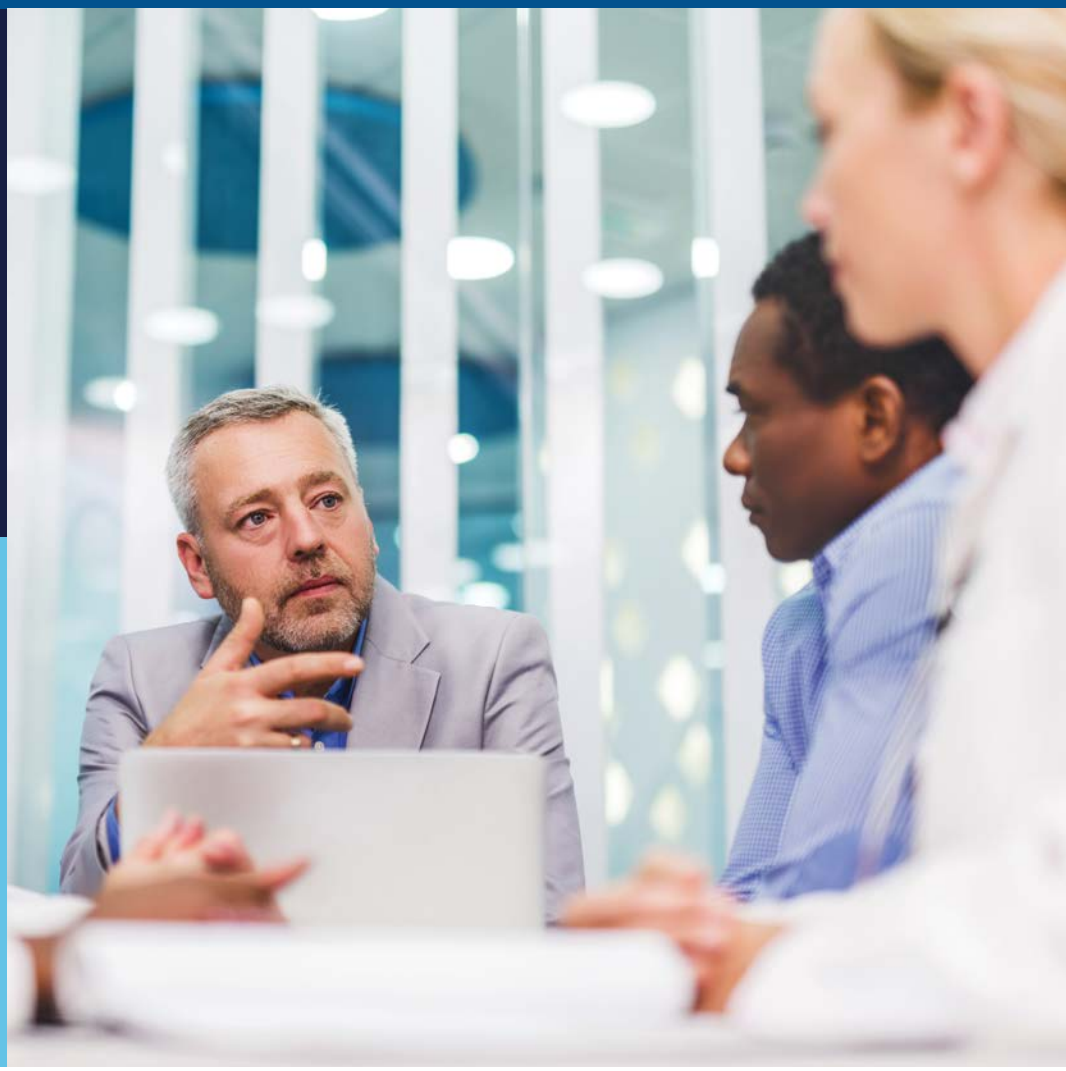
EVIDENCE COMPENDIUM

STUDY SUMMARIES SUPPORTING THE USE OF MEDTRONIC DEEP BRAIN STIMULATION FOR MOVEMENT DISORDERS



150,000
DBS PATIENTS TREATED WORLDWIDE

Medtronic
Further, Together

INTRODUCTION

Medtronic DBS™ Therapy (deep brain stimulation) for movement disorders has gained acceptance and widespread clinical use in recent years. DBS is a key therapy option for movement disorders and is included in the guidelines of the European Federation of Neurological Societies (EFNS) as a recommendation for Parkinson's disease and primary dystonias.

DBS Therapy is adjustable and reversible and may effectively manage some of the most disabling symptoms of Parkinson's disease, essential tremor, and dystonia.

This Evidence Compendium provides an educational resource consisting of summaries of key clinical trials that address various aspects of deep brain stimulation for Parkinson's disease, essential tremor, and dystonia.

Several themes, summarized in general here, are documented by clinical evidence presented in this compendium:

- Patients experience significant improvement in motor function with deep brain stimulation for movement disorders.
- Individual treatment decisions will require the consideration of the risk/benefit ratio between expected patient benefit and the potential for surgical complications and adverse events.

Parkinson's Disease

- DBS Therapy plus medication provides an additional 4 to 5 hours a day of "on" time without dyskinesia.[1-4]
- STN DBS Therapy is associated with a 32-63% average reduction in medication depending upon study, comparator, and time point.[1-5]
- When DBS Therapy is started earlier in the progression of the disease (i.e., when the patient experiences troubling motor symptoms not effectively controlled by medications), DBS Therapy provides increased benefits when compared with medical therapy alone.[6]
- Improvement in motor functioning led to improvement in measurements of activities of daily living, emotional well-being, stigma, and bodily discomfort; cognition, mood, and overall psychiatric functioning were unchanged.[2]
- Disease-related quality of life improves significantly from baseline to 24 months in patients receiving DBS Therapy; there is a minor decline in quality of life in patients receiving medical therapy alone.[6]
- Marked improvement in motor function is still evident at 5-year follow-up.[5]
- Since both STN and GPi stimulation are effective in improving motor function, targets can be selected based on individual patients and symptoms.[4]
- For motor fluctuations and dykinesia, Metronic DBS in the STN received the top recommendation (Level A) from the Movement Disorder Society European Section (MDS-ES) in collaboration with the EFNS. In comparison, Intrajejunal levodopa infusion subcutaneous apomorphine continuous infusion pumps received level C.[7]

Essential Tremor

- Studies have shown that Medtronic DBS Therapy is effective in controlling essential tremor.[8]
- DBS can effectively suppress severe tremor in patients with essential tremor for more than 6 years after implantation.[8]

Dystonia

- Bilateral GPi stimulation demonstrated benefit for patients through improvement in movement symptoms, functional disability, and quality of life scores at 1 year.[9]
- Significant, sustained improvements in dystonia ratings occurred at 5 years after surgery for patients with primary generalized or segmental dystonia treated by DBS Therapy.[10]
- Use of medication to treat dystonia was significantly reduced after surgery.[11]
- Similar symptomatic benefit occurred in patients with generalized or segmental dystonia.[10,11]

1. Weaver F, Follet K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009;301(1):63-73.
2. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep brain stimulation for Parkinson's disease. N Engl J Med. 2006;355(9):896-908.
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4. Weaver FM, Follett KA, Stern M, Luo P, Harris CL, Hur K, et al. Randomized trial of deep brain stimulation for Parkinson's disease: 36-month outcomes. Neurology. 2012; 79: 55-65.
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8. Rehncrona S, Johnels B, Widner H, Tornqvist A-L, Hariz M, Sydow O. Long-term efficacy of thalamic deep brain stimulation for tremor: Double-blind assessments. Movement Disorders. 2003;18:163-170.
9. Vidailhet M, Vercueil L, Houeto J, et al. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med. 2005;352:459-467.
10. Volkmann J, Wolters A, Kupsch A, et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol. 2012;11:1029-1038.
11. Kupsch A, Benecke R, Muller J, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N Engl J Med.2006; 355:1978-90.

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BMT best medical therapy
DBS deep brain stimulation
GPi pars interna of the globus pallidus
STN subthalamic nucleus
EFNS European Federation of Neurological Societies

DEEP-BRAIN STIMULATION OF THE SUBTHALAMIC NUCLEUS OR THE PARS INTERNA OF THE GLOBUS PALLIDUS IN PARKINSON'S DISEASE

The Deep-Brain Stimulation for Parkinson's Disease Study Group. N Engl J Med. 2001;345:956-963

OBJECTIVE

To evaluate deep brain stimulation of the subthalamic nucleus (STN) or the pars interna of the globus pallidus (GPi) in patients with advanced Parkinson's disease.

Study Type

Prospective, multicenter, crossover

Design

134 patients with advanced Parkinson's disease, ages 30 to 75 years, received bilateral implantation in the STN (n = 96) or GPi (n = 38). Patients were evaluated for immediate effects of stimulation 3 months after implant, using a double-blind, randomized, crossover method. Motor function was evaluated unblinded at 2 weeks pre-implant, and 1-, 3-, and 6-months post-implant.

RESULTS

- Significant interaction effects between dopaminergic drugs and stimulation were observed ($P < 0.001$), suggesting a synergistic effect between stimulation and medication.
- The beneficial effect of STN and GPi stimulation was stable over time ($P = 0.58$ and $P = 0.72$, respectively).

Subthalamic Nucleus

- Stimulation was associated with a median improvement in the UPDRS motor score of 49%, as compared with no stimulation ($P < 0.001$).
- Good mobility without dyskinesia during the waking day increased from 27% to 74% between baseline and 6 months ($P < 0.001$).
- Daily levodopa dose equivalents were reduced from a mean of 1218 ± 575 mg at baseline to 764 ± 507 mg at 6 months (37% reduction) ($P < 0.001$).

Pars Interna of the Globus Pallidus

- Stimulation was associated with a median improvement in the UPDRS motor score of 37%, as compared with no stimulation ($P < 0.001$).
- Good mobility without dyskinesia during the waking day increased from 28% to 64% between baseline and 6 months ($P < 0.001$).
- Mean daily levodopa dose equivalents were unchanged between baseline (1090 ± 543 mg) and 6 months (1120 ± 537 mg).

ADVERSE EVENTS

- 7 patients experienced intracranial hemorrhage, 4 of whom required surgical decompression.
  - 6 of the 7 patients had neurological deficits; 4 of those resulted in persistent dysfunction.
  - Risk of hemorrhage was correlated with the number of microelectrode insertions used to determine target location.
- Seizures occurred in 4 patients, all of which could be controlled with medication.
- 2 patients had infections necessitating electrode removal.
- 5 patients experienced stimulation-induced dyskinesia.

