EVIDENCE COMPENDIUM

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

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INTRODUCTION

Medtronic DBS Therapy (deep brain stimulation) for movement disorders has gained acceptance and widespread clinical use in recent years. The therapy is adjustable and reversible in most cases, 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.*

This compendium summarizes the clinical evidence for efficacy and adverse events of deep brain stimulation in patients with 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.
- The risks associated with the implant procedure for Medtronic DBS Therapy may include serious and sometimes fatal complications such as intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications, meningitis, encephalitis, brain abscess, cerebral edema, and aseptic cyst formation. Contraindications include diathermy, Transcranial Magnetic Stimulation and certain MRI procedures. Once implanted, device related infection, skin erosion and/or system migration may occur. Tunneling the extension may cause nerve or vascular injury, and extension fibrosis may occur. Medtronic DBS Therapy could suddenly cease because of mechanical or electrical problems. The DBS system may interact with other medical devices and other sources of electromagnetic interference which may result in serious patient injury or death, system damage or changes to the neurostimulator or to stimulation. Any of these situations may require additional surgery or cause symptoms to return or worsen. Medtronic DBS Therapy may cause new or worsening neurological or psychiatric symptoms. In patients receiving Medtronic DBS Therapy for Parkinson's disease or essential tremor, new onset or worsening depression, suicidal ideations, suicide attempts, and suicide have been reported. In patients receiving Medtronic DBS Therapy for dystonia, epilepsy or obsessive-compulsive disorder, depression, suicidal ideations, and suicide have been reported, although no direct cause-and-effect relationship has been established.
- For additional safety information, please refer to Indications, Safety and Warnings on the back of this Compendium or at medtronic.com.

Parkinson's Disease

- Patients experience significant improvement in motor function with deep brain stimulation for movement disorders in both patients with recent onset of motor complications as well as in patients with long-standing motor complications.[1]
- Quality of life and activities of daily living improve from baseline to 24 months in PD patients of recent onset of motor complications receiving DBS Therapy plus best medical treatment.[1]

- DBS therapy plus best medical treatment provides additional "on" time without troublesome dyskinesia for patients with recent onset of motor complications.[1]
- DBS therapy can lead to a reduction in medication and reduction in drug-related complications for patients with recent onset of motor complications.[1]
- Marked improvement in motor function is still evident at 5-year follow-up.[2]
- Since both STN and GPi DBS are effective in improving motor function, these targets can be selected based on individual patients and symptoms.[3]

Essential Tremor

- Unilateral thalamic stimulation is indicated for the suppression of tremor in the upper extremity.
- DBS can effectively suppress severe tremor in patients with essential tremor for more than 6 years after implantation.[4]

Dystonia

- Medtronic DBS Therapy is approved under a Humanitarian Device Exemption (HDE) for dystonia.*
- The following results were reported:
  - Bilateral GPi stimulation demonstrated some improvement in movement symptoms.[5]
  - Sustained improvements in dystonia ratings occurred at 5 years after surgery.[5]
  - Use of medication to treat dystonia was reduced after surgery.[6]
  - Similar symptomatic effects were seen in patients with generalized or segmental dystonia.[6,7]

**Humanitarian Device: Medtronic DBS Therapy has been authorized by Federal (U.S.A.) law for the use as an aid in the management of chronic, intractable (drug refractory) primary dystonia. The effectiveness of the devices used for the treatment of dystonia has not been demonstrated.*

1. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's Disease with early motor complications. *N Eng J Med*. 2013;368:610-622.
2. Krack R, Batir A, Van Blercom N, at al. Five-Year Follow-up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson's disease. *N Engl J Med*. 2003; 349: 1925-34.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.

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 largely unchanged (3% increase) between baseline (1090 ± 543 mg) and 6 months (1120 ± 537 mg).

Adverse Events

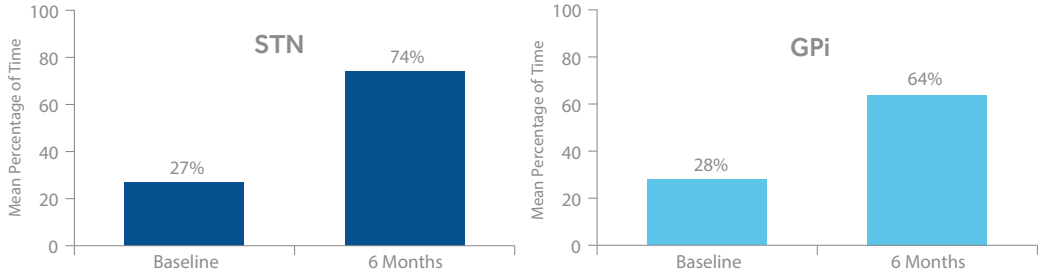
- 7 patients experienced intracranial hemorrhage, 4 of whom required surgical decompression.
  - 6 of the 7 patients had neurological deficits; 4 of those resulted in persistent dysfunction.
  - Risk of hemorrhage was correlated with the number of microelectrode insertions used to determine target location.
- 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.
- Reported adverse events included intracranial hemorrhage, seizures, and infection.

