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ORIGINAL COMMUNICATION

Economic evaluation of deep-brain stimulation for Tourette's syndrome: an initial exploration

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Abstract

Background Deep-brain stimulation (DBS) can be effective in controlling medically intractable symptoms of Tourette's syndrome (TS). There is no evidence to date, though, of the potential cost-effectiveness of DBS for this indication.

Objective To provide the first estimates of the likely cost-effectiveness of DBS in the treatment of severe TS.

Methods We conducted a cost-utility analysis using clinical data from 17 Australian patients receiving DBS. Direct medical costs for DBS using non-rechargeable and rechargeable batteries and for the alternative best medical treatment (BMT), and health utilities for BMT were sourced from the literature. Incremental cost-effectiveness ratios (ICERs) were estimated using a Markov models with a 10-year time horizon and 5% discount rate.

Results DBS increased quality-adjusted life year (QALY) gained from 2.76 to 4.60 over a 10-year time horizon. The ICER for DBS with non-rechargeable (rechargeable) batteries, compared to BMT, was A$33,838 (A$15,859) per QALY. The ICER estimates are sensitive to DBS costs and selected time horizon.

Conclusions Our study indicates that DBS may be a cost-effective treatment for severe TS, based on the very limited clinical data available and under particular assumptions. While the limited availability of data presents a challenge, we also conduct sensitivity analyses to test the robustness of the results to the assumptions used in the analysis. We nevertheless recommend the implementation of randomised controlled trials that collect a comprehensive range of costs and the use of a widely accepted health-related quality of life instrument to enable more definitive statements about the cost-effectiveness of DBS for TS.

Keywords Economic evaluations · Cost-effectiveness · Deep-brain stimulation · Tourette's syndrome

Introduction

An analysis of the cost-of-illness (COI) in a sample of German outpatients treated for Gilles de la Tourette's syndrome (TS) in 2006–2007 reported annual direct and indirect costs of €620 and €2731, respectively [1]. The study reported the direct costs of TS were smaller than other neurological diseases because cheaper generic drugs such as haloperidol, instead of patent-protected medications, were used to treat this neurological condition. The costs were primarily indirect costs attributed to productivity (€2511) and income (€220) losses. At the time this COI study was published in the *Journal of Neurology*, deep-brain stimulation (DBS) was still an emerging and largely experimental treatment for patients with severe TS. No patients in the German sample ($n = 200$) had received DBS. While the benefits of treating TS with DBS may be substantial [2–4], the costs of the surgery itself are also substantial. Dodel et al. [1] concluded that:

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> "…further health economic studies, especially cost-effectiveness studies, are necessary for a basis for rational resources allocation" (Dodel et al. [1], p. 1055).

A systematic review of health economics studies of DBS was published in 2019 [5], however, found that there are still no economic studies on the treatment of TS with DBS. Here, we seek to fill this gap in the literature by providing the first estimates of the probable cost-effectiveness of DBS for TS using the best available results from the literature and an Australian study of 17 recipients of the treatment. More definitive results on the cost-effectiveness of DBS for this indication would be possible following the conduct of suitably designed randomised controlled trials (RCTs). The indicative results presented in this paper may provide the motivation to extend the clinical research on DBS for TS to include suitable cost and quality-of-life measures in prospective RCTs.

We conduct an indicative economic evaluation by developing a Markov model to examine the costs and effects of treating severe TS with DBS compared to best medical treatment (BMT). DBS can be effective in controlling medically intractable symptoms of TS [2]. For less severe symptoms, antipsychotics, such as haloperidol and pimozide, can control tics, and alpha agonists, such as clonidine and guanfacine, can control tics and comorbid attention-deficit hyperactivity disorder [6]. A cost-utility analysis (CUA) is undertaken using parameter values derived from the extant literature on DBS and TS. The conduct of CUA essentially involves estimating the costs and consequences of two alternative treatment pathways and comparing their cost-effectiveness. A commonly used measure of output (or outcome), which we apply in this study, is the quality-adjusted life year (QALY) gained. By estimating the costs of the two alternative treatment pathways and the QALYs produced by them, an incremental cost-effectiveness ratio (ICER) can be computed, which expresses the difference in costs and the difference in QALY outcomes of the two treatments of interest. The resulting ratio is a "cost per QALY gained". As this measure is commonly used in health sector economic evaluations, the output of such analyses may be comparable (subject to some important *caveats*) across different interventions and health conditions.

Methods

Treatment costs for DBS and the comparator, BMT, were obtained from the international literature. Clinical indices of health status pre- and post-procedure were obtained from a clinical trial of 17 Australian patients treated with DBS for TS [2]. Standardised coefficients obtained from a reference population of 200 German outpatients receiving BMT for TS [3] were used to estimate the increase in QALYs attributable to DBS (see Supplemental Table S1 and Supplemental Figure S1 for demographic and clinical details). The methods are described as follows.

Treatment costs

Costs [2008 Australian dollars (A$)], for surgical implantation, non-rechargeable internal pulse generator (IPG), inpatient stay and related complications were obtained from the report "*Deep brain stimulation for essential tremor and dystonia*" published by Australia Medical Services Advisory Committee [7]. The IPG replacement protocols for dystonia and essential tremor were reported to be 2 and 5 years, respectively. Our analysis assumed a 2-year protocol for TS patients [8]. Costs (2015-€) for rechargeable Medtronic IPGs with a 9-year replacement protocol [9] were obtained from a Dutch analysis of DBS for obsessive–compulsive disorder (OCD) [10] and utilised for a sensitivity analysis (Supplemental Table S2).

