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Article

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REVIEW

Long-Term Outcomes of Surgical Therapies for Parkinson's Disease

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ABSTRACT: The surgical lesion of different brain structures has been used as a treatment for Parkinson's disease (PD) for several decades. More recently, the favored therapeutic approach has involved the administration of levodopa and the use of DBS. These two major therapeutic advances have greatly modified both the clinical condition of patients and the history of the disease. With the introduction of L-dopa in 1967, patients could regain mobility, because their akinesia, tremor, and rigidity were greatly improved, with consequent significant improvement in quality of life and increased life expectancy. However, after the so-called "honeymoon" period in which the disease seemed to be controlled, motor fluctuations and L-dopa-induced dyskinesias mitigated the initial enthusiasm. In the 1990s, unilateral pallidotomy and DBS of the globus palllidus internus and STN reduced these motor fluctuations and dyskinesias remarkably, thereby inaugurating a new era in the surgical treatment of PD. Short- and medium-term follow-up studies of patients who underwent surgery have documented sustained, significant motor benefits. However, given the progressive nature of PD and the purely symptomatic effects of pallidotomy and DBS, the long-term clinical evolution of these surgical patients currently seems to be associated with a new PD phenotype, mainly characterized by axial motor problems and cognitive impairment. Here, we analyze the long-term clinical outcomes of surgical PD patients with at least 5-year follow-up, focusing on the long-term motor symptoms that were initially responsive to surgery.

Key Words: Parkinson's disease; surgery; deep brain stimulation; long-term evolution

During the 1950s and 1960s, functional stereotactic surgery targeting the globus pallidus internus (GPi; pallidotomy) and the ventralis intermedius (Vim) nucleus of the thalamus (thalamotomy) was the main treatment for Parkinson' disease (PD). With the introduction of levodopa in 1967, the number of surgical interventions for PD declined dramatically.[1–3] However, after the so-called "honeymoon" period in which the disease seemed to be well controlled by the L-dopa treatment, motor fluctuations and L-dopa-induced dyskinesia became very difficult to manage. Thus, only two decades later, the dramatic reduction of L-dopa-induced dyskinesia observed with pallidotomy,[4] the improved surgical techniques, a better understanding of PD pathophysiology,[5] and the development of DBS[6] led to a resurgence in the use of surgery in PD patients. At present, unilateral pallidotomy and STN as well as globus pallidus internus (GPi) DBS are considered to be effective treatments for the motor fluctuations and dyskinesias associated with PD, according to evidence-based criteria. Thalamotomy or thalamic stimulation appears to be useful only to suppress tremors.[7] Short- and medium-term follow-up studies in advanced PD patients with bilateral STN DBS have documented a sustained, significant benefit in motor features, coupled with reduced dopaminergic

Additional Supporting Information may be found in the online version of this article.

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TABLE 1. Summary of the data available on the effect of STN DBS in the off-medication state in studies with a follow-up of at least 5 years

	Romito et al.[12]	Wider et al.[13]	Gervais-Bernard et al.[14]	Schüpbach et al.[11]	Krack et al.[9]	Moro et al.[15]	Fasano et al.[16]	Zibetti et al.[17]	Castrioto et al.[10]
No.of patients	20	21	23	30	42	35	20	14	18
Follow-up, years	5	5	5	5	5	5-6	8	9	10
Versus baseline									
Improved	UPDRS-III Rigidity Tremor rest Bradykinesia Axial[a] Gait Time in Off Dystonia	UPDRS-III Rigidity Axial[b]	UPDRS-III Rigidity Tremor Bradykinesia Gait UPDRS-II	UPDRS-III Axial[c] UPDRS-II	UPDRS-III Rigidity Tremor Akinesia Postural stability Gait UPDRS-II Freezing	UPDRS-III Rigidity Tremor Akinesia Postural stability Gait UPDRS-II Dystonia	UPDRS-III Rigidity Tremor (rest and postural) Akinesia Gait	UPDRS-III Rigidity Tremor Bradykinesia Gait Time in Off	UPDRS-III Rigidity Tremor (rest and action) Rigidity UPDRS-II Freezing
Not improved	Postural stability Speech	Bradykinesia Axial[b]	Postural stability	Not detailed	Speech	Speech	Speech Postural stability[g]	Postural stability Speech Other axial[e] UPDRS-II Freezing	Bradykinesia Axial[f] Speech Arise form chair Posture Gait
Worsening in the interim analysis	3 months, 1 and 3 years	6 months versus 5 years	5 versus 1 year	5 versus 2 years	5 versus 1 year	5–6 versus 3–4 years	8 versus 5 years	9 versus 5 years	10 versus 5 years
	None	UPDRS-III	Speech Gait Postural stability	UPDRS-III Axial[c] UPDRS-II	UPDRS-III Akinesia Speech Gait UPDRS-II Freezing	UPDRS-III Akinesia	UPDRS-III Akinesia Postural tremor Axial[d] Postural stability UPDRS-II	Other Axial[e] Postural stability UPDRS-II Freezing	UPDR-III

