

Continuous Subcutaneous Apomorphine Infusion before Subthalamic Deep Brain Stimulation: A Prospective, Comparative Study in 20 Patients

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ABSTRACT: Background: Studies comparing the clinical efficacy of apomorphine infusion (APO) with subsequent subthalamic deep brain stimulation (STN-DBS) in advanced Parkinson's disease (aPD) are currently lacking. Retrospective data have shown that patients treated with APO are usually older, have a more prolonged disease, and a more severe phenotype.

Objective: To compare the benefit of APO with that of STN-DBS on motor, non-motor, cognitive, and quality of life in the same patient when given sequentially.

Methods: We prospectively analyzed 20 aPD patients over 3 different treatment phases: baseline (optimized medical treatment), during APO treatment, and during subsequent STN-DBS treatment. The APO and STN-DBS phases were stable for 6 months, and evaluation of the different treatments was separated by 6 months.

Results: Compared to baseline, APO, and STN-DBS reduced mean daily off time by 70.5% and 89.3% ($P = 0.012$), respectively, and scores for Unified Parkinson's Disease Rating Scale (UPDRS) IV by 27.5% and 80.5% ($P < 0.001$), Non-motor symptoms scale (NMSS) by 24.6% and 49.3% ($P < 0.001$), Montgomery Asberg depression scale (MADRS) by 7.4% and 39.0% ($P = 0.27$), Starkstein apathy scale (SAS) by 51.1% and 39.9% ($P = 0.734$), Parkinson's disease sleep scale 2 (PDSS-2) by 25.7% and 56.7% ($P < 0.001$), and Parkinson's disease questionnaire 39 item (PDQ-39) by 39.6% and 64.9% ($P < 0.001$). Global cognition did not change with either therapy, but phonetic fluency worsened after STN-DBS compared to APO ($P = 0.022$).

Conclusions: Both APO and STN-DBS improved motor and non-motor symptoms and quality of life compared to optimized medical treatment in aPD. Overall, STN-DBS was the most effective treatment, but APO showed a pronounced benefit on motor symptoms. Effective treatment for aPD should not be delayed, even when waiting for surgery.

Apomorphine infusion (APO) and subthalamic deep brain stimulation (STN-DBS) have proven efficacy for the treatment of advanced Parkinson's disease (PD, aPD) and are widely used in clinical practice. However, the level of scientific evidence supporting each of these treatments differs. Although several prospective, randomized, and multicenter clinical trials support the

use of STN-DBS, only 1 randomized, double-blind clinical trial, the TOLEDO study^{1,2} has been undertaken with APO.^{1,2} Despite its long-standing use, many studies that support the use of APO are retrospective and with small sample sizes.^{3–10} In terms of motor symptoms, STN-DBS seems to provide greater clinical improvement than APO, which is generally restricted to

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Relevant disclosures and conflicts of interest are listed at the end of this article.

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infusion during the patient's waking hours and shows a variable effect on dyskinesia. Both treatments are well tolerated by PD patients with normal cognition.

The EUROINF 2 study collects data from patients treated with the 3 device-aided therapies for aPD—APO, STN-DBS, and levodopa-carbidopa intestinal gel infusion. The patients treated with APO are usually older, with longer disease duration and more severe symptoms than patients treated with STN-DBS.¹¹ This is the current medical practice because aPD patients meeting the criteria for STN-DBS are usually recommended this therapy. This gives rise to a significant bias when evaluating APO or comparing APO with STN-DBS because many patients treated with APO do not meet the criteria for STN-DBS.^{4,7}

To date, only 2 non-randomized and prospective studies have compared APO and STN-DBS in patients meeting the criteria for STN-DBS.^{12,13} In both, APO was offered because of the long waiting list for STN-DBS treatment. In the first study, the authors analyzed the clinical and neuropsychological evolution at 12 months of 13 patients treated with APO and 12 treated with STN-DBS. The patients who underwent STN-DBS had better results for reduction of *off* time, dyskinesia, and oral anti-parkinsonian medication. However, they showed worse verbal fluency and Neuro-Psychiatric Inventory scores.¹² In the second study, the authors evaluated memory, executive, and visuospatial function at 6 and 12 months in 9 patients treated with STN-DBS and 7 treated with APO. They observed a statistically significant decline in verbal fluency and naming speed at 6 months after the intervention. This was not observed in the APO group.¹³

We, therefore, undertook a study to compare the effect of APO and subsequently STN-DBS in the same patient.

Methods

This study was a prospective, non-randomized, observational study comparing APO and STN-DBS, conducted by the Movement Disorder Unit of the Hospital Clínico Universitario de Santiago de Compostela, Spain, from March 2017 to February 2020. Inclusion criteria were (1) patients with aPD selected for bilateral STN-DBS who started APO while waiting for surgery, at the discretion of their neurologist; (2) minimum expected APO duration for 6 months; and (3) informed consent obtained. STN-DBS criteria were based on the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD)¹⁴ with some modifications including (1) advanced stage PD; (2) disease duration over 5 years; (3) reduction in Unified Parkinson's Disease Rating Scale (UPDRS) part III motor scores over 50% after levodopa or apomorphine challenge test; (4) age below 71 years; (5) magnetic resonance imaging with no significant vascular damage or structural abnormalities; (6) absence of significant cognitive decline according to selected neuropsychological scales; (7) lack of serious psychiatric conditions, except drug-induced psychosis; (8) absence of *on*-time major gait problems; (9) good general health; and (10) realistic

expectations. Exclusion criteria included (1) patients with previous STN-DBS; (2) patients previously treated with APO (previous apomorphine pen injection was permitted); and (3) patients previously treated with levodopa infusion.

