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Australian Chapter of the
International League Against Epilepsy

September 12th, 2009

Dr Brian Richards, Executive Manager and Medical Advisor
Mr Phil Dunkley, Senior Project Manager
Medicare Services Advisory Committee Projects
Health Technology and Medical Services Group
Department of Health and Ageing
GPO Box 9848
Canberra ACT 2601

Dear Dr Richards and Mr Dunkley

Re: MSAC Application 1118 – Vagus Nerve Stimulation (VNS) Therapy Submitted March 2007 and rejected September 2008

We write in response to the MSAC submission for procedural item numbers for Vagus Nerve Stimulation (VNS) Therapy, submitted by the Epilepsy Society of Australia (ESA) in March 2007 and rejected by the MSAC in September 2008. You will have on file the ESA's initial response to your Committee's rejection and notes from a meeting in your office on November 17th, 2008. The ESA submission was endorsed by the Joint Epilepsy Council of Australia (JECA), the Neurosurgical Society of Australasia (NSA) and the Australian and New Zealand Association of Neurologists (ANZAN).

Our neurologist colleagues in the ESA and non-medical colleagues in Epilepsy Australia and Epilepsy Action remain disappointed by the MSAC's response to the VNS submission, dismayed by MSAC's evaluation of VNS efficacy, concerned about the now doomed prospects of gaining public funding for VNS by state health services, and worried for people with uncontrolled epilepsy who will be unable to access VNS therapy.

Feedback from the MSAC and other sources suggests that overall, the application and supporting data were satisfactory but several points of concern ultimately led to the final decision to not approve VNS for privately-insured patients. We understand that there is no formal review process for a MSAC submission but we hope that your Committee might reconsider the application in the light of comments made and additional data provided below, separated according to the points of concern raised by the MSAC.

VNS has a low seizure free rate

This is a true statement, seizure free rates from VNS being less than 5%. However, **seizure freedom is an inappropriate measure of efficacy of VNS**, and one that is not applied to antiepileptic drug (AED) evaluation. In the epileptic population in whom VNS might be considered, that is patients who have failed multiple AEDs and possibly a ketogenic diet and epilepsy surgery, seizure freedom is an unrealistic expectation of any therapy.

In randomised clinical trials (RCTs) of AEDs, efficacy is measured in terms of percentage seizure reduction from baseline or responder rates (percentage of patients with $\geq$50% seizure frequency reduction), with seizure free rate being rarely reported and not required for regulatory approval. Typically, responder rates for new AEDs compared to placebo are about

10-40%, in RCTs of adjunctive therapy in uncontrolled partial epilepsy in adults, with seizure free rates <5% (see table). These measurements are typically made at the end of 8-12 week double-blind phases of RCTs, with long-term efficacy (and tolerability) of AEDs being significantly lower, as evidenced by low retention rates in open-label extension trials. Clinical experience with AEDs corroborates these RCT findings, with initial response to new AEDs followed by seizure relapse or intolerability of side effects with time.

Antiepileptic Drug	**Daily Dose(s)**[^]	**Responder Rate**[#] (~3 mths)	**Seizure-free Rate**[*] (~3 mths)	**Retention Rate**[**] (> 1 yr)
pregabalin	600 mg	36 – 39%	1.4%	32%
oxcarbazepine	1200-2400 mg	28 – 37%	2.6%	
gabapentin	600-1800 mg	8 – 26%	1%	10-25%
lamotrigine	300 mg	20 – 22%	0.8	29-60%
topirimate	200 mg	27%		30%
tiagabine	15-56 mg	20 – 36%		
zonisamide	100-200 mg	13 – 15%	3%	29%
levetiracetam	1000-3000 mg	12 – 29 %	4-7%	60-75%

[^] Dose used in trial equivalent to that which is typically prescribed and tolerated

[#] Difference between treatment and placebo arms of RCTs in percentage of patients achieving 50% or greater reduction in seizures at end of the double-blind phase, typically 8-12 weeks duration. Data from TGA approved Product Information and the AAN-AES report (French et al, 2004).

