J Neurosurg 103:956–967, 2005

Deep brain stimulation in Parkinson disease: a metaanalysis of patient outcomes

FRANCES WEAVER, PH.D., KENNETH FOLLETT, M.D., PH.D., KWAN HUR, PH.D., DOLORES IPPOLITO, M.P.H., AND MATTHEW STERN, M.D.

Midwest Center for Health Services and Policy Research, Edward Hines Jr. VA Hospital, Hines, Illinois; VA Iowa City Health Care System and University of Iowa, Iowa City, Iowa; Cooperative Studies Program Coordinating Center, Edward Hines Jr. VA Hospital, Hines, Illinois; and Philadelphia VA Medical Center and University of Pennsylvania, Philadelphia, Pennsylvania

Object. Deep brain stimulation (DBS) to treat advanced Parkinson disease (PD) has been focused on one of two anatomical targets: the subthalamic nucleus (STN) and the globus pallidus internus (GPI). Authors of more than 65 articles have reported on bilateral DBS outcomes. With one exception, these studies involved pre- and postintervention comparisons of a single target. Despite the paucity of data directly comparing STN and GPI DBS, many clinicians already consider the STN to be the preferred target site. In this study the authors conducted a metaanalysis of the existing literature on patient outcomes following DBS of the STN and the GPI.

Methods. This metaanalysis includes 31 STN and 14 GPI studies. Motor function improved significantly following stimulation (54% in patients whose STN was targeted and 40% in those whose GPI was stimulated), with effect sizes (ESs) of 2.59 and 2.04, respectively. After controlling for participant and study characteristics, patients who had undergone either STN or GPI DBS experienced comparable improved motor function following surgery ($p = 0.094$). The performance of activities of daily living improved significantly in patients with either target (40%). Medication requirements were significantly reduced following stimulation of the STN (ES = 1.51) but did not change when the GPI was stimulated (ES = −0.02).

Conclusions. In this analysis the authors highlight the need for uniform, detailed reporting of comprehensive motor and nonmotor DBS outcomes at multiple time points and for a randomized trial of bilateral STN and GPI DBS.

KEY WORDS • Parkinson disease • deep brain stimulation • subthalamic nucleus • globus pallidus internus

ABLATIVE brain surgery was used as early as 1912 to treat PD.[24,66] When levodopa was introduced in the 1960s, surgical interventions for PD decreased dramatically. Within a few years, however, the therapeutic limitations of levodopa became apparent. Following the administration of levodopa, PD continued to progress and treatment-related complications including motor fluctuations and dyskinesias became a major therapeutic challenge. More recently, neurosurgical interventions experienced a renaissance in the form of ablative procedures (for example, pallidotomy).[43,44] Nonetheless, as the use of pallidotomy became more widespread, the shortcomings of this procedure were also realized. Adverse effects related to bilateral pallidotomy included speech impairment, balance and gait problems, visual field defects, and cognitive deficits.[1,21,68] The search for safer and more effective surgical treatments, particularly for bilateral symptoms, fueled interest in DBS.

Deep brain stimulation, which involves the application of electrical stimuli, produces a functional lesion within a focal area of the brain. Two targets within the brain have been stimulated to treat PD: the STN and the GPI. The first reports of DBS for the management of PD were published in the mid 1990s. Studies published since then have documented significant improvement in patient motor functioning[12,27,35,54] and quality of life following STN DBS.[10,31] Serious adverse events have also been reported including infections,[12,33,76] depression, mood changes, and psychosis requiring intervention[5,72,76,81] as well as equipment issues such as lead fractures and dislodgements.[12,54,81] Authors of studies on GPI stimulation have also reported improved motor function and time spent in the on state[12,21,29,38,42,47,55,82] as well as an enhanced perceived quality of life.[67,78] Serious complications reported for bilateral GPI DBS include hematomas,[12,47] infections,[63,81] and equipment issues.[12] Oh and colleagues[52] reported a hardware-related complication rate (including lead fractures, migrations, erosions, and infections) of 25% for DBS, whereas authors of a long-term follow-up study on STN DBS found 5% of patients with dementia and/or hallucinations and 12% with apathy not responsive to increased dopaminergic therapy.[34] Although mortality rates have been low (< 1% in the 1st year postprocedure), the rate of serious complications reveals the need to systematically track, record, and compare adverse outcomes according to the stimulation target.

As evidenced by the increase in publications in the last

Abbreviations used in this paper: ADL = activities of daily living; CI = confidence interval; DBS = deep brain stimulation; ES = effect size; GPI = globus pallidus internus; PD = Parkinson disease; SD = standard deviation; STN = subthalamic nucleus; UPDRS = United Parkinson's Disease Rating Scale.

several years, DBS for PD has gained widespread acceptance. Data from an analysis of practice patterns confirm that DBS is now the preferred surgical treatment for PD.[15] Significant questions regarding DBS remain, however, including which stimulation target site leads to better outcomes. It is not yet known whether certain patients or particular symptoms respond better to stimulation of one target than another. To our knowledge, in only one small study (10 patients) have the authors randomly assigned patients to receive bilateral GPI or STN stimulation and evaluated outcomes in a blinded fashion.[9] In this study improvements in motor function were documented regardless of the stimulation target. Levodopa intake decreased following DBS in the STN-targeted group but remained unchanged in the GPI-targeted group. Given the small sample size, however, a larger trial is needed to determine whether these findings are robust.

In lieu of a large randomized trial, we conducted a systematic review of the work completed to date to quantify what has been learned about the outcomes of DBS for PD. In this metaanalysis we synthesized the results of published research on patient outcomes following bilateral DBS of the STN and GPI targets in the brain.

Clinical Material and Methods

Literature Search and Article Selection

Several strategies were undertaken to identify all published reports on outcomes of bilateral DBS of either the STN or the GPI. We began with a MEDLINE search using the following MeSH terms: "Parkinson's disease," "deep brain stimulation," "subthalamic nucleus," and "globus pallidum." This search was supplemented by examining the bibliography published with a recent Food and Drug Administration report in which the literature on bilateral DBS of the STN and GPI was reviewed.[75] In addition, we reviewed the references from articles identified in the aforementioned searches to include any additional papers related to outcomes of DBS that may have been missed.

Inclusion criteria included the following factors: study patients had idiopathic PD, therapeutic intervention involved bilateral DBS of either the STN or the GPI, reported outcomes included UPDRS motor function scores off medications at baseline and off medications/on stimulation at follow up, and follow-up assessment occurred at least 3 months post-DBS. Thus, studies documenting only nonmotor outcomes (for example, cognitive function) or surgical parameters (such as microelectrode recording) were not considered in our review. We also excluded publications with motor function results that had already been published in another paper or in which DBS surgery had been performed for another indication (for instance, essential tremor), the electrode implantation site was neither the STN nor the GPI or it was not bilateral, or the study patients had previously undergone intracranial surgery for PD. Each article considered was compared with a checklist of inclusion and exclusion criteria. Only articles meeting the inclusion criteria were retained for analysis.

A data extraction table was developed to code the articles. This table included authors; journal title and year of publication; country in which the study had been performed; percentage of male patients; average age of patients; study design (single group pretest posttest, randomized trial, or quasiexperiment); intervention site (STN or GPI); number of patients undergoing each intervention; duration of follow-up periods (in months); average baseline UPDRS motor score off medication, standard deviation, and standard error or range; and average follow-up UPDRS score off medication/on stimulation, standard deviation, and standard error or range. If the study also included the ADL subscore of the UPDRS we reported the baseline and follow-up scores and the conditions in which these scores had been obtained (for example, off medication or on stimulation). Finally, if the study included the average medication dosage in levodopa equivalents at baseline and follow up, we recorded this information.

Dependent Variables

The primary outcome of interest in our metaanalysis is the UPDRS[17] motor score (Part III) in the off-medication/on-stimulation state. The motor subscale consists of 14 items, with score totals ranging from 0 to 104;[3] higher scores are indicative of greater impairment. This subscale enables assessments of facial expression, speech, tremors, rigidity, gait, posture, and bradykinesia and is scored based on a trained assessor's observation of the patient. This motor outcome score is the most commonly reported in DBS studies and reflects the effect of stimulation on patient motor function without medication. Regarding the more recently published studies—that is, those from 2001 and thereafter—in which UPDRS motor scores were not reported, we attempted to contact the authors to obtain this information, a successful strategy in only three cases.[30,39,74]

Other frequently reported outcomes of interest include the UPDRS ADL score (Part II) and medication requirements based on levodopa equivalents before and after DBS. The UPDRS ADL are self-reported by the patient and focus on activities such as walking, writing, dressing, and speaking. The ADL scores can range from 0 (no functional impairment) to 52 (maximal functional impairment). The levodopa equivalent measure involves converting doses of antiparkinsonian medications into comparable units of levodopa. Most authors refer to the convention of Pahwa, et al.,[55] who stated that 1 unit antiparkinsonian medication = 100 mg standard levodopa = 125 mg sustained-release levodopa = 100 ml liquid levodopa = 1 mg pergolide = 10 mg bromocriptine. These outcomes were examined only in the papers that also included UPDRS motor scores. In one case, we were able to obtain UPDRS ADL scores directly from the authors even though they had not been reported in the paper.[65] Although we tried to reach some authors of earlier reports to obtain additional information, either we were unable to reach these individuals or they no longer had the information we needed.