Clinical Assessment

The clinical assessment included (1) motor: *off* daily hours (an average for the previous week), UPDRS part III, UPDRS part IV and dyskinesia score (section A from UPDRS part IV); (2) concomitant medication use: levodopa and levodopa equivalent daily dose (LEDD);¹⁵ (3) non-motor: Non-Motor Symptoms Scale (NMSS), Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease-Rating Scale (QUIP-RS), Montgomery Asberg depression scale (MADRS), Starkstein apathy scale (SAS), and Parkinson's disease sleep scale 2 (PDSS-2); (4) cognition: Mattis rating dementia scale (MDRS) and verbal fluency; and (5) quality of life: Parkinson's disease questionnaire 39 item (PDQ-39).

We evaluated the patients at 3 different time points: (1) baseline (optimized medical treatment; ON-MED); (2) APO (in the 4 weeks before the STN-DBS surgery); and (3) STN-DBS

TABLE 1 Patients' baseline characteristics

	n = 20
Age	59.30 ± 6.40
Sex (male)	10
PD evolution (y)	8.40 ± 3.60
UPDRS III <i>off</i> meds	38.41 ± 10.91
Past impulse control disorder	3

TABLE 2 Treatment characteristics of patients receiving apomorphine infusion

	n = 20
Duration of APO (months)	9.35 ± 2.46
APO dose (mg/day)	75.5 ± 20.73
APO hours (day)	15.6 ± 2.78
Adverse effects	6 (30%)
Nodules (complicated)	2
Nausea	0
Somnolence	1
Rash	0
Illusion	1
Impulse control disorder	1
Hypotension	0
Edema	1

(*on stim/on meds*; at 6 months after surgery). In this way, within a timeframe of 12–18 months, all patients were evaluated in 3 separate clinical treatment settings, each of them stable for at least 6 months.

The following were excluded for the analysis: (1) patients who withdrew from APO, either voluntarily or because of a medical indication; (2) patients treated with APO for over

12 months; (3) patients who did not eventually get STN-DBS surgery; (4) patients who did not stop APO within the first 4 weeks after surgery; (5) patients with severe complication during or immediately after surgery; and (6) patients with a major complication in the first 6 months after STN-DBS surgery, involving partial or total removal of the stimulation system. Data derived from these assumptions were analyzed separately.

TABLE 3 Results of clinical assessments for all 3 treatments

	<i>On-MED</i>	<i>APO</i>	<i>STN-DBS</i>	<i>p</i> value <i>On-MED</i> vs. <i>APO</i>	<i>p</i> value <i>On-MED</i> vs. <i>STN-DBS</i>
<i>off</i> time (hours)	5.15 ± 2.41	1.52 ± 1.53	0.55 ± 0.84	≤0.001	≤0.001
UPDRS II <i>on</i>	8.20 ± 3.83	6.40 ± 3.72	4.90 ± 4.68	0.033	≤0.001
UPDRS III <i>on</i>	12.75 ± 5.41	11.60 ± 6.43	9.90 ± 6.03	0.365	0.004
UPDRS IV	7.45 ± 2.46	5.40 ± 2.54	1.45 ± 1.79	0.017	≤0.001
Dyskinesia score	3.05 ± 2.11	3.20 ± 2.31	0.65 ± 1.18	1	≤0.001
LEDD (mg)	1432 ± 483	1712 ± 532	776 ± 340	0.003	≤0.001
Levodopa (mg)	1149 ± 447	846 ± 420	695 ± 319	0.002	≤0.001
NMSS ^a	53.65 ± 27.83	40.45 ± 28.18	27.20 ± 18.60	≤0.001	≤0.001
Sleep/fatigue	11.15 ± 5.33	7.90 ± 5.06	3.20 ± 3.78	0.002	≤0.001
Mood	13.80 ± 11.19	9.85 ± 14.18	7.65 ± 8.45	0.001	0.001
Gastrointestinal	4.05 ± 5.61	4.00 ± 5.28	2.65 ± 4.16	0.703	0.514
Urinary	6.60 ± 5.34	5.00 ± 5.01	6.10 ± 4.77	0.182	0.922
Sexual	6.00 ± 6.62	4.45 ± 5.61	2.80 ± 4.70	0.256	0.08
Miscellaneous	10.05 ± 7.17	7.45 ± 8.55	3.85 ± 4.37	0.006	≤0.001
MADRS	13.45 ± 10.98	12.45 ± 9.29	8.20 ± 8.38	0.152	0.024
SAS	6.90 ± 7.17	3.10 ± 2.88	4.15 ± 5.64	0.41	0.41
QUIP-RS	2.20 ± 2.88	2.65 ± 6.73	0.90 ± 3.06	0.767	0.691
PDSS-2	22.75 ± 8.33	16.90 ± 8.63	9.85 ± 5.57	≤0.001	≤0.001
MDRS	135.75 ± 4.29	135.70 ± 5.66	135.20 ± 7.14	0.937	0.937
Phonetic fluency	12.40 ± 4.73	13.50 ± 4.08	10.80 ± 4.72	0.07	0.07
Semantic fluency	16.60 ± 4.39	16.85 ± 4.28	14.75 ± 3.82	0.93	0.091
PDQ-39	32.08 ± 12.49	19.37 ± 12.48	11.27 ± 9.41	≤0.001	≤0.001
Mobility	46.38 ± 25.49	22.00 ± 25.03	12.84 ± 15.65	≤0.001	≤0.001
Daily life activities	39.98 ± 22.03	19.17 ± 15.96	10.21 ± 12.44	≤0.001	≤0.001
Emotional wellbeing	39.56 ± 19.00	30.62 ± 19.42	21.48 ± 15.56	0.071	0.006
Stigma	22.51 ± 32.98	15.31 ± 24.79	4.38 ± 9.54	0.058	0.009
Social support	5.41 ± 12.16	6.25 ± 21.44	1.25 ± 5.59	0.484	0.484
Cognition	12.42 ± 10.09	14.70 ± 15.48	8.14 ± 12.52	1	0.086
Communication	17.49 ± 19.84	15.41 ± 18.58	14.59 ± 23.71	0.748	0.748
Bodily discomfort	34.99 ± 25.73	20.00 ± 21.02	8.76 ± 14.93	≤0.001	≤0.001

