

Dopaminergic therapy and subthalamic stimulation in Parkinson's disease: a review of 5-year reports

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Abstract The long-term efficacy and safety of deep brain stimulation (DBS) implant for Parkinson's disease (PD) is described in several recent papers. This procedure has been reported to permit a stable reduction of dopaminergic therapy requirements for up to 5 years, although some expectation of deterioration in non-dopaminergic signs has been recently stated. Our aim is to perform a literature-based review of papers available describing long-term post-operative follow-up after a bilateral implant for subthalamic DBS (STN-DBS). Only peer-reviewed published papers with a post-operative follow-up of at least 5 years were considered. Clinical outcome, disease progression and side effects were assessed at baseline and 2 (or 3 years) and 5 years after surgery. Seven papers were included in the review. A total of 238 patients were analyzed. STN-DBS was confirmed to be an effective treatment for selected patients with PD. In all studies, off-related motor symptoms improved dramatically, compared with pre-implant, at 2 (or 3, according to the study) years and this result persisted at 5-year evaluations. Antiparkinsonian drug reductions, improvements in motor fluctuations and dyskinesias, functional measures and the progression of underlying PD were also reported in all series. Some axial scores, in particular postural stability and speech, improved transiently. Persisting adverse effects included eyelid opening apraxia, weight gain, psychiatric disorders, depression, dysarthria, dyskinesias, and apathy. The present review of the 5-year observations confirms that STN-

DBS is a powerful method in the management of PD, but its long-term effects must be thoroughly assessed.

Keywords Parkinson's disease · Deep brain stimulation · DBS · Surgery · Subthalamus · Levodopa

Abbreviations

IPG	Implantable pulse generator
LEDD	Levodopa-equivalent daily dose
PD	Parkinson's disease
DBS	Deep brain stimulation
VIM	Ventro-intermediate nucleus of thalamus
GPi	Globus pallidus internum
STN	Subthalamic nucleus
TEED	Total electrical energy delivered
UPDRS	Unified Parkinson's Disease Rating Scale

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with a progressive clinical course [19], characterized by motor and nonmotor manifestations, including cognitive, behavioural and autonomic symptoms [1, 8, 21]. The management of PD is mainly pharmacological: levodopa and dopamine agonists are able to provide adequate symptomatic control in the first 5–10 years of therapy. Long-term evolution is accompanied in the majority of patients by complications, such as fluctuations in the motor state (the 'wearing-off' and 'on-off' phenomena), dyskinesias, psychiatric and behavioural side-effects [32, 34].

In the past three decades, the introduction of chronic high-frequency deep brain stimulation (DBS) of different

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targets [2], mainly the ventro-intermediate nucleus of the thalamus (VIM) [6], the globus pallidus internum (GPi) [30] and the subthalamic nucleus (STN) [5], has injected a great deal of excitement into the armamentarium of severe PD treatment, with major results and potential new insights into pathophysiological mechanisms of the disease.

Currently, high frequency STN-DBS is considered the preferred surgical method for treating PD patients, as it has effectively provided significant symptomatic relief and allowed reduction of antiparkinsonian medication [4, 20]. There are several papers reporting 3–4 year post-operative follow-ups of the implant of this target [16, 23, 25, 28, 33, 38], while there is still a paucity of data at longer term; in this study we aimed to give an overview of the most remarkable papers covering the clinical outcome, the dopaminergic therapy modification and the complications 5 years or more after STN-DBS procedures.

Methods

Literature searches were performed in electronic databases including Medline (1996–2010) and the Cochrane, and also by a systematic checking of reference lists published in review articles and original clinical reports. We based the data set of this review on the papers published in peer-review international journals reporting prospective trials that enrolled patients with an established diagnosis of Parkinson's disease [14], fulfilled recognized inclusion and exclusion criteria and the recommendations of the CAP-SIT-PD panel [10], used objective scales for measuring outcomes, and had post-operative follow-ups of at least 5 years after a bilateral implant for high frequency STN-DBS. After paper selection, a descriptive analysis of patients, surgical procedures, clinical outcome and adverse events reported in each study was then carried out, in order to build a general overview of long-term STN-DBS.

