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Cost-utility analysis of vagus nerve stimulators for adults with medically refractory epilepsy

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***Introduction*:** The cost-utility of vagus nerve stimulator (VNS) devices for medically refractory epilepsy has yet to be estimated.
***Methods*:** Using a meta-analysis of randomised controlled trials of VNS, we estimate that six people require implantation in order for one person to experience a 50% reduction in seizure frequency. Costs averted from improved epilepsy control were ascertained from published literature. Values for health states were obtained from a series of 42 seizure clinic attenders using time trade-off techniques and the EQ-5D health status instrument. The cost per quality adjusted life year gained was estimated and the values obtained were tested in a sensitivity analysis.
***Results*:** Improved epilepsy control averted, on average, £745 health care costs per annum. People with epilepsy had great difficulty performing the time trade-off experiment, but those who managed to complete the task valued a 50% reduction in their own seizure frequency at 0.285 units. For a programme of six implants, the baseline model estimated the cost per quality adjusted life year gained at £28 849. The most favourable estimate was equal to £4785 per quality adjusted life year gained, assuming that the number needed to treat was similar to published series in which one response was obtained for every three implants. The least favourable estimate was equal to £63 000 per quality adjusted life year gained, when EQ-5D utility values were used. The cost per quality adjusted life year gained was not sensitive to changes in length of stay, nor complication rates, but was significantly influenced by cost of device and device battery life expectancy.
***Conclusion*:** There is not a strong economic argument against a programme of VNS implantation, although care should be taken to try and identify and treat those most likely to benefit.

Key words: epilepsy; economic evaluation; costs; vagus nerve stimulator.

INTRODUCTION

There is now evidence to support the use of vagus nerve stimulator (VNS) devices for medically refractory epilepsy[1]. However, these devices cost about £5500 to purchase and little is known about their relative costs and benefits. In chronic disorders, such as epilepsy, health care staff are being asked to assess the relative costs and benefits of new and existing interventions. Local funding decisions may await an estimate of the relative costs and benefits of treatment, as resources for healthcare are finite[2]. Many epilepsy specialists, particularly in the United Kingdom have had difficulty obtaining funds for vagus nerve stimulation programmes, as there have been no original economic evaluations to date.

Recently the American Academy of Neurology[3] stated that:

> . . . Vagus nerve stimulator devices and implantation surgery are costly. This modality would be cost-effective only if studies could show decreased doctor and emergency visits, reduced dependence upon anti-epileptic drugs, and improved quality of life. Such an outcome analysis remains to be done.

We report an economic evaluation of vagus nerve stimulators for the treatment of medically refractory

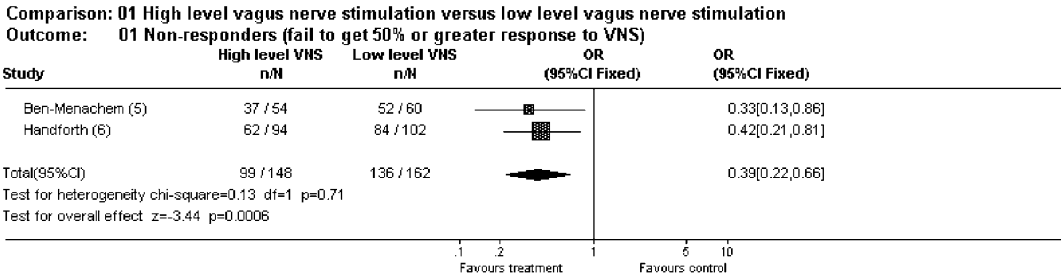

Fig. 1: Meta-analysis of randomised controlled trials of high versus low frequency vagus nerve stimulation.

epilepsy, using health state valuations of people with epilepsy.

METHODS

The cost per quality adjusted life year gained is equal to the net costs from a programme of implantation sufficiently large to benefit at least one person, divided by the net gain in quality adjusted life years. Methods are described to (i) estimate the efficacy of VNS devices; (ii) calculate costs of implantation; (iii) estimate costs averted from improved epilepsy control; and (iv) estimate the number of quality adjusted life year gained by valuing the health gained from improved epilepsy control.