Improved and unimproved parkinsonian features with respect to the baseline state, and their progression over time, are shown.
[a]Axial is the sum of the scores for the following items of UPDRS-III: speech; postural stability, and gait.
[b]Axial is the sum of the scores for the following items of UPDRS-III: rising from a chair; posture; gait; and postural stability.
[c]Axial is the sum of the scores for the following items of UPDRS-III: speech; rising from a chair; posture; postural stability; and gait.
[d]Axial is the sum of the scores for the following items of UPDRS-III: gait; postural stability; and speech.
[e]Other axial is the sum of the scores for the following items of UPDRS-III: rising from a chair; posture; and facial expression.
[f]Axial is the sum of the scores for the following items of UPDRS-II: speech; falling; freezing; and walking.
[g]Worsened.
Freezing = item 14 in UPDRS-II; gait = item 29 in UPDRS-III.

treatment.[8] However, the long-term outcomes of STN DBS have shown that whereas some of the motor signs remained improved by stimulation, axial signs and cognition deteriorated over time.[9,10]

In this review, we have analyzed the long-term clinical outcomes of uni- or bilateral surgery in PD patients with a well-documented long-term follow-up of at least 5 years. We have paid particular attention to the long-term motor symptoms that were initially responsive to surgery. As such, nonmotor signs after surgery have not been systematically reviewed. The literature search was performed using PubMed from 1960 to April 2012 using the following terms: deep brain stimulation; globus pallidus; pallidotomy; Parkinson; subthalamic nucleus; surgery; thalamus; and thalamotomy. Only English-language publications were retrieved. In addition, concerning the older stereotactic literature, relevant work known to the authors not listed in PubMed was also considered.

Long-Term Evolution of PD in Patients Treated With DBS

There are no long-term data available for unilateral STN or GPi DBS, and thus only bilateral stimulation has been considered.

Subthalamic Stimulation

Motor Effects of Stimulation Alone

In the Off-medication condition and in comparison with preoperative scores, STN DBS significantly improved the total motor UPDRS-III scores in all studies

TABLE 2. Summary of the data available on the effect of STN DBS on the on-medication state in studies with at least a 5-year follow-up

	Romito et al.[12]	Wider et al.[13]	Gervais-Bernard et al.[14]	Schüpbach et al.[11]	Krack et al.[9]	Moro et al.[15]	Fasano et al.[16]	Zibetti et al.[17]	Castrioto et al.[10]
No. of patients	20	37	23	30	42	35	20	14	18
Year of evolution	5	5	5	5	5	5–6	8	9	10
Versus baseline									
Improved	Freezing Dyskinesias Motor fluctuations	UPDRS-III Bradykinesia Axial[a] UPDRS-IV	UPDRS-IV Motor fluctuations Dyskinesias	UPDRS-IV Motor fluctuations Dyskinesias	UPDRS-IV Dyskinesias	Rigidity UPDRS-IV Motor fluctuations Dyskinesias	UPDRS-III Tremor Rigidity Akinesia Gait UPDRS-IV	UPDRS-IV Dyskinesia	Tremor rest Dyskinesias Motor fluctuations UPDRS-IV
Not improved	UPDRS-II S & E	Rigidity Tremor	UPDRS-III UPDRS-II[e]	UPDRS-III Axial[b] UPDRS-II	UPDRS-III[e] Tremor Rigidity Akinesia[e] Speech[e] Gait[e] Postural stability	UPDRS-III Speech Gait UPDRS-II Postural stability[e]	Speech Postural stability	UPDRS-III[e] Speech[e] Other axial[c,e] Post. stability[e] Gait[e] UPDRS-II[e] Freezing[e] UPDRS-IV[e] Dyksinesia[e] Off-duration[e]	UPDRS-III[e] Bradykinesia* Axial[d,e] Rise from a chair[e] Posture[e] Gait[e] Postural stability[e] Speech[e] Falling[e] UPDRS-II[e]
Worsening in the interim analysis	5 versus 1 year Postural stability Speech	6 months versus 5 years Axial[a] UPDRS-II LEDD	5 versus 1 year UPDRS-II LEDD	5 versus 2 years UPDRS-III Axial[b] UPDRS-II	5 versus 1 year UPDRS-III Akinesia Speech Postural stability Gait UPDRS-II Freezing	5–6 versus 4 years UPDRS-III Gait Akinesia UPDRS-II	8 versus 5 years Not done	9 versus 5 years UPDRS-III Other axial[c] Postural stability Gait UPDRS-II Freezing	10 versus 5 years UPDRS-III Bradykinesia

