context of a decrease in the number of seizures in epileptic patients is a fact that was already described in Landolt's theory of forced normalization in the middle of the XX century. Through this clinical case, we propose several mechanisms that aim to give a general explanation to the physiopathology of this condition. Among them, the theory which suggests increased alertness as a result of inhibitory mechanisms secondary to a long lasting epileptic condition stands out. In addition, we consider the possibility that left vagus nerve stimulation (VNS), a procedure used as a second line treatment in epileptic patients refractory to multiple drug therapy, may cause an inhibitory reaction of similar characteristics as the previously described, and could therefore lead to different psychiatric disorders. Lastly, we bring up several alternatives that will try to throw some light on the physiopathological condition that leads to the chronification of this disease, the theory regarding a cognitive deterioration associated to the appearance of negative symptoms in patients with temporal lobe epilepsy standing out. Vagus nerve stimulation and psychosis. A single case report.

25. **Biraben A, Stefani C. [Vagal nerve stimulation as a treatment of epilepsy].** ***Rev Neurol (Paris).*** **2005;161:128-32.** [French]
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. Vagal nerve stimulation as a treatment of epilepsy.

26. **Hajnsek S, Sporis D, Poljakovic Z, Basic S, Bielen I. [Minimally invasive neurosurgical methods in treatment of pharmacoresistant epilepsy].** ***Acta Med Croatica.*** **2005;59:51-4.** [Croatian]
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. Minimally invasive neurosurgical methods in treatment of pharmacoresistant epilepsy.

27. **Gil-Nagel A. [News treatments in epilepsy.].** ***Neurologia.*** **2004;19(suppl 2):22-27.** [Spanish]
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. News treatments in epilepsy.

28. **Magdaleno-Madrigal VM. [Electrical stimulation of the vagal nerve: from experimental to clinical aspects.].** ***Rev Neurol.*** **2004;39:971-977.** [Spanish]
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. Electrical stimulation of the vagal nerve: from experimental to clinical aspects.

29. **Landre E. [Vagus nerve stimulation and refractory partial epilepsies].** ***Rev Neurol (Paris).*** **2004;160 Spec No 1:5S280-7.** [French]
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. Vagus nerve stimulation and refractory partial epilepsies.

30. **Halasz P, Vajda J, Czirjak S. [Surgical treatment of epilepsy].** ***Ideggyogy Sz.*** **2004;57:189-205.** [Hungarian]
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 resistent 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 hemispherial epilepsies). The algorhythms of the presurgical evaluation and the current methods for study the pacemaker area, forbidden zones, and hemispherial functions are treated. The currently used type and techniques of surgery, such as lesionectomy, temporal lobe resections, hemispherotomy, callosotomy, multiple subpial transsections 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. Surgical treatment of epilepsy.

31. **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;38:161-9; discussion 170-1.** [Polish]
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. Vagus nerve stimulation in drug-resistant epilepsy. Experience with 23 patients.

32. **Chang KH, Hanaoka K. [Intraoperative coronary spasm in non-cardiac surgery].** ***Masui.*** **2004;53:2-9.** [Japanese]
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. Intraoperative coronary spasm in non-cardiac surgery.

33. **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;37:1113-25.** [Polish]
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. 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.

34. **Cuellar R, Molinero M. [The treatment of children with difficult to control epilepsy].** ***Rev Neurol.*** **2003;37:371-375.** [Spanish]
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. The treatment of children with difficult to control epilepsy.

35. **Kellinghaus C, Loddenkemper T, Moddel G, et al. [Electric brain stimulation for epilepsy therapy].** ***Nervenarzt.*** **2003;74:664-676.** [German]
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"). Electric brain stimulation for epilepsy therapy.

36. **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;37:573-86.** [Polish]
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. Vagus nerve stimulation (VNS) in the treatment of drug-resistant epilepsy. A 4-year follow-up evaluation of VNS treatment efficacy.

37. **Nakken KO, Henriksen O, Roste GK, Lossius R. Vagal nerve stimulation--the Norwegian experience.** ***Seizure.*** **2003;12:37-41.**
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. Vagal nerve stimulation--the Norwegian experience.

38. **Zhang J, Zhang J. [The influence of vagus nerve stimulation on NMDAR1 mRNA and GABAAR alpha 1 mRNA in thalamic reticular neucus of pentylenetetrazole-induced epileptic rats].** ***Sheng Wu Yi Xue Gong Cheng Xue Za Zhi.*** **2002;19:566-8.** [Chinese]
Abstract: To study the antiepileptic mechanism of vagus nerve stimulation (VNS), we used the methods of in situ hybridyzation and image analysis to detect the expression of NMDAR1 mRNA and GABAA receptor alpha 1 subunit mRNA (GABAAR alpha 1 mRNA) in the thalamic reticular nuclus. The results show that the NMDAR1 mRNA expression of rats administered pentylenetetrazole(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 nuclus 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(GABAR) in thalamic reticular nuclus. So the formation and development of seizures are inhibited. The influence of vagus nerve stimulation on NMDAR1 mRNA and GABAAR alpha 1 mRNA in thalamic reticular neucus of pentylenetetrazole-induced epileptic rats.

39. **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]
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. Indications and results of nonpharmacological treatments of epilepsies: vagal stimulation, ketogenic diet and gamma rays.

40. **Rush AJ, Linden M, Zobel A. [Vagus nerve stimulation. A potential therapy for chronic/recurrent depression?]. *Fortschr Neurol Psychiatr.* 2002;70:297-302.** [German]
Abstract: Vagus Nerve Stimulation (VNS) is since the 1990 a clinically useful anticonvulsant therapy for treatment-resistant epilepsy. Open acute and longer term data suggest the potential clinical utility of VNS as an antidepressant therapy especially in treatment refractory depression. The vagus nerve has connections to the limbic system and other brain structures which modulate affect. PET studies showed functional changes under VNS in such critical areas, which can explain the mechanisms of action of VMS. Ongoing studies will have to better establish its acute and longer-term efficacy, and specific indications in the treatment of depression. Vagus nerve stimulation. A potential therapy for chronic/recurrent depression?

41. **Iriarte J, Urrestarazu E, L zaro D, Schlumberger E. [Vagal stimulation in the treatment of epilepsy]. *Rev Neurol.* 2002;34:511-518.** [Spanish]
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. Vagal stimulation in the treatment of epilepsy.

42. **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;145:2229-2234.** [Dutch]
Abstract: OBJECTIVE: To describe the mechanism and first results of vagus nerve stimulation at the Medisch Spectrum Twenty, 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. Vagus nerve stimulation in patients with drug-resistant epilepsy.

43. **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;145:2223-2228.** [Dutch]
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 I 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. Dutch Collaborative Epilepsy Surgery Program: reduction of seizures, operative complications and tapering of medication in 338 patients, 1973-1998.

44. **Kirchner A, Birklein F, Stefan H, Handwerker HO. [Vagus nerve stimulation - a new option for the treatment of chronic pain syndromes?].** ***Schmerz.*** **2001;15:272-277.** [German]
Abstract: Electrical stimulation of the vagal nerve (VNS) has become an established method for treating medically refractory epilepsies. From animal experiments it is well known that depending on the stimulation intensity VNS can elicit both inhibition and facilitation of nociception. Recent physiologic investigations demonstrated a similar influence of VNS on pain perception in patients treated by chronic VNS. However, in humans, a more marked effect was shown for the pain inhibition which is probably mediated by neurobiochemical mechanisms. These findings are discussed in consideration of the physiologic mechanisms underlying the modulation of pain and seizures by VNS known from animal studies. First reports of attenuation of chronic pain by VNS indicate that the method might be an option for pain treatment in the future. Vagus nerve stimulation - a new option for the treatment of chronic pain syndromes?

45. **Sadzot B, Martin D. [How I treat ... refractory epilepsy by vagal nerve stimulation]. *Rev Med Liege.* 2001;56:407-410.** [French]
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. How I treat ... refractory epilepsy by vagal nerve stimulation.

46. **Nakken KO, Henriksen O, Roste GK, Lossius R. [Chronic intermittent vagal nerve stimulation--a new therapeutic approach in epilepsy]. *Tidsskr Nor Laegeforen.* 2001;121:1582-1585.** [Norwegian]
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? Chronic intermittent vagal nerve stimulation--a new therapeutic approach in epilepsy.

47. **Devaux B, Chassoux F, Landre E, et al. [Functional neurosurgery for epilepsy]. *Ann Fr Anesth Reanim* . 2001;20:137-144.** [French]
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. Functional neurosurgery for epilepsy.

48. **Spatt J, Pelzl G, Mamoli B, Zartl M. [Current problems in epilepsy]. *Wien Klin Wochenschr.* 1999;111:705-712.** [German]
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. Current problems in epilepsy.

49. **Bednarek N, Motte J. [Treatment and followup of epilepsy in children]. *Rev Prat.* 1999;49:1532-1539.** [French]
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. Treatment and followup of epilepsy in children.

50. **Archila R, Papazian O. [Lennox-Gastaut syndrome]. *Rev Neurol.* 1999;29:346-349.** [Spanish]
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. Lennox-Gastaut syndrome.

51. **Alvarez LA, Dean P, Jayakar P, et al. [Epilepsy treatment by vagal stimulation]. *Rev Neurol.* 1999;29:385-387.** [Spanish]
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 pectorial 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. Epilepsy treatment by vagal stimulation.

52. **Hajnsek S, Poljakovic Z. [A new minimally invasive neurosurgery method in the treatment of refractory epilepsy: vagus nerve stimulator implantation]. *Lijec Vjesn.* 1999;121:42.** [Croatian] A new minimally invasive neurosurgery method in the treatment of refractory epilepsy: vagus nerve stimulator implantation.

53. **Mauguiere F. [Intermittent chronic stimulation of the vagus nerve: a last chance for palliative treatment of drug-resistant epileptic seizures?]. *Rev Neurol (Paris).* 1996;152:231-233.** [French] Intermittent chronic stimulation of the vagus nerve: a last chance for palliative treatment of drug-resistant epileptic seizures?

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

55. **Tomovic M. [Therapy of epilepsy with stimulation of the vagus nerve].** ***Vojnosanit Pregl.*** **1994;51:143-146.** [Serbian] Therapy of epilepsy with stimulation of the vagus nerve.

56. **Shioya T, Kagaya M, Onodera A, Miura S, Miura K, Miura M. [The bronchodilating effect of pirenzepine].** ***Arerugi.*** **1991;40:1334-8.** [Japanese]
Abstract: The purpose of this study was to clarify the bronchodilating effect of pirenzepine (PZ) and to verify its mechanism. Ten asthmatic patients (6 men, 4 women: aged 20 to 65, 5 atopic 5 non-atopic) and ten non-asthmatic volunteers (8 men, 2 women: aged 25 to 60) were studied. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1.0) and peak expiratory flow rate (PEFR) were measured after intravenous administration of 20 mg PZ. PZ increased FVC, FEV1.0 and PEFR significantly by 15%, 29% and 37% respectively in asthmatic patients (p less than 0.01). We also studied the effects of PZ on the contractile responses of tracheal smooth muscle to intra-arterially administered acetylcholine (ACh) and the electrical stimulation of the vagus nerves (VNS) using isometric technique in situ in 5 mongrel dogs. PZ significantly inhibited the contractile responses elicited with ACh at doses larger than 1000 micrograms/kg (p less than 0.01). PZ also significantly inhibited the contractile responses elicited by VNS at doses larger than 100 micrograms/kg (p less than 0.01). These data demonstrate that intravenously administered PZ dilates the airway in asthmatic patients and also suggest that the bronchodilating effect of PZ related to inhibition of the M1 and M3 muscarinic receptors. The bronchodilating effect of pirenzepine.

Nursing Perspective

1. **Kennedy PA, Schallert G. Practical issues and concepts in vagus nerve stimulation: a nursing review . J Neurosci Nurs 2001:33: 105-112.**
   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. Practical issues and concepts in vagus nerve stimulation: a nursing review.

2. **Doerksen K, Klassen L. Vagus nerve stimulation therapy: nurses role in a collaborative approach to a program. Axone 1998:20: 6-9.**
   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. Vagus nerve stimulation therapy: nurses role in a collaborative approach to a program.

3. **Durm K. Vagal stimulator helps patients control seizures. Nurs Spectr (Wash D C) 1998:8: 7.** Vagal stimulator helps patients control seizures.

4. **Harkins M, Thomas T, Cooper H. Vagal nerve stimulation: nursing implications. Clin Nurs Pract Epilepsy 1997:4: 11-12.** Vagal stimulator helps patients control seizures.

5. **Michael JE. Vagal nerve stimulation in treatment of intractable partial seizures: nursing implications. J Neurosci Nurs 1992:24: 19-23.**
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. Vagus nerve stimulation for intractable seizures: one year follow-up.

Outcome Measures for VNS Therapy

1. **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: 375-8.**
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. Outcome measurement after vagal nerve stimulation therapy: proposal of a new classification.

2. **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: 222-225.**
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. Seizure control after stimulation of the vagus nerve: clinical outcome measures.

Parameters

1. **Manta S, Dong J, Debonnel G, Blier P. Optimization of vagus nerve stimulation parameters using the firing activity of serotonin neurons in the rat dorsal raphe. *Eur Neuropsychopharmacol.* 2009;19:250-5.**
Abstract: Vagus nerve stimulation (VNS) is a recently approved adjunctive intervention for treatment-resistant depression. This therapy enhances the firing rate of rat norepinephrine neurons after 1 h and that of serotonin (5-HT) neurons only after 14 days. Various stimulation parameters were thus tested on their capacity to enhance 5-HT neuronal firing because of the delayed action of VNS on the 5-HT system and its important role in the antidepressant response. Rats were implanted with a stimulator and treated for 14 days, each group of rats having only one stimulation parameter modified from the standard ones (0.25 mA, 20 Hz, 500 micros, 30 s ON/5 min OFF). Electrophysiological recordings showed that the usual parameters utilized in depressed patients, with the exception of current intensity, produced an optimal activation of 5-HT neurons. Excessive enhancement of the charge delivered to the nerve can lead to a loss of VNS effect on 5-HT neuronal firing. Optimization of vagus nerve stimulation parameters using the firing activity of serotonin neurons in the rat dorsal raphe. *Eur Neuropsychopharmacol.*

2. **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;5:275-86.**
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. A comparative study of three techniques for diameter selective fiber activation in the vagal nerve: anodal block, depolarizing prepulses and slowly rising pulses.

3. **Bunch S, DeGiorgio CM, Krahl S, et al. Vagus nerve stimulation for epilepsy: is output current correlated with acute response? *Acta Neurol Scand.* 2007;116:217-20.**
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. Vagus nerve stimulation for epilepsy: is output current correlated with acute response?

4. **Labiner DM, Ahern GL. Vagus nerve stimulation therapy in depression and epilepsy: therapeutic parameter settings. *Acta Neurol Scand.* 2007;115:23-33.**
Abstract: Vagus nerve stimulation (VNS) therapy is an effective adjunctive treatment for chronic or recurrent treatment-resistant depression in adults, and for pharmacoresistant 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 micros. 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. Vagus nerve stimulation therapy in depression and epilepsy: therapeutic parameter settings.

5. **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;15:615-20.**
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. Effects of two different cycles of vagus nerve stimulation on interictal epileptiform discharges.

6. **DeGiorgio C, Heck C, Bunch S, et al. Vagus nerve stimulation for epilepsy: randomized comparison of three stimulation paradigms. *Neurology.* 2005;65:317-9.**
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. Vagus nerve stimulation for epilepsy: randomized comparison of three stimulation paradigms.

7. **Morris GL 3rd. A retrospective analysis of the effects of magnet-activated stimulation in conjunction with vagus nerve stimulation therapy. *Epilepsy Behav.* 2003;4:740-5.**
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. A retrospective analysis of the effects of magnet-activated stimulation in conjunction with vagus nerve stimulation therapy.

8. **Heck C, Helmers SL, DeGiorgio CM. Vagus nerve stimulation therapy, epilepsy, and device parameters: scientific basis and recommendations for use. *Neurology.* 2002;59(suppl 4):S31-S37 .**
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). Vagus nerve stimulation therapy, epilepsy, and device parameters: scientific basis and recommendations for use.

9. **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.**
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. Vagus nerve stimulation for epilepsy, clinical efficacy of programmed and magnet stimulation.

10. **Koo B, Ham SD, Sood S, Tarver B. Human vagus nerve electrophysiology: a guide to vagus nerve stimulation parameters. *J Clin Neurophysiol.* 2001;18:429-433.**
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. Human vagus nerve electrophysiology: a guide to vagus nerve stimulation parameters.