Efficacy of vagus nerve stimulator devices

We derived an overall estimate of the efficacy of VNS devices from meta-analysis of published trials. We identified two randomised controlled trials[4,5] from a search of MEDLINE, EMBASE, The Cochrane Controlled Trials Register and hand search of abstracts from a satellite symposium on the use of VNS[6]. We estimated that for every six (95% CI 3–14) people implanted and stimulated at high frequency that there would be at least one person with a 50% or greater reduction in seizure frequency (Fig. 1).

Costs of epilepsy

We identified seven cost of epilepsy studies[7–13] from 356 abstracts located by a MEDLINE and EMBASE search using the terms ‘cost’ and ‘epilepsy’. Costs were inflated or deflated to UK 1996 prices using the UK Retail Price Index. Prices from other countries were inflated or deflated to 1996 US prices using the Bureau of Labour Statistics Consumer Price Index. Purchasing Power Parity calculations were used to convert the value of US goods and services to UK values, where US$1.00 purchased £0.641 of UK goods and services in 1996[14]. From these studies we estimated that a reduction in seizure frequency equivalent to the impact of a successful VNS implantation would avert £745 of healthcare costs (Table 1). One study which specifically described the costs averted from a programme of VNS implantation, and estimated that £2958 of costs were averted per year of successful VNS implantation[13]. As our pre-specified methods had stated that we would take a mean cost across all studies, we present a baseline estimate using the mean costs from all studies, and used data from the single study which specifically examined VNS costs in our sensitivity analysis.

Cost of VNS implantation

We obtained costs for theatre usage, and in-patient stay from the Scottish Healthcare Purchasing Information Centre, based at Ninewells Hospital and Medical School. The cost of a VNS device was £5500.

Quality adjusted life years gained

A literature search using MEDLINE and EMBASE identified a single study which computed utility values for an appropriate population of people with epilepsy[15]. That study used a time trade-off method[16] to value health states of people with epilepsy (Table 2). Using this data, a VNS candidate could have a baseline utility of either 0.40 or 0.66, and if successfully treated with a VNS device, could increase their utility value to 0.79 (Table 2—50% reduction in seizure frequency). Accordingly, values of quality adjusted life years gained of 0.13 or 0.39 per year of successful treatment could be derived. We sought to reproduce these values in a population of 42 people with medically refractory epilepsy attending the Epilepsy Clinic at Ninewells Hospital and Medical School, Dundee. We obtained Ethics Committee approval and participants gave written consent before completing the

Table 1: Costs averted by improved seizure control.

Author (study size and price base year)	Definition of active epilepsy	Definition of less active epilepsy	Annual cost per person with active epilepsy (1996 £)	Cost per person per annum less active epilepsy (1996 £)	Additional cost per year of less active epilepsy (1996 £)
van Hout *et al.*[7] ($N = 300$, US$ 1993)	>1 per day	<1 seizure per day, >1 seizure per week	2856	1860	997
Jacoby *et al.*[8] ($N = 789$, UK£ 1993)	>1 seizure per month	<1 seizure per month	1655	895	760
Cockerell *et al.*[9] ($N = 1682$, UK£ 1994/1989)	≥1 seizure in last 24 months	Seizure free in last 24 months	567	89	478
Begley *et al.*[10] (US$ 1990)	Non-institutionalised with frequent seizures	Persistent but rare seizures	(26064) (lifetime cost)	(10312) (lifetime cost)	(15752) (lifetime cost)
Selai *et al.*[11] ($N = 47$, UK£ 1997)	Pre-TPX	Successful treatment with TPX (includes 50% reduction in seizure frequency)	0	1494	−1494
Selai *et al.*[11] ($N = 26$, UK£ 1997)	Pre-LMT	Successful treatment with LMT (includes 50% reduction in seizure frequency)	0	1822	−1822
Malmgren *et al.*[12] ($N = 52$, US$ 1991)	Median 12 seizures per month	≥50% reduction in seizure frequency	1177	1023	154
Boon *et al.*[13] ($N = 15$, US$ 1995–1998)	26 seizures per month	11 seizures per month	5660	2702	2958

Summary of eight published studies. LMT, lamotrigine; TPX, topiramate; VGB, vigabatrin.

