Antiparkinsonian Drug Reduction After Directional Versus Omnidirectional Bilateral Subthalamic Deep Brain Stimulation

Dávid Pintér, MD, PhD¹; Evelyn Járdaházi, MA¹; István Balás, MD, PhD²; Márk Harmat, MD¹; Tamás Makó, MD¹; Annamária Juhász, MD¹; József Janszky, MD, DSc^{1,3}; Norbert Kovács, MD, DSc^{1,3}

ABSTRACT

Background: Several pilot trials and the Clinical Evaluation of the Infinity Deep Brain Stimulation System (PROGRESS) study have found that directional stimulation can provide a wider therapeutic window and lower therapeutic current strength than omnidirectional stimulation.

Objective: We conducted a single-center, open-label, registry-based, comparative trial to test the hypothesis that directional stimulation can be associated with a greater reduction in the total daily dose of antiparkinsonian medications (ApMeds) than omnidirectional stimulation.

Materials and Methods: A total of 52 patients with directional and 57 subjects with omnidirectional bilateral subthalamic deep brain stimulation (STN-DBS) were enrolled. Preoperatively and 12 months postoperatively, the dose of different ApMeds, the number of tablets used daily, the severity of motor and nonmotor symptoms using the Movement Disorder Society-sponsored Unified Parkinson Disease Rating Scale, and the health-related quality of life (HRQoL) using the 39-item Parkinson's Disease Questionnaire (PDQ-39) were assessed.

Results: According to the changes in the levodopa equivalent daily dose, directional STN-DBS led to a 13% greater reduction in the total daily dose of ApMed. The 10.3% greater reduction in the dose of levodopa was the main contributor to this difference. The number of different ApMed types also could be decreased in a greater manner with directional stimulation. The improvement in the severity of motor and nonmotor symptoms was comparable; however, we detected a 15.8% greater improvement in the global HRQoL among patients with directional stimulation according to the changes in the summary index of the PDQ-39. The total electrical energy delivered per second was comparable between the groups at 12-month postoperative visit, whereas the amplitude of stimulation was significantly lower and the impedance was significantly higher with directional leads.

Conclusions: Directional programming can further increase the reduction in the total daily dose of ApMed after STN-DBS. In addition, directional stimulation can have additional beneficial effects on the global HRQoL. The greater reduction of ApMed doses did not require more energy-consuming stimulation with directional stimulation.

Keywords: Deep brain stimulation, directional stimulation, levodopa equivalent daily dose, Parkinson disease, therapeutic window

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Address correspondence to: Dávid Pintér, MD, PhD, Department of Neurology, University of Pécs, 7623, Pécs, Rét utca 2, Hungary. Email: david.pinter@outlook.com

¹ Department of Neurology, Medical School, University of Pécs, Pécs, Hungary;

² Department of Neurosurgery, Medical School, University of Pécs, Pécs, Hungary; and

³ MTA-PTE Clinical Neuroscience MR Research Group, Pécs, Hungary

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INTRODUCTION

Pharmaceutical treatment of advanced Parkinson disease (PD) can be highly challenging. At the later stages of the disease, the balancing of symptomatic improvement with drug-related complications is difficult or completely impossible.¹ In addition, the long duration of antiparkinsonian pharmacotherapy and the frequently applied complex drug combinations^{2,3} impose a high economic burden on both the patients and the health care system.^{4,5} In advanced PD cases, subthalamic deep brain stimulation (STN-DBS) can be both a highly effective and cost-effective treatment option.^{6–14} The reduction in antiparkinsonian medication (ApMed) dosing and costs is considered as one of the most important contributors to the cost-effectiveness of this therapy.^{15–19}