For this study, we considered preoperative and the postoperative evaluations at two (or at three, if not otherwise available) years, and at 5 years. We considered for the postoperative assessments three consecutive Unified Parkinson's Disease Rating Scale (UPDRS) evaluations: (a) in the practically defined off condition without antiparkinsonian medication and with stimulation turned off; (b) without antiparkinsonian medication, after switching stimulation on; and (c) with antiparkinsonian medication and stimulation. Condition (a) intended to evaluate the progression of underlying PD motor signs without the influence of treatment; condition (b) was used to measure the efficacy of STN stimulation alone on PD motor signs; and condition (c) served to evaluate the patients' functioning during their best motor condition.

Outcome measures

We examined and compared several motor and functional indexes, as obtained by the considered papers. In particular, upper and lower limb akinesia (generally the sum of 23, 24, 25 and 26 items of the UPDRS), total axial score (generally, encompassing speech, gait and postural stability items, respectively, UPDRS items 18, 29 and 30). Freezing of gait was evaluated using item 14 of the UPDRS part II. The duration of off-periods was determined based on item 39 of the UPDRS, part IV. Dyskinesias were calculated by the sum of the dyskinesia duration and disability UPDRS part IV scores (Items 32 and 33) measured preoperatively in the condition with medication and postoperatively in the condition with medication and stimulation turned on. Activities of daily living were evaluated with the UPDRS part II score in the patients' best functional state (condition c above). Levodopa-equivalent daily dosage (LEDD, measured in milligrams) was computed for each antiparkinsonian medication by multiplying the total daily dosage of each drug by its potency relative to a standard levodopa preparation assigned the value of 1. The conversion factors varied slightly between the different studies, so we decided to utilize only the percent variation for the analysis. Adverse events were classified as transient, persistent (if not improved by turning off stimulation for a short time), stimulation-induced (present at optimal stimulation parameters, but improved when stimulation was turned off or stimulation parameters were modified), device-related, or unrelated to the procedure or stimulation [26].

Statistical analysis

The significance of the comparisons of data before STN implant and the various follow-ups, is indicated in the text and tables as provided by the papers included in our review.

Results

Seven full paper citations met the criteria previously determined for paper inclusion and were considered for the analysis [12, 17, 24, 27, 29, 31, 37]; they all reported prospective open trials. A total of 238 patients were analyzed; among them, 186 (78% of the total number) reached the five-year post-operative evaluation. Table 1 reports patients' demographic and clinical characteristics.

Surgical procedures

The target was located using a combination of methods, which varied according to the surgical centre. Preoperative stereotaxic MRI was used in all centres. Microrecordings

Table 1 Preoperative characteristics of the patients enrolled in the different studies

	Krack et al. [17]	Schüpbach et al. [29]	Romito et al. [27]	Wider et al. [37]	Piboolnurak et al. [24]	Simonin et al. [31]	Gervais-Bernard et al. [12]
Patients (<i>n</i>)	42	37	20	50	33	33	23
Gender	24 M/25 F	24 M/13 F	11 M/9 F	30 M/20 F	24 M/9 F	NA	17 M/6 F
Age at time of surgery (years) mean $\pm$ SD	NA	54.9 $\pm$ 9.1	56.4 $\pm$ 6.9	64.9 $\pm$ 7.6	53.4 $\pm$ 8.3	NA	55.1 $\pm$ 7.2
Disease duration (years) mean $\pm$ SD	14.6 $\pm$ 5.0	15.2 $\pm$ 5.3	14.3 $\pm$ 6.2	14.4 $\pm$ 4.9	13.5 $\pm$ 4.7	NA	12.9 $\pm$ 3.2

were used in most centres [12, 17, 24, 29, 31, 37] to localize subthalamic neuronal activity. In all studies, intra-operative test stimulation and a postoperative neuroimaging (MRI and CT scan)-based reconstruction were performed in order to confirm the correct position of the definitive leads.

