

Motor features and response to oral levodopa in patients with Parkinson's disease under continuous dopaminergic infusion or deep brain stimulation

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Background: Subthalamic nucleus deep brain stimulation (STN DBS) and continuous dopaminergic infusions (jejunal levodopa or subcutaneous apomorphine) are indicated in complicated Parkinson's disease (PD), although it remains unsettled how they compare to each other.

Methods: We investigated the daytime motor condition in patients with advanced PD under monotherapy with jejunal levodopa, subcutaneous apomorphine, or STN DBS and also measured the motor changes produced by an additional standard morning dose of levodopa. Motor performance was assessed with the UPDRS-III, hand taps, the AIMS dyskinesia score and patients' diaries. Outcome measures were time to best motor 'on' after start of morning treatment, daytime variability of motor condition, motor scores.

Results: The time to 'on' was longest in the jejunal levodopa group. DBS and jejunal levodopa treatments produced stable motor conditions without appreciable 'off' episodes. Continuous apomorphine infusion was associated with the worst motor scores (UPDRS-III and taps) and the most frequent off-states. Jejunal levodopa infusion was associated with the highest AIMS scores. Addition of a levodopa dose produced shortening of time to 'on' and a transient motor improvement in the jejunal levodopa group without increase in dyskinesias; in the DBS and apomorphine groups, there was an increase in dyskinesias without changes in UPDRS-III or taps.

Conclusions: STN DBS provided adequate trade-off between motor improvement and dyskinesia control, although dyskinesias could be elicited by adding oral levodopa. Jejunal levodopa infusion produced adequate motor improvement with slow time to 'on' and moderate dyskinesias. Apomorphine infusion produced insufficient motor control and negligible dyskinesias.

Introduction

Amongst the most challenging problems in the management of Parkinson's disease (PD) is the development of severe, long-term motor complications that oral medication is no longer able to control adequately at tolerable doses. The gradual worsening of these disabling symptoms has a significant impact on quality of life of the patients and their carers [1]. In addition, the management costs of patients with motor complications are threefold higher than those of PD patients with stable motor conditions [2]. Because currently neither a

curative nor restorative therapy is available for PD, the role of the neurologist is to ensure that PD patients with motor complications receive those advanced continuous treatment strategies that will most effectively control their particular symptoms and delay disability.

At present, there are three main alternatives to oral medication in patients with complicated PD: subthalamic nucleus (STN) deep brain stimulation (DBS), apomorphine via continuous subcutaneous infusion, and jejunal infusion of levodopa via gastrostomy. These treatments provide continuous symptomatic antiparkinsonian action through different mechanisms, namely high-frequency stimulation of the STN, stimulation of the post-synaptic dopamine receptors, and presynaptic delivery of levodopa. All these strategies are effective in controlling PD motor complications [3–5], but it remains unsettled how they compare to each other. The

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recently published European guidelines on complicated PD indicate that infusions of jejunal levodopa, subcutaneous apomorphine, and STN DBS can be considered in patients with severe motor fluctuations or peak-dose dyskinesias if oral therapy fails [6]. Three randomized controlled studies have recently established the superiority of STN DBS over best medical treatment in the management of PD motor complications [7–9], leaving unsettled the issue of how the three continuous treatments compare to each other. Patients under these treatments may receive additional oral medications, consisting mainly of levodopa and dopamine agonists [10–12], but the effects of adjunct oral medication have not been explored. We studied a series of consecutive patients with stabilized jejunal levodopa, subcutaneous apomorphine, or STN DBS treatments and analyzed their daily motor performance and the motor effects observed following the addition of a standard morning oral levodopa dose.