Analysis of Data

Effect size expresses in terms of SD units the magnitude of a treatment difference between two groups.[25] It allows for comparisons across studies and is commonly used in metaanalyses. In our study, the primary outcome variables were converted to ESs, which were measured using a standardized mean difference between pre- (baseline) and post-DBS (follow up) for each separate outcome for the STN and GPI studies. To calculate ES, the pre- and post-DBS means and

TABLE 1

*Literature review of bilateral STN DBS studies**

Authors & Year	Study Origin	No. of Patients	Mean Patient Age (yrs)†	% Male	Follow Up (mos)	Mean Baseline UPDRS Motor Score†	Follow-Up UPDRS Motor Score†‡	% Change
Limousin, et al., 1995	France	3	52	100	3	58.3 ± 7.6	20.3 ± 16.2	65.2
Krack, et al., 1997	France	15	60 ± 8	60	NA	63.0 ± 15.0§	28.0 ± 15.0§	55.6
Limousin, et al., 1997	France	6	53 ± 4	67	NA	53‖	22 ± 8	58
Krack, et al., 1998[38]	France	8	51 ± 10	63	6	57.5 ± 14.5	17.1 ± 8.2	70.3
Brown, et al., 1999	France & Spain	6	53	67	8.3 (mean)	63.3 ± 11.3§	21.7 ± 8.3§	65.7
Burchiel, et al., 1999	US	6	62.8 ± 12	70**	12	49.0 ± 12	27.4‖	44
Figueiras-Méndez, et al., 1999	Spain	1	68	100	3	51.0	37.0	27.5
Moro, et al., 1999††	Italy	7	57.4 ± 5.5	14	1, 3, 6, & 12	67.6 ± 9.9	43.5 ± 11.5	35.7
Pinter, et al., 1999	Austria	9	56.8 ± 9.6	67	3	60.0 ± 14.3	27.8 ± 5.8	53.7
Houeto, et al., 2000	France	23	53 ± 2	70	6	51.7 ± 14.4	17.1‡‡	66.9
Molinuevo, et al., 2000	Spain	15	60.9 ± 6.8	67	6	49.6 ± 14.0§	16.9 ± 7.0§	65.9
Pillon, et al., 2000	France	48	55.7 ± 7.5	56	3	55.4 ± 12.8	18.1 ± 11.8	67.3
		15	53.5 ± 9.7	67	6	56.1 ± 17.9	19.4 ± 20.4	65.4
Rodriguez-Oroz, et al., 2000	Spain	15	59.9 ± 7.03	80	3, 6, & 12	56 ± 16.42‖	22.4‖	60
Beric, et al., 2001	US	23	58	70	6	33	11	66.6
Broggi, et al., 2001	Italy	17	59 ± 6.06	65	8.2 (mean)	52.07 ± 17.49	32.93 ± 12.99	36.2
DBSPDSG, 2001	multiple countries	96	59 ± 15.1	62	6	54.0 ± 15.1	25.7 ± 14.1	52.4
Krause, et al., 2001	Germany	12	58.7	NA	3, 6, & 12	57.9 ± 4.6	34.6 ± 6.0§§	40.2
Lopiano, et al., 2001	Italy	20	61.2	60	3 & 12	58	25.7	55.7
Volkmann, et al., 2001	Germany	16	60.2 ± 9.8	NA	6	56.4 ± 11.62	18.6 ± 14.12	37.8
Figueiras-Méndez, et al., 2002	Spain	22	57 ± 12	64	12 & 24	49	18	63.3
Iansek, et al., 2002	Australia	10‖‖	54.1 ± 12.6	60	6 & 12	29.5 ± 13.9	18.20 ± 10.94	38.3
Ostergaard, et al., 2002	Denmark	26	59 ± 8	81	3 & 12	51.3 ± 21.1	20.1 ± 13.6	60.8
Simuni, et al., 2002	US	12	58 ± 11	83	3, 6, & 12	43.5 ± 3.6	25.5 ± 2.8	41.4
Thobois, et al., 2002	France	18	56.9 ± 6	50	6 & 12	44.9 ± 13.4	20.2 ± 10	55
Vesper, et al., 2002	Germany	38	55.6	68	1, 6, & 12	48.3	26.8	44.5
Vingerhoets, et al., 2002	Switzerland	20	63 ± 8	70	3, 6, 12, & 24	48.8 ± 14.6	27.1 ± 10.9***	44.5
Bronte-Stewart, et al., 2003	US	19	59.4 ± 9.3	NA	6 & 12	40.4 ± 11.7	8.1 ± 5.0	80
Chen, et al., 2003	China	7	57.3 ± 8.8	86	6	65.7 ± 21.7§	32.8 ± 20.1§	53
Kleiner-Fisman, et al., 2003	Canada	25	57.2 ± 11.7	60	12	50.1 ± 12.3	24.6 ± 7.3	50.9
Varma, et al., 2003	United Kingdom	7	61.0 ± 8.1	100	6	74.29 ± 10.13§§	36.57 ± 14.68§§	61
summary		565	57.8	66	6 (median)			54.3

* All reported probability levels were significant at a value < 0.05; authors of 14 studies did not provide probability values. Abbreviations: DBSPDSG = Deep-Brain Stimulation for Parkinson's Disease Study Group; NA = not available.

† Not all authors reported an SD.

‡ Assessment data used were obtained from the 6-month postintervention follow up or the follow up closest to 6 months postsurgery.

§ Motor scores ranged from 0 to 108 (scores were rescaled in the calculation); otherwise, assume a range from 0 to 104.

‖ Calculation based on other information available.

** This study was a randomized trial; 70% of patients who underwent STN and GPI stimulation were male; the breakdown of sex by surgical site was not provided.

†† Six patients at the 6-month follow up.

‡‡ Follow-up score calculated (reported 67% improvement).

§§ Information provided through email correspondence with author (one patient was lost to follow up).

‖‖ Fourteen patients received DBS, but follow-up data were only available in 10 cases.

*** One patient did not complete the 6-month assessment.

some measure of variance (that is, SD, standard error, or values for tests of significance) were needed.[22] For studies with no variance information, SDs were estimated. The average ratio of means to SDs was obtained from studies that had both means and SDs. Then, SDs were estimated by dividing the means for studies with no variance by the average ratio. To examine the impact of using estimated SDs, the overall ESs between including and excluding the studies with estimated SDs were compared. A test for the homogeneity of outcome variables was performed to address whether all studies shared the same ES. In cases in which results were not homogeneous, the overall mean ES for each outcome was obtained from a random-effects model.[13] To figure statistical significance and to assist in determining the clinical importance of ES, 95% CIs were calculated for each individual study and all studies combined.

Possible sources of heterogeneity were explored by comparing the mean ESs for subgroups of studies categorized according to selected study level characteristics by using a formal random-effects metaregression analysis that included these characteristics as covariates. Subgroup analyses were conducted for the STN and GPI target groups separately, and metaregressions were performed for the STN and GPI combined data. In the metaregression, the dependent variable was the ES for each outcome of interest, and the independent variables were the mean age of the sample, percentage of male participants, study location (European compared with non-European), duration of follow up, study publication year, and study sample size. To evaluate the relative effectiveness of the anatomical target of stimulation (STN compared with GPI) on the UPDRS motor score, this target was included as a covariate in the model. All statisti-