Recently, the technique of DBS has undergone a remarkable improvement. The development of directional leads is one of the most important milestones in this technical evolution. With this innovative technology, the direction of electric field spread can be focused to the targeted anatomical structure more precisely, which may offer more programming flexibility for optimizing the efficacy of stimulation and decreasing the risk for adverse events.^{20,21} Single-center pilot studies that used directional leads for intraoperative test stimulation and examined the low number of cases with permanently implanted directional leads have found that the maximal stimulation amplitude that causes side effect can lie higher in single-segment activation mode, and the minimal stimulation amplitude required to achieve meaningful therapeutic benefit (therapeutic current strength [TCS]) also can be lower than with omnidirectional stimulation. Therefore, single-segment activation can provide a wider therapeutic window (TW).^{22–26}

The Clinical Evaluation of the Infinity Deep Brain Stimulation System (PROGRESS) study, an international, multicenter, prospective, crossover trial on the efficacy of the Abbott St Jude Infinity™ DBS system (Abbott Laboratories, Chicago, IL), has thus far been the largest scale investigation that compared the TWs provided by directional and omnidirectional programming during STN-DBS. It has been shown that directional stimulation increased the TW by 41%, and the TW percentage (TW%, the ratio of TW and TCS) also was 69% larger. In addition, to achieve these therapeutic benefits, 30% less energy was required. According to these results, directional stimulation can provide more programming range with less energy.^{27,28}

Based on the initial pilot trials and the first large-scale analysis of the PROGRESS study, single-segment activation seems to have better efficacy and safety profile (lower TCS, wider TW, and better TW%) than omnidirectional stimulation. However, comparative data on the postoperative oral ApMed reduction after the implantation of directional and conventional leads are lacking. We assume that the wider TW provided by directional stimulation may enable a higher reduction in the dose of ApMeds. To test this hypothesis, we conducted a single-center, open-label, registry-based trial comparing the changes in the daily administered doses of ApMeds during directional vs omnidirectional bilateral STN-DBS in advanced PD.

MATERIALS AND METHODS

Study Population and Protocol

All study-related procedures were approved by the National Ethical Board (031037/2015/OTIG and OGYÉI/6916/2021).

This study was based on the prospective movement disorder registry of the Movement Disorder Unit of the Department of Neurology, University of Pécs. All patients in the registry who received directional leads (St Jude Medical Infinity™ 6170 8-Channel Directional Lead, Abbott Laboratories) in the subthalamic nuclei bilaterally for PD were included (directional stimulation group). Subsequently, from the same registry, a semiautomated software selected a matching group of patients with PD who underwent bilateral omnidirectional (Medtronic 3389 Quadripolar Omnidirectional Lead, Medtronic, Minneapolis, MN) STN-DBS implantation (omnidirectional stimulation group) based on demographic characteristics (eg, age, sex, and education), disease-specific data including type of PD, duration of disease, comorbidities, baseline (BL) rating scales (Movement Disorders Society-sponsored Unified Parkinson Disease Rating Scale [MDS-UPDRS] and the 39-item Parkinson's Disease Questionnaire [PDQ-39]), and ApMeds. The patients were treated with DBS according to the approved local guidelines and the actual CE mark of the respective devices. To enable contemporaneous comparison between the groups and minimize period effect, almost all patients in the omnidirectional cohort underwent surgery after the implantation of directional leads started in our center, and implantations were performed almost in parallel in the two groups by the same neurosurgeon using the same technique. The determination of the optimal theoretical STN target was based on previously reported coordinates (9–12 mm lateral [X coordinate], 1–3 mm posterior [Y coordinate], and 3–5 mm inferior [Z coordinate] to the midcommissural point).²⁹ During the preoperative planning that was performed with the StealthStation™ surgical navigation system (Medtronic), the theoretical coordinates were individualized based on the cerebral anatomical characteristics of patients. The final postoperative lead locations and active contact level coordinates at 12 months postoperatively (M12) were determined using postoperative computed tomography images in the StealthStation™ system and considering the characteristics of implanted electrodes (eg, lead diameter, contact height, and spacing). The detailed inclusion and exclusion criteria for the prospective data set on which the analysis is based can be found in the [Supplementary Data](#).