Improved and unimproved parkinsonian features, with respect to the baseline state and their progression over time, are shown. LEDD was reduced in all studies with respect to the basal dose.
[a]Axial is the sum of the scores for the following items of the UPDRS-III: rising from a chair; posture; gait; and postural stability.
[b]Axial is the sum of the scores for the following items of the UPDRS-III: speech; rising from a chair; posture; postural stability; and gait.
[c]Other axial is the sum of the scores for the following items of the UPDRS-III: rising from a chair; posture; and facial expression.
[d]Axial is the sum of the scores for the following items of the UPDRS-II: speech; falling; freezing; and walking.
[e]Worsened with respect to baseline.
Freezing = item 14 in UPDRS-II; gait = item 29 in UPDRS-III.

where a 5- to 10-year evolution was assessed[9–17] (Table 1). When analyzing the motor subscores, rigidity and tremor showed a stable improvement at all time points, whereas improvement in bradykinesia was maintained up to 8 to 9 years,[16,17] but not at 10 years.[10] Gait and freezing improved up to 9 to 10 years,[10,17] whereas the improvement in postural stability was inconsistent after 5 years[9,12,14,15] and did not improve in longer follow-ups.[10,16,17] Speech was not improved at any time throughout the studies, but actually deteriorated. Indeed, in studies with an interim analysis, a worsening in the total UPDRS-III scores, and in some subscores, was observed (Table 1) over time. Moreover, akinesia, gait, and speech showed an earlier deterioration than postural stability (within the first 5 years), the latter worsening between 8 or 9 years of evolution.[16,17] Only in one study did postural stability deteriorate between 1 and 5 years.[14] Although a gradual worsening was observed in interim analyses,[9,11,16,17] the activities of daily living (ADL) (UPDRS-II) scores overall improved, with the exception of one 9-year follow-up study.[17]

Motor Effects of L-dopa Alone

In their blind evaluation at 10 years, Castrioto et al. showed that L-dopa did not significantly improve total UPDRS-III scores any further, nor the cardinal signs or axial features.[10] The response to L-dopa was progressively lost over time also in other studies,[14,15] decrementing from an UPDRS-III improvement of 68% at baseline to 60% at 1 year and to 45% at 9-year follow-up[17] (See Supporting Information Table).

Motor Effects of Stimulation and L-dopa

In the On-medication condition and compared with the preoperative state, STN stimulation did not improve UPDRS-III scores, except in two studies with 5- and 8-year follow-up.[13,16] However, the total motor scores

TABLE 3. Summary of the data available on the effect of GPi DBS in the Off- and On-medication states in studies with a follow-up of at least 5 years

	Moro et al.[15]	Volkmann et al.[33]
No. of patients	16	6
Follow-up, years	5–6	5
Off-medication versus baseline		
Improved	UPDRS-III Rigidity Tremor UPDRS-II	Rigidity
Not improved	Speech Postural stability Akinesia Gait	UPDRS-III Bradykinsia Tremor Posture and gait Speech and swallowing UPDRS-II
Worsening over time	5–6 versus 3–4 years Gait trend ($P = 0.06$)	3 years and 1 year versus baseline 1 year versus baseline: no improvement in speech and swallowing 3 years versus baseline: no improvement in rigidity, tremor, speech, swallowing, and UPDRS-II
On-medication versus baseline		
Improved	UPDRS-IV Dyskinesias	Dyskinesias
Not improved	UPDRS-III Speech Tremor Rigidity Akinesia Postural stability Gait UPDRS-II	UPDRS-III Bradykinesia Rigidity Tremor Posture and gait Speech and swallowing UPDRS-II
Worsening over time	5–6 versus 3–4 years UPDRS-III Speech Akinesia (trend; $P = 0.05$) UPDRS-II	In 4 of 11 patients, there was a worsening of Off motor signs and motor fluctuations after the first year. These patients were submitted to further STN DBS surgery with a successful outcome.

