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Long-term results of vagal nerve stimulation for adults with medication-resistant epilepsy who have been on unchanged antiepileptic medication

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ABSTRACT

Purpose: Several studies suggest that vagal nerve stimulation (VNS) is an effective treatment for medication-resistant epileptic patients, although patients' medication was usually modified during the assessment period. The purpose of this prospective study was to evaluate the long-term effects of VNS, at 18 months of follow-up, on epileptic patients who have been on unchanged antiepileptic medication.
Methods: Forty-three patients underwent a complete epilepsy preoperative evaluation protocol, and were selected for VNS implantation. After surgery, patients were evaluated on a monthly basis, increasing stimulation 0.25 mA at each visit, up to 2.5 mA. Medication was unchanged for at least 18 months since the stimulation was started. The outcome was analysed in relation to patients' clinical features, stimulation parameters, epilepsy type, magnetic resonance imaging (MRI) results, and history of prior brain surgery.
Results: Of the 43 operated patients, 63% had a similar or greater than 50% reduction in their seizure frequency. Differences in the responder rate according to stimulation intensity, age at onset of epilepsy, duration of epilepsy before surgery, previous epilepsy surgery and seizure type, did not reach statistical significance. Most side effects were well tolerated.
Conclusions: 62.8% of our series of 43 medication-resistant epileptic patients experienced a significant long-term seizure reduction after VNS, even in a situation of on unchanged medical therapy. Patient characteristics predictive of VNS responsiveness remain subject to investigation. Controlled studies with larger sample sizes, on VNS for patients with medication-resistant epilepsy on unchanged medication, are necessary to confirm VNS efficacy for drug-resistant epilepsy, and to identify predictive factors.

1. Introduction

Several studies have suggested that vagal nerve stimulation (VNS) is an effective therapy for reducing seizure frequency in medication resistant epileptic patients, who are poor candidates for resection or in those in whom resection has failed.[2,4,5,8–10,12,13,29] In previous published series, VNS achieved a 50% greater seizure frequency reduction in 50–60% of implanted patients after 1 year of therapy.[18,19,25] In those studies, concomitant changes in antiepileptic drugs were allowed.[3,4,13,22,23,37,51] A progressive decline in seizure frequency is usually found during the first year of stimulation, and it remains uncertain if the progressive improvement seen with longer VNS exposures might be ascribable to a modification in the medical therapy, rather than to sustained VNS.[14,16,17,30] To date, there is only one study performed in the adult population on unchanged medical therapy during the postoperative evaluation.[30] In this study, the patients' outcome was assessed 1 year after surgery. It has been reported that no specific antiepileptic drugs seem to have additive antiseizure effects with VNS; however, to precisely evaluate the net impact of vagal stimulation in operated patients, it is essential to maintain stable doses of the administered drugs. The purpose of this study was to prospectively evaluate the long-term effects of VNS, at 18 months of follow-up, on epileptic patients who have been on unchanged antiepileptic medication.

2. Materials and methods

Forty-three adult patients with medication-resistant epilepsy were treated with VNS in our institution, from 2005 to 2009. Preoperatively, all patients had undergone a complete preoperative epilepsy evaluation protocol,[39,47] which includes videoelectroencephalogram (VEEG), 1.5 T magnetic resonance imaging (MRI), interictal single-photon emission computed tomography

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(SPECT), and neurologic, psychiatric and neuropsychologic assessment. Findings of the presurgical evaluation were discussed at a multidisciplinary case conference, where decisions were made about the possibility and type of brain surgery, as well as VNS, or the need for further investigations.

The implanted system was the ®Cyberonics VNS Therapy™, and the surgical technique has been previously described[23,37]; all of the implantations were performed by the same surgeon. Chronic stimulation was activated 15 days after the surgery. The initial parameters were: 0.25 mA; 20 Hz, 250 μs, 30 s stimulus on-time and 5 min stimulus off-time. Patients were evaluated on a monthly basis, increasing stimulation by 0.25 mA at each visit up to 2.5 mA, if there were no major adverse effects (except for one case, in whom the stimulation was set at 2.75 mA). When patients reached this level of stimulation, they were reviewed every 6 months, except for those that needed more frequent follow-ups due to medical reasons.

