Medtronic

Evidence compendium

Study summaries supporting
the use of deep brain stimulation
for movement disorders

Glossary

ADL	activities of daily living
ALDS	academic medical center linear disability scale
BFMDRS	Burke-Fahn-Marsden dystonia rating scale
BJLOT	Benton judgment of line orientation test
BMT	best medical treatment
CDQ-24	craniocervical dystonia questionnaire-24
CDRS	clinical dyskinesia rating scale
CSF	cerebrospinal fluid
DOT	digit ordering test
DBS	deep brain stimulation
ETRS	essential tremor rating scale
FWIT	interference naming strop task
GPi	internal globus pallidus
HRQoL	health-related quality of life
LEDD	levodopa equivalent daily dose
MDRS	Mattis dementia ratting scale
MRI	magnetic resonance imaging
MWT-A	multiple choice vocabulary test
NVLT	non-verbal learning test
PDQ	Parkinson's disease questionnaire
QoL	quality of life
RWT	Regensburg's word fluency test
SCOPA-PS	scales for outcomes in Parkinson's disease - psychosocial questionnaire
SF-36	short form 36
STN	subthalamic nucleus
TEA	test of everyday attention
TWSTRS	Toronto western spasmodic torticollis rating scale
UPDRS	unified Parkinson's disease rating scale
VLMT	verbal learning and memory test
VOSP	visual object and space perception
WMS-R	Wechsler memory scale - revised version

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 help 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.

Disclaimer: Medtronic sponsors clinical research and may have provided financial support to the studies described in these articles. Please review individual articles for disclosures of financial support.

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 (cerebrospinal fluid) 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 (magnetic resonance imaging) 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 or epilepsy 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 device manual or consult the Medtronic website at www.medtronic.eu.

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 longstanding motor complications.[1,8]
- In PD patients of recent onset of motor complications, from baseline to 24 months, DBS therapy plus best medical treatment can improve quality of life and activities of daily living, provide additional "on" time without troublesome dyskinesia, lead to a reduction in medication and reduction in drug-related complications.[1]
- Marked improvement in motor function is still evident at 5-year follow-up in patients with advanced PD.[2]
- Both STN (subthalamic nucleus) and GPi (internal globus pallidus) DBS are effective in improving motor function, from baseline to 36 months.[3]

Essential tremor

- DBS can effectively suppress severe tremor in patients with essential tremor for more than 6 years after implantation.[4]

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.[6]
  - Use of medication to treat dystonia was reduced after surgery.[6]
  - Similar symptomatic effects were seen in patients with generalized or segmental dystonia after 6 months of neurostimulation[7]. Then, efficacy of neurostimulation, assessed by Burke-Fahn-Marsden dystonia rating scale motor score, progressively increased in patients with generalised dystonia whereas it remained stable in segmental dystonia at 5 years.[6]

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, et 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.
8. Deuschl et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;355:896-908

Table of contents

Lead author	Year	Abbreviated title	Journal	Page
Essential tremor				
Rehncrona S	*2003*	Long-term efficacy of thalamic DBS for tremor	*Movement Disorders*	31
Dystonia				
Vidailhet M	*2005*	Bilateral DBS of the GPi in primary generalized dystonia	*N Engl J Med*	33
Kupsch A	*2006*	Pallidal DBS in primary generalized or segmental dystonia	*N Engl J Med*	34
Mueller J	*2008*	Pallidal DBS on quality of life in generalized or segmental dystonia	*Movement Disorders*	36
Volkmann J	*2012*	Pallidal DBS in primary generalized or segmental dystonia: 5-year follow-up	*Lancet Neurol*	38
Volkmann J	*2014*	Pallidal DBS in cervical dystonia	*Lancet Neurol*	40
Dinkelbach L	*2015*	Cognitive outcome of pallidal DBS for primary cervical dystonia	*Parkinsonism Relat Disord*	42

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, conducted between 1995 and 1999.

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 at 6 months post-implant were reported.

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

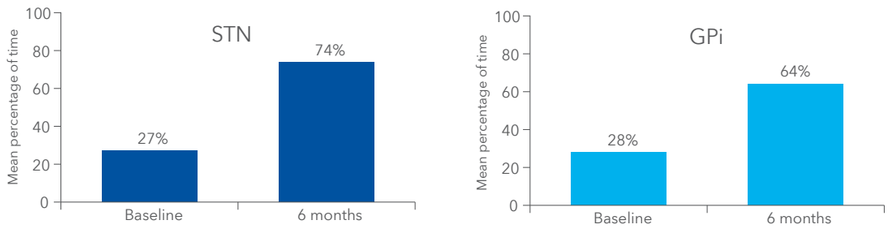
- 7 patients experienced intracranial hemorrhage, 4 of whom required surgical decompression.
  - 6 of the 7 patients had neurological deficits; 4 of those resulted in persistent dysfunction.
  - Risk of hemorrhage was correlated with the number of microelectrode insertions used to determine target location.
- 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 at one, three, and five years.

Results

- In the off-medication state,
  - Motor function scores while off medication improved by 54% at 5 years compared with baseline ($P < 0.001$).
  - Activities of daily living (ADL) scores improved by 49% at 5 years ($P < 0.001$).
- Levodopa (or equivalent) requirement significantly decreased from 1409 ± 605 mg at baseline to 518 ± 33 mg at 5 years ($P < 0.001$).

Adverse events

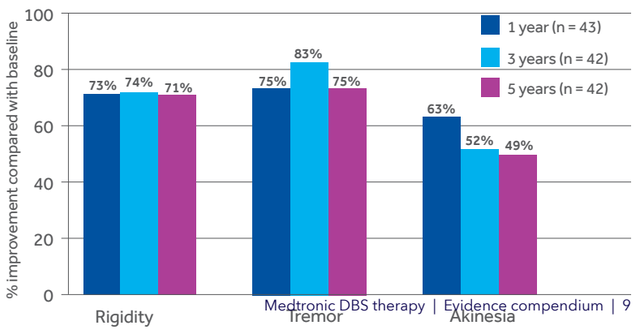
- Severe adverse events included 3 deaths: intracerebral hemorrhage, myocardial infarction, suicide.
- 2 patients developed permanent dementia.
- 15 of 49 patients (31%) had eyelid-opening apraxia in the first 3 months; this remained a problem for 8 patients throughout the follow-up.
- 1 patient had an infection that required temporary removal of the subcutaneous extension lead and pulse generator.

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.
- In the off-medication state, postural stability, gait and freezing of gait improved at 5 years while speech did not improve at 5 years.
- 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. Patients were screened between 2001 and 2004.