TABLE 2
*Literature review of bilateral GPI DBS studies**

Authors & Year	Study Origin	No. of Patients	Mean Patient Age (yrs)	% Male	Follow Up (mos)	Mean Baseline UPDRS Motor Score†	Follow-Up UPDRS Motor Score†‡	% Change
Limousin, et al., 1997	France	6	50	83	NA	43§	26 ± 11	40
Pahwa, et al., 1997‖	US	3	57	100	3	48 ± 12.77	15.3 ± 11.78	68.1
Ghika, et al., 1998	Swiss	6	55	NA	3, 6, 12, 15, 18, & 24	66.0	31.0	53.0
Krack, et al., 1998[38]	France	5	51	80	6	53.6 ± 10.4	32.5 ± 12.4	39.4
Brown, et al., 1999**	France & Spain	6	50.7	67	8.3 (mean)	54.2 ± 9.2	27.2 ± 12.0	49.8
Burchiel, et al., 1999	US	4	46.5	70	12	67.0 ± 24	40.87§	39
Durif, et al., 1999††	France	6	64	33	6	36 ± 2	23 ± 5	36.1
Kumar, et al., 2000	Canada, France, & Spain	22‡‡	52.7	68	6	53.4 ± 3.3	37.1 ± 3.8	31
Pillon, et al., 2000	France	8	52.5	75	3	55.4 ± 8.5	37.1 ± 13.3	33.0
		5	55.2	60	6	41.6 ± 14.1	27.0 ± 12.5	35.1
DBSPDSG, 2001	multiple countries	38	55.7	71	6	50.8 ± 11.6	33.9 ± 12.3	33.3
Krause, et al., 2001§§	Germany	6	58.5	NA	6	43.8 ± 8.2	39.2 ± 4.9	10.5
Volkmann, et al., 2001	Germany	11	56.6	NA	6	52.5 ± 14.16	22.9 ± 15.48	56.4
Loher, et al., 2002	Switzerland & Germany	10‖‖	64.6	50	3 & 12	63.4 ± 17.4	40.3 ± 10.3	36.4
summary		136	55.0	69	6 (median)			40.1

* All reported probability levels were significant at a value < 0.05, except in Durif, et al., 1999; six studies did not include probability values.
† Not all authors reported an SD.
‡ Assessment data used were obtained from the 6-month postintervention follow up or the follow up closest to 6 months postsurgery.
§ Calculated based on other information available; note that one patient did not complete the 6-month assessment.
‖ Results for three patients with bilateral GPI only; measures were obtained during the on stimulation/on medication state.
** Motor scores ranged from 0 to 108 (scores were rescaled in the calculation); otherwise, assume a range from 0 to 104.
†† This study included one patient who underwent unilateral electrode implantation.
‡‡ Demographic information is based on 22 patients; of these, 17 underwent bilateral and five underwent unilateral surgery. Outcome data were obtained in the 17 bilateral cases only.
§§ Information provided through email correspondence with author (one patient was lost to follow up).
‖‖ There were 16 cases total, of which 10 were bilateral DBS cases.

cal analyses were done using STATA (version 8.2; StataCorp., L.P., College Station, TX).

Results

Description of Studies and Study Patients

We initially identified 65 studies through September 2003, with the first paper on bilateral DBS published in 1995. (Note that some papers were counted more than once if the authors reported findings separately for STN and GPI cases [for example, Krack, et al.[38]]. In one study,[56] there were separate samples of cases in two different geographic locations for both STN and GPI cases, resulting in four sets of findings). Of this total, 20 studies were excluded: five did not include UPDRS motor scores pre- and post-DBS,[10,62–64,71] six consisted of already reported data on patients in another primary DBS study,[2,35,41,49,73,80] five had either only pretest[59,60] or only posttest UPDRS motor scores,[4,20,69] one had on-medication motor scores only,[67] one included uni- and bilateral cases combined,[32] and two involved only unilateral DBS on further inspection.[23,83] As a result, our analysis included 45 studies: 23 with STN targets only, six with GPI targets only, and eight with both STN and GPI targets, although results were reported separately for each target.

The UPDRS motor scores at baseline and postsurgery as well as the characteristics of each study included in the metaanalysis are detailed in Tables 1 (STN) and 2 (GPI). The first report of bilateral DBS was published in 1995.[46] Most of the published studies had been conducted in six European countries, with fewer studies originating in the US, Canada, or elsewhere. Thirty papers and one published abstract on bilateral STN published through September 2003 documented motor function outcomes in patients with PD. Burchiel and colleagues[9] performed the only randomized trial in which STN and GPI targets were directly compared. For purposes of our metaanalysis, however, we report the findings on the site of surgery separately. All other reports were pre- and postintervention studies. The mean sample size per study was 18 patients. The patients had a mean age of 57.8 years at the time of surgery, and 66% of those with an STN target were male. Because most studies (58%) included 6-month postsurgical outcomes, we examined 6-month outcome data or those from the time period closest to 6 months after surgery. If a 6-month follow up had not been conducted, we used data from the 3-month assessment (16%). In some cases 8-month (7%) or 12-month (9%) data only were available.

There were 13 published reports on bilateral GPI DBS (Table 2). Again, most originated in European countries, and all were pre- and postintervention designs with sample sizes ranging from three to 38 patients (mean 10 patients). The mean age of patients was 55 years and 69% were male. Only one GPI study has been published since 2001,[47] whereas one third (11 studies) of the STN reports were published between 2002 and 2003.

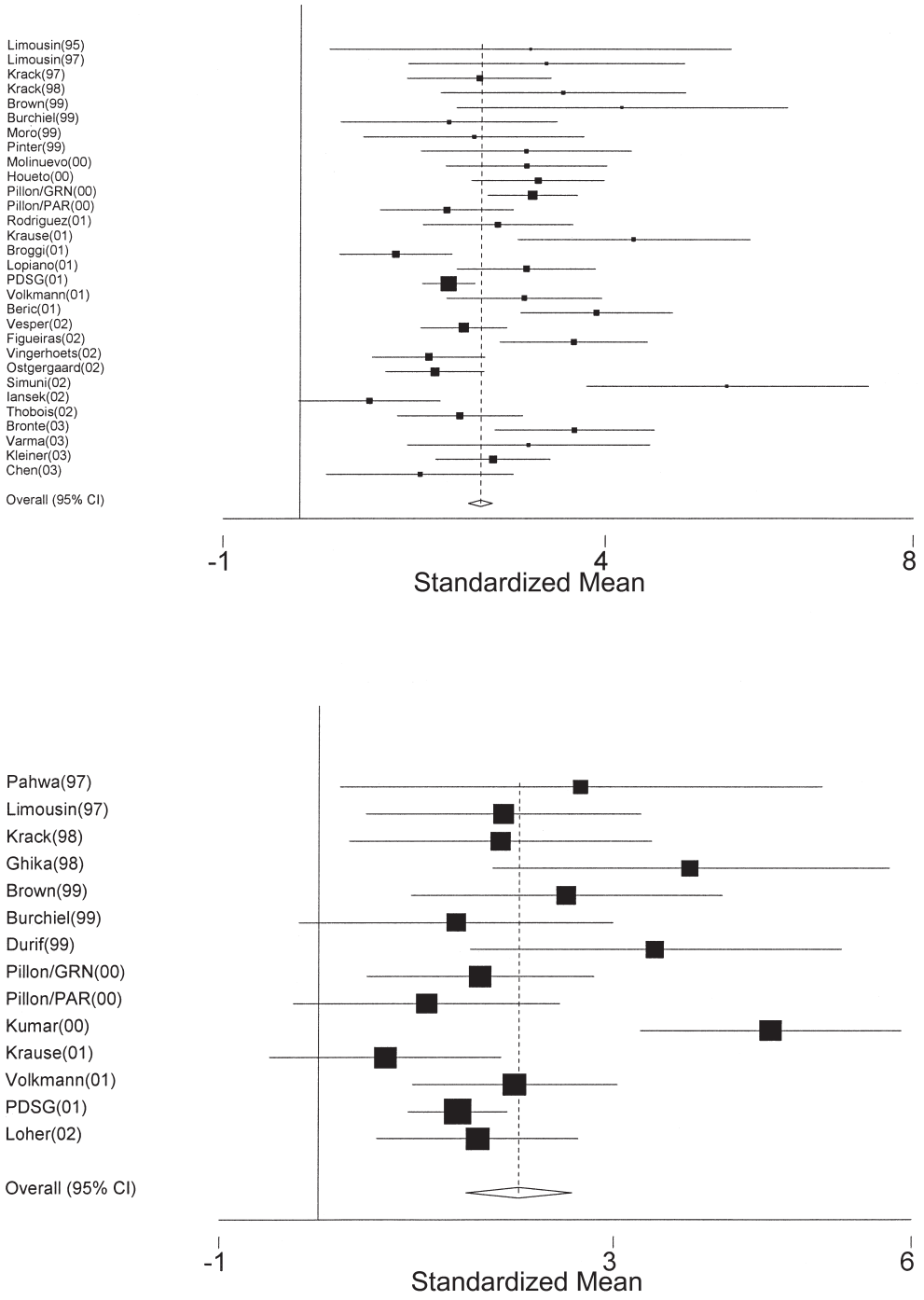

FIG. 1. *Upper:* Graph demonstrating the ESs and 95% CIs for each study and overall, based on the UPDRS motor function in the stimulation on/medication off state in patients who had undergone STN DBS. *Lower:* Graph depicting the ESs and 95% CIs for each study and overall, according to the UPDRS motor function score in the stimulation on/medication medication off state in patients who underwent GPI DBS. Krack(98) refers to Krack, et al., 1998[38] in all figures.

