

Deep brain stimulation for Alzheimer disease: a decision and cost-effectiveness analysis

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Abstract Alzheimer disease (AD) is characterized by impairments in memory function. Standard AD treatment provides marginal improvements in this domain. Recent reports, however, suggested that deep brain stimulation (DBS) may result in improved memory. Given significant equipment costs and health expenses required for DBS surgery, we determine clinical and economic thresholds required for it to be as effective as standard AD treatment. Literature review yielded annual AD progression probabilities, health-related quality of life (QoL), and costs by AD stage. Our 5-year decision analysis model compared cumulative QoL in quality-adjusted life years (QALYs) and costs of standard therapy to theoretical DBS treatment of various success rates, using known complication rates and QoL data. The base case was a patient with mild-stage AD. DBS success was defined as regression to and maintenance

of minimal stage AD, which was defined as midway between mild and no dementia, for the first year, and continuation of the natural course of AD for the remaining 4 years. Compared to standard treatment alone, DBS for mild-stage AD requires a success rate of 3 % to overcome effects of possible surgical complications on QoL. If DBS can be delivered with success rates above 20 % (\$200 K/QALY) or 74 % (\$50 K/QALY) for mild AD, it can be considered cost-effective. Above a success rate of 80 %, DBS treatment is both clinically more effective and more cost-effective than standard treatment. Our findings demonstrate that clinical and economic thresholds required for DBS to be cost-effective for AD are relatively low.

Keywords Alzheimer's disease · Cost-effectiveness/economic · Decision analysis · Harm/risk (analysis) · Deep brain stimulation

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Introduction

Alzheimer disease (AD) is a neurodegenerative condition characterized by functional impairment in memory. This disease affects more than 27 million people worldwide, accounting for an annual economic burden of more than \$600 million [1–3]. Deep brain stimulation (DBS) is of interest as a potential therapeutic option for AD, because it can directly target and modulate activity of structures implicated in memory functioning.

DBS of basal ganglionic structures is currently considered to be standard of care for well-selected patients with essential tremor and Parkinson's disease (PD) [4, 5]. It has been successful in restoring control of motor function, and has a limited side effect profile that can be attributed to electrode implantation surgery [5]. Due to its effectiveness

Table 1 Annual AD stage transition probabilities and DBS complication probability

Probabilities	<i>N</i>	Mean	SD	References
Transitions from				
Minimal to death		0.011		By definition ^a
Mild	2496			[32, 33]
Remain mild		0.614	0.010	
To moderate		0.322	0.009	
To severe		0.042	0.004	
Die		0.022	0.003	
Moderate	999			
To mild		0.039	0.006	
Remain moderate		0.565	0.016	
To severe		0.339	0.015	
Die		0.052	0.007	
Severe	1501			
To mild		0	0	
To moderate		0	0	
Remain severe		0.847	0.009	
Die		0.153	0.009	
Probability of				
Complications with DBS	4568	0.194	0.006	[8]

Where applicable, data are pooled from indicated sources

^a Minimal stage AD defined as midway between mild and perfect health. Thus, probability of death is half of mild-stage AD probability of death

and safety profile, there is growing interest in expanding the application of DBS to other conditions [6–8]. Indeed, DBS is currently in trial for multiple psychiatric disorders, including depression, obsessive–compulsive disorder, and substance abuse, and is being evaluated in preclinical studies for binge eating disorder [9–13].

Recently, Laxton et al. [14] performed DBS in the fornix/hypothalamus of 6 AD patients in a phase I clinical trial. It was hypothesized that stimulation of the fornix would alter the activity of the medial temporal memory circuits, and thus delay and/or reverse memory loss in AD. After 6–12 months, Laxton et al. [14] noted improvement and/or slowing in the progression of AD in some of the patients, according to measurements of two commonly used measures of global cognitive function. In a recent review of the literature, Laxton et al. [15] also found two additional studies that demonstrate limited evidence that DBS of the fornix or nucleus of Meynert can influence the pathologic neurological circuits involved in AD as well as PD-related dementia.

The purpose of this study is to assess the success rate DBS would require to achieve results superior to standard treatments of AD, both clinically and economically. With healthcare costs rising, it is necessary to consider

economics/costs in addition to clinical efficacy when evaluating DBS for AD treatment.