[*] Analysis includes only those that completed the RCT, a more clinically-meaningful figure than that reported from intention to treat analyses (Gazzola et al, 2007).

[**] Percentage of patients continuing on AED in extension phase of RCTs for > 1 year (longest period reported).

French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new AEDs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2004;62:1261.

Gazzola DM, Balcer LJ, French JA. Seizure-free outcome in randomized add-on trials of the new antiepileptic drugs. *Epilepsia* 2007;48:1303.

Zaccara G, Messori A, Cincotta M, Burchini G. Comparison of the efficacy and tolerability of new antiepileptic drugs: what can we learn from long-term studies? *Acta Neurol Scand* 2006;114:157.

Yuen AW, Singh R, Bell GS et al. The long-term retention of pregabalin in a large cohort of patients with epilepsy at a tertiary referral centre. *Epilepsy Res* 2009; electronic publication

Lhatoo SD, Wong IC, Polizzi G, Sander JW. Long-term retention rates of lamotrigine, gabapentin, and topiramate in chronic epilepsy. *Epilepsia* 2000;41:1592.

Wroe SJ, Yeates AB, Marshall A. Long-term safety and efficacy of zonisamide in patients with refractory partial-onset epilepsy. *Acta Neurol Scand* 2008;118:87.

As MSAC noted from the ESA submission and the MSAC's review of VNS trial data, VNS responder rates are approximately 40% (higher in open-label paediatric studies), with seizure reduction typically being delayed by 6-12 months but increasing over time, in striking contrast to AEDs in which seizure control is gradually lost. Furthermore, long-term tolerability of VNS is significantly greater than with AEDs. The greater tolerability and gradual improvement of efficacy with VNS is reflected in long-term retention rates which are high for VNS, being greater than 78% at 3 years in the long-term studies and extension phases of the RCTs. **For patients with AED resistant epilepsy, <u>sustained</u> seizure reduction is greater with VNS than with further trials of AEDs.**

VNS extension trials and long-term studies	Stimulation	Responder Rate	Seizure-free Rate	Retention Rate
International (n=454) RCT (EO1- EO5) then open Morris & Mueller, 1999		1 yr = 37% 3 yrs = 44%		1 yr = 97% 3 yrs = 78%
USA (n=195) Uncontrolled and open DeGiorgio et al, 2000		1 yr = >39%		
USA (n=46 children) Uncontrolled and open Alexopoulos et al, 2006	<2.5mA (9% cycle)	2 yrs = 59%	2 yrs = 10%	3 yrs = 78%
Belgium (n=138) Uncontrolled and open De Herdt et al, 2007	Mean 1.8 mA	3 yrs = 59%	3 yrs = 9%	
Czech Republic (n=90) Uncontrolled and open Kuba et al, 2008	Mean 1.4mA (10-35% cycle)	1 yr = 44% 2 yrs = 59% 5 yrs = 64%	5 yrs = 5%	5 yrs = 94%

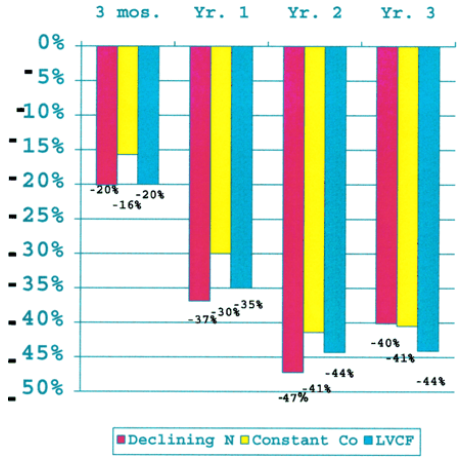
Morris GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. *Neurology* 1999;53:1731.

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.

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.

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.

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



Patients with more than a 50% seizure reduction from combined studies E01 - E05. Declining numbers (n = 440 at 3 months, 396 at 12 months, 188 at 24 months, 93 at 36 months); constant cohort (n = 93); last visit carried forward (n = 440). From Morris and Mueller, 1999.