The included patients had scheduled and standard examinations at BL (within three months before the surgery) and M12. In addition to recording detailed demographic (eg, age, sex, and level of education), disease-specific (eg, duration of disease, type of PD, and ApMeds), and comorbidity-related data, detailed neurological and health-related quality of life (HRQoL) measures were assessed at each visit. Stimulation parameters also were recorded at M12.

Assessed Scales

The cognitive performance was measured by the Hungarian validated versions (7.1, 7.2, and 7.3) of the Montreal Cognitive

Assessment (MoCA).³⁰ The severity of PD was globally measured by the Hungarian validated version of the MDS-UPDRS.³¹ To evaluate the HRQoL, the Hungarian validated versions of the PDQ-39³² and the nondisease specific EuroQoL five-dimension five-level health questionnaire (EQ-5D-5L)³³ were used.

All scales were assessed at both BL and M12. All preoperative examinations were performed in the "best" on-medication state, whereas all postoperative measures were obtained in the medication-on and stimulation-on state.

Primary End points

The main outcome measures of the study included the differences in the change in the levodopa equivalent daily dose (LEDD) representing the total daily dose of all ApMeds³⁴ from BL to M12, the number of patients receiving monotherapy in oral medication after STN-DBS, the number of subjects not receiving levodopa after STN-DBS, the number of tablets of the required daily ApMeds, and the number of different antiparkinsonian drug types after STN-DBS between the directional and omnidirectional stimulation groups.

Secondary End points

In this study, we also compared the level of changes in the severity of motor symptoms measured by Parts II and III of the MDS-UPDRS, the severity of nonmotor symptoms assessed by Part I of the MDS-UPDRS, the severity of motor complications evaluated by Part IV of the MDS-UPDRS, and the HRQoL measured by the summary index of the PDQ-39 and the EQ-5D-5L from BL to M12 between the directional and omnidirectional stimulation groups.

Statistical Analysis

Data were analyzed retrospectively. To test normality, the Kolmogorov-Smirnov test was used. Because most data from the applied scales followed the normal distribution, mean and SD values were calculated. For continuous data, independent *t*-tests were used, whereas for nominal and ordinal data, χ^2 tests were used. The level of statistical significance was set at 0.05. All statistical analyses were performed using the IBM SPSS software package (version 24.0.2, IBM Inc, Armonk, NY).

RESULTS

A total of 57 patients were considered for inclusion in the directional stimulation group. In the omnidirectional stimulation group, based on an automated script-based selection method ensuring balanced BL characteristics, the number of subjects also was 57. Of the directional stimulation group, three patients were excluded because ring mode was used at M12, and two subjects were excluded because of missing values in key data (MDS-UPDRS and PDQ-39); therefore, data of 52 patients could be finally analyzed in this group.

Sociodemographic, disease-specific, and medication-specific data of the two groups at BL are shown separately in Table 1. Almost all the BL characteristics were comparable, with only the rescue drug, the water-soluble levodopa usage, differing significantly. The coordinates of active contact levels on DBS electrodes also were comparable (Table 2).

Changes in the key variables from BL to M12 can be found in Table 3. In the directional stimulation group, the LEDD decreased from 1267.8 ± 661.9 mg to 525.1 ± 400.4 mg, whereas in the omnidirectional stimulation group, there was a decrease in the LEDD from 1139.8 ± 429.5 mg to 619.9 ± 406.2 mg. At M12, LEDD

was comparable between the two groups ($p = 0.223$); however, the magnitude of decrease was significantly higher with directional stimulation (-742.6 ± 550.7 mg vs -519.9 ± 376.9 mg, $p = 0.015$). This primary end point was met.

At M12, the levodopa equivalent dose (LED) for drugs containing levodopa was comparable between patients with directional and omnidirectional stimulation (295.5 ± 376.2 mg vs 321.7 ± 331.1 mg, $p = 0.699$). However, the magnitude of decrease in the LED for levodopa was significantly higher in the directional stimulation group (-606.2 ± 416.6 vs -423.7 ± 308.9 , $p = 0.010$). The LED for dopamine agonists and the magnitude of change in the LED for dopamine agonists did not differ significantly between the two groups (191.2 ± 229.6 vs 254.4 ± 228.4 , $p = 0.153$ and -51.8 ± 231.8 vs -27.7 ± 214.4 , $p = 0.575$ regarding directional and omnidirectional stimulation, respectively). According to these results, the greater reduction in the LEDD in the directional stimulation group mainly resulted from the greater decrease in the daily used dose of levodopa.