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 motor symptoms (UPDRS-III without medication) was found in the neurostimulation group but remained unchanged in the medication group.
- About 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 without dyskinesias (increased by 4.4 hours), shorter periods of immobility (decreased by 4.2 hours), and longer periods of sleeping (increased by 0,7 hour).

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

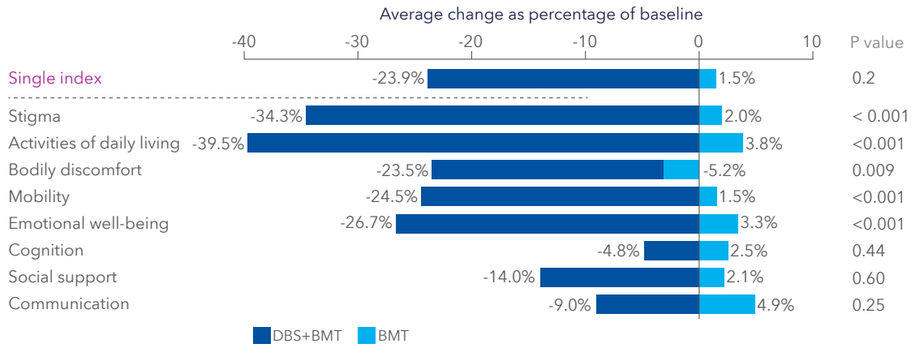
- Severe adverse events included 3 (3.9%) deaths in the neurostimulation group (hemorrhage, pneumonia, suicide) and 1 (1.3%) death in the medical management group (motor vehicle accident).
- All other severe adverse events resolved without permanent complications.

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

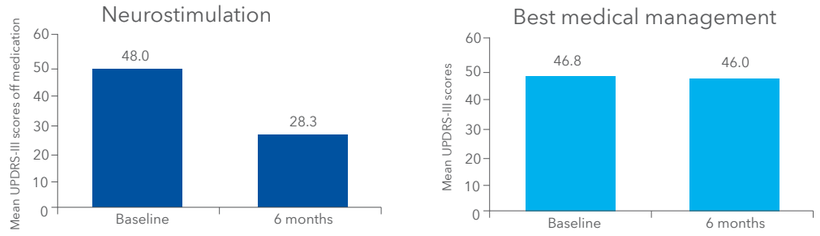
(negative score indicates improvement)



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. Patients enrolled between 2002 and 2005.

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	BMT group (n=134) – mean (SD)		DBS group (n=121) – mean (SD)		P value (*)
	Baseline	6 months	Baseline	6 months	
"On" time without troublesome dyskinesia (patient diaries) – hours/day	7.0 (2.9)	7.1 (3.3)	6.4 (2.7)	10.9 (4.2)	< 0.001
Quality of life (PDQ-39 single index)	44.3 (13.1)	44.8 (13.4)	44.9 (13.2)	37.3 (16.0)	< 0.001
Motor function without medication (UPDRS III score)	43.2 (11.3)	41.6 (12.7)	43.0 (13.5)	30.7 (14.5)	< 0.001
Medication (levodopa equivalents in mg)	1289 (546)	1303 (532)	1281 (521)	985 (633)	< 0.001

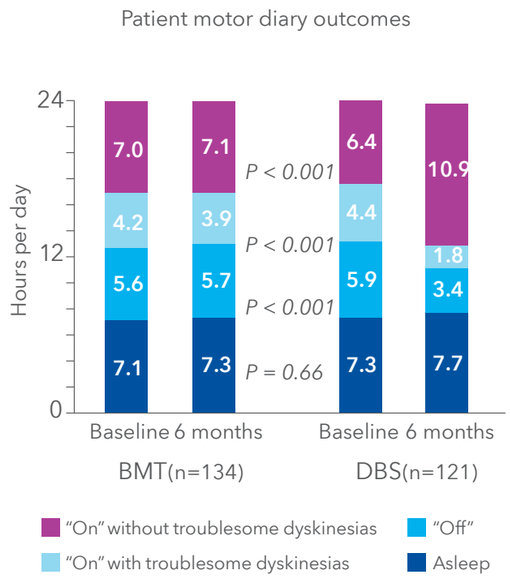
(*) Test for the change scores from baseline to 6 months between the BMT group and the DBS group.
Decrease in PDQ-39 and UPDRS III scores mean improvement.
UPDRS = Unified Parkinson's Disease Rating Scale. PDQ-39 = Parkinson's Disease Questionnaire-39 score.

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. 1 patient died due to cerebral hemorrhage that occurred 24h after lead implantation. The overall incidence risk of experiencing a serious adverse event was 3.8 times higher (95% CI, 2.3-6.3) in deep brain stimulation patients than in best medical therapy patients.

Key conclusions

- Deep brain stimulation was more effective than 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 within 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, intention-to-treat analysis).
- 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

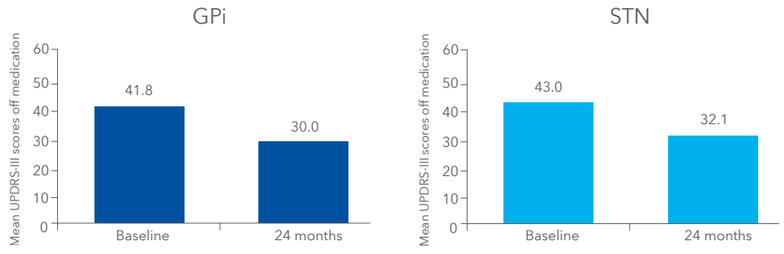
- Serious adverse events occurred in 56% of patients receiving STN stimulation and in 51% of patients receiving GPi stimulation.
- 99% of serious adverse events were resolved by the 24-month follow-up. 1 patient (STN stimulation subgroup) died to intracranial hemorrhage 24h after surgery. 1 patient (GPI stimulation subgroup) committed suicide. Other deaths were attributed to aspiration pneumonia (n=3), myocardial infraction with sepsis (n=1), intestinal perforation with sepsis (n=1), breast cancer (n=1), arteriosclerotic heart disease (n=1), sepsis with multiple organ failure (n=1), drug toxicity (n=1), injuries sustained in a motorcycle accident (n=1), and severe Parkinson’s disease with cachexia (n=1).

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 motor and 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.