Motor Function According to the UPDRS

As shown in Table 1, all authors documented improvement in motor function following STN DBS, with 50% reporting outcomes at 6 months postintervention. The mean improvement in motor function according to the UPDRS motor score was 54.3%, a decrease from a mean baseline motor score of 51.9 to 22.8 at the follow up. Calculated ESs and 95% CIs for each study and the overall mean ES are presented in Fig. 1 *upper*. Note that the study by Figueiras-Méndez and colleagues[18] had only one patient and so was not included in the ES calculation. Effect sizes of the individual studies ranged from 0.9 to 5.58. The 95% confidence limits of the ESs did not include 0 except for one study. The

overall mean ES calculated from the random-effects model was 2.59 (95% CI 2.23–2.91), which was significantly greater than 0 ($p < 0.001$). The UPDRS motor scores decreased significantly after STN DBS, signifying improved motor function. These studies were not homogeneous in terms of ES ($Q = 92.8$, $df = 29$, $p < 0.001$). The results of subgroup analyses to examine possible sources of heterogeneity showed that there was no significant difference in the ESs when comparing studies conducted in Europe and those in other countries (2.53 compared with 2.77, respectively), studies with a mean patient age of 55 years or younger and those with a mean patient age greater than 55 years (2.62 compared with 2.6, respectively), studies with sample sizes of 10 or fewer patients and those with sample sizes greater than 10 patients (2.44 compared with 2.65, respectively), and studies published between 2001 and 2003 and those published in 2000 or earlier (2.53 compared with 2.74, respectively). The calculated ESs for studies that did not include SDs and those that did were 2.9 and 2.48, respectively (the probability value was not significant).

Similarly, Fig. 1 *lower* provides motor function data for individuals who underwent bilateral GPI stimulation. Six-month follow-up outcomes were reported for most cases. These reports documented a mean UPDRS motor score of 52.2 at baseline and a mean score of 32.5 on follow up, as well as a 40% improvement in motor function in the on-stimulation/off-medication state following GPI DBS (Table 2). Individual ESs ranged from 0.68 to 4.58. There were three studies in which the 95% confidence limits included 0. The overall mean ES from the random-effects model was 2.04 (95% CI 1.5–2.58), which indicated that the UPDRS motor scores significantly decreased following GPI DBS. Again, there was significant heterogeneity between the ESs ($Q = 32.57$, $df = 13$, $p < 0.0021$). Results of subgroup analyses for GPI DBS revealed that the differences in the ESs between subgroups were more pronounced than the differences in the ESs for STN DBS subgroups. Nonetheless, there was no significant difference in the ESs when comparing the studies conducted in Europe and those in other countries (2.07 compared with 1.77, respectively), studies with a mean patient age of 55 years or younger and those with a mean patient age of 55 years (2.48 compared with 1.57, respectively), studies with sample sizes of 10 or fewer patients and those with samples greater than 10 patients (1.81 compared with 2.57, respectively), and studies published between 2001 and 2003 and those published in 2000 or earlier (1.44 compared with 2.42, respectively). The calculated ESs for reports that included no SD and those with SDs were not statistically significant (2.2 compared with 2.01, respectively; probability level not significant).

Patient (age and sex) and study characteristics (study location, duration of study follow up, publication year of study, and sample size) were not significantly associated with the ES for the UPDRS motor score in the metaregression analysis. The surgical target (STN or GPI) was not statistically significant ($p = 0.361$) after adjusting for the aforementioned dichotomous independent variables (excluding sex because five studies were missing this information). When the analysis was repeated including studies with sex information (37 studies) and adjusting for all patient and study characteristics, the surgical target was not significant ($p = 0.743$), indicating that patients in whom either target was used had comparable improvement in motor function following DBS. When STN and GPI sites were compared without adjusting for any covariates, greater improvement was associated with the STN than the GPI, but this result was not statistically significant ($p = 0.09$).

Because of the progressive nature of PD, we were also interested in examining the long-term effects of DBS. Unfortunately, only 11 STN and three GPI studies included 12-month or longer outcomes; therefore, we examined all studies with 12-month outcomes and those with 6-month outcomes if the 12-month results were not available. This approach resulted in 26 STN studies with a mean motor function improvement of 56.5% and 11 GPI studies with a mean functional improvement of 39.8%.[3] The overall ESs (95% CIs) for these studies of STN and GPI targets were 2.63 (2.29–2.97) and 2.21 (1.47–2.95), respectively. Results of a metaregression analysis adjusting for patient and study characteristics (that is, patient age and sex, study origin, year of study, and sample size) revealed that the overall ESs between STN and GPI surgical sites were not statistically different, indicating that stimulation of either of these sites was equally effective in improving motor function. As in the earlier analyses, the ESs between studies were not homogeneous for either STN or GPI reports ($p < 0.001$ for each).

Activities of Daily Living According to the UPDRS

Authors of 50% of the STN DBS studies reported UPDRS ADL scores before and after stimulation in the off-medication state, as did 57% of the authors of the GPI DBS studies. Effect sizes and their 95% CIs for the individual studies are presented in Fig. 2. In all studies, the ESs for STN DBS were positive and none of the 95% confidence limits included 0. The overall mean ES from the random-effects model was 1.81 (95% CI 1.62–2), indicating significant improvement in ADL following STN DBS. Similarly, there was only one negative ES for GPI DBS. The overall mean ES from the random-effects model of GPI studies was 1.48 (95% CI 1.14–1.81), indicating significantly improved ADL functioning after DBS. There was significant heterogeneity for both STN and GPI studies ($p < 0.001$ for each). Results of the subgroup analyses indicated that the ES for studies published in 2000 or earlier was greater than the ES for studies published between 2001 and 2003 (4.03 compared with 1.82, respectively, for STN and 3.89 compared with 1.1, respectively, for GPI). The ES for both STN and GPI studies with a mean patient age of 55 years or younger was greater than that for studies with a mean patient age greater than 55 years. In the metaregression analysis (excluding studies with missing sex information), the ESs for the ADL score were significantly smaller for studies with sample sizes of 10 or fewer patients, those published more recently (2001–2003), and those with a mean patient age greater than 55 years; the remaining independent variables that characterize these studies were not significantly associated with ADL. The site of surgery did not differentially affect improvement in ADL functioning in the off-medication state, with ADL scores improving by a mean of 40% over baseline for both surgical sites. The mean ADL scores in the off-medication state at baseline and follow up were 27.9 and 14.8 for STN DBS studies and 28 and 17.2, respectively, for GPI DBS studies.