The number of patients receiving oral antiparkinsonian monotherapy increased from 6 (11%) to 31 (59.6%) in the directional stimulation group from BL to M12, whereas this number increased from 3 (5.3%) to 27 (47.4%) among patients with omnidirectional stimulation. Although the number of patients treated with oral monotherapy at M12 was higher in the directional stimulation group, the difference did not reach the level of statistical significance ($p = 0.201$). Therefore, this primary end point was not met.

From BL to M12, the number of patients not receiving levodopa increased from 0 to 23 (44.2%) among patients with directional stimulation, whereas this number increased from 0 to 17 (29.8%) in the omnidirectional stimulation group. Although the number of patients not receiving levodopa was in the directional stimulation group, the difference did not reach the level of statistical significance ($p = 0.119$). Therefore, this primary end point was not met.

The number of tablets of oral ApMeds used daily decreased from 7.8 ± 3.0 to 4.0 ± 2.7 in the directional stimulation group from BL to M12, whereas this number decreased from 7.5 ± 2.3 to 4.8 ± 2.8 among patients with omnidirectional stimulation. At M12, the number of tablets used daily was comparable in the two groups ($p = 0.136$); therefore, this primary end point was not met either.

The number of different antiparkinsonian drug types decreased from 2.8 ± 1.1 to 1.4 ± 0.7 among patients with directional stimulation from BL to M12; this number decreased from 2.6 ± 0.8 to 1.6 ± 0.7 in the omnidirectional stimulation group. The number of different ApMed types was comparable between the two groups ($p = 0.099$); therefore, this primary end point was not met. However, the magnitude of decrease was significantly higher in the directional stimulation group (-1.3 ± 1.0 vs -0.9 ± 0.9 , $p = 0.036$). Preoperative and postoperative doses of different ApMed types can be found in the [Supplementary Data Tables S1 and S2](#).

The secondary outcomes are summarized in Table 4. Regarding the different parts of the MDS-UPDRS, neither the postoperative values nor the postoperative changes from BL to M12 differed significantly between the groups. From BL to M12, the summary index of the PDQ-39 improved from 28.4 ± 15.0 points to 17.3 ± 10.8 points in the directional stimulation group, whereas it decreased from 24.5 ± 12.2 points to 18.9 ± 13.9 points among patients with omnidirectional stimulation. Although the level of the HRQoL was comparable between the two groups at M12 ($p = 0.529$), the magnitude of improvement in the summary index of the PDQ-39 was significantly higher in the directional stimulation group (-11.1 ± 12.3 vs -5.7 ± 11.6 , $p = 0.028$).

Table 1. BL Characteristics of the Study Population.