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.

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 (ADL) scores significantly improved at 5 years ($P < 0.001$).
- Levodopa (or equivalent) requirement significantly decreased from 1409 ± 605 mg at baseline to 518 ± 33 mg at 1 year ($P < 0.001$).

Adverse Events

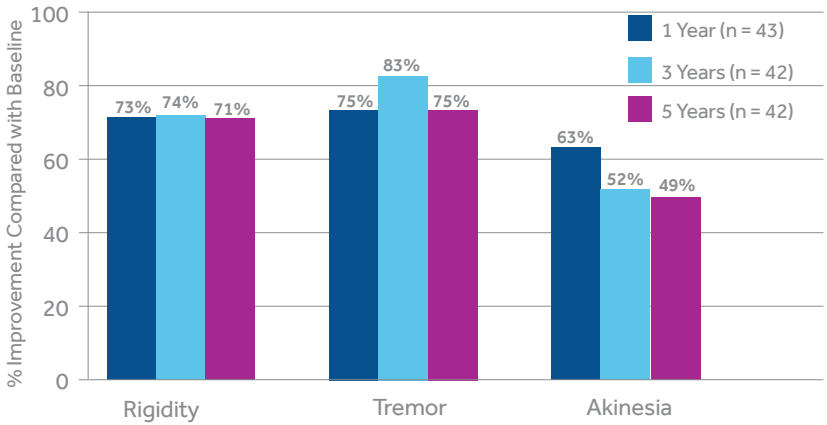
- Severe adverse events included 3 deaths: intracerebral hemorrhage, myocardial infarction, suicide.
- 2 patients developed permanent dementia.
- 15 of 49 patients (31%) had eyelid-opening apraxia in the first 3 months; this remained a problem for 8 patients throughout the follow-up.

KEY CONCLUSIONS

- Bilateral STN stimulation in patients off medication led to significant post-operative improvements in ADL scores and 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.

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

- Significant improvement in motor symptoms (UPDRS-III , $P < 0.001$) was found in the neurostimulation group but remained unchanged in the medication group.
- 25% improvement in quality of life (PDQ-39 summary index) was recorded for the neurostimulation group; there was a 1.5% decline in the medication group.
- Patients' diaries revealed significant changes only in the neurostimulation group. This included: longer periods of mobility (4.4 hours), shorter periods of immobility (decreased by 4.2 hours), and shorter periods with troubling dyskinesia.

Adverse Events

	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

- 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.

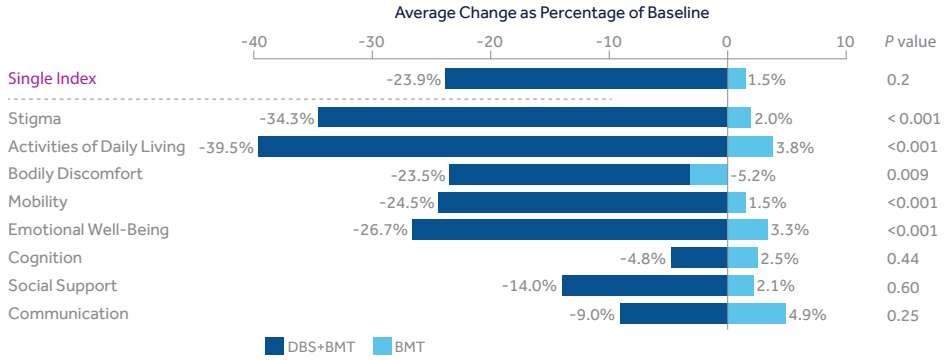
KEY CONCLUSIONS

- 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 duration of periods of immobility and dyskinesia.
- Improvement in motor function led to improvement in PDQ-39 measurements of mobility, activities of daily living, emotional well-being, stigma, and bodily discomfort; cognition, social support, and communication improved but not significantly.
- The prospect of improved quality of life resulting from deep brain stimulation must be weighed against the risks of surgical intervention.

