Bilateral Deep Brain Stimulation is the Procedure to Beat for Advanced Parkinson Disease: A Meta-Analytic, Cost-Effective Threshold Analysis for Focused Ultrasound

Uma V. Mahajan, BS[*]
Vinod K. Ravikumar, MD[‡]
Kevin K. Kumar, MD, PhD[‡]
Seul Ku, SM[‡]
Disep I. Ojukwu, MD, MBA, MPH[‡]
Camilla Kilbane, MD[*][§]
Pejman Ghanouni, MD, PhD[‡]
Joshua M. Rosenow, MD[¶]
Sherman C. Stein, MD[||]
Casey H. Halpern, MD[‡]

[*]Case Western Reserve University School of Medicine, Cleveland, Ohio; [‡]Stanford University School of Medicine, Stanford, California; [§]University Hospitals Cleveland Medical Center, Cleveland, Ohio; [¶]Northwestern University School of Medicine, Chicago, Illinois; [||]University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Correspondence:
Casey H. Halpern, MD,
Stanford University School of Medicine,
300 Pasteur Dr,
Stanford, CA 94305, USA.
Email: chalpern@stanford.edu

Received, January 6, 2020.
Accepted, August 27, 2020.
Published Online, December 9, 2020.

BACKGROUND: Parkinson disease (PD) impairs daily functioning for an increasing number of patients and has a growing national economic burden. Deep brain stimulation (DBS) may be the most broadly accepted procedural intervention for PD, but cost-effectiveness has not been established. Moreover, magnetic resonance image-guided focused ultrasound (FUS) is an emerging incisionless, ablative treatment that could potentially be safer and even more cost-effective.

OBJECTIVE: To (1) quantify the utility (functional disability metric) imparted by DBS and radiofrequency ablation (RF), (2) compare cost-effectiveness of DBS and RF, and (3) establish a preliminary success threshold at which FUS would be cost-effective compared to these procedures.

METHODS: We performed a meta-analysis of articles (1998-2018) of DBS and RF targeting the globus pallidus or subthalamic nucleus in PD patients and calculated utility using pooled Unified Parkinson Disease Rating Scale motor (UPDRS-3) scores and adverse events incidences. We calculated Medicare reimbursements for each treatment as a proxy for societal cost.

RESULTS: Over a 22-mo mean follow-up period, bilateral DBS imparted the most utility (0.423 quality-adjusted life-years added) compared to (in order of best to worst) bilateral RF, unilateral DBS, and unilateral RF, and was the most cost-effective (expected cost: $32 095 ± $594) over a 22-mo mean follow-up. Based on this benchmark, FUS would need to impart UPDRS-3 reductions of ~16% and ~33% to be the most cost-effective treatment over 2- and 5-yr periods, respectively.

CONCLUSION: Bilateral DBS imparts the most utility and cost-effectiveness for PD. If our established success threshold is met, FUS ablation could dominate bilateral DBS's cost-effectiveness from a societal cost perspective.

KEY WORDS: Deep brain stimulation, Radiofrequency ablation, Magnetic resonance guided focused ultrasound, Cost-effectiveness, Utility, Quality of life

Neurosurgery 88:487–496, 2021 DOI:10.1093/neuros/nyaa485 www.neurosurgery-online.com

Radiofrequency lesioning (RF), most frequently targeting globus pallidus pars interna (GPi), was an early, efficacious surgical treatment for advanced Parkinson disease (PD).[1,2] Due to risk of permanent complications,[3] deep brain stimulation (DBS) emerged as an often preferred intervention because of its relative reversibility.[4] Recently, magnetic resonance imaging-guided focused ultrasound (FUS) has garnered strong interest in revisiting lesioning given its incisionless nature.[5] Randomized controlled trials evaluating

ABBREVIATIONS: AE, adverse effect; **DBS,** deep brain stimulation; **ET,** essential tremor; **FUS,** focused ultrasound; **GPi,** globus pallidus pars interna; **ICER,** incremental cost-effectiveness ratio; **MDS,** Movement Disorder Society; **PD,** Parkinson disease; **QALYs,** quality-adjusted life-years; **RF,** radiofrequency; **STN,** subthalamic nucleus; **UPDRS,** Unified Parkinson Disease Rating Scale

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FUS for PD have shown promising results (NCT03319485 for pallidotomy and NCT03454425 for subthalamotomy).[6] Given real-time symptom assessment can be paired with magnetic resonance imaging to guide lesioning without an incision, complications and procedural morbidity appear to be less than RF.[5-7] Nevertheless, it is unclear the efficacy and adverse event rate required for FUS to surpass available procedural options. Moreover, cost-effectiveness of DBS vs RF has never been assessed.

We performed a meta-analysis and critical comparison of surgical treatments for PD. First, we compared DBS and RF for utility (a metric of efficacy corrected by adverse effects (AEs), derived from percent change in functional disability), by examining reduction in Unified Parkinson Disease Rating Scale (UPDRS) Motor Section (UPDRS-3) scores from each procedure as well as the incidence of AEs along with published parameters. Then, we investigated the cost-effectiveness of these 2 treatments utilizing Medicare reimbursement as a proxy for societal cost. Major guidelines regarding the application of cost-effectiveness analyses have recommended the "societal perspective" for purposes of public interest, consistency, and comparability.[8,9] Thus, our analysis does not examine costs to hospitals directly. Finally, we used these results to establish a success threshold for FUS for PD to inform evaluation of clinical trial outcomes. Best medication therapy was not included here because DBS has previously been found to be cost-effective compared to it.[10-12]

METHODS

Details on literature search, data management, meta-analytic statistical analysis, utility, and treatment costs are included in **Text, Supplemental Digital Content 1** and **Tables, Supplemental Digital Content 2-4**.