Methods

We constructed a decision analysis model in which AD patients receive either standard treatment alone or DBS plus standard treatment (DBS treatment), and projected the outcomes over 5 years. Mean cumulative health-related quality of life (QoL) and costs associated with each treatment over 5 years were estimated for different DBS success rates and compared to those associated with standard treatment.

The base case and outcomes

The base case was a 65-year-old subject with AD of mild severity, as defined by the Consortium to Establish a Registry for Alzheimer Disease (CERAD) [16]. We defined DBS success as immediate improvement to and 1-year maintenance of minimal stage AD. Minimal stage AD is not a CERAD category, but is defined as half the mortality rate and morbidity of mild-stage AD, such that QoL and annual cost of treatment were midway between mild-stage AD and perfect health. Minimal stage AD is a necessary endpoint since it is unrealistic to assume DBS would result in improvement to and maintenance of no AD symptoms for patients who were symptomatic at base line. After 1 year at a minimal severity, the AD patient would then resume the natural rate of disease progression.

Our model provided that patients received either standard or DBS treatment, the latter being either successful or unsuccessful. Regardless of DBS success, patients who underwent DBS implantation may incur complications from the procedure. Patients may worsen due to normal disease progression under standard treatment or unsuccessful DBS treatment. Possible outcomes are illustrated in Fig. 1 and include deterioration or improvement from mild, moderate, and severe stage AD as well as death. Regardless of the treatment received in the first year of the model, all patients continue the remaining 4 years of the model at the natural rate of progression of AD.

Three secondary analyses with varied assumptions were performed and are detailed in the supplementary Online Resource. One analysis explored a scenario starting with a subject with moderate-stage AD instead of mild-stage AD. Here, DBS success was defined as improvement to and maintenance of mild-stage AD for the first year of the model. Two additional analyses considered implications of DBS success lasting for the full 5 years of the model with either mild- or moderate-stage AD patients at baseline. Longer term success of DBS treatment may be achievable

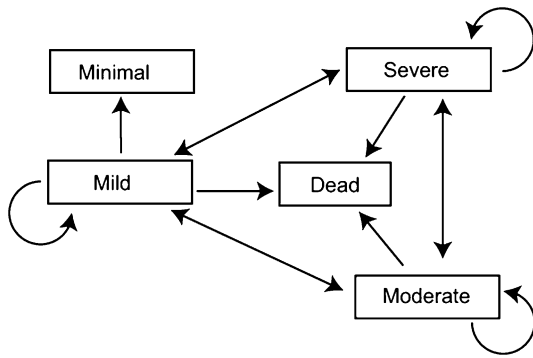


Fig. 1 Conceptual state-transition diagram, showing Markov processes for patients with mild-stage Alzheimer disease (AD). With each annual cycle, a patient may improve or deteriorate, remain unchanged, or die (transition probabilities per Table 1). Patients with unsuccessful DBS follow the same clinical course as patients receiving standard treatment but may also have treatment complications. Successfully treated patients, with or without complications, improve to minimal stage for 1 year (by definition), then return to mild state and follow the natural history of the disease until the end of the 5-year follow-up period

with effective manipulation of the stimulation parameters. The methodology, timeline, and outcomes were evaluated as described above for the mild-stage AD scenario.

The data

We performed Medline searches for English language publications between January 1990 and August 2012 for data on probabilities of disease progression, QoL of AD, and complications of DBS, as well as medical costs associated with DBS and various stages of AD. For transition probabilities, we searched for key words ‘Alzheimer’s disease, progression, natural history or transition probabilities,’ and obtained seven results. Two studies reported full sets of annual transition probabilities between stages of AD and death. Similarly, for QoL data, we searched for key words ‘Alzheimer’s disease, utility or quality of life’, and obtained 20 results. Eight studies identified by Shearer et al. [17] in a January 2012 review of this subject were used as inputs for the AD QoL data. Lastly, for economic data, we searched for key words ‘Alzheimer’s disease and cost’ and obtained nine results. One study reported data with a sufficient level of detail necessary for this decision analysis [18]. This study summarized direct costs of care (e.g., medications, nursing home costs) and indirect costs to society (e.g., lost productivity of informal caretakers) at each stage of AD in the US. Furthermore, it adjusted average cost figures for each CERAD stage of AD to account for varying portions of patients requiring formal vs. informal care. We extracted annual direct medical and indirect cost of care by AD stage.