Methods

Patients were eligible for enrollment if they had a diagnosis of idiopathic PD according to the British PD Society Brain Bank criteria [13] with at least five years of disease duration and had been under treatment for at least one year with one of the following procedures: STN DBS, jejunal levodopa, or subcutaneous apomorphine. All the patients were stabilized with optimal settings and at maximum tolerated doses. After implant, stimulation or infusion settings were up-titrated to provide the best possible control on motor signs. When necessary, oral medication was gradually reintroduced after implant and was maintained at each follow-up evaluation to the minimum dose necessary to permit optimal motor control in addition to stimulation or continuous infusion. At the time of implant, all patients had excellent and sustained response to levodopa, with disabling motor fluctuations (prolonged and at least occasionally unpredictable 'off' periods); at least 25% of the waking day spent in the off state and on-period dyskinesias; were Hoehn-Yahr stage $\geq$ III in the practically defined off condition; fulfilled recognized inclusion and exclusion criteria and the recommendations of the CAPSIT-PD panel [14]. No formal randomization was performed, but patients were offered the opportunity to choose between the three procedures; many chose duodopa or apomorphine infusion also because of the long waiting list for DBS.

The patients were enrolled consecutively in the study. They were admitted to the neurological ward and evaluated according to a standard protocol approved by the Besta Institute internal review board, after signing an informed consent. The levodopa equivalent

daily dose (measured in mg) was obtained by adding to the standard levodopa dose all dopaminergic medications converted to the relative potency of standard levodopa; the total energy delivered (TED, measured in μ J) was computed in patients receiving DBS by the formula $TED = (\text{amplitude}^2 \times \text{pulse width} \times \text{frequency rate})/\text{impedance}$ [15,16].

The patients were subject to a standard diet of 2000 kcal and 15% of protein intake and received meals at standard time. Few days after admittance, they were kept without treatment and without stimulation for 12 h overnight. Starting at 8 AM, they received the continuous drug infusion or DBS according to their previously individualized regimen. Outcome measures were recorded for 12 h during the day of observation. On a separate day, all patients were subject to the same treatment regimen with the addition of a standard oral levodopa/carbidopa (250/25 mg) dose administered at 8 AM. The same morning dose of levodopa was used for all the patients. No other antiparkinsonian medication was administered during the two days of observation. The patients were allowed to take domperidone, and all received 20 mg of domperidone 1 h before the acute levodopa challenge.

Outcome measures were the UPDRS motor score [17], the AIMS dyskinesia scale [18], (both administered every 90 min), and patients' self-rating of motor condition and the hand tapping test (both administered every 30 min), where the patients were required to tap two buttons on a plastic plate and the number of contacts was measured. The subject's task was to alternately tap one button after the other, as fast as possible, for 15 s with the right-hand palm and for another 15 s with the left hand; the average number of taps was calculated. Every 30 min, the patients were also asked to identify their motor condition as 'on' with troublesome dyskinesia, 'on' with non-troublesome dyskinesia, 'on' without dyskinesia, or 'off'.

The objective of the study was to evaluate the time to best motor 'on', the daytime variability of motor conditions, and the motor effect of a superimposed standard oral levodopa dose in the three different treatment conditions. Time to best motor 'on' was the time elapsed between the start of advanced continuous treatment and the best motor score improvement, as shown by the hand tapping test. Daytime variability of motor conditions was measured by the number of 'off' epochs reported by patients. 'Mild' dyskinesias were those which scored between 0 and 10 on the AIMS, 'moderate' dyskinesias scored between 11 and 25, and 'severe' ones scored > 25 .

Demographic data, time to best motor 'on' and the number of 'off' epochs were expressed as means ($\pm$ SE) and evaluated using the Kruskal–Wallis test and

Mann–Whitney *U*-test for pair-wise comparison. Motor responses to advanced continuous treatment and to the treatment with added oral levodopa were compared in each group by paired Student's *t*-test. The three treatment groups were compared using repeated-measures analysis of variance of hand tapping scores, UPDRS motor scores and AIMS dyskinesia scores. Between-subjects tests were used to compare the three treatment groups and to perform pair-wise intergroup comparisons. The Bonferroni correction was used for multiple comparisons. Any *P* values < 0.05 were considered significant. Statistical analysis was performed with SPSS 12.0I for Windows (release 12.0.1, IBM Corporation, NY, USA).