Model

Figure 1 illustrates the decision analytical model used to estimate the expected utilities and costs between groups. Briefly, values for utility due to efficacy, disutility due to treatment AEs, and incidence of AEs were populated in the decision tree, and an overall utility for each treatment was outputted, as described in previously.[13] The base case for the model was a patient with PD suitable for surgical intervention, with demographic values equivalent to our mean pooled values. For this analysis, we did not stratify by brain target because target does not affect costs (and we found no difference in effectiveness of target long-term, discussed below). We chose to pool all articles and, thus, utilize the prevalences of targets in published literature.

Cost-Effectiveness Analysis

Primary analysis involved a rollback analysis to calculate overall expected costs and utilities, as described in published literature.[14] Treatment benefit involves utility and durability, calculated in terms of quality-adjusted life-years (QALYs). The difference in costs between two procedures divided by their difference in QALYs is known as the incremental cost-effectiveness ratio (ICER) and allows for direct comparison of cost-effectiveness between two procedures.[15] Generally, cost-effectiveness comparisons in the United States assume society is willing to pay $50 000 per QALY gained for a preferred treatment, although some authorities affirm that the actual QALY threshold is considerably higher.[16]

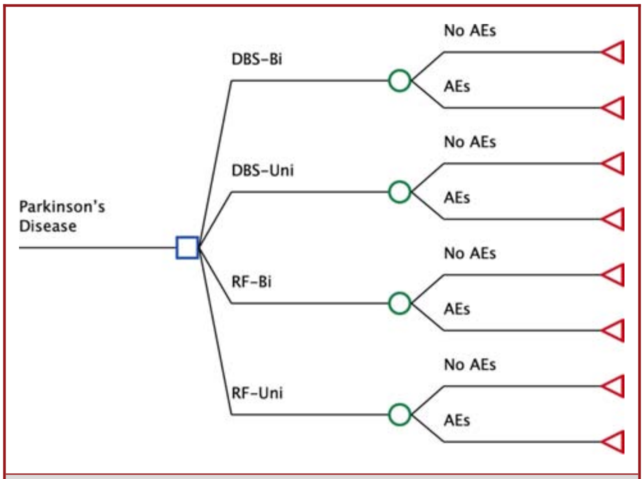


FIGURE 1. *Decision-analytic model to calculate benefits, harms, health-related utility, expected costs, and cost-effectiveness resulting from current surgical treatments of PD.*

Comparisons of utilities and costs involved sensitivity analysis with Monte Carlo simulation (100 simulated trials of 100 subjects in each treatment arm, following standard procedure[17]). Beta distributions were used for probabilities and utilities and normal distributions for costs. The cost-effectiveness model employed TreeAge Pro 2019 (TreeAge Software, Williamstown, Massachusetts).

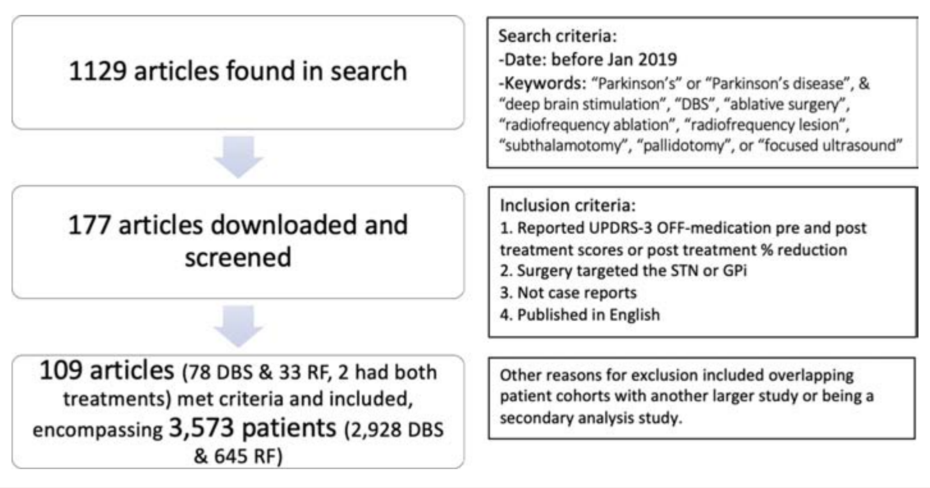
RESULTS

Literature Search

109 articles (78 DBS and 33 RF, 2 overlap) that encompassed 3573 patients (2928 DBS and 645 RF) met our screening criteria (**Table, Supplemental Digital Content 5** and Figure 2). For the minority of articles that included treatment groups with different anatomical targets or both unilateral and bilateral procedures, and with data not separable, we included data if at least 60% of cases fell in one group.

Demographics, Baseline, and Study Type Characteristics

There were no significant differences in age, sex, and disease duration between treatment groups (bilateral DBS, unilateral DBS, bilateral RF, and unilateral RF) (**Table, Supplemental Digital Content 6**). Baseline UPDRS-3 was significantly higher in the RF treatment groups compared to the DBS group. Treatment follow-up length was significantly longer in the bilateral treatment groups compared to unilateral. RF articles were significantly older than DBS articles (Figure 3). Our base case was a 59-yr-old patient with a 12-yr disease duration and UPDRS-3 OFF-medication baseline score of 44. The primary outcome (UPDRS-3 reductions) had a normal distribution ($P = .3714$; **Figure, Supplemental Digital Content 7**).



1129 articles found in search

177 articles downloaded and screened

109 articles (78 DBS & 33 RF, 2 had both treatments) met criteria and included, encompassing **3,573 patients** (2,928 DBS & 645 RF)

Search criteria:
-Date: before Jan 2019
-Keywords: "Parkinson's" or "Parkinson's disease", & "deep brain stimulation", "DBS", "ablative surgery", "radiofrequency ablation", "radiofrequency lesion", "subthalamotomy", "pallidotomy", or "focused ultrasound"

Inclusion criteria:
1. Reported UPDRS-3 OFF-medication pre and post treatment scores or post treatment % reduction
2. Surgery targeted the STN or GPi
3. Not case reports
4. Published in English

Other reasons for exclusion included overlapping patient cohorts with another larger study or being a secondary analysis study.

