Deep brain stimulation (DBS) has evolved into a mainstream therapy for the treatment of patients with Parkinson disease (PD) since it was approved by the US Food and Drug Administration in 2002. Traditionally, DBS surgery is performed with the patient “awake,” with either indirect targeting (predefined coordinates based on stereotactic anatomical atlases are used for lead placement) or direct targeting (the anatomical structure is visualized and preoperatively selected based on MRI findings). Intraoperative microelectrode recording (MER) and test stimulation are then used to refine lead placement.

ABBREVIATIONS  
DBS = deep brain stimulation; GPI = globus pallidus internus; iCT = intraoperative CT; LEDD = levodopa equivalent daily dosage; MER = microelectrode recording; OFF/ON = off medication, on stimulation; OR = operating room; PD = Parkinson disease; PDQ-39 = 39-item Parkinson’s Disease Questionnaire; SI = single index; STN = subthalamic nucleus; UPDRS-III = Unified Parkinson’s Disease Rating Scale part III.
bidities that preclude awake surgery (e.g., obstructive sleep apnea, claustrophobia, uncontrolled hypertension). In addition, anxiety about being awake for brain surgery may deter some patients who would otherwise benefit from pursuing DBS treatment.

Recently, focus has shifted toward improving the safety and accessibility of DBS for PD patients with the “asleep” DBS technique, which, instead of MER and test stimulation, uses direct targeting coupled with intraoperative imaging for verification of stereotactic accuracy as a surgical end point. Although level 1 evidence has demonstrated that the awake DBS method for PD results in significant improvement in functional outcomes of patients, a persistent criticism of the aspnel DBS technique is that the procedure relies on the assumption that accurately placing a DBS lead at an anatomical target on MRI will correlate with improved outcomes.

Several initial series of PD patients undergoing asleep DBS have demonstrated motor and quality-of-life outcomes comparable to those in historical studies using neurophysiological testing, but few reports have made direct comparisons between asleep DBS patients and control patients undergoing traditional awake surgery. To address this gap, we report clinical outcomes for patients undergoing bilateral subthalamic nucleus (STN) or globus pallidus internus (GPi) stimulation using either awake or asleep DBS at a single institution.

Methods
Study Design

Between May 1, 2012, and January 31, 2016, data were prospectively collected for all consecutive PD patients undergoing GPi and STN DBS performed by the senior author (F.A.P.). Patient candidacy and target selection were determined by a multidisciplinary team that included a movement disorders neurologist, a neuropsychologist, and a neurosurgeon. Decisions on whether to select an STN or a GPi target took into consideration factors such as the presence of mild cognitive impairment, degree of dyskinesias, medication dosages, and severity of medication side effects. These factors were discussed in a multidisciplinary consensus meeting held twice a month.

Inclusion criteria were bilateral DBS electrode placement; age greater than 21 years; an idiopathic PD diagnosis; demonstration of definite clinical response to dopaminergic medication via on-medication and off-medication Unified Parkinson's Disease Rating Scale part III (UPDRS-III) testing; and clinical evidence of disabling motor fluctuations, dyskinesias, or clinically significant functional impairment despite optimal medical therapy. Exclusion criteria were comorbid medical conditions contraindicating surgery, evidence of a poorly controlled mood or psychiatric disorder, and a history of radiation-based therapy or DBS therapy for PD or any other movement disorder. After patients were thoroughly informed about the risks and benefits of both asleep and awake techniques, the decision to undergo awake or asleep DBS was based on the preference of the patient and approval from the movement disorders neurologist (patients were not randomized to DBS technique). This preoperative discussion emphasized that the awake technique is more established, with level 1 evidence to support its efficacy, and that the asleep method is thus far supported only by level 3b and 4 studies and is also considered an off-label use, given that the US Food and Drug Administration approval of DBS stipulates that successful intraoperative test stimulation be performed.