11. **Boon P, Vonck K, Van Walleghem P, et al. Programmed and magnet-induced vagus nerve stimulation for refractory epilepsy. *J Clin Neurophysiol.* 2001;18:402-407.** 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. Programmed and magnet-induced vagus nerve stimulation for refractory epilepsy.

Pediatric

1. **Arhan E, Serdaroglu A, Kurt G, et al. The efficacy of vagal nerve stimulation in children with pharmacoresistant epilepsy: Practical experience at a Turkish tertiary referral center. *Eur J Paediatr Neurol.* 2009.**
Abstract: BACKGROUND: Vagus nerve stimulation (VNS) is an effective therapy for pharmacoresistant 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 pharmacoresistant epilepsy treated at the Gazi University Medical Faculty Epilepsy Center, Turkey. PATIENTS AND METHODS: The study included 24 patients - all younger than 18years of age (mean age: 14.31years). Median age at the time of VNS device implantation was 11years. Median age at onset of epilepsy was 21months and median duration of epilepsy was 126months. 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 >12years of age and patients <12years of age was not significant. Mean percentage of seizure reduction after 6months-7years of treatment was, respectively, 22.5% (n=24) (6thmonth), 32% (n=20) (1styear), 42% (n=16) (2ndyear), 50.45% (n=11) (3rdyear), 52% (n=10) (4thyear), 60% (n=8) (5thyear), 61.25% (n=8) (6thyear), and 61.6% (n=6) (7thyear). 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. The efficacy of vagal nerve stimulation in children with pharmacoresistant epilepsy: Practical experience at a Turkish tertiary referral center**.**

2. **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;25:1097-100.**
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. Vagus nerve stimulation in children with intractable epilepsy: indications, complications and outcome.

3. **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;50:1220-8.**
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 >or=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. Vagus nerve stimulation for refractory epilepsy in children: More to VNS than seizure frequency reduction.

4. **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;13:115-27.**
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. Approach to pediatric epilepsy surgery: State of the art, Part II: Approach to specific epilepsy syndromes and etiologies.

5. **Arts WF, Geerts AT. When to start drug treatment for childhood epilepsy: the clinical-epidemiological evidence. *Eur J Paediatr Neurol.* 2009;13:93-101.**

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. When to start drug treatment for childhood epilepsy: the clinical-epidemiological evidence.

6. **Rossignol E, Lortie A, Thomas T, et al. Vagus nerve stimulation in pediatric epileptic syndromes. *Seizure.* 2009;18:34-7.**

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 >or=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. Vagus nerve stimulation in pediatric epileptic syndromes.

7. **Ross IB, Maleeva T, Sutherling WW. Vagus nerve stimulation. *J Neurosurg Pediatr.* 2008;2:375; author reply 375.** Vagus nerve stimulation.

8. **De Tiege X, Legros B, de Beeck MO, Goldman S, Van Bogaert P. Vagus nerve stimulation. *J Neurosurg Pediatr.* 2008;2:375-7; author reply 377.** Vagus nerve stimulation.

9. **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;23:991-8.**
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. Quality of life and seizure outcome after vagus nerve stimulation in children with intractable epilepsy.

10. **Bulteau C, Dorfmuller G, Fohlen M, Jalin C, Oliver MV, Delalande O. [Epilepsy surgery during infancy and early childhood in France]. *Neurochirurgie.* 2008;54:342-6.**
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. Epilepsy surgery during infancy and early childhood in France.

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;9:395-403.**
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. Update on the Newer Antiepileptic Drugs in Child Neurology: Advances in Treatment of Pediatric Epilepsy.

12. **Malphrus AD, Wilfong AA. Use of the newer antiepileptic drugs in pediatric epilepsies. *Curr Treat Options Neurol.* 2007;9:256-67.**
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; adrenocorticotropic 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. Use of the newer antiepileptic drugs in pediatric epilepsies.

13. **You SJ, Kang HC, Kim HD, et al. Vagus nerve stimulation in intractable childhood epilepsy: a korean multicenter experience. *J Korean Med Sci.* 2007;22:442-5.**
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 altertness 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. Vagus nerve stimulation in intractable childhood epilepsy: a Korean multicenter experience.

14. **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;23:91-7.**
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. Evaluation of quality of life and clinical status of children operated on for intractable epilepsy.

15. **Saneto RP, Sotero de Menezes MA, Ojemann JG, et al. Vagus Nerve Stimulation for Intractable Seizures in Children. *Pediatr Neurol.* 2006;35:323-326.**
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 >/=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. Vagus nerve stimulation for intractable seizures in children.

16. **Alexopoulos AV, Kotagal P, Loddenkemper T, Hammel J, Bingaman WE. Long-term results with vagus nerve stimulation in children with pharmacoresistant epilepsy. *Seizure.* 2006;15:491-503.**
Abstract: PURPOSE: To retrospectively review our experience with VNS in pediatric patients with pharmacoresistant 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. Long-term results with vagus nerve stimulation in children with pharmacoresistant epilepsy.

17. **Blount JP, Tubbs RS, Kankirawatana P, et al. Vagus nerve stimulation in children less than 5 years old. *Childs Nerv Syst.* 2006;22:1167-9.**
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. Vagus nerve stimulation in children less than 5 years old.

18. **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;22:1018-26.**
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. Vagal nerve stimulation for refractory epilepsy in children: indications and experience at The Hospital for Sick Children.

19. **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.**
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 sialorrhea 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. Vagus nerve stimulation in pediatric intractable epilepsy: a Korean bicentric study.

20. **Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Submission for Pediatric Epilepsy Surgery. *Epilepsia.* 2006;47:952-959.** Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery.

21. **Hallbook T, Lundgren J, Blennow G, Stromblad LG, Rosen I. Long term effects on epileptiform activity with vagus nerve stimulation in children. *Seizure.* 2005;14:527-33.**
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. Long term effects on epileptiform activity with vagus nerve stimulation in children.

22. **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;9:399-407.**
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. Beneficial effects on sleep of vagus nerve stimulation in children with therapy resistant epilepsy

23. **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;13:494-8.**
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. Can spikes predict seizure frequency? Results of a pilot study in severe childhood epilepsies treated with vagus nerve stimulation.

24. **Kossoff EH, Pyzik PL. Improvement in alertness and behavior in children treated with combination topiramate and vagus nerve stimulation. *Epilepsy Behav.* 2004;5:256-9.**
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. Improvement in alertness and behavior in children treated with combination topiramate and vagus nerve stimulation.

25. **Buoni S, Mariottini A, Pieri S, et al. Vagus nerve stimulation for drug-resistant epilepsy in children and young adults. *Brain Dev.* 2004;26:158-163.**

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. Vagus nerve stimulation for drug-resistant epilepsy in children and young adults.

26. **Hudgins RJ, Gilreath CL. Managing epilepsy II: surgical treatment of epilepsy in children. *Nepal J Neurosci.* 2004;1:83-91.**
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.
http://www.neuroscienceforum.org.np/Hudgins.pdf

27. **Coppola G. Treatment of partial seizures in childhood : an overview. *CNS Drugs.* 2004;18:133-156.**
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. Treatment of partial seizures in childhood : an overview.

28. **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;157:560-564.**
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. Vagal nerve stimulation in refractory epilepsy: the first 100 patients receiving vagal nerve stimulation at a pediatric epilepsy center.

29. **Buchhalter JR, Jarrar RG. Therapeutics in pediatric epilepsy, Part 2: Epilepsy surgery and vagus nerve stimulation. *Mayo Clin Proc.* 2003;78:371-378.**
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. Therapeutics in pediatric epilepsy, Part 2: Epilepsy surgery and vagus nerve stimulation.

30. **Farnalls SL, Rennick J. Parents' caregiving approaches: facing a new treatment alternative in severe intractable childhood epilepsy. *Seizure.* 2003;12:1-10.**
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. Parents' caregiving approaches: facing a new treatment alternative in severe intractable childhood epilepsy.

31. **Kirse DJ, Werle AH, Murphy JV, et al. Vagus nerve stimulator implantation in children. *Arch Otolaryngol Head Neck Surg.* 2002;128:1263-1268.**
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. Vagus nerve stimulator implantation in children.

32. **Wheless JW, Maggio V. Vagus nerve stimulation therapy in patients younger than 18 years. *Neurology.* 2002;59(suppl 4):S21-S25.**
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. Vagus nerve stimulation therapy in patients younger than 18 years.

33. **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;18:61-66.**
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. Intermittent vagal nerve stimulation in paediatric patients: 1-year follow-up.

34. **Nagarajan L, Walsh P, Gregory P, Lee M. VNS therapy in clinical practice in children with refractory epilepsy. *Acta Neurol Scand.* 2002;105:13-17.**
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. VNS therapy in clinical practice in children with refractory epilepsy.

35. **Valencia I, Holder DL, Helmers SL, Madsen JR, Riviello JJ Jr. Vagus nerve stimulation in pediatric epilepsy: a review. *Pediatr Neurol.* 2001;25:368-376.**
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. Vagus nerve stimulation in pediatric epilepsy: a review.

36. **Helmers SL, Wheless JW, Frost M, et al. Vagus nerve stimulation therapy in pediatric patients with refractory epilepsy: retrospective study. *J Child Neurol.* 2001;16:843-848.**
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. Vagus nerve stimulation therapy in pediatric patients with refractory epilepsy: retrospective study.

37. **Amar AP, Levy ML, McComb JG, Apuzzo ML. Vagus nerve stimulation for control of intractable seizures in childhood. *Pediatr Neurosurg.* 2001;34:218-223.**
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. Vagus nerve stimulation for control of intractable seizures in childhood.

38. **Wakai S, Kotagal P. Vagus nerve stimulation for children and adolescents with intractable epilepsies. *Pediatr Int.* 2001;43:61-5.**
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. Vagus nerve stimulation for children and adolescents with intractable epilepsies.

39. **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;67:119-121.**
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. Vagus nerve stimulation in pediatric patients with intractable epilepsy: case series and operative technique.

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

41. **Crumrine PK. Vagal nerve stimulation in children. *Semin Pediatr Neurol.* 2000;7:216-223.**
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? Vagal nerve stimulation in children.

42. **Labar D. Vagus nerve stimulation for intractable epilepsy in children. *Dev Med Child Neurol.* 2000;42:496-499.** Vagus nerve stimulation for intractable epilepsy in children.

43. **Robinson RO. Vagal nerve stimulation for epilepsy. *Arch Dis Child.* 2000;82:336.**
Vagal nerve stimulation for epilepsy.

44. **Murphy JV. Left vagal nerve stimulation in children with medically refractory epilepsy. The Pediatric VNS Study Group. *J Pediatr.* 1999;134:563-566.**
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. Left vagal nerve stimulation in children with medically refractory epilepsy.

45. **Camfield PR, Camfield CS. Vagal nerve stimulation for treatment of children with epilepsy. *J Pediatr.* 1999;134:532-533.** Vagal nerve stimulation for treatment of children with epilepsy.

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

47. **Hornig GW, Murphy JV, Schallert G, Tilton C. Left vagus nerve stimulation in children with refractory epilepsy: an update. *South Med J.* 1997;90:484-488.**
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. Left vagus nerve stimulation in children with refractory epilepsy: an update.

48. **Murphy JV, Hornig G, Schallert G. Left vagal nerve stimulation in children with refractory epilepsy. Preliminary observations. *Arch Neurol.* 1995;52:886-889.**
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. Left vagal nerve stimulation in children with refractory epilepsy. Preliminary observations.

Pre-Approval Studies

1. **DeGiorgio CM, Thompson J, Lewis P, et al. Vagus nerve stimulation: analysis of device parameters in 154 patients during the long-term XE5 study. *Epilepsia.* 2001;42:1017-1020.**
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.
Vagus nerve stimulation: analysis of device parameters in 154 patients during the long-term XE5 study.

2. **DeGiorgio CM, Schachter SC, Handforth A, et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. *Epilepsia.* 2000;41:1195-1200.**
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. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures.

3. **Morris GL3, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. *Neurology.* 1999;53:1731-1735.**
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. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05.

4. **Labar D, Murphy J, Tecoma E. Vagus nerve stimulation for medication-resistant generalized epilepsy. E04 VNS Study Group. *Neurology.* 1999;52:1510-1512.**
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. Vagus nerve stimulation for medication-resistant generalized epilepsy. E04 VNS Study Group.

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;73:104-108.**
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. Long-term multicenter experience with vagus nerve stimulation for intractable partial seizures: results of the XE5 trial

6. **Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology.* 1998;51:48-55.**
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. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial.

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;53:1176-80.**
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. Vagus nerve stimulation for the treatment of medically intractable seizures. Results of a 1-year open-extension trial. Vagus Nerve Stimulation Study Group.

8. **A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. *Neurology.* 1995;45:224-230.**
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 > or = 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. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group.

9. **Ramsay RE, Uthman BM, Augustinsson LE, 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;35:627-636.**
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 wrre 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. Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side effects, and tolerability. First International Vagus Nerve Stimulation Study Group.

10. **George R, Salinsky M, Kuzniecky R, 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;35:637-43.**
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. 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.

11. **Ben-Menachem E, Manon-Espaillat R, Ristanovic R, 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;35:616-26.**
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. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group.

12. **Michael JE, Wegener K, Barnes DW. Vagus nerve stimulation for intractable seizures: one year follow-up. *J Neurosci Nurs.* 1993;25:362-366.**
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. Vagus nerve stimulation for intractable seizures: one year follow-up.

13. **Uthman BM, Wilder BJ, Penry JK, et al. Treatment of epilepsy by stimulation of the vagus nerve. *Neurology.* 1993;43:1338-1345.**
Notes: This paper discusses the outcomes from a subset of the patients from the single-blind 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. Treatment of epilepsy by stimulation of the vagus nerve.

14. **Holder LK, Wernicke JF, Tarver WB. Treatment of refractory partial seizures: preliminary results of a controlled study. *Pacing Clin Electrophysiol.* 1992;15:1557-1571.**
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. Treatment of refractory partial seizures: preliminary results of a controlled study.

15. **Wilder BJ, Uthman BM, Hammond EJ. Vagal stimulation for control of complex partial seizures in medically refractory epileptic patients. *Pacing Clin Electrophysiol.* 1991;14:108-115.**
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. Vagal stimulation for control of complex partial seizures in medically refractory epileptic patients.

16. **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-S50.**
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. Efficacy and safety of vagus nerve stimulation in patients with complex partial seizures.

17. **Penry JK, Dean JC. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. *Epilepsia.* 1990;31(suppl 2):S40-S43.**
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. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results.

Pregnancy

1. **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.**
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. Pregnancy and delivery while receiving vagus nerve stimulation for the treatment of major depression: a case report.

Quality of Life

1. **Kaufman EL. Mu-metal magnetic shield box to improve the day-to-day quality of life for vagus nerve stimulator patients. *Epilepsy Behav.* 2009;14:432.** Mu-metal magnetic shield box to improve the day-to-day quality of life for vagus nerve stimulator patients.

2. **Murphy W. VNS therapy. *Can J Neurol Sci.* 2008;35:276-7.** VNS therapy.

3. **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;35:287-96.**
   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. Quality of life and memory after vagus nerve stimulator implantation for epilepsy.

4. **Kotagal P, Yardi N. The relationship between sleep and epilepsy. *Semin Pediatr Neurol.* 2008;15:42-9.**
   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. The relationship between sleep and epilepsy.

5. **Milby AH, Halpern CH, Baltuch GH. Vagus nerve stimulation for epilepsy and depression. *Neurotherapeutics.* 2008;5:75-85.**
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. Vagus nerve stimulation for epilepsy and depression.

6. **Stemper B, Devinsky O, Haendl T, Welsch G, Hilz MJ. Effects of vagus nerve stimulation on cardiovascular regulation in patients with epilepsy. *Acta Neurol Scand.* 2007.**
Abstract: Objective - To evaluate the impact of vagus nerve stimulation (VNS) on heart rate and blood pressure (BP) modulation in epilepsy patients. Material and methods - Twenty-one epilepsy patients with VNS were tested during on (60 s) and off (5 min) phases. We monitored BP, RR intervals (RRI) and respiration. Spectral analysis was performed in low- (LF: 0.04-0.15 Hz) and high-frequency bands (HF: 0.15-0.5 Hz). For coherences above 0.5, we calculated the LF transfer function between systolic BP and RRI, and the HF transfer function gain and phase between RRI and respiration. Differences between the on and off phases were evaluated using Wilcoxon test. Results - VNS did not change RRI and BP values. The LF power of BP and the LF and HF power of RRI increased significantly. There was a slight change in the RRI/BP LF gain and the RRI/respiration HF gain (ns). The HF phase between RRI and respiration decreased significantly. Conclusions - Our findings show that VNS influences both sympathetic and parasympathetic cardiovascular modulation. However, our results also show that VNS does not negatively influence autonomic cardiovascular regulation. Effects of vagus nerve stimulation on cardiovascular regulation in patients with epilepsy.