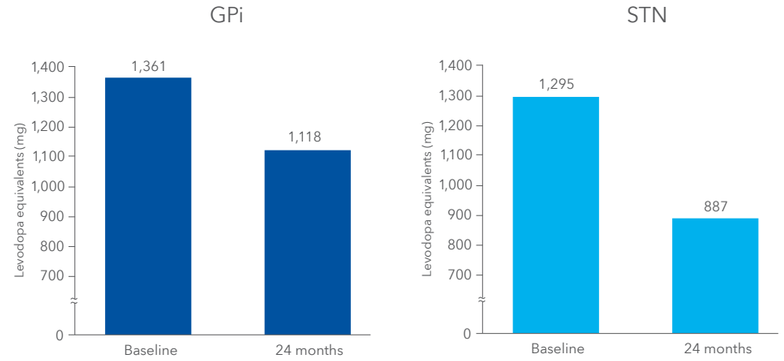
Improvement in UPDRS motor scores with DBS and without medication

(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

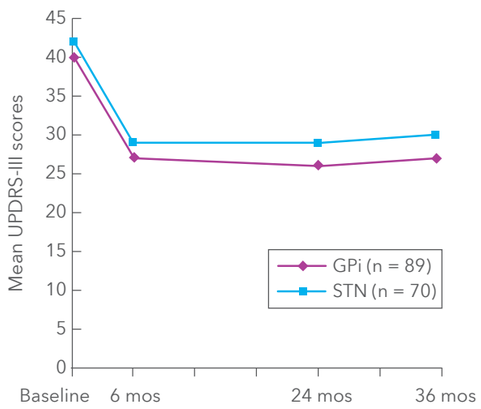
- Motor function improvement and medication reduction observed at 6 months were sustained at 36 months in both target groups.
- These changes were similar between the GPi and STN study groups and stable over time.
- Self-reported motor function, based on diaries, showed that good motor functioning (on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

Outcomes of GPi vs. STN DBS – Baseline to 3 years

On stimulation/Off medication

UPDRS-III motor scores*

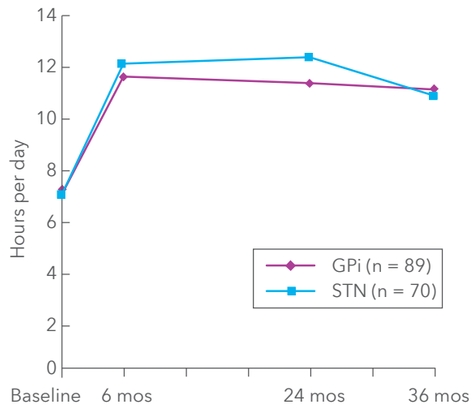
(on stimulation/off medication)



*Lower scores indicate better function

Hours of good motor function*

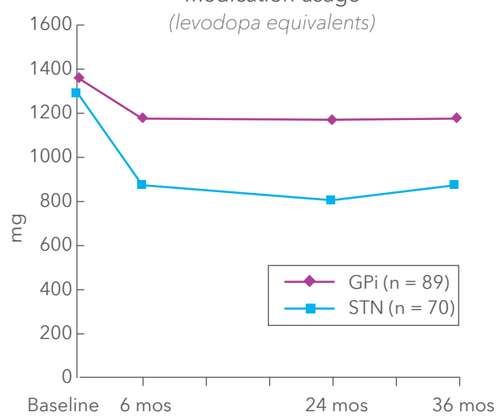
(time without troublesome dyskinesia)



*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. Patient were randomized between 2000 and 2006.

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

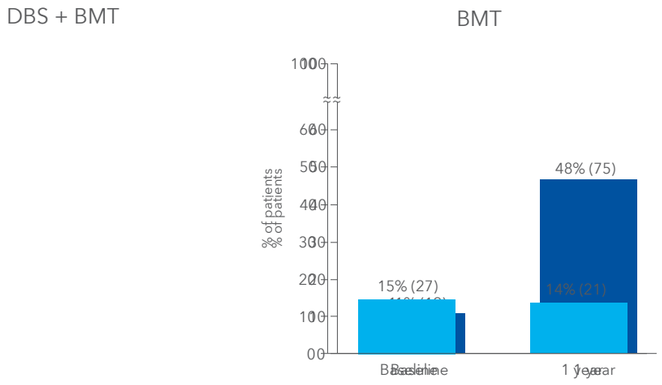
- Serious adverse events in the BMT group included 14 Parkinson's disease-related and drug-related events and 1 death (stroke).
- Serious adverse events in the DBS + BMT group included 43 surgery-related events, 25 Parkinson's disease-related and drug-related events, and 2 deaths (hemorrhage and pneumonia).
- 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), 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

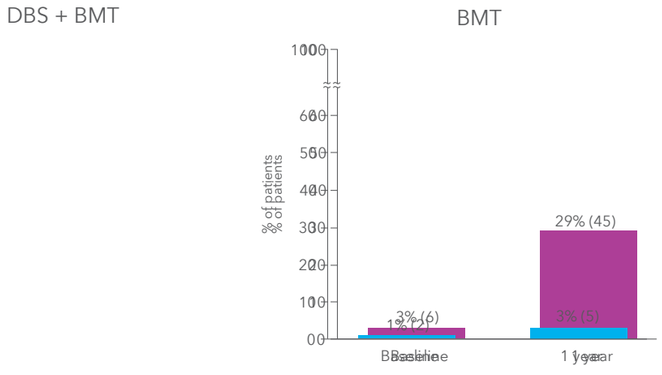
(baseline vs. 1 year)



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. Patients were enrolled from 2007 to 2011.

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.

GPI vs. STN deep brain stimulation for Parkinson's disease: 3-year follow-up

Odekerken VJJ, Boel JA, Schmand BA, et al., for the Netherlands Subthalamic and Pallidal Stimulation Study Group. *Neurology*. 2016;86:755-761.

Objective

To compare 3-year outcomes in motor symptoms, cognition, mood, and behavior for patients undergoing bilateral stimulation of the globus pallidus interna (GPi) or subthalamic nucleus (STN) in patients with advanced Parkinson's disease.

Study type – Prospective, randomized, multicenter, patient, and assessor blinded for treatment allocation

Design – 128 patients* with advanced Parkinson's disease were randomly assigned to bilateral GPi DBS or bilateral STN DBS (1:1). Patients were assessed at 3 years, during standardized off-drug and on-drug phases. Primary outcomes included 1) the Unified Parkinson's Disease Rating Scale (UPDRS) Motor Examination (ME) in the off-drug phase and 2) the number of patients with a negative composite score of cognitive, mood, and behavioral effects, and inability to participate in follow-up. Several measures were taken to assess 3-year composite score of cognitive, mood, and behavioral effects, including worsening on cognitive tests, the loss of professional activity, the loss of an important relationship (e.g., marriage), score from the Mini-International Neuropsychiatric Interview psychiatric evaluation, or missing the 3-year follow-up assessments. Secondary outcomes were symptom scales, disability status, activities of daily living. Additional measurements included sleep quality of life questionnaire, medication use, DBS settings, self-report during off-drug and on-drug phases as well as self-reported sleep disruptions, and adverse events.