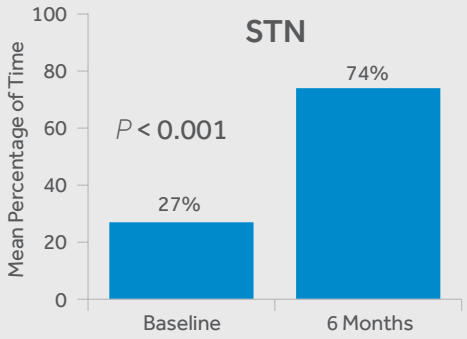
KEY CONCLUSIONS

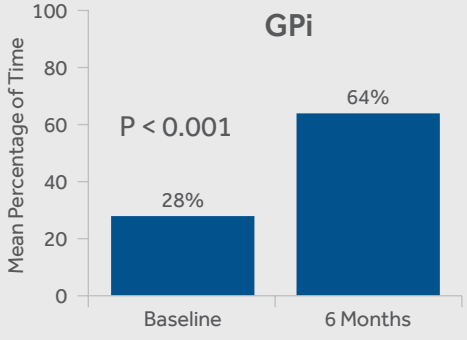
- Bilateral stimulation of the STN or GPi is associated with significant improvement in motor function in patients with advanced Parkinson's disease.
- Dyskinesia and motor fluctuations were also reduced in both groups.
- Patients in both targeted stimulation groups had a significant increase in the percentage of "on" time without dyskinesia and a significant decrease in the percentage of "off" time.
- Global evaluation scores of both physicians and patients reflected the reduction in off periods in both frequency and severity at 6 months, markedly reducing the disability.

Comparison of "On" Time with and without Deep Brain Stimulation

(mean percentage of time during waking hours)

Patients experienced a significant increase in "on" time without dyskinesia with bilateral STN or GPi stimulation (P < 0.001 for both comparisons).
On refers to good mobility. STN: subthalamic nucleus
GPi: pars interna of the globus pallidus.





This study was sponsored by Medtronic.

FIVE-YEAR FOLLOW-UP OF BILATERAL STIMULATION OF THE SUBTHALAMIC NUCLEUS IN ADVANCED PARKINSON'S DISEASE

Krack P, Batir A, Van Blercom N, et al. N Engl J Med. 2003;349:1925-1934.

OBJECTIVE

To evaluate long-term (5-year) benefits of bilateral stimulation of the subthalamic nucleus (STN) in patients with advanced Parkinson's disease.

Study Type

Prospective cohort

Design

The first 49 consecutive patients with advanced Parkinson's disease, treated with bilateral stimulation of the STN, were evaluated for 5 years with levodopa (on medication) and without levodopa (off medication). The Unified Parkinson's Disease Rating Scale (UPDRS) was used for patient assessment.

RESULTS

Motor function scores while off medication improved by 54% at 5 years compared with baseline ($P < 0.001$).

- Activities of daily living scores improved by 49% at 5 years ($P < 0.001$).
- Levodopa (or equivalent) requirement decreased from 1409 ± 605 mg at baseline to 518 ± 333 mg at 1 year ($P < 0.001$).
- At 5 years, 11 of 42 patients were no longer taking levodopa and 3 were not taking any dopaminergic drugs.

ADVERSE EVENTS

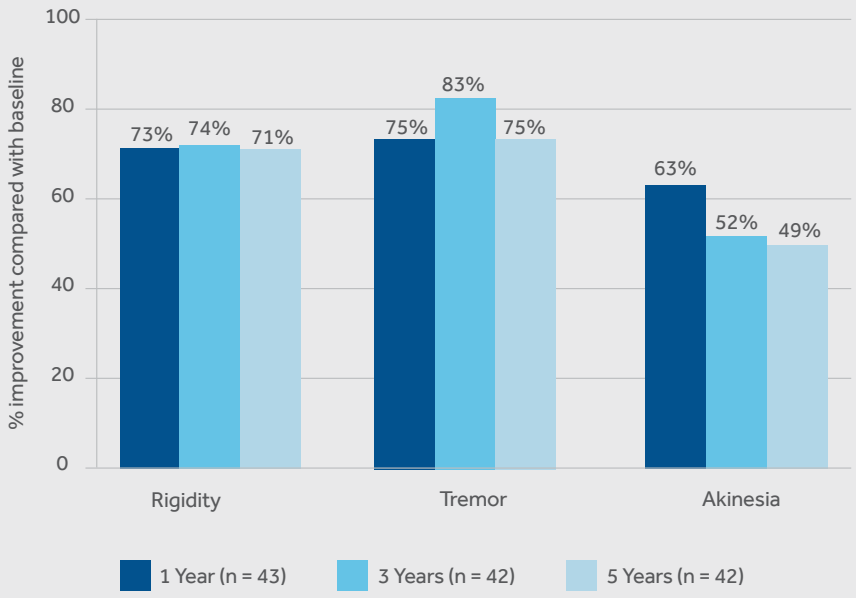
- Severe adverse events included 3 deaths: intracerebral hemorrhage, myocardial infarction, suicide.
- 2 patients developed permanent dementia.
- 15 of 49 patients (31%) had eyelid-opening apraxia in the first 3 months; this remained a problem for 8 patients throughout the follow-up.
- Surgical complications were frequent and mostly transient.
- Device-related complications were rare.

KEY CONCLUSIONS

- Bilateral STN stimulation in patients off medication led to significant post-operative improvements in some Parkinson's-related motor functions.
- Speech, postural stability, and gait freezing did not improve after DBS.
- Improvements over baseline were sustained for 5 years. When measured on dopaminergic medication and DBS, duration of dyskinesia improved substantially at 1 year and remained stable at 5 years.
- STN stimulation allows a reduction in dopaminergic medication.
- Overall, medication and stimulation changes occurred in the first year and then remained stable.
- Surgical complications were frequent and mostly temporary; device-related complications were rare.

1, 3, and 5-Year Improvement in UPDRS Motor Scores with STN Stimulation

With bilateral STN stimulation in the off-medication state, UPDRS III scores for rigidity, tremor, and akinesia improved compared with baseline (n = 49) at 1, 3, and 5 years. (P < 0.001 5 years post implant vs. baseline.)
STN: subthalamic nucleus
UPDRS: Unified Parkinson's Disease Rating Scale.



BILATERAL DEEP BRAIN STIMULATION VS BEST MEDICAL THERAPY FOR PATIENTS WITH ADVANCED PARKINSON'S DISEASE

Weaver FM, Follett KA, Stern M, et al. JAMA. 2009;301(1):63-73.

OBJECTIVE

To compare 6-month outcomes for patients with Parkinson's disease who received deep brain stimulation or best medical therapy.

Study Type

Prospective, randomized, controlled, multicenter

Design

255 patients with advanced Parkinson's disease were enrolled at 13 centers and stratified by study site and patient age (< 70 years vs. ≥ 70 years). Patients were randomized to best medical therapy (n = 134) or bilateral deep brain stimulation of the globus pallidus (GPi) (n = 61) or subthalamic nucleus (STN) (n = 60).

RESULTS

Outcomes: Change between Baseline and 6 Months by Treatment Group

Outcome	Best Medical Therapy (n = 134)	Deep Brain Stimulation (n = 121)	P Value
Motor function improvement without medication (UPDRS III)	4%	29%	< 0.001
Medication (levodopa equivalents) Change in mg over baseline (1,281 mg)	+15	-296	< 0.001
Quality of life improvement PDQ-39 single index	0.9%	17.1%	< 0.001

PDQ-39: Parkinson's Disease Questionnaire-39 score
UPDRS: Unified Parkinson's Disease Rating Scale

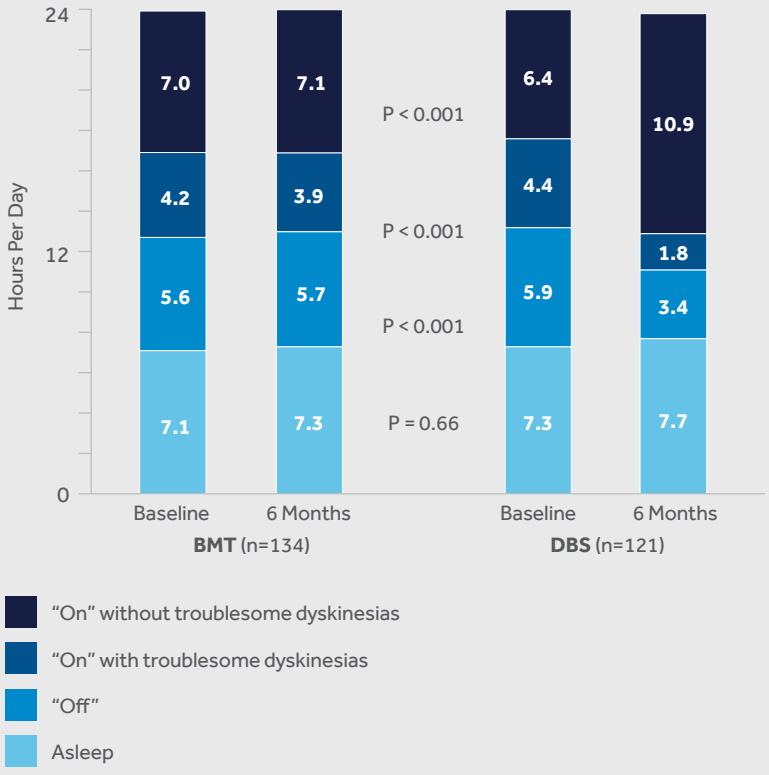
ADVERSE EVENTS

- The deep brain stimulation group reported 659 moderate or severe adverse events; the best medical therapy group reported 236 events.
- There were significantly more events in the deep brain stimulation group for: Falls ($P < 0.01$), Gait disturbance ($P = 0.03$), Depression ($P = 0.03$), and Dystonia ($P < 0.01$).
- Surgical site infection (9.9%) and surgical site pain (9.0%) were only reported in the deep brain stimulation group.
- 83% of all adverse events resolved by the 6-month follow-up.
- 99% of serious adverse events resolved by the 6-month follow-up.

KEY CONCLUSIONS

- Deep brain stimulation was superior to best medical therapy in improving "on" time without troubling dyskinesia and motor function at 6 months in patients with advanced Parkinson's disease.
- As patients improved their motor function with deep brain stimulation, they experienced improvements in quality of life.
- Overall risk of experiencing a serious adverse event was 3.8 times higher in the deep brain stimulation group than in the best medical therapy group; most were resolved at 6 months.
- The benefits of deep brain stimulation need to be weighed against the risk of complications related to surgery in each patient.