Improved and unimproved parkinsonian features are shown with respect to the baseline state and their progression over time. It was not possible to assess the LEDD reduction in either study.

significantly worsened at a 9- and 10-year follow-up.[10,17] Although freezing of gait (FOG) and axial symptoms improved for up to 5 years in two studies,[12,13] they were worse than baseline at the 9- and 10-year endpoints.[10,17] Therefore, axial symptoms tended to worsen more than other parkinsonian features in the long-term follow-up. Tremor did not improve after 5 years in any study, although there was a surprising improvement in two studies at 8 and 10 years after surgery.[10,16] In studies reporting on an interim analysis, there was a worsening in total UPDRS-III scores, bradykinesia, gait freezing, postural stability, and, in general, in axial subscores over time.[9,12,13,15,17] (Table 2). UPDRS-II scores increased gradually over time,[9,11,15,17] and at 9 and 10 years, they were worse than at baseline.[10,17]

Interestingly, in a blind evaluation after 10 years, total UPDRS-III scores, resting and action tremor, and bradykinesia and rigidity subscores, but not axial features, improved only when stimulation was combined with L-dopa, but not with L-dopa alone.[10]

Motor Complications of Dopaminergic Treatment

Total UPDRS-IV scores and motor fluctuation subscores improved for up 10 years in the follow-up.[10] However, the improvement in motor fluctuations, dyskinesia, and in UPDRS-IV scores showed a trend to progressively worsen.[10,11,17]

Antiparkinsonian Medication

A significant reduction of the L-dopa equivalent daily dosage (LEDD) was observed at all follow-up points for up to 10 years, when compared to baseline.[10] A slight LEDD increment in some,[10,11] but not all, studies[9,12,15–17] was reported over time, but it was only significant in two studies comparing the LEDD at 5 years versus 1 year[14] or 6 months of follow-up.[13]

Parameters of Stimulation

Stimulation parameters remained unmodified or only slightly changed after the 1-year follow-up. No significant variation in voltage, pulse width, and frequency over time was reported.[9,10,15] Occasionally, an increase in the total energy delivered was needed between 3 and 5 years[12] and between 5 and 8 years[16] to provide adequate motor control, suggesting that adaptability of DBS to symptoms progression may be quite limited by the potential side effects elicited by increasing the current delivered.

Preoperative Factors Influencing Outcomes

The preoperative response to L-dopa has been reported to be the best factor to predict the motor benefits from STN DBS in several short- and medium-term follow-up studies.[8,18,19,20] However, recent data indicate that the preoperative severity of axial features may better predict long-term outcomes.[10,16] Indeed, a higher gait score in the Off-medication state at baseline has been inversely correlated with long-term

TABLE 4. Summary of the available data about the effect of Vim DBS in the off-medication state

	Renchrona et al.[34*]	Kumar et al.[36]	Tarsy et al.[35]	Pahwa et al.[37**]	Hariz et al.[38***]
No. of patients	12	5	9	14	38
Follow-up, years	6–7	5.16	5.5	5	6.6
Side	Unilateral	Unilateral	5 unilateral; 4 bilateral	9 unilateral; 5 bilateral	30 unilateral; 8 bilateral
Improvement versus baseline					
	Contralateral Tremor Akinesia	Tremor Contralateral arm 86% Overall 44%	Contralateral Arm tremor rest/post/act Leg agility UPDRS-III	Contralateral tremor 82% Bilateral Tremor 90%–100%	Contralateral tremor
Evolution over time	Worsening UPDRS-III Each item but tremor Increase LEDD Stimulation stable	Worsening Dyskinesia Motor fluctuations Bradykinesia Increase LEDD	Increase LEDD Stimulation stable	Uni- and bilateral No improvement UPDRS-III Akinesia Rigidity H & Y[a] S & E[a] Stimulation stable	No improvement UPDRS-III Akinesia Rigidity Dyskinesia Axial score[a] LEDD stable Stimulation stable

Improved and unimproved parkinsonian features with respect to the baseline state, and their progression over time, is shown.
*Swedish prospective multicenter trial. Stimulation benefit was assessed by a randomized, double-blind, crossover procedure after switching off the stimulation in the Off-medication state.
**American prospective, multicenter study
***European prospective, multicenter study. In this study, the effect of stimulation was evaluated with the regular antiparkinsonian regime.
[a]Worsening.

motor benefit.[10] Worsening of gait and postural stability after surgery was more prevalent among patients with higher scores in these UPDRS-III items in the Off- and On-medication condition and in those with a higher LEDD before surgery.[16] Conversely, younger age at disease onset has been found to be a positive predictive factor in the long term.[21]

Adverse Events

The most frequent adverse effects (AEs) at 5-year follow-up were visual hallucinations and cognitive decline, probably largely related to natural PD progression.[10,13,15,22] However, it might be possible that bilateral surgery has more effect on cognitive decline than unilateral surgery.