Results

Motor condition

Thirty patients were enrolled in the study, ten in each treatment group. They were 17 women and 13 men, who tolerated well the procedures and remained on a stabilized treatment regimen for at least one year. The three groups differed only for age at disease onset and at time of evaluation (both younger in the DBS group; Table 1).

In the STN DBS group, the time to best motor 'on' averaged 186.0 ± 53.2 min from turning continuous stimulation on; when oral levodopa was administered, there was a non-significant reduction to 159.0 ± 17.9 min. Under continuous stimulation alone, the patients reported a mean of 17.6 ± 3.2 epochs of 'on' state without dyskinesias, 6.7 ± 3.1 epochs of 'off' state, 0.7 ± 0.5 epochs of 'on' state with non-troublesome dyskinesias, and no troublesome dyskinesias.

Addition of a start-up oral dose of levodopa produced a bell-shaped motor improvement, which lasted for 300 min and had its peak at 120 min (the mean improvement of taps averaged 3.2 ± 2.7 compared to

first six hours of monotherapy). Pair-wise analysis revealed no significant improvement in the hand tapping score when additional oral levodopa was administered to patients under continuous monotherapy. The addition of oral levodopa produced a bell-shaped increase in the AIMS scores with peak at 120 min (*P* < 0.01).

In the jejunal levodopa group, the time to best motor 'on' after starting infusion was 492.0 ± 59.7 min and was significantly shortened to 203.3 ± 22.2 min after addition of oral levodopa (*P* < 0.001). Patients' diaries reported a mean of 3.5 ± 0.6 epochs of 'off' state, mostly during the first three hours of observation. Addition of oral levodopa increased taps by an average of 6.7 ± 3.6 during the first six hours of monotherapy; the increase was significantly different during the first two hours (*P* < 0.01), as shown by pair-wise analysis.

Dyskinesias of moderate intensity were prominent in the jejunal levodopa group: patients reported a mean of 2.1 ± 0.5 epochs of 'on' state without dyskinesias, 18.2 ± 1.7 epochs of 'on' state with non-troublesome dyskinesias and a mean of 1.1 ± 1.1 epochs of 'on' state with troublesome dyskinesias. The addition of oral levodopa produced a non-significant bell-shaped increase in the AIMS scores with peak at 150 min.

In the apomorphine group, time to best motor 'on' after starting infusion was 199.5 ± 65.7 min and did not change after the addition of an oral levodopa dose (196.7 ± 32.5 min). Patients' diaries reported a significant incidence of 'off' related symptoms, with a mean of 3.3 ± 1.4 epochs of 'on' state without dyskinesias, 3.6 ± 1.7 epochs of 'on' state with non-troublesome dyskinesias, 0.1 ± 0.1 epochs of 'on' state with troublesome dyskinesias, 17.8 ± 2.0 epochs of 'off' state. Addition of a start-up levodopa dose produced a non-significant increase in taps from 31.5 ± 1.3 to 39.1 ± 4.6 (during the first six hours of treatment).

In the apomorphine group, there were almost no dyskinesias and a partial 'off' condition prevailed. After

Table 1 Demographic features and clinical state of the patients (mean $\pm$ SE)

	STN DBS	Jejunal levodopa	Subcutaneous apomorphine	Total
Age at time of evaluation (years)	$55.2 \pm 2.2^*$	68.4 ± 1.6	64.1 ± 2.9	62.6 ± 2.8
Age at disease onset (years)	$39.6 \pm 2.1^*$	54.4 ± 2.1	47.4 ± 2.8	47.1 ± 2.9
Disease duration (years)	15.6 ± 1.8	14.0 ± 1.7	16.7 ± 2.8	15.4 ± 2.1
Gender (% female)	40	60	70	57
Body weight	71.5 ± 3.8	65.8 ± 6.5	66.3 ± 2.4	67.9 ± 2.6
Hohen-Yahr stage	II–III	II–III	II–IV	II–IV
Oral therapy (LED)	652.0 ± 112.5	0	655.0 ± 180.0	NA
Continuous treatment	$75.9 \pm 6.8 \mu\text{J}$	$69.6 \pm 5.4 \text{ mg/h}$	$2.9 \pm 0.3 \text{ mg/h}$	NA
Duration of continuous treatment (months)	21.9 ± 5.9	13.8 ± 1.5	52.2 ± 20.5	29.3 ± 13.1