The direct medical costs for BMT (2006-€) were obtained from a published analysis of 200 German patients diagnosed with TS [1]. Treatment costs included outpatient and inpatient care, rehabilitation, physician reimbursement, medications, ancillary therapies, and auxiliary materials. All costs were estimated for a projected 10-year time frame, then adjusted to 2018-A$ using the purchasing power parity data for GDP per capita published by the International Monetary Fund [11].

Health utilities

Young TS patients with severe tics and a family history of tic disorders are more prone for poorer health-related quality of life (HRQOL) in their adulthood [12]. Comorbid conditions have been consistently addressed in the literature as key factors for lower HRQOL in young patients [3, 13–16]. Meanwhile, TS is significantly negatively correlated with HRQOL in adult patients [13] and independent factors for determining their HRQOL were depression [3], anxiety [14], tics severity and age [3]. Of importance is the treatment of tics for either young or adult TS patients, these co-morbidities also should be diagnosed and treated vigorously [3, 13, 15, 16].

Health utilities were derived from data obtained from a 2-year clinical trial conducted by Sachdev et al. [2], which evaluated the treatment of severe TS with DBS. The trial collected relevant clinical data, pre- and post-surgery for 17 patients. Data collection included: (1) tic severity with the Total Yale Global Tic Severity Scale (TYGTSS) [17], (2) depression with the Hamilton Depression Rating Scale (HDRS) [18], and (3) obsessive–compulsive behavior with

the Yale Brown Obsessive–Compulsive Scale (YBOCS) [19]. Demographic and surgical parameters were reported, also. While two disease-specific HRQOL measures, the Global Assessment of Functioning [20] and the Gilles de la Tourette Syndrome-Quality of Life (GTS-QOL) [12] were collected, no generic measure of health utility was included [21]. Hence, the incremental change in QALYs due to DBS was estimated as follows.

First, three statistically significant standardised beta coefficients (β), obtained from a multivariate regression predicting the outcome rating on the EQ-5D visual analogue scale: (1) age ($\beta = -0.153$), (2) depression ($\beta = -0.495$) measured with the Beck Depression Inventory (BDI), and (3) tic severity ($\beta = -0.180$) measured with the Tourette Syndrome Symptom List (TSSL) [3], were matched to trial data reporting: (1) age, (2) depression measured with the HDRS, and (3) tic severity measured with the TYGTSS, pre- and post-DBS. The measures of depression (BDI and HDRS) and tic severity (TSSL and TYGTSS) have Pearson's correlation coefficients of 0.73 [22] and 0.63 [23], respectively, enabling the identified coefficients to match to our standardised trial data (Supplemental Table S3).

Second, the clinical data reporting age, HDRS and TYGTSS reported by Sachdev et al. [2] were standardised ($\mu = 0$, $\sigma = 1$) using published means and standard deviations (SDs) for age [3], HDRS [1, 2], and TYGTSS [24].

Third, the published coefficients were used to estimate average standardised health utilities, pre- and post-DBS, as follows:

$$\bar{U}_{\mathrm{DBS}} = \sum_{i=1}^{i=17} \left[\left(\mathrm{Age}_s \times -0.153 \right) + \left(\mathrm{HDRS}_s \times -0.495 \right) + \left(\mathrm{TYGTSS}_s \times -0.180 \right) \right] / n \quad (1)$$

where $\bar{U}_{\mathrm{DBS}}$ is the average standardised utility score attributable to DBS, Age_s is the standardised score for age, HDRS_s is the standardised score for depression, TYGTSS_s is the standardised score for tic severity and n is the sample size.

Fourth, the average standardised utility score was re-transformed into raw utility using summary statistics ($\mu = 0.83$, $\sigma = 0.24$) for a representative sample of TS outpatients, published by Muller-Vahl et al. [3].

Health utilities for BMT group can be inferred from these summary data ($\mu = 0.83$, $\sigma = 0.24$) [3] as follows. DBS is currently indicated for TS patients with either "severe" or "very severe" TS symptoms [2], which composed the lowest 13.5% patients on the YGTSS of the BMT sample [3] (see Supplemental Table S1; where $13.5\% = [(1 + 26)/200 \times 100]$). Assuming a standard normal distribution, the mid-point of the cumulative percentage (6.75%) implies the mean health utility for comparator group lies approximately 1.5 SDs below the average TS patient (i.e. $0.47 = 0.83 - 1.5 \times 0.24$).

Markov model

A Markov model was developed to compare the changes in costs and health utilities over 10 years between DBS and BMT to treat medically intractable TS patients (Fig. 1). Markov models are suitable for situations when events recur over a long time horizon and usually age a cohort of patients until death [25]. Death, therefore, is always used as an endpoint in the models. Since the literature reports no "stages" or "transition probabilities" for TS, only two Markov states, "Survive from background mortality" and

