**Medical therapy and subthalamic deep brain stimulation in advanced Parkinson's disease: a different long-term outcome?**

# Medical therapy and subthalamic deep brain stimulation in advanced Parkinson's disease: a different long-term outcome?

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## Abstract

**Objectives:** Few clinical trials reported the comparative short-term efficacy of subthalamic nucleus deep brain stimulation (STN-DBS) versus medical therapy in advanced Parkinson's disease (PD). However, the comparative efficacy, safety and the potential disease-modifying effect of these treatments have not been investigated over a longer follow-up period. **Methods:** In this study, we organised a 'retrospective control group' to compare medical and surgical therapies over a long-term period. We assessed a group of PD patients suitable for STN-DBS but successively treated with medical therapies for reasons not related to PD, and a group of similar consecutive STN-DBS patients. We thus obtained two groups comparable at baseline, which were re-evaluated after an average follow-up of 6 years (range 4–11). **Results:** Patients treated with STN-DBS showed a long-lasting superior clinical efficacy on motor fluctuations, with a significant reduction in the average percentage of the waking day spent in 'OFF' and in the duration and disability of dyskinesia. Moreover, operated patients showed a better outcome in the activities of daily living in 'Medication-OFF' condition. On the other hand, a similar progression of motor score and cognitive/behavioural alterations was observed between the two groups, apart from phonemic verbal fluency, which significantly worsened in STN-DBS patients. **Conclusions:** To our knowledge, this is the first long-term comparison between medical and surgical therapies; a superior efficacy of STN-DBS was observed on motor disability, while no significant differences were observed in the progression of motor symptoms and, apart from phonemic verbal fluency, of neuropsychological alterations.

## Introduction

Subthalamic nucleus deep brain stimulation (STN-DBS) is an effective treatment for patients with advanced Parkinson's disease (PD) complicated by persistent motor fluctuations.1–3

Several open studies described the medium and long-term effectiveness of STN-DBS on PD cardinal features,4–10 while no study investigated the long-term comparative efficacy of surgical and medical treatments. The only comparative data between STN-DBS and medical therapy arise from short-term

studies with a follow-up duration comprised between 6 and 18 months.11–14 Moreover, any comparison with clinical data arising from PD natural history description could be misleading,15, 16 as patients undergoing surgery usually represent a selected population of PD subjects, characterised by earlier age at onset,17 ,18 no cognitive impairment and an excellent response to dopaminergic therapies.19

Nevertheless, a possible 'neuroprotective' effect of STN-DBS has been hypothesised,20 ,21 even though comparative long-term data versus conventional therapies can only be speculative. In this context, a particular methodological procedure was adopted in this study in order to evaluate STN-

DBS and oral medical treatment over a long-term follow-up period: we assessed a series of PD patients selected for STN-DBS who did not undergo surgery for various reasons not closely related to PD (subject's lack of motivation or minor relative contraindications). These patients were assumed to be good candidates for a comparative study with a similar cohort of STN-DBS patients; indeed, both groups satisfied the strict CAPSIT-PD criteria,19 and all clinical and neuropsychological data were collected with the same methodological procedure.

The two groups, matched for all the main clinical features at baseline, were then compared after a mean follow-up period of 6 years (range 4–11).

Our main aims were: to compare the effects of long-term STN-DBS and oral levodopa treatment over PD main cardinal symptoms and motor fluctuations in order to test whether the reduction of oral levodopa doses and a more stable control of basal ganglia pathological circuitry may lead to a milder long-term outcome of PD symptoms, and to report comparative neuropsychological data between STN-DBS and oral levodopa treated patients, evaluating if a long-term STN-DBS stimulation may result in a different cognitive outcome.

## Materials and methods

As shown in *figure 1*, 180 PD patients received an indication to STN-DBS at our centre between 1998 and 2008; 157 subjects underwent surgery, while 23 subjects did not undergo surgery for the following reasons: lack of motivation (15 patients), personal preference for duodopa treatment (four patients), claustrophobia (two patients), cardiac pace-maker (one patient) and head circumference too large for the stereotactic frame (one patient).

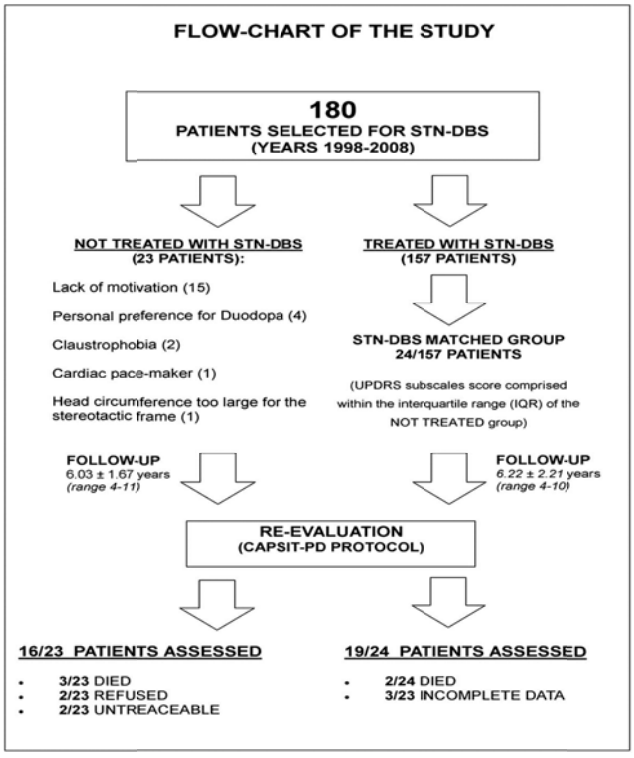


***Figure 1:*** *Flowchart of the study: 23/180 Parkinson's disease (PD) patients selected for subthalamic nucleus deep brain stimulation (STN-DBS) between 1998 and 2008 did not perform surgery for reasons not closely related to PD and were included in a long-term follow-up comparative study.*

Patients who did not undergo surgery (medical treatment group) were asked to repeat a clinical and neuropsychological evaluation after a minimum follow-up of 4 years: 16/23 subjects accepted, while the evaluation could not be performed in 7/23 subjects (two refused, two were untraceable and three died meanwhile).

