Seizure 20 (2011) 331–335

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Efficacy of vagus nerve stimulation for refractory epilepsy among patient subgroups: A re-analysis using the Engel classification

Marcus Wheeler [a,1], Veerle De Herdt [b,1,*], Kristl Vonck [b], Karen Gilbert [a], Suneetha Manem [a], Todd Mackenzie [a], Barbara Jobst [a], David Roberts [a], Peter Williamson [a], Dirk Van Roost [b], Paul Boon [b], Vijay Thadani [a]

[a] Dartmouth Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA
[b] Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium

ARTICLE INFO

Article history:
Received 7 July 2010
Received in revised form 4 January 2011
Accepted 10 January 2011

Keywords:
Vagus nerve stimulation
Refractory epilepsy
Seizure frequency outcome
Patient subgroups
Engel classification

ABSTRACT

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

1. Introduction

Electrical stimulation of the tenth cranial nerve or vagus nerve stimulation (VNS) is an extracranial form of neurostimulation that was developed more than 20 years ago.[1] In the past decade it has become a valuable therapeutic option for patients with refractory epilepsy and it is currently available in epilepsy centers worldwide. 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.[2] As for many anti-epileptic treatments, clinical application of VNS preceded the elucidation of its mechanism of action, which is unknown up to date. The first clinical studies of VNS included almost exclusively patients with focal seizures.[3] In the following years, the efficacy of VNS in other seizure types and epilepsy syndromes was assessed.[4,5] These studies reported efficacy results comparable to those seen in focal epilepsy. The current consensus is that 1/3 of patients have considerable improvement in seizure control with a seizure frequency reduction of at least 50%, and 1/3 of patients experience a worthwhile reduction of seizure frequency between 30 and 50%. Long-term follow-up studies show improved seizure control over time. However, even after long-term treatment, up to 25% of patients do not experience any positive effect of VNS.[2] These results are similar to the results of anti-epileptic drug trials in patients with refractory epilepsy. Those, as well as the VNS studies, are usually reported so that the principle seizure outcome is the "responder rate", which is defined as the proportion of patients who have a 50% or greater reduction in seizure frequency. Seizure-free rates are seldom reported, and when reported, usually less than 5%.[6]

In contrast, most trials and case series in epilepsy surgery have used the Engel classification. The Engel classification scale was proposed by Jerome Engel as a standard outcome scale after resective epilepsy surgery (Table 1).[7] This scale divides outcomes into one of four classes. A patient free of disabling seizures is classified as class I. Patients with no seizures, simple partial non-disabling seizures only, and/or a seizure free period of eight

* Corresponding author at: Reference Center for Refractory Epilepsy, Department of Neurology 1K12IA, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium. Tel.: +32 9 332 64 81; fax: +32 9 332 49 71.
E-mail address: Veerle.Deherdt@UGent.be (V. De Herdt).
[1] These authors equally contributed to the manuscript.

1059-1311/$ – see front matter © 2011 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.seizure.2011.01.002

Table 1
Classification of postoperative outcome (Engel classification).[6]

Class I	No disabling seizures
A	Completely seizure-free since surgery
B	Non-disabling simple partial seizures only
C	Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
D	Generalized convulsion with antiepileptic drug withdrawal only
Class II	Rare disabling seizures
A	Initially free of disabling seizures but has rare disabling seizures now
B	Rare disabling seizures since surgery
C	More than rare disabling seizures since surgery, but rare seizures for at least 2 years
D	Nocturnal seizures only
Class III	Worthwhile improvement
A	Worthwhile seizure reduction
B	Prolonged seizure-free intervals but less than 2 years
Class IV	No worthwhile improvement
A	Significant seizure reduction
B	No appreciable change in seizure frequency
C	Seizures are more frequent or worse

months or greater at time of latest assessment are assigned to this category. A class II outcome is one in which the patient has rare seizures at a frequency of three or less per year. Class III outcome corresponds to a "worthwhile" result occurring through a reduction either in seizure frequency or seizure intensity that improves the patient's quality of life. A patient is assigned to class IV when seizure frequency is not reduced, or reduced only to such limited extent that it does not improve day-to-day functioning. A major advantage of using the Engel classification is that not only seizure frequency is taken into account, but also the impact of seizures on quality of life. Most surgical series are reporting class I outcomes in 50–65% of patients, and combined class I and II outcomes around 80%.[8]

In this retrospective two-center study, 191 VNS patients at Dartmouth–Hitchcock Medical Center and Ghent University Hospital were evaluated using the Engel classification scale. VNS was offered here to patients who were not candidates for resective surgery, but we estimated that the use of a single scale for comparison of outcomes would be valuable. Also, since VNS is a surgical treatment, we estimated that in order to judge its efficacy we should subject it to the more stringent Engel criteria rather than the more lax standards of drug studies. Outcomes in the entire patient population were determined, as well as the outcomes in several patient subgroups, to identify predictive factors for VNS response. Characteristics examined were mental functioning, seizure type, age at VNS implantation, predisposing factors for epilepsy, and epilepsy duration.