Since none of the data were collected prospectively, they represent Level 4 evidence [19]. Observational data were pooled from multiple sources, using an inverse variance-weighted, random effects meta-analysis model for transition probabilities and QoL [20]. Mean transition probabilities describe, for a patient with a given CERAD stage of AD, the chance that the patient will be at a certain AD stage 1 year later. For example, a patient with mild-stage AD today has 0.614 probability of staying at mild-stage AD over the course of 1 year, 0.322 probability of advancing to moderate stage, 0.042 probability of advancing to severe stage, and 0.022 probability of death. Probability data are presented in Table 1. Pooled data were used to construct evidence tables, from which we calculated incidence, relative risks, summary outcomes, and costs for the two treatment strategies. Complication rates were based on a meta-analysis that determined complication rates of DBS for patients with forebrain DBS [8].

We used utility as a measure of health-related QoL, as reported in Table 2. Utility is a parametric measure of an individual’s preference for a given health state in the face of uncertainty [21]. Utility of death is 0, and perfect health is 1. This measure has the advantage of being readily converted to quality-adjusted life years (QALYs), the standard measure used in comparative effectiveness and cost-effectiveness research [22]. A QALY represents 1 year of life multiplied by the average utility for that year. Thus, 1 year of perfect health (utility = 1) is equivalent to 2 years at a utility of 0.5. Since the utility (and thus the QALY) measure is parametric, we can readily perform mathematical manipulation and statistical comparisons.

Direct and indirect medical costs (Table 2) were considered from the perspective of society and inflated from 1996 to 2013 levels as per Fox et al. [23]. Medical costs were inflated using the medical care Consumer Price Index, and indirect costs were inflated using non-farming, hourly compensation published by the Bureau of Labor Statistics [24, 25]. Specifically, dementia treatment costs included direct medical costs (e.g., medications, nursing home costs) as well as indirect costs to society (e.g., lost productivity of informal caretakers). Dementia treatment costs were weighted averages, accounting for the proportion of patients at each stage of AD in nursing homes. Costs were expressed in 2013 values, and future values of both costs and QALYs were discounted at 3 % per year [22].

We included costs of DBS implantation complications when accounting for DBS treatment costs. Costs of complications are a weighted average of costs stemming from all DBS complications. Pisapia et al. [8] noted that when complications occurred, often there was more than one complication at a time. Since we assumed 1.5 complications per patient with complication, we also needed to incorporate costs for 1.5 complications in patients with

Table 2 Additional inputs to calculate outcomes: utility-based quality of life (QoL) and annual cost of treatment (2013 US \$) for each health state

AD stage	Utility-based QoL			Treatment costs		
	N	Mean	SD	N	Cost (US \$)	References
Minimal ^a		0.826			15,096	By definition ^a
Mild	982	0.651	0.576	679	30,192	[16, 18, 34–39]
Moderate	561	0.428	1.172	679	51,448	[16, 18, 34–36, 40]
Severe	335	0.307	1.55	679	70,117	[16, 18, 34–36]
Death		0			0	[22]
Other utility considerations						
No DBS complications		1				[22]
DBS complications	4568	0.974	0.002			[8]
Other cost considerations						
DBS implantation		16,605				[41, 42]
DBS complications		2651				

^a Minimal stage AD defined as midway between mild and perfect health. Thus, utility (QoL score) and cost is midway between mild-stage AD utility and perfect health

complications. The weighted average cost was multiplied by 1.5 to estimate the cost of DBS complication per patient.

Analysis

We created a Markov model to simulate the clinical course of the average AD patient, and to calculate the annual and cumulative utility and costs during each year of the 5-year trial. The model employed 1-year cycles with half-cycle correction [26]. It calculated the likelihood of a patient being in each stage of AD and multiplied that by the utility associated with that stage to yield the expected utility for that year. The sum of these utilities, discounted to 2013 values, equaled the expected utility for the patient of a given AD stage. Half-cycle correction assumed that all transitions occur midway through the year. The same model was used to calculate expected costs. Mid-year transitions allowed for QoL and cost to be calculated more realistically by averaging the QoL and costs of two stages in the transition year. We leveraged sensitivity analyses to test how robust our model was, varying each key parameter within its calculated 95 % confidence interval and measuring its effects on both QoL and costs. Success rate of DBS, being unknown, was varied between 0 and 100 %. Our primary analysis deals with measuring rates of success for 1 year of stimulation in mild severity AD. Secondary analyses (see Online Resource) include the same analysis for patients with moderate severity AD. We also examine in the Online Resource “best-case” scenarios in which judicious manipulation of stimulation parameters maintain improvement for 5 years. Meta-analytic pooling was performed using Stata 12 (StataCorp LP; College Station, Texas). Analyses of the model employed TreeAge Pro 2012 (Tree Age Software, Inc., Williamstown, MA).