Then we selected a group of consecutive STN-DBS subjects treated at our centre between 1998 and 2008, whose baseline values of unified Parkinson's disease rating scale (UPDRS)22 section-I, -II (ON and OFF), -III (ON and OFF), -IV, -V and -VI (ON and OFF) were comprised within the IQR baseline values of the control group.

These criteria were fulfilled by 24/157 subjects (STN-DBS group), even though follow-up data at ≥4 years since surgery were available for 19 patients (three subjects did not complete the scheduled follow-up evaluation and two subjects died).

**Baseline clinical and neuropsychological assessment**

According to the Core Assessment Program for Surgical Interventional Therapies (CAPSIT) protocol for PD patient's surgical selection,19 all subjects were assessed at baseline (surgical selection) by a complete UPDRS evaluation, both in OFF condition (‘MED-OFF’; at least 12 h after the last dose of levodopa) and in ON condition (‘MED-ON’; 60 min after the administration of a levodopa challenge dose, consisting in 1.5 times the usual levodopa morning dose). UPDRS-III axial, tremor and bradykinesia subscores were also calculated as follows: the average score of items 18 (speech), 22 (neck rigidity), 27 (arising from a chair), 28 (posture), 29 (gait), 30 (postural stability) for axial subscore; items 20 (tremor at rest) and 21 (action or postural tremor of hands) for tremor subscore and items 23 (finger taps), 24 (hand movements), 25 (rapid alternating movements of hands), 26 (leg agility) and 31 (body bradykinesia and hypokinesia) for bradykinesia subscore.

Moreover, a neuropsychological evaluation consisting in a standardised battery of cognitive tests assessing reasoning, memory and frontal executive functions was performed (table 1) and, in accordance with the criteria of the Movement Disorders Society,23 the number of patients affected by dementia was reported.

***Table 1:*** *Clinical, demographic and neuropsychological variables of the two groups at baseline*

| | **Medical treatment group** | **STN-DBS group** | **p Value** |
|---|---|---|---|
| *Clinical assessment* | | | |
| N subjects | 16 | 19 | |
| Age at surgical selection (years) | 60.87±5.81 (47–68) | 60.11±5.62 (49–68) | 0.578 |
| Disease duration at surgical selection (years) | 11.06±2.93 (8–19) | 12.94±2.15 (9–16) | 0.217 |
| Motor fluctuations duration at surgical selection (years) | 3.09±1.54 (2–6) | 4.09±1.28 (1–7) | 0.243 |
| Follow-up duration (years) | 6.03±1.67 (4–11) | 6.22±2.21 (4–10) | 0.364 |
| LEDD at time of surgical selection (mg) | 1252.73±430.02 (670–2160) | 1120±328.79 (425–1500) | 0.314 |
| UPDRS-I | 2.28±1.29 (0–4) | 1.55±0.88 (0–6) | 0.128 |
| UPDRS-II 'ON' | 7.50±5.72 (1–19) | 6.00±4.61 (1–22) | 0.728 |
| UPDRS-II 'OFF' | 17.09±7.02 (6.5–26) | 21.00±5.35 (10–29) | 0.186 |
| UPDRS-III 'ON' | 19.31±8.12 (10–35) | 14.79±4.40 (5–21.5) | 0.208 |
| UPDRS-III 'OFF' | 40.16±10.92 (20–62) | 44.37±8.09 (34.5–64) | 0.236 |
| UPDRS-IV | 6.78±3.84 (2–13) | 8.30±2.51 (3–13) | 0.212 |
| UPDRS-V 'ON' | 2.34±0.40 (2–3) | 2.17±0.38 (1.5–2.5) | 0.343 |
| UPDRS-V 'OFF' | 3.41±0.49 (3–4) | 3.26±0.77 (2.5–5) | 0.323 |
| UPDRS-VI 'ON' | 90.94±8.60% (70%–100%) | 92.37±8.72% (70%–100%) | 0.554 |
| UPDRS-VI 'OFF' | 63.75±15.00% (30%–80%) | 53.89±15.21% (20%–80%) | 0.234 |
| Item 32 (dyskinesia duration) | 1.41±0.99 (0–3) | 1.80±0.89 (0.5–3) | 0.258 |
| Item 33 (dyskinesia severity) | 0.91±1.00 (0–3) | 1.42±0.93 (0–2.5) | 0.114 |
| Item 39 (% of waking day spent in 'OFF') | 1.62±0.87 (0.5–3) | 1.25±0.49 (0.5–2) | 0.247 |
| Axial 'OFF' subscore | 2.91±0.93 (0.8–4.1) | 3.20±0.67 (1–3.9) | 0.584 |
| Tremor 'OFF' subscore | 2.02±1.81 (0–5) | 2.70±1.96 (0–5) | 0.181 |
| Bradikynesia 'OFF' subscore | 3.23±1.1 (1.2–4.8) | 3.73±0.74 (1.4–4.6) | 0.419 |
| Axial 'ON' subscore | 1.50±0.72 (0.5–3.3) | 1.39±0.45 (0.6–2.6) | 0.292 |
| Tremor 'ON' subscore | 0.87±0.99 (0–3) | 0.97±0.45 (0–3) | 0.307 |
| Bradikynesia 'ON' subscore | 1.36±0.93 (0.5–2.9) | 1.25±0.67 (0.6–2.4) | 0.467 |
| *Neuropsychological assessment* | | | |
| *Reasoning* | | | |
| Raven colour matrices—PM47 | 26.5±4.3 (16–33.4) | 28.8±3.1 (22–34) | 0.109 |
| *Memory* | | | |
| Bi-syllabic words rep. test | 4.3±0.8 (3–6) | 4.3±0.7 (3–5) | 0.691 |
| Corsi's block tapping test | 4.6±1.0 (3–7) | 4.3±0.8 (2–5) | 0.885 |
| Paired associate learning | 9.4±3.3 (3–17) | 11.3±3.6 (4.5–18) | 0.344 |
| *Attentional-executive functions* | | | |
| Trail Making B | 281.6±191.8 (101–605) | 2399±98.3 (100–475) | 0.769 |
| Nelson MCST categories | 4.9±1.3 (2–6) | 5.5±1.1 (2–6) | 0.101 |
| Nelson MCST perseverations | 2.1±2.4 (0–9) | 1.4±2.3 (0–8) | 0.211 |
| *Language* | | | |
| Phonemic verbal fluency | 34.7±17.1 (4–67) | 44.3±17.7 (11–75) | 0.082 |
| Category verbal fluency | 18.2±4.3 (8.5–27.5) | 18.4±4.6 (12–26.25) | 0.987 |
| *Mood* | | | |
| Beck Depression Inventory | 17.2±11.9 (0–47) | 13±6.8 (4–26) | 0.254 |
| *Anxiety* | | | |
| State Trait Anxiety Inventory—STAI-X1 | 46.4±11.2 (20–60) | 44.5±9.7 (32–65) | 0.345 |
| STAI-X2 | 45.4±11.6 (23–61) | 45.3±8.1 (28–59) | 0.666 |