**This study uses the same patient population that is found in Odekerken VJ, van Laar T, Staal MJ, et al. for the Netherlands Subthalamic and Pallidal Stimulation Study Group. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomized controlled trial. Lancet Neurol. 2013;12:37-44.*

Results

- 90 of 128 patients enrolled in the study completed the 3-year follow-up (GPi subgroup n=47 and STN subgroup n=43).

Primary outcomes

- Greater improvement in the median off-drug phase UPDRS-ME score for STN group compared to GPi group (28 vs. 33, P=0.04, intention-to-treat analysis).
- No difference occurred between groups in the number of patients with cognitive, mood, or behavioral side effects, and missing 3-year follow-up assessments (GPi: 39 vs. STN: 37, P = 0.69).

Secondary outcomes

- No difference was found in the on-drug or off-drug phase across several symptom scales or measures of activities of daily living.
- Improvement in functioning in the off-drug phase measured by the Academic Medical Center Linear Disability Scale (ALDS) was higher in the STN group (GPi: 65.2 vs. STN: 72.6, P = 0.05).
- Improvement during on-drug phase in the Clinical Dyskinesia Rating Scale (CDRS) was detected after GPi DBS (GPi: 2.2 vs. STN: 3.3, P = 0.02)

Adverse Events

- 21 and 22 events occurred between 1 and 3 years after GPi DBS and STN DBS, respectively.
- Among the patients who completed the 3-year follow-up, reoperation to the STN due to lack of effect of pallidal stimulation was the most common adverse events among patients in the GPi DBS group (n=8). Other complications (not defined) occurred in both the GPi and STN groups, including lead migration.

Key conclusions

- STN DBS was associated with a better improvement in off-drug phase motor symptoms and functioning than GPi DBS 3 years after DBS surgery.
- No difference was found between GPi and STN targets on a composite score for cognition, mood, behavior, and the inability to participate in follow-up.

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. Patients were enrolled between 2006 and 2009.

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).

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

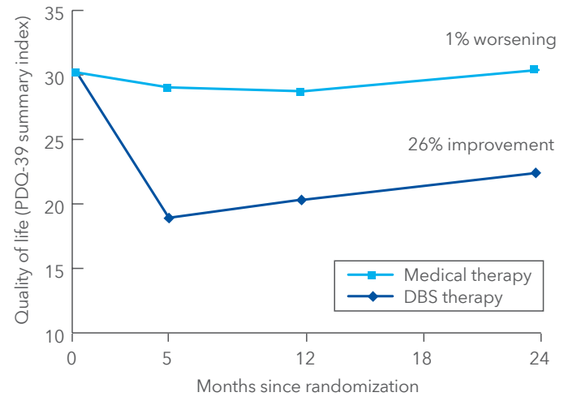
- The Schuepbach, et al. (NEJM) study is a large randomized controlled trial of DBS therapy for Parkinson's disease that confirms the impact of the therapy earlier in the progression of the disease. It is also the first comparison of DBS therapy to medical therapy at 24 months.
- This study showed consistent, 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

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.

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.

Secondary analyses in patients with recent-onset of motor complications* and additional information related to Schüepbach, et al., 2013, comparing DBS plus best medical therapy to best medical therapy (BMT) alone.

Study methodology

Deuschl G, Schüepbach M, Knudsen K, et al. Stimulation of the subthalamic nucleus at an earlier disease stage of Parkinson's disease: concept and standards of the EARLYSTIM study. *Parkinsonism Relat Disord*. 2013 Jan;19(1):56-61.

- Deuschl, et al. described the goals, methodology, and issues for the randomized, multicenter, binational clinical trial of DBS in patients with recent onset of motor complications.

Nonmotor outcomes

Lhommée E, Wojtecki L, Czernecki V, et al.; EARLYSTIM study group. Behavioural outcomes of subthalamic stimulation and medical therapy versus medical therapy alone for Parkinson's disease with early motor complications (EARLYSTIM trial): secondary analysis of an open-label randomised trial. *Lancet Neurol*. 2018 Mar;17(3):223-231.

- Lhommée, et al. assessed behavioral changes in the DBS plus BMT group or BMT alone group over a 24-month follow-up
- Non-motor neuropsychiatric fluctuations decreased in the DBS plus BMT group (-0.65 [0.15] points) but did not change in the BMT alone group (-0.02 [0.15] points; P = 0.0028).
- Hyperdopaminergic behavioral disorders like impulse control disorders or behavioral addictions decreased in the DBS plus BMT group (-1.26 [0.35] points), but increased in the BMT alone group (1.12 [0.35] points; p < 0.0001).
- Although DBS has historically been thought to precipitate neuropsychiatric behaviors, this study supports the finding that patients with DBS plus BMT do not worsen compared to BMT alone group, and suggests certain behavioral outcomes improve with DBS plus BMT.

Predictors in quality of life

Schüepbach WMM, Tonder L, Schnitzler A, et al.; EARLYSTIM study group. Quality of life predicts outcome of deep brain stimulation in early Parkinson disease. *Neurology*. 2019 Mar 5;92(10):e1109-e1120.

- Schüepbach, et al. used predictive analyses to identify disease-specific quality of life variables after DBS in patients with recent onset of motor complications.
- Patients who reported having worse quality of life at the beginning of the study improved over the study period, and the improvement was more pronounced in the DBS group than the BMT group.
- The authors concluded that the most important predictor of benefit for DBS is patients who report impaired quality of life. This finding suggests that physicians should evaluate for disease specific quality of life when considering a patient for DBS.

Programming parameters

Knudsen K, Krack P, Tonder L, et al.; EARLYSTIM study group. Programming parameters of subthalamic deep brain stimulators in Parkinson's disease from a controlled trial. *Parkinsonism Relat Disord*. 2019 Aug;65:217-223.

- Knudsen, et al. applied programming guidelines, developed by experts who reached a consensus on general stimulation parameters, to patients with DBS and measured the influence of programming on clinical outcomes.
- Single monopolar lead contact stimulation was sufficient for 184 of 228 (80.7%) implanted leads. Double monopolar and bipolar stimulation (atypical stimulation) was not often required. There was no significant difference in clinical outcomes between patient groups that required contact changes and those that did not nor between typical or atypical programming.
- The authors concluded that a standardized stimulation strategy can account for favorable outcomes in patients with recent onset of motor complications.

**These studies use the same patient population that is found in Schuepbach M, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. N Eng J Med. 2013;368:610-622.*

Predicting EQ-5D-5L utilities from PDQ-39

Zahra M, Durand-Zaleski I, Górecki M, et al.; Parkinson's disease with early motor complications: predicting EQ-5D-3L utilities from PDQ-39 data in the EARLYSTIM trial. *Health Qual Life Outcomes*. 2020 Mar 2;18(1):49.