Percent Change in Quality of Life at 6 Months
Deep Brain Stimulation vs. Best Medical Therapy

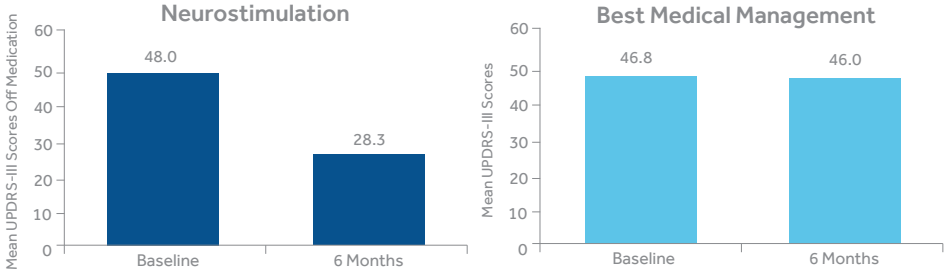
(negative score indicates improvement)



Quality of life improved by 23.9% in the neurostimulation group at 6 months, compared with a 1.5% decline in the best medical management group.
BMT = best medical therapy DBS = deep brain stimulation

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

(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.

NEUROPSYCHOLOGICAL AND PSYCHIATRIC CHANGES AFTER DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE: A RANDOMISED, 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 STN-DBS (n = 60) with best medical treatment (n = 63) on overall cognitive functioning.

*This study uses the same patient population that is 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.
- 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.

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 trial using a rater blinded to treatment for motor assessment.

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 (BMT) (n = 134)	Deep Brain Stimulation + BMT (n = 121)	P Value
Change in mobility without troublesome dyskinesia (patient diaries)	-17%	138%	< 0.001
Quality of life improvement (PDQ-39 summary index)	1%	17%	< 0.001
Motor function improvement without medication (UPDRS III)	4%	29%	< 0.001
Medication (levodopa equivalents) Change in mg over baseline (1281 mg)	1%	-23%	< 0.001

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

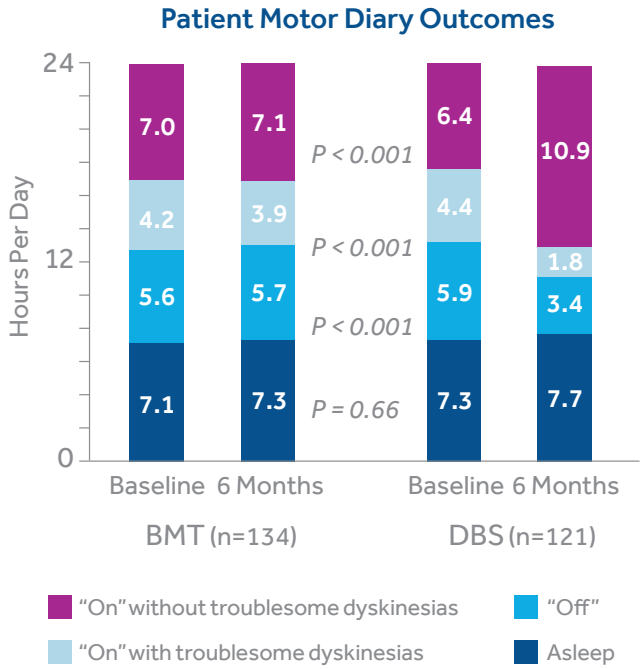
Adverse Events

- 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.
- 99% of serious adverse events resolved by the 6-month follow-up. The events were resolved, per the investigator, and may include ongoing sequelae caused by the reported events.

KEY CONCLUSIONS

- Deep brain stimulation was superior to best medical therapy in improving "on" time without troubling dyskinesia at 6 months in patients with advanced Parkinson's disease.
- Patients with deep brain stimulation experienced improvements in motor function.
- Quality of life was improved as a result of improved motor function.
- 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.



PALLIDAL VS. 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).

This is phase II of Weaver FM , Follett KA, Stern M, et al. Bilateral deep brain stimulation vs. best medical therapy for patients with advanced Parkinson's disease. *JAMA.* 2009;301(1):63-73.

Study Type — Prospective, multicenter, randomized, double-blinded

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

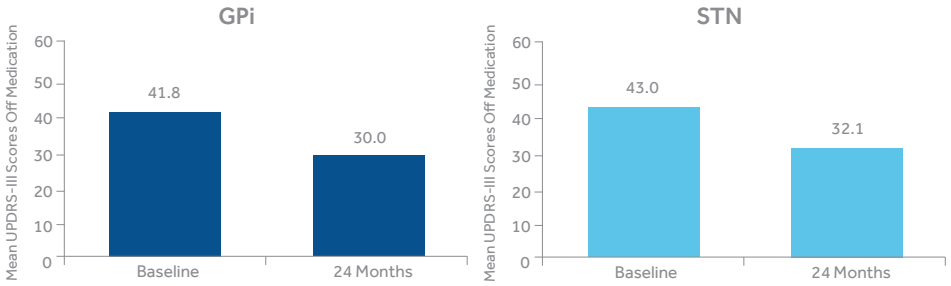
- Serious adverse events occurred in 56% of patients receiving STN stimulation and in 51% of patients receiving GPi stimulation.
- 99% of serious adverse events were resolved by the 24-month follow-up. The events were resolved, per the investigator, and may include ongoing sequelae caused by the reported events.