While freedom from all seizures and withdrawal of AEDs is an extremely rare outcome of VNS therapy, many studies (and my own personal, published experience) indicate that **VNS may lead to freedom from some specific seizure types** (eg. daytime drop attacks, recurrent bouts of status epilepticus) or **significant reductions in epilepsy severity** (eg. shorter duration seizure and postictal periods, more rapid recovery following seizures, seizure free days) are not uncommon, these being important efficacy indices that are not captured with a simple assessment of total seizure frequency and seizure freedom. These improvements are

particularly notable in paediatric epilepsies, especially the catastrophic generalised epilepsies of childhood with associated encephalopathy, such as the Lennox Gastaut syndrome.

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

Murphy JV, Torkelson R, Dowler I, et al. VNS in refractory epilepsy: the first 100 patients receiving vagal nerve stimulation at a pediatric epilepsy center. *Arch Pediatr Adolesc Med* 2003;157:560.

Lundgren J, Amark P, Blennow G, et al. VNS in 16 children with refractory epilepsy. *Epilepsia* 1998;39:809.

Patwardhan RV, Stong B, Bebin EM, et al. Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. Neurosurgery *2000*;47:1353.

Parker AP, Polkey CE, Binnie CD, et al. VNS in epileptic encephalopathies. *Pediatrics* 1999;103:778.

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

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.

Hosain S, Nikalov B, Harden C, et al. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. *J Child Neurol* 2000;15:509.

Aldenkamp AP, Van de Veerdonk SH, Majoie HJ, 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.

Majoie HJ, Berfelo MW, Aldenkamp AP, et al. Vagus nerve stimulation in patients with catastrophic childhood epilepsy, a 2-year follow-up study. *Seizure* 2005;14:10.

Andriola MR, Vitale SA. VNS in the Developmentally Disabled. *Epilepsy Behav* 2001;2:129.

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, Canada. *Childs Nerv Syst* 2006; 22:1018.

Patwardhan, RV, Dellabadia, J Jr, Rashidi, M, et al. Control of refractory status epilepticus precipitated by anticonvulsant withdrawal using left vagal nerve stimulation: a case report. *Surg Neurol* 2005; 64:170.

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

Shahwan A, Bailey C, Maixner W, Harvey AS. Vagus nerve stimulation for refractory epilepsy in children: More to VNS than seizure frequency reduction. *Epilepsia* 2009;50:1220.

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

Whether a reduction in seizure frequency and/or severity would likely translate into improvement in the patient's lifestyle, well-being and healthcare utilisation depends on the patient's age, type of epilepsy, co-morbidities and social circumstances. This issue is considered carefully by the treating neurologist and the patient/family when deciding if VNS should be undertaken. It is my (ASH) personal practice to recommend VNS to patients with AED-resistant focal or generalised epilepsy who have recurrent bouts of status epilepticus or daytime drop attacks, for which a VNS response would be significant for the patient and health service; for patients in whom a reduction in the number of their multiple daily seizures would unlikely lead to a significant change in their wellbeing, and for patients who desire seizure freedom or elimination of AEDs, I counsel against VNS.

There are poor outcomes in >50% patients undergoing VNS

By poor outcomes one assumes that MSAC means that >50% of patients do not have a significant treatment response ie. seizure freedom or greater than 50% reduction in seizure frequency. This is a true statement, dealt with in the previous section. In fact, this statement would apply more to treatment with AEDs and a ketogenic diet, with only resective epilepsy surgery affording >50% patients with complete seizure control or > 50% seizure reduction.

Is the implication of this statement that a patient with uncontrolled epilepsy should only be given a treatment if there is a >50% chance of them being cured of their epilepsy, or having a significant seizure reduction? Seemingly not, given the widespread use of AEDs to marginally reduce seizure frequency in patients with uncontrolled epilepsy. Would such a stance be taken with cancer chemotherapy or transplant treatments, that is to say that those treatments should only be undertaken if there is a >50% 5-year survival rate? While prolongation of life is easily argued as the reason for undertaking cancer chemotherapy and organ transplantion, patients with uncontrolled epilepsy live with a disabling medical condition that carries a risk of sudden death of 1 per 100 patient years.

Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol* 2008;7:1021.