Values are mean ± standard deviation; In bold, *p* < 0.05.

^aFor NMSS scores, the cardiovascular, perceptual problems, and attention/memory domains are not represented because of the high number of results with a score of 0.

Statistical Analysis

Data are expressed as a percentage for qualitative variables and as mean and standard deviation for quantitative variables. To determine statistical differences between the 3 treatments, we applied analysis of variance (ANOVA) for repeated measures or the Friedman test (equivalent to the repeated measures ANOVA for nonparametric data), depending on the parametric or nonparametric data distribution. Post hoc tests were performed to evaluate the difference between pairs of treatments: paired *t* test, after the ANOVA, or Durbin–Conover test, after Friedman’s test. The *P* values of these were adjusted using the method of Benjamini–Hochberg, to control the false discovery rate.

To evaluate the magnitude of the change of each treatment relative to baseline, we calculated the relative change ($RC = \text{mean} [\text{treatment} - \text{baseline}] \times 100 / \text{baseline mean}$) and the effect size ($ES = \text{mean} [\text{treatment} - \text{baseline}] / \text{standard deviation baseline mean}$).¹⁶ Values for ES between 0.20 and 0.49 are considered a small effect size, values between 0.50 to 0.79 are considered a moderate effect size, and values ≥ 0.80 are considered a large effect size.¹⁷

Results

A total of 24 patients participated in the study. Four patients withdrew because of their own decision, hospitalization for

TABLE 4 Magnitude of change from baseline in clinical parameters and size effect of each treatment

	Relative change from baseline (%)			Size effect	
	APO	STN-DBS	<i>p</i> value ^a	APO	STN-DBS
<i>off</i> time (hours)	−70.49	−89.32	0.012	1.51	1.91
UPDRS II <i>on</i>	−21.95	−40.24	0.033	0.47	0.86
UPDRS III <i>on</i>	−9.02	−22.35	0.022	0.21	0.53
UPDRS IV	−27.52	−80.54	≤0.001	0.83	2.44
Dyskinesia score	+4.92	−78.69	≤0.001	—	1.14
LEDD (mg)	+19.55	−45.81	≤0.001	—	1.36
Levodopa (mg)	−26.37	−39.51	0.024	0.67	1.02
NMSS ^b	−24.60	−49.30	≤0.001	0.47	0.95
Sleep/fatigue	−29.15	−71.30	≤0.001	0.61	1.49
Mood	−28.62	−44.57	0.923	0.35	0.55
Gastrointestinal	−1.23	−34.57	0.514	0.01	0.25
Urinary	−24.24	−7.58	0.182	0.30	0.09
Sexual	−16.67	−53.33	0.256	0.15	0.48
Miscellaneous	−25.87	−61.69	0.099	0.36	0.86
MADRS	−7.43	−39.03	0.27	0.09	0.49
SAS	−55.07	−39.86	0.734	0.53	0.38
PDSS-2	−25.71	−56.70	≤0.001	0.70	1.55
PDQ-39	−39.62	−64.87	≤0.001	1.02	1.67
Mobility	−52.57	−72.32	0.026	0.96	1.32
Daily life activities	−52.05	−74.46	0.003	0.94	1.35
Emotional wellbeing	−22.60	−45.70	0.064	0.47	0.95
Stigma	−31.94	−80.54	0.319	0.22	0.55
Social support	+15.53	−76.89	0.484	—	0.34
Cognition	+18.36	−34.46	0.086	—	0.42
Communication	−11.89	−16.58	0.748	0.10	0.15
Bodily discomfort	−42.84	−74.96	0.002	0.58	1.02

In bold, *p* < 0.05 and size effect >0.80.