In the postoperative visits, seizure frequency, side effects, and other significant information reported by family members and caregivers, was collected. Seizures were classified, according to their frequency, as daily seizures if the patient had 7 or more per week, as weekly seizures if the patient had from 1 to 6 a week, and as monthly seizures if the patient had less than four per month. Responders were defined as having a 50% or greater reduction in seizure frequency with respect to the mean seizure frequency during the last year before the implantation of VNS. Changes in the pharmacological treatment were not allowed during the first 18 months of postoperative follow-up.

Group mean differences in percentage of reductions in seizure frequency were tested non-parametrically if variables were not distributed normally, and using the paired Student's *t*-test for normal distributions. Normality was evaluated using the Kolmogorov–Smirnov test. The software SPSS 17.0 was used for statistical analysis. The significance level was set at $p = 0.05$. Results are shown as the mean ± SEM, except where otherwise indicated. This study was approved by the local ethics committee board.

3. Results

Clinical characteristics of the patients are shown in Table 1. The study involved 22 women and 21 men. The mean age at epilepsy onset was 9 (±9.9) years, and the mean age at implantation was 34 (±11.8) years. The majority of patients had daily multifocal or generalised seizures (51%), and 12 patients had undergone a previous surgery for epilepsy, which proved unsuccessful.

The mean seizure frequency reduction at 18 months follow-up was 46.6% (±35.5) (Table 2). Twenty-seven of the 43 patients included in the analysis (63%) were responders. Among the 27 responders, seven patients (16% of the total sample), had a greater than 90% seizure frequency reduction. Four of these 7 patients with ≥90% of seizure reduction had frontal seizures (one of them was seizure-free), one patient had occipital-temporal seizures, and 2 patients had generalised seizures. Clinical features of responders and non-responders are summarised in Table 2.

Table 1
Patient demographics.

Epilepsy type (n)	
Generalised or multifocal epilepsy	22
Temporal lobe epilepsy	5
Frontal lobe epilepsy	13
Other extratemporal locations	3
Baseline seizure rate (mean)	
Daily seizures (*n*)	34
Weekly seizures (*n*)	5
Monthly seizures (*n*)	4
Patients with previous epilepsy surgery (*n*)	12
Temporal resection	2
Extratemporal resection	7
Subpial transection	1
Callosotomy	2
Duration of epilepsy before surgery (mean years)	25 years (±9.6)

Table 2
Differences between types of patients undergoing vagal nerve stimulation at our institution, at 2 years from surgery.

Patients' features	Responders	Non-responders
Mean seizure frequency reduction	69.8% (±18.1)	4.3% (±13.6)
Mean age at surgery	33 (±10.5) years	34 (±14.16) years
Mean age at the epilepsy onset	6.9 (±5.8) years	12.8 ± 13.8 years
Mean duration of epilepsy before surgery	26 ± 9.6 years	±21, 8.8 years

Patients and caregivers reported other positive aspects derived from VNS: Ten patients referred to a reduction in seizure duration and severity; three patients reported a disappearance of the generalised tonic–clonic seizures, with persistence of the other seizure types; ten patients with mental retardation showed an improvement in alertness; and one patient experienced a non-quantified weight loss. One patient, however, reported an increase in the duration and intensity of his seizures.

Twenty-two patients experienced side-effects. The most common were mild, consisting in hoarseness, neck tingling or occasional coughing at the time when the signal was on, all of which were usually well tolerated. Two patients had intermittent dyspnoea, and another patient experienced occasional episodes of dysphagia with stimulation. Irritability was reported by two families, in the context of a general improvement in the level of alertness. Five had severe side effects, requiring their VNS generators to be inactivated or explanted. Three of the 5 patients that stopped receiving stimulation had been responders. Reasons for explantation were infection in two patients, and odynophagia, in one patient. One patient had an exacerbation of a previous behaviour disturbance, with severe aggressiveness, which improved when the stimulator was inactivated. Seizure reduction was maintained after the stimulation was stopped. Another stimulator was removed at family request, owing to a persistent abdominal pain.