During the preoperative evaluation, patients were asked to return 6 months after surgery for evaluation of motor function and other predetermined functional outcome measures. The primary outcome measure was the stimulation-induced change in motor function 6 months post-surgery, as measured by the change in the UPDRS-III score from the off-medication, off-stimulation (OFF/OFF) state to the off-medication, on-stimulation (OFF/ON) state. A movement disorders clinician who had completed UPDRS training through the International Parkinson and Movement Disorder Society performed all postoperative UPDRS-III evaluations.

Secondary outcome measures were additional medication-induced changes in motor function, measured by the difference in UPDRS-III score between the OFF/ON state and the on-medication, on-stimulation (ON/ON) state; change in quality-of-life scores, measured using the 39-item Parkinson's Disease Questionnaire (PDQ-39) single index (SI) score, 6 months postoperatively compared with baseline; change in levodopa equivalent daily dosage (LEDD) 6 months postoperatively compared with baseline; stereotactic accuracy; stimulation parameters; and adverse events. Adverse events included death, hemorrhage, infection, return to the operating room (OR) for a procedure-related complication, and any other complications noted in the patient's hospital chart or reported at 6-month follow-up. This study was approved by the St. Joseph's Hospital and Medical Center institutional review board. Patients provided written informed consent for their health information to be entered into a prospective database and reviewed in a de-identified manner.

Surgical Technique

For both STN and GPi targets, indirect methods based on anterior commissure–posterior commissure coordinates were used as an initial guide, and targeting was refined based on visualization of anatomical structures. Direct targeting was performed using preoperative MRI (3-T MRI, General Electric or Siemens) coregistered with intraoperative CT (iCT) sequences obtained using a CareTom or BodyTom mobile CT scanner (NeuroLogica). Proton density sequences (2-mm slices) were used for GPi targeting, and T2-weighted sequences (2-mm slices) were used for STN targeting. FrameLink Software (Medtronic) was used to coregister iCT images.

GPi targeting started initially at the anterior commissure–posterior commissure plane, defining a point within the GPi just ventral and slightly medial to the point of conversion between the medial medullary lamina and the accessory lamina. This point was typically approximately 4.5 mm anterior to the midcommissural point, and attention was paid to stay at least 3.6 mm away from the internal capsule, based on the data of Starr and colleagues and Zahodne and colleagues (Fig. 1A). The trajectory and entry point were subsequently planned via a parasag-
FIG. 1. A: Coronal (upper left) and axial (lower left) views of GPi direct targeting at the anterior commissure–posterior commissure plane (upper left and lower left, arrows) and with the electrode in place (upper right and lower right, arrows). B: Coronal (upper left) and axial (lower left) views of GPi targeting at the level of the optic tract (left, arrows) and with the electrode in place (right, arrows). AC = anterior commissure; L0 = contact 0; L1 = contact 1; PC = posterior commissure.
ittal approach, as close to 0° from the coronal plane as possible, just on or anterior to the coronal suture. The trajectory was then adjusted to enter on a gyrus, avoiding the ventricles and sulci, and then extended to the dorsolateral border of the optic tract (Fig. 1B).

STN targeting started initially with atlas-based coordinates: 12 mm lateral to the midline, 2 mm posterior to the midcommissural point, and 4 mm below the midcommissural plane. The target was then modified to be roughly in line with, or slightly anterior to, the ventral border of the red nucleus in the anteroposterior direction, and in the ventral portion of the postero medial corner of the STN on axial views² (Fig. 2). The entry point and trajectory were then selected to be on, or just anterior to, the coronal suture, entering on a gyrus and avoiding the ventricles and sulci.

The Medtronic 3387 electrode was used, with contact 0 placed to target for GPI electrodes and contact 1 placed to target for STN electrodes. Most leads were placed during 1 operation, with the left electrode placed first. For patients with the second electrode placed in a separate operation, clinical outcomes were measured 6 months after placement of the second electrode. As of January 2014, the pulse generator was placed in the same operation after insertion of the electrodes. Prior to January 2014, the generator was placed 7–10 days after insertion of the electrodes. Most patients underwent frame-based (Leksell, Elekta AB) stereotaxy, which is our current standard technique.