Neuropsychiatric problems, such as depression,[23] apathy,[23,24] or suicide ideation/attempt,[25] were reported within the first year after surgery, although they did not seem to have high prevalence in the long term,[9,26] especially when compared to a nonsurgical population.[27] Indeed, some behavioral issues published in long-term series indicated that these phenomena were mainly transitory.[26] The etiology of these AEs is probably multifactorial, related to LEDD reduction,[24] preoperative risks factors,[28] and the stimulation of contacts, possibly located in nonmotor areas.[29,30,31]

Dysarthria, hypophonia,[12] and eyelid opening apraxia were the most frequent stimulation-related AEs observed after a medium- and long-term follow-up.[26] Weight gain (on average, approximately 5 kg since the first year) was the most systematic side effect,[26] although weight gain seems to stabilize after the first year, and in the very long term, some weight loss may occur, even though the mean weight still appeared to be higher than that before surgery.[10]

Concerning device-related AEs, the first battery replacement occured between 5.9[19] and 6 to 7 years.[32] Lead fracture was a relatively common problem, mostly in the medium-term follow-up (3 years).[13]

In summary, STN DBS overall provided significant motor benefit, even after 10 years, and this benefit was superior to that obtained with L-dopa alone. Axial symptoms and bradykinesia improved least in the long term, whereas rigidity, tremor, and motor complications remained well controlled. It is important to note that L-dopa response declined significantly over time after surgery, especially for gait and postural stability. In addition to the worsening in axial problems, cognitive decline was frequently observed over the years.

Pallidal Stimulation

There were only two studies reporting the 5-year outcomes of GPi DBS, one coming from a single center[33] and the other representing a multicenter study.[15]

Motor Effects of Stimulation Alone

In the Off-medication condition, DBS provided significant benefit in total UPDRS-III scores as well as rigidity and tremor subscores, but not in terms of akinesia, gait, postural stability, and speech, at 5 to 6 years, compared to baseline[15] (Table 3). The UPDRS-II also remained significantly improved at 5 to 6 years.[15] In contrast to the multicenter study, only an improvement in rigidity was reported after 5 years in 6 patients who had previously showed an excellent motor response at 1- and 3-year follow-up (56% and 43% improvement in UPDRS-III scores, respectively).[33]

Motor Effects of L-dopa Alone

L-dopa response was also dampened at 5 to 6 years, when compared to the baseline state.[15]

Motor Effects of Stimulation and L-dopa

In the On-medication condition, there was no improvement in any motor sign of PD, compared to baseline, whereas a progressive worsening in total UPDRS-III scores and gait, speech, and akinesia subscores was observed (Table 3).[15] UPDRS-II scores also deteriorated over time.[15]

Motor Complications of Dopaminergic Treatment

With respect to baseline, the improvement of dyskinesia (75% in duration and 100% in severity) and in motor fluctuations was marked and sustained in the long term.[15] Dyskinesia improved by 64%, and time spent in the Off state was significantly reduced in 83% of patients.[33]

Antiparkinsonian Medication

The LEDD was not different from baseline at any time point of evolution.[15,33] L-dopa response in the On-stimulation condition did not deteriorate during the observational period to the same extent as the stimulation-induced benefit.[33] Indeed, the gap between the best possible L-dopa response and the response to pallidal stimulation progressively widened, suggesting a progressive loss of stimulation efficacy, as interpreted by the investigators, rather than the progression of the underlying disease.[33]

Parameters of Stimulation

There were no significant changes in the stimulation parameters over time in both studies.[15,33]

Adverse Events

Adverse events (AEs) related to treatment were observed in 50% of patients at 5 to 6 years,[15] the majority of which were already present at 3 to 4 years. The most prevalent AEs were cognitive decline, depression, anxiety, and speech difficulties, followed by balance and gait disorders. As previously discussed for the STN target, these AEs were attributed mainly to disease progression, but an effect of bilateral surgery or GPi stimulation itself cannot be ruled out. In the Volkmann et al. study,[33] several parkinsonian signs and motor fluctuations started to decline after the first year of surgery (Table 3), and at that time, 4 of 11 patients completely lost stimulation benefit and required another surgery in the STN. In addition, 50% of patients required a battery replacement within 5 to 6 years, with a mean battery life of 4.5 ($\pm$ 0.7) years.[15]

In summary, after 5-year evolution, patients treated with GPi DBS had fewer dyskinesia and less motor fluctuations, although axial signs deteriorated over time. Moreover, these patients had a poorer response to L-dopa as well as more cognitive and psychiatric symptoms.