FIGURE 2. *PRISMA diagram of included articles.*

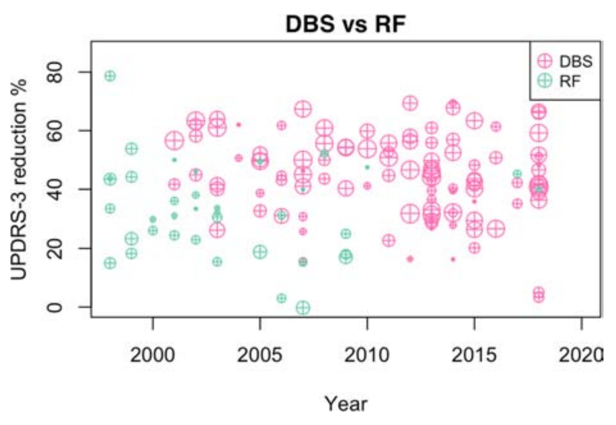


FIGURE 3. *Scatterplot demonstrating UPDRS-3 reduction by treatment type and over publication time. DBS studies were significantly newer than RF studies, though publication year was not associated with UPDRS-3 reduction. Size of data point represents number of patients in the study.*

Efficacy

When a linear mixed-effects meta-regression model was performed to test differences in efficacy outcomes (as measured by UPDRS-3 OFF-medication; the dependent variable) between groups, with 6 predictors/covariates including treatment type (DBS or RF), unilateral vs bilateral, subthalamic nucleus (STN) vs GPi, baseline UPDRS-3, follow-up length, and publication year, 2 factors significantly predicted efficacy outcomes: bilateral vs unilateral (bilateral imparting greater benefit, $P = .0002$) and follow-up length (benefit decreasing over time, $P < .0001$) (Table 1). There was a trend toward significance for target (STN imparting greater benefit, $P = .0618$; Figure 4). Treatment type ($P = .6522$), baseline UPDRS-3 ($P = .7742$; Figure 5), and publication year ($P = .7189$) were not.

When the same regression model was created with the dependent variable of long-term UPDRS-3 data (corresponding to greater than mean follow-up, >22 mo), bilateral vs unilateral (bilateral imparting greater benefit, $P < .0001$) and follow-up length (benefit decreasing over time, $P = .0001$) were still significant predictors of efficacy, but the target was no longer a predictor ($P = .4241$). When data were stratified by target, efficacy of STN decreased significantly as follow-up length increased ($P = .0001$), but efficacy of GPi was not significantly associated with follow-up length ($P = .3185$; Figure 4).

A separate sub-analysis was performed with the dependent variable of UPDRS-3 ON-medication scores (as dopamine replacement medications are generally substantially reduced after STN DBS[18]) (Figure 4). In DBS, bilateral vs unilateral

TABLE 1. Treatment Efficacy

Mean % UPDRS-3 reduction (OFF-medication)	Bilateral DBS (n = 2603 STN, n = 258 GPi)	Unilateral DBS (n = 134 STN, n = 44 GPi)	Bilateral RF (n = 42 STN, n = 43 GPi)	Unilateral RF (n = 126 STN, n = 443 GPi)
Overall	45.4% ± 3.2%	30.3% ± 3.1%	41.3% ± 4.9%	30.6% ± 5.1%
STN only	46.1% ± 3.1%	32.9% ± 3.2%	47.0% ± 5.2%	24.8% ± 3.0%
GPi only	38.5% ± 4.1%	22.3% ± 2.8%	35.8% ± 4.5%	32.2% ± 5.5%

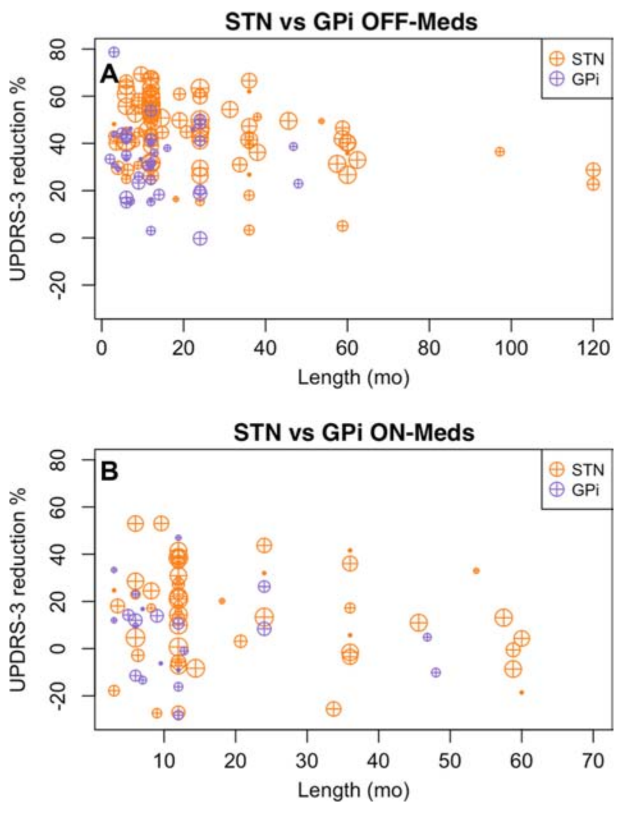


FIGURE 4. *Scatterplots demonstrating UPDRS-3 reduction by target over follow-up length.* **A**, *Off-medication. UPDRS-3 reduction decreased over time, and STN provided greater benefit than GPi.* **B**, *On-medication. STN and GPi provided equivalent benefit. Size of data point represents number of patients in the study. Note: axis scales are different in* **A** *and* **B**.