Authors of several studies (11 STN and five GPI) also

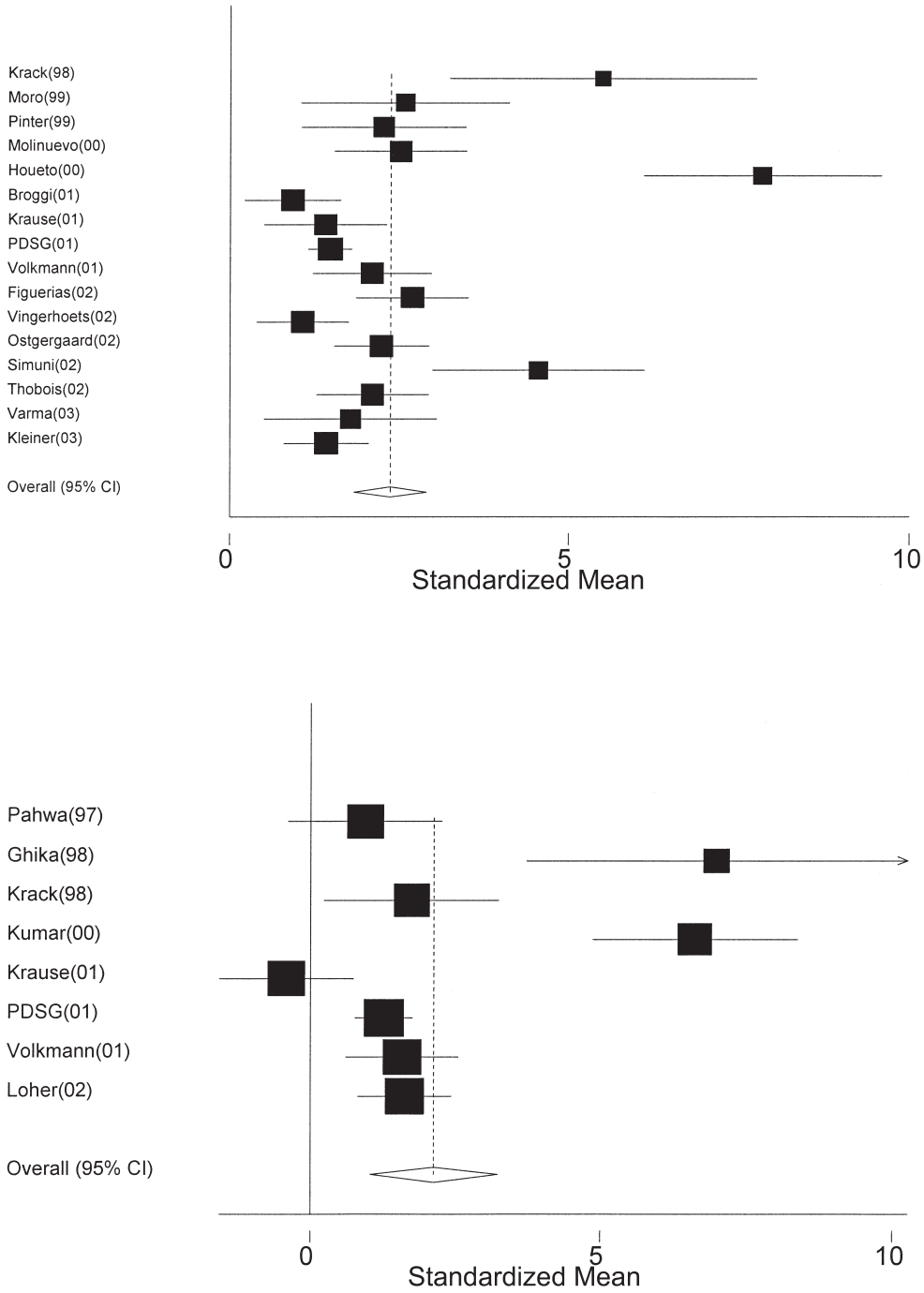

FIG. 2. *Upper:* Graph illustrating ESs and 95% CIs for each study and overall, for STN DBS, according to the UPDRS ADL score in the stimulation on/medication off state in patients who had undergone STN DBS. *Lower:* Graph exhibiting ESs and 95% CIs for each study and overall, based on the UPDRS ADL score in the stimulation on/medication off state in patients who had undergone GPI DBS.

reported UPDRS ADL scores obtained while the patient was on medication at baseline and follow up. Data from the STN studies revealed a decrease from a mean score of 11.3 at baseline to 8.5 at the follow up. Nonetheless, the ES was small (0.61) and the 95% confidence limits for more than half of the studies included 0, indicating that improvement in ADL functioning was not statistically significant. A change in the mean ADL scores from 19.4 to 12.4 in the on-medication/on-stimulation state was noted in the GPI studies. These studies had a mean ES equal to 1.6 and only one of the five studies had a confidence limit that included 0.

Medical Therapy and Levodopa Equivalents

Approximately half of the studies contained information on antiparkinsonian medication use. Authors of these analy-

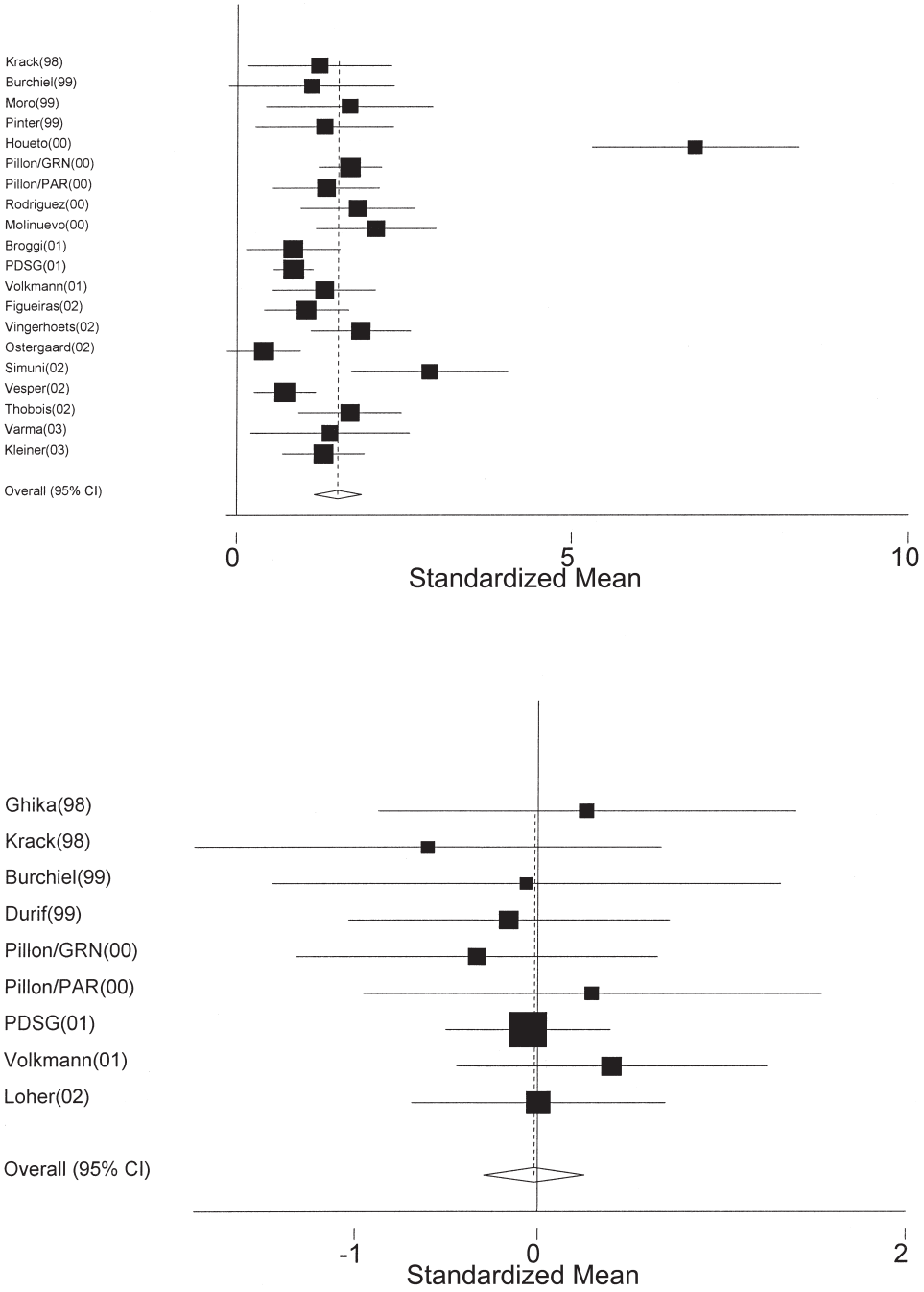

FIG. 3. *Upper:* Graph demonstrating ESs and 95% CIs for each study and overall, according to levodopa equivalents in patients who underwent STN DBS. *Lower:* Graph revealing ESs and 95% CIs for each study and overall, according to levodopa equivalents in patients who underwent STN DBS.

ses converted common PD medication dosages to comparable units called levodopa equivalents.[55] Effect sizes and their 95% CIs for the individual studies are presented in Fig. 3. Effect sizes for STN DBS ranged from 0.39 to 6.83, with an overall mean ES of 1.51 (95% CI 1.15–1.87), indicating a significant reduction in medication use following DBS. On average, authors of these studies reported a 52% reduction in daily medication dosage. Effect sizes for GPI DBS ranged from −0.6 to 0.4, and the mean ES was −0.02 (95% CI −0.29–0.26). The ES was positive in four studies (50%) and all 95% confidence limits included 0, which indicated that in none of the studies was medication use significantly reduced following GPI DBS. There was significant heterogeneity of ESs for STN DBS ($p < 0.001$) but not for GPI DBS ($p = 0.948$).

Discussion

Data from an analysis of several dozen studies of bilateral STN and GPI DBS for PD indicated that motor function

based on the UPDRS motor subscale improves significantly after DBS, regardless of the stimulation target. The beneficial effect was greater, although not statistically significantly so, in STN compared with GPI cases. Medication dosages were reduced by 50% following STN DBS but did not change in patients who had undergone GPI DBS. Activities of daily living functioning improved equally in both groups in the off-medication state; GPI DBS (but not STN DBS) also led to improvement in ADL in the on-medication state.