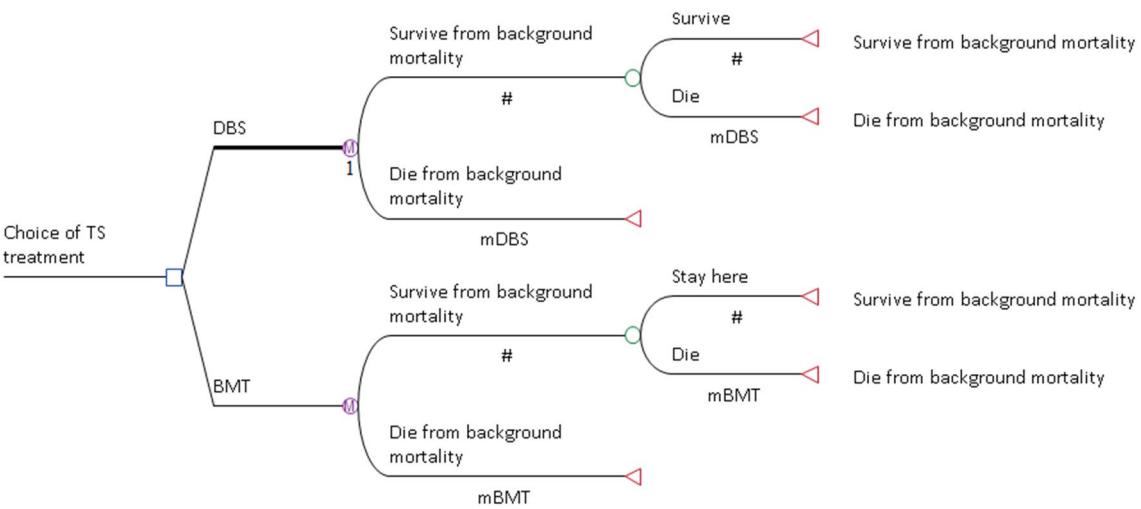

Fig. 1 Markov model. *TS* Tourette syndrome, *DBS* deep-brain stimulation, *BMT* best medical treatment, *mDBS* probability of mortality due to DBS, *mBMT* probability of mortality due to BMT

"Die from background mortality", were designated. TS is reported to be positively correlated with suicide [26], mortality rates in the "Die from background mortality" states thus were adjusted (Supplemental Table S4). The model assumes: (1) survival has constant-utility, (2) no withdrawal from treatment, and (3) a discount rate of 5% for costs and effects [7, 27, 28].

The ICER was calculated as follows:

$$\text{ICER} = \frac{\text{Cost}_{\text{DBS}} - \text{Cost}_{\text{BMT}}}{\text{QALY}_{\text{DBS}} - \text{QALY}_{\text{BMT}}} \quad (2)$$

Sensitivity analysis

The assumptions used to calculate ICERs for DBS using, non-rechargeable and rechargeable IPGs, were tested using deterministic sensitivity analysis (DSA). Treatment costs were varied by 50% [29, 30]. Although DBS is associated with a large upfront cost to the patient, its long-term costs may be sustainably reduced in comparison to long-term BMT [31]. Previous studies have shown that on average 25% [2, 24, 32–35] of TS patients required no medications following DBS. For those who continued pharmacotherapy after DBS, the reduced percentage of medications used was between 25 and 66% [24, 35, 36]. The reduced medication costs (between A$13,584 for a 25% reduction, i.e. 25% × A$54,335 of the BMT total cost, and A$35,861 for a 66% reduction) can be covered within the ±50% range of the DBS cost in the DSA.

In the DSA, health utilities were varied by one SD around the mean [28]. Mortality rates for DBS and BMT were arbitrarily varied by 50%. Discount rates of 3.5% and 7.5% [28] were tested, as were treatment time horizons of 5 and 20 years [28].

Probabilistic sensitivity analysis (PSA) was used to test the robustness of our model. Monte Carlo simulations were run with 10,000 iterations. Gamma and beta distributions were used for costs and utilities, respectively [37]. Mortality rates were not subject to PSA due to the unavailability of SD parameters. Five and 20-year treatment time horizons were used in the PSA [28] (Supplemental Table S5).

This study is not subject to an ethical review due to the use of published data [1–3, 7, 10].

Results

Estimated mean health utility for DBS was 0.78 (SD = 0.16) and for BMT was 0.47 (SD = 0.24). Itemised cost estimates for DBS (using non-rechargeable and rechargeable IPGs) and BMT are reported in Table 1.

The total cost of DBS with a non-rechargeable IPG was A$159,448, of which IPG replacement makes up the largest component (53%). The calculated ICER of non-rechargeable DBS compared to BMT was A$33,838/QALY [28, 38]. DBS with a rechargeable IPG was associated with higher upfront costs (A$69,010 vs. A$48,685), but substantially lower IPG replacement costs (A$83,778 vs. A$16,755) and complication costs (A$12,904 vs. A$2,111). The total cost of DBS using rechargeable IPG was A$101,997 and the ICER vis-à-vis BMT was A$15,859/QALY (Table 2).

The DSA, presented as a combined tornado diagram, indicate that ICER estimates are most sensitive to variations in the costs of DBS and choice of time horizon in both scenarios (Fig. 2). For example, in non-rechargeable scenario, a 50% increase in the cost of DBS increased the ICER to A$61,468/QALY. A shorter time horizon, 5 years, increased the ICER estimate to A$68,729/QALY. However, ICER estimates were less sensitive to variations in health utilities for DBS and costs of BMT, and less sensitive still, to variations in other potentially influential variables, including the discount rates for costs and utilities, health utilities associated with BMT, and mortality rates.

The PSA, presented as ICER scatterplots, indicates that 95% of the replicated ICERs lie in the northwest, northeast and southeast quadrants, of which 56% (61%) are located in the northeast quadrant in the non-rechargeable (rechargeable) scenario, indicating DBS is more costly but more effective than BMT (Figs. 3, 4).