For awake patients, the head of bed was positioned at 30° to aid airway patency and facilitate patient comfort. Patients underwent MER and intraoperative test stimulation at 0–10 V, 90-usec pulse width, and 180-Hz frequency. An electrophysiology-trained movement disorders neurologist (R.D.) ran the MER, performed the test stimulation, and interpreted the results. Leads were repositioned if microelectrode tracts were nonconfirmatory, if no clinical benefit was noted, or if the patient had an unacceptably low side-effect threshold. A postplacement iCT was obtained to evaluate and confirm lead placement after skin closure. For asleep patients, the head of bed was maintained at 0° throughout the entirety of the procedure after anesthesia induction. A postplacement iCT was obtained after electrode implantation before skin closure. The radial error was calculated on FrameLink software based on the principal contact. For asleep cases, if the error was ≥ 2 mm, the electrode was repositioned, and another iCT was obtained to reevaluate accuracy. For both awake and asleep cases, the radial error was calculated based on the final lead location relative to the intended stereotactic plan (i.e., if a lead was repositioned in an awake patient based on electrophysiology, the calculated error reflected the distance between the ultimate lead location after repositioning and the preoperatively planned location).

**Case and OR Times**

Case time reflects the time from skin incision to skin closure. OR time refers to the duration from when the patient was wheeled into the OR to the time he or she was wheeled out. Patients undergoing staged electrode placement (n = 9), with each electrode placed in a separate operation, were excluded from this analysis. For patients undergoing battery placement in a second procedure 7–10 days after the initial electrode implantation, the case and OR times for the first bilateral electrode implantation procedure were analyzed. Our practice changed around January 2014 (19 months into the study period), primarily to place the generator during the same operation as the electrodes.

**DBS Programming**

Patients were referred from 21 neurologists, who subsequently performed postoperative neurostimulator programming and medication adjustments 1–2 weeks after implantation of the pulse generator. An initial monopolar review of all electrode contacts was performed. Voltage-limiting side effects and ranges within which PD symptoms improved were documented and used to guide chronic stimulation parameters. Programming frequency and final settings were determined by the clinical assessments and preferences of the neurologists.

**Statistical Analysis**

The cohort was described using counts with percentages and means with standard deviations. Between-group differences were assessed using independent-samples t-tests with corrections applied as appropriate based on Levine’s test for equality. The study was powered at 80% and was sufficient to detect a large effect size of Cohen’s d = 0.9, based on the awake versus asleep STN groups with sample sizes of 13 and 39, and assuming a mean difference of 9.3 ± 10.0, conducted as a 2-sided test with alpha set at 0.05. To validate that unequal group sample size did not impact results, we performed a secondary analysis on the primary outcome with all awake patients and a random subset of the asleep patients to create equal sample sizes. Although these secondary analyses resulted in different means and p values, the significance for all comparisons remained the same (data not shown). Data are presented as mean ± SD; p values < 0.05 were considered statistically significant. IBM SPSS Statistics for Windows (version 22.0, IBM Corp.) was used for analyses. Power analysis was performed using PASS 14 Power Analysis and Sample Size Software (NCSS, LLC).

**Results**

**Patients**

During the study period, 433 patients underwent DBS at our institution. Of these patients, 158 patients underwent bilateral GPI; DBS (38 awake and 120 asleep); 1 awake patient, who presented to us initially for revision surgery, was excluded. Of the remaining 157 patients, 78 (49.7%) returned for 6-month follow-up and were included in this analysis. No significant differences were found in mean age (p = 0.48), sex (p = 0.19), or duration of disease (p = 0.59) between patients who did and did not return for follow-up. Baseline characteristics of the 16 awake and 62 asleep patients included in this study were similar (p ≥ 0.51; Table 1). Most leads were placed during 1 operation; only 4 awake patients and 1 asleep patient underwent staged electrode placement.