Characteristics	Omnidirectional leads (n = 57)	Directional leads (n = 52)	p Value
Demographic data			
Age (y)	59.7 ± 9.5	60.3 ± 7.5	0.747
Sex			
Men	37 (64.9)	33 (63.5)	0.875
Women	20 (35.1)	19 (36.5)	
Handedness			
Right	56 (98.2)	50 (96.2)	0.505
Left	1 (1.8)	2 (3.8)	
Education (y)	13.1 ± 2.5	13.2 ± 3.0	0.980
MoCA (version 7)	24.7 ± 2.6	25.8 ± 2.8	0.124
Disease-specific data			
Duration of disease (y)	10.3 ± 4.1	9.7 ± 4.4	0.416
Type of disease			
Tremor-dominant	10 (17.5)	8 (15.4)	0.938
Rigid-akinetic	29 (50.9)	28 (53.8)	
Mixed	18 (31.6)	16 (30.8)	
MDS-UPDRS Part I	12.2 ± 5.8	12.7 ± 5.8	0.631
MDS-UPDRS Part II	14.9 ± 7.0	16.9 ± 7.7	0.171
MDS-UPDRS Part III	26.8 ± 9.3	25.6 ± 13.3	0.604
MDS-UPDRS Part IV	6.5 ± 3.7	7.0 ± 3.7	0.469
EQ-5D-5L summary index	0.666 ± 0.193	0.605 ± 0.203	0.111
PDQ-39 summary index	24.5 ± 12.2	28.4 ± 15.0	0.144
ApMed			
Levodopa treatment	57 (100)	52 (100)	N/A
Dopamine agonist treatment	41 (71.9)	36 (69.2)	0.757
Monoamine oxidase inhibitor treatment	18 (36.1)	17 (32.7)	0.901
Catechol-O-methyltransferase inhibitor treatment	42 (73.7)	35 (67.3)	0.465
Anticholinergic treatment	2 (3.5)	0 (0.0)	0.173
Monotherapy	3 (5.3)	6 (11.5)	0.234
Number of different antiparkinsonian drug types			
0	0 (0.0)	0 (0)	0.266
1	3 (5.3)	6 (11.5)	
2	24 (42.1)	15 (28.8)	
3	24 (42.1)	19 (36.5)	
4	5 (8.8)	8 (15.4)	
5	1 (1.8)	4 (7.7)	
Number of different antiparkinsonian drug types	2.6 ± 0.8	2.8 ± 1.1	0.356
Number of tablets (pieces/day)	7.5 ± 2.3	7.8 ± 3.0	0.569
LED for drugs containing levodopa (mg)	745.4 ± 351.3	903.6 ± 517.6	0.063
LED for dopamine agonists (mg)	282.1 ± 244.1	243.0 ± 245.1	0.406
LEDD (mg)	1139.9 ± 429.5	1267.8 ± 661.9	0.230

Data are presented as mean ± SD or count (%).

N/A, not available.

The total electrical energy delivered (TEED) per second calculated based on the method by Koss et al³⁵ was comparable between the omnidirectional and directional stimulation groups

(146.6 ± 68.1 µJ vs 147.7 ± 67.1 µJ, $p = 0.944$) at M12. The amplitude of stimulation was significantly lower (2.2 ± 0.6 mA vs 2.6 ± 1.0 mA, $p = 0.022$), whereas the impedance was significantly higher

Table 2. Coordinates of Active Contact Levels.

Coordinates	Omnidirectional leads (n = 57)	Directional leads (n = 52)	p Value
Left lead			
X (mm)	11.7 ± 0.6	11.6 ± 1.1	0.889
Y (mm)	2.7 ± 0.5	2.8 ± 0.5	0.837
Z (mm)	4.1 ± 2.1	2.8 ± 1.1	0.259
Right lead			
X (mm)	12.3 ± 0.6	11.5 ± 0.8	0.120
Y (mm)	2.3 ± 0.7	2.6 ± 0.6	0.491
Z (mm)	3.7 ± 2.5	3.1 ± 1.4	0.623

Table 3. The Primary Outcomes at the 12-Month Follow-Up Visit.

