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GUEST EDITORIAL

Vagus nerve stimulation for epilepsy: a review

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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.

Key words: vagus nerve stimulation; epilepsy.

INTRODUCTION

Vagal nerve stimulation (VNS) is a relatively novel method of treatment for medically intractable epilepsy, introduced in 1988, and used increasingly widely since efficacy and safety were established by clinical trials in the mid-1990s. It involves intermittent stimulation of the left vagus in the neck by implanted electrodes connected to a subcutaneous generator located below the clavicle.

The use of VNS in epilepsy arises from the serendipitous experimental finding that extracranial vagal stimulation desynchronizes the EEG in animals[1,2]. As hypersynchrony is a feature of epileptic discharges and arousal with EEG desynchronization blocks interictal epileptiform activity in animal models and in man, it was reasonable to test VNS for antiepileptic action in experimental epilepsy. Several studies have shown that VNS prevents, terminates or attenuates seizures in various animal models (Table 1), including both generalized seizures (PTZ, strychnine, maximal electroshock) and partial (penicillin and alumina-gel foci, amygdala kindling).

Zabara[3] showed VNS suppressed within 0.5–5 seconds seizures induced by continuous strychnine infusion in the dog. Seizures returned 10 minutes after termination of VNS. Thus the effects are rapid, but outlast stimulation by some minutes, being half maximal 5 minutes after termination[4]. Sustained stimulation over a period of 60 minutes has a cumulative effect[4]. Such observations, together with considerations of battery life and the need to avoid damage to the vagal nerve by prolonged stimulation, have led to the general use in humans of a schedule of 30 second stimulation at 5 minute intervals.

Despite extensive experimental studies and some human data (Table 2), the mode of action of VNS is unknown. With the stimulus parameters used in clinical practice, vagal C-fibres are unlikely to be stimulated, and destruction of C-fibres by capsaicin does not

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Table 1: Anticonvulsant effects of VNS in experimental epilepsies.

Year	Investigators	Model	Animal	Result
1938	Bailey and Bremer[1]	NA	cat	Induced frontal fast activity
1952	Zanchetti *et al.*[2]	Strychnine	cat	Blocked interictal spiking
1961	Magnes *et al.*[51]	NA	cat	Desynchronized EEG
1966	Chase *et al.*[22]	NA	cat	Synchronized or desynchronized EEG in thalamus and cortex
1968	Stoica and Tudor[52]	Strychnine	cat	Increased or decreased cortical spiking
1971	O'Brien *et al.*[53]	NA	monkey	Elicited cortical evoked potentials
1977	Puizillout and Foutz[54]	NA	cat	Induced REM sleep
1985	Zabara[3, 55]	Strychnine	dog	Aborted seizures
1992				
1990	Lockard *et al.*[56]	Alumina	monkey	Reduced seizure frequency
1991	Woodbury & Woodbury[57]	Maximal electroshock	rat	Reduced seizure severity
1993	McLachlan[9]	Penicillin/PTZ	rat	Reduced interictal spikes and seizure duration
1999	Fernandez-Guardiola *et al.*[58]	Amygdala kindling	cat	Delayed kindling, stage IV never reached

reduce the efficacy of VNS in animals[5]. The main central afferent connection of the vagus is the nucleus of the tractus solitarius (NTS), which projects to the locus coeruleus (LC) and adjacent parabrachial nucleus, dorsal raphe, nucleus ambiguus, cerebellum, hypothalamus, thalamus, insula, medullary reticular formation and other brainstem structures, several of which are known to modulate seizures in various models[6–10]. Both chronic lesioning and acute inactivation of the LC reduce the anticonvulsant effects of VNS[11]. However, the locus coeruleus has extensive diencephalic, brainstem and cortical projections and the role of these has not been explored by lesioning studies. Another possibly relevant pathway is the projection of the NTS through the parabrachial nuclei to the substantia innominata and zona incerta. Stimulation of the areas facilitates, and inhibition may suppress generalized seizures[12, 13]. An alternative anatomical interpretation is proposed by Rafael and Moromizato[14], who suggest that stimulation at mid-cervical level activates only nocioceptive and proprioceptive afferents, which terminate in subnuclei of the spinal trigeminal nucleus (but not the NTS). These have projections to the cerebellum, medial accessory olivary nucleus, brainstem reticular nuclei, LC, raphe and superior central nuclei. Changes in various neurotransmitters have been demonstrated (Table 2), including an elevation of c.s.f. GABA in man[15] but whether these are secondary or have a primary role in the mechanism of action of VNS is unknown.