Of all 433 patients, 108 patients underwent bilateral
FIG. 2. A: STN direct targeting (arrows) on a T2-weighted MR sequence. Coronal (upper left), axial (lower left), and sagittal (upper right) views. Trajectory view (lower right). B: Post–electrode placement CT scans showing contact 1 placed to target (arrows). Coronal (upper left), axial (lower left), and sagittal (upper right) views. Trajectory view (lower right).
STN DBS (23 awake and 85 asleep); 1 awake patient and 1 asleep patient who underwent initial lead placement at an external facility were excluded. Of the remaining 106 patients, 55 (51.9%) returned for 6-month follow-up and were included in our analysis. No significant differences were found in mean age (p = 0.50), sex (p = 0.84), or duration of disease (p = 0.34) between patients who did and did not return for follow-up. Baseline characteristics of the 14 awake and 41 asleep patients were comparable (p ≥ 0.31; Table 1). Most leads were placed in 1 operation; only 3 awake patients and 1 asleep patient underwent staged electrode placement.

**Motor Function**

In the GPi cohort, complete motor function scores were available for 16 awake and 59 asleep patients. UPDRS-III OFF/OFF scores were not significantly different between awake and asleep groups (p = 0.40). The primary outcome, stimulation-induced change in mean UPDRS-III motor score (OFF/OFF to OFF/ON state), did not differ significantly between awake versus asleep groups for the GPi target, with a 20.8-point improvement for the awake group and an 18.8-point improvement for the asleep group (p = 0.45). The difference in percentage change of the mean score from the OFF/OFF state to the OFF/ON state was not significantly different between awake (38.5%) and asleep (37.5%) groups (p = 0.81; Fig. 3).

In the STN cohort, complete scores were available for 13 awake and 39 asleep patients. The mean UPDRS-III OFF/OFF scores were similar between the groups (p = 0.99). The primary outcome did not differ between awake versus asleep groups, with a 21.6-point improvement in the awake group and a 26.1-point improvement in the asleep group (p = 0.20). The percentage change was also similar between awake (40.3%) and asleep (48.8%) groups (p = 0.06; Table 2 and Fig. 3).

For the GPi patients, after medication was administered (ON/ON state), an additional 8.9-point decrease in mean score was observed in the awake group, and an 8.2-point decrease was observed in the asleep group (p = 0.74). The STN patients had an additional 8.0-point reduction in the awake group and a 7.9-point reduction in the asleep group (p = 0.95; Table 2 and Fig. 3).

**Quality of Life**

In the GPi cohort, baseline and postoperative PDQ-39 data were available for 9 awake and 52 asleep patients. In the STN cohort, complete data were available for 8 awake and 38 asleep patients. The mean baseline scores were similar for the awake and asleep groups for both the GPi (p = 0.74) and STN (p = 0.90) targets (Fig. 4). The mean percentage improvement in PDQ-39 SI at 6 months compared with baseline was similar in both the awake (34.7%) and asleep (32.4%) groups (p = 0.80) for the GPi target. Within the STN cohort, similar improvements were observed in the awake (36.1%) and asleep (37.9%) groups (p = 0.85).

**Medication Reduction**

Medication dosages were available for all patients. The mean LEDD reduction at 6 months compared with baseline was similar between awake and asleep groups for both GPi and STN targets. Baseline medication dosages were similar between awake and asleep patients for both the GPi target (p = 0.58) and the STN target (p = 0.78). For the GPi patients, the mean LEDD reduction was 287 mg (22.2%) for the awake group and 216 mg (17.6%) for the asleep group (p = 0.80 for mean milligram reduction; p = 0.54 for percentage reduction). For the STN patients, the mean LEDD reduction was 425.8 mg (39.6%) for the awake group and 423.0 mg (34%) for the asleep group (p = 0.85 for milligram reduction; p = 0.49 for percentage reduction; Fig. 4).

**Stereotactic Accuracy**

For the GPi cohort, the mean radial error for the awake group (1.0 ± 0.5 mm) was similar to that for the asleep group (1.1 ± 0.4 mm). The mean radial error for the asleep group (1.5 ± 0.6 mm) was also similar to that for the awake group (1.2 ± 0.5 mm).
group (0.8 ± 0.4 mm; p = 0.14). The mean number of brain penetrations was higher in awake patients (1.4 ± 0.6) than in asleep patients (1.1 ± 0.2; p = 0.05). For the STN cohort, the mean radial error was 0.9 ± 0.3 mm for both the awake and asleep groups (p = 0.70), and the mean number of brain penetrations was similar for the awake (1.1 ± 0.2) and asleep (1.1 ± 0.3) patients (p = 0.97). The between-group differences in stereotactic coordinates or trajectory angles were not significant (GPi, p ≥ 0.18; STN, p ≥ 0.15; Table 3).