Primary outcomes	Omnidirectional leads (n = 57)	Directional leads (n = 52)	p Value
LED for drugs containing levodopa (mg)	321.7 ± 331.1	295.5 ± 376.2	0.699
Change in the LED for drugs containing levodopa (mg)	−423.7 ± 308.8	−606.2 ± 416.6	0.010
LED for dopamine agonists (mg)	254.4 ± 228.4	191.2 ± 229.6	0.153
Change in the LED for dopamine agonists (mg)	−27.7 ± 214.4	−51.8 ± 231.8	0.575
LEDD (mg)	619.9 ± 406.2	525.1 ± 400.4	0.223
Change in the LEDD (mg)	−519.9 ± 376.9	−742.6 ± 550.7	0.015
Number of different antiparkinsonian drug types	1.6 ± 0.7	1.4 ± 0.7	0.099
Change in the number of different antiparkinsonian drug types	−0.9 ± 0.9	−1.3 ± 1.0	0.036
Number of tablets (pieces/day)	4.8 ± 2.8	4.0 ± 2.7	0.136
Change in the number of tablets (pieces/day)	−2.6 ± 3.1	−3.7 ± 2.9	0.063
Monotherapy	27 (47.4)	31 (59.6)	0.201
Change in the monotherapy status			
Achieved	24 (42.1)	26 (50.0)	0.376
Unchanged	33 (57.9)	25 (48.1)	
Lost	0 (0.0)	1 (1.9)	
Levodopa treatment	40 (70.2)	29 (55.8)	0.119
Change in levodopa treatment			
Stopped	17 (29.8)	23 (44.2)	0.119
Unchanged	40 (70.2)	29 (55.8)	
Initiated	0 (0.0)	0 (0.0)	
Dopamine agonist treatment	39 (68.4)	30 (57.7)	0.246
Change in dopamine agonist treatment			
Stopped	7 (12.3)	10 (19.2)	0.605
Unchanged	45 (78.9)	38 (73.1)	
Initiated	5 (8.8)	4 (7.7)	
Monoamine oxidase inhibitor treatment	3 (5.3)	0 (0.0)	0.093
Change in monoamine oxidase inhibitor treatment			
Stopped	16 (28.1)	17 (32.7)	0.566
Unchanged	40 (70.2)	35 (67.3)	
Initiated	1 (1.8)	0 (0.0)	
Catechol-O-methyltransferase inhibitor treatment	29 (50.9)	19 (36.5)	0.132
Change in catechol-O-methyltransferase inhibitor treatment			
Stopped	14 (24.6)	18 (34.6)	0.375
Unchanged	42 (73.7)	32 (61.5)	
Initiated	1 (1.8)	2 (3.8)	
Anticholinergic treatment	0 (0.0)	0 (0.0)	N/A
Change in anticholinergic treatment			
Stopped	2 (3.5)	0 (0.0)	0.173
Unchanged	55 (96.5)	52 (100)	
Initiated	0 (0.0)	0 (0.0)	

Data are presented mean ± SD or count (%).

N/A, not available.

(1698.3 ± 444.2 Ω vs 1160.5 ± 355.5 Ω, $p < 0.001$) with directional leads (Table 5).

There were no intracranial bleedings or infections in any of the included patients, and the frequency and severity of stimulation-related side effects were comparable between the study groups.

DISCUSSION

Although an increasing body of research has revealed the superiority of directional stimulation over omnidirectional DBS,^{22–28} the effects of benefits provided by directional leads on antiparkinsonian pharmacotherapy have remained unknown. To address this question, we performed a single-center, open-label, registry-based, comparative study on the changes in the daily administered doses of ApMeds measured in LEDD during directional vs omnidirectional bilateral STN-DBS among patients with advanced PD.

One of the main findings of this study was that a greater reduction in the LEDD could be achieved with directional programming, which mainly resulted from the greater reduction in the daily used dose of medications containing levodopa. The magnitude of reduction in the total daily dose of ApMeds reached the 30% to 60% decrease that has been found in previous studies of STN-DBS^{15–17} in both study groups; however, the reductions in the total daily doses of ApMeds and levodopa were 13% (−58.6% vs 45.6%) and 10.3% (67.1% vs 56.8%), respectively, higher with directional stimulation. In addition, with directional stimulation, the oral antiparkinsonian treatment also could be simplified to a greater extent by reducing the numbers of different drug types and tablets used daily in a greater manner. These together not only may contribute to the higher cost-effectiveness of antiparkinsonian therapy but also may increase therapeutic adherence.

In line with the preliminary findings of the PROGRESS trial,^{27,28} this study also found no difference in the level of control of

Table 4. The Secondary Outcomes at the 12-Month Follow-Up Visit.