Clinical outcome

STN-DBS was confirmed to be an effective treatment for selected patients with PD (Table 2). In all studies, off-related motor symptoms improved dramatically, compared with pre-implant, at 2 (or 3, according to the study) years and this result persisted at 5-year evaluations [12, 17, 24, 27, 29, 31, 37]; at last evaluation, the percentage of improvement ranged between 30 and 55% and in most series, a slight though not significant decrease of the improvement between medium-term evaluation and 5 years after surgery was recorded. Rest tremor, rigidity, gait, and limb akinesia, in decreasing order, were generally improved. Some axial scores, in particular postural stability and speech, improved transiently [17, 24, 27, 29, 31, 37] or even worsened [12].

LEDD was consistently reduced by 36–63% at 5 years (Table 2): it also did not remain stable during the observation period. Levodopa-induced dyskinesias and duration of off-periods also improved over time, with usually a >60% reduction on related scales (Table 2). This improvement paralleled the reduction in daily dopaminergic drug intake and was maintained over 5 years.

On-period freezing of gait showed a stable improvement during the 5 years of follow-up only in one study [27], while a worsening after 3 and 5 years when compared to baseline was indicated in another study [17].

There were generally no variations in UPDRS-activities of daily living (ADL) compared to the pre-implant state (Table 2), but in three studies a worsening of ADL at 5 years was evidenced [12, 17, 37].

When the patients were evaluated without medication and with stimulation turned off 5 years after implant, there was no difference in the total UPDRS motor score compared to baseline without medication; rigidity, speech, gait and postural stability had non-significant variations.

Adverse events

In all series, only a minority of the patients (Table 3) reported persistent and severe adverse events. Hypophonia occurred in 5 to 70% of patients and was generally associated with dysarthria and related to the surgical procedure or to the stimulation. Eyelid opening apraxia was also frequent and generally resolved by adequate botulinum toxin treatment. Many series reported patients with tetanic limb or face contractions clearly related to stimulation [12, 17, 27, 29] and resolved with botulinum toxin treatment or with a change of stimulation parameters. Most series reported a significant weight gain after surgery; in some patients it was associated to health risk. Suicide attempts or ideations [17, 24, 29] and suicides [12, 17, 37] were reported. A total of 17 deaths not related to suicide were recorded [12, 17, 37] among the implanted patients followed during the 5-year period.

Neuropsychiatric side effects (such as mood change, confusion, depression and apathy) were not infrequent after STN-DBS; they could be transient or persistent. Some series also reported cognitive decline, especially in older patients [37].

Discussion

In all analyzed series, the long-term effect of STN stimulation on PD patients resulted in a sustained and marked improvement of the dopaminergic-responsive motor symptoms, with reduction of severity and duration of dyskinesias and of off-periods compared to the pre-implant state. LEDD was markedly reduced up to 5 years after STN implant, and this contributed to dyskinesia reduction, though prolonged continuous STN stimulation may also exert an indirect antidyskinetic action, mediated by plastic changes of corticostriatal terminals that counteract the effects of dopaminergic priming [3, 22] and also a specific antidyskinetic effect of STN stimulation, due to stimulation of the ansa lenticularis containing pallidal outflow to the thalamus [13, 15].

The worsening of some motor signs (mainly speech, postural stability, freezing), and the reported cases of

Table 2 Efficacy of stimulation and progression of motor signs in PD patients, evaluated at different times after STN implant