Thalamic (Vim) Stimulation (Table 4)

Contralateral parkinsonian tremor was significantly controlled by Vim DBS, with no deterioration for up to 7 years.[34] With the exception of two studies in which an amelioration of bradykinesia was observed,[34,35] thalamic DBS did not improve rigidity, bradykinesia, and axial signs.[34–38] There was a worsening in total UPDRS-III scores, rigidity and akinesia subscores,[34,36] motor fluctuations, dyskinesia,[36] axial sign subscores,[38] and H & Y and Schwab and England (S & E) scores over time.[37] The use of anti-PD drugs increased significantly in some studies,[34,36,38] whereas stimulation parameters remained stable over the follow-up period.[34,35,37,38]

Although in one study there were no major complications,[34] dystonia[38] and, mainly, dysarthria and balance disturbances[35,37] were not infrequent in patients treated with Vim DBS, mostly after bilateral surgery.

Long-Term Evolution of PD in Patients Treated With Lesions

Pallidotomy

Because bilateral pallidotomy was associated with high incidence of severe AEs (e.g., cognitive impairment, dysarthria, and dysphagia),[39] unilateral lesions have been usually performed over the last few years. We have mainly reviewed outcomes from patients with unilateral pallidotomy, with the exception of a few patients who received bilateral pallidotomies[40] (Table 5).

At 5 years after unilateral pallidotomy, motor UPDRS improved by 19% to 27%,[41,42] overall disability in the On-medication condition (S & E scores) was stable,[41] and ADL in the Off-medication state improved.[42] Mean tremor reduction was 65% after 4 to 5 years,[41] and, if initially controlled by surgery,

TABLE 5. Summary of the data available on the efficacy of pallidotomy and thalamotomy in the off-medication state versus the baseline state in studies with a follow-up of at least 5 years

	Unilateral Pallidotomy				Unilateral Thalamotomy		
	Hariz and Bergenheim[40]	Fine et al.[41]	Kleiner-Fisman et al.[43]*	Strutt et al.[42]	Speelman[45]	Schuurman et al.[46]	Moriyama et al.[48]**
No. of patients	13	20	10	18	41 (10 bilateral; 31 unilateral)	14	44
Follow-up, years	10	4–5	12	5	19	5	8.8
Main results	↓ Tremor ↓ Dyskinesia ↑ L-dopa ↑ H & Y ↑ Akinesia ↑ FOG Cognitive decline Five patients needed further surgery for their PD 4 months to 11 years after the initial pallidotomy.	↓ UPDRS-III Off-medication 19% ↓ Contralateral Tremor 65% Rigidity 43% Bradykinesia 18% Dyskinesia 70% Stable S & E	↓ Dyskinesia	↓ UPDRS-III Off-medication ↓ UPDRS-total Off-medication ↓ Dyskinesia ADL improved	↓ Contralateral Tremor Rigidity ↑ Disability ↑ Hypokinesia ↑ Postural instability ↑ Speech disturbance	↑ UPDRS-III ↑ Postural instability ↑ Gait disorders ↑ LEDD ↓ Tremor 92% of patients ADL worsened ↑ Gait disturbance	↓ Contralateral Tremor Rigidity ↓ LEDD ADL improved

*This study is the follow-up of the Fine et al. study.
**Only upper limb tremor, rigidity, and bradykinesia were evaluated.

contralateral tremor remained improved up to 10 years.[40] At 4 to 5 years, contralateral rigidity and bradykinesia were reduced by 43% and 18%, respectively,[41] although, in most patients, there was a gradual recurrence of bradykinesia and an increase in FOG at 10-year follow-up.[40] Only moderate disease progression was observed over 10 years,[40] as shown by an increase in mean H & Y stage from 3 at baseline to 3.7 at the last follow-up.

Cognitive decline was reported after 5[42] and 10 years of disease evolution,[40] whereas LEDD increased in all patients who were followed for up to 10 years, without recurrence or induction of dyskinesia contralateral to pallidotomy.[40] Severity of dyskinesia contralateral to pallidotomy diminished by 70% to 75% (UPDRS-IV subscores)[41,42] after 5 years. Moreover, in a small subgroup of patients followed for up to 12 years, there was a tendency toward a sustained improvement in dyskinesia, although other parkinsonian signs did not improve.[43]

In conclusion, the long-term effect of unilateral pallidotomy on contralateral dyskinesia was highly reproducible and stable over time. The benefit on contralateral tremor and rigidity was also maintained in a large proportion of patients, although contralateral bradykinesia only improved in the short term. Axial symptoms were not improved and progressed over time, and, together with the cognitive decline that occurred at the long follow-up (10 years),[40] axial worsening led to increased disability.