Secondary outcomes	Omnidirectional leads (n = 57)	Directional leads (n = 52)	p Value
MoCA (version 7)	25.2 ± 3.0	25.1 ± 2.7	0.870
Change in MoCA*	0.3 ± 3.1	−0.3 ± 1.9	0.478
MDS-UPDRS Part I	9.8 ± 7.0	8.8 ± 6.1	0.410
Change in MDS-UPDRS Part I*	−2.3 ± 6.5	−3.9 ± 7.0	0.229
MDS-UPDRS Part II	10.6 ± 7.0	11.2 ± 7.5	0.685
Change in MDS-UPDRS Part II*	−4.3 ± 7.5	−5.6 ± 7.6	0.390
MDS-UPDRS Part III	23.8 ± 10.9	24.1 ± 12.7	0.898
Change in MDS-UPDRS Part III ^{*,†}	−3.0 ± 11.1	−1.4 ± 15.9	0.557
MDS-UPDRS Part IV	2.8 ± 3.1	4.0 ± 4.1	0.082
Change in MDS-UPDRS Part IV*	−3.6 ± 3.6	−3.0 ± 4.2	0.392
EQ-5D-5L summary index	0.755 ± 0.157	0.708 ± 0.189	0.171
Change in EQ-5D-5L summary index*	0.086 ± 0.208	0.092 ± 0.203	0.878
PDQ-39 summary index	18.9 ± 13.9	17.3 ± 10.8	0.529
Change in PDQ-39 summary index*	−5.7 ± 11.6	−11.1 ± 12.3	0.028

Data are presented as mean ± SD.

*Changes were calculated as the difference between the M12 and the BL values.

[†]MDS-UPDRS Part III was assessed in "best" ON state at BL and on-medication and on-stimulation state at M12.

parkinsonian symptoms between directional and omnidirectional stimulation, despite the lower mean current strength used during directional stimulation. A possible explanation for this finding may be that directional leads can produce higher charge density with the same amplitude of current to the targeted brain structure and an increased volume of tissue activation compared with conventional omnidirectional leads.³⁵ This increase in the activated volume of the targeted tissue can lead to a better symptomatic control, and as a result, lower dosages of additional oral medications may be needed to achieve the desired therapeutic effect. Furthermore, lower current thresholds for beneficial effects can prevent dose-limiting motor or nonmotor side effects resulting from the undesirable spread of stimulation into areas outside the target and can prevent an optimal outcome. In addition, reduced amplitude settings also can partially counterbalance the increased tissue impedance of smaller contacts, which may be relevant in terms of energy consumption.³⁶

According to the summary index of the PDQ-39, we detected a 15.8% greater (39.1% vs 23.3%) improvement in the global HRQoL during directional STN-DBS. The change in the HRQoL was slightly inferior to that observed in previous studies of omnidirectional STN-DBS (−24% to 38%)¹⁴ in the omnidirectional programming group, whereas the improvement exceeded that range with directional stimulation. The difference detected in the global HRQoL between the two groups was not just statistically significant but also clinically relevant, considering the minimal clinically

important difference threshold for improvement established for the summary index of the PDQ-39 (4.72 points).³² In this study, directional stimulation provided the same symptomatic improvement and control as omnidirectional stimulation and greater improvement in the global HRQoL with less ApMeds, which may indicate the superior efficacy of directional vs omnidirectional stimulation.

Frequently applied complex drug combinations are among the main expenses of treatment in advanced PD.^{4,5} By reducing the dose of oral medications, STN-DBS can improve the cost-effectiveness of antiparkinsonian therapy.^{15,16,18,19} The PROGRESS study found that directional programming can be associated with lower energy consumption than omnidirectional stimulation.^{27,28} In this study, although directional stimulation was superior to omnidirectional stimulation in decreasing the total daily dose of oral ApMeds, the TEED per second was comparable. This means that the greater reduction of ApMed doses did not require more energy-consuming stimulation to achieve the desired symptomatic control. Furthermore, we detected a greater improvement in the global HRQoL that also has been considered as an important factor in previous analyses on the economic aspects of neurostimulation.^{37–39} Based on these findings, the use of directional leads may further improve the cost-effectiveness of DBS in PD.