A cost-effectiveness threshold has not been explicitly set by The Pharmaceutical Benefits Advisory Committee (PBAC) for reimbursement in Australia [39]. George et al. [40] reported a range between A$37,000/QALY and A$69,000/QALY thresholds in their analysis of the consistency of PBAC funding decisions during the period of 1991–1996. Another study by Clement et al. [41] presented the most likely threshold around which PBAC recommended listing to be A$60,000/QALY in 2009 (Clement et al., eFigure 2). We, therefore, utilised A$70,000/QALY as the implied maximal willingness-to-pay threshold in this study, similar to that was applied by a published cost-effectiveness analysis of rotavirus vaccination in Australia [39].

The probability of cost-effectiveness under a threshold of A$70,000/QALY increases to 66% for the non-rechargeable and 75% for the rechargeable scenario (Fig. 5). Cost-effectiveness is positively correlated with the time horizon. Given a willingness-to-pay of A$70,000/QALY, DBS is 45% (76%) more likely to be cost-effective with 5-year (20-year) time horizon in the non-rechargeable scenario, and is 61% (80%) more likely to be cost-effective with 5-year (20-year) time horizon in the rechargeable scenario (Fig. 5).

Jointly, the DSA and PSA suggest the estimated ICERs are reasonably robust. Differences in single variables

Table 1 Direct medical costs of DBS and BMT over 10 years in two scenarios

Items	Quantity	Per unit	Costs, non-rechargeable IPGs (2008-A$)	Costs, rechargeable IPGs (2018-A$)
A. DBS				
Hardware—Kinetra[*]				
IPG	1	15,060	15,060	
Deep-brain electrode lead	2	4150	8300	
Extension lead	2	2100	4200	
Patient activator	1	1400	1400	
Sub-total hardware			28,960	
Insertion of implant				
Bilateral implantation of electrodes	1	3579	3579	
Unilateral implantation of IPG	2	308	615	
Unilateral target localisation (neurologist)	2	1827	3653	
Programming 2.5 times per year	25	171	3471	
Sub-total implantation			11,319	
Other surgical costs				
Pre-operative MRI of brain	2	336	672	
Management of anaesthesia for scans (MRI; computerised axial tomography; and digital subtraction angiography)	2	136	273	
Management of anaesthesia for intracranial procedures	1	269	269	
Management of anaesthesia for surgery of the anterior part of the chest	2	54	107	
Sub-total surgery			1,321	
Total DBS devices and procedures			41,600	69,010
IPG replacement every 2 years			71,586	16,755[**]
Inpatient stay			12,066	14,121
Complications			11,026	2,111[**]
Grand total 10-year cost (2008-A$)			136,278	
Grand total 10-year cost (2018-A$)			159,448	101,997
B. BMT				
Items	Costs (mean (SD)) (2006-€)			
Outpatient care	14.0 (40.6)			
Inpatient care	195.8 (1267.8)			
Rehabilitation	98.8 (993.6)			
Physicians	26.7 (81.9)			
Medications	223.1 (430.4)			
Ancillary therapy	51.9 (137.4)			
Auxiliary materials	0.3 (3.9)			
Total 3-month cost (2006-€)	620 (1697.1)			
Total 10-year cost (2018-A$)	54,335 (148,728)			54,335 (148,728)

[*]71% (12/17) of DBS patients of the Australian sample used the Kinetra device (single IPG for both sides)

[**]Calculations are shown in Supplemental Table S2

DBS deep-brain stimulation, *BMT* best medical treatment, *IPG* internal pulse generator, *MRI* magnetic resonance imaging, *A$* Australian dollars, *€* Euros

associated with DBS and BMT do not affect overall cost-effectiveness substantially.

Discussion

In this paper, we investigated the cost-effectiveness of treating severe TS with DBS using clinical data obtained from a

Table 2 Markov model inputs and outputs in two scenarios

Strategy	Markov model inputs		Markov model outputs		
	Data	Mean	Estimates	Incremental	ICERs
Non-rechargeable IPGs					
BMT	Cost (A$)	54,335	33,093	–	–
	Utility (EQ-5D)	0.47	2.76 QALYs	–	
	Probability of mortality	0.0079			
DBS	Cost (A$)	159,448	97,153	64,084	34,959
	Utility (EQ-5D)	0.78	4.60 QALYs	1.83 QALYs	
	Probability of mortality	0.0075			
Rechargeable IPGs					
BMT	Cost (A$)	54,335	33,093	–	–
	Utility (EQ-5D)	0.47	2.76 QALYs	–	
	Probability of mortality	0.0079			
DBS	Cost (A$)	101,997	62,148	29,054	15,856
	Utility (EQ-5D)	0.78	4.60 QALYs	1.83 QALYs	
	Probability of mortality	0.0075			

BMT best medical treatment, *DBS* deep-brain stimulation, *EQ-5D* EuroQol 5 dimensions, *ICERs* incremental cost-effectiveness ratios, *QALYs* quality-adjusted life years