Patient Motor Diary Outcomes



The Department of Veterans Affairs Cooperative Studies Program and the National Institute of Neurological Disorders and Stroke contributed to the study design. The sponsors were not involved in the conduct, collection, management, analysis, and/or interpretation of the study results and preparation, review, or approval of the manuscript. Medtronic provided financial support for monitoring and collecting data at 3 years of patient follow-up.

PALLIDAL VERSUS SUBTHALAMIC DEEP-BRAIN STIMULATION FOR PARKINSON'S DISEASE

Follett KA, Weaver FM, Stern M, et al. N Engl J Med. 2010;362:2077-2091.

OBJECTIVE

To compare 24-month outcomes in motor function for patients undergoing bilateral stimulation of the globus pallidus interna (GPi) or subthalamic nucleus (STN).

Study Type

Prospective, multicenter, randomized, double-blind

Design

299 patients with Parkinson's disease, across 13 centers, were randomly assigned to receive STN stimulation (n = 147) or GPi stimulation (n = 152). The primary outcome was change in motor function as assessed with the UPDRS-III. Secondary outcomes included self-reported function, quality of life, neurocognitive function, and adverse events.

RESULTS

- Motor function significantly improved with stimulation and no medication in both the GPi and STN stimulation subgroups as measured by change in the UPDRS-III (GPi: -28.2%, STN: -24.9%. No significant difference between the groups).
- This primary outcome was stable over 24 months.
- Two-thirds of patients in both groups had at least a 5-point improvement in the UPDRS-III score at 24 months as measured while receiving stimulation without medication.
- Average medication use decreased 408 mg (32%) in patients receiving STN stimulation (from 1295 mg to 887 mg) and decreased 243 mg (18%) in patients receiving GPi stimulation (from 1361 mg to 1118 mg) (P = 0.02).
- Quality of life as measured by the PDQ-39 improved for both groups.

ADVERSE EVENTS

- Serious adverse events occurred in 56% of patients receiving STN stimulation and in 51% of patients receiving GPi stimulation.
- 99% of serious adverse events were resolved by the 24-month follow-up.

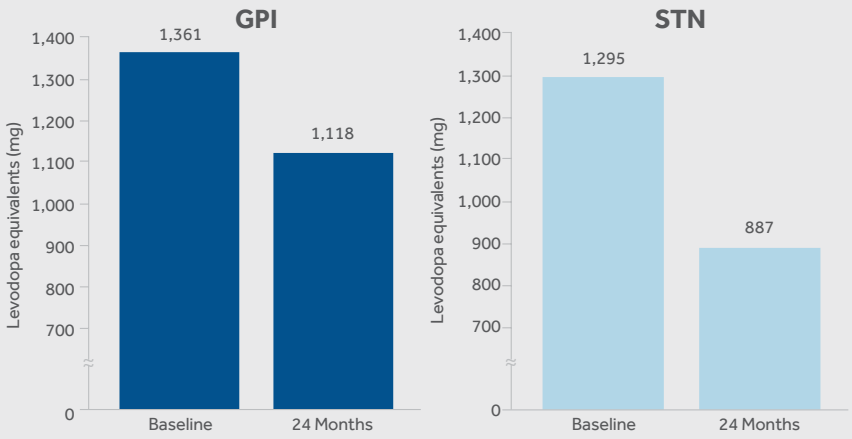
KEY CONCLUSIONS

Deep brain stimulation improved motor function in patients with Parkinson's disease who underwent either GPi or STN stimulation.

- Benefits observed at 6 months were sustained through 24 months of follow-up in both study groups.
- The choice of surgical target can take into consideration non-motor symptoms and the level of dopaminergic medications, both of which contribute to quality of life.
- There was no significant difference between the study groups in the type or frequency of adverse events at 24 months.

Decrease in Medication at 24 Months with Deep Brain Stimulation

The average levodopa equivalent use decreased more in the STN stimulation group (a reduction of 408 mg) than in the GPi group (a reduction of 243 mg) (P = 0.02).



The Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development and the National Institute of Neurological Disorders and Stroke provided financial support for this study and contributed to the study design. Medtronic provided financial support. The stimulators were purchased from the manufacturer, which had no role in the study design, data accrual, data analysis, or manuscript preparation.

RANDOMIZED TRIAL OF DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE: 36-MONTH OUTCOMES

Weaver FM, Follett KA, Stern M, et al. Neurology. 2012;79:55-65.

OBJECTIVE

To compare 36-month outcomes in motor function for patients undergoing bilateral stimulation of the globus pallidus interna (GPi) or subthalamic nucleus (STN).

This is the 36-month outcomes report of the Veterans Affairs Cooperative Studies Program (CSP) 486 trial. It consists of an extended follow-up subset of patients from the previous study: Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010;362:2077-2091.

Study Type

Prospective, multicenter, randomized, blinded

Design

Patients were randomly assigned to GPi (n = 89) or STN (n = 70) deep brain stimulation (DBS) and followed for 36 months. The primary outcome was motor function assessed by the UPDRS-III, on stimulation/off medication. Secondary outcomes included self-reported motor function, quality of life (QOL), and neurocognitive function.

RESULTS

- Motor benefit of both GPi and STN DBS improved between baseline and 36 months, as assessed by the UPDRS-III, on stimulation/off medication. Improvements were maintained at 36 months (DBS overall, trend over time: $P < 0.001$).
- Improvements in UPDRS-III were similar between GPi and STN study groups and stable over time (GPi vs. STN, trend over time: $P = 0.59$).
- On time without dyskinesia improved following DBS and remained stable at 36 months, based on self-reported motor function ($P = 0.48$). Gains over baseline:
  - 4.6 hours/day – GPi
  - 4.1 hours/day – STN
- The initial decreases in post-implant medication usage in both groups were maintained at 36 months (GPi vs. STN, trend over time: $P = 0.07$).

Medication Usage: GPi vs. STN Baseline, 6 Mo, 36 Mo

DBS Target	Baseline (mg*)	6-mo post-DBS (mg*)	36-mo post-DBS (mg*)
GPi (n = 89)	1356	1106	1115
STN (n = 70)	1270	831	817

**levodopa equivalent*

ADVERSE EVENTS

- Authors did not comment on adverse events.

KEY CONCLUSIONS

- Motor function improvement and medication reduction observed at 6 months were sustained at 36 months in both target groups.
- These changes were similar between the GPi and STN study groups and stable over time.
- Self-reported motor function, based on diaries, showed that good motor functioning (on time without dyskinesia) improved after DBS and was stable at 36 months.
- Both GPi and STN target sites are options for treating motor symptoms associated with PD.
- Targets can be selected based on individual patients and symptoms.

- A gradual decline in neurocognitive function occurred with similar rates of decline for both targets in most parameters. Exceptions were the Mattis Dementia Rating Scale and the Hopkins Verbal Learning Test, in which there was no change in the GPi group and worsening in the STN group by 36 months.
- The extent of initial improvements in PDQ-39 scores observed in both the STN and GPi groups was not sustained over time ($P < 0.001$). However, in all but three domains (emotional role well-being, social support and cognition), PDQ-39 scores at 36 months were still significantly lower (improved) than baseline.
- There was no difference in the PDQ-39 trends over time between STN and GPi DBS ($P < 0.38$).

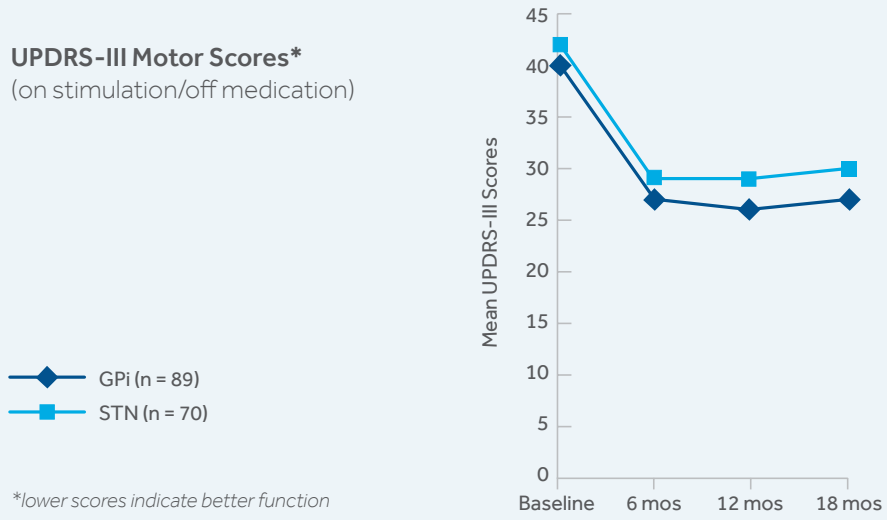
The Department of Veterans Affairs Cooperative Studies Program and the National Institute of Neurological Disorders and Stroke contributed to the study design. The sponsors were not involved in the conduct, collection, management, analysis, and/or interpretation of the study results and preparation, review, or approval of the manuscript. Medtronic provided financial support for monitoring and collecting data at 3 years of patient follow-up.

RANDOMIZED TRIAL OF DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE: 36-MONTH OUTCOMES

Weaver FM, Follett KA, Stern M, et al. Neurology. 2012;79:55-65.