STN DBS, subthalamic nucleus deep brain stimulation; LED, levodopa equivalent dose; NA, not applicable; *Significantly different from jejunal levodopa and subcutaneous apomorphine (*P* < 0.01).

the addition of oral levodopa, a significant bell-shaped increase in the AIMS scores occurred ($P = 0.021$) with a plateau from 90 min to 300 min and a duration of about 210 min.

Intergroup comparisons indicated that the time required to reach the best 'on' was significantly longer in the jejunal levodopa group compared to STN DBS ($P < 0.01$) or apomorphine ($P < 0.01$), with no difference between the apomorphine and the STN DBS groups (Fig. 1). The variability of motor conditions had consistent intergroup variations, with a higher number of 'off' states in the apomorphine group compared to the STN DBS or jejunal levodopa groups ($P < 0.01$; Fig. 2). Apomorphine subcutaneous infusion provided the worst UPDRS motor scores (different from STN DBS and jejunal levodopa, $P < 0.001$) and the worst hand tapping scores (different from STN DBS, $P < 0.01$). There were no differences under monotherapy between the jejunal levodopa and the STN DBS group, either on UPDRS or on tapping measurements. This picture was unaltered by the addition of a single morning oral levodopa dose, as UPDRS motor scores and tapping scores were worst in the apomorphine group ($P < 0.01$ vs. STN DBS, $P < 0.001$ vs. levodopa); there were no differences, instead, between the levodopa and the STN DBS groups (Table 2). Patients treated with jejunal levodopa had the highest AIMS dyskinesia scores ($P < 0.001$ compared to STN DBS or apomorphine), whereas the STN DBS group retained the lowest AIMS scores and the least of dyskinesias epochs, even when a start-up levodopa dose was added ($P < 0.05$ compared to levodopa or apomorphine; Fig. 3).

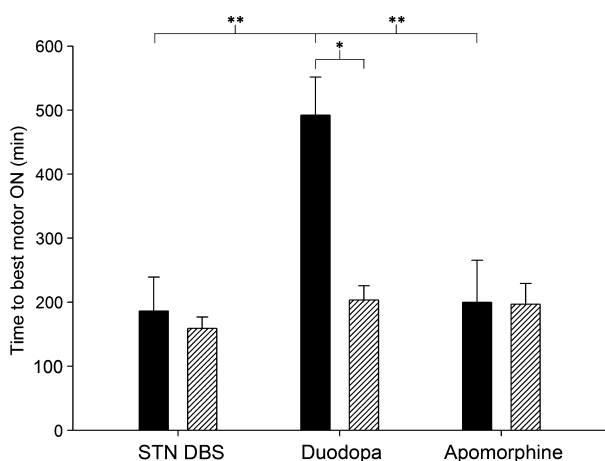


Figure 1 Time to best motor 'on' in patients with monotherapy (solid bars) and after a start-up oral levodopa dose (dashed bars). Comparison of the three treatment groups are indicated by horizontal brackets: *, ($P < 0.05$); **, ($P < 0.01$).