**Stimulator Settings**

At 6 months, for the GPi cohort, the average amplitude was similar between the awake group (3.3 ± 0.9 V) and the asleep group (3.1 ± 0.9 V; p = 0.50), as were pulse width (awake 80.9 ± 20.8 μsec vs asleep 78.6 ± 15.8 μsec; p = 0.63) and frequency (awake 164.8 ± 23.2 Hz vs asleep 164.5 ± 26.0 Hz; p = 0.96). For the STN cohort at follow-up, amplitude was also similar for the awake group (2.7 ± 0.7 V) and the asleep group (3.0 ± 0.7 V; p = 0.13), as were pulse width (awake 78.8 ± 17.9 μsec vs asleep 68.5 ± 11.0 μsec; p = 0.08) and frequency (awake 162.9 ± 20.4 Hz vs asleep 158.3 ± 20.3 Hz; p = 0.49). For all subgroups (both GPi and STN, awake and asleep), the most frequent active contact was contact 1 for left-sided leads and contact 9 for right-sided leads.

**Case and Operating Room Times**

Case and OR durations are listed in Table 4. Forty-nine patients underwent battery placement in a second operation, and 75 patients underwent generator and electrode placement in 1 procedure. When electrode placement only was evaluated, the asleep group mean case time (127.6 ± 46.1 minutes) was significantly shorter than that for the

---

### Table 2. Primary outcome and additional UPDRS-III motor scores

<table>
<thead>
<tr>
<th>Target</th>
<th>Score</th>
<th>Point Change (% change)</th>
<th>Point Change (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Awake</td>
<td>Asleep</td>
<td>From OFF/OFF to OFF/ON</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p Value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Awake</td>
</tr>
<tr>
<td>GPi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS-III OFF/OFF</td>
<td>54.3 ± 13.3</td>
<td>50.7 ± 15.6</td>
<td>20.8 ± 8.7</td>
</tr>
<tr>
<td>UPDRS-III OFF/ON</td>
<td>33.5 ± 11.9</td>
<td>31.9 ± 12.3</td>
<td>(38.5 ± 13.1)</td>
</tr>
<tr>
<td>UPDRS-III ON/ON</td>
<td>24.7 ± 11.1</td>
<td>23.6 ± 11.9</td>
<td>21.6 ± 7.3</td>
</tr>
<tr>
<td>STN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS-III OFF/OFF</td>
<td>53.7 ± 17.0</td>
<td>53.8 ± 16.4</td>
<td></td>
</tr>
<tr>
<td>UPDRS-III OFF/ON</td>
<td>32.2 ± 12.1</td>
<td>27.6 ± 11.3</td>
<td>40.3 ± 9.9</td>
</tr>
<tr>
<td>UPDRS-III ON/ON</td>
<td>24.2 ± 11.3</td>
<td>19.8 ± 11.1</td>
<td>21.6 ± 7.3</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. There were 16 awake and 59 asleep patients with GPi DBS and 13 and 39 patients, respectively, with STN DBS.
awake group (178.3 ± 44.8 minutes; p = 0.003); however, there was no significant difference in overall average OR time between asleep (215.9 ± 50.7 minutes) and awake (240.6 ± 64.8 minutes) groups (p = 0.20). Among the patients undergoing generator and electrode placement in the same procedure, there were no significant differences in case time (p = 0.15) or OR time (p = 0.78).