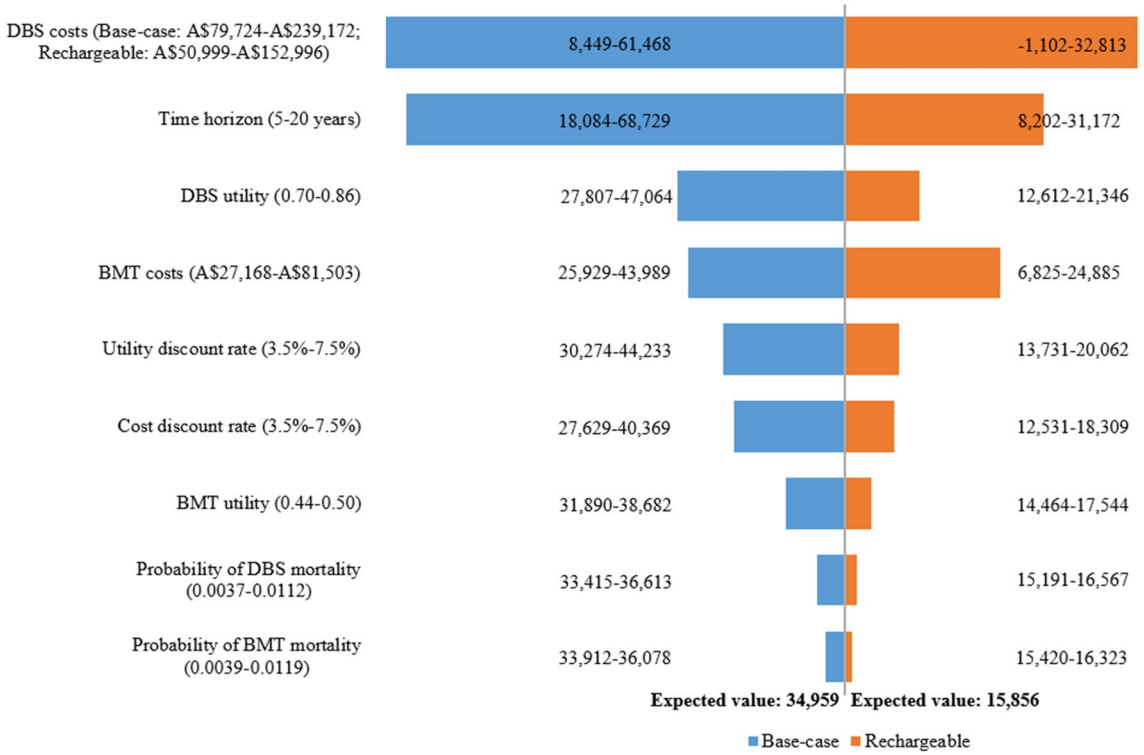

Fig. 2 Strength of effect of input parameters on the ICER in two scenarios. The ranges of ICER values when the parameters were varied were presented in the middle of the base-case and rechargeable panels. The longer the bars, the stronger the effect of a parameter. *ICER* incremental cost-effectiveness ratio, *A$* Australian dollar; *DBS* deep-brain stimulation, *BMT* best medical treatment

clinical trial combined with published coefficients obtained from a representative sample of TS patients in two scenarios: DBS using non-rechargeable and rechargeable IPGs. The ICER for non-rechargeable (rechargeable) DBS was A$33,838/QALY (A$15,859/QALY) and the PSA indicated cost-effectiveness in 66% (75%) of trials, given a threshold of A$70,000/QALY. The ICER estimates are sensitive to DBS costs and selected time horizon.

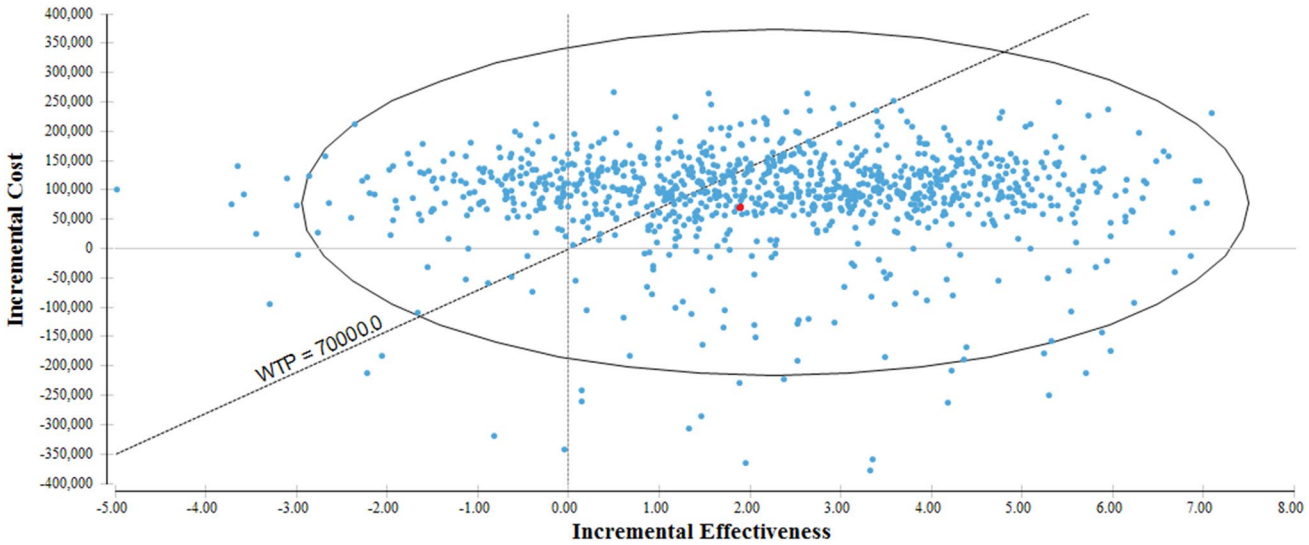

Fig. 3 Scatterplot of simulated ICERs in non-rechargeable scenario. Notes: The ellipsis represents the 95% confidence interval. The red dot represented the expected ICER. The dashed lines represent the willingness-to-pay threshold of A$70,000/QALY