The results presented in the current metaanalysis should be interpreted cautiously. Only one study was a randomized trial and numerous factors limited our ability directly to compare outcomes according to the anatomical target of stimulation. Among these factors are differences in sample sizes, enrollment criteria, and selection criteria for DBS at one site as opposed to the other (for example, physician and patient preferences or predominant symptom). Physician experience[3] and patient expectations[58] may have a significant impact on outcomes and cannot be assessed in the existing literature. Other factors including targeting techniques, final location of implanted electrodes, and the extent to which stimulation is fine-tuned after DBS can also affect outcomes. This information is neither reported nor easily synthesized when available. Generalization of our findings to the general PD population may be limited, given that the mean age of patients reported in the literature (~ 56 years) and the age at onset of the disease (62.4 years) differ from the average age of the general PD population.[70] Nevertheless, the findings are quite robust; when we excluded certain studies based on sample size, year of study publication, study origin, or duration of follow up, the results remained relatively stable.

A differential effect of the stimulation target was found when medication requirements were examined. Medication requirements decreased in all studies following STN DBS but not following bilateral GPI DBS. We do not know whether STN DBS and GPI DBS have differential effects on medication requirements or whether the difference is an artifact resulting from assumptions about medication needs following stimulation at these sites. In general, STN DBS allows reduced medication without adversely affecting motor function. Furthermore, STN DBS may exacerbate dyskinesias, and reduction of dyskinesias following this therapy is dependent on a reduction in PD medications. In contrast, GPI DBS may have a direct antidyskinetic effect that is not dependent on a reduction in medications, and many providers do not attempt to reduce medication in this group.[79] Whether medications can be reduced following GPI stimulation without negative consequences has not been studied, nor have differences in medication requirements after STN and GPI DBS been compared in a prospective, blinded fashion.

Mounting evidence suggests that medication withdrawal after surgery for PD may not be desirable in all patients. The withdrawal of medication after surgery may exacerbate nonmotor symptoms, especially neuropsychological dysfunction such as affective and personality disorders.[28,34,36,81] In some patients, adverse effects of STN DBS on nonmotor symptoms can negate improvement in motor symptoms. Reinstitution of medical therapy can correct these problems in some patients.[16,34] In light of these observations, data indicating better ADL and disability outcomes in the on-medication state in patients undergoing GPI DBS, compared with STN DBS, are interesting. Our data revealed that patients undergoing GPI and STN DBS had improvement of ADLs in the off-medication state, but only patients who had undergone GPI DBS showed improvement in ADLs while in the on-medication state as well. Burchiel and colleagues[9] reported that medical therapy might have a synergistic effect with GPI but not with STN DBS. The Deep-Brain Stimulation for Parkinson's Disease Study Group[12] reported disability scores (rated separately by physicians and patients) before and after DBS for treatment of PD. The degree of improvement in disability was greater in patients who had undergone GPI DBS than in those who had undergone STN DBS (the degree of significance was not indicated). The better ADL and disability scores in patients who underwent GPI DBS support the presence of a synergistic effect between medical therapy and GPI DBS. Perhaps this result occurs through better control of nonmotor symptoms by continued medication therapy in the patients treated using GPI DBS.

In this metaanalysis we used the UPDRS motor score as its primary measure for a comparison between STN DBS and GPI DBS because this measure is most commonly reported in the published literature pertaining to the surgical treatment of PD. Objective motor function as scored using the UPDRS is relatively easy for physicians to assess but may not be the outcome of greatest functional significance to patients. Other patient and physician-related outcomes that can influence the superiority of DBS at one site compared with another include time in the on state without dyskinesias, functional disability and ADLs, complications of therapy, mood, mentation, and complexity of patient care. Whether the relative superiority of STN DBS in improving functional (UPDRS) motor scores is sufficient in and of itself to place STN DBS at the forefront of surgical therapy for PD remains unsettled. The better UPDRS motor scores achieved through STN DBS must be balanced by the postprocedural potential for increased cognitive dysfunction[26] and greater frequency of mood changes compared with those in patients who undergo GPI DBS.[53,79]

Complications and adverse events of DBS are also important to consider in a comparison of STN and GPI stimulation but were not examined in this metaanalysis. It was not possible to synthesize these findings across studies because not all authors reported adverse events, definitions of any reported adverse events were not uniform across studies, and it was not always possible to distinguish among stimulation effects (modifiable), transient effects, and adverse events that resulted in permanent changes.

Limitations of metaanalyses pertaining to surgery for PD have been described by Bakay.[3] Chief among these limitations is the adverse impact of including poor-quality, nonuniform data in the metaanalysis. Our review of the existing literature reveals significant variability in the quality of published reports. We have tried to minimize the inherent limitations of metaanalyses through careful selection and evaluation of published reports detailing outcomes of STN and GPI DBS. Only those reports that met our strict inclusion criteria were incorporated into the analysis. Some reports may have included patients whose data were also detailed in other publications, but this duplication was not always clear. We therefore attempted to identify and use data only from the most recent, most relevant, and/or most

complete publication. Additionally, in several studies the sample size changed between the baseline and follow-up assessments and it was not always clear on what sample the analysis had been conducted. Although most authors only examined outcomes at a single time point (for example, 6 months postintervention), a few reported outcomes at multiple points (for example, 1, 3, and 12 months post-DBS). We selected the time closest to 6 months postsurgery for all studies to have a more uniform assessment. In fact, 12-month data in some studies showed that the effect of DBS on motor function is greater than that found in assessments closer to the time of surgery (perhaps reflecting fine-tuning of medications and stimulation over time). Furthermore, we included three studies in which the authors did not specifically report when follow up had been conducted. When analyses were redone limiting studies to those with 6- or, preferably, 12-month outcomes, the results did not change. Finally, although we excluded studies that combined unilateral and bilateral cases if the data were not presented separately, we did include one paper in which one patient had received a unilateral implant and the rest of the sample had received bilateral implants.[14] We could not control some factors that directly affect surgical outcomes, such as physician experience, lack of blinded assessments, targeting techniques, location of implanted electrodes, and postoperative stimulation management.

Subthalamic nucleus DBS has gained significant popularity and, based on improvement in motor function and decreased medication requirements, the STN is considered the preferred site of bilateral stimulation by most PD specialty centers. Data from our analysis indicates that motor function improves equally in the GPI-targeted cases, while medication needs do not change. Additional important questions about DBS target sites remain unanswered. What are the effects of the stimulation target site on other outcomes such as cognitive and psychosocial functioning, speech, balance, gait, and quality of life? Do patients value improvement in some symptoms more than others? Are there differential costs and is cost-effectiveness dependent on the target site? Are there differential surgical risks and management complexities? These issues are critically important to the field: DBS is an expensive therapy, its use requires a long-term commitment on the part of patients as well as physicians, and there are many potential candidates for the procedure.

Conclusions

A review of the published literature and the results of our metaanalysis reveal the need for a large randomized controlled trial of STN and GPI DBS to evaluate the relative effectiveness of stimulation targets based on multiple patient outcomes at multiple time points. Within the context of a large randomized trial, patient factors such as age, sex, and race and disease factors such as the predominant symptom (for example, tremor, dyskinesia, or postural instability) that may differentially affect outcomes of DBS can be distinguished. Long-term effects (that is, those present $>$ 1 year postsurgery) of DBS on patient functioning should also be considered. In all likelihood, certain types of patients and/or particular disease symptoms may respond better to stimulation at one target than another, but we cannot determine the difference based on the existing literature. Therapy-specific factors that could influence target selection for DBS might also be identified in a large-scale trial, for instance, incidence and severity of surgical complications, stimulation-related side effects, and management complexity. Given the promise of DBS for long-term management of advanced PD, clinicians and patients should make treatment decisions based on evidence from well-designed trials that minimize bias and provide valid findings to inform clinical practice.

Acknowledgments

We thank Todd Lee, Ph.D., and William Henderson, Ph.D., for their reviews of earlier versions of this paper.

