ARTICLE CLASS OF EVIDENCE

Deep brain stimulation in early-stage Parkinson disease

Five-year outcomes

Mallory L. Hacker, PhD, MSCI, Maxim Turchan, MS, Lauren E. Heusinkveld, BS, Amanda D. Currie, MD, Sarah H. Millan, BA, Anna L. Molinari, JD, Peter E. Konrad, MD, PhD, Thomas L. Davis, MD, Fenna T. Phibbs, MD, MPH, Peter Hedera, MD, PhD, Kevin R. Cannard, MD, Li Wang, MS, and David Charles, MD

Correspondence
Dr. Hacker
Mallory.Hacker@vumc.org

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Abstract

Objective

To report 5-year outcomes from the subthalamic nucleus (STN) deep brain stimulation (DBS) in early-stage Parkinson disease (PD) pilot clinical trial.

Methods

The pilot was a prospective, single-blind clinical trial that randomized patients with early-stage PD (Hoehn & Yahr II off medications) to receive bilateral STN DBS plus optimal drug therapy (ODT) vs ODT alone (IDEG050016, NCT0282152, IRB040797). Participants who completed the 2-year trial participated in this observational follow-up study, which included annual outpatient visits through 5 years. This analysis includes 28 patients who were taking PD medications for 6 months to 4 years at enrollment. Outcomes were analyzed using both proportional odds logistic regression and linear mixed effects models.

Results

Early STN DBS + ODT participants required lower levodopa equivalent daily doses ($p = 0.04$, $\beta = -240$ mg, 95% confidence interval [CI] −471 to −8) and had 0.06 times the odds of requiring polypharmacy at 5 years compared to early ODT participants ($p = 0.01$, odds ratio [OR] 0.06, 95% CI 0.00 to 0.65). The odds of having worse rest tremor for early STN DBS + ODT participants were 0.21 times those of early ODT participants ($p < 0.001$, OR 0.21, 95% CI 0.09 to 0.45). The safety profile was similar between groups.

Conclusions

These results suggest that early DBS reduces the need for and complexity of PD medications while providing long-term motor benefit over standard medical therapy. Further investigation is warranted, and the Food and Drug Administration has approved the conduct of a prospective, multicenter, pivotal clinical trial of DBS in early-stage PD (IDEG050016).

Classification of evidence

This study provides Class II evidence that DBS implanted in early-stage PD decreases the risk of disease progression and polypharmacy compared to optimal medical therapy alone.

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From the Departments of Neurology (M.L.H., M.T., L.E.H., A.D.C., S.H.M., A.L.M., T.L.D., F.T.P., P.H., D.C.), Neurosurgery (P.E.K.), and Biostatistics (L.W.), Vanderbilt University Medical Center, Nashville, TN; and Department of Neurology (K.R.C.), Walter Reed National Military Center, Bethesda, MD.

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Glossary

AE = adverse event; **CI** = confidence interval; **CRC** = Clinical Research Center; **DBS** = deep brain stimulation; **FDA** = Food and Drug Administration; **IPG** = implanted pulse generator; **IRB** = institutional review board; **LEDD** = levodopa equivalent daily dose; **ODT** = optimal drug therapy; **OR** = odds ratio; **PD** = Parkinson disease; **PDQ-39** = Parkinson's Disease Questionnaire–39; **STN** = subthalamic nucleus; **TEED** = total electrical energy delivered; **UPDRS-III** = Unified Parkinson's Disease Rating Scale, part III.

Clinical trials evaluating deep brain stimulation (DBS) in mid-stage and advanced-stage Parkinson disease (PD) consistently demonstrate the symptomatic superiority of DBS plus medications vs medications alone, motivating investigations into whether DBS applied in early-stage PD could extend or even enhance its benefits. A prospective, randomized, single-blind clinical trial was conducted at Vanderbilt University Medical Center and was the first investigation into the safety and tolerability of subthalamic nucleus (STN) DBS in early-stage PD (IDEG050016, NCT0282152, IRB040797, CRC1363).[1–8]

Thirty patients with early-stage PD (Hoehn & Yahr II off medication, aged 50–75 years, medication duration 6 months to 4 years, without dyskinesia or other motor fluctuations) were randomized 1:1 to bilateral STN DBS plus optimal drug therapy (ODT) (early STN DBS + ODT) or ODT alone (early ODT) and evaluated every 6 months for 2 years. Medication management for both groups and stimulation measures for participants randomized to receive early STN DBS were performed by the patient's primary neurologist (not the principal investigator), according to standard of care practice and the physician's clinical judgment.