Photon emission tomography (PET) studies in man have shown changes in blood flow in numerous cortical and subcortical structures but with inconsistent results between subjects[16–18]. Similarly, fos-staining has indicated activation by VNS at several apparently unrelated sites[19].

In experimental animals VNS can produce desynchronization or synchronization of the EEG, depending on the stimulus parameters used[20–22]; but significant EEG changes in man have not been demonstrated[23–25].

PRACTICAL AND SURGICAL DETAILS

Human experience is confined to a single device, the Neurocybernetic Prosthesis (NCP®) developed and marketed by Cyberonics (Webster, TX, USA). The system comprises: a pulse generator, a lead incorporating a bipolar electrode, tether and connectors, a tunnelling tool, a programming wand with control software and a magnet.

The electrode array comprises 2 silicone helices each with three turns, with a platinum ribbon electrode within the middle turn. Threads are attached to position the coils around the nerve. A third helical coil is located further caudally to tether the lead to the nerve.

The generator is a disc of 55 mm diameter and 13.2 mm thick, weighing 55 mg. Both before and after implantation it can be interrogated and programmed by radio-frequency signals from the wand which is connected to the serial port of a laptop computer. Output current, pulse width and frequency, the duration of each stimulus train and intervals between trains can be selected. The software also tests the integrity of the generator and lead during implantation. The settings can subsequently be recovered by interrogating the generator.

A hand-held magnet can be used to turn on stimulation when briefly placed over the generator and settings for magnet-activated stimulation can also be programmed. If the magnet is left in place over the generator, the device is inactivated; this facility can be used to suspend stimulation at times when side-effects would be inconvenient (see below).

Implantation is performed under general anaesthesia and the surgical procedure takes approximately 1 hour in experienced hands. The electrodes are placed

Table 2: Evidence on mode of action of VNS.

Functional anatomy:-	
	Multiple projection pathways identified, through nucleus of the tractus solitarius to: locus coeruleus, parabrachial nucleus, dorsal raphe, nucleus ambiguus, cerebellum, hypothalamus, thalamus, insula, medullary reticular formation, substantia innominata, zona incerta.
	Lesioning/inactivation of locus coeruleus reduces the anticonvulsant effect[5].
PET:-	
	Blood flow increased in rostral medulla, right post-central gyrus, hypothalami, thalami, insulae, cerebellum.
	Blood flow decreased in hippocampi, amygdalae, posterior cinguli[17].
Electrophysiology:-	
	EEG desynchronized or synchronized in cat[22, 51].
	Little effect on in man[23, 25].
	Evoked potential latencies increased in man[59], or no effect[24].
Neurochemistry:-	
	Serotoninergic: csf 5-hydroxyindole acetic acid increase[60].
	Serotoninergic: Activation of loculus coeruleus[11].
	Dopaminergic: csf homovanillic acid elevated[15].
	GABAergic: csf GABA elevated[15]; Vth nerve nucleus response to Gasserian stimulation reduced[61]; vagal nerve lesioning by ibotenic acid reduces threshold to picrotoxin & bicuculline but not strychnine (Godlevsky *et al.* 1994).
	VNS induces *fos* production in superior colliculus, amygdala, cortex, post-lateral thalamus and hypothalamus[19].

through an incision over the anterior border of the left sternomastoid midway between the mastoid process and the clavicle. The nerve is identified in the carotid sheath, is mobilized and lifted with vessel loops. The coils are applied to the vagus and gentle traction applied to the threads to wrap them around the nerve. A horizontal incision is then made, centred on a point below the mid-point of the left clavicle and a subcutaneous pouch is prepared to receive the generator. The tunnelling tool is used to pass the connectors of the lead from the cervical to the thoracic incision. The lead is plugged into the generator. This is then interrogated by means of the wand and a lead integrity test is run.

Procedures for starting stimulation vary. It is recommended that stimulation be withheld for 2 weeks as current may track along pathways formed by post-operative oedema. Subsequent ramping up of current is determined by clinical response, tolerability and timing outpatient visits to suit the convenience of the patient. An increase in current as small as 0.25 mA is generally experienced as disagreeable. The patient complains of discomfort or pain in the neck, jaw, face or teeth, and may suffer a paroxysm of coughing. The voice may be strikingly altered. These symptoms rapidly subside, so that after two or three cycles of stimulation the patient reports them as being unpleasant but tolerable and within a few hours significant discomfort has generally disappeared. Current escalation continues until a good therapeutic response is obtained, or adverse symptoms become persistent (see below) or until the maximum available setting of 3.5 mA is reached.