7. **Pardo JV, Sheikh SA, Kuskowski MA, et al. Weight loss during chronic, cervical vagus nerve stimulation in depressed patients with obesity: an observation. *Int J Obes (Lond).* 2007;31:1756-9.**
Abstract: Fourteen patients were treated over 2 years with cervical vagus nerve stimulation (VNS) for adjunctive therapy of severe, treatment-resistant depression. Here, we report the serendipitous observation that this treatment was associated with highly significant, gradual weight loss despite the patients' report of not dieting or exercising. The weight loss was

proportional to the initial BMI, that is, the more severe the obesity, the greater the weight loss. Weight loss did not correlate with changes in mood symptoms. The vagus nerve carries visceral information to and from the brain; modulation of its activity may alter eating behavior. Chronic cervical VNS may merit controlled study for the treatment of severe obesity. Weight loss during chronic, cervical vagus nerve stimulation in depressed patients with obesity: an observation

8. **Borghetti D, Pizzanelli C, Maritato P, et al. Mismatch negativity analysis in drug-resistant epileptic patients implanted with vagus nerve stimulator. *Brain Res Bull.* 2007;73:81-5.**
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. Mismatch negativity analysis in drug-resistant epileptic patients implanted with vagus nerve stimulator.

9. **Brodtkorb E, Mula M. Optimizing therapy of seizures in adult patients with psychiatric comorbidity. *Neurology.* 2006;67:S39-44.**
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. Optimizing therapy of seizures in adult patients with psychiatric comorbidity.

10. **Shafique S, Dalsing MC. Vagus nerve stimulation therapy for treatment of drug-resistant epilepsy and depression. *Perspect Vasc Surg Endovasc Ther.* 2006;18:323-7.**
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. Vagus nerve stimulation therapy for treatment of drug-resistant epilepsy and depression.

11. **Ghacibeh GA, Shenker JI, Shenal B, Uthman BM, Heilman KM. The influence of vagus nerve stimulation on memory. *Cogn Behav Neurol.* 2006;19:119-22.**
Abstract: BACKGROUND: Vagus nerve stimulation (VNS) has been shown to improve memory. OBJECTIVE: The purpose of this study was to learn at which stage of memory formation this influence occurs. METHODS: Ten subjects who had been implanted with vagus nerve stimulators for the treatment of intractable seizures performed tasks that assessed learning and retention (Hopkins Verbal Learning Test) during actual and sham VNS. RESULTS: We found that VNS had no effect on learning but enhanced consolidation, which led to improved retention. CONCLUSIONS: The means by which VNS improves retention is probably related to the increased activity in the nucleus of the tractus solitarius and the locus coeruleus-central adrenergic system that activates the amygdala and increases long-term potentiation in the hippocampus. The influence of vagus nerve stimulation on memory.

12. **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;140:1443-51.**
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. Vagus nerve stimulation does not affect spatial memory in fast rats, but has both anti-convulsive and pro-convulsive effects on amygdala-kindled seizures.

13. **Wheless JW. Intractable epilepsy: a survey of patients and caregivers. *Epilepsy Behav.* 2006;8:756-64.**
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. Intractable epilepsy: A survey of patients and caregivers.

14. **Ghacibeh GA, Shenker JI, Shenal B, Uthman BM, Heilman KM. Effect of vagus nerve stimulation on creativity and cognitive flexibility. *Epilepsy Behav.* 2006;8:720-725.**
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. Effect of vagus nerve stimulation on creativity and cognitive flexibility.

15. **Boon P, Moors I, De Herdt V, Vonck K. Vagus nerve stimulation and cognition. *Seizure.* 2006;15:259-63.**
Abstract: Vagus nerve stimulation (VNS) has been developed as an add-on treatment for patients with refractory epilepsy. Based on the clinical observation of improved cognition in many epilepsy patients who received VNS, we reviewed the recent literature for evidence concerning the cognitive effects of this treatment. From most of these studies it seems that, with currently used stimulation parameters, the effects on memory are only of

theoretical importance. However, some animal studies suggest positive effects on specific modalities of memory function. In studies in epilepsy patients, there is no evidence of adverse effects on cognition but clear-cut positive effects cannot be expected either. Preliminary results of VNS in the treatment of diseases associated with cognitive decline such as Alzheimer's disease seem promising but need to be further investigated. Vagus nerve stimulation and cognition.

16. **Koren MS, Holmes MD. Vagus nerve stimulation does not lead to significant changes in body weight in patients with epilepsy. *Epilepsy Behav.* 2006;8:246-9.**
Abstract: BACKGROUND: Vagus nerve stimulation (VNS) is an FDA-approved treatment for medically intractable epilepsy. The effect of this therapy on body weight is unclear. VNS could cause weight loss by engaging vagal afferents from the gastrointestinal tract mediating satiety. METHODS: We performed a retrospective analysis of body weight changes over a period up to 2 years following VNS implantation. We studied 21 patients (13 M/8 F) 35 +/- 12 years old, who received a Cyberonics VNS Therapy System for medically intractable epilepsy between April 1998 and May 2004. The mean +/- SD duration of follow-up was 613.1 +/- 389.1 days. The study had 80% power with a type I error of 0.05 to detect a 5% weight change. Data were analyzed with repeated-measures ANOVA. RESULTS: Weight changes relative to baseline at 30, 60, 120, 360, 480, and 720 days were -0.17 +/- 2.33, +0.33 +/- 2.64, -0.32 +/- 3.56, +1.09 +/- 5.97, +1.06 +/- 7.47, and +0.33 +/- 3.69%, respectively. At all time points these differences failed to reach statistical significance. CONCLUSIONS: Vagus nerve stimulation with parameters typically used in the treatment of patients with epilepsy was not associated with clinically significant weight changes. A well-controlled prospective study is necessary for more precise evaluation of the effect of VNS therapy on body weight. Vagus nerve stimulation does not lead to significant changes in body weight in patients with epilepsy.

17. **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;14:504-13.**
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), Wechlser 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 Birleson 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. Vagus nerve stimulation in 15 children with therapy resistant epilepsy; its impact on cognition, quality of life, behaviour and mood.

18. **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;64:170-3.**
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. Control of refractory status epilepticus precipitated by anticonvulsant withdrawal using left vagal nerve stimulation: a case report.

19. **Martin CO, Denburg NL, Tranel D, Granner MA, Bechara A. The effects of vagus nerve stimulation on decision-making. *Cortex.* 2004;40:605-12.**
Abstract: Subcortical and brainstem structures are increasingly becoming recognized as important contributors to higher cognitive functioning. Decision-making is one such function, particularly as viewed within the framework of the somatic marker hypothesis (SMH). The SMH views the participation in decision-making by the body proper as integral to emotional biasing and hence key to choosing in an advantageous manner. This study focuses on the vagus nerves as a possible conduit for somatic afferent signals pertinent to decision-making. We tested eight epileptic patients with implanted left vagus nerve stimulators. To assess decision-making we used the gambling task, which is sensitive to real-life decision-making deficits. Using a counterbalanced design, each participant performed the gambling task under a condition in which low-level vagus nerve stimulation (VNS) was covertly delivered, and another condition in which no VNS was delivered.

Participants showed improved performance, that is, made more advantageous choices, in the stimulated relative to the unstimulated condition. Although these results should be viewed as preliminary, they suggest that the vagus nerve is a conduit for afferent somatic signals that can influence decision-making. The effects of vagus nerve stimulation on decision-making.

20. **Schachter SC. Vagus nerve stimulation: mood and cognitive effects. *Epilepsy Behav.* 2004;5 Suppl 1:S56-9.**
Abstract: Many antiepileptic medications modulate affective and cognitive functions. In keeping with these observations, a growing body of literature suggests that vagus nerve stimulation (VNS) may have similar effects. This review evaluates the published evidence for VNS-associated changes in mood and cognition in patients with neuropsychiatric disorders. Vagus nerve stimulation: mood and cognitive effects.

21. **Krishnamoorthy ES . Treatment of depression in patients with epilepsy: problems, pitfalls, and some solutions. *Epilepsy Behav.* 2003;4(suppl 3):46-54.**
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. Treatment of depression in patients with epilepsy: problems, pitfalls, and some solutions.

22. **Rizzo P, Beelke M, De Carli F, et al. Chronic vagus nerve stimulation improves alertness and reduces rapid eye movement sleep in patients affected by refractory epilepsy. *Sleep.* 2003;26:607-611.**
Notes: This study showed that VNS improved alertness and the quality of awakeness 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. Chronic vagus nerve stimulation improves alertness and reduces rapid eye movement sleep in patients affected by refractory epilepsy.

23. **Chavel SM, Westerveld M, Spencer S. Long-term outcome of vagus nerve stimulation for refractory partial epilepsy. *Epilepsy Behav.* 2003;4:302-9.**
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 >or=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. Long-term outcome of vagus nerve stimulation for refractory partial epilepsy.

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

25. **Galli R, Bonanni E, Pizzanelli C, et al. Daytime vigilance and quality of life in epileptic patients treated with vagus nerve stimulation. *Epilepsy Behav.* 2003;4:185-91.**
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 (<or=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. Daytime vigilance and quality of life in epileptic patients treated with vagus nerve stimulation.

26. **McLachlan RS, Sadler M, Pillay N, et al. Quality of life after vagus nerve stimulation for intractable epilepsy: is seizure control the only contributing factor? *Eur Neurol.* 2003;50:16-19.**
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. Quality of life after vagus nerve stimulation for intractable epilepsy: is seizure control the only contributing factor?

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

28. **Harden CL. The co-morbidity of depression and epilepsy: epidemiology, etiology, and treatment. *Neurology.* 2002;59(suppl 4):S48-S55.**
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. The co-morbidity of depression and epilepsy: epidemiology, etiology, and treatment.

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

30. **Elger CE, Hoppe C. Vagus nerve stimulation and mood. In: Trimble M, Schmitz B, Eds. *The Neuropsychiatry of Epilepsy*. Cambridge: Cambridge University Press; 2002:283-295.**

Book Chapter

http://www.cambridge.org/catalogue/catalogue.asp?isbn=9780521005166

31. **Boylan LS. Peri-ictal behavioral and cognitive changes. *Epilepsy Behav.* 2002;3:16-26.**
Abstract: Peri-ictal behavioral and cognitive changes contribute substantially to disability and distress among people with epilepsy. Psychosis, depression, and suicide may all occur as complications of seizures. Greater appreciation and understanding of the peri-ictal period is clinically important and might open novel therapeutic windows. At the same time this period provides a model for understanding basic mechanisms underlying mood and thought disorders and the substrates of cognition, volition, emotion, and consciousness. This review will discuss behavioral and cognitive antecedents of seizures, including the preictal milieu, reflex seizures, and self-induced seizures. Behavioral and cognitive treatment approaches that have been undertaken are reviewed. Both acute and delayed postictal emotional, behavioral, and cognitive changes will be discussed. Finally, possible mechanisms by which epileptic brain activity and behavior may modify each other are considered. Peri-Ictal Behavioral and Cognitive Changes.

32. **Helmstaedter C, Hoppe C, Elger CE. Memory alterations during acute high-intensity vagus nerve stimulation. *Epilepsy Res.* 2001;47:37-42.**
Abstract: Left cervical vagus nerve stimulation (VNS) is an accepted add-on treatment for pharmacoresistant 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 pharmacoresistant 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. Memory alterations during acute high-intensity vagus nerve stimulation.

33. **Cramer JA. Exploration of changes in health-related quality of life after 3 months of vagus nerve stimulation. *Epilepsy Behav.* 2001;2:460-465.**
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. Exploration of Changes in Health-Related Quality of Life after 3 Months of Vagus Nerve Stimulation.

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

35. **Brazdil M, Chadim P, Daniel P, et al. Effect of vagal nerve stimulation on auditory and visual event-related potentials. *Eur J Neurol.* 2001;8:457-61.**
Abstract: Chronic unilateral vagal nerve stimulation (VNS) has been recently introduced into the therapy for intractable epileptic seizures. Its effect on cognitive functions in VNS-treated patients remains controversial. The aim of the present study was to evaluate the possible impact of therapeutic VNS on cognitive functions by means of event-related potentials analysis. Ten patients with medically intractable epilepsy, who had been implanted with VNS devices, participated in the study. Auditory and visual event-related potentials (ERPs) were repeatedly recorded, first just before the implantation of VNS devices, and then again 3-6 months after the device activation. The effect of lower intensity stimulation on the P3 component of ERPs was assessed. No significant differences were found in auditory ERPs; the latencies of P3 as well as N2/P3 peak-to-peak amplitudes were virtually identical. The same was true for mean P3 latencies of visual ERPs. However, higher visual N2/P3 peak-to-peak amplitudes were observed in the responses to targets that followed VNS, with a significant finding at the electrodes investigated. When comparing the effect of VNS on visual N2/P3 amplitude in each electrode separately, the most expressive differences were found in the frontal region. This observation supports the theory of a possible positive effect of low-intensity VNS on the cognitive functions. Effect of vagal nerve stimulation on auditory and visual event-related potentials.

36. **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;2:335-342.**
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. Self-Reported Mood Changes following 6 Months of Vagus Nerve Stimulation in Epilepsy Patients.

37. **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;2:351-356.**
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. No Evidence for Cognitive Side Effects after 6 Months of Vagus Nerve Stimulation in Epilepsy Patients.

38. **Ergene E, Behr PK, Shih JJ. Quality-of-Life Assessment in Patients Treated with Vagus Nerve Stimulation. *Epilepsy Behav.* 2001;2:284-287.**
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. Quality-of-Life Assessment in Patients Treated with Vagus Nerve Stimulation.

39. **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.* 2001;1:93-99.**
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. A Pilot Study of Mood in Epilepsy Patients Treated with Vagus Nerve Stimulation.

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

41. **Dodrill CB, Morris GL. Effects of vagal nerve stimulation on cognition and quality of life (letter). *Epilepsy Behav.* 2001;2:162.** Effects of vagal nerve stimulation on cognition and quality of life.
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.

42. **Dodrill CB, Morris GL. Effects of Vagal Nerve Stimulation on Cognition and Quality of Life in Epilepsy. *Epilepsy Behav.* 2001;2:46-53.**
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. Effects of Vagal Nerve Stimulation on Cognition and Quality of Life in Epilepsy.

43. **Labar DR. Effects of vagal nerve stimulation on cognition and quality of life. *Epilepsy Behav.* 2001;2:161-162.** Effects of vagal nerve stimulation on cognition and quality of life.

44. **Harden CL. Mood changes in epilepsy patients treated with vagus nerve stimulation. *Epilepsy Behav.* 2001;2:S17-S20.**

45. **Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res.* 2000;42:203-210.**
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. Vagus nerve stimulation is associated with mood improvements in epilepsy patients.

46. **Clark KB, Naritoku DK, Smith DC, Browning RA, Jensen RA. Enhanced recognition memory following vagus nerve stimulation in human subjects. *Nat Neurosci.* 1999;2:94-98.**
Notes: First major article on the qualitative benefits of VNS. VNS at low levels (0.5 mA) enhanced retention in humans, but high stimulation (0.75 to 1.5 mA) did not improve retention. Findings are consistent with those in rodent studies. Improvements could not be attributed to strictly seizure decrease alone. These memory-improvement benefits may also be of value to patients who experience cognitive impairment as a result of traumatic injury or disease.
Abstract: Neuromodulators associated with arousal modulate learning and memory, but most of these substances do not freely enter the brain from the periphery. In rodents, these neuromodulators act in part by initiating neural messages that travel via the vagus nerve to

the brain, and electrical stimulation of the vagus enhances memory. We now extend that finding to human verbal learning. We examined word-recognition memory in patients enrolled in a clinical study evaluating the capacity of vagus nerve stimulation to control epilepsy. Stimulation administered after learning significantly enhanced retention. These findings confirm in humans the hypothesis that vagus nerve activation modulates memory formation similarly to arousal. Enhanced recognition memory following vagus nerve stimulation in human subjects.

47. **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;24:230-234.**
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. Chronic stimulation of the left vagus nerve in epilepsy: balance effects.

48. **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;24:226-9.**
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 (SI) 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. Chronic stimulation of the left vagus nerve: cognitive motor effects.