That safety and tolerability study was designed to collect preliminary data on the effects of early STN DBS. The trial met its primary safety endpoint at 24 months,[4] and prior publications describe the study design,[2] enrollment[1] and surgical[5] experiences, primary results,[4,9] and post hoc analyses from the 2-year dataset.[10–12] Results from this pilot trial provided Class II evidence that STN DBS implanted in very early-stage PD slows the progression of rest tremor.[13] This finding, as well as the overall safety and efficacy of DBS in early-stage PD, must next be tested in a large, multicenter clinical trial. The Food and Drug Administration (FDA) has approved the conduct of a prospective, double-blind, placebo-controlled, phase III, pivotal trial evaluating DBS in early-stage PD across 20 US centers (IDEG050016).

Despite numerous prospective, randomized studies demonstrating safety and efficacy of DBS in mid-stage and advanced-stage PD, there are limited reports of long-term follow-up through 5 years. Sustained motor benefits of DBS after 5–10 years have been reported in prospectively followed advanced-stage PD cohorts,[14–17] although none of these studies had a control group randomized to medications alone. Therefore, there are no published reports of long-term follow-up of patients with PD at any stage treated with DBS from a randomized clinical trial.[18] Furthermore, understanding the durability of STN DBS therapy is even more critical when considering its application in early-stage PD due to the added length of time patients would be exposed to the device. The adoption of STN DBS as an adjunctive therapy for early-stage PD will require not only a demonstration of safety and efficacy in a multicenter, pivotal trial but also lasting benefit and safety in studies evaluating the long-term effects of early DBS. This study's objective was to report 5-year outcomes from the safety and tolerability trial of DBS in early-stage PD.

Methods

Standard protocol approvals, registrations, and patient consents

The STN DBS in early PD pilot was a prospective, randomized, controlled, single-blind clinical trial (ClinicalTrials.gov NCT00282152) that was approved by the FDA (IDEG050016) and Vanderbilt institutional review board (IRB) (IRB040797).[4] All 29 participants who completed the 2-year pilot trial provided written informed consent to participate in an observational follow-up study that included annual outpatient visits at 3, 4, and 5 years after baseline (IRB040797).

Participants

Due to a gap in study funding, only 8 early ODT and 9 early STN DBS + ODT participants were evaluated at the year 3 study visit, but all participants completed visits in years 4 and 5. Although 30 participants were randomized, this analysis includes 28 participants who were taking PD medications 6 months to 4 years at enrollment and completed at least 1 follow-up visit: 1 early ODT participant dropped out after the baseline visit, and 1 early STN DBS + ODT participant was discovered after the trial concluded to have not met the inclusion criteria for the medication duration at enrollment, and this participant was excluded from the primary analysis. After completing the 2-year clinical trial, participants in this observational follow-up study were permitted to pursue any standard-of-care treatment for PD, including levodopa infusion pumps or DBS for participants randomized to the early ODT group.

Assessments

Participants returned to the Vanderbilt Clinical Research Center (CRC) for annual outpatient study visits at years 3, 4, and 5, undergoing evaluations similar to the day 1 assessments conducted during the initial 2-year trial.[4] The Unified

Parkinson's Disease Rating Scale, part III (UPDRS-III) was videotaped on therapy (on medications, on stimulation, if applicable), and all video assessments were scored in a randomized, blinded manner at the conclusion of the follow-up study by the same rater who evaluated UPDRS-III for the first 2 years of the pilot trial (K.R.C.).[4] All items of the motor examination were scored except for rigidity, which cannot be evaluated by videotape. Levodopa equivalent daily dose (LEDD) was calculated as previously described.[19] Total electrical energy delivered (TEED) was calculated using the formula (voltage^2 × frequency × pulse width)/impedance.[20] Stimulation amplitude (voltage) and TEED for each participant was averaged between left and right leads. One participant was missing impedance values on one side of the brain at year 4. All adverse events (AEs) collected at years 3, 4, and 5 were coded using the preferred term in the Medical Dictionary for Regulatory Activities (MedDRA)[21] and classified as mild, moderate, severe, or serious.

Statistical analysis

This analysis was conducted to provide Class II evidence of the long-term effect of STN DBS on disease progression and medication utilization when applied in very early-stage PD. In this intention-to-treat analysis, participants were evaluated in the treatment group to which they were randomized. Statistical analyses were performed using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

A proportional odds logistic regression model was used with assessment scores as the outcome and baseline score, time, and treatment assignment as the independent variables. Interactions between treatment assignment and time were not included in the model due to the small sample size (n = 28). Because each participant had multiple assessments throughout the study period, the Huber-White cluster sandwich covariance estimator was used with each participant as a cluster in order to adjust the variance of the model to account for these repeated measures. A linear mixed effects model was used to compare the overall trend in outcomes for the 2 groups that included fixed effects of baseline value, time, and treatment assignment, random effects of participants, and an autoregressive covariance structure to account for repeated measures at baseline and 6-, 12-, 18-, 24-, 36-, 48-, and 60-month evaluations for each participant. Polypharmacy status was defined, per participant, as being prescribed more than 1 class of PD medication at the study visit.[11,22] Fisher exact test was used to compare baseline and 5-year polypharmacy status between the groups.