Lack of Class I evidence from a RCT of VNS

As the MSAC knows well, **Class I evidence from RCTs of therapeutic devices is rare**, due to problems with blinding. Sham VNS is not possible, due to the laryngeal effects of stimulation, preventing a VNS placebo which could be blind to the patient and investigator in an RCT. The pivotal early trials of VNS therapy were thus performed with low- versus high-current stimulation, these being of a sufficiently high trial-design standard and yielding sufficiently robust findings to enable regulatory approval in Europe, the USA, Australia and most of Asia. One would not envisage that any further sponsored RCTs of VNS in epilepsy would be forthcoming.

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.

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.

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.

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

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.

Additionally, it appeared that the MSAC excluded from their analysis pivotal RCTs of VNS if they did not meet the MSAC criterion of specifically stating that the patients studied were not eligible for epilepsy surgery. The application of this supplementary indication for VNS (having failed or being unsuitable for epilepsy surgery) to regulatory trials performed 15 years ago seems ludicrous, as this view of the clinical place of VNS only became apparent after completion of these pivotal RCTs and experience with VNS in clinical practice.

It is unclear why these trial data were **suitable evidence of efficacy for the TGA and the rest of the world**, but considered by the MSAC as "insufficient evidence of effectiveness and net benefit of VNS for patients with medically refractory epilepsy". If MSAC considerations are broader than the efficacy and safety issues that underpin regulatory approval, why did MSAC not accept the efficacy and safety data approved by the TGA and consider the more clinical, social and economic data?

Improved quality of life is difficult to determine and the best indicator is reduced seizure frequency

The MSAC claimed that the effectiveness of VNS in improving patient quality of life (QOL) was difficult to determine, that the instruments used were insensitive, and that the best indicator of QOL is seizure freedom. We disagree strongly with these statements, pointing out that **QOL measures improved consistently in the numerous controlled and open studies of VNS in adults and children**, where such assessments were made (listed previously here, in the MSAC submission, and below). As with seizure reduction during VNS therapy, improvement in some QOL measures also increases over time. Furthermore, **some of the QOL improvements following VNS appear to be a direct effect of VNS, independent of seizure frequency reduction** (next paragraphs).

Cramer, JA. Exploration of Changes in Health-Related Quality of Life after 3 Months of Vagus Nerve Stimulation. *Epilepsy Behav* 2001; 2:460.

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.

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.

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

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

There is evidence that **VNS improves mood** and other depressive symptoms in patients with epilepsy. VNS was approved by the FDA in 2005 for treatment-resistant major depression. This positive mood effect in epilepsy is in striking contrast to the effects of AEDs which, according to the FDA and TGA analyses of the regulatory trials of AEDs, increase suicidal thoughts and the risk of suicide.

Elger G, Hoppe C, Falkai P, et al. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res* 2000; 42:203.

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.

Schachter SC. Vagus nerve stimulation: mood and cognitive effects. *Epilepsy Behav* 2004; 5 (Suppl 1):S56.

Marangell LB, Suppes T, Zboyan HA, et al. A 1-year pilot study of vagus nerve stimulation in treatment-resistant rapid-cycling bipolar disorder. *J Clin Psychiatry* 2008;69:183.

Park MC, Goldman MA, Carpenter LL, Price LH, Friehs GM. VNS for depression: rationale, anatomical and physiological basis of efficacy and future prospects. *Acta Neurochir Suppl* 2007;97:407.

Neuropsychopharmacology. 2006 Jul;31(7):1345-55. Epub 2006 Apr 19. LinksErratum in:

Nemeroff CB, Mayberg HS, Krahl SE, et al. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. *Neuropsychopharmacology* 2006;31:1345.

Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* 2001;25:713.

Daban C, Martinez-Aran A, Cruz N, Vieta E. Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. *J Affect Disord* 2008;110:1.

FDA report on AEDs and Suicidality, May 2008 (http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf)

VNS improves daytime alertness and vigilance, even in patients without significant reduction in seizure frequency, potentially by stimulation of brainstem centres controlling alertness. As with the dramatic seizure reductions seen in some children with severe generalised epilepsies, improvements in alertness are often striking in children with severe

developmental disabilities such as autism, intellectual disability, cerebral palsy and Rett syndrome, again independent of seizure control.