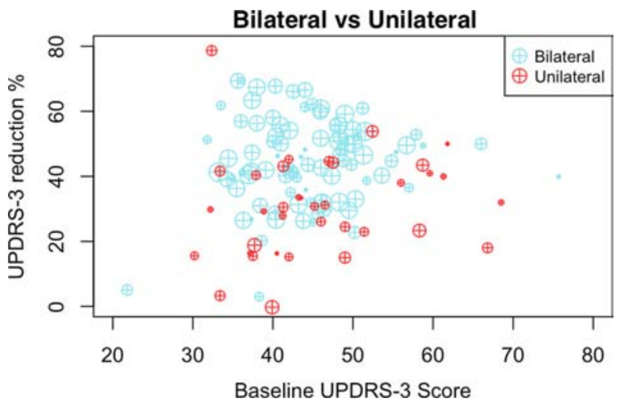


FIGURE 5. *Scatterplot demonstrating UPDRS-3 reduction for bilateral vs unilateral, over baseline UPDRS-3 scores. Bilateral treatment provided greater efficacy than unilateral treatment. There was no association between baseline score and efficacy outcome or baseline score and bilateral vs unilateral. Size of data point represents number of patients in the study.*

(bilateral imparting greater benefit, $P = .0190$) and follow-up length (benefit decreasing over time, $P < .0001$) were significant predictors of UPDRS-3 ON-medication scores; target ($P = .7839$) and baseline UPDRS-3 ON-medication score ($P = .7742$) were not. In RF, target (STN imparting greater benefit, $P = .0015$) was a significant predictor of UPDRS-3 ON-medication scores; bilateral vs unilateral ($P = .4512$), follow-up length ($P = .3777$), and baseline ($P = .6360$) were not.

We tested if the efficacy of the most prevalent treatment, bilateral DBS, was affected by disease course and severity, as measured by disease duration and baseline UPDRS-3, respectively. We found no significant association ($P = .9411$ for disease duration and $P = .1937$ for baseline UPDRS-3).

Adverse Effects

Table 2 and **Figure, Supplemental Digital Content 8** show incidence of each AE category for each treatment (**Table, Supplemental Digital Content 9** shows incidence stratified by target). Overall, speech-related difficulties were the most common, followed by movement disorders (including dyskinesia and hemiballismus), anxiety, and mood-related events. Bilateral RF had the highest incidence of AEs, followed by bilateral DBS, unilateral RF, and then unilateral DBS.

Fisher's exact tests revealed a lower risk of AEs with bilateral DBS than bilateral RF ($P = .0096$), and likewise, unilateral DBS had a lower risk of AEs than unilateral RF ($P = .0096$). Bilateral DBS and unilateral RF exhibited no difference ($P = .4671$). Bilateral DBS was associated with a higher risk than unilateral DBS ($P = .0096$), and bilateral RF was associated with a higher risk than unilateral RF ($P = .0096$).

To ensure our reported AEs incidences were not skewed because of changes in reporting practices over time, we tested whether there were temporal trends. We found that reporting of AEs was not associated with publication year in either treatment group (DBS $P = .114$, RF = 0.717).

Utility

Table 3 displays utility imparted by treatment efficacy, disutility imparted by AEs, and overall utility (which also factors incidence of AEs) of all treatments. Overall utilities imparted were (higher value indicates more preferred health state) 23.1% ± 0.6%, 20.4% ± 0.5%, 15.9% ± 0.4%, and 15.5% ± 0.4% for bilateral DBS, bilateral RF, unilateral DBS, and unilateral RF, respectively. A one-way ANOVA with Tukey's post hoc test revealed all four groups imparted a significantly different overall utility ($P < .001$ for all comparisons).

Costs

Table 4 displays the expected costs for each treatment, including expected complication costs. As stated in our Methods, the DBS device cost is not included in Medicare reimbursements because it is paid for by the hospital. Given that mean postoperative follow-up among pooled studies was 22.0 mo, we factored in costs for 7 outpatient follow-up visits for DBS programming

TABLE 2. Treatment-Related AEs

	DBS-bilateral		DBS-unilateral		RF-bilateral		RF-unilateral	
AEs	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Speech-related difficulties	0.048	0.005	0.000	0.000	0.176	0.041	0.054	0.010
Movement disorders[a]	0.030	0.004	0.016	0.016	0.118	0.035	0.050	0.010
Anxiety/mood related	0.035	0.004	0.016	0.016	0.000	0.000	0.008	0.004
Weight change related	0.032	0.004	0.000	0.000	0.012	0.012	0.010	0.004
Infection related	0.029	0.004	0.048	0.027	0.012	0.012	0.008	0.004
Cognitive/concentration related	0.026	0.004	0.000	0.000	0.012	0.012	0.016	0.006
Depression related	0.014	0.003	0.016	0.016	0.035	0.020	0.010	0.004
Hematoma/hemorrhage	0.011	0.002	0.000	0.000	0.000	0.000	0.022	0.007
Weakness related	0.007	0.002	0.000	0.000	0.012	0.012	0.024	0.007
Device related (not infection)	0.013	0.003	0.000	0.000	0.000	0.000	0.000	0.000
Vascular related	0.009	0.002	0.016	0.016	0.012	0.012	0.006	0.003
Falls and related	0.012	0.002	0.000	0.000	0.000	0.000	0.000	0.000
Death	0.006	0.002	0.000	0.000	0.000	0.000	0.010	0.004
Face related	0.002	0.001	0.000	0.000	0.012	0.012	0.016	0.006
Seizure related	0.003	0.001	0.000	0.000	0.012	0.012	0.012	0.005
Vision related	0.001	0.001	0.000	0.000	0.012	0.012	0.016	0.006
Pneumonia and related	0.005	0.002	0.000	0.000	0.000	0.000	0.000	0.000
Urological related	0.002	0.001	0.000	0.000	0.000	0.000	0.004	0.003
Total	0.284	0.046	0.113	0.091	0.424	0.190	0.267	0.083

Incidence of AEs per patient in each treatment group. Table is sorted from top to bottom by greatest overall incidence.