### Adverse Events

Adverse events are listed in Table 5. No patient had a hemorrhage, seizure, or infection during the follow-up period, and no patient died during follow-up. In the GPi cohort, 13 adverse events occurred in 7 of 16 patients undergoing awake DBS, and 63 adverse events occurred in 36 of 62 patients undergoing asleep DBS. There were no intergroup differences in type and frequency of events (p ≥ 0.44). Two asleep patients underwent pulse generator revision due to discomfort. In the STN cohort, a total of 16 adverse events occurred in 8 of 14 awake patients, and a total of 41 adverse events occurred in 27 of 41 asleep patients. Two patients underwent battery revision because of discomfort, and 1 patient required unilateral lead repositioning because of unacceptably low motor thresholds discovered during initial programming. With the exception of hypomania (2 awake and 0 asleep patients; p = 0.01), intergroup differences in frequency of specific complications did not differ significantly (p ≥ 0.14). Follow-up documentation did not specify whether adverse events were stimulation related; therefore, the events documented in Table 5, in particular “balance difficulty,” “speech disturbance,” and “hypomania,” may reflect either stimulation-related or procedure-related side effects.

### Discussion

To our knowledge, this report is the first to directly compare functional outcomes between awake and asleep methods for PD patients undergoing either bilateral GPi or STN DBS using an iCT-guided technique for asleep DBS electrode placement. For both GPi and STN targets, we found no differences in motor outcomes, quality-of-life outcomes, degree of medication reduction, stereotactic accuracy, or adverse events between awake and asleep groups.

### Primary Outcome

In patients undergoing GPi stimulation, the primary outcome of stimulation-induced change in UPDRS-III...
score was no different for awake patients (20.8 ± 8.7 points, 38.5% ± 13.1% improvement) and asleep patients (18.8 ± 9.2 points, 37.5% ± 14.1% improvement) (p = 0.45 and p = 0.81, respectively; Table 2). In patients undergoing STN stimulation, we also found no difference in the UPDRS-III score change with stimulation between awake patients (21.6 ± 7.3 points, 40.3% ± 9.9% improvement) and asleep patients (26.1 ± 12.0 points, 48.8% ± 14.5% improvement) (p = 0.20 and p = 0.06, respectively; Table 2).

A recent multicenter European trial of 40 PD patients undergoing bilateral STN stimulation also found no significant difference in motor function outcomes of patients undergoing DBS with general anesthesia and those of patients who underwent DBS under conscious sedation. Additionally, in a study of 14 asleep patients and 68 awake patients undergoing bilateral STN stimulation, Nakajima and colleagues found no difference in the percentage improvement in postoperative OFF/ON UPDRS-III scores compared with preoperative off-medication scores between awake (30.8%) and asleep (52.8%) groups (p = 0.96). For patients who underwent the asleep DBS technique, the percentage of motor score improvement was similar to that previously reported in awake DBS studies (GPi, 28%-33%; STN, 25%-52%).

No significant differences were observed in the percentage of LEDD reduction between awake and asleep groups for either the GPi or STN target. Nakajima et al. also found no difference in degree of LEDD reduction between 68 awake patients and 14 asleep patients undergoing bilateral STN DBS (p = 0.51). Similarly, Saleh et al. compared 23 awake and 14 asleep patients undergoing bilateral STN stimulation and observed no difference in the percentage of postoperative LEDD improvement between awake (38.3%) and asleep (49.3%) groups (p = 0.45).

The mean radial error for asleep DBS in our series was less than 1 mm for both targets (GPi 0.8 ± 0.4 mm, STN 0.9 ± 0.3 mm), which is in line with that in previous reports of MRI- and CT-guided asleep DBS techniques (0.6–1.2 mm). The incidence of specific adverse events did not differ significantly between awake and asleep cohorts. Balance and speech disturbances were the most commonly reported symptoms at 6-month follow-up across all groups, and incidences were in line with those previously published for awake and asleep DBS series.