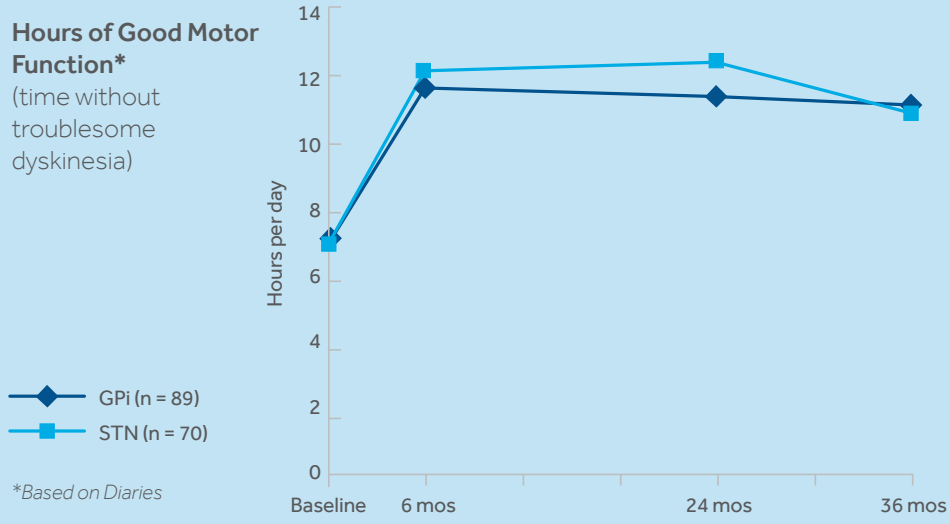
Outcomes of GPi vs. STN DBS – Baseline to 3 Years
On Stimulation/Off Medication

UPDRS-III Motor Scores*
(on stimulation/off medication)



**lower scores indicate better function*

Hours of Good Motor Function*
(time without troublesome dyskinesia)

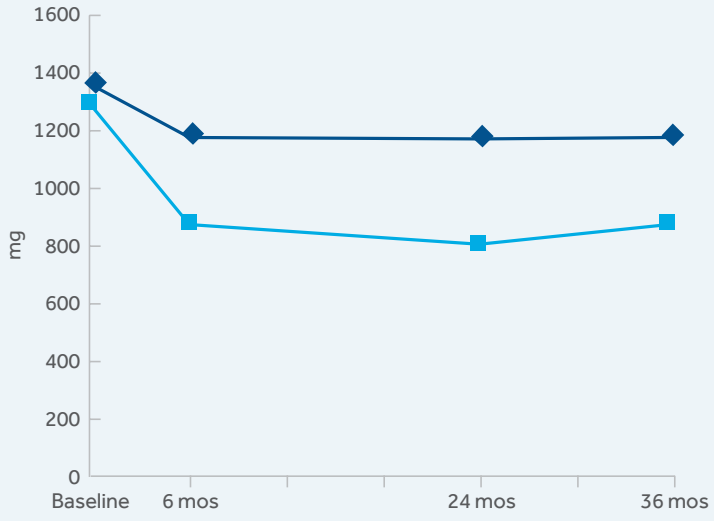


**Based on Diaries*

Motor function improvement (diary-reported and UPDRS-III-assessed) and medication reduction observed at 6 months were sustained at 36 months in both GPi and STN DBS target groups.

These changes were similar between the two groups and were stable over time.

Medication Usage
(levodopa equivalents)



SUBTHALAMIC NUCLEUS VERSUS GLOBUS PALLIDUS BILATERAL DEEP BRAIN STIMULATION FOR ADVANCED PARKINSON'S DISEASE (NSTAPS STUDY): A RANDOMISED CONTROLLED TRIAL

Odekerken VJJ, van Laar T, Staal MJ, Mosch A, Hoffmann CFE, et al. Lancet Neurol. 2013; 12(1):37-44.

OBJECTIVE

To assess the difference in functional improvement resulting from deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) compared with the subthalamic nucleus (STN) in patients with advanced Parkinson's disease (PD).

Study Type

Prospective, randomised, controlled, multicentre

Design

128 patients from 5 centres, ≥ 18 years old with advanced idiopathic PD, were randomised to either GPi DBS or STN DBS (1:1). A minimisation procedure was applied to drug use (levodopa equivalent dose < 1000 mg vs. ≥ 1000 mg) and treatment centre. Patients were assessed at baseline and 12 months, during standardised off-drug and on-drug phases. Primary outcomes included 1) functional health measured by the Academic Medical Center Linear Disability Scale (ALDS), which is weighted by time spent in the off phase and on phase, and 2) a composite score for cognitive, mood, and behavioural effects up to 1 year after surgery. Secondary outcomes were symptom scales, activities of daily living scales, a quality of life questionnaire, medication use, and the occurrence of adverse events.

RESULTS

Primary outcomes

- No difference was found in the mean off-on phase-weighted ALDS change score between the GPi group and the STN group (3.0 vs. 7.7, P = 0.28).
- No difference occurred between groups in the number of patients with cognitive, mood, and behavioural side effects (GPi: 36 vs. STN: 35, P = 0.94).

Table 1. Percent Improvement, Baseline to 12 Months (mean change)

Outcome	Gpi DBS	STN DBS	P Value – Difference Between Treatment Groups
	Off-drug (n = 125)		
UPDRS motor examination (range 0 – 108)	26% (11.4)	46% (20.3)	0.03
ALDS (range 0 – 100)	22% (11.8)	42% (20.3)	0.04
Schwab and England scale (range 0 – 100)	20% (10.0)	50% (20.0)	0.02
	Off-drug (n = 125)		
Clinical dyskinesia rating scale (CDRS, range 0 – 28)	57% (3.0)	23% (1.1)	0.01

ADVERSE EVENTS

- 290 adverse events occurred in the GPi group; 303 in the STN group.
- No statistically significant differences were recorded between the two groups.

KEY CONCLUSIONS

- No difference was found between GPi and STN targets in the primary outcomes: weighted ALDS and composite score for cognition, mood, and behavioural effects.
- In secondary analyses, STN DBS was associated with a better improvement in off-drug phase motor symptoms and disability than was GPi DBS. The authors feel this is clinically relevant.
- The authors suggest that STN may be the preferred target for DBS in PD because of more substantial improvement in symptoms and disability in the off-drug phase, combined with a reduced need for medication and lower battery consumption.

Secondary outcomes

- In the off-drug phase, larger improvements were found in the STN group compared with the GPi group in UPDRS motor examination scores, ALDS scores, and the Schwab and England scale (Table 1).
- In the on-drug phase, dyskinesias were reduced more in the GPi group than the STN group (Table 1).
- The mean levodopa equivalent dose reduction was greater in the STN group than in the GPi group from baseline to 12 months (Table 2).
- DBS amplitude and pulse widths were on average lower in the STN group (Table 3).
- No statistically significant differences were found between groups in the other secondary outcomes.

Table 2. Reduction in Levodopa Equivalent Dose (mg)

	Gpi DBS		STN DBS		P Value – Difference Between Treatment Groups
	Baseline	Reduction (%)	Baseline	Reduction (%)	
Levodopa equivalent dose (mg) (n = 125)	1331	-208 (16%)	1254	-546 (44%)	0.01

Table 3. 12-Month DBS Stimulation Settings

Parameter (n = 125)	Gpi DBS	STN DBS	P Value – Difference Between Treatment Groups
Amplitude (V)	2.9	2.6	0.004
Pulse width (µs)	73.0	63.9	0.008

DEEP BRAIN STIMULATION PLUS BEST MEDICAL THERAPY VERSUS BEST MEDICAL THERAPY ALONE FOR ADVANCED PARKINSON'S DISEASE (PD SURG TRIAL): A RANDOMIZED, OPEN-LABEL TRIAL

Williams A, Gill S, Varma T, et al, on behalf of the PD SURG Collaborative Group. Lancet Neurol. 2010;9:581-591.

OBJECTIVE

To assess whether deep brain stimulation (DBS) and best medical therapy (BMT) improved self-reported quality of life more than best medical therapy alone for patients with advanced Parkinson's disease.

Study Type

Prospective, randomized, open label, multicenter

Design

366 patients with advanced Parkinson's disease were enrolled at 13 centers and randomized to bilateral deep brain stimulation plus best medical therapy (n = 183) or to best medical therapy alone (n = 183). The primary endpoint was the patient's self-reported quality of life using the Parkinson's Disease Questionnaire (PDQ-39), comparing the change between baseline and 1 year.

RESULTS

Outcomes: Change Between Baseline and 1 Year by Treatment Group (Negative Change = Improvement)

- At 1 year, the mean improvement in PDQ-39 scores for mobility, activities of daily living, bodily discomfort, and the summary index was significantly greater in the DBS + BMT group than in the BMT alone group (see table above for detail).
- The improvement was also significantly greater for the UPDRS Parts I-IV scores, on and off medication, in the DBS + BMT group (see table above for detail).
- At 1 year, patients receiving DBS were on a mean levodopa equivalent dose of 894 mg/day. Those in the medical therapy group were on 1,347 mg/day. The difference represents a 34% reduction in mean drug dose in the surgery group compared to best medical therapy alone.

ADVERSE EVENTS

- Serious adverse events in the BMT group included 14 Parkinson's disease-related and drug-related events and 1 death (stroke).
- Serious adverse events in the DBS + BMT group included 43 surgery-related events, 25 Parkinson's disease-related and drug-related events, and 2 deaths (hemorrhage and pneumonia).
- The most common surgery-related serious adverse event was infection (n = 16).

KEY CONCLUSIONS

- At 1 year, deep brain stimulation plus best medical therapy improved patient-evaluated motor function and quality of life, and clinical assessment, more than best medical therapy alone.
- Substantial benefits of deep brain stimulation occurred in the time and severity of dyskinesia and off periods.
- When patients were asked their reasons for considering deep brain stimulation, the most common reasons were dyskinesia (73%), severe off periods (77%), and tremor (40%).
- The amount of drug therapy required in the DBS group was 34% lower than the amount required by patients receiving best medical therapy alone.
- Substantially more patients undergoing deep brain stimulation had serious adverse events than did patients receiving medical therapy only.
- The most common disease- and drug-related serious adverse events were worsening of Parkinson's disease symptoms or uncontrolled Parkinson's disease symptoms.

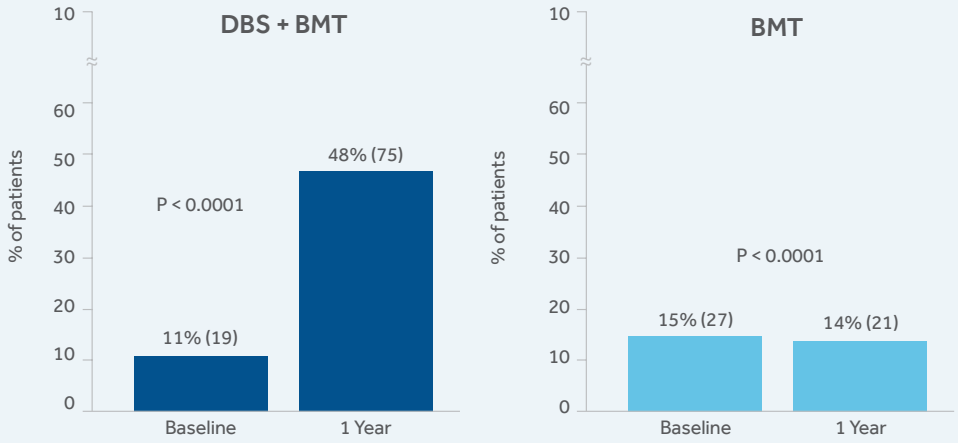
Table 1. Percent Improvement, Baseline to 12 Months (mean change)