- Zahra, et al. predicted health-related quality of life (HRQoL) metrics, or utilities, from disease-specific HRQoL data using two algorithms based on PDQ-39 scores. The authors also investigated performance terms within and between the DBS and BMT groups, and distribution by the severity of the patients' disease.
- Both algorithms predicted a significant change from baseline predicted mean utilities up to 24 months in the DBS group (P < 0.001). Only one algorithm precited a significant change from baseline predicted mean utilities up to 12 months for patients in the BMT group (P = 0.04). The difference in change from baseline predicted mean utilities between the DBS and BMT groups favored DBS at all follow-up visits (P < 0.001). Predicted utilities deteriorated with increasing disease severity measured by the Hoehn and Yahr scale.
- The authors concluded that using utilities predicted by algorithms that use PDQ-39 data demonstrate a clinically meaningful improvement with DBS compared with BMT.

Social and occupational functioning

Stoker V, Krack P, Tonder L, et al.; EARLYSTIM Study Group. Deep Brain Stimulation Impact on Social and Occupational Functioning in Parkinson's Disease with Early Motor Complications. *Mov Disord Clin Pract*. 2020 Aug 3;7(6):672-680.

- Stoker, et al. compared the impact of DBS plus BMT and BMT alone on social, psychological, and occupational functioning in patients who were 60 years or younger with recent onset of motor complications at baseline and 24-month follow-up.
- Psychosocial (-2.1 [0.7]; P = 0.023), social and occupational (9.8 [1.9] points; P < 0.001) function improved in the DBS plus BMT group. Compared to the BMT alone group, the DBS plus BMT group did not improve patient's ability to engage in work-related activities; a subjective lack of motivation, or apathy, may contribute to a patient's ability to work.
- The authors concluded that the DBS plus BMT group had significant improvements in social, occupational, and psychosocial function compared to the BMT alone group 2 years after DBS surgery. Actual work engagement did not improve in the DBS plus BMT group.

Interpretation of health-related quality of life

Martinez-Martin P, Deuschl G, Tonder L, et al. EARLYSTIM Study Group. Interpretation of health-related quality of life outcomes in Parkinson's disease from the EARLYSTIM Study. *PLoS One*. 2020 Aug 21;15(8):e0237498.

- Martinez-Martin, et al. determined whether health-related quality of life (HRQoL) outcomes were clinically significant among patients with DBS over a 24-month follow-up.
- DBS showed benefits in HRQoL in the majority of patients; the improvement was considerable in almost 60%. In the BMT group, about 66% of patients were stable or worse at the 24-month follow-up.
- Almost 90% of patients in the DBS group improved. The proportions for patients stating "much" or "very much" improvement was different between the groups (80.8% for DBS and 22% for BMT).
- For those patients that improved more than their respective minimal change for "much" and "very much" improved, the proportion was also different (DBS: 56.7%; BMT: 30.3%).
- The authors concluded that DBS significantly and moderately improved most patients' health-related quality of life 2 years after DBS surgery.

Anatomical correlations

Tödt I, Al-Fatly B, Granert O, et al. The Contribution of Subthalamic Nucleus Deep Brain Stimulation to the Improvement in Motor Functions and Quality of Life. *Mov Disord*. 2022 Feb 3;37(2):291-301.

- Tödt, et al. explored the relationship between lead placement in the stimulated portions of the STN and its impact on clinical outcomes.
- The authors saw a positive correlation between improvements in the UPDRS motor score, the PDQ-39 score and positioning of the lead in the sensorimotor STN, specifically in the posteroventral spatial location.
- The authors concluded that the larger stimulated portions of the sensorimotor STN correspond to less motor severity and better quality of life for the patient.

Long-term data* on DBS therapy for Parkinson's disease

The table below provides an educational resource consisting of information from three clinical studies that address outcomes of long-term use of deep brain stimulation (DBS) for Parkinson's disease (PD). The selected studies included at least 50 patients and provided follow-up data for patients who have had DBS therapy for at least 10 years. These studies also measured the effects of DBS on disease severity with the Unified Parkinson's Disease Rating Scale (UPDRS) part II (activities of daily living), part III (motor subsection), and part IV (complications of therapy), and/or one of several available dyskinesia rating scales in both the off and on medication periods.

**The long-term safety and effectiveness of Medtronic DBS therapy for Parkinson's Disease has not been established beyond 36 months.*

	Castrioto, et al. (2022)[1**]	Park, et al. (2022)[2]	Bove, et al. (2021)[3]
Main study objective(s)	Capture the evolution of independence in activities of daily living among PD patients with STN DBS.	Investigate survival rate and long-term outcome of advanced PD patients with bilateral STN DBS	Evaluate the effects of STN DBS on motor complications in PD patients.
Number of patients	85 patients included in the analysis (complete data for the primary outcome available for 76 patients)	81 patients included in the analysis	51 patients included in the analysis
Longest follow-up period	> 10 years after DBS surgery	> 10 years after DBS surgery	> 15 years after DBS surgery
Primary objective	Change in the Schwab & England Activities of Daily Living (ADL) Scale (UPDRS VI) from baseline to the last follow-up.	Survival rate and long-term outcomes measured by the UPDRS III scores.	Change in UPDRS IV (time spent with dyskinesia and time in the "off" state) from baseline to the long-term follow-up.

Primary outcomes

Castrioto, et al. (2022)[1]**

Schwab & England ADL scale (UPDRS Part VI)

	Pre-op	> 10 years post-op with DBS On	P value
Off medication	51.3	63.2	< 0.001
On medication	89.6	70.4	< 0.001

Park, et al. (2022)[2]

Motor examination (UPDRS Part III)

	Pre-op	> 10 years post-op with DBS On	P value
Off medication	39.8 (n = 69)	29.5 (n = 46)	0.000
On medication	20.1 (n = 69)	28.3 (n = 38)	0.026

Cumulative survival rate after DBS surgery:

- 98% at 1 year
- 95% at 5 years
- 79% at 10 years
- Thirty-five patients (43%) died during the 11-year follow-up period.