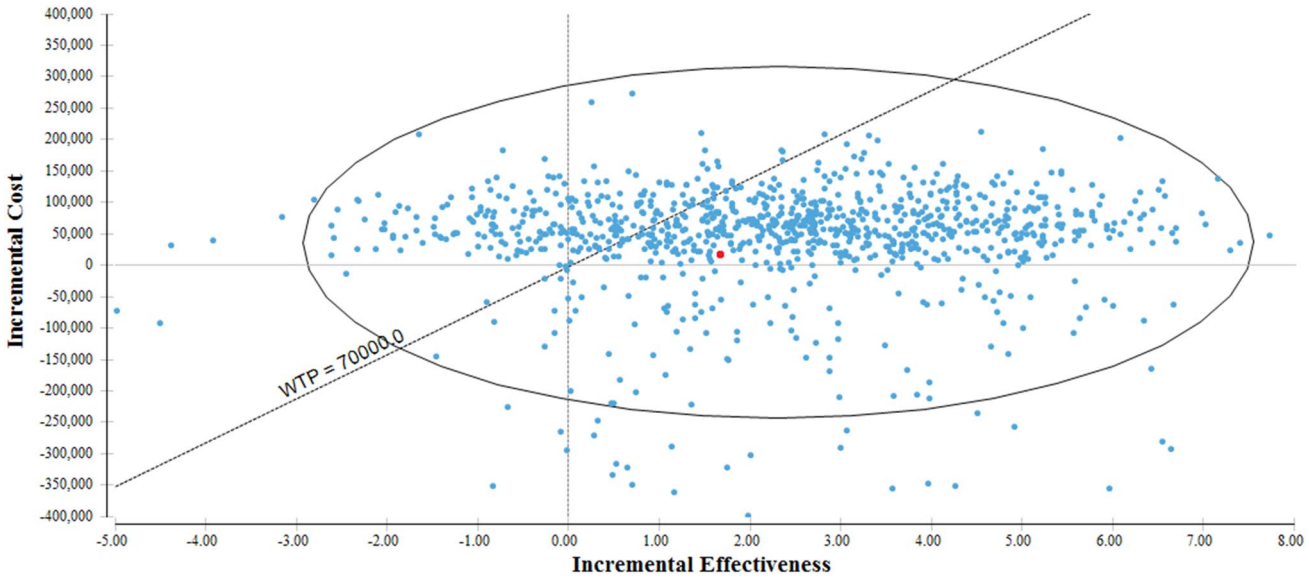

Fig. 4 Scatterplot of simulated ICERs in rechargeable scenario. Notes: The ellipsis represents the 95% confidence interval. The red dot represented the expected ICER. The dashed lines represent the willingness-to-pay threshold of A$70,000/QALY

Although the use of ICER thresholds has been controversial for their failure to represent the uncertain nature of dynamic changes in opportunity costs of next-best health interventions forgone [42], the replicated ICERs are typically less than A$70,000/QALY, which may be considered as cost-effective in Australian analyses [28, 38–41]. As such, the economic evidence we present offers promising, but by no means conclusive evidence, that DBS is a cost-effective treatment for severe TS.

The clinical efficacy of medical treatment should be established before its economic effectiveness can be confirmed [25]. Baldermann et al. [4] conducted a pooled meta-analysis of 57 studies that evaluated the clinical effectiveness of DBS for TS in 156 patients using the YGTSS. They found that DBS was emerging as a promising treatment for TS that was otherwise resistant to traditional medical treatments. However, the evidence analysed was deemed to be at a very high risk of bias, i.e. a level IV on the American Academy of Neurology's four-tired