2. Methods

2.1. Patient population

Two epilepsy centers participated in this open retrospective study: Dartmouth–Hitchcock Medical Center, Lebanon, New Hampshire, USA and Ghent University Hospital, Gent, Belgium. All patients included in the study underwent presurgical evaluation including long-term video-EEG monitoring and MRI with an epilepsy protocol that included additional coronal temporal views and T2 weighted or FLAIR sequences. All patients were for various reasons considered to be unsuitable candidates for resective surgery, and were subsequently treated with VNS. Patients with a post-implantation follow-up of at least 12 months were included in this analysis. For each patient, data on age at seizure onset, types of seizures, age at time of implantation, seizure frequency before and after VNS treatment, level of mental functioning, VNS stimulation parameters, number of antiepileptic drugs (AEDs) taken before implantation and at maximum follow-up, and predisposing factors for epilepsy, were collected from the patient's medical records. Approval of the Ethical Committee of Ghent University Hospital and Dartmouth–Hitchcock Medical Center was obtained prior to the start of the study.

2.2. Seizure outcome using the Engel classification

Each patient included in this study was assigned to an outcome class, using the Engel classification. This assessment was done at latest follow-up by a thorough review of the patients' seizure diaries and medical files, and by taking into account changes in seizure frequency, seizure intensity, and the impact of these changes on the patients' quality of life. Outcome class was determined principally by seizure frequency, but in patients with mental retardation, caregivers' assessment of quality of life was taken into account in deciding between class III and class IV outcomes. Since the Engel classification defines class III as "worthwhile improvement" we felt justified in taking factors other than seizure frequency into account for class III, but not for classes I and II.

2.3. Seizure outcome in different patient subgroups

Patients were divided into two groups with regard to mental functioning, using a full scale IQ score (FSIQ) obtained during the presurgical neuropsychological examination. Patients with a FSIQ of 70 or more were placed in the group of "normal mental functioning" and those with scores of 69 or less were classified as having "impaired mental functioning". Some patients were so severely retarded that they could not be tested in a reliable way and were assigned to the "impaired mental functioning" group for obvious reasons.

Another analysis divided patients into three groups based on seizure type. One group contained patients with only focal seizures. A second group contained patients with tonic clonic seizures. Idiopathic and symptomatic epilepsies were not distinguished, and patients with focal seizures and occasional tonic clonic seizures were also included in this group. A third group contained patients with other seizures types such as atonic or tonic seizures, myoclonic seizures and absence seizures, often in combination with tonic clonic seizures. This group contained a large proportion of patients with Lennox–Gastaut syndrome.

Subgroup analysis was also done according to predisposing factors for developing epilepsy. These factors included head trauma preceding the onset of epilepsy, history of intracranial infection, history of birth complications, and history of febrile seizures. Patients were divided into groups with one of the above risk factors, a group with more than one of the previously mentioned risk factors or with other risk factors including brain tumors and neuronal migration disorders, and a group with no identifiable risk factors before epilepsy onset.

Age was looked at in two ways. First, patients were divided according to their age at the time of VNS implantation. For this purpose, they were divided into 3 age groups with 20 year intervals. Second, patients were divided into 2 groups depending on the duration of their epilepsy at the time of VNS implantation. One group contained patients with an epilepsy duration of 0–10 years, the other group contained patients with an epilepsy duration of more than 10 years.

2.4. Statistics

Statistical analysis was performed by means of the independent samples *T*-test and Chi square test where indicated. To simplify the

statistical analysis of small numbers, classes I and II, and classes III and IV were pooled when comparing subgroups. All calculations were performed by SPSS 15.0. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient population

189 Patients (102M/87F) were included in the study (89/189 Ghent University Hospital, 100/189 Dartmouth–Hitchcock Medical Center). Mean follow-up was 41 months (range 12–144 months). Mean age at time of VNS implantation was 30 years (range 2–60 years) and mean duration of epilepsy was 21 years (range 1–60 years). The mean number of AEDs remained unchanged before implantation and at maximum follow-up (3, range: 0–5).