Table 2: Utility values from a study of Lamotrigine add-on therapy for epilepsy, Messori *et al.*[15].

Epilepsy severity	*N*	Mean utility	SD	Range
Level 1	9	0.40	0.07	0.32–0.50
Level 2	12	0.66	0.08	0.56–0.78
Level 3	30	0.79	0.13	0.51–1.00
Level 4	15	0.91	0.09	0.74–1.00
Level 5	15	0.96	0.04	0.88–1.00
All	81	0.78	0.19	0.32–1.00

Level 1: non-responder, withdrawal of LMT due to toxicity. Level 2: no response. Level 3: at least 50% reduction in seizure frequency >1 seizure per month. Level 4, at least 50% reduction <1 seizure per month. Level 5 seizure free.

Liverpool Epilepsy Battery[17], the EQ-5D Health Status Instrument[18], and a time trade-off experiment[16] for their own health state and a hypothetical health state in which their seizure frequency is reduced by 50%. The utility values were used to estimate quality adjusted life years gained from successful epilepsy treatment with a VNS. We used to social tariff for the EQ-5D Health Status Instrument to derive utility values[19].

Cost-utility analysis

The cost per quality adjusted life year gained is equal to the net cost divided by the total number of quality adjusted life years gained. The net cost is equal to the total cost of an implantation programme minus the costs averted. The values used in baseline cost-utility models are summarised (Table 3).

Other model assumptions

We assumed that the life expectancy of a device battery was 5 years, which means that after this period of time a further procedure (as a day case) is required to maintain the device. The model was therefore restricted to a 5 year time horizon, which is a reasonable assumption as a longer time horizon implies that no other effective therapy is likely to emerge during that time. We also examined the published literature to determine a device removal rate of 2.7% and an infection risk of 1.1%, each requiring in-patient treatment. We assumed that an infected device would require 7 days in-patient treatment with intravenous antibiotics and would eventually require removal. Future costs were discounted at a rate of 6% (UK Government Treasury Rate), and future health gains (quality adjusted life years) were discounted at a rate of 2%. Discounting is a way of taking into account the fact that people generally prefer, and therefore place greater value on, goods that are immediately available than those available at a point in the future[20,21].

Sensitivity analysis

A sensitivity analysis[22] was performed to assess the impact of changes in model assumptions on the final cost per quality adjusted life year gained.

RESULTS

Quality adjusted life years gained

In our own population we found that people with epilepsy found the time trade-off very difficult to accomplish and out of 43 consented participants, 42 gave responses to some or all the questions. Time trade-off experiments were extremely difficult for the patient population. Six people were unable to give any answer. Thirty people either did not wish to trade any time at all or traded an infinitesimally small amount of time, i.e. seconds or minutes out of a 20 year period. The reason for this reluctance to trade is unclear, as

Table 3: Baseline inputs for calculation of cost per quality adjusted life year gained from VNS implantation.

Input	Value	Comment
Number needed to treat	6 (95% CI 3–14)	From meta-analysis
Cost per implant	£5500	Values from local neuroscience directorate. Used value of £5000 for sensitivity analysis
Cost per day of in-patient stay	£315	From Scottish Healthcare Purchasing Information Centre
Length of in-patient stay	3 days	Range 1–3 days for sensitivity analysis
Cost per hour of theatre time	£395	Assume 1.5 hours theatre time per implant
Cost per infected device	£3100	Cost of 7 days as inpatient receiving IV antibiotics plus explant procedure. (Scottish Healthcare Purchasing Information Centre)
Quality adjusted life years gained per implant	0.285	Values from seven valid time trade-off values. Used range 0.13–0.39 (Messori *et al.*[15]) and 0.167 (EQ-5D values[19]) for sensitivity analysis
Life expectancy of implant battery	5 years	Range 4–6 years for sensitivity analysis

Table 4: Sensitivity analysis: seven selected models for the cost per quality adjusted life year gained from vagus nerve stimulation (values as per baseline unless otherwise stated).