49. **Clarke BM, Upton AR, Kamath M, Griffin HM. Electrostimulation effects of the vagus nerve on balance in epilepsy. *Pacing Clin Electrophysiol.* 1992;15:1614-1630.**
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. Electrostimulation effects of the vagus nerve on balance in epilepsy.

50. **Clarke BM, Upton AR, Griffin HM. Cognitive motor function after electrical stimulation of the vagus nerve. *Pacing Clin Electrophysiol.* 1992;15:1603-1607.**
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. Cognitive motor function after electrical stimulation of the vagus nerve.

51. **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;15:1608-1613.**
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. Acute effects of high frequency vagal nerve

stimulation on balance and cognitive motor performance in epilepsy: three case study reports.

52. **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;14:77-85.**
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. Balance and cognitive impairment in two epileptic patients before and after vagal nerve stimulation.

Real-World Outcomes

1. **Kuba R, Brazdil M, Kalina M, et al. Vagus nerve stimulation: longitudinal follow-up of patients treated for 5 years. *Seizure.* 2009;18:269-74.**
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. Vagus nerve stimulation: longitudinal follow-up of patients treated for 5 years.

2. **Abubakr A, Wambacq I. Long-term outcome of vagus nerve stimulation therapy in patients with refractory epilepsy. *J Clin Neurosci.* 2008;15:127-9.**
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. Long-term outcome of vagus nerve stimulation therapy in patients with refractory epilepsy.

3. **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;16:579-85.**
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 pharmacoresistant 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 pharmacoresistant 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 =1 9), 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 pharmacoresistant 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. Vagus nerve stimulation for medically refractory epilepsy: a long-term follow-up study.

4. **De Herdt V, Boon P, Ceulemans B, et al. Vagus nerve stimulation for refractory epilepsy: a Belgian multicenter study. *Eur J Paediatr Neurol.* 2007;11:261-9.**
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. Vagus nerve stimulation for refractory epilepsy: a Belgian multicenter study.

5. **Sakas DE, Korfias S, Nicholson CL, et al. Vagus nerve stimulation for intractable epilepsy: outcome in two series combining 90 patients. *Acta Neurochir Suppl.* 2007;97:287-91.**
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). Vagus nerve stimulation for intractable epilepsy: outcome in two series combining 90 patients.

6. **Spanaki MV, Allen LS, Mueller WM, Morris GL 3rd. Vagus nerve stimulation therapy: 5-year or greater outcome at a university-based epilepsy center. *Seizure.* 2004;13:587-90.**
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. Vagus nerve stimulation therapy: 5-year or greater outcome at a university-based epilepsy center.

7. **Uthman BM, Reichl AM, Dean JC, et al. Effectiveness of vagus nerve stimulation in epilepsy patients: a 12-year observation. *Neurology.* 2004;63:1124-6.**
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. Effectiveness of vagus nerve stimulation in epilepsy patients: a 12-year observation.

8. **Labar D. Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs. *Seizure.* 2004;13:392-8.**
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. Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs.

9. **Vonck K, Thadani V, Gilbert K, et al. Vagus nerve stimulation for refractory epilepsy: a transatlantic experience. *J Clin Neurophysiol.* 2004;21:283-9.**
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. Vagus nerve stimulation for refractory epilepsy: a transatlantic experience.

10. **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;117:58-61.**
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. Vagus nerve stimulation for refractory epilepsy: long term efficacy and side-effects.

11. **Chavel SM, Westereld M, Spencer S. Long-term outcome of vagus nerve stimulation for refractory partial epilepsy. *Epilepsy Behav.* 2003;4:302-309.**
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 >or=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. Long-term outcome of vagus nerve stimulation for refractory partial epilepsy.

12. **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;105:9-13.**
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%), pharingodinia 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 pharmacoresistant epileptic seizures. Vagus nerve stimulation for treatment of medically intractable seizures. Evaluation of long-term outcome.

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

14. **Scherrmann J, Hoppe C, Kral T, Schramm J, Elger CE. Vagus nerve stimulation: clinical experience in a large patient series. *J Clin Neurophysiol.* 2001;18:408-414.**
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. Vagus nerve stimulation: clinical experience in a large patient series.

15. **Morrow JI, 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;9:442-445.**
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. Vagal nerve stimulation in patients with refractory epilepsy. Effect on seizure frequency, severity and quality of life.

16. **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;8:328-334.**
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 rest (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. Long-term results of vagus nerve stimulation in refractory epilepsy.

17. **FineSmith RB, Zampella E, Devinsky O. Vagal nerve stimulator: a new approach to medically refractory epilepsy. *N J Med.* 1999;96:37-40.**
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. Vagal nerve stimulator: a new approach to medically refractory epilepsy.

18. **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;52:1265-1267.**
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. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years.

Reimbursement Assessment for VNS Therapy

1. **Blue Cross and Blue Shield Association. Chronic vagus nerve stimulation for treatment of seizures. Tecnologica MAP Suppl 1998: 3-5.**

Rett Syndrome

1. **Wilfong AA, Schultz RJ. Vagus nerve stimulation for treatment of epilepsy in Rett syndrome. *Dev Med Child Neurol.* 2006;48:683-6.**
   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 >or=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. Vagus nerve stimulation for treatment of epilepsy in Rett syndrome.

Epilepsy Review

1. **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;74:24-6.**
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. Electrical stimulation of the olfactory mucosa: an alternative treatment for the temporal lobe epilepsy?

2. **Rosenfeld WE, Roberts DW. Tonic and atonic seizures: what's next--VNS or callosotomy? *Epilepsia.* 2009;50 Suppl 8:25-30.**
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. Tonic and atonic seizures: what's next--VNS or callosotomy?

3. **Lulic D, Ahmadian A, Baaj AA, Benbadis SR, Vale FL. Vagus nerve stimulation. *Neurosurg Focus.* 2009;27:E5.**
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. Vagus nerve stimulation

4. **Boon P, Raedt R, de Herdt V, Wyckhuys T, Vonck K. Electrical stimulation for the treatment of epilepsy. *Neurotherapeutics.* 2009;6:218-27.**
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. Electrical stimulation for the treatment of epilepsy.

5. **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.**
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 serotoninergic and adrenergic systems. This manuscript reviews the clinical studies investigating efficacy and side effects in patients and the experimental studies aiming to elucidate the mechanims of action. Vagal nerve stimulation--a 15-year survey of an established treatment modality in epilepsy surgery.

6. **Schomer DL, Black PM. A 24-year-old woman with intractable seizures: review of surgery for epilepsy . *JAMA.* 2008;300:2527-38.**
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. A 24-year-old woman with intractable seizures: review of surgery for epilepsy.

7. **O'Brien DF. Epilepsy surgery: a proven neurosurgical treatment and a multi-disciplinary team practice. *Ir Med J.* 2008;101:266-7.** Epilepsy surgery: a proven neurosurgical treatment and a multi-disciplinary team practice.

8. **Mapstone TB. Vagus nerve stimulation: current concepts. *Neurosurg Focus.* 2008;25:E9.**
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. Vagus nerve stimulation: current concepts.

9. **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:E10.**
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. Trends in the use of vagus nerve stimulation for epilepsy: analysis of a nationwide database.

10. **Balabanov A, Rossi MA. Epilepsy surgery and vagal nerve stimulation: what all neurologists should know. *Semin Neurol.* 2008;28:355-63.**
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. Epilepsy surgery and vagal nerve stimulation: what all neurologists should know.

11. **Implantable nerve stimulators.** ***Clin Privil White Pap*** **. 2008;1-20.** Implantable nerve stimulators.

12. **Janicak PG. An interview with Philip G. Janicak, MD: Neuromodulation by Norman Sussman, MD.** ***CNS Spectr.*** **2008;13:370-4.** An interview with Philip G. Janicak, MD: Neuromodulation by Norman Sussman, MD.

13. **Elger CE, Schmidt D. Modern management of epilepsy: A practical approach.** ***Epilepsy Behav.*** **2008;12:501-39.**
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. Modern management of epilepsy: A practical approach.

14. **Sun FT, Morrell MJ, Wharen RE Jr. Responsive cortical stimulation for the treatment of epilepsy.** ***Neurotherapeutics.*** **2008;5:68-74.**
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. Responsive cortical stimulation for the treatment of epilepsy.

15. **Ramani R. Vagus nerve stimulation therapy for seizures. *J Neurosurg Anesthesiol.* 2008;20:29-35.**
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. Vagus nerve stimulation therapy for seizures.

16. **Wilong AA. Complications and consequences of epilepsy surgery, ketogenic diet, and vagus nerve stimulation. *Semin Pediatr Neurol.* 2007;14:201-3.**
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. Complications and consequences of epilepsy surgery, ketogenic diet, and vagus nerve stimulation.

17. **Amar AP. Vagus nerve stimulation for the treatment of intractable epilepsy. *Expert Rev Neurother* . 2007;7:1763-73.**
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. Vagus nerve stimulation for the treatment of intractable epilepsy.

18. **Vesper J, Steinhoff B, Rona S, et al. Chronic high-frequency deep brain stimulation of the STN/SNr for progressive myoclonic epilepsy. *Epilepsia.* 2007;48:1984-9.**
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. Chronic high-frequency deep brain stimulation of the STN/SNr for progressive myoclonic epilepsy.

19. **Gross M, Goyal M. Central therapeutic effects of peripheral vagus nerve stimulation. *Am J Electroneurodiagnostic Technol.* 2007;47:47-52.**
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. Central therapeutic effects of peripheral vagus nerve stimulation.

20. **Krapohl BD, Deutinger M, Komurcu F. Vagus nerve stimulation: treatment modality**

for epilepsy. *Medsurg Nurs.* 2007;16:39-44; discussion 45, 54.
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. Vagus nerve stimulation: treatment modality for epilepsy.

21. **Theodore WH, Fisher R. Brain stimulation for epilepsy. *Acta Neurochir Suppl.* 2007;97:261-72.**
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. Brain stimulation for epilepsy.

22. **Karceski S. Electrical stimulation devices in the treatment of epilepsy. *Acta Neurochir Suppl.* 2007;97:247-59.**
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. Electrical stimulation devices in the treatment of epilepsy.

23. **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;97:273-80.**
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. Clinical experience with vagus nerve stimulation and deep brain stimulation in epilepsy.

24. **Ansari S, Chaudhri K, Al Moutaery KA. Vagus nerve stimulation: indications and limitations. *Acta Neurochir Suppl.* 2007;97:281-6.**
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. Vagus nerve stimulation: indications and limitations.

25. **Alexopoulos AV, Gonugunta V, Yang J, Boulis NM. Electrical stimulation and gene-based neuromodulation for control of medically-refractory epilepsy. *Acta Neurochir Suppl.* 2007;97:293-309.**
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. Electrical stimulation and gene-based neuromodulation for control of medically-refractory epilepsy.

26. **Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Perucca E, Tomson T. Progress report on new antiepileptic drugs: A summary of the Eigth Eilat Conference (EILAT VIII).** ***Epilepsy Res.*** **2006.**
Abstract: The Eigth 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, valrocemide, 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. Progress report on new antiepileptic drugs: A summary of the Eigth Eilat Conference (EILAT VIII).

27. **Blum AS, Morvarid B. Neurostimulation for epilepsy.** ***Med Health R I.*** **2006;89:127-9.**
Neurostimulation for epilepsy.

28. **Tecoma ES, Iragui VJ. Vagus nerve stimulation use and effect in epilepsy: what have we learned?** ***Epilepsy Behav.*** **2006;8:127-36.**
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. Vagus nerve stimulation use and effect in epilepsy: what have we learned?

29. **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: Taylor & Francis; 2006:608-613.**

30. **Helmers SL, Holmes MD. Vagus nerve stimulation: history and overview. In: Miller JW, Silbergeld DL, eds. *Epilepsy Surgery: Principles and Controversies*. New York: Taylor & Francis; 2006:597-607.**

31. **Atkinson PB, Labiner DM. Shocking the wandering nerve: Vagus nerve stimulation after a decade of widespread use. *US Neurological Disease.* 2006.**

32. **Ryvlin P. The modern challenges of drug resistant epilepsy. *Epileptic Disord.* 2005;7(suppl 1):1-2.** The modern challenges of drug resistant epilepsy.

33. **Ben-Menachem E, A French J. VNS Therapy versus the latest antiepileptic drug. *Epileptic Disord.* 2005; 7(suppl 1):22-26.**
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 l988, 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. VNS Therapy versus the latest antiepileptic drug.

34. **Turner MD, Glickman RS. Epilepsy in the oral and maxillofacial patient: current therapy. *J Oral Maxillofac Surg.* 2005;63:996-1005.** Epilepsy in the oral and maxillofacial patient: current therapy.

35. **Oommen J, Morrell M, Fisher RS. Experimental electrical stimulation therapy for epilepsy. *Curr Treat Options Neurol.* 2005;7:261-271.**
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. Experimental electrical stimulation therapy for epilepsy.

36. **Nadkarni S, LaJoie J, Devinsky O. Current treatments of epilepsy. *Neurology.* 2005;64(suppl 3):S2-S11.**
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. Current treatments of epilepsy.

37. **Sheth RD, Stafstrom CE, Hsu D. Nonpharmacological treatment options for epilepsy. *Semin Pediatr Neurol.* 2005;12:106-113.**
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. Nonpharmacological treatment options for epilepsy.

38. **Groves DA, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. *Neurosci Biobehav Rev.* 2005;29:493-500.**
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. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects.

39. **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;2:175-89.**
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. Improving the lives of patients with medically refractory epilepsy by electrical stimulation of the nervous system.

40. **Wolf P. From precipitation to inhibition of seizures: rationale of a therapeutic paradigm. *Epilepsia.* 2005;46 Suppl 1:15-16.**
Abstract: Summary: 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. From precipitation to inhibition of seizures: rationale of a therapeutic paradigm.

41. **Guberman A. Vagus nerve stimulation in the treatment of epilepsy. *CMAJ.* 2004;171:1165-1166.** Vagus nerve stimulation in the treatment of epilepsy.

42. **Polkey CE. Brain stimulation in the treatment of epilepsy. *Expert Rev Neurother.* 2004;4:965-972.**
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. Brain stimulation in the treatment of epilepsy.

43. **Jellinger KA. Vagus nerve stimulation. *Eur J Neurol.* 2004;11:721.**

44. **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;61:1-48.**
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 valrocemide (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. Progress report on new antiepileptic drugs: a summary of the Seventh Eilat Conference (EILAT VII).

45. **Wheless JW, Baumgartner J. Vagus nerve stimulation therapy. *Drugs Today (Barc).* 2004;40:501-15.**
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. Vagus nerve stimulation therapy.

46. **Theodore WH, Fisher RS. Brain stimulation for epilepsy. *Lancet Neurol.* 2004;3:111-8.**
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. Brain stimulation for epilepsy.

47. **Leonard EC Jr. Did some 18th and 19th century treatments for mental disorders act on the brain? *Med Hypotheses.* 2004;62:219-221.**
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. Did some 18th and 19th century treatments for mental disorders act on the brain?

48. **Kernich CA. Vagus nerve stimulation. *Neurologist.* 2004;10:57-58.**
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. Vagus nerve stimulation.

49. **Sackeim HA. Vagus nerve stimulation. In: Lisanby SH, ed. *Brain Stimulation in Psychiatric Treatment.* Washington: American Psychiatric Publishing; 2004:99-143.**

50. **Kelso AR, Cock HR. Advances in epilepsy. *Br Med Bull.* 2004;72:135-148.**
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. Advances in epilepsy.

51. **Goodman JH. Brain stimulation as a therapy for epilepsy. *Adv Exp Med Biol.* 2004;548:239-247.**
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. Brain stimulation as a therapy for epilepsy.

52. **Vonck K, Boon P, Goossens L, et al. Neurostimulation for refractory epilepsy. *Acta Neurol Belg.* 2003;103:213-7.**
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 mechanims of action of DBS for epilepsy. Neurostimulation for refractory epilepsy.

53. **Litt B. Evaluating devices for treating epilepsy. *Epilepsia.* 2003;44 Suppl 7:30-37.**
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. Evaluating devices for treating epilepsy.

54. **DeGiorgio CM, Shewmon DA, Whitehurst T. Trigeminal nerve stimulation for epilepsy. *Neurology.* 2003;61:421-422.** Trigeminal nerve stimulation for epilepsy.

55. **Albensi BC. A comparison of drug treatment versus electrical stimulation for suppressing seizure activity. *Drug News Perspect.* 2003;16:347-352.**
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. A comparison of drug treatment versus electrical stimulation for suppressing seizure activity.