**LEDD**, levodopa equivalent daily dose; **STN-DBS**, subthalamic nucleus deep brain stimulation; **UPDRS**, Unified Parkinson's disease rating scale.

### STN-DBS surgical procedure

The bilateral stereotactical STN implantation was performed under local anaesthesia, using MRI/CT image fusion for anatomical targeting, intraoperative electrophysiological recording and microstimulation to evaluate clinical effects, as previously described in detail elsewhere.24

### Follow-up evaluation

The Medical treatment group follow-up evaluation comprised an UPDRS scale assessment both in 'Med-OFF' and in 'Med-ON' condition and the same neuropsychological and neuropsychiatric battery of tests performed at baseline.

The STN-DBS group follow-up evaluation comprised a complete UPDRS scale evaluation in four conditions (Stimulation ON/Medication OFF ('Stim-ON/Med-OFF'; after at least 12 h of medication washout); Stimulation OFF/Medication OFF ('Stim-OFF/Med-OFF'; after at least 60 min the stimulator was turned off); Stimulation OFF/Medication ON ('Stim-OFF/Med-ON'; 60 min after the administration of a supramaximal levodopa dose of 1.5 times the usual preoperatively morning dose); Stimulation ON/Medication ON ('Stim-ON/Med-ON'; 60 min after the stimulator was turned on)). The neuropsychological and neuropsychiatric battery of tests performed at baseline was also repeated in the best clinical condition ('Stim-ON/Med-ON').

### Statistical analysis

Descriptive statistics (mean, SD, median and range) were used for continuous variables. The non-parametric Wilcoxon rank sum test and Mann–Whitney U test were applied for comparison within the same group and between the two groups. When appropriate, a general linear model for repeated measures was applied for the comparison of outcomes between groups. Mortality rates were compared by means of Kaplan–Meier survival analysis log-rank test and a regression analysis was performed in order to investigate the possible role of levodopa dose changes on UPDRS-I, -II, -III, -IV, -VI, item 32 (dyskinesia duration), item 33 (dyskinesia severity) and item 39 (% of waking day spent in OFF) clinical outcomes.

All p values reported are two-tailed and a probability (p) value $<0.05$ was considered statistically significant. The analyses were performed using SPSS V.18 for Windows.

The ethical committee approved this study and an informed consent was obtained by all the patients who participated in the study.

## Results

### Baseline comparison between groups

As shown in table 1, no significant differences were observed between the two groups at baseline (presurgical evaluation): the age at surgical selection was approximately 60 years, with an average

disease duration of 11–13 years; the two groups did not differ for the main clinical and neuropsychological scores and were equally affected by disabling dyskinesias and/or OFF periods. Concerning the neuropsychological functions, tests assessing reasoning, memory, executive functions and language were similar, as well as mood and anxiety, and no patient was affected by dementia at baseline.

**Follow-up evaluation**

The clinical and neuropsychological data of the two groups were compared after an average follow-up duration of 6.22 years in the STN-DBS group (range 4–10) and 6.03 years (range 4–11) in the Medical treatment group.