3.2. Seizure outcome using the Engel classification

11/189 (5.8%) Patients were assigned to a class I outcome, and 25/189 (13.2%) patients had class II outcomes. The class I and class II groups were combined into a group representing very good seizure outcome, thus making a total of 36 patients (19.0%). Another 92 patients (48.7%) had a "worthwhile" improvement with regard to seizure control and/or quality of life, and were assigned class III outcomes. 61/189 Patients (32.3%) had no improvement in their condition after VNS implantation and were regarded as class IV outcomes.

3.3. Stimulation output

Mean stimulation output current at latest follow-up was 1.6 mA (range 0–3.5). In two patients, stimulation output current was programmed to 0 mA after at least 12 months of VNS treatment, due to lack of efficacy. The combined class I and class II groups were programmed to receive significantly ($p < 0.01$, independent samples *T*-test) lower stimulation output currents (1.2 mA; range 0.25–2.5) when compared to the combined class III and class IV groups (1.75 mA; range 0–3.5).

3.4. Seizure outcome in different patient subgroups

3.4.1. Mental functioning (Table 2)

When the outcome classification of the 117 patients with normal mental functioning was compared with the outcome of the 72 patients with mental impairment, a statistically significant better outcome was found in patients with normal mental functioning ($p = 0.029$).

3.4.2. Seizure type (Table 3)

53/189 Patients had partial seizures without secondary generalization. 14/53 (26%) showed a class I or II outcome. 95 Patients experienced primary or secondarily generalized tonic clonic seizures. 18/95 (18.9%) had a class I or II outcome. 41 Patients had other seizures types. 4/41 (10%) had a class I or II outcome. Seizure type did not affect seizure outcome after VNS in a statistically significant manner.

Table 2
Comparison of subgroups regarding mental functioning.

		Class I and II	Class III	Class IV
IQ ≥ 70	*N* = 117	28 (24%)*	59 (50%)	30 (26%)
IQ < 70	*N* = 72	8 (11%)	33 (46%)	31 (43%)

Outcomes following the Engel classification are given in subgroups regarding mental functioning.
* Statistical significance ($p < 0.05$, Chi square test).

Table 3
Comparison of subgroups regarding seizure type.

		Class I and II	Class III	Class IV
Partial seizures	*N* = 53	14 (26%)	21 (40%)	18 (34%)
Tonic clonic seizures	*N* = 95	18 (19%)	53 (56%)	24 (25%)
Multiple seizure types	*N* = 41	4 (10%)	18 (44%)	19 (46%)

Outcomes following the Engel classification are given in subgroups regarding seizure type.

3.4.3. Predisposing factors for epilepsy (Table 4)

A total of 25/189 patients had experienced head trauma as sole risk factor preceding the onset of their seizures. 10/25 (40%) had a class I or II outcome. Of the 15/189 patients who had a history of intracranial infection, 4/15 (27%) had a class I or II outcome. The percentage of class I or II outcomes for the 20/189 patients with a history of birth complication was 1/20 (5%). Of the 13/189 patients with a history of febrile seizures, 2/13 (15%) had a class I or II outcome. 46/189 Patients had a combination of the previously defined risk factors or had other risk factors predisposing them to develop epilepsy. Of those patients, 8/46 (17.5%) had class I or II outcomes. Finally, 70/189 patients had no or unknown risk factors for seizures. 11/70 (16%) had a class I or II outcome. The differences between the groups were not statistically significant.

3.4.4. Age at time of VNS implantation (Table 5)

45/189 Patients were implanted at the age of 20 years or younger and 13% of them had a class I or II outcome. 98/189 Patients had VNS between the ages of 21 and 40 years and 18% had a class I or II outcome. VNS implantation at 41 years and older yielded 26% class I and II outcomes. No statistically significant differences could be demonstrated.

3.4.5. Epilepsy duration (Table 6)

No statistical differences were found between the group with epilepsy duration of less than 10 years and the group with epilepsy duration of more than 10 years.

4. Discussion

In this study, VNS at Dartmouth–Hitchcock Medical Center and Ghent University Hospital was shown to be an effective add-on

Table 4
Comparison of subgroups regarding predisposing factors for epilepsy.