KEY CONCLUSIONS

- Deep brain stimulation improved motor function in patients with Parkinson's disease who underwent either GPi or STN stimulation.
- Motor function improvement and medication reduction 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.
- There was no significant difference between the study groups in the type or frequency of adverse events at 24 months.

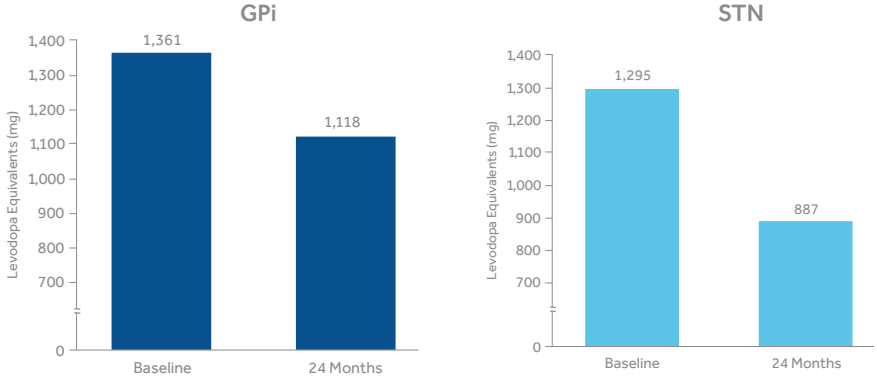
Improvement in UPDRS Motor Scores with DBS and without Medication

(lower scores indicate better function)



UPDRS III scores improved in both study groups but did not differ significantly according to the surgical target (difference - 1.1 points; 95% confidence interval, -4.3 to 2.1; P=0.50).
UPDRS III = Unified Parkinson's Disease Rating Scale, part III.
DBS = deep brain stimulation.

Decrease in Medication at 24 Months with DBS



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).

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 vs. 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*

- 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 lower (improved) than baseline.
- There was no difference in the PDQ-39 trends over time between STN and GPi DBS ($P = 0.38$).

Adverse Events

- Authors did not comment on adverse events.

KEY CONCLUSIONS

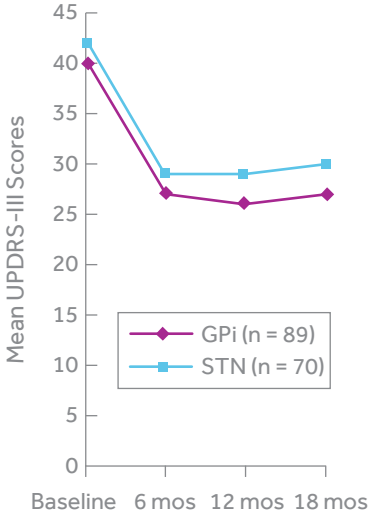
- Motor function improvement and medication reduction observed at 6 months were sustained at 36 months in both target groups.
- These changes were similar between the GPi and STN study groups and stable over time.
- Self-reported motor function, based on diaries, showed that good motor functioning (on 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.

Outcomes of GPi vs. STN DBS — Baseline to 3 Years

On Stimulation/Off Medication

UPDRS-III Motor Scores*

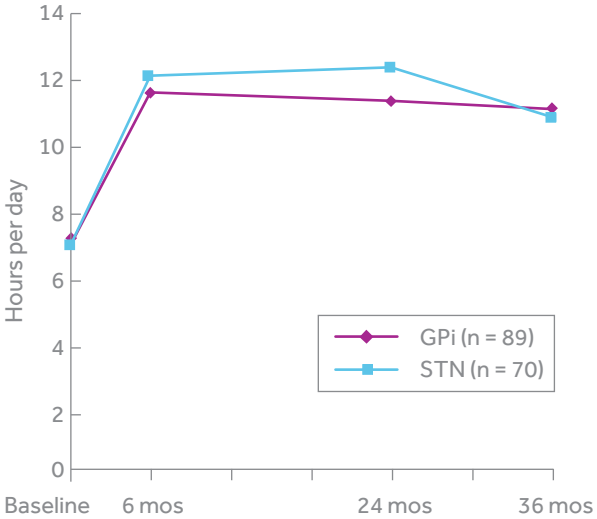
(on stimulation/off medication)