**Motor symptoms**

A significant worsening of UPDRS-III score in 'Med-OFF' and 'Med-ON' condition was observed in patients of both groups.

As shown in figure 2, the Medical treatment group UPDRS-III score in 'Med-OFF' condition ranged from 40.16 (±10.92) to 53.16 (±13.08) (p 0.007), while the STN-DBS group 'Med-OFF' versus 'Stim-OFF/Med-OFF' condition ranged from 45.37 (±8.09) to 53.47 (±16.81) (p 0.009), without evidence of different clinical evolution between groups (p 0.681).

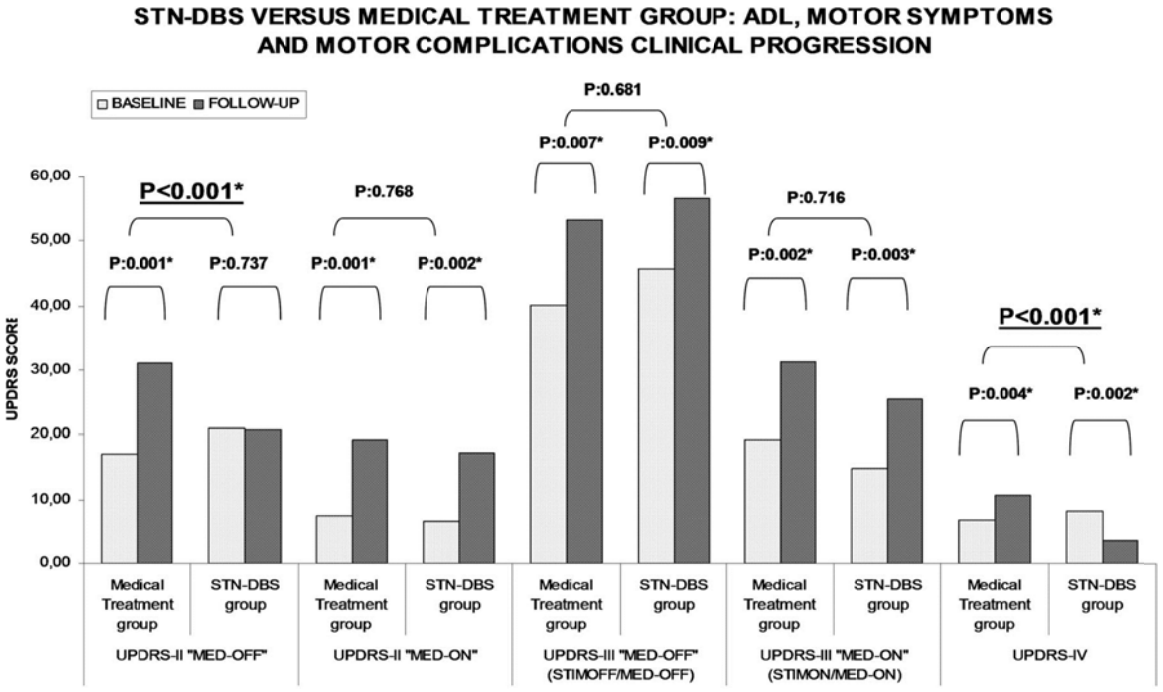


***Figure 2:*** *Subthalamic nucleus deep brain stimulation (STN-DBS) treated patients showed a significantly better evolution in activities of daily living (Unified Parkinson's disease rating scale (UPDRS)-II) in 'Med-OFF' condition and in complications of therapy (UPDRS-IV), while no other significant differences of outcomes were observed between groups.*

Similar results were observed for the UPDRS-III score in 'Med-ON' condition, which increased from 19.31 (±8.12) to 31.30 (±12.21) in the Medical treatment group (p 0.002), while the UPDRS-

III score in 'Med-ON' versus 'Stim-ON/Med-OFF' condition ranged from 14.79 (±4.40) to 33.50 (± 13.50) ($p<0.001$) and the 'Med-ON' versus 'Stim-ON/Med-ON' condition ranged from 14.79 (±4.40) to 24.97 (±14.16) (p 0.003) in the STN-DBS group.

Also in this case no significant differences of clinical evolution were observed between the two groups, neither at the comparison between 'Med-ON'→'Med-ON' and 'Med-ON'→'Stim-ON/Med-ON' condition (p 0.716) nor at the comparison between 'Med-ON'→'Med-ON' and 'Med-ON'→'Stim-ON/Med-OFF' condition (p 0.235). Moreover, similar findings were observed comparing the effect of L-dopa alone in the two groups ('Med-ON' versus 'Stim-OFF/Med-ON' condition); in this case, the STN-DBS group UPDRS-III score ranged from 14.79 (±4.40) to 34.84 (±15.58) ($p<0.001$) and no significant differences of clinical evolution were observed between groups (p 0.684).

As shown in figure 3, a similar progression between groups was observed also for UPDRS-III axial and bradykinesia subscore, which similarly worsened both comparing 'Med-OFF'→'Med-OFF' Medical treatment group versus 'Med-OFF'→'Stim-OFF/Med-OFF' STN-DBS group and 'Med-ON'→'Med-ON' Medical treatment group versus 'Med-ON'→'Stim-ON/Med-ON' STN-DBS group.