56. **Sirven JI. The current treatment of epilepsy: a challenge of choices. *Curr Neurol Neurosci Rep.* 2003;3:349-356.**
Notes: Current epilepsy treatmentsAEDs, surgery, VNS, and ketogenic dietare 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. The current treatment of epilepsy: a challenge of choices.

57. **Nguyen DK, Spencer SS. Recent advances in the treatment of epilepsy. *Arch Neurol.* 2003;60:929-935.**
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.
Abstract: Great progress has been seen in the treatment of epilepsy during the past decade, with the marketing of eight new anticonvulsants and an innovative neurostimulation device. This plethora of options creates dilemmas for physicians faced with treatment decisions. This article reviews recent advances in epilepsy treatment, in the context of available evidence. Recent advances in the treatment of epilepsy.

58. **George MS, Nahas Z, Kozol FA, et al. Mechanisms and the current state of transcranial magnetic stimulation. *CNS Spectr.* 2003;8:496-514.**
Abstract: Transcranial magnetic stimulation (TMS) is unique among the current brain stimulation techniques because it is relatively non-invasive. TMS markedly differs from vagus nerve stimulation, deep brain stimulation and magnetic seizure therapy, all of which require either an implanted prosthesis or general anesthesia, or both. Since its rebirth in its modern form in 1985, TMS has already shown potential usefulness in at least three important domains-as a basic neuroscience research instrument, as a potential clinical diagnostic tool, and as a therapy for several different neuropsychiatric conditions. The TMS scientific literature has now expanded beyond what a single summary article can adequately cover. This review highlights several new developments in combining TMS with functional brain imaging, using TMS as a psychiatric therapy, potentially using TMS to enhance performance, and finally recent advances in the core technology of TMS. TMS' ability to non-invasively and focally stimulate the brain of an awake human is proving to be a most important development for neuroscience in general, and neuropsychiatry in particular. Mechanisms and the current state of transcranial magnetic stimulation.

59. **Polkey CE. Alternative surgical procedures to help drug-resistant epilepsy - a review. *Epileptic Disord.* 2003;5:63-75.**
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. Alternative surgical procedures to help drug-resistant epilepsy - a review.

60. **Waterhouse E. New horizons in ambulatory electroencephalography. *IEEE Eng Med Biol Mag.* 2003;22:74-80.**
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 evolvefrom 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. New horizons in ambulatory electroencephalography.

61. **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.**
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. Neuroprotection trek--the next generation: neuromodulation I. Techniques--deep brain stimulation, vagus nerve stimulation, and transcranial magnetic stimulation.

62. **Cohen-Gadol AA, Stoffman MR, Spencer DD. Emerging surgical and radiotherapeutic techniques for treating epilepsy. *Curr Opin Neurol.* 2003;16:213-219.**
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. Emerging surgical and radiotherapeutic techniques for treating epilepsy.

63. **Salinsky MC. Vagus nerve stimulation as treatment for epileptic seizures. *Curr Treat Options Neurol.* 2003;5:111-120.**
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. Vagus nerve stimulation as treatment for epileptic seizures.

64. **Romano CJ. Another option for seizure control. *Neurology Reviews.* 2003;9.**

65. **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;78:238-48.**
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. Neurostimulation therapy for epilepsy: current modalities and future directions.

66. **Murphy JV, Patil A. Stimulation of the nervous system for the management of seizures: current and future developments. *CNS Drugs.* 2003;17:101-15.**
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 >/=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. Stimulation of the nervous system for the management of seizures: current and future developments.

67. Special groups of patients. Refractory epilepsy. *Epilepsia.* 2003;44(suppl 6):81-82.
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.”

68. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet Neurol.* 2002;1:477-482.
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. Vagus-nerve stimulation for the treatment of epilepsy.

69. **Wild D. Epilepsy therapies have similar impact on quality of life. CNS News. 2002:12.**

70. **Schachter SC, Wheless JW. The evolving place of vagus nerve stimulation therapy. *Neurology.* 2002;59:S1-2.**
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. The evolving place of vagus nerve stimulation therapy.

71. **Schachter SC. Vagus nerve stimulation therapy summary: five years after FDA approval. *Neurology.* 2002;59(suppl 4):S15-S20.**
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. Vagus nerve stimulation therapy summary: five years after FDA approval.

72. **George MS, Nahas Z, Bohning DE, et al. Vagus nerve stimulation therapy: a research update. *Neurology.* 2002;59:S56-61.**
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. Vagus nerve stimulation therapy: a research update.

73. **Karceski S. Devices in the treatment of epilepsy. *Semin Neurol.* 2002;22:259-268.**
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. Devices in the treatment of epilepsy.

74. **Labar D, Dean A. Neurostimulation therapy for epilepsy. *Curr Neurol Neurosci Rep.* 2002;2:357-64.**
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-Gastuat syndome. 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. Neurostimulation therapy for epilepsy.

75. **Schachter SC. Vagus nerve stimulation: where are we? *Curr Opin Neurol.* 2002;15:201-206.**
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. Vagus nerve stimulation: where are we?

76. **Lanska DJ. J.L. Corning and vagal nerve stimulation for seizures in the 1880s. *Neurology.* 2002;58:452-459.**
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. Corning and

vagal nerve stimulation for seizures in the 1880s.

77. **Upton A. Vagal stimulation for intractable seizures. *Adv Exp Med Biol.* 2002;497:233-239.**
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. Vagal stimulation for intractable seizures.

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

79. **Boon P, Vonck K, De Reuck J, Caemaert J. Vagus nerve stimulation for refractory epilepsy. *Seizure.* 2001;10:448-55.**
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. Vagus nerve stimulation for refractory epilepsy.

80. **Boon PA. Vagus nerve stimulation for refractory epilepsy. *J Clin Neurophysiol.* 2001;18:393.** Vagus nerve stimulation for refractory epilepsy.

81. **Chadwick D. Vagal-nerve stimulation for epilepsy. *Lancet.* 2001;357:1726-1727.** Vagal-nerve stimulation for epilepsy.

82. **Krishnamoorthy ES . Psychiatric issues in epilepsy. *Curr Opin Neurol.* 2001;14:217-224.**
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. Psychiatric issues in epilepsy.

83. **Weinstein S. The anticonvulsant effect of electrical fields. *Curr Neurol Neurosci Rep.* 2001;1:155-161.**
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. The anticonvulsant effect of electrical fields.

84. **Schachter SC. Epilepsy. *Neurol Clin.* 2001;19:57-78.**
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.

85. **Wheless JW. Vagus nerve stimulation. In: Wyllie E, ed. *The Treatment of Epilepsy. Principles and Practice*. Philadelphia: Lippincott Williams & Wilkins; 2001:1007-1015.**

86. **Schmidt D. Vagus nerve stimulation for the treatment of epilepsy. *Epilepsy Behav.* 2001;2:S1-S5.**

87. **Karceski S, Morrell M, Carpenter D. The expert consensus guideline series: treatment of epilepsy. *Epilepsy Behav.* 2001;2:A1-A50.**

88. **Chayasirisobhon S , Koulouris S, Parker E, et al. Vagus nerve stimulation for refractory epilepsy. *The Permanente Journal.* 2001;5:21-26.**

89. **Benbadis SR, Tatum WO, Vale FL. When drugs don't work: an algorithmic approach to medically intractable epilepsy. *Neurology.* 2000;55:1780-1784.** When drugs don't work: an algorithmic approach to medically intractable epilepsy.

90. **Aiken SP, Brown WM. Treatment of epilepsy: existing therapies and future developments. *Front Biosci.* 2000;5:E124-E152 .**
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. Treatment of epilepsy: existing therapies and future developments.

91. **Vagus nerve stimulation for epilepsy. *Clin Privil White Pap.* 2000;1-8.**

92. **Wilkins DE. Reassessment: vagus nerve stimulation for epilepsy. *Neurology.* 2000;54:2027.** Reassessment: vagus nerve stimulation for epilepsy.

93. **Uthman BM. Vagus nerve stimulation for seizures. *Arch Med Res.* 2000;31:300-303.**
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%). Vagus nerve stimulation for seizures.

94. **Binnie CD. Vagus nerve stimulation for epilepsy: a review. *Seizure.* 2000;9:161-169.**
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. Vagus nerve stimulation for epilepsy: a review.

95. Ben-Menachem E. New antiepileptic drugs and non-pharmacological treatments. *Curr Opin Neurol.* 2000;13:165-170.
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. New antiepileptic drugs and non-pharmacological treatments.

96. Nerve stimulator useful in treating epilepsy. *Mayo Clin Health Lett.* 1999;17:4. Nerve stimulator useful in treating epilepsy.

97. 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;39:489-495.
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. Experience with vagus nerve stimulation for intractable epilepsy: some questions and answers.

98. **Devinsky O. Patients with refractory seizures. *N Engl J Med.* 1999;340:1565-1570.** Patients with refractory seizures.

99. **Lesser RP. Unexpected places: how did vagus nerve stimulation become a treatment for epilepsy? *Neurology.* 1999;52:1117-1118.** Unexpected places: how did vagus nerve stimulation become a treatment for epilepsy?

100. **Privitera MD. Evidence-based medicine and antiepileptic drugs. *Epilepsia.* 1999;40(suppl 5):S47-S56 .**
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. Evidence-based medicine and antiepileptic drugs.

101. **Snively C, Counsell C, Lilly D. Vagus nerve stimulator as a treatment for intractable epilepsy. *J Neurosci Nurs.* 1998;30:286-289.**
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. Vagus nerve stimulator as a treatment for intractable epilepsy.

102. **Henry TR. Most commonly asked questions about vagus nerve stimulation for epilepsy. *The Neurologist.* 1998;4:284-289.**

103. **Herman ST, Pedley TA. New options for the treatment of epilepsy. *JAMA.* 1998;280:693-694.** New options for the treatment of epilepsy.

104. **Schachter SC, Saper CB. Vagus nerve stimulation. *Epilepsia.* 1998;39:677-686.**
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. Vagus nerve stimulation.

105. **Marks WJ Jr, Garcia PA. Management of seizures and epilepsy. *Am Fam Physician.* 1998;57:1589-1600, 1603-1604.**
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. Management of seizures and epilepsy.

106. **Sander JW. New drugs for epilepsy. *Curr Opin Neurol.* 1998;11:141-148.**
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.

107. **McLachlan RS. Vagus nerve stimulation for treatment of seizures? *Arch Neurol.* 1998;55:232-233.** Vagus nerve stimulation for treatment of seizures?

108. **Hachinski V. Vagus nerve stimulation therapy. *Arch Neurol.* 1998;55:234.** Vagus nerve stimulation therapy.

109. **Ben-Menachem E. Vagus nerve stimulation for treatment of seizures? *Arch Neurol.* 1998;55:231-232.** Vagus nerve stimulation for treatment of seizures?

110. **Schachter SC. Vagus nerve stimulation: current status and clinical applications. *Expert Opin Investig Drugs.* 1997;6:1327-1335.**
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. Vagus nerve stimulation: current status and clinical applications.

111. **Phillips P. Current view of advances in epilepsy. *JAMA*. 1997;278:883-886.** Current view of advances in epilepsy.

112. **McLachlan RS. Vagus nerve stimulation for intractable epilepsy: a review. *J Clin Neurophysiol.* 1997;14:358-368.**
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. Vagus nerve stimulation for intractable epilepsy: a review.

113. **Ben-Menachem E. Modern management of epilepsy: Vagus nerve stimulation. *Baillieres Clin Neurol.* 1996;5:841-848.**
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. Modern management of epilepsy: Vagus nerve stimulation.

114. **Neufeld MY, Korczyn AD. New drugs and vagal stimulation for treatment of epilepsy--the Israeli experience. *Neurol Neurochir Pol.* 1996;30(suppl 2):113-120.**
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. New drugs and vagal stimulation for treatment of epilepsy--the Israeli experience.

115. **Shimizu H, Ishijima B, Nakamura K, et al. Effect of vagal stimulation on intractable epilepsy. *Psychiatry Clin Neurosci.* 1995;49:S254-S255.** Effect of vagal stimulation on intractable epilepsy.

116. **Rafael H, Moromizato P. Vagus stimulator for seizures. *J Neurosurg.* 1993;79:636-637.** Vagus stimulator for seizures.

117. **McLachlan RS. Suppression of interictal spikes and seizures by stimulation of the vagus nerve. *Epilepsia.* 1993;34:918-923.**
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 < 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 +/- 15.7 s without stimulation to 5.0 +/- 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. Suppression of interictal spikes and seizures by stimulation of the vagus nerve.

118. **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-S60.** Vagus nerve stimulation for the control of epilepsy.

Right-Sided VNS Therapy

1. **Zhang Y, Ilsar I, Sabbah HN, Ben David T, Mazgalev TN. Relationship between right cervical vagus nerve stimulation and atrial fibrillation inducibility: therapeutic intensities do not increase arrhythmogenesis. *Heart Rhythm.* 2009;6:244-50.**
Abstract: BACKGROUND: Strong vagus nerve stimulation (VNS) is routinely used to induce and maintain atrial fibrillation (AF) in acute animal studies. Taken as a surrogate of increased vagal tone, such observations suggest an arrhythmogenic role of VNS in AF. In contrast, VNS has been demonstrated to have profound therapeutic effects in heart failure and other ailments. OBJECTIVE: The purpose of this study was to examine the relationship between right cervical VNS and AF, especially the potential arrhythmogenic effects of therapeutic VNS. METHODS: The relationship between VNS intensities and AF inducibility was studied in eight acute dogs at baseline and four different levels of VNS, which were set to prolong spontaneous sinus cycle length (SCL) by 20%, 40%, 60%, or 100%. The effect of mild VNS treatment on AF induction was further investigated in six chronically instrumented conscious dogs. These dogs were implanted with right cervical VNS stimulators and specialized atrial pacemakers. VNS intensity was titrated to slow the sinus rate by 10%. RESULTS: In acute studies, it was found that mild to moderate VNS (i.e., producing < or =40% SCL prolongation) did not increase AF inducibility, while strong VNS (i.e., producing > or =60% SCL prolongation) did. In chronic studies, compared with controls, AF induction did not change during the 4-week VNS treatment. CONCLUSIONS: AF inducibility by right cervical VNS is intensity dependent: strong VNS (producing > or =60% SCL prolongation) facilitates AF, while moderate VNS (producing < or =40% SCL prolongation) appears not to affect AF. The nonarrhythmogenic effect of therapeutic chronic VNS was further verified in conscious animals. We conclude that VNS with moderate intensities can be used to deliver therapeutic benefits without arrhythmogenic risk. Relationship between right cervical vagus nerve stimulation and atrial fibrillation inducibility: therapeutic intensities do not increase arrhythmogenesis.

2. **Spuck S, Nowak G, Renneberg A, Tronnier V, Sperner J. Right-sided vagus nerve stimulation in humans: an effective therapy? *Epilepsy Res.* 2008;82:232-4.**
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. Right-sided vagus nerve stimulation in humans: an effective therapy?

3. **Tubbs RS, Salter EG, Killingsworth C, et al. Right-sided vagus nerve stimulation inhibits induced spinal cord seizures. *Clin Anat.* 2007;20:23-6.**
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. Right-sided vagus nerve stimulation inhibits induced spinal cord seizures.

4. **McGregor A, Wheless J, Baumgartner J, Bettis D. Right-sided vagus nerve stimulation as a treatment for refractory epilepsy in humans. *Epilepsia.* 2005;46:91-6.**
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. Right-sided vagus nerve stimulation as a treatment for refractory epilepsy in humans.

5. **McGregor A, Wheless J. Response: Right-sided vagus nerve stimulation. *Epilepsia.* 2005;46:1152-1153.** Response: Right-sided vagus nerve stimulation.

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;56:1-4.**
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. Right-sided vagus nerve stimulation reduces generalized seizure severity in rats as effectively as left-sided.

Ring Chromosome 20 Syndrome

1. **Herrgard E, Mononen T, Mervaala E, et al. More severe epilepsy and cognitive impairment in the offspring of a mother with mosaicism for the ring 20 chromosome. *Epilepsy Res.* 2007;73:122-128.**
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 nondysmophic, 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. More severe epilepsy and cognitive impairment in the offspring of a mother with mosaicism for the ring 20 chromosome.

2. **Parr JR, Pang K, Mollett A, et al. Epilepsy responds to vagus nerve stimulation in ring chromosome 20 syndrome. *Dev Med Child Neurol.* 2006;48:80.** Epilepsy responds to vagus nerve stimulation in ring chromosome 20 syndrome.