*Lower scores indicate better function

Hours of Good Motor Function*

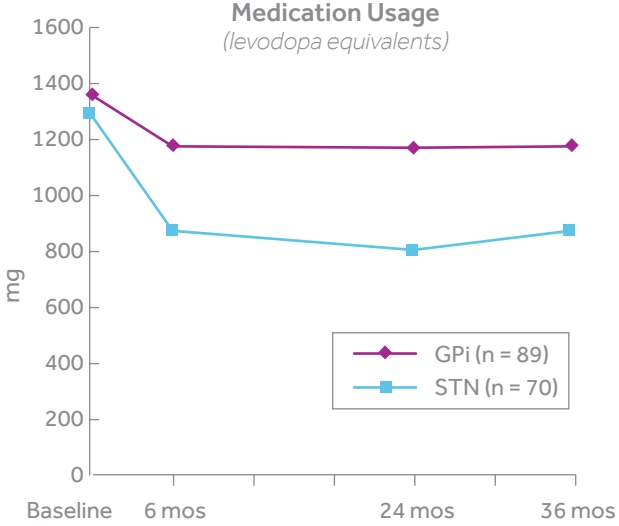
(time without troublesome dyskinesia)



*Based on diaries

Medication Usage

(levodopa equivalents)



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.

DEEP BRAIN STIMULATION PLUS BEST MEDICAL THERAPY VERSUS BEST MEDICAL THERAPY ALONE FOR ADVANCED PARKINSON'S DISEASE (PD SURG TRIAL): A RANDOMISED, 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, controlled, 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)

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
UPDRS Parts I-IV			
Total score: On medication	1.6	-6.6	< 0.0001
Total score: Off medication	-0.9	-27.4	< 0.0001

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

- At 1 year, the mean improvement in the PDQ-39 summary index was significantly greater in the DBS+BMT group compared with 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 BMT alone.

Adverse Events

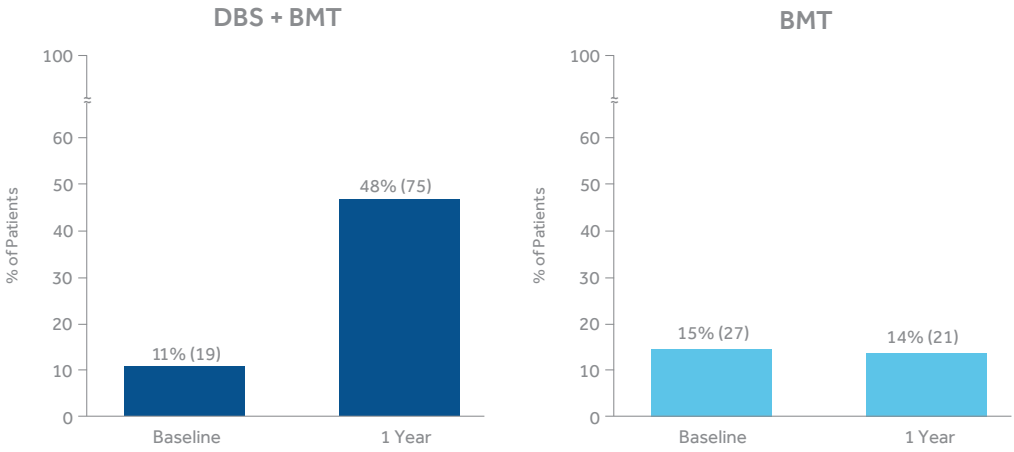
- Serious adverse events in the BMT group included 14 Parkinson's disease-related and drug-related events and 1 death (stroke).
- Serious adverse events in the DBS + BMT group included 43 surgery-related events, 25 Parkinson's disease-related and drug-related events, and 2 deaths (hemorrhage and pneumonia).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

KEY CONCLUSIONS

- At 1 year, DBS plus BMT improved patient-evaluated motor function and quality of life, and functional clinical assessment (UPDRS and DRS II), more than BMT 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 lower than the amount required by patients receiving BMT 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.