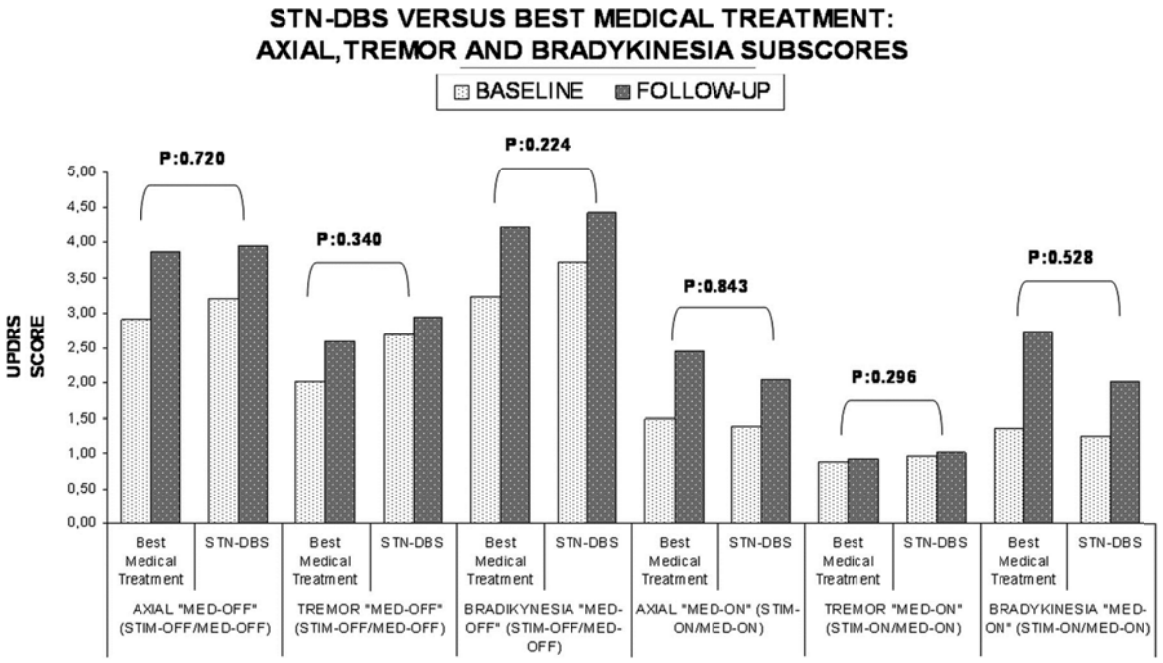


***Figure 3:*** *Comparison of axial, tremor and bradykinesia subscores between the two groups. STN-DBS, subthalamic nucleus deep brain stimulation.*

On the other hand, a sustained control of tremor was observed in both groups, with only a slight worsening of the UPDRS tremor subscore in 'Med-ON'→'Med-ON' Medical treatment group and in 'Med-ON'→'Stim-ON/Med-ON' STN-DBS group (figure 3).

**Activities of daily living**

According to the UPDRS-II mean score (figure 2), activities of daily living (ADL) in 'Med-ON' condition significantly worsened in both groups from baseline to follow-up: the Medical treatment group UPDRS-II score ranged from 7.50 (±5.72) to 19.27 (±8.24) (p 0.001), while the STN-DBS group scores ranged from 6.00 (±4.61) to 17.94 (±8.87) (p 0.002) (no significant differences of clinical evolution between groups (p 0.768)).

On the contrary, the UPDRS-II score in 'Med-OFF' condition showed a significant worsening in patients of the Medical treatment group, ranging from 17.09 (±7.02) to 31.10 (±8.48) (p 0.001), but remained stable in the STN-DBS ('Stim-ON/Med-OFF condition') group (from 21.00 (±5.35) to 20.14 (±9.00) (p 0.737)); in this case, a significant different evolution was observed between groups ($p<0.001$).

The Schwab and England scale, which provides global information on the patient's autonomy in ADL, showed a significant worsening in 'Med-ON' condition in both groups: the 'Med-ON' score ranged from 90.94 (±8.60%) to 70.00 (±13.63%) in the Medical treatment group (p 0.001), and from 92.37 (±8.72%) to 73.61 (±19.69%) (p 0.003) in the STN-DBS group (no significant differences of clinical evolution between groups (p 0.735)).

However, similar to the UPDRS-II, the Schwab and England scale 'Med-OFF' score worsened only in the Medical treatment group, ranging from 63.75% (±15.00) to 46.25% (±15.86) (p 0.004), while it remained substantially stable in the STN-DBS ('Stim-ON/Med-OFF condition') group (from 52.89% ±15.21 to 46.33% ±22.71 (p 0.332)). Nevertheless, in this case, the inter-group comparison of outcome did not reach the statistical threshold (p 0.091).

**Complications of therapy**

A significantly different outcome was observed in therapy complications, as measured by the UPDRS-IV score; the average score of the Medical treatment group (figure 2) significantly increased from 6.78 (±3.84) to 10.75 (±3.38) (p 0.004), while the UPDRS-IV score of the STN-DBS group improved, decreasing from 8.30 (±2.51) to 3.17 (±3.03) (p 0.002) (a significantly different evolution was observed between groups ($p<0.001$)).

The duration (item 32 of UPDRS-IV) and severity (item 33 of UPDRS-IV) of dyskinesias showed a marked improvement after STN-DBS (figure 4), while their scores did not change significantly in the Medical treatment group. Moreover, the average percentage of waking day spent in 'OFF' (item 39 of UPDRS-IV) increased in the Medical treatment group (p 0.015), while it moderately decreased (p 0.204) in the STN-DBS group (a significant different evolution was observed between groups (p 0.005)).