3. **Alpman A, Serdaroglu G, Cogulu O, Tekgul H, Gokben S, Ozkinay F . Ring chromosome 20 syndrome with intractable epilepsy. *Dev Med Child Neurol.* 2005;47:343-346.**
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. Ring chromosome 20 syndrome with intractable epilepsy.

4. **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;17:778-780.**
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. Intractable epilepsy with ring chromosome 20 syndrome treated with vagal nerve stimulation: case report and review of the literature.

Safety

1. **Zaaimi B, Grebe R, Berquin P, Wallois F. Vagus nerve stimulation induces changes in respiratory sinus arrhythmia of epileptic children during sleep. *Epilepsia.* 2009;50:2473-80.**
Abstract: PURPOSE: This study analyzed the direct short-term effect of vagus nerve stimulation (VNS) on respiratory sinus arrhythmia (RSA) in children with pharmacoresistant 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(2)) 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. Vagus nerve stimulation induces changes in respiratory sinus arrhythmia of epileptic children during sleep.

2. **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;25:195-7.**
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. Cardiac rhythm disturbance in a depressed patient after implantation with a vagus nerve stimulator.

3. **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;120:139-42.**

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. Application of a vagal nerve stimulator in an epilepsy patient with cardiac pacemaker after post-ictal cardiac arrest.

4. **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;18:339-42.**
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. Mode of vagus nerve stimulation differentially affects sleep related breathing in patients with epilepsy.

5. **Roebling R, Huch K, Kassubek J, Lerche H, Weber Y. Cervical spinal MRI in a patient with a vagus nerve stimulator (VNS). *Epilepsy Res.* 2009;84:273-5.**
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. Cervical spinal MRI in a patient with a vagus nerve stimulator (VNS).

6. **Iriarte J, Urrestarazu E, Alegre M, et al. Late-onset periodic asystolia during vagus nerve stimulation. *Epilepsia.* 2009;50:928-32.**
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 bradyarrythmia 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. Late-onset periodic asystolia during vagus nerve stimulation.

7. **Air EL, Ghomri YM, Tyagi R, Grande AW, Crone K, Mangano FT . Management of vagal nerve stimulator infections: do they need to be removed. Clinical article? *J Neurosurg Pediatr.* 2009;3:73-8.**
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. Management of vagal nerve stimulator infections: do they need to be removed.

8. **Ebben MR, Sethi NK, Conte M, Pollak CP, Labar D. Vagus nerve stimulation, sleep apnea, and CPAP titration. *J Clin Sleep Med.* 2008;4:471-3.**
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 H2O 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. Vagus nerve stimulation, sleep apnea, and CPAP titration.

9. **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;20:229-30.** Case report of an interaction of a vagal nerve stimulation system with a microwave current from a body fat analyzer.

10. **Papathanasion ES, Papacostas SS. Sleep-related breathing disorders in children with vagal nerve stimulators. *Pediatr Neurol.* 2008;39:142; author reply 142.** Sleep-related breathing disorders in children with vagal nerve stimulators.

11. **Rauchenzauner M, Haberlandt E, Ortler M, et al. N-terminal pro-brain natriuretic peptide (NT-proBNP) release in children with vagus nerve stimulation. A prospective case series. *J Neurol.* 2008;255:980-5.**
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. N-terminal pro-brain natriuretic peptide (NT-proBNP) release in children with vagus nerve stimulation. A prospective case series.

12. **Keller S, Lichtenberg P. Psychotic exacerbation in a patient with seizure disorder treated with vagus nerve stimulation. *Isr Med Assoc J.* 2008;10:550-1.** Psychotic exacerbation in a patient with seizure disorder treated with vagus nerve stimulation.

13. **Rijkers K, Berfelo MW, Cornips EM, Majoie HJ. Hardware failure in vagus nerve stimulation therapy. *Acta Neurochir (Wien).* 2008;150:403-5.**
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. Hardware failure in vagus nerve stimulation therapy.

14. **Pearl PL, Conry JA, Yaun A, et al. Misidentification of vagus nerve stimulator for intravenous access and other major adverse events. *Pediatr Neurol.* 2008;38:248-51.**
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. Misidentification of vagus nerve stimulator for intravenous access and other major adverse events.

15. **Hsieh T, Chen M, McAfee A, Kifle Y. Sleep-related breathing disorder in children with vagal nerve stimulators. *Pediatr Neurol.* 2008;38:99-103.**
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. Sleep-related breathing disorder in children with vagal nerve stimulators.

16. **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;107:519-20.**
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. Preservation of a subcutaneous pocket for vagus nerve stimulation pulse generator during magnetoencephalography. Technical note.

17. **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;109:849-52.**
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. Cardiac responses of vagus nerve stimulation: intraoperative bradycardia and subsequent chronic stimulation.

18. **Khurana DS, Reumann M, Hobdell EF, et al. Vagus nerve stimulation in children with refractory epilepsy: unusual complications and relationship to sleep-disordered breathing. *Childs Nerv Syst.* 2007;23:1309-12.**
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. Vagus nerve stimulation in children with refractory epilepsy: unusual complications and relationship to sleep-disordered breathing.

19. **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;109:788-90.**
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. Vocal cord paralysis after vagus nerve stimulator battery replacement successfully treated with medialization thyroplasty.

20. **Sinclair R, Bajekal RR. Vagal nerve stimulation and reflux. *Anesth Analg.* 2007;105:884-5; author reply 885.** Vagal nerve stimulation and reflux.

21. **Zaaimi B, Grebe R, Berquin P, Wallois F. Vagus nerve stimulation therapy induces changes in heart rate of children during sleep. *Epilepsia.* 2007;48:923-30.**
Abstract: PURPOSE: This study analyzed changes in the heart rates of children receiving vagus nerve stimulation (VNS) therapy for pharmacoresistant epilepsy. METHODS: Changes in the heart rates of ten children receiving VNS therapy for pharmacoresistant 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 pharmacoresistant epilepsy, cardiorespiratory variations occurred while the VNS therapy pulse generator was delivering stimulation. Understanding these variations may allow further optimization of VNS parameters. Vagus nerve stimulation therapy induces changes in heart rate of children during sleep.

22. **Amark P, Stodberg T, Wallstedt L. Late onset bradyarrhythmia during vagus nerve stimulation. *Epilepsia.* 2007;48:1023-4.**
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. Late onset bradyarrhythmia during vagus nerve stimulation.

23. **Papacostas SS, Myrianthopoulou P, Dietis A, Papathanasiou ES. Induction of central-type sleep apnea by vagus nerve stimulation. *Electromyogr Clin Neurophysiol.* 2007;47:61-3.**
Abstract: Vagus nerve stimulation (VNS) is an acceptable and effective adjunctive therapy for pharmacoresistant 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. Induction of central-type sleep apnea by vagus nerve stimulation.

24. **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;115:260-7.**
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. Predictors of laryngeal complications in patients implanted with the Cyberonics vagal nerve stimulator.

25. **Rychlicki F, Zamponi N, Cesaroni E, et al. Complications of vagal nerve stimulation for epilepsy in children. *Neurosurg Rev.* 2006;29:103-7.**
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. Complications of vagal nerve stimulation for epilepsy in children.

26. **Pruvost M, Zaaimi B, Grebe R, Wallois F, Berquin P, Perlitz V. Cardiorespiratory effects induced by vagus nerve stimulation in epileptic children. *Med Biol Eng Comput.* 2006;44:338-47.**
Abstract: Vagus nerve stimulation (VNS) is used in pharmaco-resistant epilepsy to decrease the number of seizures. Although it is well known that VNS affects respiration, there are only a few reports concerning an effect of VNS on heart rate or heart rate variability (HRV). We investigated the relationship between respiratory frequency and the high frequency (HF) domain of the discrete Fourier transform (DFT) of the RR interval

function during night sleep recordings of ten subjects treated with VNS. Our results show that VNS shifts the frequency of maximal power spectrum density (PSD) in the HF-band, decreases the related PSD and induces a partial cardiorespiratory decoupling. Cardiorespiratory effects induced by vagus nerve stimulation in epileptic children.

27. **Ronkainen E, Korpelainen JT, Heikkinen E, Myllylä VV, Huikuri HV, Isojärvi JI. Cardiac autonomic control in patients with refractory epilepsy before and during vagus nerve stimulation treatment: a one-year follow-up study. *Epilepsia.* 2006;47:556-562.**
Abstract: Summary: Purpose: To elucidate possible effect of vagus nerve stimulation (VNS) therapy on interictal heart rate (HR) variability in patients with refractory epilepsy before and after 1-year VNS treatment. Methods: A 24-hour electrocardiogram (ECG) was recorded at the baseline and after 12 months of VNS treatment in 14 patients with refractory epilepsy, and once in 28 healthy age- and sex-matched control subjects. Time and frequency domain measures, along with fractal and complexity measures of HR variability, were analyzed from the ECG recordings. Results: The mean value of the RR interval ($p = 0.008$), standard deviation of N-N intervals (SDNN) ($p < 0.001$), very-low frequency (VLF) ($p < 0.001$), low-frequency (LF) ($p = 0.001$), and high-frequency (HF) ($p = 0.002$) spectral components of HR variability, and the Poincare components SD1 ($p = 0.005$) and SD2 ($p < 0.001$) of the patients with refractory epilepsy were significantly lower than those of the control subjects before VNS implantation. The nocturnal increase in HR variability usually seen in the normal population was absent in patients with refractory epilepsy. VNS had no significant effects on any of the HR-variability indexes despite a significant reduction in the frequency of seizures. Conclusions: HR variability was reduced, and the nocturnal increase in HR variability was not present in patients with refractory epilepsy. One-year treatment with VNS did not have a marked effect on HR variability, suggesting that impaired cardiovascular autonomic regulation is associated with the epileptic process itself rather than with recurrent seizures. Cardiac autonomic control in patients with refractory epilepsy before and during vagus nerve stimulation treatment: a one-year follow-up study.

28. **Zaaimi B, Heberle C, Berquin P, Pruvost M, Grebe R, Wallois F. Vagus nerve stimulation induces concomitant respiratory alterations and a decrease in SaO2 in children. *Epilepsia.* 2005;46:1802-9.**
Abstract: PURPOSE: To analyze respiratory alterations and effects on SaO(2) caused by vagus nerve stimulation (VNS) in children with epilepsy. METHODS: Polysomnographic recordings, including electroencephalography, thoracoabdominal distention, nasal airflow, SaO(2), and VNS artifact were evaluated in 10 children with pharmacoresistant 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(2) 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(2). It is possible that VNS has a neuroprotective effect, and this possibility calls for further investigation. Vagus nerve stimulation induces concomitant respiratory alterations and a decrease in

SaO2 in children

29. **Carius A, Schulze-Bonhage A. Trigeminal pain under vagus nerve stimulation. *Pain.* 2005;118:271-3.**
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. Trigeminal pain under vagus nerve stimulation.

30. **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;116:2501-2504.**
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/cm2/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. A lack of effect from transcranial magnetic stimulation (TMS) on the vagus nerve stimulator (VNS).

31. **Stamboulis E, Catsaros N, Gatzonis S, Siafakas A, Georgacoulias N, Sakas D. Cardiac vagal tests and vagus nerve stimulation in epilepsy. *Clin Auton Res.* 2005;15:54-56.**
Cardiac vagal tests and vagus nerve stimulation in epilepsy.

32. **Shaffer MJ, Jackson CE, Szabo CA, Simpson CB. Vagal nerve stimulation: clinical and electrophysiological effects on vocal fold function. *Ann Otol Rhinol Laryngol.* 2005;114:7-14.**
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. Vagal nerve stimulation: clinical and electrophysiological effects on vocal fold function.

33. **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;127:401-402.**
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. Identification and treatment of bronchoconstriction induced by a vagus nerve stimulator employed for management of seizure disorder.

34. **Srinivasan B, Awasthi A. Transient atrial fibrillation after the implantation of a vagus nerve stimulator. *Epilepsia.* 2004;45:1645.** Transient atrial fibrillation after the implantation of a vagus nerve stimulator.

35. **Ali II, Pirzada NA, Kanjwal Y, et al. Complete heart block with ventricular asystole during left vagus nerve stimulation for epilepsy. *Epilepsy Behav.* 2004;5:768-771.**
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. Complete heart block with ventricular asystole during left vagus nerve stimulation for epilepsy.

36. **Jandial R, Aryan HE, Hughes SA, Levy ML. Effect of vagus nerve stimulator magnet on programmable shunt settings. *Neurosurgery.* 2004;55:627-630.**
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. Effect of vagus nerve stimulator magnet on programmable shunt settings.

37. **Patel NC, Edwards MS. Vagal nerve stimulator pocket infections. *Pediatr Infect Dis J.* 2004;23:681-683.**
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. Vagal nerve stimulator pocket infections.

38. **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;25:356-361.**
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. In vitro study of the electromagnetic interaction between wireless phones and an implantable neural stimulator.

39. **Rizzo P, Beelke M, De Carli F, et al. Modifications of sleep EEG induced by chronic vagus nerve stimulation in patients affected by refractory epilepsy. *Clin Neurophysiol.* 2004;115:658-64.**
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. Modifications of sleep EEG induced by chronic vagus nerve stimulation in patients affected by refractory epilepsy.

40. **Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. *Circulation.* 2004;109:120-124.**
Abstract: BACKGROUND: Diminished cardiac vagal activity and higher heart rate predict a high mortality rate of chronic heart failure (CHF) after myocardial infarction. We investigated the effects of chronic electrical stimulation of the vagus nerve on cardiac remodeling and long-term survival in an animal model of CHF after large myocardial infarction. METHODS AND RESULTS: Two weeks after the ligation of the left coronary artery, surviving rats were randomized to vagal- and sham-stimulated groups. Using an implantable miniature radio-controlled electrical stimulator, we stimulated the right vagal nerve of CHF rats for 6 weeks. The intensity of electrical stimulation was adjusted for each rat, so that the heart rate was lowered by 20 to 30 beats per minute. The treated rats had significantly lower left ventricular end-diastolic pressure (17.1+/-5.9 versus 23.5+/-4.2 mm Hg, $P<0.05$) and higher maximum dp/dt of left ventricular pressure (4152+/-237 versus 2987+/-192 mm Hg/s, $P<0.05$) than the untreated rats. Improvement of cardiac pumping function was accompanied by a decrease in normalized biventricular weight (2.75+/-0.25 versus 3.14+/-0.22 g/kg, $P<0.01$). Although the 140-day survival of the untreated group was only half, vagal stimulation markedly improved the survival rate (86% versus 50%, $P=0.008$). Vagal stimulation therapy achieved a 73% reduction in a relative risk ratio of death. CONCLUSIONS: Vagal nerve stimulation markedly improved the long-term survival of CHF rats through the prevention of pumping failure and cardiac remodeling. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats.

41. **Hunter TB, Yoshino MT, Dzioba RB, Light RA, Berger WG. Medical devices of the head, neck, and spine. *Radiographics.* 2004;24:257-285.**
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. Medical devices of the head, neck, and spine.

42. **Holmes MD, Chang M, Kapur V. Sleep apnea and excessive daytime somnolence induced by vagal nerve stimulation. *Neurology.* 2003;61:1126-9.**
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. Sleep apnea and excessive daytime somnolence induced by vagal nerve stimulation.

43. **Smyth MD, Tubbs RS, Bebin EM, Grabb PA, Blount JP. Complications of chronic vagus nerve stimulation for epilepsy in children. *J Neurosurg.* 2003;99:500-3.**
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%). Complications of chronic vagus nerve stimulation for epilepsy in children.

44. **De Herdt V, Boon P, Vonck K, et al. Are psychotic symptoms related to vagus nerve stimulation in epilepsy patients? *Acta Neurol Belg.* 2003;103:170-5.**
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. Are psychotic symptoms related to vagus nerve stimulation in epilepsy patients?