For the 38 patients that continued receiving stimulation, intensity fluctuated between 0.5 mA and 2.75 mA. Mean seizure

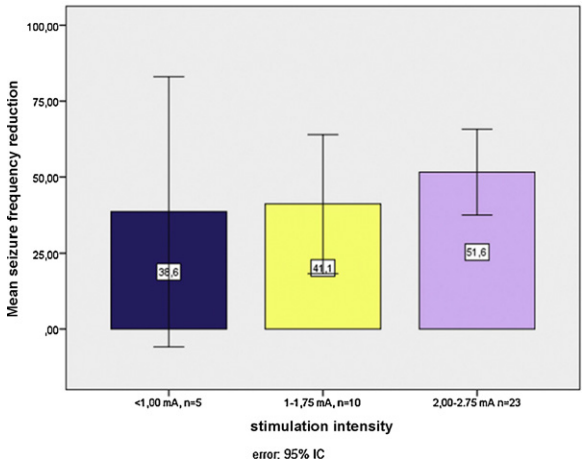

Fig. 1. Seizure reduction rate by stimulation intensity, in our series of patients on unchanged medication undergoing vagal nerve stimulation for medication-resistant epilepsy, at the second year follow-up. mA, miliamperes.

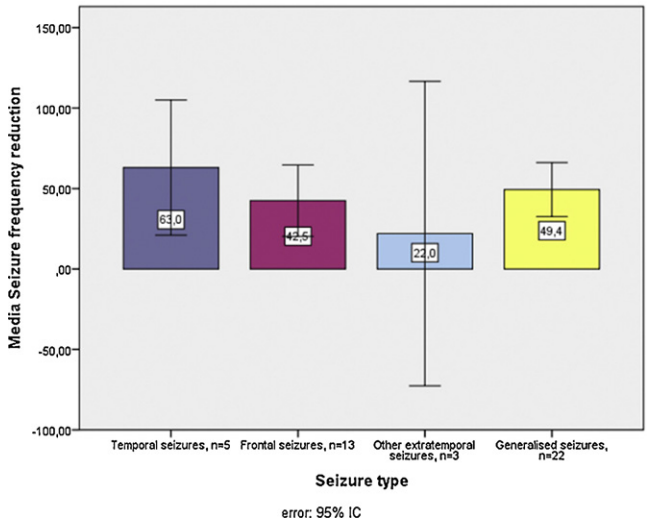

Fig. 2. Seizure frequency reduction rate by type of epilepsy, in our cohort of patients treated with vagal nerve stimulation for medication-resistant epilepsy, on unchanged medication, at the second year follow-up.

frequency reduction by stimulation intensity is represented in Fig. 1. Two patients receiving stimulation at 0.25 mA, obtained a greater than 90% reduction in the frequency of their seizures. The responder rate for patients at $\geq$2 mA was 71% (17 out of 24 patients, whereas it was 53% for those at $<$2 mA (7 out of 19 patients).

The relationship between the clinical outcome and the intensity of stimulation, epilepsy type and location, and frequency did not reach statistical significance. Patients with generalised epilepsy had a mean seizure frequency reduction of 49.4 $\pm$ 34.8%, and those with focal epilepsy, 44.5 $\pm$ 35.6%. Among them, patients with temporal epilepsy had a seizure reduction rate of 63.0 $\pm$ 34.8% (Fig. 2). We analysed the percentage of responders by epilepsy location, and we found that 4 out of 5 (80%) of the patients with temporal lobe epilepsy, 15 out of 22 (74%) of the patients with generalised epilepsy, 6 out of 13 (46%) of the patients with frontal epilepsy, and 1 out of 3 (33%) of those with other extratemporal seizures, were responders.