[a] Includes dyskinesis, hemiballismus.

TABLE 3. Overall Expected Utility of Each Treatment

	Bilateral DBS (n = 2861)	Unilateral DBS (n = 178)	Bilateral RF (n = 85)	Unilateral RF (n = 569)
Utility added by treatment efficacy[a]	25.0% ± 1.7%	16.7% ± 1.7%	22.7% ± 2.7%	16.8% ± 2.8%
Disutility imparted by AEs[a]	72.9% ± 4.4%	59.0% ± 4.9%	76.7% ± 4.2%	72.2% ± 4.5%
Incidence of AEs	28.4% ± 4.6%	11.3% ± 9.1%	42.4% ± 4.6%	26.7% ± 8.3%
Overall utility imparted	23.1% ± 0.6%	15.9% ± 0.4%	20.4% ± 0.5%	15.5% ± 0.4%

[a] For both utility and disutility values, higher values indicate more preferred health states.

TABLE 4. Expected Costs for Each Treatment[a]

	Bilateral DBS	Unilateral DBS	Bilateral RF	Unilateral RF
Cost	$32 095 ± $594	$29 283 ± $415	$35 035 ± $632	$33 001 ± $597

For DBS, nonstaged costs were used, because we previously found (in Ravikumar et al.[7]) that staging for DBS is not cost-effective.

Costs include treatment costs and expected complication costs.

sessions. A total of $35 035 ± $632, $33 001 ± $597, $32 095 ± $594, and $29 283 ± $415 was yielded for bilateral RF, unilateral RF, bilateral DBS, and unilateral DBS, respectively. A one-way ANOVA with Tukey's post hoc test revealed was all four groups had a significantly different expected cost ($P < .001$ for all comparisons).

Cost-Effective Comparisons

When both utility and cost values were considered, bilateral DBS was the most cost-effective treatment (Figure 6). Over a 22-mo follow-up period, bilateral DBS added 0.423 QALYs (eg, overall utility imparted (0.231) multiplied by follow-up years (1.83)), compared to 0.375 added by bilateral RF, 0.292

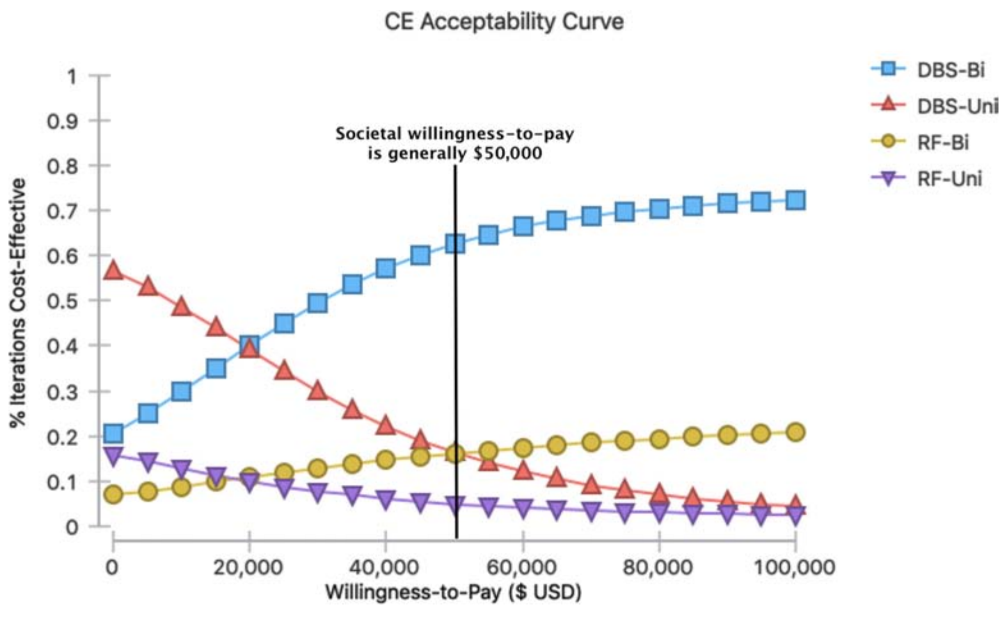


FIGURE 6. *Cost-effectiveness acceptability curve. Bilateral DBS is consistently the most cost-effective treatment at willingness-to-pay thresholds at and above $20,000.*

TABLE 5. Success Thresholds for FUS

	FUS
Expected cost	$17 074 ± 380
UPDRS % reduction threshold 2-yr	15.5% ± 0.4%
UPDRS % reduction threshold 5-yr	32.8% ± 0.5%
UPDRS % reduction threshold 10-yr	38.1% ± 0.5%

The expected cost, and efficacy thresholds needed to be more cost-effective than bilateral DBS over 2-, 5-, and 10-yr periods.

added by unilateral DBS, and 0.284 added by unilateral RF. The ICERs (eg, difference in costs divided by difference in QALYs) of bilateral DBS compared to the other three treatments were: $21 708 (unilateral DBS), −$59 620 (bilateral RF), and −$6049 (unilateral RF) per QALY. The ICERs of bilateral DBS compared to RF were negative because bilateral DBS is less costly and more effective than RF.

FUS Thresholds

Inputting the treatment cost, the estimated AE incidence, and utility values for FUS from Ravikumar et al[7] yields the percent reduction thresholds in UPDRS-3-Off to achieve superior cost-effectiveness compared to the procedure to beat, ie, bilateral DBS (Table 5). The model indicates that FUS needs to achieve UPDRS-3-Off reductions of 15.5% (Figure 7A) and 32.8% (Figure 7B) to achieve cost-effectiveness over 2- and 5-yr periods, respectively (Table 3), given an AE incidence rate of 16.2% (**Table, Supplemental Digital Content 10**).