References

1. Anonymous: Management of Parkinson's disease: an evidence-based review. **Mov Disord 17 (Suppl 4):**S1–S166, 2002
2. Ardouin C, Pillon B, Peiffer E, Bejjani P, Limousin P, Damier P, et al: Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. **Ann Neurol 46:**217–223, 1999
3. Bakay R: Metaanalysis, pallidotomy, and microelectrodes. **J Neurosurg 97:**1253–1256, 2002 (Letter)
4. Bejjani BP, Gervais D, Arnulf I, Papadopoulos S, Demeret S, Bonnet AM, et al: Axial parkinsonian symptoms can be improved: the role of levodopa and bilateral subthalamic stimulation. **J Neurol Neurosurg Psychiatry 68:**595–600, 2000
5. Beric A, Kelly P, Sterio D, Rezai A, Mogilner AY, Zonenshayn M: Six-month clinical outcome of bilateral subthalamic deep brain stimulation in Parkinson's disease. **Stereotact Funct Neurosurg 77:**146, 2001
6. Broggi G, Franzini A, Ferroli P, Servello D, D'Incerti L, Genitrini S, et al: Effect of bilateral subthalamic electrical stimulation in Parkinson's disease. **Surg Neurol 56:**89–96, 2001
7. Bronte-Stewart H, Courtney T, McGuire K, Shaw H, Fujikami G, Heit G: Bilateral subthalamic nucleus deep brain stimulation (B-STN DBS) changes the expected course of advanced Parkinson's disease (PD). American Academy of Neurology 55th Annual Meeting, 2003. **Neurology 60 (Suppl 1):**A121, 2003
8. Brown RG, Dowsey PL, Brown P, Jahanshahi M, Pollak P, Benabid AL, et al: Impact of deep brain stimulation on upper limb akinesia in Parkinson's disease. **Ann Neurol 45:**473–488, 1999
9. Burchiel KJ, Anderson VC, Favre J, Hammerstad JP: Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of a randomized, blinded pilot study. **Neurosurgery 45:**1375–1384, 1999
10. Capus L, Melatini A, Zorzon M, Torre P, Carraro N, Moretti D, et al: Chronic bilateral electrical stimulation of the subthalamic nucleus for the treatment of advanced Parkinson's disease. **Neurol Sci 22:**57–58, 2001
11. Chen CC, Lee ST, Wu T, Chen CJ, Chen MC, Lu CS: Short-term effect of bilateral subthalamic stimulation for advanced Parkinson's disease. **Chang Gung Med J 26:**344–351, 2003
12. Deep-Brain Stimulation for Parkinson's Disease Study Group: Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. **N Engl J Med 345:**956–963, 2001
13. DerSimonian R, Laird N: Meta-analysis in clinical trials. **Control Clin Trials 7:**177–188, 1986
14. Durif F, Lemaire J, Debilly B, Dordain G: Acute and chronic effects of anteromedial globus pallidus stimulation in Parkinson's disease. **J Neurol Neurosurg Psychiatry 67:**315–322, 1999
15. Eskandar EN, Flaherty A, Cosgrove GR, Shinobu LA, Barker FG II: Surgery for Parkinson disease in the United States, 1996 to 2000: practice patterns, short-term outcomes, and hospital charges in a nationwide sample. **J Neurosurg 99:**863–871, 2003

16. Esselink RA, de Bie RM, de Haan RJ, Lenders MW, Nijssen PC, Staal MJ, et al: Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: a randomized trial. **Neurology 62:** 201–207, 2004
17. Fahn S, Elton RL: Unified Parkinson's Disease Rating Scale, in Fahn S, Marsden CD, Goldstein M (eds): **Recent Developments in Parkinson's Disease, ed 2.** New York: Macmillan, 1987, pp 153–163
18. Figueiras-Méndez R, Marín-Zarza F, Molina JA, Jiménez-Jiménez FJ, Ortí-Pareja M, Magariños C, et al: Subthalamic nucleus stimulation improves directly levodopa induced dyskinesias in Parkinson's disease. **J Neurol Neurosurg Psychiatry 66:** 549–550, 1999
19. Figueiras-Méndez R, Regidor I, Riva-Meana C, Magariños-Ascone CM: Further supporting evidence of beneficial subthalamic stimulation in Parkinson's patients. **Neurology 58:** 469–470, 2002
20. Fukuda M, Ghilardi MF, Carbon M, Dhawan V, Ma Y, Feigin A, et al: Pallidal stimulation for parkinsonism: improved brain activation during sequence learning. **Ann Neurol 52:**144–152, 2002
21. Ghika J, Villemure JG, Fankhauser H, Favre J, Assal G, Ghika-Schmid F: Efficiency and safety of bilateral contemporaneous pallidal stimulation (deep brain stimulation) in levodopa-responsive patients with Parkinson's disease with severe motor fluctuations: a 2-year follow-up review. **J Neurosurg 89:**713–718, 1998
22. Glass GV, McGaw B, Smith ML: **Meta-Analysis in Social Research.** Beverly Hills: SAGE Publications, 1981
23. Gross C, Rougier A, Guehl D, Boraud T, Julien J, Bioulac B: High-frequency stimulation of the globus pallidus internalis in Parkinson's disease: a study of seven cases. **J Neurosurg 87:** 491–498, 1997
24. Guridi J, Lozano AM: A brief history of pallidotomy. **Neurosurgery 41:**1169–1183, 1997
25. Hedges LV, Olkin I: **Statistical Methods for Meta-Analysis.** San Diego: Academic Press, 1985
26. Hershey T, Revilla FJ, Wernle A, Schneider Gibson P, Dowling JL, Perlmutter JS: STN stimulation-induced impairment in cognitive control in PD. **Society for Neuroscience meetings:** New Orleans, Nov. 12, 2003
27. Houeto JL, Damier P, Bejjani PB, Staedler C, Bonnet AM, Arnulf I, et al: Subthalamic stimulation in Parkinson disease: a multidisciplinary approach. **Arch Neurol 57:**461–465, 2000
28. Houeto JL, Mesnage V, Mallet L, Pillon B, Gargiulo M, du Moncel ST, et al: Behavioural disorders, Parkinson's disease, and subthalamic stimulation. **J Neurol Neurosurg Psychiatry 72:** 701–707, 2002
29. Iacono RP, Lonser RR, Maeda G, Kuniyoshi S, Warner D, Mandybur G, et al: Chronic anterior pallidal stimulation for Parkinson's disease. **Acta Neurochir (Wien) 137:**106–112, 1995
30. Iansek R, Rosenfeld JV, Huxham FE: Deep brain stimulation of the subthalamic nucleus in Parkinson's disease. **Med J Aust 177:** 142–146, 2002
31. Just H, Ostergaard K: Health-related quality of life in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nuclei. **Mov Disord 17:**539–545, 2002
32. Katayama Y, Kasai M, Oshima H, Fukaya C, Yamamoto T, Mizutani T: Double blinded evaluation of the effects of pallidal and subthalamic nucleus stimulation on daytime activity in advanced Parkinson's disease. **Parkinsonism Relat Disord 7:** 35–40, 2000
33. Kleiner-Fisman G, Fisman DN, Sime E, Saint-Cyr JA, Lozano AM, Lang AE: Long-term follow up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson disease. **J Neurosurg 99:**489–495, 2003
34. Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al: Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. **N Engl J Med 349:**1925–1934, 2003
35. Krack P, Benazzouz A, Pollak P, Limousin P, Piallat B, Hoffmann D, et al: Treatment of tremor in Parkinson's disease by subthalamic nucleus stimulation. **Mov Disord 13:**907–914, 1998
36. Krack P, Fraix V, Mendes A, Benabid AL, Pollack P: Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. **Mov Disord 17 (3 Suppl):**S188–S197, 2002
37. Krack P, Pollak P, Limousin P, Benazzouz A, Benabid AL: Stimulation of subthalamic nucleus alleviates tremor in Parkinson's disease. **Lancet 350:**1675, 1997
38. Krack P, Pollak P, Limousin P, Hoffmann D, Xie J, Benazzouz A, et al: Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. **Brain 121:**451–457, 1998
39. Krause M, Fogel W, Heck A, Hacke W, Bonsanto M, Trenkwalder C, et al: Deep brain stimulation for the treatment of Parkinson's disease: subthalamic nucleus versus globus pallidus internus. **J Neurol Neurosurg Psychiatry 70:**464–470, 2001
40. Kumar R, Lang AE, Rodriguez-Oroz MC, Lozano AM, Limousin P, Pollack P, et al: Deep brain stimulation of the globus pallidus pars interna in advanced Parkinson's disease. **Neurology 55 (12 Suppl 6):**S34–S39, 2000
41. Kumar R, Lozano AM, Kim YJ, Hutchison WD, Sime E, Halket E, et al: Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. **Neurology 51:** 850–855, 1998
42. Kumar R, Lozano AM, Montgomery E, Lang AE: Pallidotomy and deep brain stimulation of the pallidum and subthalamic nucleus in advanced Parkinson's disease. **Mov Disord 13 (Suppl 1):** 73–82, 1998
43. Laitinen LV, Bergenheim AT, Hariz MI: Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. **J Neurosurg 76:**53–61, 1992
44. Lang AE, Lozano AM, Montgomery E, Duff J, Tasker R, Hutchinson W: Posteroventral medial pallidotomy in advanced Parkinson's disease. **N Engl J Med 337:**1036–1042, 1997
45. Limousin P, Greene J, Pollak P, Rothwell J, Benabid AL, Frackowiak R: Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. **Ann Neurol 42:**283–291, 1997
46. Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E, et al: Effect on Parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. **Lancet 345:**91–95, 1995
47. Loher TJ, Burgunder JM, Pohle T, Weber S, Sommerhalder R, Krauss JK: Long-term pallidal deep brain stimulation in patients with advanced Parkinson disease: 1-year follow-up study. **J Neurosurg 96:**844–853, 2002
48. Lopiano L, Rizzone M, Perozzo P, Tavella A, Torre E, Lanotte M, et al: Deep brain stimulation of the subthalamic nucleus: selection of patients and clinical results. **Neurol Sci 22:**67–68, 2001
49. Martínez-Martín P, Valldeoriola F, Tolosa E, Pilleri M, Molinuevo JL, Rumiá J, et al: Bilateral subthalamic nucleus stimulation and quality of life in advanced Parkinson's disease. **Mov Disord 17:**372–377, 2002
50. Molinuevo JL, Valldeoriola F, Tolosa E, Rumiá J, Valls-Solé J, Roldán H, et al: Levodopa withdrawal after bilateral subthalamic nucleus stimulation in advanced Parkinson disease. **Arch Neurol 57:**983–988, 2000
51. Moro E, Scerrati M, Romito MA, Roselli R, Tonali P, Albanese A: Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. **Neurology 53:**85–90, 1999
52. Oh MY, Abosch A, Kim SH, Lang AE, Lozano AM: Long-term hardware-related complications of deep brain stimulation. **Neurosurgery 50:**1268–1276, 2002
53. Okun MS, Green J, Saben R, Gross R, Foote KE, Vitek JL: Mood changes with deep brain stimulation of STN and GPi: results of a pilot study. **J Neurol Neurosurg Psychiatry 74:**1584–1586, 2003
54. Ostergaard K, Sunde N, Dupont E: Effects of bilateral stimulation of the subthalamic nucleus in patients with severe Parkinson's disease and motor fluctuations. **Mov Disord 17:**693–700, 2002
55. Pahwa R, Wilkinson S, Smith D, Lyons K, Miyawaki E, Koller WC: High-frequency stimulation of the globus pallidus for the treatment of Parkinson's disease. **Neurology 49:**249–253, 1997