Twenty-three out of 34 (67%) patients with daily seizures responded to stimulation, whereas those with monthly or 5 weekly seizures had a responder rate of 50% (2 out of 5, and 2 out of 4 patients, respectively). Eight out of 12 (66%) patients with a history of previous epilepsy surgery were responders, while of those without a previous operation, 10 out of 21 (50%) responded to stimulation.

4. Discussion

Given the complexity and degree of disability of patients treated with VNS, most of the studies have allowed modification of the patients' antiepileptic medication types and doses after the implantation[32,33]; this may significantly affect the analysis of the results.[36,41,44–46,48,49] To our knowledge, this is the only long-term prospective study that has been performed on VNS for adults with no changes in the medical treatment during the follow-up (6).

In our series, the percentage of epileptic patients that achieved a 50% or greater seizure frequency reduction, 18 months after VNS implantation, was 63%, and the mean reduction in seizure frequency was 46.6%. In various published series, an equal or higher than 50% reduction in seizure frequency was achieved in about 50% of patients (18.4–67%), and the mean reduction in the frequency of seizures was 42.8% (range 28–66%).[7,15,21,35,43,53] In the only study to date, performed on an adult population where medication type and doses were held totally constant during the postoperative period, the median reduction in seizure frequency, 1 year after the stimulation was started, was 63%.[30]

The implantation of VNS implies frequent visits to clinic and therefore the possibility of a more careful adjustment of medical therapy; moreover, patients might derive an improvement in seizure frequency from the administration of new drugs. On the other hand, our results are similar to those obtained in institutions with extensive experience in epilepsy and vagal stimulation, suggesting that changes in medication therapy during the period of adjustment of parameters do not appear to benefit patients.[30] The absence of medication changes, which can interfere with the evaluation of seizure frequency and side effects, may be helpful in optimising stimulation settings and thus, in improving response rates. Moreover, as most neurologists and patients hope to decrease the number of medications after VNS placement, it is possible that a reduction in the medication regime might have had a detrimental effect on patients undergoing VNS.

There are several studies suggesting that high intensity of stimulation corresponds to better outcome, although some other authors consider the time of exposure to the treatment, and not the intensity of stimulation, the key factor that leads to appropriate responses.[15,18,26,30,40] In our series, the relationship between the clinical outcome and the intensity of stimulation was independently analysed for the duration of stimulation, since the outcome was uniformly considered at 18 months. Outcome differences according to intensity of stimulation were not statistically significant, and there were also some very satisfactory results besides the usual therapeutic values of stimulation.[31,34] Other than frontal focal epilepsy and younger age at the VNS implantation, have also been considered positive predictive factors for VNS response in various studies,[26,30] although no definite conclusions have been drawn.[23,26–28] In our series, 15 out of 22 patients with generalised epilepsy were responders, and 4 of the 7 patients that obtained a frequency reduction of more than 90% had frontal epilepsy. It is also of note that our patients' mean epilepsy duration at the time of surgery (25 years), was very high.[30,42] Finally, the existence of a previous surgery has been suggested as a negative predictive factor after VNS.[4] It is of importance to confirm these results, because they might substantially modify VNS patient selection. In our series, 8 out of 12 patients with a previous surgery attained satisfactory results from stimulation. Further studies on VNS for epileptic patients on unchanged medication are needed to elucidate which are the main predictive factors of responsiveness to VNS.

The impact of the VNS in other domains of interest has been documented in several studies.[20,42,43] The improvement in mood and cognitive performance has led to indicate VNS for patients with chronic depression, although later results have been conflicting.[42,43] In our series, a positive effect on alertness has been observed in almost a quarter of the patients. Reduction in seizure frequency and independent mechanisms for regulation of various centroencephalic nuclei have been implicated in these processes, although they have not been yet elucidated.[23,42,43,50] It must be said that, occasionally, the improvement of the level of alertness has not been linked to an improvement in the quality of life, since patients are more aware of the limitations of their illness. In our series, previous behaviour disorders were exacerbated.[1,6,22,23,52,54]