Patients with both electrodes within the STN had higher rates of survival and continued follow-up (Group I [both electrodes within STN: 51.9% vs. group II [1 electrode within STN and the other outside:
35% vs. group III [both electrodes outside STN]: 14.3%, P = 0.85)

Bove, et al. (2021)[3]

Motor fluctuations and dyskinesias (UPDRS Part IV)

	Pre-op	LFU	P value
Time spent w/ dyskinesia	1.64	0.41	< 0.001
Time spent in the "off" state	1.85	0.74	< 0.001

Additional outcomes

Castrioto, et al. (2022)[1]**

- Cognition (n = 66): worse than baseline (P < 0.001)
- Depression (n = 63): No difference between baseline and beyond 10 years
- Off dystonia (n = 77): improved from baseline (P < 0.001)
- Motor fluctuations (n = 76): improved from baseline (P < 0.001)
- Activities of daily life (UPDRS II; n = 76):
  - Improved from baseline in the off-medication condition (P < 0.01).
  - Deterioration at last follow-up in the on-medication condition (P < 0.001).
- Levodopa equivalent daily dose (LEDD): improved from baseline (P < 0.001)
- Predictors of long-term independence included younger age at surgery (P < 0.0005), lower preoperative UPDRS I (non-motor symptoms) score, and male gender (P < 0.05).
- MDRS score predictive of quality of life via PDQ-37 emotional subscore (P = 0.05)

Park, et al. (2022)[2]

- UPDRS II:
  - Total score improved from baseline when patients were on medication and on stimulation, but remained the same from baseline when patients were off medication and on stimulation (both Ps = 0.000)
  - Freezing subscore improved from baseline when patients were on medication and on stimulation, but remained the same from baseline when patients were off medication and on stimulation (both Ps = 0.012)
- UPDRS IV:
  - Dyskinesia duration and disability decreased from baseline when patients were on medication and on stimulation.
  - Off duration remained the same when patients were on medication and on stimulation
- LEDD decreased from baseline when patients were on medication and on stimulation

Bove, et al. (2021)[3]

- Quality of life (PDQL; n = 27): Improved by 13.8% at long-term follow-up (P < 0.001)
  - Subscores, emotional function: improved 13.6% (P = 0.001)
  - Subscores, social function: 29.9% (P < 0.001)
  - Parkinsonian symptoms: Remained the same from baseline (P = 0.95)
  - Systemic symptoms: Remained the same from baseline (P = 0.07)
- Activities of daily living (UPDRS II and in the "on" condition; n = 40): Worse than baseline (P < 0.001)
- UPDRS motor scores (UPDRS III and "on" stimulation/ "on" medication during chronic medication compared to preoperative "on" condition; n = 51): Worse than baseline (P < 0.001)
- LEDD: Reduced by 50.6% at long-term follow-up (P < 0.001)

Adverse events

Castrioto, et al. (2022)[1]**

85 pts:
- Severe akinetic crisis (n = 5)
- Skin erosion (n = 3)
- Replacement of connection cable (n = 2)
- Lead replacement 8 years after DBS surgery (n = 1)
- Surgical cleansing and replacement of connection cable (n = 1)
- Infection (n = 1)

Park, et al. (2022)[2]

81 pts:
- Weight gain > 10 kg (n = 8)
- Transient confusion or decreased consciousness (n = 3)
- Dysarthria (n = 2)
- Track hemorrhage (n =1)
- Neurostimulator pocket abscess (n = 1)
- Apraxia of eyelid opening (n = 1)
- Severe depression requiring medication (n =1)
- Abulia (n = 1)

Bove, et al. (2021)[3]

Adverse event (number of events):
- Stimulation-/treatment-related (294)
- Device-related (47)
- Surgery-related (19)

***Medtronic provided financial support, but no role in study design, data analysis/interpretation, writing the manuscript.*
LFU = Last follow-up, MDRS = Mattis Dementia Rating Scale, PDQ = Parkinson's Disease Questionnaire, UPDRS = Unified Parkinson's Disease Rating Scale

Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. *Nat Rev Neurol.* 2019 Feb;15(4):234-242.

Limousin and Foltynie (2019) wrote a review summarizing the findings of 18 studies that report long-term outcomes (at least 5 years after DBS surgery) of subthalamic nucleus (STN) and globus pallidus interna (GPi) DBS (15 and 3 studies, respectively). The authors concluded that STN DBS can provide long-term improvements in motor function for patients with PD, while GPi DBS improves dyskinesias in the long term. However, further studies on GPi DBS are needed to further examine potential benefits of therapy. They also commented that DBS does not prevent the progression of PD, so quality-of-life scores typically fall to preoperative levels after 5 years. Deterioration of quality of life often reflects medication or stimulation-resistant motor or nonmotor impairments related to gait, balance, and speech. Long-term management may be complex, requiring a systematic approach to distinguishing stimulation-induced adverse event from disease progression. Finally, the authors concluded that long-term outcomes are related to a combination of factors, including patient selection, lead targeting, stimulation programming, and medication adjustments.

1. Castrioto A, Debu B, Cousin E, et al. Long-term independence and quality of life after subthalamic stimulation in Parkinson disease. *Eur J Neurol*. 2022;29(9):2645-2653. http://dx.doi.org/10.1111/ene.15436
2. Park HR, Im HJ, Park J, et al. Long-Term Outcomes of Bilateral Subthalamic Nucleus Deep Brain Stimulation for Patients With Parkinson's Disease: 10 Years and Beyond. *Neurosurgery*. 2022;91(5):726-733. http://dx.doi.org/10.1227/neu.0000000000002117
3. Bove F, Mulas D, Cavallieri F, et al. Long-term Outcomes (15 Years) After Subthalamic Nucleus Deep Brain Stimulation in Patients With Parkinson Disease. *Neurology*. 2021. http://dx.doi.org/10.1212/WNL.0000000000012246
4. Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. *Nat Rev Neurol*. 2019;15(4):234-242. http://dx.doi.org/10.1038/s41582-019-0145-9

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. Patients were enrolled between 1992 and 1994.

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.

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

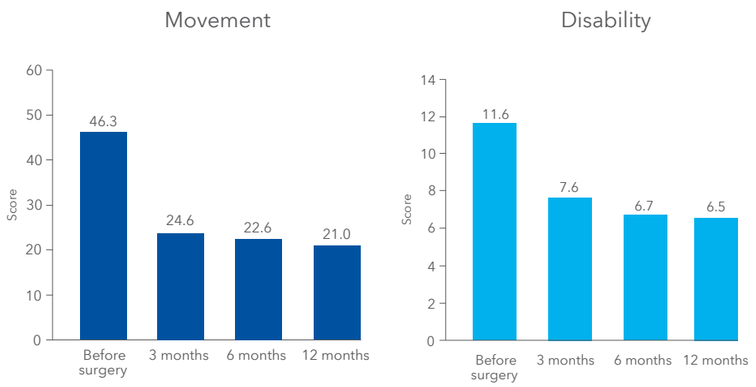
- 3 patients had 5 adverse events in the post-operative period.
- All events resolved rapidly with no permanent neurological sequelae.

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.

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. Patients were enrolled between 2002 and 2004.