56. Pillon B, Ardouin C, Damier P, Krack P, Houeto JL, Klinger H, et al: Neuropsychological changes between "off" and "on" STN or GPi stimulation in Parkinson's disease. **Neurology 55:**411–418, 2000
57. Pinter MM, Alesch F, Murg M, Seiwald M, Helscher RJ, Binder H: Deep brain stimulation of the subthalamic nucleus for control of extrapyramidal features in advanced idiopathic Parkinson's disease: one year follow-up. **J Neural Transm 106:**693–709, 1999
58. Pollo A, Torre E, Lopiano L, Rizzone M, Lanotte M, Cavanna A, et al: Expectation modulates the response to subthalamic nucleus stimulation in Parkinsonian patients. **Neuroreport 13:** 1383–1386, 2002
59. Rizzone M, Lanotte M, Bergamasco B, Tavella A, Torre E, Faccani G, et al: Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: effects of variation in stimulation parameters. **J Neurol Neurosurg Psychiatry 71:**215–219, 2001
60. Rodriguez MC, Guridi OJ, Alvarez L, Mewes K, Macias R, Vitek J, et al: The subthalamic nucleus and tremor in Parkinson's disease. **Mov Disord 13 (Suppl 3):**111–118, 1998
61. Rodriguez-Oroz MC, Gorospe A, Guridi J, Ramos E, Linazasoro G, Rodriguez-Palmero M, et al: Bilateral deep brain stimulation of the subthalamic nucleus in Parkinson's disease. **Neurology 55 (Suppl 6):**S45–S51, 2000
62. Schuurman PR, Bosch DA, Bossuyt PM, Bonsel GJ, van Someren EJ, de Bie RM, et al: A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. **N Engl J Med 342:**461–468, 2000
63. Scotto di Luzio AE, Ammannati F, Marini P, Sorbi S, Mennonna P: Which target for DBS in Parkinson's disease? Subthalamic nucleus versus globus pallidus internus. **Neurol Sci 22:**87–88, 2001
64. Siegfried J, Taub E, Wellis GN: Long-term electrostimulation of the ventroposterolateral pallidum in the treatment of Parkinson's disease. **Adv Neurol 80:**623–626, 1999
65. Simuni T, Jaggi JL, Mulholland H, Hurtig HI, Colcher A, Siderowf A, et al: Bilateral stimulation of the subthalamic nucleus in patients with Parkinson disease: a study of efficacy and safety. **J Neurosurg 96:**666–672, 2002
66. Speelman JD, Bosch DA: Resurgence of functional neurosurgery for Parkinson's disease: a historical perspective. **Mov Disord 13:** 582–588, 1998
67. Straits-Troster K, Fields JA, Wilkinson SB, Pahwa R, Lyons KE, Koller WC, et al: Health-related quality of life in Parkinson's disease after pallidotomy and deep brain stimulation. **Brain Cogn 42:**399–416, 2000
68. Taha JM, Favre J, Burchiel KJ: Bilateral pallidotomy for the treatment of Parkinson's disease, in Krauss JK, Grossman RG, Jankovic J (eds): **Pallidal Surgery for the Treatment of Parkinson's Disease and Movement Disorders.** Philadelphia: Lippincott-Raven, 1998, pp 173–178
69. Tamma F, Rampini P, Egidi M, Caputo E, Locatelli M, Pesenti A, et al: Deep brain stimulation for Parkinson's disease: the experience of the Policlinico-San Paolo Group In Milan. **Neurol Sci 24:** S41–S42, 2003
70. Tanner CM, Goldman SM: Epidemiology of Parkinson's disease. **Neurol Clin 12:**317–335, 1992
71. Tavella A, Bergamasco B, Bosticco E, Lanotte M, Perozzo P, Rizzone M, et al: Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: long-term follow-up. **Neurol Sci 23 (Suppl 2):**S111–S112, 2002
72. Thobois S, Mertens P, Guenot M, Hermier M, Mollion H, Bouvard M, et al: Subthalamic nucleus stimulation in Parkinson's disease: clinical evaluation of 18 patients. **J Neurol 249:**529–534, 2002
73. Umemura A, Jaggi JL, Hurtig HI, Siderowf AD, Colcher A, Stern MB, et al: Deep brain stimulation for movement disorders: morbidity and mortality in 109 patients. **J Neurosurg 98:**779–784, 2003
74. Varma TR, Fox SH, Eldridge PR, Littlechild P, Byrne P, Forster A, et al: Deep brain stimulation of the subthalamic nucleus: effectiveness in advanced Parkinson's disease patients previously reliant on apomorphine. **J Neurol Neurosurg Psychiatry 74:** 170–174, 2003
75. Vatz JB: **Bilateral Deep Brain Stimulation (DBS) of the Subthalamic Nucleus (STN) or the Globus Pallidus Interna (GPi) for Treatment of Advanced Parkinson's Disease.** Chicago: Blue Cross & Blue Shield Association, 2002
76. Vesper J, Klostermann F, Stockhammer F, Funk T, Brock M: Results of chronic subthalamic nucleus stimulation for Parkinson's disease: a 1-year follow-up study. **Surg Neurol 57:**306–313, 2002
77. Vingerhoets FJG, Villemure JG, Temperli P, Pollo C, Pralong E, Ghika J: Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up. **Neurology 58:**396–401, 2002
78. Vingerhoets G, Lannoo E, van der Linden C, Caemaert J, Vandewalle V, van den Abbeele D, et al: Changes in quality of life following unilateral pallidal stimulation in Parkinson's disease. **J Psychosom Res 46:**247–255, 1999
79. Vitek JL: Deep brain stimulation for Parkinson's disease. A critical re-evaluation of STN versus GPi DBS. **Stereotact Funct Neurosurg 78:**119–131, 2002
80. Voges J, Volkmann J, Allert N, Lehrke R, Koulousakis A, Freund HJ, et al: Bilateral high-frequency stimulation in the subthalamic nucleus for the treatment of Parkinson disease: correlation of therapeutic effect with anatomical electrode position. **J Neurosurg 96:**269–279, 2002
81. Volkmann J, Allert N, Voges J, Weiss PH, Freund HJ, Sturm V: Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. **Neurology 56:**548–551, 2001
82. Volkmann J, Sturm V, Weiss P, Kappler J, Voges J, Koulousakis A, et al: Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. **Ann Neurol 44:** 953–961, 1998
83. Yokoyama T, Sugiyama K, Nishizawa S, Yokota N, Ohta S, Uemura K: Subthalamic nucleus stimulation for gait disturbance in Parkinson's disease. **Neurosurgery 45:**41–49, 1999

Manuscript received November 22, 2004.
Accepted in final form June 6, 2005.
The research reported here was supported by the Department of Veterans Affairs, Veterans Health Administration. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

Address reprint requests to: Frances Weaver, Ph.D., Midwest Center for Health Services and Policy Research, Hines VAMC, P.O. Box 5000 (151H), Hines, Illinois 60141-5000. email: Frances.Weaver@va.gov.