^aPaired *t* test after ANOVA between APO and STN-DBS evaluations.

^bFor NMSS, cardiovascular, perceptual problems and attention/memory domains are not represented because of the high number of results with a score of 0.

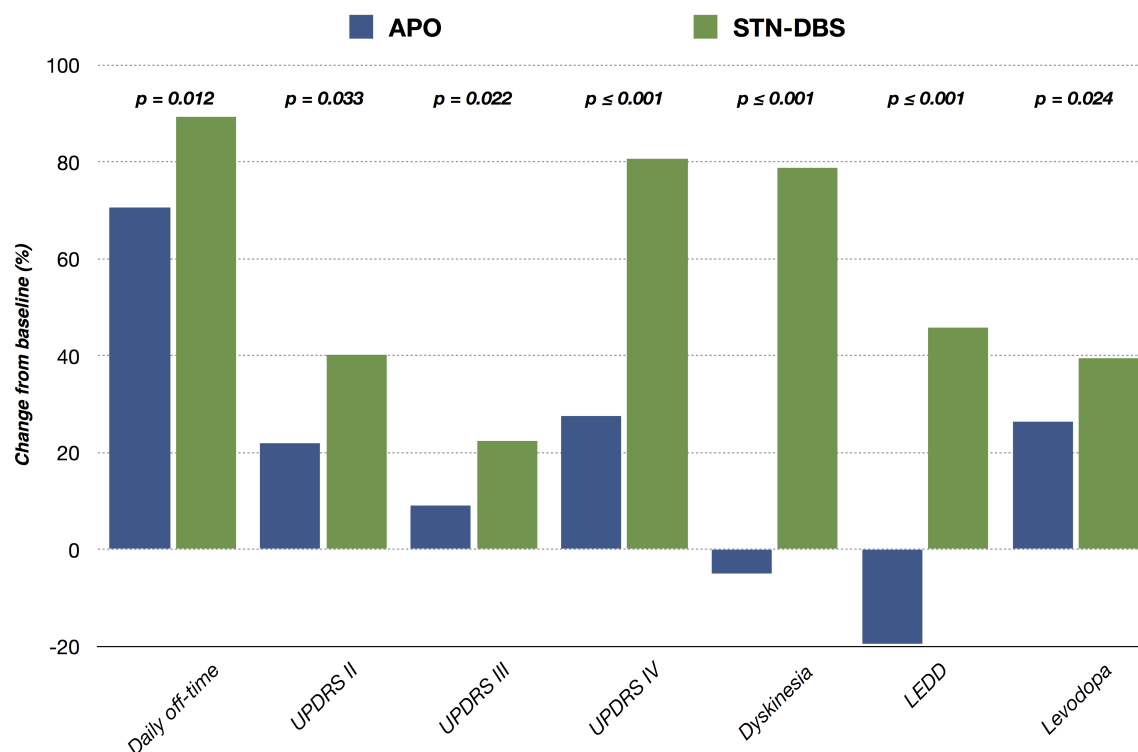


FIG 1. Change in motor and concomitant medication use relative to baseline for each treatment.

drug-induced psychosis (see Discussion), extended APO over 12 months, and heart pacemaker implantation. This last patient is still being treated with APO, with a moderate clinical response. The baseline and APO characteristics of the remaining 20 patients are in Tables 1 and 2.

Table 3 shows the results for each motor, non-motor and cognitive evaluation, concomitant medication use, and quality of life variables, and the pair-to-pair analysis for the baseline evaluation. Table 4 displays the magnitude of the change in these parameters for each device-aided therapy relative to baseline.

Motor Outcome and Medication

Compared to baseline, mean daily *off* time was reduced by 70.5% with APO and 89.3% with STN-DBS, showing a large effect size in each case (1.51 and 1.91, respectively) (Fig. 1). The difference between these treatments was statistically significant ($P = 0.012$). Mean UPDRS IV score improved by 27.5% after APO and by 80.5% after STN-DBS, with a large effect size in each case (0.83 and 2.44, respectively). The difference between APO and STN-DBS was significant ($P \leq 0.001$). Mean dyskinesia score did not improve with APO, but showed a 78.7% reduction after STN-DBS, with a large effect size (1.14). STN-DBS significantly improved mean UPDRS III score compared to baseline and APO ($P = 0.004$ and $P = 0.022$, respectively).

Mean daily levodopa dosage was reduced by 26.8% after APO (moderate effect size, 0.67) and by 39.5% after STN-DBS (large effect size, 1.02). Despite this, mean LEDD was increased by 19.6% with APO. The difference between APO and STN-DBS was statistically significant for both levodopa dose reduction ($P = 0.024$) and LEDD reduction ($P \leq 0.001$).