Percent of Patients Experiencing No Dyskinesia During Waking Hours

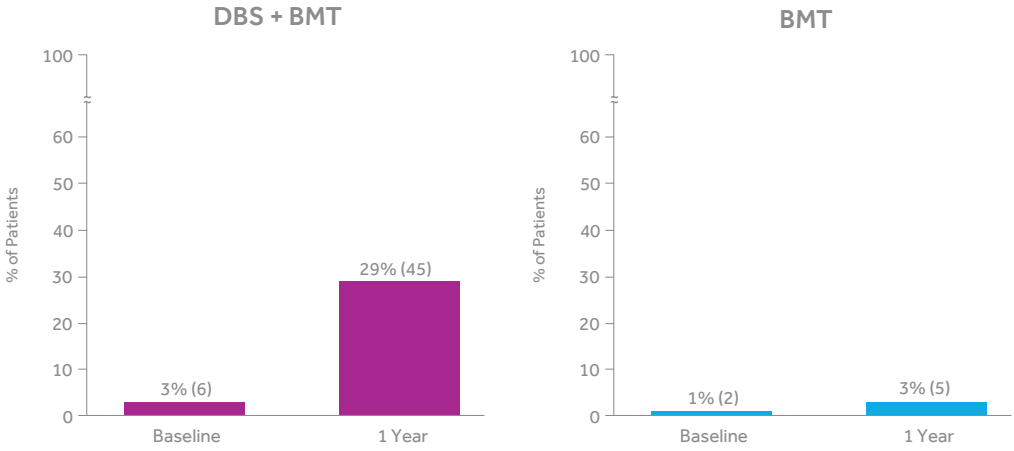
(baseline vs. 1 year)



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).

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, $P = 0.94$).

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 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
On-drug (n = 125)			
Clinical dyskinesia rating scale (CDRS, range 0 – 28)	57% (3.0)	23% (1.1)	0.01

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

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.

NEUROSTIMULATION FOR PARKINSON'S DISEASE WITH EARLY MOTOR COMPLICATIONS

Schuepbach M, Rau J, Knudsen K, et al. *N Eng J Med.* 2013;368:610-622.

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 Outcome — 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).

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 20 months — P <0.05*

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 26 (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-month follow-up.
- Serious adverse events related to motor problems, impulse control disorders, and psychotic manifestations were more frequent in the best medical therapy group.

KEY CONCLUSIONS

- The Schuepbach et al (NEJM) 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.

Reference

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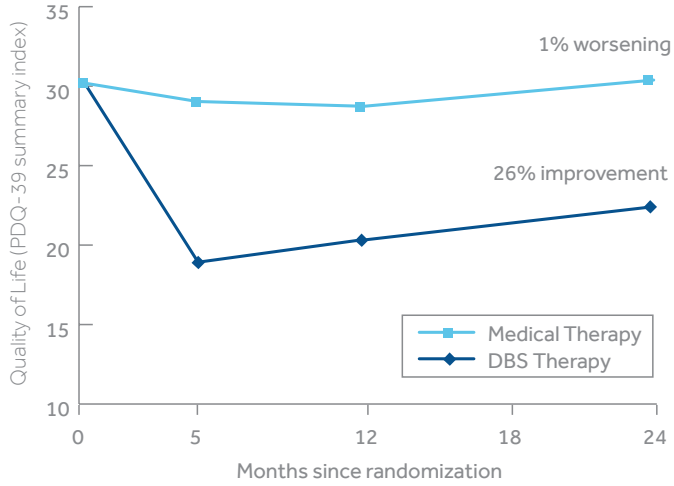
Quality of Life Scores with DBS therapy vs. Medical therapy — PDQ-39 Summary Index, Baseline to 24 Months

(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.

This physician-initiated study received financial support from Medtronic.

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 time frames ($P < 0.025$).

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.

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 was related to the surgical procedure or to the implanted devices.
- 1 patient with Parkinson's disease experienced unpleasant paraesthesias.
- Lead fracture led to DBS lead replacement in 1 patient.

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.

Humanitarian Device: The effectiveness of this device for the treatment of dystonia has not been demonstrated.

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 Rating Scale. Movement scores were evaluated via videotape review by a blinded observer. At the 3-month follow-up, patients were assessed in a double blind manner 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.
- Neurostimulation improved all subscores except speech.

Adverse Events

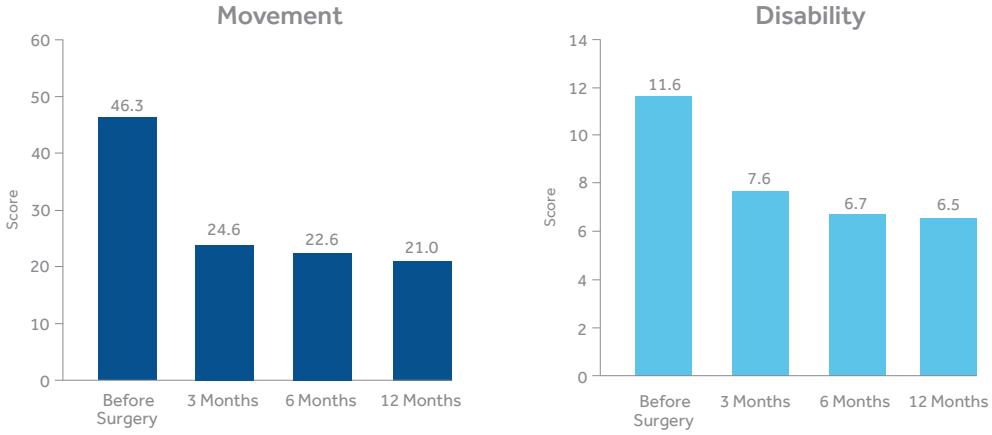
- 3 patients had 5 adverse events in the post-operative period.
- All events resolved rapidly with no permanent neurological sequelae.