		Class I and II	Class III	Class IV
Head trauma	*N* = 25	10 (40%)	11 (44%)	4 (16%)
Intracranial infection	*N* = 15	4 (27%)	8 (53%)	3 (20%)
Birth complication	*N* = 20	1 (5%)	14 (70%)	5 (25%)
Febrile seizures	*N* = 13	2 (15%)	10 (77%)	1 (8%)
Multiple/other	*N* = 46	8 (17.5%)	18 (39%)	20 (43.5%)
No/unknown	*N* = 70	11 (16%)	31 (44%)	28 (40%)

Outcomes following the Engel classification are given in subgroups regarding predisposing factors for epilepsy.

Table 5
Comparison of subgroups regarding age at time of implantation.

		Class I and II	Class III	Class IV
0–20 years	*N* = 45	6 (13%)	17 (38%)	22 (49%)
21–40 years	*N* = 98	18 (18%)	50 (51%)	30 (31%)
>41 years	*N* = 46	12 (26%)	25 (54%)	9 (20%)

Outcomes following the Engel classification are given in subgroups regarding age at time of implantation.

Table 6
Comparison of subgroups regarding epilepsy duration.

		Class I and II	Class III	Class IV
0–10 years	$N=46$	7 (15%)	21 (46%)	18 (39%)
>10 years	$N=143$	29 (20%)	71 (50%)	43 (30%)

Outcomes following the Engel classification are given in subgroups regarding epilepsy duration.

treatment for patients with refractory epilepsy. 19% of patients had a very good (class I and II) outcome with VNS and 48.7% had a worthwhile (class III) improvement of their condition, when using the Engel classification for seizure outcome after epilepsy surgery. Although important differences exist between VNS therapy and resective surgery, using the same classification for seizure outcome has some advantages. In most studies analyzing VNS efficacy and trying to identify prognostic factors for seizure reduction, a >50% seizure frequency reduction has been the primary outcome measurement. But even in refractory epilepsy patients, achieving seizure freedom is still the ultimate epilepsy care goal. The Engel classification is well known to epileptologists, clearly identifies those who are seizure free or almost seizure free, and takes into account not only seizure frequency, but also the impact of the seizures on daily life. Moreover, this allows a comparison between VNS and resective surgery, both of which are invasive epilepsy treatments.

In a previous publication, we demonstrated that VNS outcomes in the Dartmouth–Hitchcock Medical Center and in the Ghent University Hospital patient population using % seizure frequency reduction as an outcome measure, were comparable with those described in literature.[9] One recent study by McHugh et al. compared a new classification system for VNS outcome with the Engel classification. 6/48 (12%) of the patients included in that study were assigned to Engel classes I and II.[10] However, the VNS outcome classification proposed by McHugh et al. has five outcome categories and is difficult to compare with resective surgical outcomes, and equally difficult to compare with drug study outcomes. We therefore believe that analyzing VNS outcome data with both the Engel approach and the % seizure reduction approach yields the best comparisons.

When the outcome of VNS presented in this study is compared to the outcome of other epilepsy treatments in a refractory population, the relatively small number of a very good outcome becomes more acceptable. With regard to the use of antiepileptic drugs (AEDs), one third to one half of newly treated epilepsy patients are refractory to initial treatment. Of those, only 5–10% will obtain seizure freedom with the use of additional AEDs, and usually less than one half will have a 50% reduction in seizure frequency with any new drug.[6,11] This is true for both the older drugs and the new generation of drugs, that despite having fewer side effects, seem to have the same level of efficacy.[12] Of the one third of patients who are medically refractory, perhaps half are candidates for resective epilepsy surgery. For temporal lobe surgery, outcomes are very good and in one study of 215 patients by Salanova et al. a seizure-free rate of 89% was achieved.[13] Long term outcome studies are showing seizure-free rates of 60–70% and combined Engel class I and II outcomes are around 80%.[8] In frontal lobe epilepsy surgery, Worrel et al. found an overall success rate of 52%.[14] In cases where other extra-temporal regions are involved, surgery can be risky and yield rather poor results. One example comes from a study by Aykut-Bingol et al. in which seizure-freedom in patients who had surgery for occipital lobe epilepsy, varied from 17 to 56%.[15]

Among patients with unresectable seizure foci, or those who have failed resective surgery, options are limited. Additional drug trials offer very low rates of seizure freedom, and most studies report less than 50% of patients having a 50% reduction in seizure frequency. Other surgical options such as callosotomy, subpial transsections, and experimental surgical treatments such as deep brain stimulation, offer no better results.[16–18] In this context, VNS results such as those reported here, with 18% very good outcomes and another 49% showing worthwhile improvement, seem quite attractive.