Outcome	Best Medical Therapy (n = 150)	Deep Brain Stimulation + Best Medical Therapy (n = 160)	P Value
	PDQ-39		
Summary index	-0.3	-5.0	0.001
Mobility	0.7	-8.2	0.0004
Activities of daily living	0.1	-12.3	< 0.0001
Bodily discomfort	-2.4	-9.8	0.004
	UPDRS Parts I-IV		
Total score: On medication	1.6	-6.6	< 0.0001
Total score: Off medication	< 0.0001	-27.4	< 0.0001

PDQ-39 = Parkinson's Disease Questionnaire-39 score UPDRS = Unified Parkinson's Disease Rating Scale

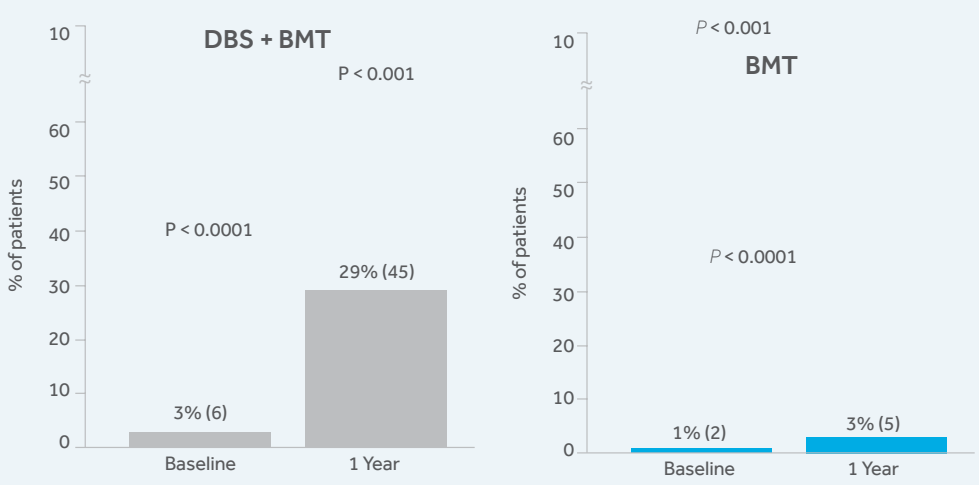
DEEP BRAIN STIMULATION PLUS BEST MEDICAL THERAPY VERSUS BEST MEDICAL THERAPY ALONE FOR ADVANCED PARKINSON'S DISEASE (PD SURG TRIAL): A RANDOMIZED, OPEN-LABEL TRIAL

Williams A, Gill S, Varma T, et al, on behalf of the PD SURG Collaborative Group. Lancet Neurol. 2010;9:581-591.



At 1 year, 75 patients in the surgery group, and 21 in the medical therapy group, reported no waking day dyskinesia (P < 0.0001). DBS = deep brain stimulation. BMT = best medical therapy.

Percent of Patients Experiencing No "Off" Time During Waking Hours (baseline vs. 1 year)



At 1 year, 45 patients in the surgery group and 5 in the medical therapy group reported no waking day "off time" (P < 0.0001).

STIMULATION OF THE SUBTHALAMIC NUCLEUS AT AN EARLIER DISEASE STAGE OF PARKINSON'S DISEASE: CONCEPT AND STANDARDS OF THE EARLYSTIM-STUDY

Deuschl G, Schüpbach M, Knudsen K, et al. Parkinsonism Relat Disord. 2013;19:56-61.

OBJECTIVE

To describe the general aims, the methodological approach, and the critical issues of the EARLYSTIM study, a randomized controlled trial to assess the effect of subthalamic nucleus (STN) stimulation in patients at an early stage of Parkinson's disease (PD). Baseline data are provided.

Study Type

Concepts and standards paper relating to EARLYSTIM, a randomized, multicenter, bi-national pivotal trial

Design of EARLYSTIM

366 patients with advanced Parkinson's disease were enrolled at 13 centers and randomized to bilateral deep brain stimulation plus best medical therapy (n = 183) or to best medical therapy alone (n = 183). The primary endpoint was the patient's self-reported quality of life using the Parkinson's Disease Questionnaire (PDQ-39), comparing the change between baseline and 1 year.Enrolled patients (n = 251) were 60 years or younger with levodopa-induced motor complications of no more than 3 years, and preserved social and occupational functioning. The criteria excluded patients with advanced PD (Hoehn and Yahr stage was ≤ 2.5 in the best condition). Disease duration was ≥ 4 years to likely exclude atypical disease. Various assessments were compared in patients randomized to deep brain stimulation (DBS) or to best medical treatment (BMT) only. Patients were followed for 24 months.

DISCUSSION POINTS

Study authors hypothesize that STN DBS improves quality of life at an earlier stage of PD – after the honeymoon phase ends and the levodopa-induced complications start to be experienced from medical treatment.

- Thorough attention and effort were given to quality of care and standardized algorithms for patients receiving best medical treatment and for those receiving neurostimulation. This will improve the ability to compare outcomes between treatment groups and to provide the best clinical outcomes for both groups.
- The rigorous methodological framework applied in this study may be a solution for critical aspects in future clinical research of DBS in Parkinson's disease, as well as in routine care of patients.
- Strict safety assessments and documentation of all adverse events were implemented in both treatment groups to improve the ability of comparison to published literature.

OVERVIEW

Primary Endpoint

Difference in mean change in disease-related quality of life, measured by the PDQ-39 summary index at 24 months.

Secondary Endpoints

Major secondary endpoints were motor scores off medication (UPDRS-III), activities of daily living in the worst condition (UPDRS-II), levodopa-induced complications (UPDRS-IV), and hours of good mobility without troubling dyskinesia (patient diary). Minor secondary (exploratory) endpoints included other motor, neuropsychological, and psychosocial outcomes measured by established scales and questionnaires.

Methodological Framework

Methodologies and procedures were standardized to strengthen the study design and to optimize patient care. Descriptions of methodology and procedures are included in this paper:

- **Blinded video assessments**
  The UPDRS-III, except rigidity, was assessed by two independent, blinded raters based on standardized video recording
- **Standardized neurosurgery**
  Neurosurgical standards were defined by the involved neurosurgeons to assure an optimal approach
- **Defined stimulator programming**
  Stimulation parameter settings were defined based on expert consensus, in the absence of evidence-based recommendations
- **Reinforced best medical treatment**
  A procedure was developed to reinforce BMT using evidence-based medicine in Parkinson's disease
- **Suicide risk surveillance**
  A procedure was developed to improve monitoring for suicidal ideation and behavior, allowing immediate intervention if needed

Baseline Results

Patients were younger and had a shorter duration of PD compared to other large randomized trials of DBS (Table 1)

Table 1. Baseline Results of EARLYSTIM Compared to Other Large Trials

Randomized Trials	Patients (n=)	Age at Surgery	Disease Duration (yrs)
Deuschl G, et al. 20061	156	61	13.4*
Williams A, et al. 20122	366	59	11.4
Follett K, et al. 20103	299	62	11.7*
Okun M, et al. 20124	136	60	12.0
EARLYSTIM (current study)	251	52.6	7.5

**Duration of dopaminergic treatment*

References

1. *Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med. 2006;355:896-908.*
2. *Williams A, Gill S, Varma T, et al, Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomized, open-label trial. Lancet Neurol. 2010;9:581-591.*
3. *Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010;362:2077-2091.*
4. *Okun MS, Gallo BV, Mandybur G, et al. Subthalamic deep brain stimulation with a constant current device in Parkinson's disease: an open-label randomised controlled trial. Lancet Neurol. 2012;11:140-149.*

This physician-initiated study received financial support from Medtronic.

NEUROSTIMULATION FOR PARKINSON'S DISEASE WITH EARLY MOTOR COMPLICATIONS EARLYSTIM STUDY

Schüpbach M, Rau J, Knudsen K, et al. N Eng J Med. 2013; 368:610-22.

OBJECTIVE

To assess the effect of subthalamic nucleus (STN) stimulation on the quality of life in patients at an earlier stage of Parkinson's disease (PD).

Study Type

Multicenter, bi-national (Germany, France), randomized, controlled trial

Design

251 patients were randomized to deep brain stimulation (DBS) therapy plus medical therapy (n = 124) or medical therapy only (n = 127). Patients were 60 years or younger with levodopa-induced motor complications of no more than 3 years, Hoehn and Yahr stage of ≤ 2.5 on medications, and preserved social and occupational functioning. The primary outcome was the difference in the mean change in quality of life (QOL), measured by the PDQ-39 summary index. Major secondary outcomes were motor scores, activities of daily living, levodopa-induced complications, and hours of good mobility

RESULTS

Primary outcomes
Quality of life measured by the PDQ-39 summary index

- The DBS therapy group improved by 26% (7.8 points) from baseline to 24 months; the medical therapy group worsened by 1% (0.2 points).
- The difference in change between the treatment groups was highly significant (8.0 points), in favor of DBS therapy (P = 0.002).
- The maximum effect of DBS therapy was reached at 5 months and remained stable at 24 months..

Secondary outcomes

- DBS therapy was superior to medical therapy in motor scores, activities of daily living, levodopa-induced motor complications, time in good mobility without dyskinesia, and reduction of levodopa-equivalent dosage (Table 1).

SERIOUS ADVERSE EVENTS

- Serious adverse events occurred in 68 patients (54.8%) in the DBS therapy group and in 56 patients (44.1%) in the medical therapy group.
- Serious adverse events related to surgery or the implanted device occurred in 22 (17.7%) surgical patients; all but one (cutaneous scarring) resolved completely.
- Two DBS therapy patients and one medical therapy patient died by suicide.
- Suicidal ideation and suicide attempts were of similar frequency in both groups; depression was more frequent in the DBS therapy group, yet the Beck Depression Inventory had an overall reduction of 18% in the DBS group with no change in the BMT group at the 24 months follow-up.
- Serious adverse events related to motor problems, impulse control disorders, and psychotic manifestations were more frequent in the best medical therapy group.