EVIDENCE OF EFFICACY

The first patient treated by VNS, showed a marked reduction in seizure frequency[26]. Single-blind (designated E01 and E02) studies followed in 14 patients, also giving results sufficiently encouraging to justify more formal trials (Table 4).

There are obvious practical difficulties in assessing a treatment which involves surgery and produces obvious side-effects. Randomized, controlled trials have been conducted, using a parallel, add-on design under so far as possible double-blind conditions. Both were multicentre studies using similar designs, designated E03[27] and E05[28], and involving 114 and 199 patients, respectively. The patients (Table 3) had medically intractable partial seizures, with or without secondary generalization. After a baseline period of 3 to 4 months, they were randomized to one of two treatments. The standard protocol (designated 'high stimulation') was that thought from previous studies to be most effective. It comprised 30 second periods of stimulation at 5 minute intervals, at the maximum tolerated current. The alternate treatment ('low stimulation') was regarded as a less effective active control, but it is uncertain whether it was in fact of minimal or zero efficacy. It used a 30 second stimulation period at 60–180 minute intervals, and a lower pulse rate and duration, at a current level just above the threshold for sensation; magnet-triggered stimulation was disabled. At each site, physical examination, and documentation of seizure frequency and adverse events were performed by blinded investigators, and, programming of the generator by an independent investigator.

Table 3: Studies E03 and E05—patient characteristics.

	E03	E05
Inclusion criteria		
age	over 12 yrs	12–65
seizures	6 or more per month maximum interval 14 days refractory predominantly partial	6 or more complex partial maximum interval 21 days refractory
AEDs	1–3	1–3 with stable levels
contraception		acceptable method
documentation		patient or carer can accurately record seizures
Exclusion criteria		
progressive neurological disorder	+	
unstable medical condition	+	
pregnancy	+	
investigational AED	+	
active peptic ulcer		+
current		+
cardiac/pulmonary disease		
prior vagotomy or VNS		+
AEDs prn		+
>2 episodes of status in past year		+
previous resective epilepsy surgery		+
non-epileptic seizures		+
Patient characteristics		
number	114	198
age (mean yrs)	33	33
male %	62	47
mean seizures/day	1.62	1.26
duration of epilepsy	22 yrs	23 yrs
number of AEDs	2.08	2.1
% with secondary GT-C seizures	35	51

Table 4: Efficacy of VNS in trials E01, 2, 3, 4, and 5.

Study	% Change in seizure frequency (n)			% with >50% seizure reduction		
	High	Low	P	High	Low	P
E01/2	−28.2 (14)	NA	<0.05	14.3	NA	NS
E03	−24.5 (54)	−6.1 (60)	<0.01	31.0	13.0	<0.02
E04	−21.5 (116)	NA	<0.001	29.3	NA	NS
E05	−27.9 (94)	−15.2 (102)	0.039	23.4	15.7	NS

One hundred and twenty-five patients were enrolled for the E03 study, 114 of whom underwent randomization. For E05, 254 were recruited but 55 were withdrawn during the baseline period, and one was withdrawn due to infection of the implant site; thus 199 were randomized. In both studies, the clinical characteristics of the two treatment groups were closely similar. The primary efficacy measure was percentage change in seizure frequency with respect to baseline during the 12 weeks following ramp up. A secondary outcome measure was the proportion of subjects experiencing a 50% seizure reduction. In E03, mean seizure frequency fell by 24.5% on high and 6.1% on low stimulation; in E05 the reductions were 28% and 15%, respectively; a significant difference in favour of high stimulation in both cases. Fifty percent seizure reduction was achieved by 31% of the high and 13% of the low stimulation groups in E03 ($P < 0.02$). In E05, there was a 50% reduction in 23.4% on high and 15.7% on low stimulation, a difference which was not significant; however, 10.6 and 2.0, respectively, achieved a 75% reduction ($P < 0.015$). Only three patients (two in E03 and one in E05) became seizure-free after the 3-month acute period of the assessment.