45. **Galli R, Limbruno U, Pizzanelli C, et al. Analysis of RR variability in drug-resistant epilepsy patients chronically treated with vagus nerve stimulation. *Auton Neurosci.* 2003;107:52-59.**
Notes: This was a 36-month study that looked at the short-term (1 month) and long-term (36 months) effects of VNS Therapy on autonomic cardiac function compared with baseline (n=7). Although a slight reduction of the high-frequency component of the spectrum during the night and a flattening of sympathovagal circadian changes were seen during the study in the long term, no clinically relevant cardiac side effects were seen with VNS Therapy. No arrhythmias or heart failure were associated with long-term VNS. This study confirmed that VNS is an effective and safe adjunctive treatment for refractory epilepsy.
Abstract: Vagus nerve stimulation (VNS) has been suggested as an adjunctive treatment for drug-resistant epilepsy when surgery is inadvisable. The overall safety profile of VNS seems to be favorable as only minor adverse effects have been described. The purpose of this study was to determine if cardiac vagal tone is eventually modified by short- and long-term VNS. The effects of short- and long-term VNS were evaluated in seven subjects with intractable epilepsy. Autonomic cardiac function has been carried out by means of a 24-h analysis of RR variability at baseline (t(0)), 1 month (t(1), short-term VNS) and 36 months after VNS initiation (t(2), long-term VNS). Frequency- and time-domain parameters were calculated. Periodic cardiological and neurological evaluations were performed.Clinically relevant cardiac effects were not observed throughout the study. Despite the limited

number of patients and the variety of data among them, for all the patients, a common trend towards a nocturnal decrease in the high-frequency (HF) component of the spectrum was observed after long-term VNS (mean+/-S.D.: 40+/-18 normalized units (nu) at t(0), 38+/-17 nu at t(1), 18+/-10 nu at t(2); $p<0.05$ of t(2) vs. either t(0) or t(1)). The day-to-night changes in the power of low-frequency (LF) and HF components were significantly blunted after long-term VNS (LF day-to-night change: +16+/-13 nu at t(0) and +15+/-8 nu at t(1) vs. +3+/-13 nu at t(2), $p<0.02$; HF day-to-night change: -18+/-13 nu at t(0) and -13+/-11 nu at t(1) vs. +3+/-12 nu at t(2), $p<0.003$). No significant changes were observed with regard to the time-domain parameters of the heart rate variability.Throughout the neurological follow-up, one subject became seizure-free, three experienced a seizure reduction of >50%, two patients of <50% and one had no changes in his seizure frequency. Our findings suggest that long-term VNS might slightly affect cardiac autonomic function with a reduction of the HF component of the spectrum during night and a flattening of sympathovagal circadian changes, not inducing, however, clinically relevant cardiac side effects. Analysis of RR variability in drug-resistant epilepsy patients chronically treated with vagus nerve stimulation

46. **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;30:224-7.**
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, i 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. Respiratory pattern changes in sleep in children on vagal nerve stimulation for refractory epilepsy.

47. **Marzec M, Edwards J, Sagher O, Fromes G, Malow BA. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. *Epilepsia.* 2003;44:930-5.**
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. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients.

48. **Ronson RS, Puskas JD, Thourani VH, et al. Controlled intermittent asystole cardiac therapy induced by pharmacologically potentiated vagus nerve stimulation in normal and hibernating myocardium. *Ann Thorac Surg.* 2003;75:1929-1936.**
Abstract: BACKGROUND: Pharmacologically potentiated electrical stimulation of the right vagus nerve achieves controlled intermittent asystole cardiac therapy. The present study examined pathophysiologic consequences of repetitive intermittent asystoles on contractile function, myocardial blood flow, and vagus nerve function and morphology. METHODS: Open-chest anesthetized canines, with either normal left anterior descending (LAD) coronary arteries (n = 8) or severely stenotic LADs (n = 8), received pharmacologic pretreatment with pyridostigmine (0.5 mg/kg), propranolol (80 microg/kg), and verapamil (50 microg/kg) before vagus nerve stimulation. Time-matched control animals with normal (n = 4) or severely stenotic LADs (n = 6) received drugs but no vagus nerve stimulation. The vagus nerve was stimulated for 12 seconds ("on") and rested for 15 seconds ("off"). This algorithm was repeated for 15 on-off cycles, simulating using controlled intermittent asystole during the placement of 15 sutures in a distal coronary anastomosis. This 15-cycle sequence was repeated twice more, simulating a three-vessel bypass. RESULTS: Normal coronary arteries: Ninety minutes after three sets of controlled intermittent asystole, LAD blood flow was unchanged from base line (36.6 +/- 4.5 versus 33.0 +/- 4.2 mL/min, p = 0.4), and global left ventricular performance (impedance catheter, end-systolic pressure-volume relations) was similar to baseline (7.4 +/- 1.2 versus 7.2 +/- 1.0 mm Hg/mL, p = 0.1). Left anterior descending coronary artery stenosis model: Ninety minutes after CIA, there were no significant differences versus control animals in regional LAD blood flow (27 +/- 4 versus 29 +/- 5 mL/min, p = 0.4) or fractional shortening of LAD myocardium (sonomicrometry; 6.2% +/- 1.8% versus 5.4% +/- 1.2%, p = 0.1). Vagus nerve conduction and morphology were unchanged from baseline. CONCLUSIONS: Repetitive controlled intermittent asystole does not impair poststimulation coronary blood flow, cardiac contractile function, or vagus nerve function. Controlled intermittent asystole may be useful to facilitate off-pump or endoscopic coronary artery bypass grafting. Controlled intermittent asystole cardiac therapy induced by pharmacologically potentiated vagus nerve stimulation in normal and hibernating myocardium.

49. **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;44:855-858.**
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. Pharyngeal dysesthesia in refractory complex partial epilepsy: new seizure or adverse effect of vagal nerve stimulation?

50. **Shih JJ, Devier D, Behr A. Late onset laryngeal and facial pain in previously asymptomatic vagus nerve stimulation patients. *Neurology.* 2003;60:1214.**
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. Late onset laryngeal and facial pain in previously asymptomatic vagus nerve stimulation patients.

51. **Vassilyadi M, Strawsburg RH. Delayed onset of vocal cord paralysis after explantation of a vagus nerve stimulator in a child. *Childs Nerv Syst.* 2003;19:261-3.**
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. Delayed onset of vocal cord paralysis after explantation of a vagus nerve stimulator in a child.

52. **Klein JP, Jean-Baptiste M, Thompson JL, Bowers MB. A case report of hypomania following vagus nerve stimulation for refractory epilepsy. *J Clin Psychiatry.* 2003;64:485.**
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. A case report of hypomania following vagus nerve stimulation for refractory epilepsy.

53. **Zalvan C, Sulica L, Wolf S, Cohen J, Gonzalez-Yanes O, Blitzer A. Laryngopharyngeal dysfunction from the implant vagal nerve stimulator. *Laryngoscope.* 2003;113:221-225.**
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. Laryngopharyngeal dysfunction from the implant vagal nerve stimulator.

54. **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;43:1268-1270.** Vagus nerve stimulation in a case of epilepsy with CSWSS: respiratory side effects during sleep.

55. **Kersing W, Dejonckere PH, van der Aa HE, Buschman HP. Laryngeal and vocal changes during vagus nerve stimulation in epileptic patients. *J Voice.* 2002;16:251-7.**
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. Laryngeal and vocal changes during vagus nerve stimulation in epileptic patients.

56. **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;96:949-951.**
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. Self-inflicted vocal cord paralysis in patients with vagus nerve stimulators. Report of two cases.

57. **Sucholeiki R, Alsaadi TM, Morris GL 3rd, Ulmer JL, Biswal B, Mueller WM. fMRI in patients implanted with a vagal nerve stimulator. *Seizure.* 2002;11:157-62.**
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. fMRI in patients implanted with a vagal nerve stimulator. fMRI in patients implanted with a vagal nerve stimulator.

58. **Bernik TR, Friedman SG, Ochani M, et al. Pharmacological stimulation of the cholinergic antiinflammatory pathway. *J Exp Med.* 2002;195:781-788.**
Abstract: Efferent activity in the vagus nerve can prevent endotoxin-induced shock by attenuating tumor necrosis factor (TNF) synthesis. Termed the "cholinergic antiinflammatory pathway," inhibition of TNF synthesis is dependent on nicotinic alpha-bungarotoxin-sensitive acetylcholine receptors on macrophages. Vagus nerve firing is also stimulated by CNI- 1493, a tetravalent guanylhydrazone molecule that inhibits systemic inflammation. Here, we studied the effects of pharmacological and electrical stimulation of the intact vagus nerve in adult male Lewis rats subjected to endotoxin-induced shock to determine whether intact vagus nerve signaling is required for the antiinflammatory action of CNI-1493. CNI-1493 administered via the intracerebroventricular route was 100,000-fold more effective in suppressing endotoxin-induced TNF release and shock as compared with intravenous dosing. Surgical or chemical vagotomy rendered animals sensitive to TNF release and shock, despite treatment with CNI-1493, indicating that an intact cholinergic antiinflammatory pathway is required for antiinflammatory efficacy in vivo. Electrical stimulation of either the right or left intact vagus nerve conferred significant protection against endotoxin-induced shock, and specifically attenuated serum and myocardial TNF, but not pulmonary TNF synthesis, as compared with sham-operated animals. Together, these results indicate that stimulation of the cholinergic antiinflammatory pathway by either pharmacological or electrical methods can attenuate the systemic inflammatory response to endotoxin-induced shock. Pharmacological stimulation of the cholinergic antiinflammatory pathway.

59. **Sanossian N, Haut S. Chronic diarrhea associated with vagal nerve stimulation. *Neurology.* 2002;58:330.** Sanossian N, Haut S. Chronic diarrhea associated with vagal nerve stimulation.

60. **Dardis R, Selway R, Koutromanidis M, Polkey CE. Vagal nerve stimulators and anaesthesia: 2. *Anaesthesia.* 2001;56:1210.** Vagal nerve stimulators and anaesthesia: 2.

61. **Aziz E, Radcliffe JJ. Vagal nerve stimulators and anaesthesia: 1. *Anaesthesia.* 2001;56:1209-1210.** Vagal nerve stimulators and anaesthesia: 1.

62. **Charous SJ, Kempster G, Manders E, Ristanovic R. The effect of vagal nerve stimulation on voice. *Laryngoscope.* 2001;111:2028-2031.**
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. The effect of vagal nerve stimulation on voice.

63. **Sato K, Shamoto H, Yoshimoto T. Severe bradycardia during epilepsy surgery. *J Neurosurg Anesthesiol.* 2001;13:329-332.**
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. Severe bradycardia during epilepsy surgery.

64. **Blumer D, Davies K, Alexander A, Morgan S. Major psychiatric disorders subsequent to treating epilepsy by vagus nerve stimulation. *Epilepsy Behav.* 2001;2:466-472.**
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. Major Psychiatric Disorders Subsequent to Treating Epilepsy by Vagus Nerve Stimulation.

65. **Benbadis SR, Nyhenhuis J, Tatum WO 4th, Murtagh FR, Gieron M, Vale FL. MRI of the brain is safe in patients implanted with the vagus nerve stimulator. *Seizure.* 2001;10:512-515.**

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. MRI of the brain is safe in patients implanted with the vagus nerve stimulator.

66. **Liporace J, Hucko D, Morrow R, et al. Vagal nerve stimulation: adjustments to reduce painful side effects. *Neurology.* 2001;57:885-886.**
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. Vagal nerve stimulation: adjustments to reduce painful side effects.

67. **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;127:125-133.**
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. High strength stimulation of the vagus nerve in awake humans: a lack of cardiorespiratory effects.

68. **Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. *J Clin Neurophysiol.* 2001;18:415-418.**
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. Vagus nerve stimulation, side effects, and long-term safety.

69. **Tubbs RS, Patwardhan R, Palmer CA, et al. Histological appearance of a chronically stimulated vagus nerve in a pediatric patient. *Pediatr Neurosurg.* 2001;35:99-102.**
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. Histological appearance of a chronically stimulated vagus nerve in a pediatric patient.

70. **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;42:1007-1016.**
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. Left vagus nerve stimulation with the neurocybernetic prosthesis has complex effects on heart rate and on its variability in humans.

71. **Lewis ME, Al-Khalidi AH, Bonser RS, et al. Vagus nerve stimulation decreases left ventricular contractility in vivo in the human and pig heart. *J Physiol.* 2001;534:547-52.**
Abstract: 1. Studies of the effect of vagus nerve stimulation on ventricular myocardial function in mammals are limited, particularly in the human. 2. The present study was designed to determine the effect of direct electrical stimulation of the left vagus nerve on left ventricular contractile state in hearts paced at 10 % above the natural rate, in anaesthetised pigs and anaesthetised human subjects undergoing open chest surgery for coronary artery bypass grafting. 3. Contractility of the left ventricle was determined from a series of pressure-volume loops obtained from a combined pressure and conductance (volume) catheter placed in the left ventricle. From the measurements a regression slope of the end-systolic pressure-volume relationship was determined to give end-systolic elastance (Ees), a load-independent measure of contractility. 4. In six anaesthetised open chest pigs, stimulation of the peripheral cut end of the left cervical vagus nerve induced a significant decrease in Ees of 26 +/- 14 %. 5. In nine patients electrical stimulation of the left thoracic vagus nerve close to its cardiac branch resulted in a significant drop in Ees of 38 +/- 16 %. 6. The effects of vagal stimulation were blocked by the muscarinic antagonist glycopyrronium (5 mg kg(-1)). 7. Administration of the beta-adrenoreceptor antagonist

esmolol (1 mg kg(-1)) also attenuated the effect of vagal stimulation, indicating a degree of interaction of vagal and sympathetic influences on contractility. 8. These studies show that in the human and pig heart the left vagus nerve can profoundly decrease the inotropic state of the left ventricular myocardium independent of its bradycardic effect. Vagus nerve stimulation decreases left ventricular contractility in vivo in the human and pig heart.

72. **Tovey G, Griffiths R. Vagal nerve stimulators and anaesthesia. *Anaesthesia.* 2001;56:703-704.** Vagal nerve stimulators and anaesthesia.

73. **Prater JF. Recurrent depression with vagus nerve stimulation. *Am J Psychiatry.* 2001;158:816-817.** Recurrent depression with vagus nerve stimulation.

74. **Kim W, Clancy RR, Liu GT. Horner syndrome associated with implantation of a vagus nerve stimulator. *Am J Ophthalmol.* 2001;131:383-384.**
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. Horner syndrome associated with implantation of a vagus nerve stimulator.

75. **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;42:133-135.**
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. Deep wound infection after vagus nerve stimulator implantation: treatment without removal of the device.

76. **Murray BJ, Matheson JK, Scammell TE. Effects of vagus nerve stimulation on respiration during sleep. *Neurology.* 2001;57:1523-1524.** Effects of vagus nerve stimulation on respiration during sleep.

77. **Iriarte J, Artieda J, Alegre M, et al. Spasm of the sternocleidomastoid muscle induced by vagal nerve stimulation. *Neurology.* 2001;57:2319-2320.** Spasm of the sternocleidomastoid muscle induced by vagal nerve stimulation.

78. **Malow BA, Edwards J, Marzec M, Sagher O, Fromes G. Effects of vagus nerve stimulation on respiration during sleep: a pilot study. *Neurology.* 2000;55:1450-4.**
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. Effects of vagus nerve stimulation on respiration during sleep: a pilot study.

79. **Koutroumanidis M, Hennessy MJ, Binnie CD, Polkey CE. Aggravation of partial epilepsy and emergence of new seizure type during treatment with VNS. *Neurology.* 2000;55:892-893.** Aggravation of partial epilepsy and emergence of new seizure type during treatment with VNS.

80. **Duhaime AC, Melamed S, Clancy RR. Tonsillar pain mimicking glossopharyngeal neuralgia as a complication of vagus nerve stimulation: case report. *Epilepsia.* 2000;41:903-905.**
Notes: This is a case report of delayed stimulation-related severe tonisllar 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 reinstitution 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. Tonsillar pain mimicking glossopharyngeal neuralgia as a complication of vagus nerve stimulation: case report.

81. **Zumsteg D, Jenny D, Wieser HG. Vocal cord adduction during vagus nerve stimulation for treatment of epilepsy. *Neurology.* 2000;54:1388-1389.** Vocal cord adduction during vagus nerve stimulation for treatment of epilepsy.

82. **Lesser RP. Ventricular asystole during vagus nerve stimulation for epilepsy in humans. *Neurology.* 2000;54:776.** Ventricular asystole during vagus nerve stimulation for epilepsy in humans.

83. **Lanska DJ. Ventricular asystole during vagus nerve stimulation for epilepsy in humans. *Neurology.* 2000;54:775-776.** Ventricular asystole during vagus nerve stimulation for epilepsy in humans.

84. **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;40:1452-4.**
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%. Bradycardia and asystole with the use of vagus nerve stimulation for the treatment of epilepsy: a rare complication of intraoperative device testing.

85. **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;35:1-11.**
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. Cardiorespiratory variables and sensation during stimulation of the left vagus in patients with epilepsy.