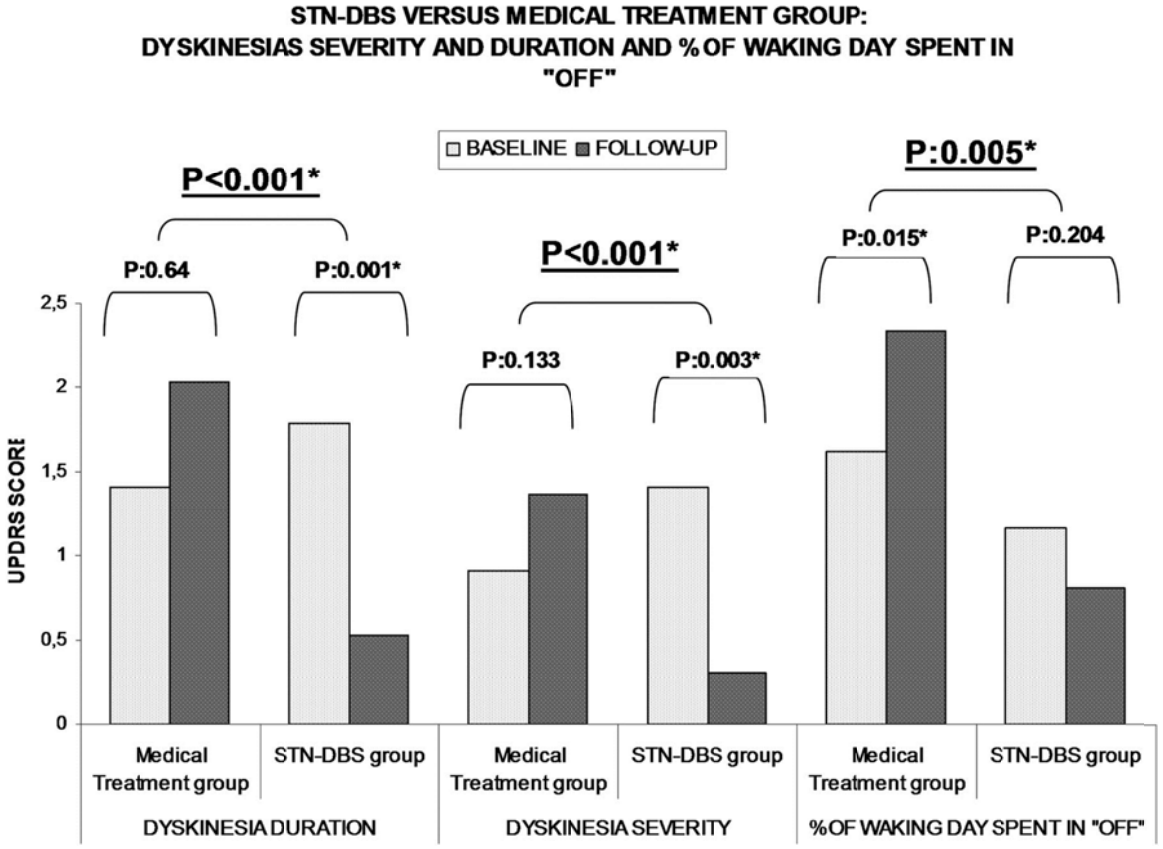


***Figure 4:*** *Subthalamic nucleus deep brain stimulation (STN-DBS) treated patients showed a significantly better evolution in the duration and severity of dyskinesia and in the average percentage of waking day spent in 'OFF'.*

Some STN-DBS patients showed surgical-related and/or stimulation-induced side effects: one subject developed pulmonary thromboembolism after 10 years since surgery; one subject developed eyelid apraxia after 4 years, partially improved after the change of DBS setting; and four subjects developed stimulus-related speech abnormalities (dysarthria or hypophonia) after 4, 5, 6 and 9 years of chronic STN-DBS. A replacement of the impulse generator was required in 9/19 patients during the follow-up period.

On the other hand, complications were observed also in the Medical treatment group: two patients developed pulmonary thromboembolism after 4 and 8 years since the surgical selection, two patients developed severe constipation after 3 and 6 years, one patient had a sepsis after 5 years and one patient developed a mammalian cancer 4 years after the surgical selection.

Suicidal behaviour was not observed in the Medical treatment or in the STN-DBS group.

**Levodopa equivalent daily dose**

The STN-DBS patients' levodopa equivalent daily dose decreased from 1120 (±328.79) mg/day to 510.78 (±295.75) mg/day (p 0.001), while a minimal reduction of dopaminergic therapies was observed in the Medical treatment group (from 1252.73 (±430.02) mg/day to 1141.50 (±490.79) mg/day (p 0.638)), with a significant difference between groups (p 0.001). The L-dopa dose decreased from 782.24 (±283.74) mg/day to 442.11 (±271.45) mg/day in the STN-DBS group (p 0.003), and from 1042.50 (±367.66) mg/day to 994.57 (±41 776) in the Medical treatment group (p

0.654), with a significant inter-group difference (p 0.01). The percentage of subjects treated with dopaminergic agonists decreased both in the Medical treatment group, ranging from 87.5% to 68.8% of patients, and in the STN-DBS group, decreasing from 89.5% to 47.0% (no significant differences between groups (p 0.146)).

In the Medical treatment group, the regression analysis revealed a correlation between levodopa dose reduction and milder dyskinesia duration severity (p 0.043), while no other significant correlations were found between clinical outcomes and levodopa doses changes in both groups.