Figure 8 displays how changes in FUS safety and incidence affect 2-yr cost-effectiveness. These reduction thresholds would result in ICERs of approximately $50 000 (standard for being cost-effective) for FUS compared to bilateral DBS, which is the amount above which the more effective treatment is no longer cost-effective. Since the AE incidence and utility values utilized were based on essential tremor (ET) data, we performed a sensitivity analysis (Figure 9), which showed that these varying values have a limited effect on the ICERs.

A sub-analysis was performed with an additional FUS cost included (which is currently a hospital cost but may be reimbursed by Medicare in the future, detailed in **Table, Supplemental Digital Content 4F**). This cost was estimated to be $1910.06 (equivalent to the unilateral RF professional reimbursement), and FUS success thresholds of 19.1% and 34.4% were yielded for 2- and 5-yr periods, respectively.

DISCUSSION

This work represents the first study utilizing meta-analytic and cost-effective analyses to compare available procedural interventions for PD. We observed that bilateral DBS imparts the highest utility (0.231 utils per year, or 0.423 QALYs added over the 22-mo follow-up). Bilateral DBS incurred lower direct costs than either unilateral or bilateral RF (DBS device costs are not included in Medicare reimbursement, as the hospital covers the cost) and

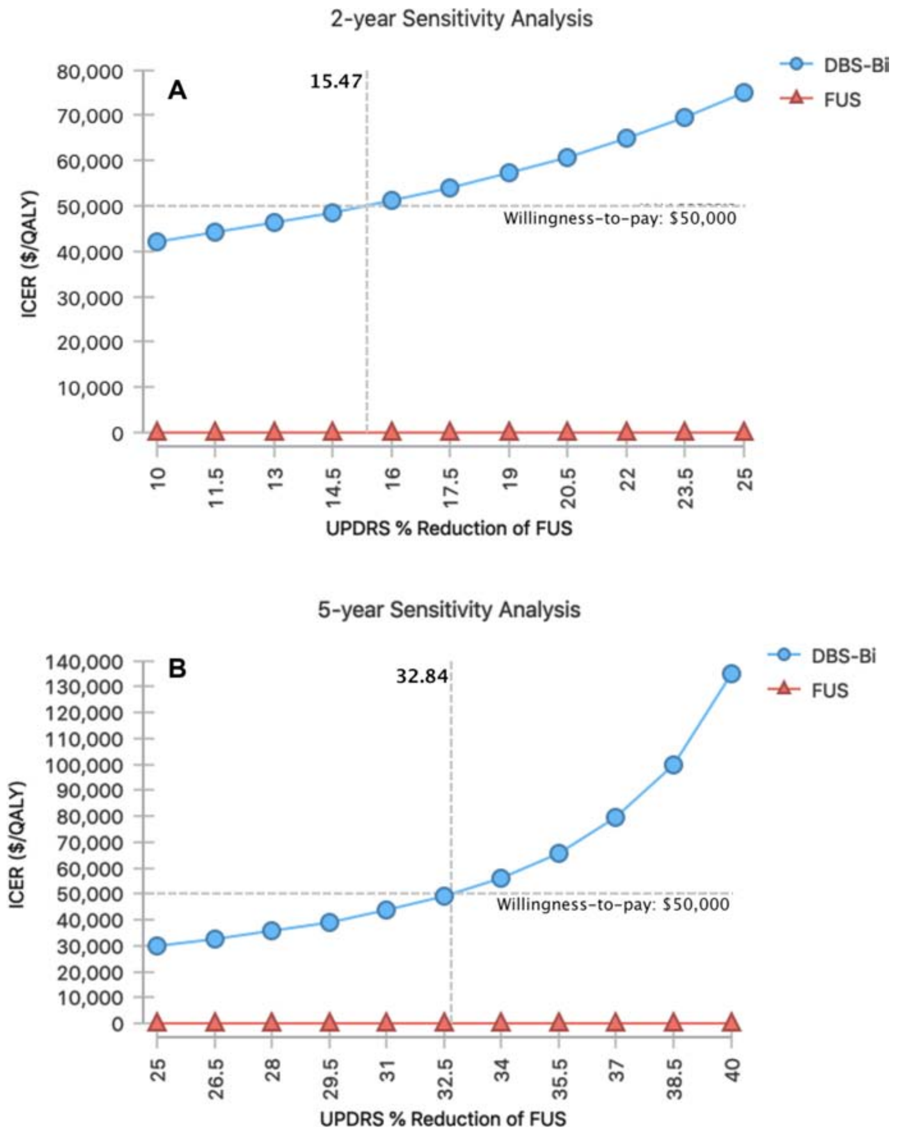


FIGURE 7. *Sensitivity analysis demonstrating the UPDRS-3 OFF % reduction that FUS would have to meet in order to be more cost-effective than bilateral at various ICER values.* **A**, *2-yr timescale.* **B**, *5-yr timescale.*

was overall more cost-effective. In 2010, the national economic burden of PD was approximately $22 800 per patient.[19] As the population ages and the expected number of people in the United States living with PD increases, the cumulative economic burden will continue to increase.[20] The majority of treatment costs in PD are associated with managing increasing disability (specifically costs related to increasing need for care),[20] and thus, there remains a critical need to provide cost-effective treatments that stave off disability for as long as possible. Because DBS has generally replaced RF in treatment for PD particularly bilaterally,[21] it is encouraging to observe that DBS is also cost-effective.