Table 1. Outcomes: Percent Change from Baseline to 24 Months by Treatment Group

Outcome	DBS therapy	Medical therapy	P Value Difference Between Treatment Groups
Improvement in quality of life PDQ-39 summary index	+26%*	-1%	0.002
Improvement in motor score UPDRS-III (off medication)	+53%*	4%	< 0.001
Improvement in activities of daily living (ADL)	+30%*	-12%*	< 0.001
Improvement in UPDRS-IV (levodopa-induced complications)	+61%*	-13%*	< 0.001
Increased hours of good mobility without troublesome dyskinesia (Patient diary)	+20%*	2%	0.012
Improved SCOPA-PS (SCales for Outcomes in PArkinson's disease –PsychoSocial questionnaire)	+28%*	3%	0.023
Within group change in daily levodopa-equivalent dosage	-39%*	+21%*	< 0.001

**Within group change from baseline to 24 months - P < 0.05*

NEUROSTIMULATION FOR PARKINSON'S DISEASE WITH EARLY MOTOR COMPLICATIONS EARLYSTIM STUDY

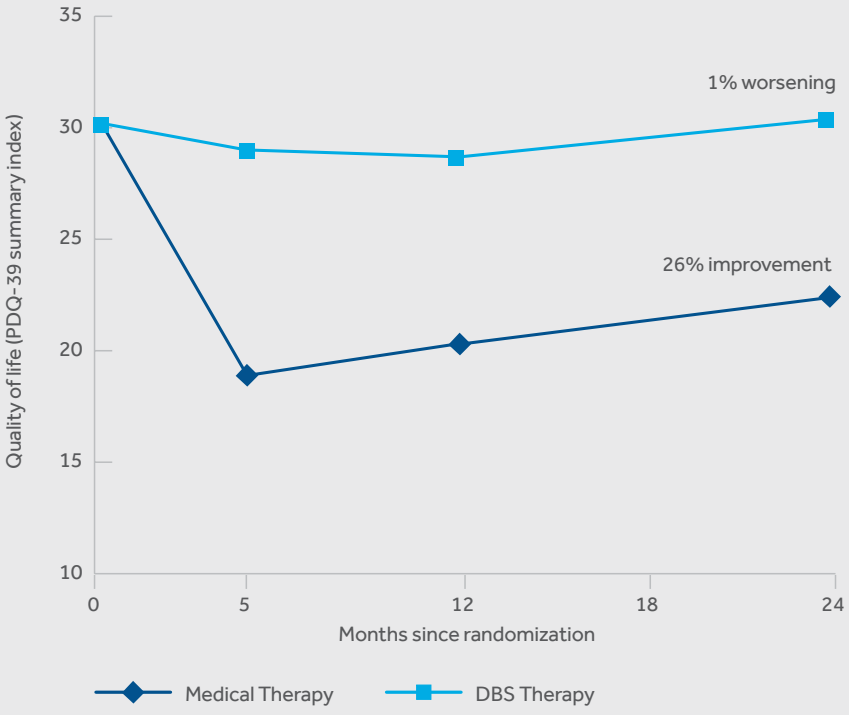
Schüpbach M, Rau J, Knudsen K, et al. N Eng J Med. 2013; 368:610-22.

KEY CONCLUSIONS

- The EARLYSTIM study is a large randomized controlled trial of DBS therapy for Parkinson's disease that confirms the impact of the therapy earlier in the progression of the disease. It is also the first comparison of DBS therapy to medical therapy at 24 months.
- This study showed consistent, significant findings that DBS therapy for patients with early motor complications is superior to medical therapy in the evaluation of multiple outcomes, including the primary and major secondary objectives.
- Disease-related quality of life improves significantly from baseline to 24 months in patients receiving DBS therapy; there is no change in quality of life in patients receiving medical therapy alone.
- Safety outcomes were similar in both treatment groups.
- This study provides additional insights into patient selection criteria for successful DBS therapy outcomes.

Quality of Life Scores with DBS therapy vs. Medical therapy – PDQ-39 Summary Index, Baseline to 24 Months

(lower score indicates improvement)



PDQ-39 summary index scores are shown at baseline, 5, 12, and 24 months for both treatment groups.

The DBS Therapy group improved by 26% from baseline to 24 months (P = 0.002); the medical therapy group remained unchanged.

References

[1] *Deuschl G, Schüpbach M, Knudsen K, et al. Stimulation of the subthalamic nucleus at an earlier disease stage of Parkinson's disease: concept and standards of the EARLY STIM study. Parkinsonism Relat Disord. 2013;19:56-61.*

This physician-initiated study received financial support from Medtronic.

EFNS GUIDELINE ON NEUROLOGICAL MANAGEMENT LATE (COMPLICATED) PARKINSON'S DISEASE

Oertel WH, Berardelli A, Bloem BR, et al. In: Gilhus NE, Barnes MP, Brainin M, eds. European Handbook of Neurological Management: Volume 1. 2nd ed. Oxford, UK: Blackwell Publishing Ltd.; 2011:237-267.

OBJECTIVE

To provide guidance in the therapeutic management of patients with advanced Parkinson's disease (PD). Guidance represents a peer-reviewed statement of minimum desirable standards of practice based on scientifically proven, evidence-based criteria.

Study Type

Guidance paper developed using unified criteria for standards of reporting within the framework established by an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS).[1] Refer to Table 1 below for rating of recommendations and evidence classification scheme.

RESULTS

Recommendations:

Note: Interventions and recommendations are summarized here for motor-related complications and general sleep problems only. Recommendations for non-motor complications are included in the paper but not summarized here.

Symptomatic Control of Severe Motor Fluctuations

If pharmacological therapy is unsuccessful at improving marked to severe fluctuations in motor performance, the following strategies can be recommended:

Deep brain stimulation of the subthalamic nucleus (STN)

- Effective against motor fluctuations and dyskinesia (Level A)
- Recommended for patients < 70 years old without major psychiatric problems or cognitive decline because of risk for adverse events
- Other stimulation targets may be effective; results are less well documented

Subcutaneous apomorphine as injection (Level A) or continuous infusion (Level C)
Intrajejunal levodopa/carbidopa enteric gel administered through percutaneous gastrostomy (Level C)

Symptomatic Control of Unpredictable ON-OFF

Deep brain stimulation (Level A)
Specific oral medical strategies—insufficient evidence exists for recommendation

Symptomatic Control of Peak-Dose Dyskinesia

Reduce individual levodopa dose size

- May increase OFF time
- Compensate by increasing the number of doses of levodopa or dopamine agonist (Level C)

Discontinue or reduce dose of MAO-B inhibitors or COMT inhibitors (good practice point [GPP])

- May worsen wearing-off (end-of-dose) akinesia

Add amantadine (Level A)

- Benefit may last < 8 months
- Other antiglutamatergic drug use is investigational

Deep brain stimulation

- Allows reduction of dopaminergic treatment (Level A)
- GPi (globus pallidus interna) stimulation may also inhibit severe dyskinesia (Level C)

Add atypical antipsychotics, clozapine, or quetiapine (Level C)

- Clozapine is associated with serious adverse events including agranulocytosis and myocarditis, limiting its use (GPP)

Apomorphine continuous subcutaneous infusion allows reduction of levodopa therapy (Level C)

Intrajejunal levodopa infusion in patients with marked peak dose dyskinesia and motor fluctuations (Level C)

Symptomatic Control of Off-Period and Early Morning Dystonias

Strategies for wearing-off can be applied in case of off-period dystonia (GPP)

Additional night doses of levodopa or dopamine agonist therapy may control night or early morning dystonia (GPP)

Deep brain stimulation of the STN (Level A) or GPi (Level C)

Botulinum toxin (GPP)

Treatment of Sleep Problems

Levodopa, standard or prolonged-release dose, at bedtime (Level B)

Transdermal rotigotine, pramipexole, and prolonged-release ropinirole for patients with motor fluctuations (Level A)

Deep brain stimulation of the STN except for nocturnal motor phenomena of sleep disorders (Level B)

EFNS GUIDELINE ON NEUROLOGICAL MANAGEMENT LATE (COMPLICATED) PARKINSON'S DISEASE

KEY CONCLUSIONS

Weaver FM, Follett KA, Stern M, et al. Neurology.2012;79:55-65.

- Recommendations for the therapeutic management of patients with advanced PD are systematically graded according to the strength of available scientific evidence.
- Deep brain stimulation of the STN is among the highest recommendations for treatment and control of symptoms associated with late (complicated) Parkinson's disease.

Table 1. EFNS Evidence Classification Scheme for a Therapeutic Intervention (adapted from Brainin M, et al. Eur J Neurol. 2004;11:577-581).[1]

Rating of Recommendation	
Level A	Established as effective, ineffective, or harmful. Requires ≥ 1 convincing class I study or ≥ 2 consistent, convincing class II studies.
Level B	Probably effective, ineffective, or harmful. Requires ≥ 1 convincing class II study or overwhelming class III evidence.
Level C	Possibly effective, ineffective, or harmful. Requires ≥ 2 convincing class III studies.
Class of Evidence	
Class I	An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population, or An adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations **The following are required:** a. randomization concealment b. primary outcome(s) is/are clearly defined c. exclusion/inclusion criteria are clearly defined d. adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias e. relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class III	Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above, or A randomized, controlled trial in a representative population that lacks one criteria a–e
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion
GPP (good practice point)[1]	Used in exceptional clinical areas for which no high class evidence is available or likely to become available in the near future Not grounded on more than class IV evidence, implying large clinical uncertainty Based on the experience and consensus of the guideline development group

**Within group change from baseline to 24 months - P < 0.05*

References

1. *Brainin M, Barnes M, Baron J-C, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004;11:577-581.*

A RANDOMIZED TRIAL OF DEEP-BRAIN STIMULATION FOR PARKINSON'S DISEASE

Deuschl G, Schade-Brittinger C, Krack P, et al. for the German Parkinson Study Group, Neurostimulation Section. N Engl J Med. 2006;355:896-908.

OBJECTIVE

To compare deep brain neurostimulation with best medical management for changes from baseline to 6 months in motor function and quality of life in patients with advanced Parkinson's disease. Secondary endpoints included changes in a dyskinesia scale and in activities of daily living, with and without medication

Study Type

Prospective, multicenter, randomized pairs

Design

156 patients with advanced Parkinson's disease and severe motor symptoms, under 75 years, were enrolled as pairs and randomly assigned to neurostimulation of the subthalamic nucleus or best medical management.

RESULTS

- 41% Improvement in severity of symptoms index (UPDRS-III) was found in the neurostimulation group but remained unchanged in the medication group.
- Neurostimulation was associated with a 25% improvement in the quality of life summary (PDQ-39); change in the medication group was insignificant.
- Patients' diaries revealed profound and significant changes, only in the neurostimulation group, with longer periods of mobility, shorter periods of immobility, shorter periods with troubling dyskinesia, and longer periods of sleep.

ADVERSE EVENTS

- Severe adverse events included 3 (3.9%) deaths in the neurostimulation group (hemorrhage, pneumonia, suicide) and 1 (1.3%) death in the medical management group (motor vehicle accident).
- All other severe adverse events resolved without permanent complications.