Dyskinesia was considered present at the study visit if a participant had a score of ≥1 on item 32 of the UPDRS part IV.[23] Fisher exact tests were used to compare presence of dyskinesia at baseline and 5 years. Presence and severity of dyskinesia was defined as the sum of UPDRS section IVa (items 32–35; range 0–13)[24] and, due to the small number of distinct observed values, the same proportional odds logistic regression model as previously described was used. Following completion of the study, it was discovered that UPDRS-IV question 36 was incorrectly worded. Sensitivity analyses were conducted to exclude UPDRS-IV question 36, and the exclusion of this question did not affect results of this report or prior publications.[4,10] Sensitivity analyses were also conducted including the STN DBS + ODT participant who did not meet inclusion criteria, excluding rest tremor from the UPDRS-III score, excluding scores prior to implanted pulse generator (IPG) replacements, and as-treated to account for the temporal crossover to bilateral STN DBS for a subset of early ODT participants. In all cases, p values less than 0.05 were considered significant.

Data availability

The individual de-identified participant data and related study documents are not being publicly shared at this time as they are currently being used for the development of a proprietary, multicenter, phase III, pivotal clinical trial (IDE G050016).

Results

Participant follow-up

At the 5-year study visit, the 28 participants from the STN DBS in early-stage PD pilot trial analyzed were 66.1 ± 6.4 years old and had been taking PD medications for 7.2 ± 1.2 years. There were no deaths through 5 years of follow-up. Four participants who were randomized to early ODT elected to receive bilateral STN DBS as standard of care prior to study visits at year 3 (n = 1), year 4 (n = 2), and year 5 (n = 1). These 4 participants were evaluated in the treatment group assigned at randomization, following an intention-to-treat analysis comparing early STN DBS + ODT (intervention) to early ODT (standard of care).

Clinical outcomes

Annual clinical assessments for early ODT and early STN DBS + ODT groups are reported in table 1. Groups were compared using both proportional odds logistic regression and linear mixed effect models (table 2 and table 3, respectively) for UPDRS (I–IV, total), LEDD, and Parkinson's Disease Questionnaire–39 (PDQ-39) Summary Index. The odds of having worse motor symptoms (UPDRS-III) through 5 years among early STN DBS + ODT participants were 0.42 times those of early ODT participants (p = 0.08, odds ratio [OR] 0.42, 95% confidence interval [CI] 0.15 to 1.12). The between-group difference in mean UPDRS-III score due to randomization was 3.70, which represents a clinically important difference[25] (p = 0.12, β = −3.70, 95% CI −8.42 to 1.01; figure 1A).

Symptomatic rest tremor control

Because the pilot trial provided Class II evidence that early STN DBS + ODT slows the progression of rest tremor,[13] the on therapy rest tremor item of the UPDRS-III was evaluated separately. The odds of having worse rest tremor for early STN DBS + ODT participants were 0.21 times those of early ODT participants (p < 0.001, OR 0.21, 95% CI 0.09 to 0.45). In addition, the between-group difference in mean rest tremor score favored participants randomized to early STN DBS +