Non-Motor Outcome

Compared to baseline, mean NMSS score was reduced by 24.6% with APO, near to a moderate effect (0.47) (Fig. 2). The sleep/fatigue domain had the most pronounced improvement, and was the only domain that achieved a moderate effect size. After STN-DBS, mean NMSS score was reduced by 49.3% with a large effect size (0.95). Sleep/fatigue and miscellaneous domains had the largest effect sizes, followed by the mood domain. The differences between APO and STN-DBS were statistically significant for total NMSS score ($P \leq 0.001$) and sleep/fatigue ($P \leq 0.001$). Mean score for depression, assessed using MADRS, did not improve with APO, but was reduced by 39.0% after STN-DBS ($P = 0.024$), with a moderate effect size (0.49). Nevertheless, the difference between treatments was not statistically significant. Mean score for apathy, evaluated using SAS, improved to a greater extent with APO, 55.1%, with a moderate effect size (0.53), than with STN-DBS, 39.9%, but did not reach statistical significance. QUIP-RS score did not show reliable

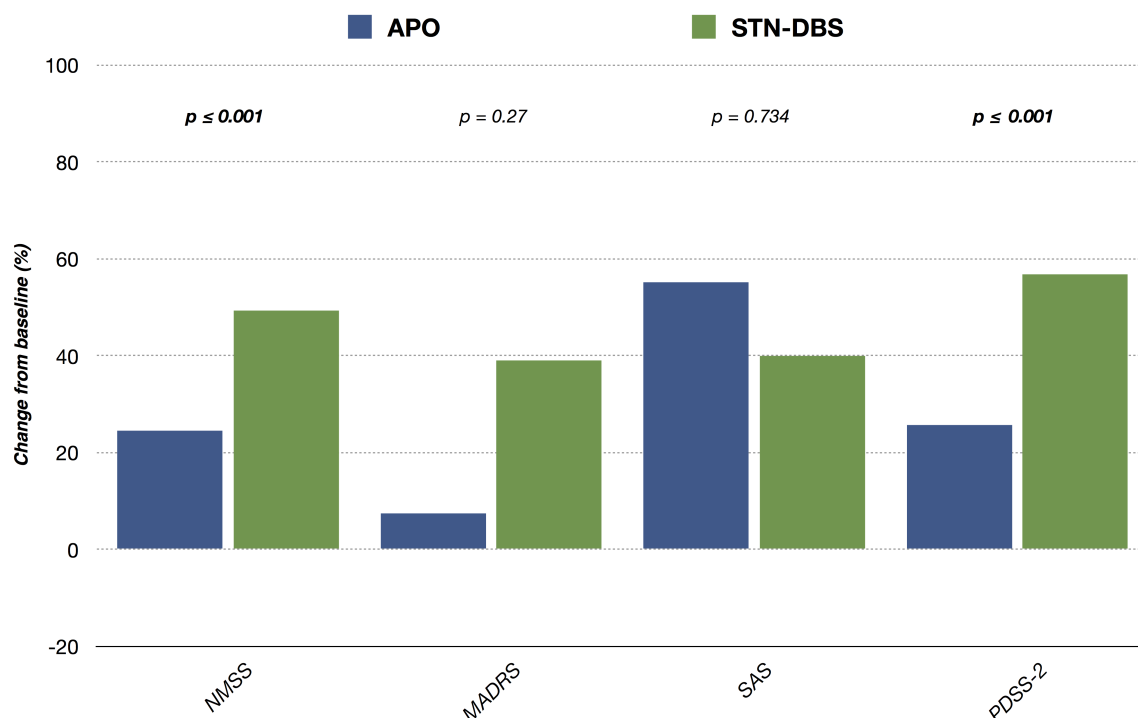


FIG 2. Change in non-motor scores relative to baseline for each treatment.

changes over the study period (see discussion). Finally, mean PDSS-2 score was improved by 25.7% with APO and by 56.7% with STN-DBS, achieving a moderate effect size (0.70) and large effect size (1.55), respectively. The difference between APO and STN-DBS was statistically significant ($P \leq 0.001$).

Cognition

The global cognitive status of the patients remained unchanged either with APO and STN-DBS. Neither MADRS nor any of its subscales showed statistically significant differences between the 3 treatment phases. However, when verbal fluency was specifically assessed, we have observed a worsening after the STN-DBS surgery. Phonetic fluency was significantly reduced with STN-DBS compared to APO ($P = 0.022$) and also reduced compared to baseline, close to statistical significance ($P = 0.07$). Semantic fluency also showed lower values after the STN-DBS, although they did not reach statistical significance.

Quality of Life

Compared to baseline, both APO and STN-DBS resulted in a substantial improvement in patients' quality of life (Fig. 3). Mean total PDQ-39 score was reduced by 39.6% with APO and 64.9% with STN-DBS, both achieving a large effect size (1.02 and 1.67, respectively). Mobility and daily life activities showed greater improvement with APO with a large effect size and

bodily discomfort with a moderate effect size. STN-DBS reached a large effect size in mobility, daily life activities, emotional wellbeing, and bodily discomfort, and had a moderate effect size on stigma. The differences between APO and STN-DBS were statistically significant for total PDQ-39 score ($P \leq 0.001$), mobility, daily life activities, and bodily discomfort.

Discussion

To our knowledge, this is the first prospective study that compares APO and subsequent STN-DBS in the same patient. Our unit previously published the data of 18 patients treated with APO before the STN-DBS surgery.¹⁰ In that scenario, we had observed that, despite not reaching the effectiveness of STN-DBS, APO had achieved adequate control of the disease when the conventional oral/transdermal medication was no longer effective. In addition to the lack of randomized and prospective studies comparing these 2 treatments, the data derived from recent studies^{1,4,5,7,11} reveal that patients treated with APO are usually in a much more advanced stage than STN-DBS patients.