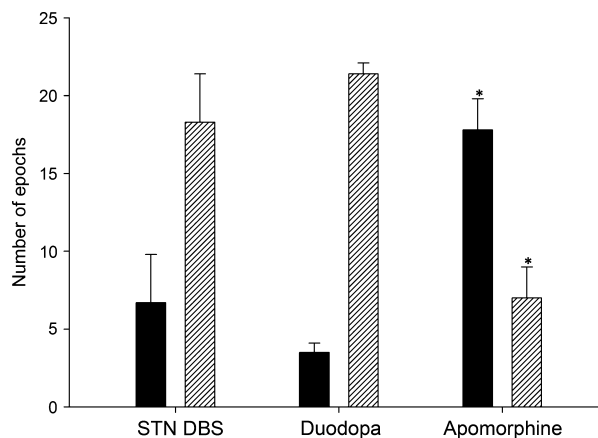


Figure 2 Number of 'off' state epochs (solid bars) and of 'on' state epochs (dashed bars) in patients under continuous monotherapy. *Significantly different from jejunal levodopa and from subthalamic nucleus deep brain stimulation ($P < 0.001$).

Safety

Safety was assessed in all thirty patients. In the DBS group, one patient developed mild transient hypotension during the first two weeks after surgery; in another patient, one electrode had to be replaced three months after surgery because of fracture. In the duodopa group, five patients reported one or more technical problems which did not lead to discontinuation in any of them. One patient reported transient bleeding from gastrostomy on the day after surgery. In the apomorphine group, mild-to-moderate skin nodules (reflecting focal panniculitis) occurred in five patients and transient excessive daytime sleepiness occurred in two patients. One patient suffered from mild hallucinations about five years after starting apomorphine, requiring treatment with low quetiapine doses. Events related to the procedures are listed in Table 3.

Discussion

Continuous dopaminergic infusions and STN DBS provide a background motor improvement for patients with PD. Differences in daily motor outcome in patients with complicated PD have been outlined by this study. STN DBS and jejunal levodopa provided stable motor conditions without appreciable 'off' episodes in most patients, whereas a partial 'off' state was observed with subcutaneous apomorphine. Mild-to-moderate dyskinesias occurred with jejunal levodopa infusion, but not with STN stimulation or apomorphine infusion.

The most important pharmacokinetic property of levodopa is its short plasma half-life of 90 min. In PD, with loss of functional dopaminergic nerve terminals in the striatum, the half-life of dopamine produced

Table 2 Mean motor scores ($\pm$ SE) observed with continuous therapy or with an additional start-up oral levodopa dose

		Experimental groups		
		STN DBS	Jejunal levodopa	Subcutaneous apomorphine
Morning 'on' with home treatment	UPDRS-III	12.0 $\pm$ 1.5	17.3 $\pm$ 3.1	26.3 $\pm$ 4.7
Morning 'off' after overnight withdrawal	UPDRS-III	29.4 $\pm$ 3.4	38.8 $\pm$ 4.8	47.8 $\pm$ 5.2
Best motor 'on' with continuous monotherapy	UPDRS-III	16.9 $\pm$ 2.1	17.8 $\pm$ 2.7	36.9 $\pm$ 4.3*
Mean scores under continuous therapy (12 h)	Hand tapping	48.9 $\pm$ 2.9	41.3 $\pm$ 2.2	31.7 $\pm$ 4.5*
	UPDRS-III	21.0 $\pm$ 2.4	23.1 $\pm$ 3.9	44.4 $\pm$ 4.6**
Mean scores after additional start-up oral levodopa (6 h)	Hand tapping	52.8 $\pm$ 2.9	45.7 $\pm$ 2.8	39.1 $\pm$ 4.6*
	UPDRS-III	15.6 $\pm$ 2.2	20.1 $\pm$ 5.2	35.6 $\pm$ 5.9**

STN DBS, subthalamic nucleus deep brain stimulation; UPDRS-III, unified Parkinson's disease rating scale motor score; *Different from STN DBS ($P < 0.01$); **Different from STN DBS and jejunal levodopa ($P < 0.001$). All the other comparisons are not significant.