Thalamotomy

Before Vim DBS,[6] bilateral thalamotomy was only performed in exceptional cases, because the risk for severe AEs (mainly speech and swallowing difficulties) was estimated to be too high.[44,45] As such, only results from unilateral thalamotomy were available (Table 5).

The longest follow-up was reported by Speelman in 1991,[45] where permanent improvement of tremor in the contraleral arm was observed in 87% of patients. After 19-year follow-up, disability, bradykinesia and postural instability worsened in 90% of the patients, as did speech and gait disturbances.[45] No tremor or mild tremor in contralateral limbs was reported after a follow-up of 5[46] or 8.8[47] years, and contralateral rigidity improved in most of these patients.[45,48] An increase in motor UPDRS score was observed 5 years after surgery, mainly the result of increased postural instability and gait disorders.[46] Accordingly, LEDD increased and ADL worsened.[46] By contrast, improved ADL and reduced L-dopa dosage have also been reported at 8.8 years.[48] Although not prospectively studied, L-dopa-induced dyskinesia did not seem to be an issue at 19-year follow-up.[45] Interestingly, patients were not demented according to the Mini–Mental State Examination (MMSE) 19 years after surgery in a series of young patients with tremor-dominant PD.[45] Although it is known that the MMSE is not the proper instrument to assess dementia in PD, these findings might be related to the type of PD (tremor-dominant PD is known to have a lower risk of dementia), younger age, and shorter duration of the disease at time of surgery.

In summary, Vim thalamotomy appears to be highly effective in combating contralateral tremor in the long term, and although contralateral rigidity and dyskinesia could be improved, bradykinesia and axial symptoms were not improved, and ADL apparently worsened over time.

Discussion and Future Directions

We have summarized the long-term (≥5 years) outcomes of DBS and ablative surgery involving different targets (STN, GPi, and Vim) in PD patients. Studies with bilateral DBS surgery, particularly STN DBS, clearly dominate the literature, when compared with the studies on lesions or unilateral interventions. Although the data coming from these long-term studies are difficult to compare, particularly as they differ in many parameters, including the follow-up duration, laterality, methods of evaluation, and so forth, it appears that the long-term outcomes vary in function of the specific clinical signs of PD.

STN and GPi DBS can induce long-lasting stable, effective improvement in tremor, rigidity, and motor complications (i.e., fluctuations and dyskinesia). However, the long-term clinical phenotype of the surgical PD patient seems to be mostly dominated by bradykinesia, dysarthria, postural instability, and FOG. In addition, cognitive decline, hallucinations, and dementia become increasingly evident in the studies with longer follow-up. These stimulation- and L-dopa-resistant signs have been considered to be mainly related to the progression of the disease to nondopaminergic systems, and they are associated with a progressive decline in autonomy.

It has to be acknowledged that these results can be biased, because they might represent outcomes coming only from patients with good evolution, whereas drop-out patients (usually frequently reported as very numerous in DBS studies) could be the ones with the worst outcome. However, in the 5-year follow-up study by Krack et al.,[9] in which only 7 of 49 patients were lost to follow-up, the results were the same as in other studies with similar follow-up, but higher drop-out rates.

STN Versus GPi DBS in the Long Term

Although STN and GPi DBS were introduced almost simultaneously, there are more long-term outcome reports available for the STN, rather than the GPi DBS. There are several issues that might account for this disparity, as outlined below.