APO and STN-DBS both resulted in substantial motor improvements in this study, reducing daily off time and the complications resulting from conventional medication. In both cases, the effect of STN-DBS was superior to APO, notably in the case of UPDRS IV score. Dyskinesia, which improved dramatically

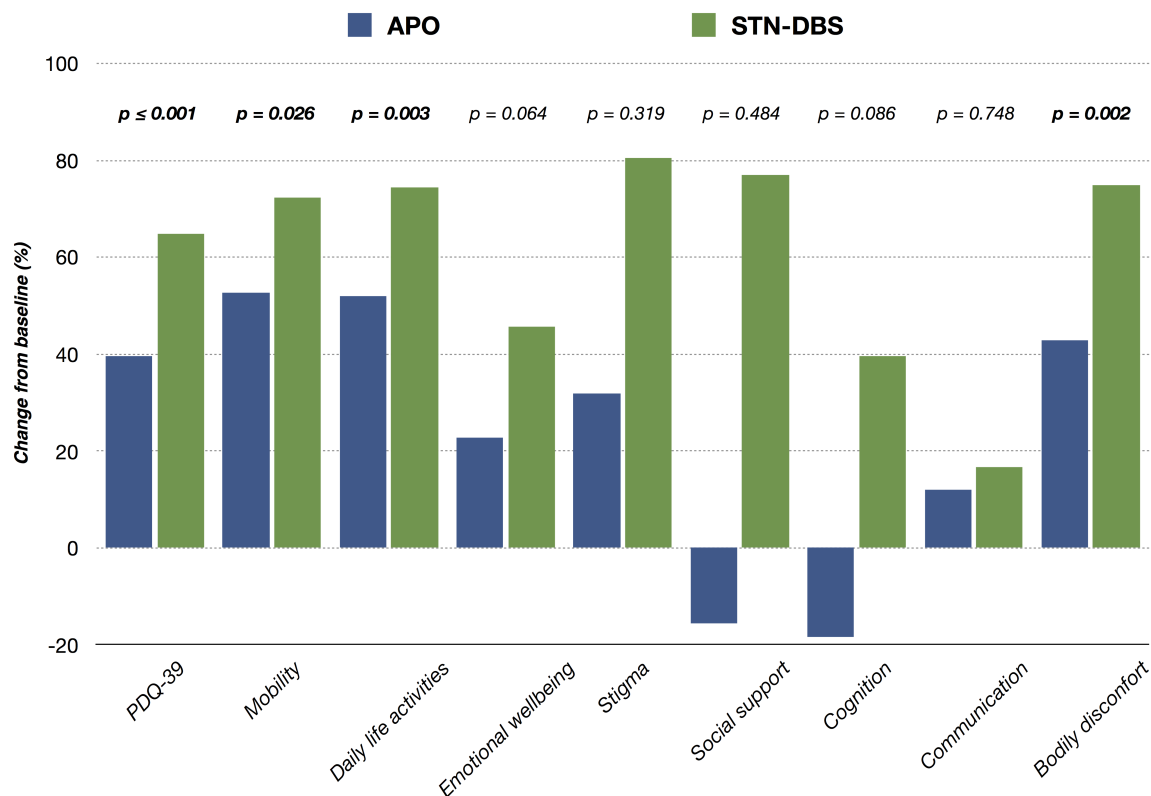


FIG 3. Change in patient's quality of life (PDQ-39 and its domains) relative to baseline for each treatment.

after STN-DBS surgery, did not worsen with APO, despite the LEDD increase. The APO effect on dyskinesia remains controversial. Studies have shown either improvement^{6,18–20} or no change.^{4,7,9,10,12} A compensatory hypersensitivity of the D1 receptors in PD has been linked to dyskinesia,^{21,22} but it might be balanced by a decrease in the dopaminergic pulsatile stimulus.¹⁷

UPDRS III score after STN-DBS surgery, evaluated in the *ON stim/on meds* situation, was significantly lower compared to APO. The most comprehensive studies of STN-DBS also demonstrate this improvement in comparison to conventional medication.^{23,24} This is not easy to explain. On one hand, the effect of STN-DBS on tremor usually exceeds that of medication, and in fact, severe tremor is a common indication for surgery.²⁵ On the other hand, it is believed that levodopa has a greater effect on distal akinesia.^{26,27} This opinion is still controversial.²⁸ Nevertheless, what is consistent throughout these studies is that the *ON stim/on meds* situation obtains the best results.

STN-DBS resulted in a substantial overall effect on non-motor symptoms, measured by the NMSS scale, whereas the impact of APO was more modest. There was a large difference for the total score, however, despite scores for individual domains were lower after STN-DBS—except for urinary symptoms—only the sleep/fatigue domain showed differences

between treatments. In our study cohort, the non-motor symptoms burden was low. Patients were selected for STN-DBS, and therefore, were in an early advanced stage, so cardiovascular or cognitive items were scarcely represented. Compared to baseline, STN-DBS was more beneficial for depressive mood, whereas APO was more beneficial for apathy, although the differences between treatments were not significant. In our study, depression and apathy scores after the STN-DBS were similar to those found in other studies.^{23,24} Sleep quality significantly improved with both treatments, although STN-DBS showed greater benefit than APO. In addition to changes in sleep structure, in aPD, insomnia reflects a prolonged *off* periods, because of insufficient dopaminergic replacement during the night.²⁹ The improvement in sleep quality is mainly driven by the nocturnal motor control achieved with STN-DBS, whereas the effect of APO is focused on waking hours.