Although the mean case time for electrode placement was significantly lower for the asleep group than the awake group (215.9 ± 50.7 vs 240.6 ± 64.8 minutes; p = 0.003), the OR time for electrode placement did not differ significantly between groups (215.9 ± 50.7 vs 240.6 ± 64.8 minutes; p = 0.20; Table 4). This finding might be related to the potential effects of surgeon consistency when evaluating case times only, whereas OR times can be influenced by variations in anesthetic practices as well as OR staffing and workflow variables. Although this finding suggests that OR times could potentially become shorter if there was a consistent anesthetic team for each case, it might also reflect the longer duration of time needed to induce general anesthesia and subsequently awaken a patient from the anesthetic compared with the time needed to perform conscious sedation only. The similar case and OR times within the group of patients who underwent a single procedure for electrode and IPG placement may be attributable to factors not captured in our data analysis, such as variations in duration between skin closure for electrode placement and skin incision for IPG placement (which includes stereotactic frame removal, patient positioning, and prepping for the second procedure), and differences in the degree of teaching and resident participation between cases.

Secondary Outcomes

There are limited data comparing the degree of improvement in quality of life between awake and asleep DBS techniques. Foltynie et al. reported a mean 18% improvement in PDQ-39 SI scores 1–2 years after bilateral STN stimulation in 79 asleep DBS patients, which is lower than the mean percentage improvement observed in the present asleep STN group (38%). The higher percentage improvement in our patients may be related to the higher baseline mean PDQ-39 SI score (56.1 points), compared with that of the Foltynie group (30.2 points), and to a follow-up point of 6 months in the current series compared with a follow-up of 1–2 years in their study. Nonetheless, our results are in line with those reported recently by Leccano et al. of 69 patients undergoing awake bilateral STN DBS who had a mean baseline PDQ-39 SI score of 41.1 points and a 36.5% score improvement at 1-year follow-up.
Clinical Implications

Primary and secondary outcomes in this study suggest that it may no longer be merely an assumption that stereotactic accuracy correlates with clinical benefit in asleep DBS. Submillimeter stereotactic error in the asleeep group for both targets correlated with similar improvements in motor function outcomes, quality-of-life outcomes, and medication reduction compared with those in the awake group. Furthermore, the lack of significant difference in stereotactic error between the asleep and awake groups suggests that, regardless of technique, the initial target was consistently being hit. These data support previous results of asleep DBS series that have demonstrated improvements in motor function that are comparable to those of historical awake DBS studies.18,23,28

Limitations

Although this study provides a strong comparison between the 2 DBS implantation techniques, several limitations must be considered. Patients were monitored and data were collected prospectively, with end points for this study defined at the onset. However, patients were not randomized to implantation technique, thus allowing for potential selection and observer bias. Our concurrent attempt at randomization to obtain higher-quality data failed to enroll patients, given that most patients were unwilling to undergo randomization after being fully informed about the risks and benefits of each technique. After the trial failed to reach enrollment levels at 6 months, it was closed (Trial Comparing Functional Outcomes of Awake vs. Asleep Deep Brain Stimulation [DBS] for Parkinson’s Disease; clinicaltrials.gov, registration no. NCT02401308).

Approximately one-half of the patients monitored in our prospective database returned for their 6-month follow-up (GPI, 49.7% [78 of 157 patients]; STN, 51.9% [55 of 106 patients]), resulting in sample sizes smaller than those of previously published randomized DBS trials. The COMPARE (Cognition and Mood in Parkinson Disease) trial had 86.5% follow-up at 7 months (45 of 52 patients);2 the Veterans Affairs study had 87.8% follow-up at 6 months (224 of 255 patients);3 and Follet et al.8 reported 93.3% follow-up at 6 months (279 of 299 patients). Recent smaller asleep DBS series have reported 82.3% follow-up at 6 months (14 of 17 patients)22 and 76.9% follow-up at 12 months (20 of 26 patients).23 Several factors likely contributed to our lower follow-up rates. Perhaps one of the most significant contributors was that all patients undergoing DBS for PD were enrolled in the study (no patient declined to have their outcome data prospectively collected), although we did not require their commitment to return at 6 months as a criterion for enrollment. Outcome evaluations were not conducted in the offices of the patients’ treating or programming neurologists, and the 6-month follow-up visit was purely for research purposes. Therefore, a patient may have decided to opt out of the 6-month follow-up appointment. However, it is certainly also possible that patients experiencing adverse events or programming challenges (i.e., stimulation-related side effects) would be more likely to return for follow-up than patients who were doing well with programming and had no clinical issues. If so, this likelihood may contribute to a selection bias when analyzing the patient group that did undergo follow-up.