Table 4 summarizes the efficacy data from the randomized trials E03 and E05, the early studies, E01-2, and a subsequent, larger open study E04. That high level VNS was associated with seizure reduction is not in doubt, but the strength of the effect is impossible to assess. In all studies there may have been a 'placebo effect', including possible regression to mean seizure frequency in patients who were recruited during a temporary exacerbation of their epilepsy. As it is not known whether low stimulation had any antiepileptic action, it is impossible to assess the placebo effect. Nevertheless it may be noted that, irrespective

of any possible placebo component, response rates for high stimulation, by all measures used (except possibly subjects becoming seizure-free) were similar to those in trials, in similar patient populations, of recently registered new antiepileptic drugs[29, 30].

SAFETY AND TOLERABILITY

This method of treatment raises issues about safety in several areas. Electrical damage to tissue should not occur at the maximum settings of current and duty cycle available (maxima 3.5 mA, 14 V and 0.36, respectively) and indeed there is no evidence of nerve injury[31, 32]. Magnetic resonance image (MRI) scanning could in theory cause heating of the leads, but is approved in the USA, provided only a head coil is used, and by KEMA in Europe. The device is not affected by microwave transmissions, cellular phones or airport security systems, but the author knows one patient whose stimulator was twice activated during take-off or landing, presumably by fields from actuators used to operate the spoilers or undercarriage.

Some surgical complications may be expected, particularly from insertion of a prosthetic device. In the E03 study, the battery of one generator failed. Another generator locked in continuous high output mode, causing left vocal cord paralysis. In one case the lead became disconnected from the generator and had to be re-connected. One patient suffered a reversible left lower facial paresis and one had an infection at the implant site which was controlled by antibiotics. In the E05 study, operative and technical complications were all reversible and comprised: left vocal cord paresis (two patients), left lower facial paresis[2] fluid accumulation around the generator[1] and infection around the device requiring removal[3]. No damage to the common carotid artery has been reported during post-marketing surveillance of some 4500 patients (Cyberonics internal data).

Possible peripheral vagal effects are a further concern, but measures are adopted to minimize these. Only the left vagus is used for VNS; this is mainly afferent and in particular contains less cardiac efferent fibres than the right. In both the randomized controlled trials particular attention was directed to possible peripheral vagal effects. In the E03 study, vital signs, routine EKG, Holter monitoring (in 28 subjects) and assays of gastric acid (14 patients) were investigated. In E05, vital signs were checked and Holter monitoring (mean heart rate, lowest and peak heart rate, heart rate variability and episodes of bradycardia) were checked in all subjects at baseline and after ramp up, as were fasting serum gastrin and pulmonary function. No evidence of adverse effects of peripheral vagal stimulation was found. There are reports of reversible asystole during intraoperative testing of the stimulator in five patients[33, 34]. This may have been due to anaesthesia, as various anaesthetic agents differentially suppress both sympathetic and parasympathetic tone, with the possibility of increasing cardiac effects of vagal stimulation[35, 36]. Until further evidence is obtained it would appear advisable to initiate VNS during implantation only with great care and under cardiac monitoring and to inactivate the generator during any subsequent general anaesthetic.

No patient died during the E03 and E05 trials, but cases of sudden, unexpected death (SUDEP) have been reported. A study by Annegers *et al.*[37] of 791 patients followed over 1335 patient years, found an incidence of definite or probable SUDEP in patients undergoing VNS of 4.5 per 1000 patient years, which is no greater than expected in such a population.

One patient in E03 suffered a non-fatal myocardial infarct and was withdrawn. In E05, two patients were withdrawn after randomization, one because of postictal Cheyne–Stokes respiration which continued after deactivation of the device, the other because of multiple symptoms present before, during and after termination of VNS.

Levels of co-medication, serum chemistry, haematology and urinalysis were checked in both trials and, not unexpectedly, no adverse effects were detected.

Subjective stimulus-related adverse experiences are reported by all patients able to communicate, and include pain or discomfort, alteration of the voice, breathlessness and coughing. These are generally mild and show rapid habituation until the maximum tolerated current setting is reached. Voice changes are usually mild, but during stimulation the speaker may sound anxious or appear to have a sore throat. This may not be obvious to any but the most attentive listener, but can be embarrassing to the patient whose work brings them into contact with the public. Coughing and dyspnoea may be troublesome to those who engage in vigorous exercise, but can be avoided by strapping a magnet over the generator to inactivate the device during physical exertion. Some patients with learning disability suffer dysphagia and aspiration has been reported[38]. This too may be avoidable by application of the magnet at mealtimes.