Table 1 Annual outcomes

	Early ODT							Early STN DBS + ODT						
Outcome	**Baseline**	**1 y**	**2 y**	**3 y**	**4 y**	**5 y**	**Δ Baseline to 5 y**	**Baseline**	**1 y**	**2 y**	**3 y**	**4 y**	**5 y**	**Δ Baseline to 5 y**
No.	14	14	14	8	14	14	14	14	14	14	8	14	14	14
Hoehn & Yahr	1.8 (0.4)	2.0 (0.1)	2.1 (0.4)	2.2 (0.4)	2.2 (0.3)	2.3 (0.3)	0.5	1.7 (0.5)	2.0 (0.1)	2.2 (0.2)	2.1 (0.2)	2.3 (0.4)	2.4 (0.3)	0.7
Schwab & England	90.7 (5.5)	89.6 (4.1)	86.8 (8.9)	86.2 (7.4)	86.4 (4.6)	83.2 (10.3)	−7.5	91.8 (3.7)	90.7 (4.3)	90.0 (6.5)	90.6 (6.3)	89.3 (6.5)	83.2 (8.9)	−8.6
UPDRS-I	1.8 (1.2)	2.2 (1.3)	2.9 (2.0)	2.9 (1.8)	2.4 (1.9)	2.5 (1.2)	0.7	1.7 (1.4)	2.9 (2)	2.7 (2.1)	2.9 (2.5)	3.2 (2.1)	3.0 (1.9)	1.3
UPDRS-II	7.9 (4.6)	8.2 (4.9)	10.2 (5.9)	8.2 (4.7)	10.4 (5.2)	13.3 (5.1)	5.4	8.7 (4.3)	9.8 (5.1)	11.8 (6.5)	13.1 (7.2)	12.5 (5.7)	16.4 (5.8)	7.7
UPDRS-III "on"[a]	21.3 (9.2)	25.0 (10.5)	24.4 (9.5)	23.8 (10.9)	24.9 (9.0)	28.4 (9.5)	7.1	24.8 (12.0)	23.5 (11.5)	25.1 (13.2)	23.7 (11.0)	23.3 (9.7)	26.5 (11.9)	1.7
UPDRS-IV	1.9 (1.9)	2.5 (2.1)	3.8 (2.2)	4.0 (1.9)	4.6 (2.4)	4.1 (2.7)	2.2	2.0 (2.0)	2.5 (3.4)	2.4 (1.6)	3.9 (3.4)	3.1 (1.8)	4.4 (2.8)	2.4
Total UPDRS[b]	33.4 (13.3)	37.9 (13.2)	41.2 (16.2)	38.9 (11.3)	42.4 (12.9)	48.3 (13.1)	14.9	37.2 (15)	38.7 (14.6)	41.9 (18.5)	43.6 (17.2)	42.1 (13.7)	50.3 (16.9)	13.1
Timed test, dominant, s	69.1 (15.6)	72.4 (18.4)	70.6 (18.8)	70 (15.9)	65.2 (13.3)	59.4 (12.9)	−9.7	65.6 (13.7)	65.9 (18)	64.7 (21.6)	63.9 (22.8)	64.2 (13.2)	62.9 (16.5)	−2.7
Timed test, nondominant, s	62.0 (11)	64.4 (14.2)	65.1 (17.1)	63.4 (15.5)	67.8 (12.0)	60.4 (12.9)	−1.6	63.5 (11.3)	64.7 (14.1)	62.6 (17.5)	63.6 (11.8)	65.2 (21.0)	62.6 (21.3)	−0.9
Stand-walk-sit steps	19.0 (3.6)	18.4 (3.3)	17.9 (3.5)	18.0 (2.1)	21.0 (6.2)	18.6 (3.2)	−0.4	19.0 (3.1)	18.8 (5.1)	18.8 (3.8)	18.8 (3.1)	18.8 (3.8)	21.0 (5.4)	2.0
Stand-walk-sit time, s	11.7 (2.8)	12.6 (3.5)	11.8 (3.1)	11.6 (1.8)	13.6 (3.4)	13.1 (3.0)	1.4	12.3 (2.7)	12.8 (2.5)	13.6 (3.6)	13.8 (3.3)	13.9 (3.3)	15.7 (6.1)	3.4
LEDD, mg	490.7 (216.2)	641.1 (319.5)	705.2 (377.1)	946.6 (545.3)	964.9 (472.2)	1,157.8 (677.5)	667.1	409.0 (316.4)	462.1 (345.3)	526.7 (313.0)	715.2 (493.1)	676.1 (520.2)	773.6 (590.3)	364.6
PDQ-39 Summary Index	13.4 (9.1)	16.4 (12.4)	22.0 (18.1)	24.4 (9.1)	21.4 (13.6)	26.2 (15.7)	12.8	13.7 (10.7)	20.8 (14.7)	19.8 (14.3)	27.4 (14.9)	27.0 (15.1)	28.9 (16.1)	15.2

Abbreviations: DBS = deep brain stimulation; LEDD = levodopa equivalent daily dose; ODT = optimal drug therapy; PDQ-39 = Parkinson's Disease Questionnaire–39; STN = subthalamic nucleus; UPDRS-III = Unified Parkinson's Disease Rating Scale, part III.
Values are mean (SD).
[a] Excludes rigidity.
[b] UPDRS total reported as the sum of UPDRS parts I, II, III, and IV.

Table 2 Proportional odds analysis

Outcome	OR (95% CI)	*p* Value
UPDRS I	1.34 (0.49–3.66)	0.56
UPDRS II	1.62 (0.57–4.64)	0.37
UPDRS III	0.42 (0.15–1.12)	0.08
UPDRS IV	0.65 (0.29–1.43)	0.28
Total UPDRS	0.75 (0.28–2.00)	0.56
LEDD, mg	0.26 (0.09–0.78)	0.02
PDQ-39 SI	1.38 (0.48–3.98)	0.56

Abbreviations: CI = confidence interval; LEDD = levodopa equivalent daily dose; OR = odds ratio; PDQ-39 SI = Parkinson's Disease Questionnaire–39 Summary Index; UPDRS = Unified Parkinson's Disease Rating Scale.
Model adjusted for baseline scores; n = 28.