	Baseline	Daycase implantation	Costs averted from VNS cost study (Boon *et al.*[13])	Costs averted from VNS study and daycase surgery	EQ-5D health state valuations[19]	Messori health state valuation 1 (Table 2)	Messori health state valuation 2 (Table 2)	10% complication rate	Targeted to most likely responders
Number needed to treat	6								3
Cost per VNS device	£5500								
Length of hospitalisation	3 days	1 day		1 day					
Cost of devices plus surgical procedures	£39465	£34725		£34725				£39776	
Costs averted	£745 per annum of successful treatment		£2958	£2958					£2958
Quality adjusted life years gained per successful device	0.285				0.167	0.130	0.390		
Cost per quality adjusted life year gained	£28849	£25384	£20599	£17134	£49233	£63245	£21082	£29076	£4785
Change from baseline cost per quality adjusted life year gained	Baseline	−12%	−29%	−41%	+71%	+119%	−27%	+1%	−83%

other responses made it clear that they did have significant health problems at the time of interview. Of the remaining 37 participants, only 7 appeared to trade in a manner described in the health state valuation literature. These seven people valued a 50% reduction in seizure frequency with a utility value of 0.285. Using the EQ-5D quality of life instrument people with a seizure frequency of less than one per month had a mean utility of 0.848 ($n = 17$) compared to a mean utility value of 0.681 for those with a seizure frequency of greater than 1 per month ($n = 25$). For a 50% reduction in seizure frequency, the mean gain in health could reasonably be valued as 0.167 quality adjusted life years.

Using these utility values, and estimates for the costs incurred and costs averted (Table 3) we estimate that the baseline cost per quality adjusted life year gained from a programme of six VNS implants, each with a battery life of 5 years, gaining 0.285 quality adjusted life years per annum, and averting £745 of health care costs to be £28 950 (1996 prices). Using the 95% confidence intervals (CI) for the number needed to treat, the range of possible values has to lie between £13 000 and £71 000 per quality adjusted life year gained.

Sensitivity analysis

Clearly there are many potential permutations for this economic model. However, we present seven reasonable alternatives to explore the effect of changes to important variables or examine the effect of different neurological or neurosurgical practice (Table 4).

The range of values from sensitivity analysis was between £4785 for a model which assumed that the device could be targeted to those with a 33% chance of response to £63 245 per quality adjusted life year gained when unfavourable values for health gains were used (Table 4). If we decreased the life expectancy of the device to 4 years, the baseline cost per quality adjusted life year gained rose sharply to £36 161, but a small increase in the life expectancy of the device to 6 years caused a 17% fall in the value to £24 000 per quality adjusted life year gained (Table 4). If the device cost fell by 10% to £5000, the cost per quality adjusted life year gained would be, all other things being equal, £26 656 (Table 4).

DISCUSSION

Our model suggests that the economic argument against VNS implantation (with a 1 in 6 response rate) is weak, particularly given the clinical imperative to treat in an otherwise no win situation of medically intractable epilepsy. As VNS is a last resort treatment, with a good chance of a meaningful reduction in seizure frequency, a case can be made for adopting the new technology.

The cost per quality adjusted life year gained from our model is probably an overestimate as we have failed to capture important health benefits such as those of carers. Our baseline value of 0.285 quality adjusted life years gained per year of successful epilepsy treatment may also be an underestimate. Messori *et al.*[15] imply that a good responder could gain up to 0.39 quality adjusted life years per year of successful stimulation (Table 2), and in such a case the cost per QALY gained would be close to £20 000. Follow-up studies of VNS patients have shown trends towards improvements in seizure control over time[23]. While this observation needs confirmation, it again implies that the health benefits may not be constant over time and could increase—which would make the device more attractive from a purely economic perspective.

We are concerned that the majority of our clinic attenders were unable to complete the time trade-off valuations, even in the presence of a research nurse (SM). Nonetheless, the minority who completed the valuations produced results consistent with Messori *et al.*[15]. The values from the EQ-5D instrument are arguably more robust, but were associated with a higher ratio of cost to quality adjusted life years gained (£49 233).

The model was relatively insensitive to changes in length of stay or complication rates, as an increase in the complication rate to 10% had very little impact on the final cost per quality adjusted life year ratio. Accordingly, there is not a strong economic imperative to perform implantation as a daycase.