### Neuropsychological outcome

According to the neuropsychological assessment (table 2), the cognitive evolution was similar in the two groups of patients, with a slight global worsening over time; the only neuropsychological function showing a different inter-group evolution was phonemic verbal fluency, which resulted more impaired in STN-DBS patients (p 0.023).

***Table 2 :*** *Comparison of neuropsychological outcomes*

| | **Medical treatment intragroup comparison** | | | **STN-DBS intragroup comparison** | | | **Inter-group comparison of outcomes (p value)** |
|---|---|---|---|---|---|---|---|
| | **Pre** | **Post** | **p Value** | **Pre** | **Post** | **p Value** | |
| Reasoning | | | | | | | |
| Raven colour matrices—PM47 | 26.5±4.3 (16–33.4) | 22.3±11.0 (0–34) | 0.05 | 28.8±3.1 (22–34) | 22.6±9.2 (0–35) | 0.007* | 0.604 |
| Memory | | | | | | | |
| Bi-syllabic words rep. test | 4.3±0.8 (3–6) | 3.9±0.9 (2–6) | 0.083 | 4.3±0.7 (3–5) | 3.8±0.5 (3–5) | 0.033* | 0.955 |
| Corsi's block tapping test | 4.6±1.0 (3–7) | 4.2±1.0 (2–6) | 0.157 | 4.3±0.8 (2–5) | 3.9±1.1 (0–5) | 0.376 | 0.862 |
| Paired associate learning | 9.4±3.3 (3–17) | 9.1±3.9 (0–16) | 0.346 | 11.3±3.6 (4.5–18) | 10.7±3.2 (5.5–17) | 0.568 | 0.244 |
| Attentional-executive functions | | | | | | | |
| Trail Making B | 281.6±191.8 (101–605) | 308.1±219.7 (85–600) | 0.075 | 2399±98.3 (100–475) | 413.6±179.5 (116–600) | 0.006* | 0.258 |
| Nelson MCST categories | 4.9±1.3 (2–6) | 4.1±2.3 (0–6) | 0.114 | 5.5±1.1 (2–6) | 4.4±1.9 (0–6) | 0.03* | 0.906 |
| Nelson MCST perseverations | 2.1±2.4 (0–9) | 4.4±4.6 (0–11) | 0.035* | 1.4±2.3 (0–8) | 5.1±4.2 (0–12) | 0.05 | 0.570 |
| Language | | | | | | | |
| Phonemic verbal fluency | 34.7±17.1 (4–67) | 25.7±17.9 (0–56) | 0.131 | 44.3±17.7 (11–75) | 24.5±13.8 (7–59) | 0.001* | 0.023* |
| Category verbal fluency | 18.2±4.3 (8.5–27.5) | 16.3±7.7 (0–26.75) | 0.306 | 18.4±4.6 (12–26.25) | 15.2±5.5 (7–26) | 0.031* | 0.544 |
| Mood | | | | | | | |
| Beck Depression Inventory | 17.2±11.9 (0–47) | 12.9±8.4 (0–26) | 0.959 | 13±6.8 (4–26) | 15.1±9.1 (4–33) | 0.232 | 0.432 |
| Anxiety | | | | | | | |
| State Trait Anxiety Inventory—STAI-X1 | 46.4±11.2 (20–60) | 38.3±10.7 (25–56) | 0.374 | 44.5±9.7 (32–65) | 44.7±13.1 (11–62) | 0.711 | 0.450 |
| STAI-X2 | 45.4±11.6 (23–61) | 40.7±12.8 (20–61) | 1.00 | 45.3±8.1 (28–59) | 47.3±12.7 (10–68) | 0.533 | 0.357 |

- *denotes p< 0.05
- **STN-DBS**, subthalamic nucleus deep brain stimulation.

On the other hand, the percentage of subjects affected by dementia was similar: 25% of patients of the Medical treatment group and 21% of patients of the STN-DBS group developed cognitive alterations suggestive of dementia during follow-up (no significant intergroup difference (p 0.467)).

Tests investigating reasoning (PM47) significantly worsened in both groups (table 2). Memory tests (Bi-syllabic Words Rep. test (BWT), Corsi's Block Tapping test (CBT), Paired Associate Learning (PAL)) showed a similar trend in the two cohort of patients: both spatial short-term memory (CBT) and verbal learning (PAL) did not change significantly during follow-up, while BWT scores showed a trend towards worsening in both groups (statistically significant only in the STN-DBS group). The two groups showed a slight worsening in the attentional and executive functions, significant for the Nelson Modified Wisconsin Card Sorting Test (MCST) perseveration in both groups and for the other tests (Trail Making B, Nelson MCST categories, phonemic and category verbal fluency) only in the STN-DBS group (table 2).

Mood and anxiety tests (Beck Depression Inventory, State Trait Anxiety Inventory (STAI)-X1, STAI-X2) did not change significantly between baseline and follow-up in the two cohorts and showed a similar progression at the inter-group analysis (table 2).

**Mortality rate**

A similar mortality rate was observed between the two groups (p 0.628). Three patients died in the Medical treatment group (one for myocardial infarction about 1.5 years and two for pneumonia after 5 and 7 years since presurgical selection), while two deaths were observed in the STN-DBS group (intestinal infarction after 5 years and pulmonary embolism after 3 years since surgery).