Attempts were made to obtain clinical follow-up for patients with mailed letters and telephone reminders; however, patients were not pressured to return. Ultimately, patients may have decided not to return to our clinic for various reasons, including personal inconvenience, other medical issues, or geographic distance (many patients in Arizona live out of state for various parts of the year, and some patients are permanent out-of-state residents). Improved follow-up would likely have required testing to take place in the office of the programming neurologist as part of routine clinical care; however, with 21 referring neurologists, such a requirement would have been impractical and would have introduced the added confounder of interrater reliability. When the first 3 years of the study period (May 2012–April 2015) were subdivided into 12-month increments, the yearly follow-up rate ranged from 48.6% to 56.4% for GPI patients and from 43.9% to 72.2% for STN patients, demonstrating a relatively consistent follow-up rate throughout the study period.

Although UPDRS-III scores were determined by a uniform rater at follow-up, the clinician was not blinded to the DBS technique; thus, the results are subject to observer bias. In addition, postoperative adverse events were not categorized on the basis of whether the event was stimulation related, associated with the underlying PD, or related to another pathology. Thus, the adverse events reported in this series may be either procedure or stimulation related, and we cannot compare differences in stimulation-related adverse events between awake and asleep groups. Furthermore, the “speech disturbances” that were documented were self-reported by patients, rather than captured from an official speech therapist evaluation. Thus, the severity of speech decline could be variable, and the incidence of objective speech disturbances may have been underestimated.

These limitations emphasize the need for caution when interpreting the motor outcome results in correlation with stereotactic accuracy, given that potential stimulation-related side effects (e.g., paresthesias, speech declines), despite good motor outcomes, may reflect suboptimal targeting. Although we speculate that there would be no difference in disabling or bothersome stimulation-related side effects based on the lack of a significant difference in the overall number of speech disturbances, gait and balance abnormalities, and incidences of hypomania that were reported, we were unable to provide a direct subcomparison between awake and asleep groups for each of these adverse events. We have since modified our protocol to specifically distinguish adverse events from stimulation-related side effects.

Lastly, all operations were performed by a single surgeon using the iCT-MRI fusion method for lead placement. Although this treatment approach allows for uniformity in procedural technique, it may limit the generalizability of our results to other institutions. Despite these limitations, an outcomes comparison between a relatively large cohort of awake DBS patients and a control cohort of asleep patients, performed during the same study period at a single institution, provides a valuable addition to the medical lit-
Conclusions

For PD patients undergoing either bilateral GPi or STN DBS, a single-institution experience demonstrates that the asleep DBS technique with patients under general anesthesia correlates with changes in postoperative motor scores, as compared to those of the traditional awake MER-guided technique.

Acknowledgments

We thank Loraine Escalante for her assistance with patient care coordination and the staff of the Neuroscience Publications Office at Barrow Neurological Institute for assistance with manuscript preparation.

References


Disclosures
Ms. Lambert and Dr. Chapple: financial funding from the Barrow Center for Neuromodulation. Dr. Ponce: consultant for Medtronic.

Author Contributions
Conception and design: Ponce, Chen. Acquisition of data: Chen, Mirzadeh, Lambert, Shill, Moguel-Cobos, Tröster, Dhall. Analysis and interpretation of data: Chen, Mirzadeh, Chapple, Shill, Moguel-Cobos, Tröster, Dhall. Drafting the article: Ponce, Chen, Mirzadeh, Chapple. Critically revising the article: Ponce, Chen. Reviewed submitted version of manuscript: Ponce. Statistical analysis: Chen, Chapple. Administrative/technical/material support: Lambert. Study supervision: Ponce.

Correspondence
Francisco A. Ponce: c/o Neuroscience Publications, Barrow Neurological Institute, St. Joseph’s Hospital and Medical Center, Phoenix, AZ. neuropub@barrowneuro.org.