	Krack et al. [17]		Schüpbach et al. [29]		Romito et al. [27]		Wider et al. [37]		Piboolnurak et al. [24]		Simonin et al. [31]		Gervais-Bernard et al. [12]	
	3 years	5 years	2 years	30	5 years	3 years	5 years	2 years	5 years	3 years	5 years	1 year	5 years	1 year
Patients (n)	42	42	32	30	20	20	20	19	21	33	33	23	23	23
Efficacy of STN stimulation (%) ^a														
UPDRS-motor score	−59.0*	−53.7*	−65.3*	−49.5*	−47.8*	−54.2*	−47.2*	−47.2*	−29.7*	−35.2*	−43.8*	−40.3*	−60.7*	−54.7*
Rest tremor	−82.7*	−75.0*	NA	NA	−86.9*	−95.3*	−75.5*	−75.5*	−67.4*	−74.6*	NA	NA	−82.0*	−73.5*
Rigidity	−73.9*	−70.9*	NA	NA	−41.1*	−56.3*	−69.8	−69.8	−44.8*	−35.9*	NA	NA	−61.0*	−66.1*
Upper/lower limb akinesia	−52.4*	−48.7*	NA	NA	−33.5*	−40.8*	−40.9	−40.9	−22.2*	−24.0*	NA	NA	−61.3*	−59.1*
Axial scores			−56.9 ^e , *	−39.7 ^e , *			−30.1 ^h , *		+1.6 ^h					
Speech	−5.3	0.0			−21.7	−13.0				+11.8	NA	NA	−10.0*	+26.9*
Postural stability	−48.0*	−44.0*			−50.0	−44.4				−33.3	NA	NA	−76.2*	−17.5*
Gait	−61.3*	−51.6*			−45.8*	−50.0*				−26.3	NA	NA	−74.0*	−37.0*
UPDRS, activities of daily living ^b	+49.6*	+91.8*	−13.0	+24.4	−18.3	−21.1	+28.0		+89.0*	+17.9	NA	NA	+62.8*	+141.5*
Freezing of gait	+133.3*	+300.0*	NA	NA	−66.7*	−58.3*	NA		NA	NA	NA	NA	NA	NA
Dyskinesia score	−71.4 ^d , *	−71.4 ^d , *	−71.0 ^f , *	−59.4 ^f , *	−82.9*	−80.5*	−83.3*		−85.4*	−76.5 ^d , *	−60.7*	−83.3*	−85.0 ⁱ , *	−60.0 ⁱ , *
Off-period duration	NA	NA	−83.0 ^g , *	−70.2 ^f , *	−95.0*	−98.0*	−76.3*		−84.2*	−50.0*	−54.5*	−54.5*		
Evaluation of underlying PD (%) ^c														
UPDRS-motor score	NA	NA	−18.1	−1.2	−7.3	−7.8	NA		NA	+3.1	−7.0	−12.1	−3.7	6.5
Rigidity	NA	NA	NA	NA	+4.5	+1.8	NA		NA	+3.3	NA	NA	NA	NA
Speech	NA	NA	−20.7 ^e	−1.7 ^e	−4.3	−4.3	NA		NA	+23.5	NA	NA	NA	NA
Postural stability	NA	NA			−11.1	−16.7	NA		NA	−16.6	NA	NA	NA	NA
Gait	NA	NA			−16.7	−16.7	NA		NA	+5.2	NA	NA	NA	NA
LEDD	−58.5*	−62.7*	−55.6*	−54.6*	−62.2*	−61.9*	−65.3*		−56.9*	−46.5*	−43.1*	−35.8*	−70.5*	−54.4*

Values are given as percentage variation between the various FUs and the baseline

LEDD levodopa equivalent daily dose; UPDRS Unified Parkinson's Disease Rating Scale; NA not available

* *p* Significant compared with the values before surgery in the same drug condition; all the other comparisons were not significant

^a Efficacy is evaluated with stimulation turned on, but without antiparkinsonian medication

^b UPDRS, activities of daily living are evaluated with stimulation turned on and with antiparkinsonian medications

^c Underlying PD is evaluated with stimulation turned off and without antiparkinsonian medication. Negative values (minus sign) indicate a reduction in the scores and therefore an improvement; positive values (plus sign) indicate an increase and therefore worsening of the scores