During the interpretation of our findings, some limitations should be considered. First, patients were allocated to the treatment arms in a nonrandom fashion. In addition, the study is limited

Table 5. DBS Therapy Characteristics at the 12-Month Follow-Up Visit.

Stimulation parameters	Omnidirectional leads (n = 57)	Directional leads (n = 52)	p Value
Amplitude (mA)	2.6 ± 1.0*	2.2 ± 0.6	0.022
Pulse width (μs)	62.8 ± 9.9	63.7 ± 11.4	0.725
Frequency (Hz)	146.5 ± 24.9	141.5 ± 23.0	0.399
Impedance (Ω)	1160.5 ± 355.5	1698.3 ± 444.2	<0.001
TEED per second (μJ)	146.6 ± 68.1	147.7 ± 67.1	0.944

Data are presented as mean ± SD.

*Because in the omnidirectional stimulation group, constant current devices were used, voltage values were converted to current values based on Ohm's law.

by its open-label and single-center design; our results might have been influenced by factors related specifically to the institution and/or the country. Because there is no unified strategy for programming, other movement disorder centers may use programming algorithms different from that used by our group. In our center, each patient undergoes monopolar review one month postoperatively. During this procedure, all segments are tested with standard parameters, namely, 60- μ s pulse width and 130-Hz frequency, and single segments are activated immediately after the monopolar review. If the outcomes justify it, single-segment activation is the default stimulation mode. During follow-up visits, if modifications to stimulation settings are needed, mainly the amplitude, occasionally the pulse width or the frequency, is adjusted instead of returning to ring mode. Strategic reduction of ApMeds after the initiation of DBS also may differ among centers.⁴⁰ Our group prefers reducing the dose of levodopa in most of the cases and tries to achieve monotherapy with lowered doses of dopamine agonists. In addition, we tested more than one outcome; therefore, a type I error might have occurred that could be addressed with more in-depth analyses (eg, correction for multiple comparisons).⁴¹ Finally, because the study was based on the retrospective analysis of registry data, our findings provide class III evidence⁴² on the difference in the reduction of ApMeds during omnidirectional vs directional STN-DBS.

In conclusion, compared with omnidirectional stimulation, directional STN-DBS can be associated with a greater reduction in the total daily dose of ApMeds, which mainly results from the reduction in the daily used doses of drugs containing levodopa. Therefore, it can be suggested that the use of directional leads that also have been found to have lower energy consumption may enable a more cost-effective antiparkinsonian treatment. Although the total daily dose of ApMeds can be reduced in a greater manner, the efficacy of directional DBS remains comparable with that of omnidirectional stimulation. Moreover, directional stimulation can lead to a greater improvement in the HRQoL of patients with PD. According to some previous findings, the reduced and simplified antiparkinsonian pharmacologic treatment and the improvement in the HRQoL can be sustainable even for years after the initiation of STN-DBS.^{43–45} Further longer-term studies should be conducted to decide whether observed differences in the level of antiparkinsonian drug reduction and the level of improvement in the HRQoL between directional and omnidirectional stimulation persist in the long term. Our findings support the suspected superiority of directional over omnidirectional stimulation from a previously unstudied aspect and can be useful for future efficacy and cost-effectiveness analyses that are warranted to judge the clinical and economic relevance of our results.

Authorship Statements

Dávid Pintér and Norbert Kovács participated in all aspects of the research project and manuscript draft, review, and critique. Evelyn Járdaházi, Annamária Juhász, and Márk Harmat participated in the organization of the research project, the execution of the statistical analysis, and the review and critique of the manuscript. István Balás participated in the execution of the research project and the review and critique of the statistical analysis and the manuscript. Tamás Makó participated in the organization of the research project and the review and critique of the statistical analysis and the manuscript. József Janszky participated in the conception of the research

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at <https://doi.org/10.1016/j.neurom.2022.01.006>.

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