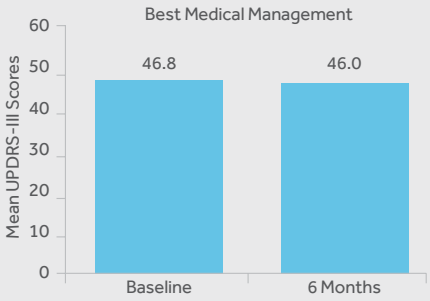
	Neurostimulation	Medical Management	P Value
Serious Adverse Events	10 (12.8%)	3 (3.8%)	0.04
Adverse Events	39 (50%)	50 (64.1%)	0.08

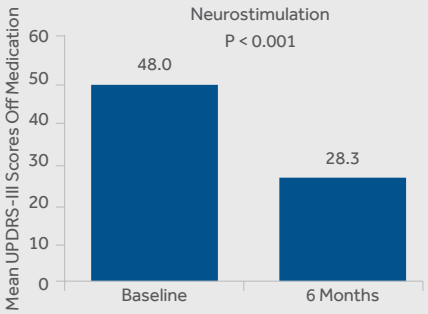
KEY CONCLUSIONS

- Neurostimulation of the subthalamic nucleus was more effective than best medical management in patients with advanced Parkinson's disease and severe motor complications.
- An improvement in quality of life resulted from a decrease in the severity and duration of periods of immobility and dyskinesia.
- Improvement in motor functioning led to improvement in measurements of activities of daily living, emotional well-being, stigma, and bodily discomfort; cognition, mood, and overall psychiatric functioning were unchanged.
- The prospect of improved quality of life resulting from deep brain stimulation must be weighed against the risks of surgical intervention.

Changes in Motor Scores Best Medical Management vs. without Medication Neurostimulation

(lower scores indicate better function)





Neurostimulation resulted in a 41% improvement in motor symptom scores in patients when off medication ($P < 0.001$). Scores remained unchanged in the best medical management group.
UPDRS III= Unified Parkinson's Disease Rating Scale, part III.

This physician-initiated study received limited financial support from Medtronic.

NEUROPSYCHOLOGICAL AND PSYCHIATRIC CHANGES AFTER DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE: A RANDOMIZED, MULTICENTRE STUDY

Witt K, Daniels C, Reiff J, et al. Lancet Neurol. 2008;7:605-614.

OBJECTIVE

To prospectively compare the postoperative changes in cognitive function and psychiatric symptoms in patients with advanced Parkinson's disease who are receiving deep brain stimulation (DBS) or best medical treatment (BMT) over a 6-month period.

Study Type

Prospective ancillary protocol to a controlled, multicenter, randomized trial

Design

123 patients* with advanced Parkinson's disease had neuropsychological and psychiatric examinations to assess changes between baseline and 6 months post implantation. The primary outcome was to compare the effect of DBS (n = 60) with best medical treatment (n = 63) on overall cognitive functioning.

**This study uses the same patient population that found in Deuschl G, Schade-Brittinger C, Krack P, et al. for the German Parkinson Study Group. A randomized trial of deep-brain stimulation for Parkinson's disease. Neurostimulation Section. N Engl J Med. 2006;355:896-908*

RESULTS

- Overall cognition did not differ significantly between DBS and BMT groups.
- The DBS group experienced significantly greater negative changes in semantic (P = 0.03) and phonemic (P = 0.02) fluency scores of the verbal fluency test; this was not associated with changes in scores in quality of life or psychiatric scales.
- Changes in dysarthria score (P = 0.24) and other neuropsychological tests after DBS were not significantly different compared with BMT.
- Anxiety was significantly reduced in the DBS group (P < 0.0001) but remained unchanged in the BMT group.
- DBS resulted in significant improvement in motor function (P = 0.004) and associated quality of life measures (P < 0.0001) compared with best medical treatment.

ADVERSE EVENTS

- Severe psychiatric adverse events occurred in 10 patients in the DBS group (13%) and 8 patients in the BMT group (10%).

Serious Adverse Events in the Psychiatric Domain		
Event	**DBS (n = 78)**	**BMT (n = 78)**
Death in a psychotic episode	0	1
Depression	4	0
Psychosis	4	7
Severe loss of affect (apathy)	1	0
Suicide	1	0

DBS = deep brain stimulation
BMT = best medical treatment

KEY CONCLUSIONS

- Overall cognitive function, verbal memory, working memory, and attention were unchanged after DBS.
- Patients in the best medical treatment group mostly had medication-induced psychosis, whereas patients treated with DBS more often had adverse events due to hypodopaminergic stimulation.
- The most frequently reported serious adverse events in the DBS group were depression and psychosis.

LONG-TERM EFFICACY OF THALAMIC DEEP BRAIN STIMULATION FOR TREMOR: DOUBLE-BLIND ASSESSMENTS

Rehncrona S, Johnels B, Widner H, Törnqvist A-L, Hariz M, Sydow O. Movement Disorders. 2003;18:163-170.

OBJECTIVE

To study the long-term effect (6-7 years) of thalamic deep brain stimulation in patients with severe tremor.

Study Type

Prospective, randomized, multicenter

Design

39 patients with severe tremor (20 Parkinson's disease, 19 essential tremor) received deep brain stimulation to the ventrointermediate nucleus of the thalamus. Patients were evaluated at 2 years and 6-7 years post-implant, in a double-blind manner with the Unified Parkinson's Disease Rating Scale (UPDRS) and Essential Tremor Rating Scale (ETRS), to evaluate long-term efficacy of therapy.

RESULTS

Stimulation parameters for Parkinson's disease and essential tremor—including amplitude, pulse width, and frequency—were stable over time.

Essential Tremor

Effects on Tremor

- Stimulation significantly reduced action tremor in the upper extremity at:
  - 2 years in all patients
  - 6-7 years in all but 3 patients
  - Results for postural tremor were similar
- Stimulation significantly improved tremor and hand function compared to off-stimulation conditions and compared to preoperative baseline evaluations at both follow-up timeframes ($P < 0.025$).

Disease Progression

- No obvious differences in the off-stimulation scores between baseline and follow-up were observed.
- Before surgery, 5 of the 13 patients were taking either beta-blockers or primidone; at 6.5 years these medications were terminated.

KEY CONCLUSIONS

- Deep brain stimulation can effectively suppress severe tremor in patients with Parkinson's disease and essential tremor for more than 6 years after implantation.
- Side effects were few, mild, and reversible.

Parkinson's Disease

Effects on Tremor

- Stimulation significantly suppressed:
  - Tremor in both upper and lower extremities at 2 years and at 6-7 years ($P < 0.025$)
  - Kinetic tremor ($P < 0.025$)

Disease Progression

- Total motor score, including rigidity and akinesia, deteriorated significantly at 6-7 years with the neurostimulator off ($P < 0.025$).
- With stimulation on, total motor score improved significantly compared to no stimulation,
- by suppressing tremor and by decreasing akinesia ($P < 0.025$).
- Speech and postural stability declined during the follow-up period and were not improved by stimulation.
- Mean daily intake of levodopa increased by 490 ± 360 mg from baseline in the entire Parkinson's disease group (mean baseline dose for total group not provided in article).

Adverse Events for Essential Tremor and Parkinson's Disease

- No surgical complications were recorded.
- None of the 7 deaths that occurred during the follow-up period were related to the surgical procedure or to the implanted devices.
- 1 patient with Parkinson's disease experienced unpleasant paraesthesias.
- Lead fracture led to DBS electrode replacement in 1 patient.

BILATERAL DEEP-BRAIN STIMULATION OF THE GLOBUS PALLIDUS IN PRIMARY GENERALIZED DYSTONIA

Vidailhet M, Vercueil L, Houeto J-L, Krystkowiak P, Benabid A-L, Cornu P, for The French SPIDY Study Group. N Engl J Med. 2005;352:459-467.

OBJECTIVE

To evaluate the effects of bilateral stimulation of the globus pallidus (GPi) on motor impairment, functional disability, quality of life, cognition, and mood in patients with primary generalized dystonia.

Study Type

Prospective, controlled, multicenter

Design

22 patients with primary generalized dystonia were evaluated before surgery and at 3, 6, and 12 months after bilateral GPi deep brain stimulation. Severity of dystonia was assessed with neurostimulation using the movement and disability subscores of the Burke-Fahn-Marsden Dystonia Scale. Movement scores were evaluated via videotape review by a blinded observer. At the 3-month follow-up, patients were assessed double blindly with neurostimulation on and off

RESULTS

- Movement symptoms significantly improved at 3 months and persisted at 1 year, with 51% improvement in mean dystonia movement scores ($P < 0.001$).
- Global disability score, and general health and physical functioning subscores, all improved significantly after surgery ($P < 0.001$, $P = 0.04$, $P = 0.007$, respectively).
- Cognition and mood were unchanged at 1 year.
- All subscores except speech were worse without neurostimulation than with it.

ADVERSE EVENTS

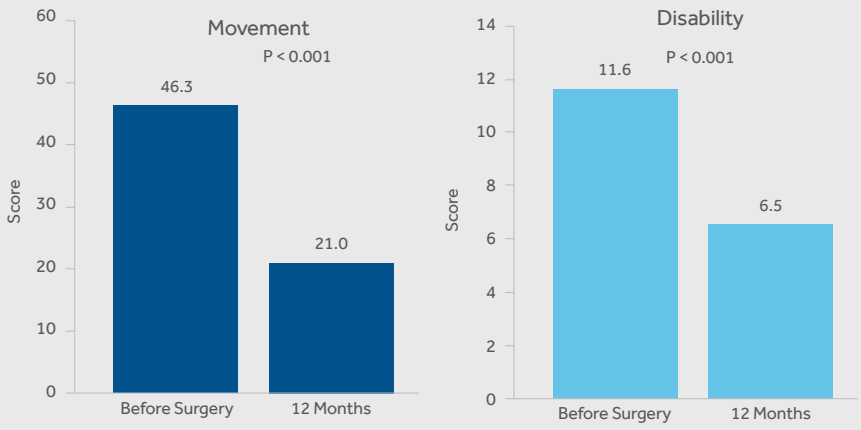
- 3 patients had 5 adverse events in the post-operative period.
- All events resolved rapidly with no permanent neurological sequelae.

KEY CONCLUSIONS

- Bilateral GPi stimulation demonstrated sustained benefit for patients through improvement in motor symptoms, functional disability, and quality of life at 1 year.
- Authors did not observe any worsening of cognition or mood, nor any permanent adverse effects.
- Use of medication to treat dystonia was reduced after surgery.

Improvement in Outcome Scores in Patients with Primary Dystonia
(higher scores indicate more severity)

Significant improvement in movement and disability was reported through 12 months as compared with baseline in patients with primary generalized dystonia treated with bilateral deep brain stimulation ($P < 0.001$). Mean scores are provided from the Burke-Fahn-Marsden Dystonia Scale.