In our study there was a significantly lower VNS output current in the group of patients with class I and II seizure outcomes. Similarly, Labar found that patients with better clinical outcomes had their VNS programmed at a significantly lower output current than patients who had a poorer outcome. He also found that 13 patients who stayed on exactly the same VNS settings and AED regimen, had a decline in seizure rate reduction from 36% after 3 months to 85% after 12 months of follow-up.[19] This suggests that VNS responders tend to respond quite early, which halts the process of further ramping-up of the stimulation intensity by the physician, and that there is not always the need to continuously adjust stimulation settings for optimizing seizure outcome. Ideal stimulation parameters may be different for each individual, but this has yet to be studied in randomized prospective studies with different stimulation paradigms.

When it comes to the identification of VNS responders, large patient groups have been examined retrospectively, but identification of subgroups most likely to benefit, prior to implantation, seems one of the most difficult issues in VNS treatment. One study by Janszky et al. in 47 patients found that the absence of bilateral interictal epileptiform discharges was associated with a statistically significant increase in the likelihood of a seizure-free outcome after VNS.[20] In our study we used the Engel classification to identify predictive factors for seizure outcome. A significantly larger proportion of patients with normal intelligence had a class I or II outcome. Despite the smaller chance of highly successful outcomes, one might still recommend VNS for mentally impaired patients because of the 50% chance for a class III outcome in addition to improvement in their mood and overall condition.[21]

Since the subpopulations were small, it was difficult to prove statistical significance for the other subgroups. However, future prospective studies should target specific subpopulations based upon their unique characteristics. In such trials one will need to look not only at rates of seizure control but also at improvement in quality of life using validated scales.

Acknowledgements

Prof. P. Boon is a Senior Clinical Investigator of the Fund for Scientific Research-Flanders and is supported by grants from FWO; grants from BOF and by the Clinical Epilepsy Grant from Ghent University Hospital. Prof. K. Vonck is supported by a BOF-ZAP grant from Ghent University Hospital.

References

1. Penry JK, Dean JC. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. *Epilepsia* 1990;**31**(Suppl. 2):S40–3.
2. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet Neurol* 2002;**1**:477–82.
3. 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.
4. 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.
5. 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.
6. French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcom-

mittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2004;**62**:1261–73.
7. Engel Jr J, Van Ness PC, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel Jr J, editor. *Surgical treatment of the epilepsies*. New York: Raven Press; 1993. p. 609–21.
8. Engel Jr J, Wiebe S, French J, Sperling M, Williamson P, Spencer D, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology* 2003;**60**:538–47.
9. Vonck K, Thadani V, Gilbert K, Dedeurwaerdere S, De Groote L, De Herdt V, et al. Vagus nerve stimulation for refractory epilepsy: a transatlantic experience. *J Clin Neurophysiol* 2004;**21**:283–9.
10. 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.
11. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;**342**:314–9.
12. Nadkarni S, LaJoie J, Devinsky O. Current treatments of epilepsy. *Neurology* 2005;**64**:S2–11.
13. Salanova V, Markand O, Worth R. Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients. *Epilepsia* 2002;**43**:170–4.
14. Worrell GA, So EL, Kazemi J, O'Brien TJ, Mosewich RK, Cascino GD, et al. Focal ictal beta discharge on scalp EEG predicts excellent outcome of frontal lobe epilepsy surgery. *Epilepsia* 2002;**43**:277–82.
15. Aykut-Bingol C, Bronen RA, Kim JH, Spencer DD, Spencer SS. Surgical outcome in occipital lobe epilepsy: implications for pathophysiology. *Ann Neurol* 1998;**44**:60–9.
16. Wada JA. Callosal bisection and transcallosal secondary antiepileptogenesis. *Epilepsia* 2005;**46**(Suppl. 1):2–6.
17. Theodore WH, Fisher RS. Brain stimulation for epilepsy. *Lancet Neurol* 2004;**3**:111–8.
18. Spencer SS, Schramm J, Wyler A, O'Connor M, Orbach D, Krauss G, et al. Multiple subpial transection for intractable partial epilepsy: an international meta-analysis. *Epilepsia* 2002;**43**:141–5.
19. Labar D. Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs. *Seizure* 2004;**13**:392–8.
20. 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.
21. 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.