**Discussion**

Aiming at a comparison of STN-DBS and oral medical treatment in advanced PD patients over a long-term period, in this study we adopted a particular retrospective analysis: we focused on patients selected as good candidates for STN-DBS, who did not perform surgery for reasons unrelated to the classical contraindications of DBS. We tracked these subjects after an average follow-up period of 6 years, obtaining a ‘Medical control group’ that we compared with a similar group of STN-DBS patients selected for surgery and operated in the same period, with a similar follow-up duration.

This methodological procedure represents an artifice to obtain some comparative data between medical and surgical therapies, by-passing the ethical problems intrinsic to long-term comparison trials with sham stimulation or medical treatment.11

Several follow-up studies demonstrated the clinical efficacy of STN-DBS;4–10 however, only short-term clinical trials compared STN-DBS versus oral medical therapies.11–14 The multicentre PD SURG trial11 reported the 1 year follow-up data of 366 PD patients treated either with surgery or the best medical therapy, showing a significant improvement in DBS patient's quality of life, in spite of a 19% incidence of serious adverse events. Moreover, two large clinical trials12 ,13 reported a significant improvement in the ‘ON’ time without troubling dyskinesias and in the

quality of life in DBS patients after 6 months of treatment, and similar data were also reported by a smaller study after 18 months of follow-up.14

Natural history studies accurately described the long-term clinical and neuropsychological evolution of the general PD population,15 ,16 but these data cannot be compared with those of long-term STN-DBS follow-up since PD subjects treated with surgery represent a selected group of the general PD population.18

Therefore, keeping in mind all the limitations of our retrospective analysis, we tried to obtain some information about the long-term comparison between STN-DBS and medical therapies. We observed that UPDRS-III motor score in 'Med-OFF' and in 'Med-ON' condition equally worsened both in STN-DBS and in medically treated patients, as a possible consequence of medication-stimulation resistant features development.25 Moreover, a similar progression of UPDRS-III axial and bradykinesia subscores were observed in the two groups, as well as a sustained control of tremor with both oral levodopa and electrical subthalamic high frequency stimulation.

Nevertheless, the group of STN-DBS subjects showed a better clinical outcome in UPDRS-II 'Med-OFF' condition, which represents an index of the patient's ADL fluctuation related to the levodopa cycle of action; this finding suggests a better control of motor fluctuations in STN-DBS group, mirroring the STN-DBS group scores improvement observed in the average percentage of the waking day spent in 'OFF' and in the duration and severity of dyskinesia. Taken together, these data highlight the effectiveness of STN-DBS in improving the autonomy in ADL by lessening the severity of motor complications.

The remarkable efficacy of STN-DBS on motor fluctuations is well documented in literature5 ,6 and it is similar only to the efficacy of L-dopa infusional therapy.26–28 However, compared with oral medical therapy, our results underlie the superior long-lasting positive effect of STN-DBS on patient's autonomy in ADL, as a possible consequence of the motor complications improvement.

On the other hand, surgical-related and/or stimulation-induced side effects occurred in some patients treated with STN-DBS: in this limited series of patients, we observed one case of eyelid opening apraxia, partially improved after the change of stimulation setting, and four cases of stimulus-related speech abnormalities (dysarthria or hypophonia). The surgical-related complication rate was similar to that reported in literature,1 and no differences were observed in the mortality rates when comparing STN-DBS and the Medical treatment groups.

Moreover, despite the attentive and executive functions worsening of patients treated with STN-DBS, no significant differences were observed in the neuropsychological clinical evolution of the two groups; taking into account the contrasting data reported in literature,29–33 our findings suggest that, in this series of patients, a long-term STN stimulation did not interfere with the main cognitive domains, as well as with anxiety and mood.

The only exception was represented by phonemic verbal fluency, which significantly worsened in the group of STN-DBS patients: four subjects developed a disabling dysarthria after surgery, and a mild/moderate impairment of the verbal fluency affected most of the remaining patients. This finding is in accordance with previous studies,34–37 which suggest that verbal fluency impairment is a frequent STN-DBS side effect, correlated both to the surgical implant per se, as suggested by

Okun et al,35 who described a decline in phonemic verbal fluency also in patients receiving STN leads implantation without electrical activation, and to different mechanisms of the chronic STN stimulation.36 ,37

Overall, summarising the main findings of this study: (1) STN-DBS showed a long-lasting superior clinical efficacy on motor fluctuations than oral medical therapy, reducing the average percentage of the waking day spent in 'OFF' and improving the disability and duration of dyskinesias; (2) A better patients' autonomy in ADL was observed in the STN-DBS subjects over a long-term follow-up, according to the UPDRS-II score in 'Med-OFF' condition; (3) No significant differences were observed in the UPDRS-III motor score progression; and (4) The cognitive and behavioural assessments showed a comparable evolution in the two groups, with the exception of the phonemic verbal fluency that significantly worsened in the STN-DBS group.

Finally, we may assert that in spite of several clear limitations, represented by the retrospective analysis of data, the small samples size of patients and the average follow-up duration of 6 years, our findings may be evaluated as an original attempt to obtain a long-term comparison between STN-DBS and oral medical therapy in advanced PD.

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**Footnotes**

**Contributors** AM: organisation and execution of research project; design, execution, review and critique of statistical analysis; writing of the first draft and review and critique of manuscript. LR: organisation and execution of research project and analysis of neuropsychological data. MZ: review and critique of statistical analysis; review and critique of manuscript. CAA, EM and SA: execution of research project and analysis of data. ML and MGR: review and critique of manuscript. LL: conception and organisation of research project; critique of statistical analysis; and review and critique of manuscript.

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