from levodopa is similarly brief. The short plasma half-life of levodopa and the dependence of striatal dopamine synthesis upon external levodopa in PD mean that alterations in absorption, metabolism, and distribution to brain of levodopa will immediately translate into clinical effects [19]. Because the short-duration response roughly parallels the plasma levodopa concentrations and presumably, striatal synaptic dopamine concentrations [20], delayed 'on' is probably caused by inadequate absorption and transport of levodopa into the brain. Slowed gastric emptying, a known cause of delayed 'on' [21], was not involved in any of these patients because jejunal levodopa infusions bypassed the stomach, providing first-order pharmacokinetics [22]. In the case of jejunal levodopa, the addition of a start-up oral levodopa dose shortened the time to best motor 'on'. A possible explanation is that as the gastrointestinal metabolism of levodopa is a saturable pathway, increasing the levodopa dose resulted in a more than proportional increase in its plasma concentration [23]. In patients under jejunal levodopa bolus oral addition of levodopa caused a fast delivery of dopamine to the basal ganglia that compensated for the gradual effects of continuous duodenal infusion. In the apomorphine and DBS groups, on the other hand, time to best motor 'on' was approximately 3 h and was not influenced by the addition of a start-up levodopa dose. It is remarkable that the time to best motor 'on' provided by STN DBS and apomorphine coincided notwithstanding their different mechanisms of action.

After withdrawal of oral therapy, patients in the apomorphine group deteriorated more than patients in the other groups. Particularly in patients with apomorphine, the number of 'off' states was more than threefold compared to the jejunal levodopa and STN DBS groups. This finding is in keeping with previous studies reporting that STN DBS can provide greater reduction in dopaminergic medications and 'off' time

improvement than apomorphine infusion [24,25] and that jejunal levodopa can be more efficacious than apomorphine infusion to control motor fluctuations [26]. The present data are also in keeping with a previous report that apomorphine monotherapy fails to keep patients with PD in the 'on' state after withdrawal of oral levodopa [27] and that only a minority of patients with continuous apomorphine infusions can withdraw all other medications [28].

The severity of dyskinesias was mild or moderate in the jejunal levodopa group, never exceeding a score of 25/40. The addition of an oral levodopa dose produced a bell-shaped increase in dyskinesias in all patient groups with a time dimension corresponding to a short-duration motor response. This indicates that the anti-dyskinetic action of STN DBS was associated with the reduction in dopaminergic medication, raising the issue whether STN DBS *per se* has an anti-dyskinetic action. Other DBS targets, such as the globus pallidum internum or the center median and parafascicularis complex, may possibly have a more specific anti-dyskinetic activity [29,30].

Patients in the jejunal levodopa group had excellent control of fluctuations, but retained a high prevalence of non-severe dyskinesias that did not further increase with the addition of a start-up oral levodopa dose. Earlier series reported that dyskinesias are retained in the majority of patients under chronic jejunal levodopa infusions and are increased in about 10% of them [4,31]. A recent study reported that severe dyskinesias are reduced in these patients, but failed to analyze variations of mild dyskinesias [32]. The present observation suggests that severe dyskinesias are not seen in patients treated with jejunal levodopa, whereas mild dyskinesias are retained. This is in keeping with the observation that continuous infusion of levodopa corrects the pharmacokinetic, not the pharmacodynamic, causes of dyskinesias [33] and shifts the dyskinesia dose-response curve to the right [34].