1. According to the pioneering team in Grenoble and the first multicenter clinical trial,[49,50] STN DBS induces more-reliable improvement in bradykinesia and more L-dopa reduction than GPi DBS. The reduction of dopaminergic medication indirectly allowed by STN DBS indicates a greater antiparkisonian effect of bilateral STN DBS versus surgery on any other target. Such a reduction in medication is a comfort for the patient and also an important economic parameter to be considered. In addition, several patients with no longer benefit from pallidal DBS 3 to 5 years after surgery have been successfully treated with STN DBS.[33,51,43]
2. When compared to GPi DBS, a higher rate of short-term behavioral complications has been observed after STN DBS. Some of these, such as impulsivity and mania, are thought to be related to current diffusion to the limbic part of the STN,[52,53] whereas effects such as apathy could be related to the reduction in dopaminergic medication.[24,54] Suicide ideation and attempts are likely to be multifactorial, but the direct effect of stimulation needs to be considered.[25] However, these ''limbic'' STN DBS complications mainly occur in the first months after surgery and are usually reversible (with the exception of completed suicide).[55] After the initial months postsurgery, behavior seems to be rather stable, with few long-term behavioral complications,[9,26] when compared with those experienced when PD is only treated medically.[27] This is consistent with the notion that reduced dopaminergic therapy improves the behavioral complications of dopamine (DA)-replacement therapy.[54,56,57] However, there is very little information about the long-term behavioral, complications and future studies should address this issue.
3. The cognitive deterioration toward dementia after surgery that is observed in long-term studies has been attributed to the progression of the neurodegenerative disease, rather than to the stimulation itself,[9,22,58] although bilateral surgery could have a role. Nevertheless, bilateral DBS and unilateral ablative surgery for PD in young and nondemented patients appears to be safe from a cognitive standpoint, in that the procedure is typically associated with transient, mild, and circumscribed cognitive alterations (most commonly in verbal fluency).[59] The failure to improve quality of life after surgery may be related to baseline cognitive decline without dementia.[60] The original preference for the STN over the GPi has been recently challenged by randomized, comparative, short-term studies,[61–63] which have shown similar benefit and side effects with both targets. Therefore, the more-common choice of STN DBS in PD patients is anything but accepted as a consensus.[64] Thus, the debate into the optimal target is far from closed.[65]

The DBS Patient in Daily Clinical Practice

The large majority of the DBS patients in our daily clinical practice have bilateral STN DBS. From a purely motor perspective, the long-term STN-DBS

patient commonly observed in clinical practice has little or no tremor and rigidity in the Off-medication state. Motor fluctuations and dyskinesia remain improved, and although there is a progressive worsening in bradykinesia and axial signs, when compared with the first years after surgery, these features remain improved, compared to baseline. The clinical state of these patients will be eventually dominated by prominent dysarthia, dysphagia, FOG, festination, postural deformities, imbalance, and falls. By adding dopaminergic drugs, bradykinesia, speech, posture, and gait might improve, although the magnitude of motor response gradually decreases over years.[10,15,17] Moreover, an excessive increase in dopaminergic treatment may be associated with a worsening of speech (i.e., fast, slurred unintelligible), FOG, instability, falls, and possible psychiatric complications (i.e., impulse control disorders, hallucinations, and delusions). As such, the management of long-term DBS patients can be very challenging. No further benefit can usually be expected from changing the parameters of stimulation after the first postoperative year. As for any other patient with motor complications, nonpulsatile treatment with highly fractionated L-dopa (plus DDC inhibitors, MAO-B inhibitors, and COMT inhibitors), in combination with small doses of DA agonists, if tolerated, should be the main therapeutic strategy to adopt. Amantadine may be useful to address gait problems and dyskinesia. Moreover, there are anecdotic cases of motor instability resulting from recurrence in ''Off periods'' after more than 6 years of successful STN DBS that have been treated with continuous jejunal L-dopa infusion, producing significant improvement in the Off-time.[66] Systematic reviews about the frequency of STN DBS failure in the long term are not available, but the data indicate that, more than a therapeutic failure, the aforementioned situation is not infrequent and is mainly related to disease progression. Given the large number of patients treated with STN DBS, more-reliable information about the frequency of this problem and the efficacy of alternative therapies should become available in the forthcoming years. Balance and gait disturbances that do not respond to STN DBS and L-dopa have also been treated with lower frequency DBS[67] or with DBS of the pedunculopontine nucleus, although with questionable benefit.[68,69]

In addition to the cognitive decline and dementia, many other nonmotor aspects may occur several years after surgical treatment. These are the typical features encountered in patients with advanced PD, such as sleep disorder (i.e., REM sleep behavior disorder and diurnal somnolence), autonomic disturbances (i.e., bladder sphincter incontinence, orthostatic hypotension, constipation, and so forth), apathy, and depression, that are most likely related to the disease itself and are not the object of this review.

Conclusions

Surgically, treatment of PD patients produces good, long-term control of both dopaminergic features of the disease and motor complications of L-dopa. However, currently available surgical techniques (e.g., lesions and DBS) do not cure PD and cannot halt the progression of the underlying neurodegenerative process.[9,10,40] It is becoming evident, with the growing number of surgical patients that have been followed over the long term, that there is a new phenotype of patients[70] who—unlike patients treated with dopaminergic treatment only[71]—do not suffer from tremor, rigidity, painful dystonia, On-period dyskinesia, or motor fluctuations, but mainly display axial features, dementia, and other nonmotor problems. Thus, new therapies focused on treating these mainly nondopaminergic features of PD are clearly needed.[72] ■

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