ODT (p = 0.005, β = −2.0, 95% CI −3.4 to −0.7; figure 1B). Without rest tremor included in the UPDRS-III score, there were no between-group differences in the odds of having worse motor symptoms (p = 0.40, OR 0.65, 95% CI 0.24 to 1.79) or in the magnitude of difference in motor symptom score (p = 0.45, β = −1.49, 95% CI −5.48 to 2.50).

Medications

LEDD for early ODT participants was 491 ± 216 mg at baseline and increased to 1,158 ± 678 mg at 5 years (+667 mg; table 1). Mean LEDD for the early STN DBS + ODT group increased from 409 ± 316 mg at baseline to 774 ± 590 mg at 5 years (+364 mg).

The odds of requiring a greater LEDD for early STN DBS + ODT participants were 0.26 times those of early ODT participants (p = 0.02, OR 0.26, 95% CI 0.09 to 0.78; table 2), with the between-group difference in mean LEDD significantly favoring the early DBS + ODT group (p = 0.04, β = −240 mg, 95% CI −471 to −8; figure 2A and table 3).

Table 3 Mixed effects model analysis

Outcome	Estimate (95% CI)	*p* Value
UPDRS I	0.49 (−0.54 to 1.52)	0.34
UPDRS II	2.25 (−1.0 to 5.5)	0.17
UPDRS III	−3.70 (−8.42 to 1.01)	0.12
UPDRS IV	−0.26 (−1.20 to 0.69)	0.58
Total UPDRS	−1.19 (−8.25 to 5.87)	0.73
LEDD, mg	−239.65 (−471.39 to −7.91)	0.04
PDQ-39 SI	1.83 (−5.32 to 8.98)	0.60

Abbreviations: CI = confidence interval; LEDD = levodopa equivalent daily dose; OR = odds ratio; PDQ-39 SI = Parkinson's Disease Questionnaire–39 Summary Index; UPDRS = Unified Parkinson's Disease Rating Scale.
Model adjusted for baseline scores; n = 28.

At baseline, there was no difference between groups in the need for polypharmacy (p = 1.0). By 5 years, 93% of early ODT participants (13/14) required polypharmacy compared to 43% (6/14) of early STN DBS + ODT participants (figure 2B). The odds of requiring polypharmacy after 5 years for early STN DBS + ODT participants was 0.06 times those of early ODT participants (p = 0.01, OR 0.06, 95% CI 0.00 to 0.65).

STN stimulation

Average stimulation amplitude for the early STN DBS + ODT group started at 1.6 ± 0.2 V after surgery (6 months) and increased to 1.9 ± 0.3 V by 24 months.[4] Pulse width was fixed at 60 μs and rate remained at 130 Hz during the first 2 years. By year 5, mean amplitude for participants randomized to early STN DBS + ODT increased to 2.4 ± 0.7 V, and pulse width and frequency parameters during the follow-up study period ranged from 60 to 90 μs and 100 to 160 Hz, respectively. Mean TEED was 59.2 ± 44.5 μJ/s at year 4 and 64.7 ± 50.3 μJ/s at year 5.

Three early STN DBS + ODT participants had IPG replacements during the follow-up study at the following times in relation to scheduled study visits: 1 day after the year 4 visit, 6 months before the year 5 visit, and 1 month after the year 5 visit. A sensitivity analysis was conducted where these 2 UPDRS-III scores collected prior to IPG replacements were discarded; removing these scores did not affect the results of the primary analysis. There were no device failures during the 5-year study period.