There are limitations to our study, since a control group was not included in the analysis. It is difficult to compare previously reported series of patients with drug-resistant epilepsy under the best medical treatment with our series because of differences in the definition of drug-resistant epilepsy and patient

characteristics.[11,55–58] In previous reports, the remission rate for epileptic patients that have been resistant to at least two antiepileptic drugs oscillates between 4 and 5% per year, and around 50% of patients might be responders in the long term.[11,24,38,54,55] VNS, as any chronic implanted medical device, requires unambiguous positive evidence for therapeutic superiority over conservative treatment in regards to costs, risks, and adverse effects. Despite the fact that our study eliminates the confounding factor of medication changes during the assessment period after VNS implantation, there is a need for long-term controlled prospective studies with patients under VNS, and without changes in medication, to confirm our results.

5. Conclusions

62.8% of our series of 43 medication-resistant epileptic patients experienced a significant long-term seizure reduction after VNS, even in a situation of unchanged medical therapy. Patient characteristics predictive of VNS responsiveness remain subject to investigation. It is necessary to perform controlled studies with a larger number of subjects on unchanged antiepileptic medication to draw definitive conclusions

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References

1. Treatment-resistant depression: no panacea, many uncertainties. Adverse effects are a major factor in treatment choice. *Prescrire International* 2011;**20**:128–33.
2. Alonso-Vanegas MA, Austria-Velasquez J, Lopez-Gomez M, Brust-Mascher E. Chronic intermittent vagal nerve stimulation in the treatment of refractory epilepsy: experience in Mexico with 35 cases. *Cirugia y Cirujanos* 2010;**78**:15–23. 24.
3. Amar AP. Vagus nerve stimulation for the treatment of intractable epilepsy. *Expert Review of Neurotherapeutics* 2007;**7**:1763–73.
4. Amar AP, Apuzzo ML. Vagus nerve stimulation therapy for patients with persistent seizures after epilepsy surgery. *Stereotactic and Functional Neurosurgery* 2003;**80**:9–13.
5. 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.
6. Bagary M. Epilepsy, consciousness and neurostimulation. *Behavioural Neurology* 2011;**24**:75–81.
7. Bao M, Zhou J, Luan GM. Treatment of drug-resistant epilepsy with vagus nerve stimulation—review of 45 cases. *Chinese Medical Journal* 2011;**124**:4184–8.
8. Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. *Epilepsia* 1994;**35**:616–26.
9. Bhattacharya SK, Das BP, Rauniar GP, Sangraula H. Vagus nerve stimulation: a novel approach for prevention and control of refractory seizures. *Kathmandu University Medical Journal (KUMJ)* 2007;**5**:261–3.
10. Bunch S, DeGiorgio CM, Krahl S, Britton J, Green P, Lancman M, et al. Vagus nerve stimulation for epilepsy: is output current correlated with acute response? *Acta Neurologica Scandinavica* 2007;**116**:217–20.
11. Callaghan B, Schlesinger M, Rodemer W, Pollard J, Hesdorffer D, Allen Hauser W, et al. Remission and relapse in a drug-resistant epilepsy population followed prospectively. *Epilepsia* 2011;**52**:619–26.
12. 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.
13. Cersosimo RO, Bartuluchi M, De Los Santos C, Bonvehi I, Pomata H, Caraballo RH. Vagus nerve stimulation: effectiveness and tolerability in patients with epileptic encephalopathies. *Childs Nervous System* 2011;**27**:787–92.
14. Cersosimo RO, Bartuluchi M, Fortini S, Soraru A, Pomata H, Caraballo RH. Vagus nerve stimulation: effectiveness and tolerability in 64 paediatric patients with refractory epilepsies. *Epileptic Disorders* 2011;**13**:382–8.
15. Connor Jr DE, Nixon M, Nanda A, Guthikonda B. Vagal nerve stimulation for the treatment of medically refractory epilepsy: a review of the current literature. *Neurosurgical Focus* 2012;**32**:E12.
16. De Herdt V, Boon P, Ceulemans B, Hauman H, Lagae L, Legros B, et al. Vagus nerve stimulation for refractory epilepsy: a Belgian multicenter study. *European Journal of Paediatric Neurology* 2007;**11**:261–9.
17. DeGiorgio CM, Schachter SC, Handforth A, Salinsky M, Thompson J, Uthman B, et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. *Epilepsia* 2000;**41**:1195–200.