Results

Probabilities and outcome-associated quality of life and costs

Annual transition probabilities for patients receiving standard treatment and those not responding to DBS are listed in Table 1. AD is generally progressive, with rare cases of reversion in mild and moderate-stage AD. As noted in the Methods section, minimal stage AD was defined by the authors for this analysis as midway between mild-stage AD and perfect health. Table 1 also presents the probability of a complication for patients undergoing a DBS procedure based on data from movement disorders.

Table 2 summarizes the utility-based QoL for each AD stage. By definition, perfect health has a QoL = 1 and death has QoL = 0. As expected, QoL declines with elevated stages of AD. One year of life for someone with mild-stage AD generates 0.651 QALYs, while a year of life with severe stage AD generates 0.307 QALYs. QoL values are reduced by 2.63 % for patients who have complications from DBS implantation [7]. Since the complications are generally perioperative, this adjustment in QoL was made only to the first year in the model [7].

Relevant cost data are also summarized in Table 2. As expected, more advanced AD incurs higher annual costs of care. These values are weighted averages among patients receiving formal care (e.g., nursing homes) and patients receiving informal care from friends and family. DBS implantation and maintenance costs are based on payment figures from the Centers for Medicare and Medicaid Services. The DBS complications cost in Table 2 is adjusted to reflect the cost of 1.5 complications as discussed in the methods. All cost figures are expressed in 2013 values.

Table 3 Five-year expected costs and QALYs

Treatment strategy	Expected costs (USD) ^a	Expected QALYs ^a
Standard care	179,256	2.49
Successful DBS	175,216	2.86
Unsuccessful DBS	196,376	2.48

^a 2013 values

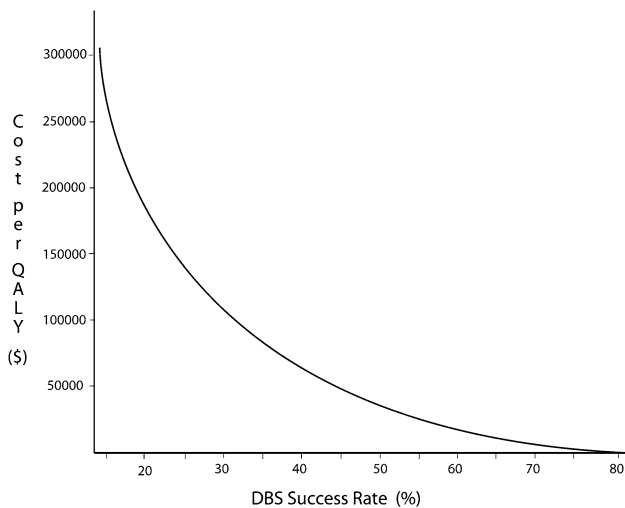


Fig. 2 Cost per QALY for DBS, as a function of DBS success rate for a mild-stage Alzheimer disease patient

DBS treatment clinical and cost-effectiveness thresholds

Clinical effectiveness of each treatment is estimated on the basis of total QALYs generated over the 5-year duration of the model while cost-effectiveness is estimated by considering the cost incurred over the same time period. Standard treatment generates 2.49 QALYs over the 5 years at a cost of \$179,256 (2013 values). Table 3 shows that successful DBS results in better clinical outcome at lower cost than standard care. In contrast, unsuccessful DBS is more costly than standard care and yields slightly poorer outcomes. When treating mild-stage AD patients, DBS treatment must have at least a 3 % success rate to be equivalent in clinical effectiveness or an 80 % success rate to be equivalent in terms of cost-effectiveness when compared to standard treatment.

A higher success rate for DBS treatment in AD patients leads to more clinically effective and overall less costly treatment. At success rates below 3 %, DBS treatment is both less effective than standard treatment and more costly, meeting neither the clinical effectiveness nor the cost-effectiveness threshold. Between 3 and 80 % DBS treatment success, DBS is more effective but also more costly than standard care. Society’s willingness to pay for incremental

QALYs must be considered (see discussion). For instance, if DBS treatment was 20 % successful, it would cost \$200,000 per QALY gained. Similarly, at a 74 % success rate, DBS costs \$50,000 per QALY gained. Figure 2 shows the declining cost per QALY treatment as success rate of DBS increases. The threshold for cost-effectiveness has been reported to fall between these two values [27].