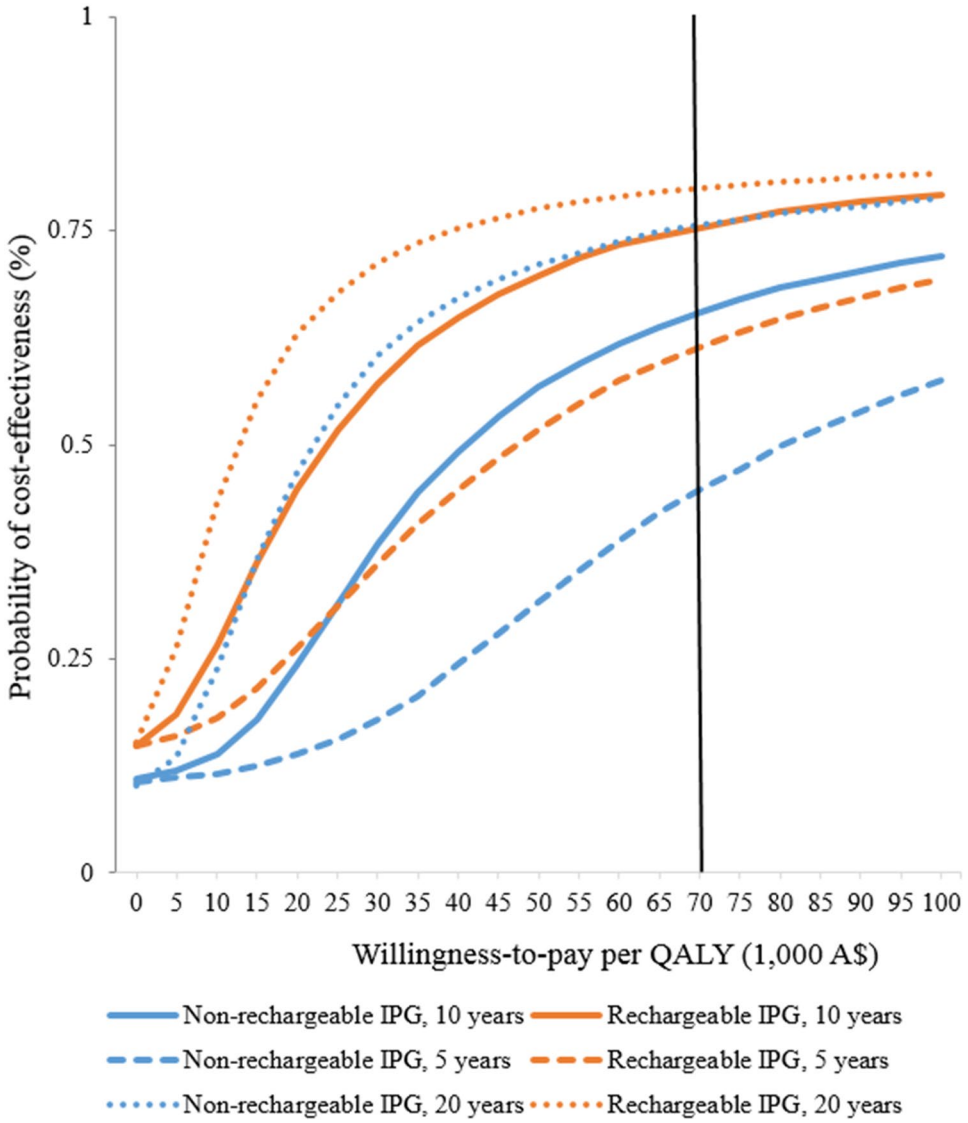

Fig. 5 Cost-effectiveness acceptability curves of each scenario in 5-year and 20-year time horizons. The curves show the probability that DBS is cost-effective compared with BMT for a range of willingness-to-pay thresholds per one QALY changed. The black vertical line represents the threshold of A$70,000/QALY. *ICERs* incremental cost-effectiveness ratios, *QALY* quality-adjusted life year, *DBS* deep-brain stimulation, *BMT* best medical treatment

classification scheme [43]. While the authors acknowledged that:

> "…there is still a lack of controlled studies and the available data is still scarce due to the small sample sizes." (Baldermann et al. [4], p. 301)

They argued that DBS for TS should no longer be regarded as a strictly experimental treatment and that a well-designed double-blind study to investigate the effectiveness of DBS for TS is warranted in the near future.

The meta-analysis, which included the study by Sachdev et al.[2], suggests that the TS patients analysed in our economic evaluation were slightly more responsive to DBS than median patient in the meta-analysis. For example, the median pre-operative (post-operative) YGTSS reported by Sachdev et al.[2] and Baldermann et al. [4] were 81 (30) and 83 (35), respectively. While Sachdev et al. [2] and Baldermann et al. [4] reported a 25% improvement in the YGTSS for 82.3% and 80.6% of their patients, respectively, Sachdev et al. [2] reported a much larger percentage of their sample achieved a 50% improvement in their YGTSS (70.6% vs. 24%). Similarly, a larger percentage reduction in motor tics (54% vs. 38.6%) and phonic tics (50% vs. 40%) was reported by Sachdev et al. [2] than Baldermann et al. [4]. Taken at face value, these data suggest that our results may slightly overestimate the cost-effectiveness of treating severe TS with DBS.

Our literature review suggests this to be the first economic evaluation of treating severe TS with DBS. Other published economic evaluations indicated that DBS can be a cost-effective treatment of PD [30, 44, 45], OCD [10, 46], and dystonia [47]. To date, the evidence suggests that the cost-effectiveness of DBS depends largely on the duration of benefit and the symptomatic severity of the patient

population that is analysed [44–46, 48, 49]. This is because DBS is a costly treatment, which means that small payback periods result in relatively high cost-to-consequence (i.e. health benefit) estimates. DBS is thus more likely to pass cost-effectiveness tests when the target patient groups experience large and longer term benefits. This study adds to that body of knowledge and confirms that DBS, compared to BMT, is most likely to be considered cost-effective only in those patient populations with severe TS.

We converted published ICERs reported for PD [30, 44, 45], OCD [10, 46] and dystonia [47] into 2018-A$ to facilitate meaningful comparisons of the cost-effectiveness of DBS for TS. The cost-effectiveness results for non-rechargeable DBS-TS (A$33,838) are considerably lower than the estimates of the cost per QALY for dystonia (A$93,418) [47] and OCD (A$56,266 [46] and A$262,282 [10]). The OCD and dystonia studies that produced larger ICERs were based on 2-year trials [10, 47], while the OCD study that produced a lower ICER was based on a Markov model [46]. The high initial cost of DBS that is typically incurred in the first year of treatment, in conjunction with the short duration of benefits measured under trial conditions, is jointly the reason that trial-based estimates of ICERs tend to be larger than longer duration Markov-based estimates in these cohorts. The inclusion of indirect costs in the OCD study, such as travel and productivity gain [10], could contribute to the difference in the ICERs estimated. The non-rechargeable DBS-TS estimate is also less than DBS-PD (A$43,152 in the UK [45], A$38,541 in Japan [30], and A$35,613 in the US [44]). The discrepancies are largely due to the exclusion of follow-up cost and medications saving after DBS in our study, as well as higher discount rates we applied to costs and effects, 5% compared to 3–3.5%.