18. DeGiorgio CM, Thompson J, Lewis P, Arrambide S, Naritoku D, Handforth A, et al. Vagus nerve stimulation: analysis of device parameters in 154 patients during the long-term XE5 study. *Epilepsia* 2001;**42**:1017–20.
19. Elliott RE, Morsi A, Kalhorn SP, Marcus J, Sellin J, Kang M, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. *Epilepsy & Behavior* 2011;**20**:57–63.
20. Englot DJ, Chang EF, Auguste KI. Efficacy of vagus nerve stimulation for epilepsy by patient age, epilepsy duration, and seizure type. *Neurosurgery Clinics of North America* 2011;**22**:443–8. v.
21. Fisher RS. Therapeutic devices for epilepsy. *Annals of Neurology* 2012;**71**:157–68.
22. 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.
23. García-Navarrete E, García MR, Sola RG MN. Vagus nerve stimulation (VNS) therapy for the treatment of pharmacoresistant epilepsy: the Spanish experience. *Epilepsia* 2007;**48**(Suppl. 6):127.
24. Hauser WA. The natural history of drug resistant epilepsy: epidemiologic considerations. *Epilepsy Research Supplement* 1992;**5**:25–8.
25. Hui AC, Lam JM, Wong KS, Kay R, Poon WS. Vagus nerve stimulation for refractory epilepsy: long term efficacy and side-effects. *Chinese Medical Journal* 2004;**117**:58–61.
26. Janszky J, Hoppe M, Behne F, Tuxhorn I, Pannek HW, Ebner A. Vagus nerve stimulation: predictors of seizure freedom. *Journal of Neurology Neurosurgery and Psychiatry* 2005;**76**:384–9.
27. Jaseja H. Vagal nerve stimulation: exploring its efficacy and success for an improved prognosis and quality of life in cerebral palsy patients. *Clinical Neurology and Neurosurgery* 2008;**110**:755–62.
28. Karceski S. Vagus nerve stimulation and Lennox-Gastaut syndrome: a review of the literature and data from the VNS patient registry. *CNS Spectrums* 2001;**6**:766–70.
29. Kuschyk J, Borggrefe M. Vagus stimulation. Mechanisms and current clinical importance in heart failure. *Herzschrittmachertherapie & Elektrophysiologie* 2011;**22**:21–6.
30. Labar D. Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs. *Seizure* 2004;**13**:392–8.
31. Magdaleno-Madrigal VM. Electrical stimulation of the vagal nerve: from experimental to clinical aspects. *Revista de Neurologia* 2004;**39**:971–7.
32. Majkowska-Zwolinska B, Zwolinski P, Roszkowski M, Drabik K. Long-term results of vagus nerve stimulation in children and adolescents with drug-resistant epilepsy. *Child's Nervous System* 2012;**28**(4):621–8.
33. 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. *Journal of Clinical Neurophysiology* 2001;**18**:419–28.
34. 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. *European Neuropsychopharmacology* 2009;**19**:250–5.
35. Martin JL, Martin-Sanchez E. Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: variable results based on study designs. *European Psychiatry* 2012;**27**:147–55.
36. Muller K, Fabo D, Entz L, Kelemen A, Halasz P, Rasonyi G, et al. Outcome of vagus nerve stimulation for epilepsy in Budapest. *Epilepsia* 2010;**51**(Suppl. 3):98–101.
37. Navas M, Navarrete EG, Pascual JM, Carrasco R, Nunez JA, Shakur SF, et al. Treatment of refractory epilepsy in adult patients with right-sided vagus nerve stimulation. *Epilepsy Research* 2010;**90**:1–7.
38. Neligan A, Bell GS, Elsayed M, Sander JW, Shorvon SD. Treatment changes in a cohort of people with apparently drug-resistant epilepsy: an extended follow-up. *Journal of Neurology Neurosurgery and Psychiatry* 2012;**83**:810–3.
39. Pastor J, Hernando-Requejo V, Dominguez-Gadea L, de Llano I, Meilan-Paz ML, Martinez-Chacon JL, et al. Impact of experience on improving the surgical outcome in temporal lobe epilepsy. *Revista de Neurologia* 2005;**41**:709–16.
40. Patwardhan RV, Dellabadia Jr J, Rashidi M, Grier L, Nanda A. Control of refractory status epilepticus precipitated by anticonvulsant withdrawal using left vagal nerve stimulation: a case report. *Surgical Neurology* 2005;**64**:170–3.
41. Polkey CE. Clinical outcome of epilepsy surgery. *Current Opinion in Neurology* 2004;**17**:173–8.
42. Renfroe JB, Wheless JW. Earlier use of adjunctive vagus nerve stimulation therapy for refractory epilepsy. *Neurology* 2002;**59**:S26–30.
43. Rizvi SJ, Donovan M, Giacobbe P, Placenza F, Rotzinger S, Kennedy SH. Neurostimulation therapies for treatment resistant depression: a focus on vagus nerve stimulation and deep brain stimulation. *International Review of Psychiatry* 2011;**23**:424–36.