Our model predicted that a lower clinical improvement threshold was needed for FUS to be more cost-effective than bilateral DBS particularly at 2 yr because of the lower treatment costs associated with FUS. Bilateral DBS is typically associated with an improvement in the UPDRS-3-OFF scale of about 45% (at 22 mo follow-up). For FUS to be as cost-effective over a 2-yr period, it requires a UPDRS-3 reduction of about 16%. FUS thresholds increase over time, as postprocedure time amortizes the surgical costs. Thus, FUS thresholds increase to match effectiveness of bilateral DBS. The mean patient age in our analysis was 59 yr, and the average 59-yr-old in the United States has a life

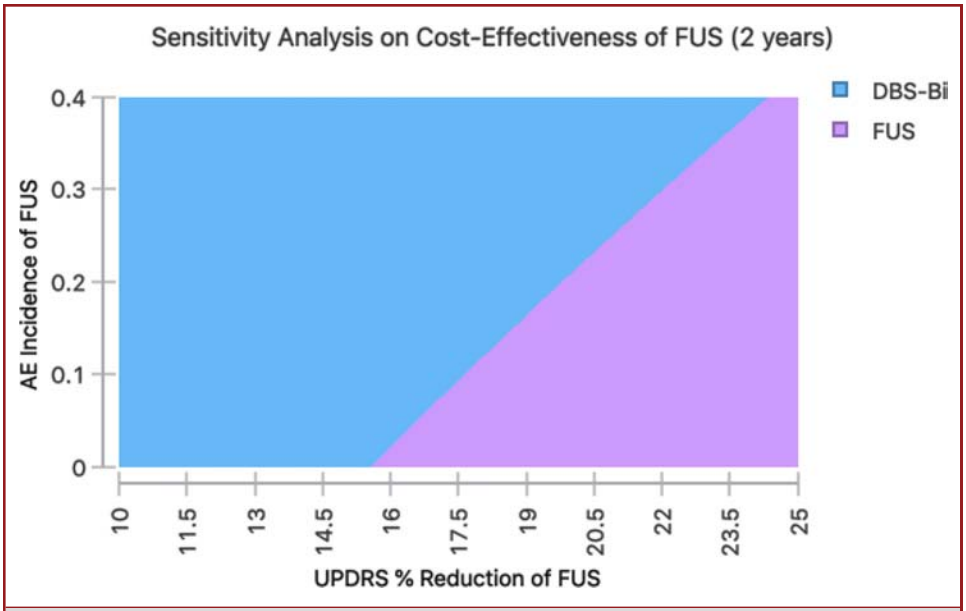


FIGURE 8. *Plot demonstrating how changes in the AE incidence and UPDRS-3% reduction of FUS affect its cost-effectiveness, over a 2-yr period. Blue shaded areas demonstrate scenarios where bilateral DBS is the most cost-effective option (if adhering to the societal $50 000 willingness-to-pay threshold). Purple shaded areas indicate scenarios where FUS is the more cost-effective option.*

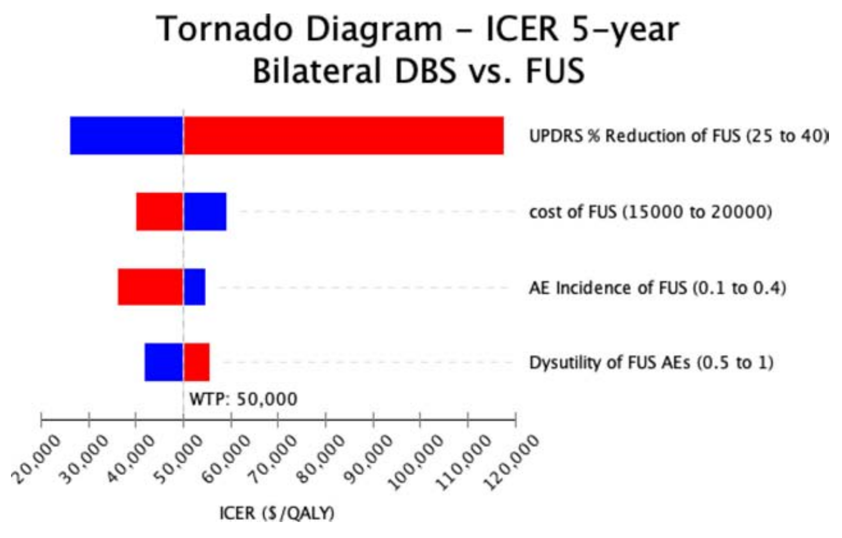


FIGURE 9. *Tornado diagram demonstrating effect of varying FUS AE incidence and disutility as well as cost and efficacy on the overall ICER of bilateral DBS compared to FUS (an ICER less than $50 000 supports DBS as more cost-effective, whereas an ICER greater than $50 000 supports FUS as more cost-effective). Red bars demonstrate the effects of an increase in the variable value and blue bars indicate the effects of a decrease in the variable value.*

expectancy of approximately 24 more years.[22] A typical patient may continue to live for two decades, over which QALYs added could accumulate, and the threshold to be a cost-effective alternative would increase.

Two FUS studies in PD patients were published in 2018. In a prospective trial of 8 patients, FUS pallidotomy resulted in a mean UPDRS-3 reduction of 39.1% after 6 mo. A series of 10 patients undergoing FUS subthalamotomy demonstrated a Movement

Disorder Society (MDS)-UPDRS-3 reduction of 35.2% after 6 mo.[6,23] Although the MDS-UPDRS differs slightly from UPDRS, these 2 scales have been shown to be highly correlated ($r = 0.96$), so percentage reductions—as opposed to absolute differences—can be compared.[24] These results supported that FUS may be a cost-effective alternative if AE incidence rates are kept low enough and efficacy is durable. Notably, FUS thalamotomy has recently been reported to be durable for unilateral ET for up to 3 yr.[25]

Our results support that DBS of the GPi and STN DBS targets demonstrated no significant differences in reducing UPDRS-3 ON-medication scores, although there was a trend for STN DBS to perform better than GPi DBS at reducing UPDRS-3 OFF-medication scores. This is expected given dopamine replacement medications are decreased more after STN DBS surgery than GPi DBS.[18] We found that RF of the STN was significantly better than RF of the GPi at reducing UPDRS-3 ON-medication scores. However, ablative STN procedures are not preferred because of a higher risk of medically resistant hemiballismus (15% incidence).[26,27] Although GPi and STN had similar AE incidences for unilateral RF procedures, STN had nearly 10 times the incidence (15.1%) of movement complications including hemiballismus and dyskinesia (**Table, Supplemental Digital Content 9**).