86. **Tatum WO 4th, Moore DB, Stecker MM, et al. Ventricular asystole during vagus nerve stimulation for epilepsy in humans. *Neurology.* 1999;52:1267-1269.**
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. Ventricular asystole during vagus nerve stimulation for epilepsy in humans.

87. **Schallert G, Foster J, Lindquist N, Murphy JV. Chronic stimulation of the left vagal nerve in children: effect on swallowing. *Epilepsia.* 1998;39:1113-4.**
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 pharmacoresistant 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.

88. **Leijten FS, Van Rijen PC. Stimulation of the phrenic nerve as a complication of vagus nerve pacing in a patient with epilepsy. *Neurology.* 1998;51:1224-1225.** Stimulation of the phrenic nerve as a complication of vagus nerve pacing in a patient with epilepsy.

89. **Lundgren J, Ekberg O, Olsson R. Aspiration: a potential complication to vagus nerve stimulation. *Epilepsia.* 1998;39:998-1000.**
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. Aspiration: a potential complication to vagus nerve stimulation.

90. **Murphy JV, Hornig GW, Schallert GS, Tilton CL. Adverse events in children receiving intermittent left vagal nerve stimulation. *Pediatr Neurol.* 1998;19:42-44.**
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. Adverse events in children receiving intermittent left vagal nerve stimulation.

91. **Setty AB, Vaughn BV, Quint SR, Robertson KR, Messenheimer JA. Heart period variability during vagal nerve stimulation. *Seizure.* 1998;7:213-217.**
Abstract: Vagal nerve stimulation is an emerging therapy for epilepsy, yet little is known regarding the effects of this stimulation on heart period variability. We selected 10 patients (two female, eight male) who were receiving high-frequency, high-intensity left vagal nerve stimulation for intractable epilepsy. Electrocardiogram data were recorded for a 7 min baseline, 2.5 min of stimulation and a 7 min post-stimulation period. We found no significant changes in average heart period, instantaneous changes of successive R-to-R intervals greater than 50 ms or fractal dimension. We also found no significant changes in the total power in the 0.0-0.04 Hz, 0.04-0.12 Hz and 0.2-0.4 Hz bands with stimulation of the left vagus nerve. This study suggests that left vagal nerve stimulation has little acute effect on the cardiac rhythm or heart period variability. Heart period variability during vagal nerve stimulation.

92. **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;18:149-154.**
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) Airway effects of direct left-sided cervical vagal stimulation in patients with complex partial seizures.

93. **Lundy DS, Casiano RR, Landy HJ, Gallo J, Gallo B, Ramsey RE. Effects of vagal nerve stimulation on laryngeal function. *J Voice.* 1993;7:359-364.**
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. Effects of vagal nerve stimulation on laryngeal function.

94. Kamath MV, Upton AR, Talalla A, Fallen EL. Neurocardiac responses to vagoafferent electrostimulation in humans. *Pacing Clin Electrophysiol.* 1992;15:1581-1587.

Abstract: To determine if cardiac vagal tone is enhanced by vagal electrostimulation (VES), we examined the heart rate autospectrum (HRA) in eight patients with implanted stimulators for complex partial seizures. In four patients the VES was activated at 30 Hz and 500-msec pulse (HiStim group) compared to 2 Hz and 130-msec pulse for the LoStim group (n = 4). Continuous ECG and respiratory waveforms were recorded for 45 minutes every 8 hours (7-8 AM; 3-4 PM 11-12 PM) during resting supine wakeful epochs both before and 15 days after surgical implantation. From the HRA cardiac sympathovagal balance was expressed as the ratio of the low frequency (LF) power to the high frequency (HF) power. RESULTS: There were no presurgical differences between the groups in heart rate, its variance, or the energies contained in any autospectral band. The LoStim group showed no significant change in heart rate (HR), HF peak power, or LF:HF ratios during 2 weeks of VES. Conversely, in the HiStim group, the LF:HF peak power ratio (an expression of sympathetic dominance) decreased from 2.5 +/- 1.5 preimplant to 1.5 +/- 0.49 ($P < 0.02$) with VES. During VES there was a significantly higher HF power in the HiStim compared to LoStim group. No diurnal variations in HRA values were seen for either group. CONCLUSIONS: (1) A relationship exists between selective vagal nerve electrostimulation and the HRA; and (2) high stimulation frequency of the vagus nerve in man is associated with sustained augmentation of cardiac vagal tone throughout a 24-hour cycle. Neurocardiac responses to vagoafferent electrostimulation in humans.

95. Kamath MV, Upton AR, Talalla A, Fallen EL. Effect of vagal nerve electrostimulation on the power spectrum of heart rate variability in man. *Pacing Clin Electrophysiol.* 1992;15:235-243.

Abstract: The power spectrum of heart rate variability contains low frequency (LF = 0.08-0.12 Hz) and high frequency (HF = 0.18-0.30 Hz) components said to represent neurocardiac rhythms. To verify whether such a relationship exists we report a unique study where the heart rate autospectrum was determined in a 28-year-old epileptic male patient with an implanted vagal electrical stimulator. The stimulator was activated at 20 Hz, 300 microseconds pulse, and 1.25 V. Continuous ECG and respiratory waveform records were obtained over 45 minutes every 8 hours (7-8 AM; 3-4 PM; 11-12 PM) with the stimulator ON, then 24 hours OFF and then 24 hours ON again. The overall LF:HF peak ratio increased from 0.64 to 1.99 (P less than 0.001) after the stimulator was turned OFF. There was a dramatic increase in the LF peak power (greater than 60%) and a corresponding decrease in the HF peak power (greater than 65%) when the stimulator was turned OFF. These values were reversed when the stimulator was turned ON again. In the early morning and late evening hours, there was a significant rightward shift in the LF peak power frequency (average 0.057 to 0.075 Hz) whenever the stimulator was ON. Otherwise, there were no significant circadian variations in any of the autospectral components. The results demonstrate an unequivocal relationship between selective vagal nerve electrostimulation and alterations in the heart rate autospectrum. Effect of vagal nerve electrostimulation on the power spectrum of heart rate variability in man.

96. Agnew WF, McCreery DB. Considerations for safety with chronically implanted nerve electrodes. *Epilepsia.* 1990;31(suppl 2):S27-S32.
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.
Considerations for safety with chronically implanted nerve electrodes.

Seizure Detection

1. **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;19:157-72.**
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. Non-invasive computerized system for automatically initiating vagus nerve stimulation following patient-specific detection of seizures or epileptiform discharges.

Status Epilepticus

1. **De Herdt V, Waterschoot L, Vonck K, et al. Vagus nerve stimulation for refractory status epilepticus. *Eur J Paediatr Neurol.* 2009;13:286-9.**
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. Vagus nerve stimulation for refractory status epilepticus.

2. **Robakis TK, Hirsch LJ. Literature review, case report, and expert discussion of prolonged refractory status epilepticus. *Neurocrit Care.* 2006;4:35-46.**
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, adrenocorticotropic 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. Literature review, case report, and expert discussion of prolonged refractory status epilepticus.

3. **Winston KR, Levisohn P, Miller BR, Freeman J. Vagal nerve stimulation for status epilepticus. *Pediatr Neurosurg.* 2001;34:190-192.**
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. Vagal nerve stimulation for status epilepticus.

SUDEP

1. **Schachter SC. Therapeutic effects of vagus nerve stimulation in epilepsy and implications for sudden unexpected death in epilepsy. *Clin Auton Res.* 2006;16:29-32.**
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. Therapeutic effects of vagus nerve stimulation in epilepsy and implications for sudden unexpected death in epilepsy.

2. **Sanya EO. Increasing awareness about sudden unexplained death in epilepsy--a review. *Afr J Med Med Sci.* 2005;34:323-7.**
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. Increasing awareness about sudden unexplained death in epilepsy--a review.

3. **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;41:549-553.**
Notes: A very favorable update on SUDEP and VNS from Annergers' 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. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death.

4. **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;39:206-212.**

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. Epilepsy, vagal nerve stimulation by the NCP system, mortality, and sudden, unexpected, unexplained death.

Temporal Lobe Epilepsy

1. **Devinsky O. Diagnosis and treatment of temporal lobe epilepsy. Rev Neurol Dis 2004:1: 2-9.**
   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. Diagnosis and treatment of temporal lobe 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: 954-956.**
   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. Vagus nerve stimulation for the treatment of bilateral independent temporal lobe epilepsy.

Tourette Syndrome

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;41:117-8.** Vagus nerve stimulation in a patient with Gilles de la Tourette syndrome and major depression.

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;21:1273-5.** 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. Effect of vagal nerve stimulation in a case of Tourette's syndrome and complex partial epilepsy.

Tuberous Sclerosis

1. **Elliott RE, Carlson C, Kalhorn SP, et al. Refractory epilepsy in tuberous sclerosis: vagus nerve stimulation with or without subsequent resective surgery. *Epilepsy Behav.* 2009;16:454-60.**
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. Refractory epilepsy in tuberous sclerosis: vagus nerve stimulation with or without subsequent resective surgery.

2. **Major P, Thiele EA. Vagus nerve stimulation for intractable epilepsy in tuberous sclerosis complex. *Epilepsy Behav.* 2008;13:357-60.**
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. Vagus nerve stimulation for intractable epilepsy in tuberous sclerosis complex.

3. **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.**
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. Tuberous sclerosis complex: a review of the management of epilepsy with emphasis on surgical aspects.

4. **Thiele EA. Managing epilepsy in tuberous sclerosis complex. *J Child Neurol.* 2004;19:680-686.**
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. Managing epilepsy in tuberous sclerosis complex.

5. **Parain D, Penniello MJ, Berquen P, Delangre T, Billard C, Murphy JV. Vagal nerve stimulation in tuberous sclerosis complex patients. *Pediatr Neurol.* 2001;25:213-216.**
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. Vagal nerve stimulation in tuberous sclerosis complex patients

Progressive Myoclonus Epilepsy of Unverricht-Lundborg Type

1. **Smith B, Shatz R, Elisevich K, Bespalova IN, Burmeister M. Effects of vagus nerve stimulation on progressive myoclonus epilepsy of Unverricht-Lundborg type. Epilepsia 2000:41: 1046-8.**
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. Effects of vagus nerve stimulation on progressive myoclonus epilepsy of Unverricht-Lundborg type.

VNS Therapy Surgical Procedure

1. **Pratap R, Farboud A, Patel H, Montgomery P. Vagal nerve stimulator implantation: the otolaryngologist's perspective. *Eur Arch Otorhinolaryngol.* 2009;266:1455-9.**
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. Vagal nerve stimulator implantation: the otolaryngologist's perspective.

2. **You SJ, Kang HC, Ko TS, et al. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. *Brain Dev.* 2008;30:195-9.**
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. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome.

3. **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;5:540-2.**
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. 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.

4. **Hatton KW, McLarney JT, Pittman T, Fahy BG. Vagal nerve stimulation: overview and implications for anesthesiologists. *Anesth Analg.* 2006;103:1241-9.**
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 neuropsychiatic 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. Vagal nerve stimulation: overview and implications for anesthesiologists.

5. **Ghanem T, Early SV. Vagal nerve stimulator implantation: an otolaryngologist's perspective. *Otolaryngol Head Neck Surg.* 2006;135:46-51.**
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. Vagal nerve stimulator implantation: an otolaryngologist's perspective.

6. **Gercek A, Ozek MM. From the anesthesiologist's perspective: placement of vagal nerve stimulator. *Anesth Analg.* 2006;102:1910.**

7. **Bauman JA, Ridgway EB, Devinsky O, Doyle WK. Subpectoral implantation of the vagus nerve stimulator. *Neurosurgery.* 2006;58:ONS-322-ONS-326.**
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. Subpectoral implantation of the vagus nerve stimulator.

8. **Slavin KV. Commentary. *Surg Neurol.* 2006;65:49-50.**
http://linkinghub.elsevier.com/retrieve/pii/S0090301905003836

9. **Patwardhan RV. Commentary. *Surg Neurol.* 2006;65:50.**
http://linkinghub.elsevier.com/retrieve/pii/S0090301905003848

10. **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;65:48-9; discussion 49-50.**
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. The use of a sump antibiotic irrigation system to save infected hardware in a patient with a vagal nerve stimulator: technical note.

11. **Lobe TE, Wright SK, Irish MS. Novel uses of surgical robotics in head and neck surgery. *J Laparoendosc Adv Surg Tech A.* 2005;15:647-652.**
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(R) 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. Novel uses of surgical robotics in head and neck surgery.

12. **Tubbs RS, Blount JP. Right-sided vagus nerve stimulation. *Epilepsia.* 2005;46:1152-1153.** Right-sided vagus nerve stimulation.

13. **MacDonald J, Couldwell WT. Revision of vagal nerve stimulator electrodes: technical approach. *Acta Neurochir (Wien).* 2004;146:567-570.**
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. Revision of vagal nerve stimulator electrodes: technical approach.

14. **Santos PM. Surgical placement of the vagus nerve stimulator. *Operative Techniques in Otolaryngology-Head and Neck Surgery.* 2004;15:201-209.**

15. **Santos PM. Evaluation of laryngeal function after implantation of the vagus nerve stimulation device. *Otolaryngol Head Neck Surg.* 2003;129:269-73.**
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. Evaluation of laryngeal function after implantation of the vagus nerve stimulation device.

16. **McKhann GM 2nd, Bourgeois BF, Goodman RR. Epilepsy surgery: indications, approaches, and results. *Semin Neurol.* 2002;22:269-278.**
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. Epilepsy surgery: indications, approaches, and results.

17. **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;36:164-166.**
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. Interscapular placement of a vagal nerve stimulator pulse generator for prevention of wound tampering. Technical note.

18. **Bernard EJ, Passannante AN, Mann B, Lannon S, Vaughn BV. Insertion of vagal nerve stimulator using local and regional anesthesia. *Surg Neurol.* 2002;57:94-8.**
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. Insertion of vagal nerve stimulator using local and regional anesthesia.

19. **Vaughn BV, Bernard E, Lannon S, et al. Intraoperative methods for confirmation of correct placement of the vagus nerve stimulator. *Epileptic Disord.* 2001;3:75-77.**
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). Intraoperative methods for confirmation of correct placement of the vagus nerve stimulator.

20. **Patil A, Chand A, Andrews R. Single incision for implanting a vagal nerve stimulator system (VNSS): technical note. *Surg Neurol.* 2001;55:103-105.**
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. Single incision for implanting a vagal nerve stimulator system (VNSS): technical note.

21. **Carey ME, Kutz S. Modified malis bayonet forceps aids application of the Cyberonics vagus nerve stimulator electrode: technical note. *Neurosurgery.* 2000;47:985-987.**
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. Modified malis bayonet forceps aids application of the cyberonics vagus nerve stimulator electrode: technical note.

22. **Maniker A, Liu WC, Marks D, Moser K, Kalnin A. Positioning of vagal nerve stimulators: technical note. *Surg Neurol.* 2000;53:178-181.**
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. Positioning of vagal nerve stimulators: technical note.

23. **Gates JR, Dunn ME. Presurgical assessment and surgical treatment for epilepsy. *Acta Neurol Belg.* 1999;99:281-294.**
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. Presurgical assessment and surgical treatment

for epilepsy.

24. **Espinosa J, Aiello MT, Naritoku DK. Revision and removal of stimulating electrodes following long-term therapy with the vagus nerve stimulator. *Surg Neurol.* 1999;51:659-664.**
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. Revision and removal of stimulating electrodes following long-term therapy with the vagus nerve stimulator.

25. **Cortese JJ. Vagus nerve stimulation: a new treatment for intractable epilepsy. *Surg Technol.* 1999;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
Abstract: 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.

26. **Amar AP, Heck CN, Levy ML, et al. An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: rationale, technique, and outcome. *Neurosurgery.* 1998;43:1265-1280.**
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. An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: rationale, technique, and outcome.

27. **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;78:26-31.**
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. Vagus nerve stimulation for complex partial seizures: surgical technique, safety, and efficacy.

28. **Tarver WB, George RE, Maschino SE, Holder LK, Wernicke JF. Clinical experience with a helical bipolar stimulating lead. *Pacing Clin Electrophysiol.* 1992;15:1545-1556.**
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. Clinical experience with a helical bipolar stimulating lead.

29. **Terry RS, Tarver WB, Zabara J. The implantable neurocybernetic prosthesis system. *Pacing Clin Electrophysiol.* 1991;14:86-93.**
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. The implantable neurocybernetic prosthesis system.

30. **Reid SA. Surgical technique for implantation of the neurocybernetic prosthesis. *Epilepsia.* 1990;31(suppl 2):S38-S39.**
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. Surgical technique for implantation of the neurocybernetic prosthesis.