KEY CONCLUSIONS

- Bilateral GPi stimulation demonstrated improvement in motor symptoms.
- Authors did not observe any worsening of cognition or mood.
- 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 Rating Scale.

Humanitarian Device: The effectiveness of this device for the treatment of dystonia has not been demonstrated.

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.

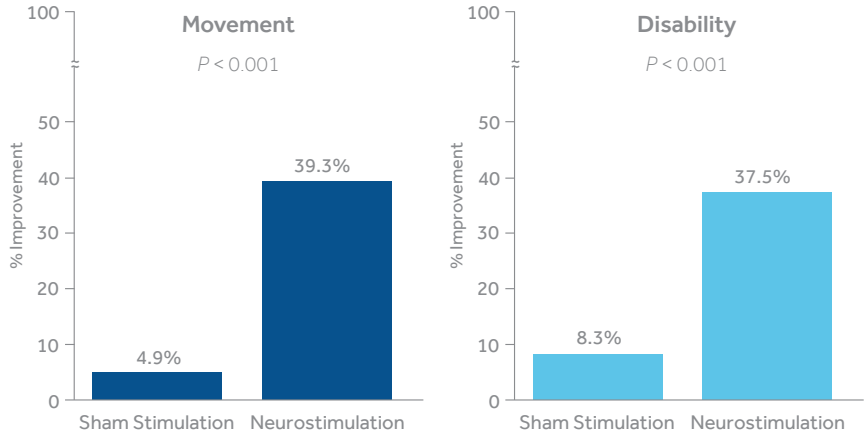
Adverse Events

- 9 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 improvement in some movement symptoms compared to baseline.
- Similar symptomatic improvement occurred in patients with generalized or segmental dystonia, suggesting that the two conditions may equally benefit from neurostimulation.
- The authors found that the clinical effects of neurostimulation were greater than that of high-dosage trihexyphenidyl.
- Infection and dysarthria were the most common adverse events.

Percent Improvement in Assessment Scores
Sham Stimulation vs. Neurostimulation



Patients receiving GPi neurostimulation for 3 months had significantly greater improvement in movement and disability 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.

Humanitarian Device: The effectiveness of this device for the treatment of dystonia has not been demonstrated.

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, 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 generalized or segmental dystonia.

Study Type — Prospective, randomized, controlled, multicenter

Design — 40 patients in the parent trial[1] were randomized 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 pre-operative baseline and the 6-month visit, as assessed by the Burke-Fahn-Marsden dystonia rating scale (BFMDRS) motor score.

RESULTS

- 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 improvements for up to 5 years.
- Improvements in the 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 generalized 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).

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 — Generalized vs. Segmental

(BFMDRS motor score)

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

NA = not available in study

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 generalized 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 sustained improvements in dystonia ratings at 5 years after surgery, for patients with primary generalized or segmental dystonia treated by bilateral pallidal neurostimulation.
- The reduction of dystonia symptoms led to substantial improvements in disability in both dystonia groups. These benefits were sustained at 5 years.
- The study provides additional evidence supporting pallidal neurostimulation as a relatively safe therapy for patients with medically intractable generalized or segmental dystonia.

1. Kupsch A, Benecke R, Muller J, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. *N Engl J Med*. 2006;355(19):1978-1990.

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Parkinson's Disease

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4. Fraix V, Houeto JL, Lagrange C, et al. Clinical and economic results of bilateral subthalamic nucleus stimulation in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2006;77(4):443-449.
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Parkinson's Disease *(cont.)*

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Dystonia

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Brief Statement: Medtronic DBS Therapy for Parkinson's Disease, Tremor and Dystonia

Medtronic DBS Therapy for Parkinson's Disease, Tremor and Dystonia: Product labeling must be reviewed prior to use for detailed disclosure of risks.