If it is possible to identify and implant a group with a high response rate extremely favourable cost per quality adjusted life year values are obtained (£4785 per QALY, if one out of every three people implanted are responders). One follow-up study reported a absolute reduction in seizure frequency of 28–33%[23], which would translate into numbers needed to treat of two or three per successful implant.

If the battery life of a vagus nerve stimulator was extended to 6 years instead of 5, the baseline cost per quality adjusted life year gained falls further (to £24 000). While it is possible to estimate cost per quality adjusted life year gained over a longer period of time, there is insufficient data to accurately model device prognosis or device efficacy beyond the current expected battery life span of 5 years. Nonetheless, it is important to keep the time horizon short as the introduction of a novel, more effective treatment for refractory epilepsy could be introduced in the near future, which would seriously undermine the conclusions of an economic model based upon a prolonged time of treatment. We would anticipate that cost per quality adjusted life year estimates from a 10 year model would be extremely favourable.

Before recommending investment in VNS devices in a resource constrained health care system, there remains the more fundamental consideration of efficacy. Arguably all people with epilepsy want seizure freedom, not partial relief (i.e. a 50% reduction in seizure frequency). Although seizure freedom is rare following VNS, our seven time trade-off respondents placed a very high value upon a 50% reduction in seizure frequency. These respondents valued a life expectancy of 20 years with their current epilepsy severity as of the same value as 14.3 years of epilepsy with a 50% reduction in seizure frequency. This undermines a widely held view that a 50% reduction in seizure frequency is of little value, and implies that a successful VNS has a clinically meaningful impact from the perspective of a person with medically refractory epilepsy.

An economic argument against VNS would be tenable if competing treatments for other people with epilepsy had a far smaller cost per quality adjusted life year gained. According to quality adjusted life year theory, the intervention with the lowest cost per quality adjusted life year gained is the intervention that will produce greatest health for a target population for a given amount of resource[24]. A successful VNS implant is of comparable efficacy to add-on anti-convulsants, i.e. for every six people treated you will get at least one good response[25]. Compared to add-on anti-convulsants, VNS has a favourable economic status, e.g. Lamotrigine add-on therapy[26] at £33 339 per quality adjusted life years gained (published as US$43 343 in 1990 values, inflated to 1996 prices and converted to £ using purchasing power parity factor of 0.641[14]). Compared to our baseline value of £28 849, VNS for medically refractory epilepsy has a more favourable cost per quality adjusted life year gained, yet the argument for VNS becomes more compelling as VNS is a final option, not one of a host of add-on therapies. Studies of anterior temporal lobectomy for epilepsy have estimated the cost per quality adjusted life year gained as £10 277[27] (published as US$15 581 in 1995 prices), and £18 463[28] (published as US$27 200 in 1994 prices). These values for anterior lobectomy are broadly comparable to the more favourable estimates presented for VNS in this paper.

The decision to invest in a novel health technology may depend on clinical factors such as the absence of alternative treatments but may equally depend upon political imperatives. Definitions of good and bad value for money have not been accurately defined. Nonetheless, cut off values of £10 000 per quality adjusted life year gained have been set as a threshold below which an intervention would represent efficient use of scarce resources[29]. Arguably, interventions above £30 000 per quality adjusted life year gained should have their implementation deferred until costs fall or political imperatives prevail[30]. If a new technology produces very small gains in health at a very high cost, there is an economic argument for not investing in that technology and considering alternatives, as these alternatives may produce greater benefits to a greater number of people[31]. Alternatively, if a new technology provided meaningful health gains at a reasonably low cost there would not be a strong economic argument against investing in the new technology[24]. In the case of VNS, the initial expense is ultimately offset by costs averted from improved epilepsy control, and most of our cost-utility estimates are within an acceptable range. The possibility of a meaningful reduction in seizure frequency for people with intractable epilepsy is very hard for patients or neurologists to resist—irrespective of the conclusions of an economic evaluation—but this economic information is demanded by purchasers in modern healthcare systems.

Vagus nerve stimulator devices have become an acceptable treatment for epilepsy. Our economic model demonstrates that the economic argument against a programme of implantation is weak, and therefore the decision to implant should be primarily on clinical and efficacy grounds.

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