This physician-initiated study received financial support from Medtronic.

PALLIDAL DEEP-BRAIN STIMULATION IN PRIMARY GENERALIZED OR SEGMENTAL DYSTONIA

Kupsch A, Benecke R, Müller J, et al, for the Deep-Brain Stimulation for Dystonia Study Group. N Engl J Med. 2006;355:1978-1990.

OBJECTIVE

To evaluate effects of bilateral deep brain stimulation of the globus pallidus (GPi) in reducing symptoms of severe primary dystonia.

Study Type

Prospective, randomized, sham-controlled, multicenter

Design

40 patients with primary segmental or generalized dystonia received an implanted device for bilateral GPi deep brain stimulation and were randomly assigned to receive either neurostimulation or sham stimulation for 3 months. Two investigators, unaware of treatment status, assessed the severity of the dystonia. Subsequently, all patients received open-label neurostimulation. Blinded assessment was repeated after 6 months of active treatment.

RESULTS

- After 6 months of continuous neurostimulation, the entire study group experienced average improvement of 46% in movement score as compared with baseline.
- Patients with generalized or segmental dystonia had similar improvement in symptoms after 6 months of neurostimulation ($P = 0.41$).
- Medication dosage was reduced by an average of 32.1% at 6 months in the 20 patients who received ongoing medical treatment for dystonia; 5 patients discontinued pharmacotherapy.

Improvement (%): Baseline to 3 Months

Outcome	Neurostimulation	Sham-Stimulation	P Value
Movement*	39.3% (n = 20)	4.9% (n = 20)	< 0.001
Disability*	37.5% (n = 20)	8.3% (n = 19)	< 0.001
Quality of life (SF-36 scale)	29.8% (n = 17)	11.4% (n = 16)	0.02

**Burke-Fahn-Marsden Dystonia Rating Scale*

ADVERSE EVENTS

6 events were reported during the 3-month randomized phase – 6 in the neurostimulation group and 3 in the sham-stimulation group.

- Infection at the neurostimulator site was the most frequent
- All resolved during the same period without permanent sequelae

13 adverse events were reported during the open-label phase in 11 subjects.

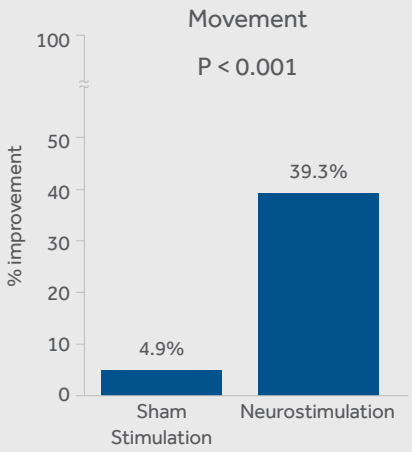
- Most were related to stimulation and resolved or improved with adjustments
- Dysarthria was the most common

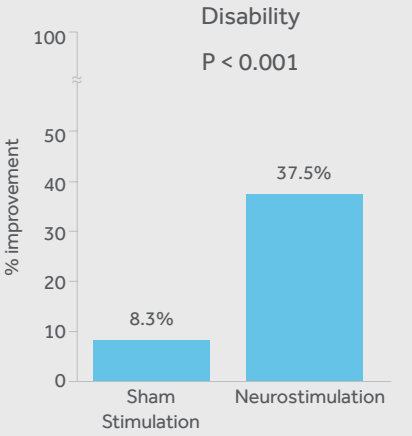
KEY CONCLUSIONS

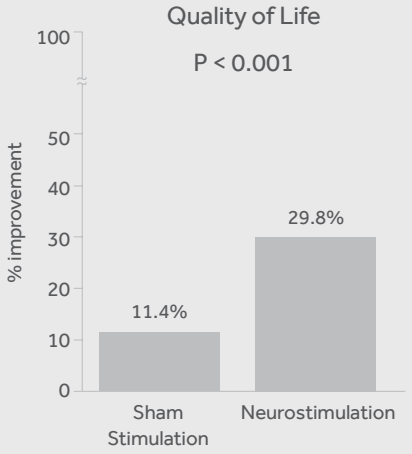
- 3 months of bilateral GPi deep brain stimulation demonstrated significant benefit for patients through reduction in disability and severity of dystonia, and improvement in quality of life, compared to baseline.
- Similar symptomatic benefit occurred in patients with generalized or segmental dystonia, suggesting that the two conditions may equally benefit from neurostimulation.
- The authors found that the clinical benefits of neurostimulation were greater than that of high-dosage trihexyphenidyl, the most potent drug for treatment of dystonia.

Percent Improvement in Assessment Scores Sham Stimulation vs. Neurostimulation

Patients receiving GPi neurostimulation for 3 months had significantly greater improvement in movement, disability, and quality of life scores compared to scores of patients receiving sham stimulation. Improvement in movement and disability was assessed by blinded ratings using the Burke-Fahn-Marsden Dystonia Rating Scale. Quality of life was assessed with the SF-36.







This physician-initiated study received financial support from Medtronic.

PALLIDAL DEEP BRAIN STIMULATION IN PATIENTS WITH PRIMARY GENERALISED OR SEGMENTAL DYSTONIA: 5-YEAR FOLLOW-UP OF A RANDOMISED TRIAL

Volkmann J, Wolters A, Kupsch A, Müller J, Kühn, Schneider G-H, et al. Lancet Neurol. 2012;11:1029-1038.

OBJECTIVE

To assess the 5-year safety and efficacy of bilateral pallidal neurostimulation in patients with primary generalised or segmental dystonia.

Study Type

Prospective, randomised, controlled, multicentre

Design

40 patients in the parent trial1 were randomised to either sham neurostimulation or neurostimulation of the internal globus pallidus for 3 months. Assessment was repeated for all patients after 6 months of active neurostimulation. 38 patients consented to participate in an open-label extension study with annual follow-up visits for up to 5 years after activation of neurostimulation. The primary endpoint, in an intention-to-treat analysis, was the change in dystonia severity at 3 years and 5 years compared with the preoperative baseline and the 6-month visit, as assessed by the Burke-Fahn-Marsden dystonia rating scale (BFMDRS) motor score.

RESULTS

- Significant improvement in dystonia severity occurred at 3 years and 5 years compared with baseline (Table 1).
- All motor symptoms (except speech and swallowing) and global clinical assessments of dystonia and pain showed significant improvements for up to 5 years.
- Improvements in the health-related quality of life physical subscores of the SF-36 obtained at 6 months were sustained at 5 years. Improvements in the mental subscores remained relatively stable after the 6-month visit but were no longer significant at 5 years compared with baseline.
- Patients with generalised dystonia experienced a progressive improvement of dystonia severity beyond 6 months of neurostimulation, whereas those with segmental dystonia showed a relatively stable change (Table 2).

ADVERSE EVENTS

- Dysarthria and transient worsening of dystonia were the most common non-serious adverse events.
- All serious adverse events in the original study phase, and 66.6% during the 5-year extension, occurred in patients with generalised dystonia.
- 21 adverse events were rated serious, 16 of which were device-related.
- All serious adverse events resolved without permanent sequelae.

KEY CONCLUSIONS

- This prospective long-term study showed significant, sustained improvements in dystonia ratings at 5 years after surgery, for patients with primary generalised or segmental dystonia treated by bilateral pallidal neurostimulation.
- The reduction of dystonia symptoms led to substantial improvements in disability and health-related quality of life in both dystonia groups. These benefits were sustained at 5 years.
- The study provides additional evidence supporting pallidal neurostimulation as an effective and relatively safe first-line treatment option for patients with medically intractable generalised or segmental dystonia.

Table 1. Improvement in Dystonia Severity Compared to Baseline (intention-to-treat, n = 40)

Outcome	6 months	3 years	5 years	P Value (5 years vs. baseline)
BFMDRS motor score	47.9%	61.1%	57.8%	< 0.0001

BFMDRS = Burke-Fahn-Marsden dystonia rating scale

Table 2. Improvement in Dystonia Severity – Generalised vs. Segmental (BFMDRS motor score)

Type of Dystonia	6 months	3 years	5 years	P Value
Generalised	44.8%	70.6%	67.0%	NA
Segmental	54.5%	60.5%	49.4%	NA

NA = not available in study

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EFNS GUIDELINES ON DIAGNOSIS AND TREATMENT OF PRIMARY DYSTONIAS

Albanese A, Asmus F, Bhatia KP, et al. Euro J Neurol. 2011:18:5-18.

OBJECTIVE

To provide guidance in the diagnosis and therapeutic management of patients with primary dystonias. Guidance represents a peer-reviewed statement of minimum desirable standards of practice based on scientifically proven, evidence-based criteria.

Study Type

Guidance paper developed using unified criteria for standards of reporting within the framework established by an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS).1 Refer to Table 1 on page 32 for rating of recommendations and evidence classification scheme.

RESULTS

Note: Recommendations for the treatment of dystonia are summarized here. Recommendations for the diagnosis of dystonia are included in the paper but not summarized here.

Pallidal Deep Brain Stimulation (DBS)

1. Considered a good option, particularly for primary generalized or segmental dystonia (Level A), after medication or botulinum toxin (BoNT) has failed to provide adequate improvement.
2. Considered a good option for cervical dystonia, after medication or BoNT has failed to provide adequate improvement (Level B).
3. Less effective, in general, in secondary dystonia with the exception of tardive dystonia (Level C).
4. Procedure requires a specialized expertise and a multidisciplinary team; not without side effects (GPP).

KEY CONCLUSIONS

- Recommendations for the therapeutic management of patients with primary dystonias are systematically graded according to the strength of available scientific evidence.
- Deep brain stimulation is considered a good option for primary generalized, segmental, or cervical dystonia, after medication or BoNT has failed.

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NOTES

INDICATIONS

Medtronic DBS Therapy for Movement Disorders is indicated for patients with disabling tremor or symptoms of Parkinson's disease. Studies have shown that deep brain stimulation with Medtronic DBS Therapy components is effective in controlling essential tremor and symptoms of Parkinson's disease that are not adequately controlled with medications.

Additionally, deep brain stimulation is effective in controlling dyskinesias and fluctuations associated with medical therapy for Parkinson's disease. Medtronic DBS Therapy for Movement Disorders is also indicated as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and segmental dystonia, hemidystonia, and cervical dystonia (torticollis) for individuals 7 years of age and older.

Refer to the appropriate information for prescribers booklet for contraindications, warnings, precautions, adverse events summary, patient selection, and component disposal.

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