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

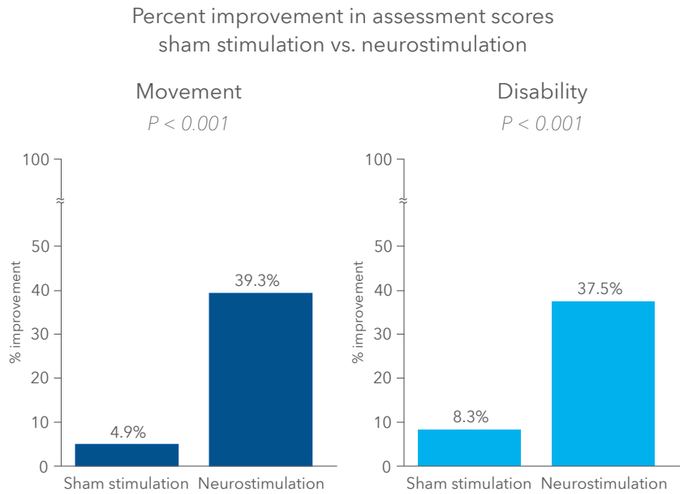
- 3 months after randomization, the movement scores improved by a mean of 15.8±14.1 points (a 39.3% reduction in symptoms) in the neurostimulation group, as compared with 1.6±4.0 points (a 4.9% reduction) in the sham stimulation group. Disability scores and quality of life, assessed by the physical component of the SF-36, also improved significantly (respectively $p<0.001$ and $p=0.02$).
- 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.



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.

Pallidal deep brain stimulation improves quality of life in segmental and generalized dystonia: results from a prospective, randomized sham-controlled trial

Mueller J, Skogseid IM, Benecke R, et al. *Mov Disord*. 2008;23(1):131-134.

Objective

To evaluate effects of deep brain stimulation on health-related quality of life (HRQoL) in patients with segmental or generalized dystonia.

Study type – Prospective, randomized, sham-controlled, multicenter

Design – 40 patients* with primary segmental or generalized dystonia underwent bilateral GPi deep brain stimulation (DBS). Patients were randomly assigned to receive either neurostimulation or sham stimulation for 3 months, then subsequently received open-label stimulation for either 3 or 6 months (totaling 6 months of neurostimulation for each group). Several measures of HRQoL were assessed, including eight multi-item variables of the Short Form 36 (SF-36), as well as measures for depression, anxiety, neuropsychiatric status, and severity of dystonia.

**This study uses the same patient population that is found in Kupsch A, Benecke R, Müller J, et al. for the Deep-Brain Stimulation for Dystonia Study Group. Pallidal Deep-Brain Stimulation in Primary Generalized or Segmental Dystonia. N Engl J Med. 2006;355:1978-1990.*

Results

- Improvement in several HRQoL variables was observed only in the active stimulation group. Depression, anxiety, and neuropsychiatric status did not change significantly in either group at 3 months compared to baseline (Table 1).
- Improvement in several HRQoL variables was still observed during the open-label trial phase. Depression was significantly reduced at 6 months of continuous DBS, while anxiety and neuropsychiatric status did not significantly change (Table 2).

Table 1. Outcomes: Change from baseline and 3 months after DBS

Variables	Stimulation		Sham stimulation		P value
	N	Mean	N	Mean	
BFMDRS movement score	20	-15.8	18	-1.6	< 0.001
BFMDRS disability score	20	-3.9	19	-0.8	< 0.001
SF-36 domain scores					
Physical function (PF)	18	27.3	18	3.0	0.001
Role physical (RP)	18	25.0	17	13.2	0.20
Bodily pain (BP)	19	22.7	18	9.7	0.04
General health (GH)	19	17.6	18	2.1	0.02
Vitality (VT)	19	14.7	18	2.0	0.047
Social function (SF)	19	21.1	18	0.7	0.07
Role emotional (RE)	19	24.6	17	13.7	0.43
Mental health (MH)	19	10.7	18	2.0	0.54
Physical component score (PCS)	17	10.1	16	3.8	0.02
Mental component score (MCS)	17	5.2	16	0.2	0.39
Beck depression inventory	14	-5.1	16	-0.5	0.42
Beck anxiety inventory	16	-6.9	19	-2.4	0.10
Brief psychiatric rating scale	18	-5.9	19	-3.0	0.09

Table 2. Outcomes: Change from baseline and 6 months after DBS

Variables	N	Mean	P value
BFMDRS movement score	36	-16.7	< 0.001
BFMDRS disability score	36	-4.1	< 0.001
SF-36 domain scores			
Physical function (PF)	33	23.1	< 0.001
Role physical (RP)	33	31.1	< 0.001
Bodily pain (BP)	34	21.8	< 0.001
General health (GH)	34	19.2	< 0.001
Vitality (VT)	34	12.9	0.003
Social function (SF)	34	18.0	0.009
Role emotional (RE)	34	24.5	0.005
Mental health (MH)	34	14.2	< 0.001
Physical component score (PCS)	34	10.6	< 0.001
Mental component score (MCS)	34	4.0	0.01
Beck depression inventory	29	-3.1	0.008
Beck anxiety inventory	34	-3.5	0.09
Brief psychiatric rating scale	33	-2.0	0.19

Adverse events

- Authors did not comment on adverse events

Key conclusions

- Pallidal deep brain stimulation for patients with primary segmental and generalized dystonia improves HRQoL, with results that may be comparable to other movement disorders.

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.

Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial

Volkmann J, Mueller J, Deuschl G, et al. for the Deep Brain Stimulation Study Group for Dystonia. *Lancet Neurol*. 2014;13(9):875-884.

Objective

To evaluate effects of bilateral deep brain stimulation of the globus pallidus (GPi) in improving symptoms in patients with cervical dystonia.

Study type – Prospective, randomized, sham-controlled, multicenter. Patients were enrolled between 2006 and 2008.

Design – 62 patients from 10 centers, ≥ 18 years old with idiopathic or inherited isolated cervical dystonia underwent bilateral GPi DBS. Patients were randomized to either neurostimulation or sham stimulation (1:1) for 3 months. A change in severity of dystonia was assessed using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score at 3 months. Treatment outcomes were assessed by standardized recorded video by masked dystonia experts, and analyzed by intention to treat. Secondary outcomes included change in TWSTRS disability and pain scores, Bain tremor score, and Craniocervical Dystonia Questionnaire-24 (CDQ-24) score. Patients were reassessed after 6 months of active, unblinded stimulation (i.e., 9 months for the patients in the sham stimulation group).

Results

Primary outcomes

- Patients in the neurostimulation group had a 26% improvement in TWSTRS severity score while patients in the sham stimulation group had a 6% improvement in the intention to treat population (improved by 5.1 points in the neurostimulation group vs. 1.3 points in the sham group, P = 0.0024).
- The mean change from baseline to 3 months between the neurostimulation and sham groups was 3.8 points, and 4.1 points for the per-protocol population.