Indications:

Medtronic DBS Therapy for Parkinson's Disease: Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Parkinson's Disease is indicated for adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's disease of at least 4 years' duration that are not adequately controlled with medication, including motor complications of recent onset (from 4 months to 3 years) or motor complications of longer-standing duration.

Medtronic DBS Therapy for Tremor: Unilateral thalamic stimulation of the ventral intermediate nucleus (VIM) using Medtronic DBS Therapy for Tremor is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with essential tremor or parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.

Medtronic DBS Therapy for Dystonia: Unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Dystonia is indicated as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above.

Contraindications: Medtronic DBS Therapy is contraindicated for patients who are unable to properly operate the neurostimulator and, for Parkinson's disease and Essential Tremor, patients for whom test stimulation is unsuccessful. The following procedures are contraindicated for patients with DBS systems: diathermy (e.g., shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy), which can cause neurostimulation system or tissue damage and can result in severe injury or death; Transcranial Magnetic Stimulation (TMS); and certain MRI procedures using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area if the patient has an implanted Soletra™ Model 7426 Neurostimulator, Kinetra™ Model 7428 Neurostimulator, Activa™ SC Model 37602 Neurostimulator, or Model 64001 or 64002 pocket adaptor.

Warnings and Precautions: There is a potential risk of brain tissue damage using stimulation parameter settings of high amplitudes and wide pulse widths and, for Parkinson's disease and essential tremor, a potential risk to drive tremor using low frequency settings. Extreme care should be used with lead implantation in patients with an increased risk of intracranial hemorrhage. Sources of electromagnetic interference (EMI) may cause device damage or patient injury. Theft detectors and security screening devices may cause stimulation to switch ON or OFF and may cause some patients to experience a momentary increase in perceived stimulation. The DBS System may be affected by or adversely affect medical equipment such as cardiac pacemakers or therapies, cardioverter/ defibrillators, external defibrillators, ultrasonic equipment, electrocautery, or radiation therapy. MRI conditions that may cause excessive heating at the lead electrodes which can result in serious injury, including coma, paralysis, or death, or that may cause device damage, include: neurostimulator implant location other than pectoral and abdominal regions; unapproved MRI parameters; partial system explants ("abandoned systems"); misidentification of neurostimulator model numbers; and broken conductor wires (in the lead, extension or pocket adaptor). The safety of electroconvulsive therapy (ECT) in patients receiving DBS Therapy has not been established. Tunneling the extension too superficially or too deeply may result in nerve or vascular injury, or tunneling through unintended anatomy. The lead-extension connector should not be placed in the soft tissues of the neck due to an increased incidence of lead fracture. Abrupt cessation of stimulation should be avoided as it may cause a return of disease symptoms, in some cases with intensity greater than was experienced prior to system implant ("rebound" effect). Onset of status dystonicus, which may be life-threatening, may occur in dystonia patients during ongoing or loss of DBS therapy. Patients using a rechargeable neurostimulator for Parkinson's disease or Essential Tremor should check for skin irritation or redness near the neurostimulator during or after recharging, and contact their physician if symptoms persist. Loss of coordination in activities such as swimming may occur. For Parkinson's disease or essential tremor, new onset or worsening depression, suicidal ideation, suicide attempts, and suicide have been reported. For Dystonia, depression, suicidal ideations and suicide have been reported, although no direct cause-and-effect relationship has been established.

Adverse Events: Adverse events related to the therapy, device, or procedure can include intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications (including pain, infection, dehiscence, erosion, seroma, and hematoma), meningitis, encephalitis, brain abscess, cerebral edema, aseptic cyst formation, device complications (including lead fracture and device migration) that may require revision or explant, extension fibrosis (tightening or bowstringing), new or exacerbation of neurological symptoms (including vision disorders, speech and swallowing disorders, motor coordination and balance disorders, sensory disturbances, cognitive impairment, and sleep disorders), psychiatric and behavioral disorders (including psychosis and abnormal thinking), cough, shocking or jolting sensation, ineffective therapy, and weight gain or loss.

Safety and effectiveness has not been established for patients with previous surgical ablation procedures, dementia, coagulopathies, or moderate to severe depression, or patients who are pregnant. Parkinson's disease and essential tremor: safety and effectiveness has not been established for patients under 18 years or patients with neurological disease other than idiopathic Parkinson's disease or Essential Tremor. Essential tremor: safety and effectiveness has not been established for bilateral stimulation or for patients over 80 years of age. Dystonia: age of implant is suggested to be that at which brain growth is approximately 90% complete or above.

Humanitarian Device (Dystonia): Authorized by Federal Law as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above. The effectiveness of the devices for treating these conditions has not been demonstrated.

USA Rx only Rev 11/19

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