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.

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.

Malow BA, Edwards J, Marzec M, et al. Vagus nerve stimulation reduces daytime sleepiness in epilepsy patients. *Neurology* 2001;57:879.

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.

Gates J, Huf R, Frost M. VNS for Patients in Residential Treatment Facilities. *Epilepsy Behav* 2001;2:563.

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

Zamponi N, Rychlicki F, Corpaci L, Cesaroni E, Trignani R. Vagus nerve stimulation is effective in treating catastrophic epilepsy in very young children. *Neurosurg Rev* 2008;31:291.

Formal economic analysis was not conducted due to lack of adequate data and uncertainty of net clinical benefit

A detailed component of our submission was a summary of the cost-effectiveness of VNS, with an estimate of the funding implications of increased private usage in Australia. Health economic evaluations in North America and Europe consistently show **decreased healthcare resource utilization and subsequent reductions in medical costs with VNS in uncontrolled epilepsy**. Aurora Bioscience, the Australian distributor of Cyberonics® VNS Therapy, have conducted a detailed analysis of the health economic literature and performed some economic modelling with Australian figures, the results of which they may forward to MSAC separately.

In one published USA study (Bernstein et al, 2007), the average use of health services declined from the year prior to VNS to the fourth year after VNS by 82% for outpatient visits, 86% for emergency room visits and 67% for hospital admissions. In this study, the average annual cost of these health services in the year prior to VNS was US$7,189 and fell by 73% to US$1,950 by the fourth year after VNS; this analysis did not consider the additional economic benefits to the community eg. return to work, reduction in caregivers' time off work, social security costs etc. Numerous other economic studies report significant cost savings with VNS therapy in appropriately selected patients, with the costs of VNS recovered in less than 5 years.

In my (ASH) personal (published) series, several children with recurrent status epilepticus prompting hospital attendance and admission ceased attending hospital for seizure exacerbations after VNS therapy was commenced, the hospital savings in one patient being equivalent to the cost of five VNS devices (Shahwan et al, 2009). Also, injuries complicating seizures in Lennox Gastaut syndrome, and their associated health costs, are significantly reduced in children with who cease having daytime drop attacks with VNS. These two clinical situations, where one sees dramatic improvements in seizure control, quality of life and medical costs, are situations where patients are <u>not</u> seizure-free.

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:S44.

Bernstein A, Barkan H, Hess T. Vagus nerve stimulation therapy for pharmacoresistant epilepsy: effect on health care utilization. *Epilepsy Behav* 2007;10:134.
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.
Boon P, Vonck K, D'Have M, et al. Cost-benefit of vagus nerve stimulation for refractory epilepsy. *Acta Neurol Belg* 1999;99:275.
Boon P, Vonck K, Vandekerckhove T, et al. Vagus nerve stimulation for medically refractory epilepsy: efficacy and cost-benefit analysis. *Acta Neurochir (Wien)* 1999;141:447-452.
Forbes RB, Macdonald S, Eljamel S et al. Cost-utility analysis of vagus nerve stimulators for adults with medically refractory epilepsy. *Seizure* 2003;12:249.
Majoie HJ, Berfelo MW, Aldenkamp AP et al. 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.
Shahwan A, Bailey C, Maixner W, Harvey AS. Vagus nerve stimulation for refractory epilepsy in children: More to VNS than seizure frequency reduction. *Epilepsia* 2009;50:1220.

Replacement of VNS pulse generators after battery exhaustion, after 6-12 years therapy using typical stimulation settings, is only performed in patients who have had a favourable response to VNS eg. significant reduction in seizure frequency or severity, abolition of a troublesome seizure type, reduction in hospital attendances for seizure exacerbations etc. The cost of replacement is about 25% less than implantation, as the stimulation lead is not replaced, the procedure for replacing the pulse generator is minor, and monthly review for stimulation increases is not needed. Presumably, the health cost savings in these patients would justify the replacement of their pulse generator.