In both trials, the adverse experience most often reported on high stimulation was hoarseness/voice change (37.2% in E03; 63% in E05). The discrepancy between the trials may reflect different methods of questioning; in E05 adverse experience reports were actively solicited. Nevertheless, all patients are aware of stimulation and, as few become seizure-free, a strategy of treating to the limits of tolerance will necessarily result in most patients eventually experiencing significant side-effects. Any reported incidence of stimulation-related side-effects less than 100% is

therefore virtually meaningless without further qualification. Discomfort and voice changes are usual, but rapidly habituate until the limits of tolerance are reached; a setting should then be selected which is acceptable to the patient.

The completion rates for the studies, 98% in E03 and 99% in E05, are strikingly higher than those for antiepileptic drug trials in similar populations; the lack of side-effect-related withdrawals suggests a high tolerability of this treatment.

LONG TERM OUTCOME

Patients randomized to low stimulation in the E03 study were subsequently switched to the high stimulus schedule. During 18 month follow-up of the first 67 patients to complete the blinded study, both groups continued to improve, but those transferred from low to high stimulation lagged behind those on the high regime. Thus after a total of 15 months on high stimulation all patients showed a similar mean seizure reduction: 43.1% in the original 'high' group and marginally less, 38.1%, in the former 'low' group (i.e. after 18 months in all)[39]. However, the degree of improvement is hard to assess as 10% of patients withdrew because of lack of efficacy, and there were missing data in others.

Salinsky *et al.*[40] analysed the results of 12 months 'high' stimulation in the E03 study on a last-visit-carried-forward basis and found 32.1% and 31.6% seizure reductions in the former high and low groups, respectively.

Despite this continuing improvement, response within the first 3 months on high stimulation was predictive of long term outcome. Twenty-eight percent of patients achieved a 50% seizure reduction after 3 months, and only 3% more did so after 1 year.

In a follow-up of the E05 study, 102 subjects were transferred from 'low' to 'high' stimulation, and '94' continued on the high schedule. After a further 3 months, the reduction in seizure frequency with respect to baseline increased from 15% to 34% in the former 'low' group, and from 28% to 46% in the 'high' group, relative improvements in seizure control of 125% and 45%[41].

The longest follow-up experience (mean 20 months, range 3 to 64 months) is reported by Ben-Menachem *et al.*[42] in 64 patients not apparently included in the E03 and E05 studies. If a new drug was introduced to improve efficacy, evaluation of VNS outcome was terminated. Forty-four percent experienced a 50% seizure reduction (5/8, 63%, both in Lennox Gastaut syndrome and 5/8 in 'primary generalized seizures').

These studies should be interpreted with caution as they were unblinded, adjustment of co-medication was permitted and some patients were lost to follow-up or withdrew because of lack of efficacy. The most comprehensive available data set analysed on a basis of last-visit-carried-forward comprised 244 patients from the E01, E02, E03 trials and a further open study, E04. There was a mean change in seizure frequency of −38.7% after 18 months, with 37.7% of patients achieving a 50% seizure reduction (Cyberonics, internal report). Despite their limitations, the follow-up studies support the contention that high stimulation is more efficacious than low, and suggest a continuing cumulative effect of VNS beyond the first 3 months of treatment.

PAEDIATRIC RESULTS

No formal controlled paediatric trials have been reported, but there is considerable reported experience of VNS in children. Murphy *et al.*[43] reported a seizure reduction of more than 90% in five out of 12 children with intractable epilepsy. Schallert *et al.*[44] and Lundgren *et al.*[45], respectively, found that 12 out of 20 and six of 16 children achieved a 50% seizure reduction. Some limited assessments of quality of life indicated worthwhile improvement in 17. Parker *et al.*[46] investigated 16 children with particularly severe symptomatic or cryptogenic generalized epilepsies, who had been found unsuitable for surgery. Initial response was poor but after 2 years of follow-up, there was a mean seizure reduction of 46%, six patients had achieved a 50% seizure reduction, one was seizure-free, and five had objective evidence of improved quality of life.

OUTSTANDING ISSUES

Mode of action. An understanding of the mode of action has not been found essential to either the acceptance or effective use of novel antiepileptic drugs (AEDs). Nevertheless, establishing the mechanisms underlying the anticonvulsant action of VNS would enhance its credibility and might facilitate the identification of optimal treatment protocols and of suitable or unsuitable co-medication, and selection of the most appropriate patients.