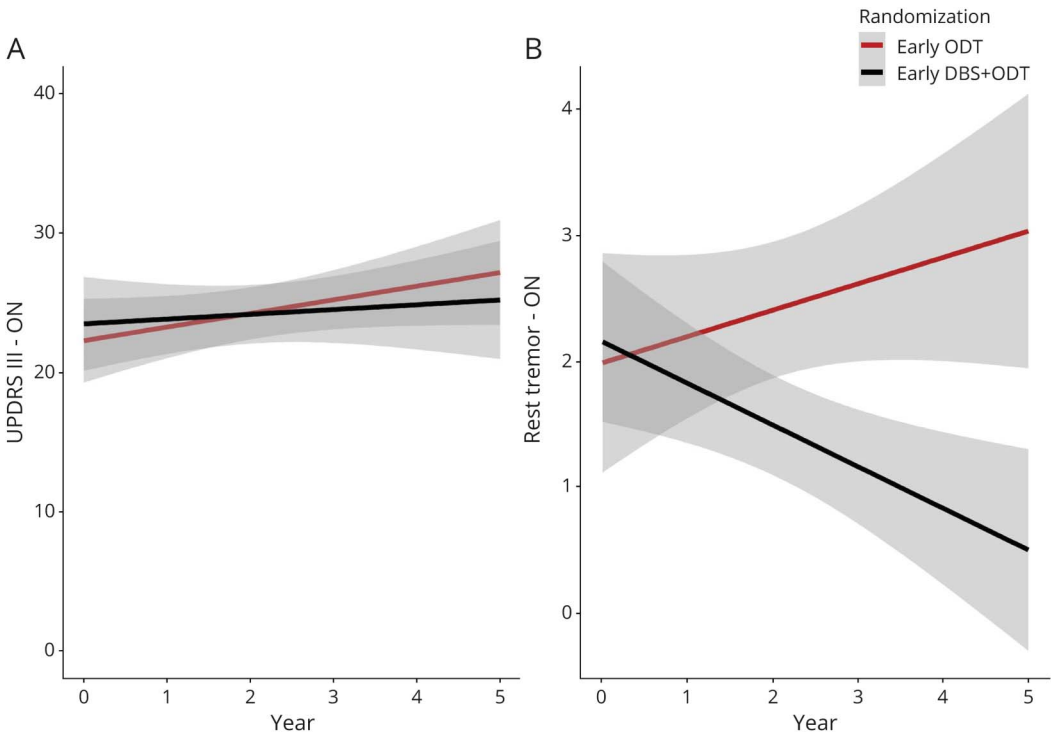
Dyskinesia emergence

Based on the significantly lower LEDD and reduced odds of requiring polypharmacy for early STN DBS + ODT participants compared to early ODT (figure 2), an analysis of the development of dyskinesia was conducted. There was no difference between groups in the presence of dyskinesia at baseline (p = 1.0). At 5 years, dyskinesia was present in 50% of early ODT participants (7/14) compared to 21% (3/14) of early STN DBS + ODT participants, but this was not statistically significant (p = 0.24). The odds of having worse dyskinesia (UPDRS-IVa) for early STN DBS + ODT participants were 0.35 times those of early ODT participants (p = 0.06, OR 0.35, 95% CI 0.12 to 1.06; figure 3).

Adverse events

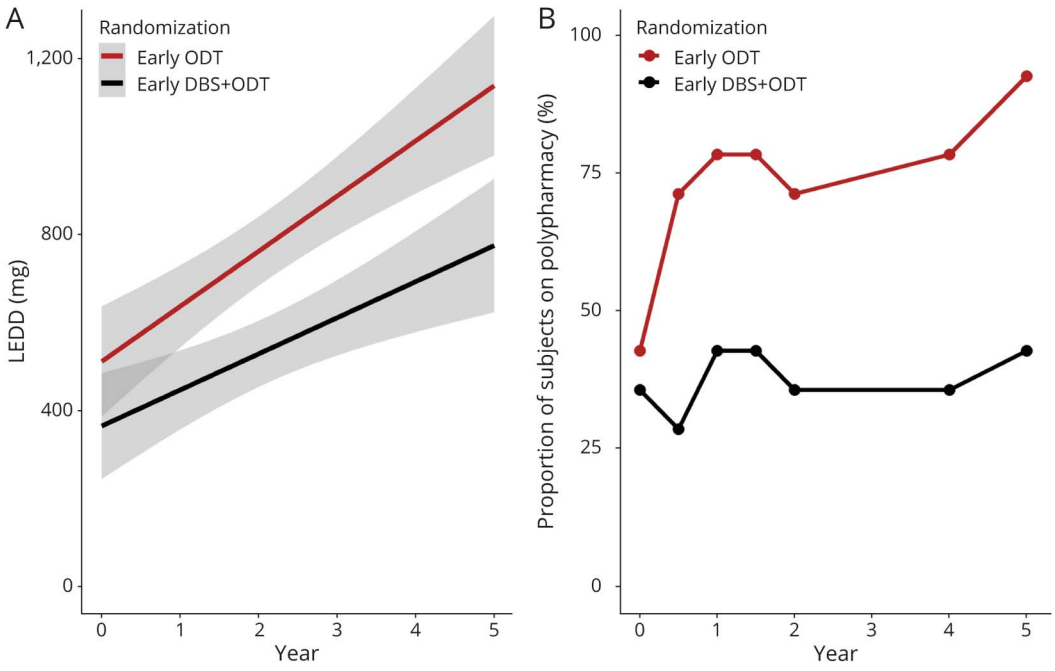
AEs from baseline to 2 years were previously reported.[4,5] The AE profile in this follow-up study was similar between the groups (table e-1, doi.org/10.5061/dryad.0p2ngf1w8). There were 134 AEs identified in the follow-up study: 66 in the early DBS + ODT group and 68 in the early ODT group (18 of which occurred in the 4 early ODT participants after receiving STN DBS surgery as standard of care). Five of the 134 AEs were related to the surgery or device: 3 in early ODT participants who received STN DBS during the extension study follow-up (cognitive disorder, confusional state, pneumocephalus) and 2 in the early STN DBS + ODT group