The resources required to conduct a clinical trial, with a properly designed economic evaluation, can be costly. As such, the economic evaluation of rare diseases and their treatments is frequently absent from the literature [50]. Another reason that economic evaluations are not always included for the analysis of trials is that, in efficacy studies, cost-effectiveness is sometimes a distant or subsidiary concern. It is also common for the importance of economic evaluations to be belatedly appreciated after efficacy trials have been completed. Where appropriate, the capacity to utilise available data to conduct ad hoc economic evaluations can offer useful preliminary insights into resource allocation. The strength of our study is its capacity to draw upon data, from Australia, Germany and the Netherlands, to construct an economic evaluation model, where none currently exists.

Characteristics of the sample selected for this evaluation, i.e. Sachdev's sample, were compared with those from three clinical trials [34, 36, 51], which evaluated the treatment of TS with DBS and had relatively larger sample size to others included in the Baldermann et al. [4] review. At baseline, our sample was a bit younger (28.5 [2] vs. 32.7 [34, 36, 51] years) and had more tics (TYGTSS: 81.2 [2] vs. 75.8 [34, 36, 51]), but less OCD (YBOCS: 13.9 [2] vs. 16.4 [34, 36, 51]) and depression (15.4 HDRS scores [2] vs. 25.3 BDI scores [34, 36, 51]. Two RCTs [36, 51] performed periods of off-stimulation, while it was not applied to our sample. Among the trials being compared, the brain targets, stimulation parameters, scales used to measure outcomes, and length of follow-up assessment, are also different, but the patient response to treatment was in similar pattern. For example, at 2 years, the average TYGTSS score had decreased (54% [2] vs. 53% [34, 36, 51]). Similarly, at 2 years the average YBOCS score for comorbid OCD had decreased (62% [2] vs. 75% [34, 36, 51]) and the average GTS-QOL score for patients' QOL had increased (62% [2] vs. 61% [51]) (Supplemental Table S6 provides further details). Notwithstanding several demographic and clinical differences, given the similarities in sample size (17 [2], 18 [34], 15 [51] and 6 [36]) and patients' outcomes, our sample and results can be regarded as representative of TS patients treated with DBS.

Our study, however, is subject to some limitations that demand a careful interpretation of the results. First, the health utility of DBS was derived from a limited sample. A sample of 17 patients is relatively small to produce statistically reliable estimates for an economic evaluation, although we believe the best database accessible at the current point of time is involved.

Second, DBS costs for dystonia (OCD) were used as a proxy for DBS costs for TS in the non-rechargeable (rechargeable) scenarios. The choice was made given three reasons: (1) no cost data of DBS for TS are available, thus costs for DBS already applied in a clinically analogous disorder could be a substitute; (2) dystonia and OCD are co-morbidities commonly associated with TS [8]; and (3) DBS for dystonia is considerably more expensive than DBS for essential tremor, given the different protocols of IPG replacement, we chose the larger to cover the upper bound of the costs.

Third, direct non-medical costs, e.g. travel costs and co-payment, and indirect costs, e.g. productivity and leisure time losses of patients and caregivers, were not included. The non-medical direct costs were unavailable for patients with DBS, although reported for patients with BMT. The exclusion productivity loss was due to concerns of double-counting. When using QALY, the QALY conceptually reflects the influence of work loss, and thus productivity. That is, the productivity loss is included in both the numerator (cost) and the denominator (effectiveness) of the ICER [52]. In addition, heterogeneity of cost data may exist, given different backgrounds of DBS (Australian and the Dutch) and BMT (German) costs.

Fourth, the chosen time horizon of 10 years may not adequately reflect the long-term productivity gains following DBS. The mean age at time of surgery was at young adulthood (i.e. 28 years) [2], implying many further years of life post-DBS. The productivity effect on utilities may also be significant as TS patients resume their work. However, a lifetime horizon is also not currently reasonable, given the lack of long-term effectiveness data.

DBS is currently implemented as a treatment of last resort in patients with TS that is refractory to medical treatment. Without Level I clinical evidence derived from a good-quality RCT, considerable uncertainty about rolling out DBS to treat severe TS remains. However, given the very limited data and under strong assumptions, our indicative economic analysis suggests that DBS maybe a cost-effective treatment strategy compared to BMT, particularly when rechargeable IPGs will be implanted. The sensitivity analysis highlighted the major impact of DBS costs, with which IPG replacement cost is the dominated component largely affected by the difference in time to battery exchange, on the ICER result.

Our findings provide context for the Australian jurisdictions when considering listing DBS for TS. We encourage further research on the costs and health consequences of using DBS to treat TS in the Australian and other settings internationally [3, 53].

Author contributions 1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique. TD: 1A, 1B, 2A, 2B, 3A, DR: 1A, 2A, 2C, 3B, JL: 3B, TC: 3B, PS: 3B, LC: 2C, 3B.

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Compliance with ethical standards

Conflicts of interest LC reports no conflicts of interest.

Ethical standards The manuscript does not contain clinical studies or patient data.

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