Overall cognition did not change with APO or STN-DBS. Phonetic fluency significantly worsened after the STN-DBS compared to APO. It was also reduced relative to baseline evaluation, close to statistical significance. In almost all STN-DBS studies, executive function assessment shows a mild worsening after surgery, which is more pronounced in the case of phonetic fluency. This worsening could be related to the stimulation of the subthalamic nucleus itself.^{30,31} Nevertheless, several factors

can play a role, such as current diffusion to non-motor regions of the subthalamic nucleus³² or certain trajectories of the electrodes.³³ These factors have not been adequately evaluated.

The patient's quality of life improved substantially after both APO and STN-DBS, but the greatest improvement occurred after STN-DBS. For all PDQ-39 domains, scores were lower after STN-DBS treatment.

Finally, 4 patients withdrew from the study, but only 2 were related to APO. One patient stopped APO by his own decision after a few weeks, and another patient developed a psychotic episode that required hospital admission. Although APO was stopped, the patients' symptoms remained unchanged, so STN-DBS was no longer a treatment option. None of 3 patients with a previous medical history of impulse control disorder developed these symptoms. Only 1 patient experienced mild hypersexuality and hobbyism with APO.

Our study has some limitations. The sample size was small, however, it is broadly similar to some APO prospective studies, particularly considering that all patients in our study also underwent STN-DBS surgery. Our study design avoided possible biases from the patient's profile. However, the APO phase may be negatively influenced by some patient's previous negative opinion of APO, which was used only as a bridge therapy before the desired STN-DBS. In addition, the open-label assessments of outcomes could have increased the difference between the treatments. The evolution of the disease is inevitable, but in the context of aPD, this would be minimized over a 6-month interval and, at the same time, clinical stability would be guaranteed with each treatment.

In conclusion, APO and STN-DBS both markedly improved motor and non-motor symptoms and quality of life compared to baseline in aPD patients. Cognition was unchanged by either treatment. Overall, STN-DBS was the most effective treatment, however, in the setting of prominent pure dopaminergic fluctuations, APO had a very robust motor benefit, far superior to previously described. As noted above, most patients treated with APO are in a more advanced phase than those treated with STN-DBS. For non-motor symptoms, although beneficial, APO effect was more modest than previously reported. We cannot discount that this might be related to treating patients with a less advanced disease in this study.

We would like to highlight the need to be proactive in the treatment of aPD, and to select and administer an appropriate treatment. Device-aided therapies, both surgery and infusion, are able to provide a substantial improvement in aPD patients' symptoms and should not be delayed. A patient who cannot undergo STN-DBS surgery immediately should be on an effective treatment, such as APO, during the waiting time.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

G.F.P.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

A.S.: 1A, 1B, 1C, 2A, 2C, 3A, 3B

B.A.: 1C, 3B

I.J.M.: 1C, 2A, 2C, 3B

M.G.: 1C

E.A.: 1C

J.L.R.: 1C

A.C.: 1C, 3B

Disclosures

Ethical Compliance Statement: The study was carried out following the Declaration of Helsinki of the World Medical Association and approved by the Research Ethics Committee of Santiago (Project identification code 2018/339). Informed consent was obtained from each patient or from their relatives, after a full explanation of the procedures. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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References

- Katzenschlager R, Poewe W, Rascol O, et al. Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, doubleblind, randomised, placebo-controlled trial. *Lancet Neurol* 2018;17(9):749–759.
- Katzenschlager R, Poewe W, Rascol O, et al. Long-term safety and efficacy of apomorphine infusion in Parkinson's disease patients with persistent motor fluctuations: results of the open-label phase of the TOLEDO study. *Parkinsonism Relat Disord* 2021;83:79–85.
- Martínez-Martín P, Reddy P, Antonini A, et al. Chronic subcutaneous infusion therapy with apomorphine in advanced Parkinson's disease compared to conventional therapy: a real life study of non motor effect. *J Parkinsons Dis* 2011;1(2):197–203.
- Drapier S, Gillioz AS, Leray E, Péron J, Rouaud T, Marchand A, Vénin M. Apomorphine infusion in advanced Parkinson's patients with subthalamic stimulation contraindications. *Parkinsonism Relat Disord* 2012; 18(1):40–44.
- Martínez-Martín P, Reddy P, Katzenschlager R, et al. EuroInf: a multicenter comparative observational study of apomorphine and levodopa infusion in Parkinson's disease. *Mov Disord* 2015;30(4):510–516.
- Auffret M, Le Jeune F, Maurus A, et al. Apomorphine pump in advanced Parkinson's disease: effects on motor and nonmotor symptoms with brain metabolism correlations. *J Neurol Sci* 2017;372:279–287.
- Sesar A, Fernández-Pajarín G, Ares B, Rivas MT, Castro A. Continuous subcutaneous apomorphine infusion in advanced Parkinson's disease: 10-year experience with 230 patients. *J Neurol* 2017;264(5):946–954.
- Borgemeester RW, Drent M, van Laar T. Motor and non-motor outcomes of continuous apomorphine infusion in 125 Parkinson's disease patients. *Parkinsonism Relat Disord* 2016;23:17–22.