As indicated in the ESA's submission to MSAC and agreed with in the MSAC assessment report, the financial implications of Medicare funding for VNS therapy procedures in privately insured patients is negligible, based on 30 patients implanted annually, the costs of the device being covered by the patient's health insurer, and the utilisation of VNS being extremely limited.

The ESA and JECA recognise that there is concern about the number of medical devices being implanted in patients for various indications. This is a growth area in medical research and therapy, and a field that health authorities need to monitor closely. We suspect that the majority of implanted medical devices in Australia are drug delivery pumps and cardiac pacemakers and defibrillators, with VNS (current and future) representing only a tiny fraction.

The MSAC process for VNS

VNS therapy was approved by the Australian TGA in 2000, but no procedural MBS item numbers or other funding arrangements were put in place. Limited public funding was gained at a few epilepsy centres around Australia, and privately-insured patients were able to obtain VNS with payment of the device and implantation procedure by their health fund. In 2005, Medicare requested that the ESA submit an application for VNS-specific procedural item numbers for billing privately-insured inpatients, forbidding further use of MBS procedural items for other neurostimulators. The ESA was given the impression that the MSAC review would be a formality, given the wealth of efficacy, safety and health economic data on VNS, the limited and restricted use of VNS in Australia, and the conservative budget modelled on implantation of other neurostimulators.

The MSAC rejection of MBS funding for privately insured patients and the threatened withdrawal of VNS therapy from the Australian Register of Therapeutic Devices came as a great shock to the ESA and the non-medical epilepsy organisations. Furthermore, the MSAC's recommendation that *"public funding arrangements for VNS for epilepsy remain unchanged"* was unrelated to the purpose of the MSAC application, ignored the fact that there are limited public funding arrangements for VNS in Australia, and potentially jeopardises applications to public hospitals and state health departments for public funding. Combined with the comparatively harsh review of VNS efficacy using seizure-freedom and responder rates, the exclusion of several pivotal RCTs from the MSAC analysis, the superficial and erroneous interpretation of non-seizure outcomes of VNS, and the disregard of positive health economic data, the ESA finds the whole process quite incredible and extremely frustrating. How a previously-approved, partially-funded medical device can have access suddenly limited, without any adverse efficacy, safety or economic data to support its limitation, defies understanding.

Conclusion

VNS therapy was approved by the Australian TGA in 2000 (following regulatory approval in Europe in 1994 and in the USA and Canada in 1998) as adjunctive therapy to reduce the frequency of seizures (not seizure freedom!) in patients with partial and generalised seizures which are refractory to AEDs. Clinical experience with VNS over the last 10 years has recognised its superiority to continued AED trials in patients with uncontrolled epilepsy, its inferiority to epilepsy surgery in appropriately-selected patients, and its relatively greater efficacy in severe childhood epilepsies and patients with recurrent status epilepticus, refining its place in clinical practice. Consensus international opinion is that VNS is a treatment option for patients with medically-refractory epilepsy who are not candidates for resective epilepsy surgery, being supported by adequate funding models in developed countries.

Fisher RS, Handforth A. Vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 1999;53:666.

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

>700 publications on VNS and epilepsy cited at Medline

The VNS funding model proposed by the ESA (Section 5.3 of MSAC application) was for continued MBS and health insurer funding for privately-insured patients around Australia, combined with hospital- or state-based applications for public funding of non-insured patients, the private and public funding being limited to patients with therapy-resistant (AEDs, surgery, ketogenic diet) partial and generalised epilepsy evaluated in recognised comprehensive epilepsy centres.

Epilepsy is a relatively, poorly-funded area of healthcare with respect to clinician reimbursement for professional services, and patient access to specialist care, specialised investigations and treatments, and social support services. Furthermore, people living with uncontrolled epilepsy are significantly disadvantaged and stigmatised, in the health and education systems and in the wider community. Those caring for people with epilepsy see the lack of public and private funding of VNS as yet another example of the hardship and disadvantage facing patients and families living with epilepsy.

The ESA and the JECA would be grateful for your considered review and response to the points raised here, if possible before the **Federal Parliamentary Inquiry into Epilepsy** on October 30th.

Yours sincerely

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