44. Scherrmann J, Hoppe C, Kral T, Schramm J, Elger CE. Vagus nerve stimulation: clinical experience in a large patient series. *Journal of Clinical Neurophysiology* 2001;**18**:408–14.
45. 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.
46. Skarpaas TL, Morrell MJ. Intracranial stimulation therapy for epilepsy. *Neurotherapeutics* 2009;**6**:238–43.
47. Sola RG, Hernando-Requejo V, Pastor J, Garcia-Navarrete E, DeFelipe J, Alijarde MT, et al. Pharmacoresistant temporal-lobe epilepsy. Exploration with foramen ovale electrodes and surgical outcomes. *Revista de Neurologia* 2005;**41**:4–16.
48. Spanaki MV, Allen LS, Mueller WM, Morris 3rd GL. Vagus nerve stimulation therapy: 5-year or greater outcome at a university-based epilepsy center. *Seizure* 2004;**13**:587–90.
49. Tanganelli P, Ferrero S, Colotto P, Regesta G. Vagus nerve stimulation for treatment of medically intractable seizures. Evaluation of long-term outcome. *Clinical Neurology and Neurosurgery* 2002;**105**:9–13.
50. Torres CV, Lozano AM. Deep brain stimulation in the treatment of therapy-refractory depression. *Revista de Neurologia* 2008;**47**:477–82.
51. Torres CV, Pastor J, Navarrete EG, Sola RG. Thalamic deep brain stimulation for refractory epilepsy. *Revista de Neurologia* 2011;**53**:99–106.
52. Tran Y, Shah AK, Mittal S. Lead breakage and vocal cord paralysis following blunt neck trauma in a patient with vagal nerve stimulator. *Journal of the Neurological Sciences* 2011;**304**:132–5.
53. Uthman BM, Reichl AM, Dean JC, Eisenschenk S, Gilmore R, Reid S, et al. Effectiveness of vagus nerve stimulation in epilepsy patients: a 12-year observation. *Neurology* 2004;**63**:1124–6.
54. Wozniak SE, Thompson EM, Selden NR. Vagal nerve stimulator infection: a lead-salvage protocol. *Journal of Neurosurgery Pediatrics* 2011;**7**:671–5.
55. Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. Likelihood of seizure remission in an adult population with refractory epilepsy. *Annals of Neurology* 2007;**62**:382–9.
56. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *New England Journal of Medicine* 2000;**342**:314–9.
57. Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on? *Seizure* 2000;**9**:464–8.
58. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. *Annals of Neurology* 2007;**62**:375–81.