9. Houvenaghel JF, Drapier S, Duprez J, et al. Effects of continuous subcutaneous apomorphine infusion in Parkinson's disease without cognitive impairment on motor, cognitive, psychiatric symptoms and quality of life. *J Neurol Sci* 2018;395:113–118.
10. Sesar A, Fernández-Pajarín G, Ares B, et al. Continuous subcutaneous apomorphine in advanced Parkinson's disease patients treated with deep brain stimulation. *J Neurol* 2019;266(3):659–666.
11. Dafsari HS, Martinez-Martin P, Rizos A, et al. EuroInf 2: subthalamic stimulation, apomorphine, and levodopa infusion in Parkinson's disease. *Mov Disord* 2019;34(3):353–365.
12. De Gaspari D, Siri C, Landi A, et al. Clinical and neuropsychological follow up at 12 months in patients with complicated Parkinson's disease treated with subcutaneous apomorphine infusion or deep brain stimulation of the subthalamic nucleus. *J Neurol Neurosurg Psychiatry* 2006;77(4):450–453.
13. Alegret M, Valdeoriola F, Martí M, Pilleri M, Junqué C, Rumià J, Tolosa E. Comparative cognitive effects of bilateral subthalamic stimulation and subcutaneous continuous infusion of apomorphine in Parkinson's disease. *Mov Disord* 2004;19(12):1463–1469.
14. Defer GL, Widner H, Marié RM, et al. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord* 1999;14(4):572–584.
15. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010;25(15):2649–2653.
16. Cohen J. Statistical power analysis for the behavioral sciences. *Academic*. 1977;8:567. <https://doi.org/10.4324/9780203771587>
17. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. *Med Care* 1989;27(3 Suppl):S178–S189.
18. Manson AJ, Turner K, Lees AJ. Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: long-term follow-up study of 64 patients. *Mov Disord* 2002;17(6):1235–1241.
19. Katzenschlager R, Hughes A, Evans A, et al. Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson's disease: a prospective study using single-dose challenges. *Mov Disord* 2005;20(2):151–157.
20. García Ruiz PJ, Sesar Ignacio A, Ares Pensado B, et al. Efficacy of long-term continuous subcutaneous apomorphine infusion in advanced Parkinson's disease with motor fluctuations: a multicenter study. *Mov Disord* 2008;23(8):1130–1136.
21. Aubert I, Guigoni C, Häkansson K, et al. Increased D1 dopamine receptor signaling in levodopa-induced dyskinesia. *Ann Neurol* 2005;57(1):17–26.
22. Feyder M, Bonito-Oliva A, Fisone G. L-DOPA induced dyskinesia and abnormal signaling in striatal medium spiny neurons: focus on dopamine D1 receptor-mediated transmission. *Front Behav Neurosci* 2011;5:71.
23. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;355(9):896–908.
24. Schüpbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med* 2013;368(7):610–622.
25. Antonini A, Moro E, Godeiro C, Reichmann H. Medical and surgical management of advanced Parkinson's disease. *Mov Disord* 2018;33(6):900–908.
26. Timmermann L, Braun M, Groiss S, et al. Differential effects of levodopa and subthalamic nucleus deep brain stimulation on bradykinesia in Parkinson's disease. *Mov Disord* 2008;23(2):218–227.
27. Dafotakis M, Fink GR, Allert N, Nowak DA. The impact of subthalamic deep brain stimulation on bradykinesia of proximal and distal upper limb muscles in Parkinson's disease. *J Neurol* 2008;255(3):429–437.
28. Nozaki T, Asakawa T, Sugiyama K, et al. Effect of subthalamic deep brain stimulation on upper limb dexterity in patients with Parkinson disease. *World Neurosurg* 2018;115:e206–e217.
29. Suzuki K, Miyamoto M, Miyamoto T, Hirata K. Parkinson's disease and sleep/wake disturbances. *Curr Neurol Neurosci Rep* 2015;15(3):8.
30. Alegret M, Junque C, Valdeoriola F, et al. Effects of bilateral subthalamic stimulation on cognitive function in Parkinson disease. *Arch Neurol* 2001;58(8):1223–1227.
31. Parsons TD, Rogers SA, Braaten AJ, Woods SP, Tröster AI. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *Lancet Neurol* 2006;5(7):578–588.
32. Frankemölle AM, Wu J, Noecker AM, et al. Reversing cognitive-motor impairments in Parkinson's disease patients using a computational modelling approach to deep brain stimulation programming. *Brain* 2010;133(Pt 3):746–761.
33. Witt K, Granert O, Daniels C, Volkmann J, Falk D, van Eimeren T, Deuschl G. Relation of lead trajectory and electrode position to neuropsychological outcomes of subthalamic neurostimulation in Parkinson's disease: results from a randomized trial. *Brain* 2013;136(Pt 7):2109–2119.