Figure 1 Motor symptoms



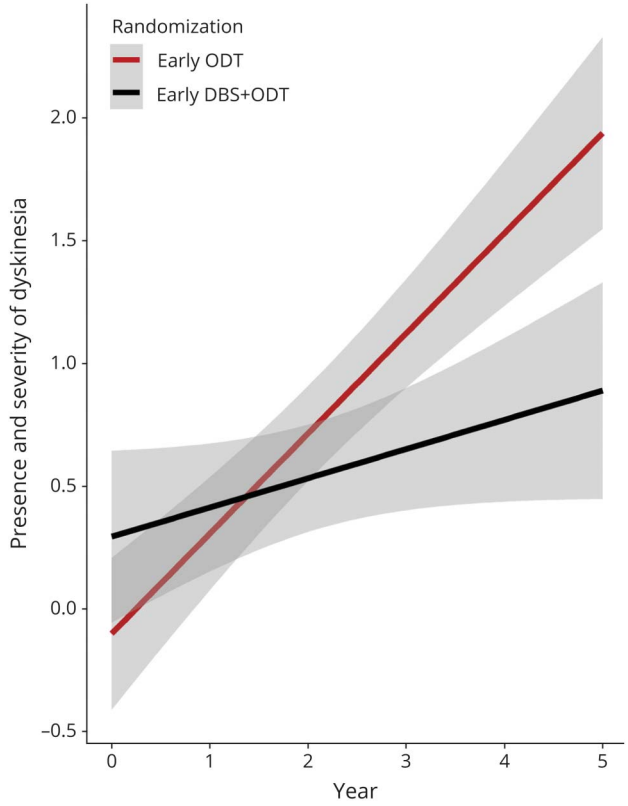
(A) Single-blind motor examination (Unified Parkinson's Disease Rating Scale, part III [UPDRS-III]) scores, baseline through 5 years (p = 0.12, β = −3.70, 95% confidence interval [CI] −8.42 to 1.01). (B) Single-blind rest tremor (UPDRS-III item 20) scores, baseline through 5 years (p = 0.005, β = −2.0, 95% CI −3.4 to −0.7). DBS = deep brain stimulation; ODT = optimal drug therapy.

Figure 2 Parkinson disease medications



(A) Levodopa equivalent daily dose (LEDD) (mg), baseline through 5 years (p = 0.04, β = −240 mg, 95% confidence interval −471 to −8). (B) Proportion of participants requiring polypharmacy at each annual study visit. DBS = deep brain stimulation; ODT = optimal drug therapy.

Figure 3 Presence and severity of dyskinesia



Baseline through 5 years (Unified Parkinson's Disease Rating Scale, part IV items 32–35). DBS = deep brain stimulation; ODT = optimal drug therapy.

(postprocedural hematoma, medical device site scar). Of 13 study-related AEs, the most common was nausea (n = 2 in early STN DBS + ODT, n = 1 in early ODT). Of 116 unrelated AEs, the most common was depression (n = 3 in early STN DBS + ODT, n = 3 in early ODT).

Discussion

Five-year outcomes from the first and only clinical trial of STN DBS in early-stage PD are reported, which represents the longest outcomes data published from a prospective, randomized, controlled clinical trial of DBS implanted in any stage of PD. Despite its novelty, this study is inherently limited by its small sample size and the open-label, single-blind design of the original pilot trial. Only 61% of patients (17/29) completed the year 3 assessments due to a gap in funding between the trial and the observational follow-up study, but all participants completed visits at years 4 and 5. Four participants originally randomized to early ODT elected to receive bilateral STN DBS during the follow-up period, and this crossover is acknowledged as a limitation. An as-treated sensitivity analysis was conducted accounting for the temporal crossover of those 4 participants to STN DBS + ODT, and the addition of DBS as standard of care for a subset of early ODT participants did not affect the outcomes of this study. The only measure of dyskinesia from the pilot trial was the patient-reported UPDRS-IV, which may underestimate the amount of dyskinesia in this cohort because patients may not know they are experiencing this complication.[26]

Importantly, the AE profile was similar between the groups in this follow-up study, which provides preliminary data to suggest long-term safety of early STN DBS therapy. There were also no statistically significant differences between the randomized groups in UPDRS scores (parts I–IV, total) and PDQ-39. A multicenter, phase III clinical trial with adequate statistical power is required to evaluate the efficacy of early STN DBS + ODT on the progression and symptomatic control of motor and nonmotor features of PD. Ultimately, adopting STN DBS as a therapy for early-stage PD will not only require evidence of significant motor improvement compared to the standard of care but also benefit in other critical domains such as quality of life and activities of daily living.