Stimulation parameters. The standard protocol of 30 second stimulation at 5 minute intervals was selected on the basis of the duration of effect in animal models, but has not been shown to be optimal in man. At least three other schedules are in use: 'rapid cycling': 7 second stimulation at 0.3 minute intervals, 1 minute continuous stimulation at 5 minute intervals, and 30 seconds at 1.8 minute intervals. No formal

studies have compared these protocols nor determined whether there are different indications for their use.

Interactions with drugs. Studies of mode of action offer some evidence that the effects of VNS are mediated by specific neurotransmitters. If this is so, there may also be synergy or antagonism between VNS and particular drugs, which need to be considered when VNS is used in patients taking AEDs, or other agents.

Identification of candidates. Although the controlled trials included only patients with partial seizures, it appears from uncontrolled reports and post-marketing experience that VNS exhibits the same, modest efficacy in a wide range of epilepsies and seizure types, both partial and generalized[47, 48]. In pharmacotherapy of epilepsy, a wide spectrum of action is generally regarded as an advantage, but until a wide spectrum of action is reliably established, or narrower indications are more clearly defined, there will be justified concern that vagal nerve stimulation is not being used optimally.

At present it appears that VNS should be considered in any patient with undoubted epilepsy, demonstrably resistant to appropriate medication administered to tolerance, who is not a candidate for potentially curative resective surgery. The definition of medical intractability may be disputed, and similar considerations will apply as in conventional surgery. It is a matter of concern that VNS may be viewed, both by physicians and patients, as a safe, inexpensive alternative to resective surgery. As the latter offers to some categories of patients a 70–85% chance of complete seizure control, it is important that VNS should only be undertaken after full consideration of other surgical options, and in the context of a comprehensive epilepsy program. Vagal nerve stimulation offers palliative treatment approximately equivalent in efficacy to callosotomy, and a randomized trial of VNS and callosotomy would be valuable.

Benefits other than seizure control. There is some anecdotal evidence that VNS improves cognition, particularly in patients with learning disability and may improve mood and quality of life. As noted above, quality of life measures were included in some uncontrolled paediatric trials and benefits were claimed. Clark *et al.*[49] report enhancement of retention memory in a robust controlled study in man. Unfortunately, this effect was seen only at levels of current too low to influence seizure frequency in most subjects. Further randomized studies of cognitive, affective and behavioural changes during VNS at therapeutic levels are urgently required.

Vagal nerve stimlation as an alternative to pharmacotherapy. Although side-effects of VNS are inescapable, they are well tolerated and cause less distress and impairment of quality of life than do the cognitive side-effects of most AEDs. If further experience of VNS in intractable epilepsies is favourable, the question must arise as to whether this treatment may not also be suitable for some patients whose seizures are controllable with AEDs, but only at a cost of unacceptable side-effects. Comparative cost/benefit studies against AEDs in less refractory populations must be the next step.

Cost-benefit. The efficacy of vagus nerve stimulation appears to be comparable to, or greater than, that of any one of the newer antiepileptic drugs; however, trial use of a drug can rapidly be abandoned if unsuccessful, whereas undertaking treatment by VNS involves a minimum commitment to the cost of the device and its implantation. Nevertheless, across a sample of 15 patients including responders and non-responders, the cost of VNS was recovered by savings in direct medical costs within 2 years[50].

Regulatory status. Vagal nerve stimulation is recognized as effective by the US Food and Drug Administration, Medicare and the central advisory board of Blue Cross-Blue Shield. The device has E.U. CE approval. A report of the American Academy of Neurology's Therapeutics and Technology Assessment Subcommittee, Fisher and Handforth[30] concludes the evidence of efficacy to be of Class I, except for use in idiopathic generalized epilepsies and children, where is it of Class III.

CONCLUSION

Vagus nerve stimulation offers a non-pharmacological palliative treatment of epilepsy, of established efficacy and safety in adults with medically refractory partial seizures which are not amenable to resective surgery. In this population the efficacy is modest but worthwhile and the tolerability excellent. Randomized controlled trials are not available in other seizure types nor in children, but VNS appears to be of similar efficacy in all forms of intractable epilepsy. Its utility in milder seizure disorders is unknown. The eventual overall role of this therapy in epilepsy has yet to be established, but is likely to be significant.

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