^d Defined as UPDRS-IV dyskinesia duration subscore

^e Axial** score defined as the sum of the following motor subscores: speech, rising from a chair, posture, postural stability and gait (UPDRS items 18, 27, 28, 29, and 30)

^f Indicated in the original text as UPDRS part IV-B (levodopa induced dyskinesias)

^g Indicated in the original text as UPDRS part IV-A (motor fluctuations)

^h "Axial signs" are defined in the original paper as the sum of UPDRS items 27–30

ⁱ Calculated as total UPDRS-IV score

Table 3 Adverse events observed in patients of the different series

	Krack et al. [17]	Schüpbach et al. [29]	Romito et al. [27]	Wider et al. [37]	Piboolnurak et al. [24]	Simonin et al. [31] ^a	Gervais- Bernard et al. [12]
Total number of analyzed patients	49	32	20	50	33	33	23
Reported adverse events							
Transient							
Disinhibition/hypomania/loss of the emotional control	4	9	2	–	–	–	2
Psychosis	1	4	3	–	–	–	–
Apathy	2	4	2	–	–	–	–
Delirium/confusion	12	6	1	8	–	–	3
Seizure (responsive to antiepileptic drug)	2	–	1	1	–	–	–
Persistent							
Apathy	5	4	1	–	1	–	1
Depression	0	8	0	8	3 (resolved)	–	8
Hypophonia/dysarthria with or without dysphagia	2	13	7	–	23	–	13
Eyelid opening apraxia	8	11	2	–	2	–	7
Disinhibition/hypomania/loss of the emotional control	1	8	–	–	1	–	9
Limb/face dystonia	–	–	5	–	–	–	3
Cognitive decline	3	8	0	11	6	–	–
Weight gain	39	12	4	–	16	–	–
Stimulation-induced							
Hypophonia/dysarthria	–	–	1	–	–	–	–
Dystonia/dyskinesia	2	8	2	–	–	–	–
Tetanic contractions	2	4	3	–	–	–	2
Device-related							
Cable/system infection	1	1	1	1	–	–	3
Unrelated to procedure or stimulation							
Severe spinal arthrosis	–	–	3	–	–	–	–
Transitory ischemic attack	–	–	2	–	–	–	–
Cardiac disorders	–	–	3	–	–	–	–
Suicide attempt/ideation	3	4	0	–	1	–	–
Suicide	1	–	0	3	–	–	1
Death not related to suicide	2	–	–	14	–	–	1

– Type of side effects/adverse events not reported or discussed

^a Side effects/adverse events not reported at all throughout the paper

cognitive decline in the long-term follow-up probably reflect the natural evolution of PD [9, 11, 17, 29, 37], with the extension of neural degeneration to non-dopaminergic areas [7], or simply do not seem to clinically support the postulated neuroprotective effect of STN inactivation [35, 36].

Individual variability in postoperative cognitive and behavioral outcome invites caution, because of the possible relations to preexisting psychiatric illness, surgery-related stress, changes in medication (apathy, depression, mania), alterations in social life associated with mismatch between the motor function improvement, adverse events and patients' expectations [11, 12, 27]. Permanent apathy parallel with a decrease in frontal cognitive function is

probably related to the natural progression of the disease; a recent preliminary paper [18], however, confirmed that apathy may be induced by STN-DBS, thus outlining the role of the subthalamic nucleus in associative and limbic circuitry in humans and suggesting that it is a key basal ganglia structure in motivation circuitry.

Overall, these data indicate that chronic STN-DBS is an efficacious method to improve levodopa-responsive parkinsonian symptoms and allows maintaining a long-lasting reduction of dopaminergic treatment for at least 5 years. Further, longer-term data, a wider number of patients and controlled designed studies, are, however, needed to better analyze the nature and magnitude of clinical and demographic specificity in surgical PD treatment.

Acknowledgments LMR conducted the research project and data analysis and wrote the first draft; AA was responsible of manuscript review and critique.

Conflict of interest The authors received funding from the Italian Ministry of University and Research (National Interest Project number 2001062543 to A.A.).

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