Sensitivity analysis

Each major variable was varied within its 95 % confidence interval; the impact on QALYs generated by DBS treatment over the 5-year duration of the model was measured. DBS success rate had the largest impact on this model. As expected, this key variable is critical in determining DBS treatment’s viability. Overall, no single input value, when varied within its 95 % confidence interval, changed the outcome (number of QALYs generated) by more than 10–15 %. The Online Resource explores the sensitivity analysis further.

Conclusions

Our threshold findings quantify critical bounds of the success rate, which DBS treatment must meet to be equivalent or superior to standard treatment for AD. For mild-stage AD, DBS requires a 3 % success rate to produce clinical outcomes superior to standard treatment, and an 80 % success rate to also be less costly. The limited efficacy of standard treatments suggests that any treatment that may slow, stop, or reverse the progression of AD requires a relatively low rate of success to produce equivalent QoL outcomes, assuming that there is low complication rate.

Since DBS in our analysis is both more effective and more costly than standard care at success rates between 3 and 80 %, its cost-effectiveness depends on society’s willingness to pay for the additional QALYs it provides over the 5-year follow-up period. Traditionally, treatments costing less than \$50,000/QALY have been deemed cost-effective, though recent studies have shown that our society’s actual willingness to pay may be \$200,000/QALY or greater [27]. As our study shows, DBS crosses these thresholds at success rates between approximately 74 and 20 %, respectively.

Prolonged effectiveness of DBS treatment for the full 5-year period of the model may be achieved with stimulation parameter optimization. In such a scenario, lower DBS treatment success rates are required for equivalency to standard treatment. For a patient with mild-stage AD at baseline, DBS success rates of 0.2 and 9.3 % are required for clinical and economic equivalency, respectively, to standard treatment. Since DBS treatment

provides longer lasting benefit in this scenario, lower success rates are required to attain equivalence to standard treatment (see Online Resource).

There are a number of limitations to this study. First, we rely on pooled data from various sources. Our sensitivity analysis, however, showed that individual input variables must change considerably (beyond their 95 % confidence intervals) to have at least a 10–15 % effect on total QALYs generated in the 5-year model duration. Still, relatively low magnitude changes in multiple variables at the same time may have a greater than 10–15 % effect on the results.

Two particularly relevant input variables pertain to the rate of post-operative complications and the transition probabilities used in post-surgical patients. Demented patients in general have a higher rate of post-operative complications and re-hospitalization, and may be less compliant with post-operative wound care, potentially increasing the incidence of skin irritation, infection, poor wound healing, or DBS malfunction [28–30]. In light of this, we tested our 5-year model with a doubled rate of surgical complication, well outside its 95 % CI. We also more than quintupled the disutility of complications (disutility = 1 – utility) from 0.006 to 0.05. At a 5 % DBS success rate, QALYs generated dropped by only 0.0177 QALYs, using the new assumptions both for higher incidence of post-operative complication and for increased severity of these complications. This minimal change of <1 % suggests that even substantial changes in the assumptions our model made for unexpected post-operative complications will have a near negligible effect on the model outcome.

A second input variable of particular interest is the set of transition probabilities that underlie the rate of disease progression in post-operative AD patients. While our model utilizes similar transition probabilities for patients who received surgery with unsuccessful outcomes and patients who did not receive any surgery, recent studies suggested that cerebral inflammation secondary to surgery and anesthesia may accelerate the rate of AD progression [31]. As with other variables, the sensitivity analysis we conducted addressed this limitation by showing how varying the transition probabilities within their 95 % CI resulted in a minimal change in the number of QALYs generated by the model.

In conclusion, our findings indicate that DBS may require an extremely low threshold of success of 3 % to be a clinically effective treatment for AD. Moreover, success rates of approximately 80 % would make DBS not only more effective for mild cases of AD, but also less costly than standard treatment. The exact DBS success rate will have to be established experimentally with clinical trials.

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Conflicts of interest David Wolk has declared his current participation in a clinical trial sponsored by Functional Neuromodulation, Ltd in the study of deep brain stimulation in AD. None of the other authors have any conflict of interests to declare.

Ethical standard No patients were engaged to obtain data for this study. As a result, no informed consent was needed or obtained by the Ethics Committee of the University of Pennsylvania Health System.

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