Our study was designed to reflect the current PD surgical treatment population. Thalamic surgeries were excluded because these primarily treat only tremor and not other cardinal symptoms of PD, such as rigidity and bradykinesia. The costs and AE parameters in our analysis were based on unilateral FUS data, similar to the current clinical trials, but bilateral FUS may be tested in the future.[28] The only significant demographic difference between the treatment groups was a lower baseline mean UPDRS-3 score in the DBS population compared to the RF population (**Table, Supplemental Digital Content 6**). Possible reasons for this finding include the superior safety profile of DBS, leading to a shift in clinical practice to considering more recently diagnosed, less severely advanced PD patients.[29] Indeed, our results suggest that it is effective to perform DBS, even early in a patient's disease course when PD is less severe (as measured by disease duration and baseline UPDRS-3). In particular, performing surgery earlier in the disease course could result in additional years gained and a greater number of QALYs added.

As our analysis was conducted from a societal perspective, we did not include equipment costs such as the DBS implants, which are incurred by the hospital (approximately $30 000 per patient). The hospital may recoup these costs in other ways, such as in the costs of battery changes and physical therapy that are passed on to patients, which even more so makes the cost-effectiveness of FUS relative to DBS favorable. However, FUS equipment can be quite costly, with a list price of approximately $2.2 million dollars (and device life of approximately 10 yr), which may limit scalability and adoption even if the procedure is cost-effective. Additionally, treatment choice will factor in individual disease characteristics and provider preferences, and is ultimately a patient decision. Thus, a greater cost-effectiveness in the setting of lower utility may still limit widespread patient adoption of a therapy. The patient experience will also factor into the decision (eg, FUS is incisionless and will not result in surgical scars) and will have to be balanced with the cost-effectiveness. Including equipment costs, 5-yr total costs in a center that performs, for example, 25 procedures per year would amount to approximately $7.76 million for DBS and $4.13 million for FUS (2-yr costs would be $3.10 million for DBS and $2.85 million for FUS).

Limitations

There were several limitations to our analysis. Mapping UPDRS-3 reduction and AEs onto a utility scale is indirect and may obscure outcome estimation but is necessary, as optimizing functional disability involves accounting for both treatment efficacy and AEs. Utilizing UPDRS-3 as the efficacy measure may bias our analysis toward motor improvement and not as well account for other aspects of PD such as neuropsychiatric profile; however, it is the most commonly reported measure because these procedures are typically considered best at ameliorating motor dysfunction. Utilizing ET parameters for AE rates for FUS are not an exact outcome estimate, but was necessary to provide an efficacy estimate because a robust FUS PD dataset is not available. Furthermore, the AE parameters used for FUS also represented intermediate values among our AE data, falling between those for DBS and RF. We utilized Medicare reimbursement as a proxy for societal cost but realize that different payment models exist in other countries, and these results may not be directly applicable outside of the United States. Hence, we have included pooled utility values in Table 3 that can be adapted for other models. Although Medicare is the most consistent way to estimate United States societal costs, improvements in productivity and activities of daily living are not assessed.

CONCLUSION

Bilateral DBS is currently the most cost-effective procedure for PD. Ongoing clinical trials of FUS for PD should be evaluated in the context of our findings. We urge further investigation of FUS to confirm durable outcomes with acceptable safety profiles given the potential for cost-effectiveness from a societal perspective.

Funding

This study did not receive any funding or financial support.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Dr Kilbane receives education grants from Medtronic, Abbot, and Boston Scientific to support a movement disorder fellowship program. Dr Halpern receives consulting fees and/or speaking honoraria from Medtronic, NeuroPace, and Boston Scientific. Research funds as site PI (for Drs Halpern and Ghanouni) were also received from Insightec to conduct the FUS pallidotomy trial NCT03319485.

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Acknowledgments

We thank Sara Banister and Silvia Villarreal of Stanford University for assistance in ensuring accuracy of the billing codes used in our analysis. We thank Professor Pingfu Fu of Case Western Reserve University for statistical advice. We would like to dedicate this work in honor of coauthor and the late Dr Stein, who made exceptional contributions in guiding the design and analysis of this study but passed before its completion.

***Supplemental digital content** is available for this article at www.neurosurgery-online.com.*

Supplemental Digital Content 1. Text. Methodology on literature search, data management, meta-analytic statistical analysis, utility, and treatment costs.
Supplemental Digital Content 2. Table. Adverse event clinical categories.
Supplemental Digital Content 3. Table. Utility of side effects and complications.
Supplemental Digital Content 4. Table. A, Unilateral non-staged DBS reimbursement calculation. **B**, Bilateral non-staged DBS reimbursement calculation. **C**, Unilateral DBS and bilateral DBS follow-up costs. **D**, Unilateral RF reimbursement calculation. **E**, Bilateral RF reimbursement calculation. **F**, Unilateral FUS reimbursement calculation.
Supplemental Digital Content 5. Table. Studies included in the analysis, listed by treatment group. A total of 109 articles (78 DBS and 33 RF, 2 overlap) that encompassed 3573 patients (2928 DBS and 645 RF) were included.
Supplemental Digital Content 6. Table. Patient demographics and treatment follow-up length.
Supplemental Digital Content 7. Figure. Histogram of UPDRS-3-Off reductions (primary outcome measure). Distribution is normal.
Supplemental Digital Content 8. Figure. Plot of complication rates (AE incidence) by treatment type. Incidence is in units of events per patient (grayscale).
Supplemental Digital Content 9. Table. Incidence of AEs by treatment target and laterality subgroups.
Supplemental Digital Content 10. Table. AE parameters for FUS, taken from Ravikumar et al.[7]