As expected with STN DBS, early STN DBS + ODT participants required significantly lower LEDD, and a significantly lower proportion of early STN DBS + ODT participants required PD polypharmacy through 5 years of follow-up. Although experts in the clinical care of PD often utilize multiple types of medications to optimally manage PD symptoms, the adverse effects of polypharmacy are well-established.[27,28] These results suggest that early STN DBS + ODT provides better control of motor symptoms while simultaneously simplifying the therapeutic regimen for patients transitioning from early to mid-stage disease.

The emergence of levodopa-induced dyskinesia is a negative milestone in the course of PD progression, and dyskinesia severity correlates with increased weight loss and social isolation.[29,30] STN DBS in mid-stage and advanced-stage PD reduces the severity of dyskinesia, and one hypothesized benefit of applying STN DBS to stable-responding, early-stage PD is delaying or even preventing the onset of this debilitating effect of levodopa utilization. Comparisons of dyskinesia severity did not reach the prespecified significance threshold in this small study ($p = 0.06$), but these data, in combination with the significant reduction in medication burden observed, suggest early STN DBS could reduce the risk of developing or worsening dyskinesia in PD.

Motor scores for participants who received early STN DBS + ODT were lower than for participants randomized to early ODT by a clinically important difference,[25] although this difference did not reach statistical significance and was largely driven by the marked improvement in rest tremor. Within the motor domain, the odds of having worse rest tremor for early STN DBS + ODT participants was 0.21 times those of the early ODT group ($p < 0.001$). This finding is clinically meaningful to the PD community because it suggests that people with early-stage PD treated with standard medical therapy are 5 times more likely to have worse rest tremor over

5 years when compared to people treated with STN DBS. This result suggests that, in addition to slowing the progression of rest tremor,[13] early STN DBS intervention also provides long-term symptomatic rest tremor benefit compared to standard medical care.

These results suggest that early STN DBS + ODT is a safe PD treatment with the potential to provide long-term, sustained motor benefit over standard medical therapy while reducing the need for, and complexity of, antiparkinsonian medications and their associated complications. A larger trial is needed to confirm these findings, and the FDA has approved the conduct of a large-scale, multicenter, pivotal clinical trial testing STN DBS in early-stage PD (IDEG050016).

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Disclosure

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Appendix Authors

Name	Location	Contribution
Mallory L. Hacker, PhD	Vanderbilt University Medical Center	Organized and executed the study, interpreted the data, drafted the manuscript for intellectual content
Maxim Turchan, MA	Vanderbilt University Medical Center	Analyzed and interpreted the data, revised the manuscript for intellectual content
Lauren E. Heusinkveld, BS	Vanderbilt University Medical Center	Executed the study, interpreted the data, revised the manuscript for intellectual content
Amanda D. Currie, MD	Vanderbilt University Medical Center	Organized and executed the study, revised the manuscript for intellectual content
Sarah H. Millan, BA	Vanderbilt University Medical Center	Executed the study, revised the manuscript for intellectual content
Anna L. Molinari, JD	Vanderbilt University Medical Center	Organized and executed the study, revised the manuscript for intellectual content
Peter E. Konrad, MD, PhD	Vanderbilt University Medical Center	Conceived and executed the study, revised the manuscript for intellectual content
Thomas L. Davis, MD	Vanderbilt University Medical Center	Conceived and executed the study, revised the manuscript for intellectual content
Fenna T. Phibbs, MD	Vanderbilt University Medical Center	Executed the study, revised the manuscript for intellectual content
Peter Hedera, MD, PhD	Vanderbilt University Medical Center	Executed the study, revised the manuscript for intellectual content
Kevin R. Cannard, MD	Walter Reed National Military Center	Executed the study, revised the manuscript for intellectual content
Li Wang, MS	Vanderbilt University Medical Center	Designed the analysis and interpreted the data, revised the manuscript for intellectual content
David Charles, MD	Vanderbilt University Medical Center	Conceived, organized and executed the study, interpreted the data, revised the manuscript for intellectual content

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