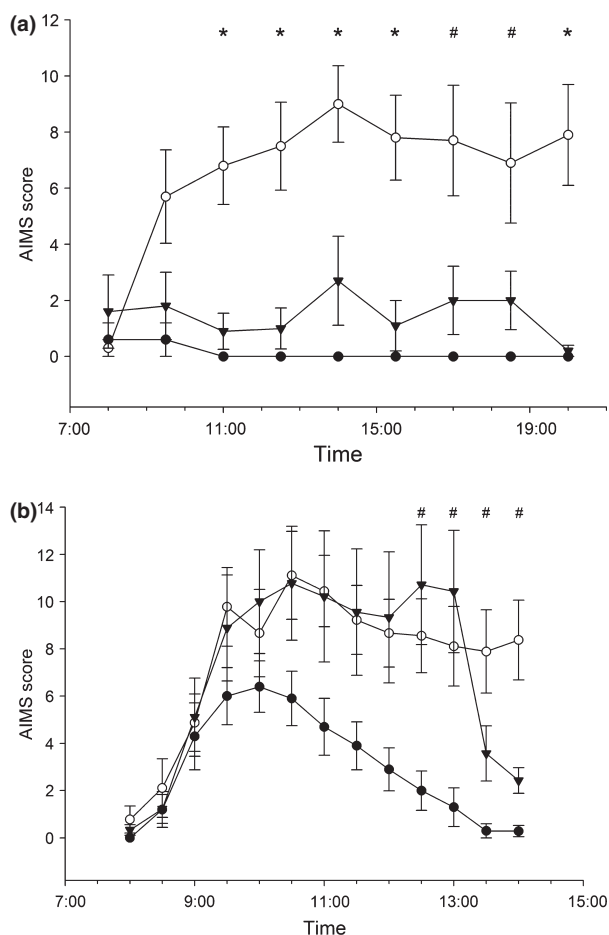


Figure 3 Dyskinesia plots in patients with continuous monotherapy (a) or with monotherapy and a standard oral levodopa dose (b). Symbols: ● subthalamic nucleus deep brain stimulation (STN DBS) group, ○ Jejunal levodopa group, ▼ Apomorphine group. *Jejunal levodopa different from apomorphine and STN DBS ($P < 0.001$); Jejunal levodopa different from STN DBS ($P < 0.001$).

This study bears some inevitable limitations. First, patients were not randomized and baseline differences might have potentially interfered with our findings. The main difference in demographic features between the three treatment groups are that patients treated with STN DBS had earlier age at the time of evaluation, in keeping with the observation that younger patients are

particularly prone to accept DBS. However, previous studies have shown that age does not modify outcome to STN DBS [35], thus limiting the relevance of this age difference. Another difference relates to the duration of continuous treatment, which was shorter in the jejunal levodopa group; but never below one year, a time span considered adequate for adaptation to continuous treatment. Finally, we observed that the DBS group had lower, albeit not statistically different, baseline UPDRS motor score than the other two groups. This difference could be related to a carryover effect of STN stimulation after overnight switch-off, which might underestimate the 'off' condition in the DBS group. Indeed, a lack of worsening of PD motor symptoms after withdrawal of stimulation and medication for 12 h has been reported [36].

Although these three strategies are indicated for PD patients with severe motor fluctuations or dyskinesias [6], we observed differences in motor outcome which may be relevant for the management of patients with complicated PD. Our study design provides short-term observations in a homogeneous clinical setting; future studies may provide long-term assessment of patients under monotherapy and comparative outcome in a randomized controlled design. Controlled trials are desirable in principle, but difficult to put into practice. This study provides a first analysis indicating similarities and differences, notwithstanding the variety of mechanisms of action. In our setting, all these treatment modalities reduced, but did not abolish, motor complications, probably because long-term changes at the post-synaptic level are required to attain a full reversal [37].

The present data identify differences in motor outcome amongst three different continuous treatments and suggest that prospective trials need to be designed to identify the precise placement of each of these continuous treatments in the management algorithm of complicated PD and to highlight their specific cost-efficacy profiles.

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Table 3 Adverse events related to procedures in the three study groups. The number of patients is shown in brackets

STN DBS	Jejunal levodopa	Subcutaneous apomorphine
Lead fracture requiring new implant (1)	Breaking of external infusion tube (3)	Mild-to-moderate skin nodules (5)
Mild transient hypotension soon after surgery (1)	Transient obstruction of the gastrointestinal tube (2)	Excessive daytime sleepiness (2)
	Transient bleeding from gastrostomy (1)	Mild, self-limiting, leg edema (1)
		Visual hallucinations (1)

STN DBS, subthalamic nucleus deep brain stimulation.

Disclosure of conflict of interest

All authors report no conflict of interest and have nothing to disclose.

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