Secondary outcomes

- Patients in the neurostimulation group had a greater percentage improvement in TWSTRS disability and Bain tremor score than those in the sham stimulation group at 3 months. Pain and health-related quality of life also improved at 3 months in both the neurostimulation and sham groups, but the difference was not significant (Table 1).
- When patients were reassessed after 6 months of active stimulation, patients who were initially assigned to sham stimulation had a 26% improvement in TWSTRS severity score, whereas patients who were initially assigned to neurostimulation had a 3% improvement from an extra 3 months of stimulation (improved by 5.0 points for patients initially assigned to sham stimulation vs. -0.4 points for patients with 3 additional months of stimulation).

Table 1. Outcomes: Mean change from baseline to 3 months by treatment group

Outcome	Neurostimulation		Sham stimulation		P value
	N	Mean	N	Mean	
TWSTRS disability score	31	-5.6	30	-1.8	0.007
TWSTRS pain score	31	-4.4	30	-3.7	0.47
Bain tremor scale	30	-2.0	29	-0.4	0.02
CDQ-24	29	-16.4	30	-10.4	0.27

Table 2. Adverse events

	Neurostimulation	Sham stimulation
Serious adverse events	5 (16%)	11 (37%)
Adverse events	21 (66%)	20 (67%)

- Serious adverse events in the neurostimulation group were surgery or device-related and medication or stimulation-related events.
- Serious adverse events in the sham stimulation group were surgery or device-related and dystonia-related (or related to another disorder) event.
- The most common serious adverse event in both groups was device infection (n = 2), but was resolved within the study period.

Key conclusions

- Bilateral pallidal neurostimulation is more effective than sham stimulation at reducing motor impairment and related disability in patients with cervical dystonia 3 months after DBS surgery.

Cognitive outcome of pallidal deep brain stimulation for primary cervical dystonia: 1-year follow-up results of a prospective multicenter trial

Dinkelbach L, Mueller J, Poewe W, et al. *Parkinsonism Relat Disord*. 2015;21(8):976-980.

Objective

To evaluate effects of bilateral deep brain stimulation of the globus pallidus (GPi) on neuropsychological outcomes in patients improving symptoms of cervical dystonia.

Study type – Prospective, randomized, sham-controlled, multicenter

Design –13 patients* with primary cervical dystonia participated in an ancillary part of the trial. Memory, executive functions, attention, visual perception, mental arithmetic, and estimated verbal intelligence were examined using a variety of tests before and after 12 months of neurostimulation. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), the Craniocervical Dystonia Questionnaire (CDQ-24), and medication were also captured before and after 12 months of neurostimulation.

**This study uses a subgroup of patients that is found in Volkmann J, Mueller J, Deuschl G, et al. for the Deep Brain Stimulation Study Group for Dystonia. Pallidal Neurostimulation in Patients with Medication-Refractory Cervical Dystonia: A Randomised, Sham-Controlled Trial. Lancet Neurol. 2014;13(9):875-884.*

Results

- Patients with cervical dystonia produced fewer words in the alternating category word fluency subtest of the Regensburg's Word fluency test (RWT) after 12 months of neurostimulation (P = 0.020). All other cognitive variables were unchanged (Table 1).
- No significant correlation was found between the change in TWSTRS severity, the change in CDQ-24 and the differences in results from the alternating categories task subtest of the RWT (TWSTRS-Severity: r 0.126, p > 0.05; CDQ-24: r 0.258, p > 0.05).

Table 1. Outcomes: Results of neuropsychological assessments at baseline and 12 months after DBS

Variables		Baseline		12 months		P value
		N	Median	N	Median	
Memory						
VLMT	Learning	13	47.0	13	41.0	0.909
	Recall	13	8.0	13	7.0	0.938
	Recognition	12	10.5	12	12.0	0.842
DOT	Digit span forward	13	6.0	13	5.0	0.221
WMS-R	Block span forward	13	7.0	13	7.0	0.828
NVLT	Figural memory	13	17.0	13	22.0	0.182
Executive functions						
DOT	Verbal working memory	13	5.0	13	5.0	0.875
RWT	Verbal fluency total	13	63.0	13	59.0	0.056
	Letter fluency	13	9.0	13	9.0	0.397
	Alternating letters	13	12.0	13	10.0	0.076
	Category fluency	13	22.0	13	20.0	0.203
	Alternating categories	13	15.0	13	13.0	0.020

Variables		Baseline		12 months		P value
		N	Median	N	Median	
Attention						
TEA	Sustained attention	8	7.0	8	7.0	1.000
	Selective attention	7	9.0	7	9.0	1.000
	Attentional switching	6	6.5	6	4.5	0.344
FWIT	Interference	13	80.0	13	87.0	0.970
Visual perception						
VOSP	Total	11	38.0	11	38.0	0.641
	Object perception	11	18.0	11	19.0	0.172
	Number location	11	9.0	11	9.0	0.531
	Cube analysis	11	10.0	11	10.0	0.500
BJLOT	Visuospatial abilities	8	24.5	8	26.5	0.594
Mental arithmetic						
Graded difficulty arithmetic test		13	19.0	13	14.0	0.064
Verbal intelligence						
MWT-A		13	30.0	13	29.0	0.787

VLMT, Verbal Learning and Memory Test; DOT, Digit Ordering Test; WMS-R, Wechsler Memory Scale – Revised Version; NVLT, Non-Verbal Learning Test; RWT, Regensburg's Word fluency Test; TEA, Test of Everyday Attention; FWIT, interference naming strop task; VOSP, Visual Object and Space Perception; BJLOT, Benton Judgment of Line Orientation Test; MWT-A, multiple choice vocabulary test.

Adverse events

- Hemiparesis or stroke (resolved; 1 in 13 pts)
- Exchange of extension cable (1 in 13 pts)
- Tethering of extension cable (1 in 13 pts)
- Dyskinesia due to DBS (1 in 13 pts)
- Worsening of dystonia due to DBS (1 in 13 pts)

Key conclusions

- No clinically relevant deterioration of cognition was found. The authors suggest that GPi DBS is safe regarding potential cognitive side effects in patients with primary cervical dystonia.

Selected articles about DBS therapy

Parkinson's disease

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Parkinson's disease: Secondary analyses in patients with recent-onset of motor complications

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2. Lhommée E, Wojtecki L, Czernecki V, et al.; EARLYSTIM study group. Behavioural outcomes of subthalamic stimulation and medical therapy versus medical therapy alone for Parkinson's disease with early motor complications (EARLYSTIM trial): secondary analysis of an open-label randomised trial. *Lancet Neurol*. 2018 Mar;17(3):223-231.
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Brief Statement

See the device manual for detailed information regarding the instructions for use, the implant procedure, indications, contraindications, warnings, precautions, and potential adverse events. For further information, contact your local Medtronic representative and/or consult the Medtronic website at www.medtronic.eu.

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