Evidence compendium

Research study summaries supporting the use of Medtronic deep brain stimulation (DBS) for Parkinson’s disease
# CONTENTS

- Introduction .......................................................................................................................... 4
- Index of study summaries ...................................................................................................... 6
- Parkinson's disease study summaries ...................................................................................... 8
- References .............................................................................................................................. 40
- Glossary .................................................................................................................................. 41
INTRODUCTION

Deep brain stimulation (DBS) is a key therapy option for movement disorders. It is included in the guidelines of the European Federation of Neurological Societies (EFNS) as a recommendation for Parkinson’s disease. DBS therapy is adjustable and reversible and may effectively manage some of the most disabling symptoms of Parkinson’s.

This Evidence Compendium presents summaries of key clinical trials that address various aspects of DBS for Parkinson’s. It therefore provides important information for anyone affected by Parkinson’s who is considering this therapy.

A glossary of terms is included at the back of this publication.

Several themes are documented by clinical evidence presented in this compendium. These can be broadly summarised as follows:

- DBS leads to a significant improvement in motor function in Parkinson’s
- Individual treatment decisions will need to consider the risk/benefit ratio, that is the ratio between expected benefits and the potential for surgical complications and adverse events.
- Due to the fact that DBS has now been in use for over 25 years, most possible complications are well known. DBS is a relatively safe surgical procedure involving established risks, some during surgery time (such as a seizure or trauma to the brain tissue), others appearing later such as skin infections that can affect about 2.5% to the brain tissue), others appearing later such as skin infections that can affect about 2.5% to 2.8% of the patients yearly.
- Not everyone will receive the same results.
- DBS therapy plus medication provides an additional 4 to 5 hours a day of “on” time without dyskinesia.
- STN DBS therapy is associated with a 32-63% average reduction in medication depending upon study, comparator, and time point.
- When DBS therapy is started earlier in the progression of the disease (i.e., when the person experiences troubling motor symptoms not effectively controlled by medications), DBS therapy provides increased benefits when compared with medical therapy alone.
- Improvement in motor functioning led to improvement in measurements of activities of daily living, emotional well-being, stigma, and bodily discomfort, cognition, mood, and overall psychiatric functioning were unchanged.
- Disease-related quality of life improves significantly from baseline to 24 months in patients receiving DBS therapy; there is a minor decline in quality of life in patients receiving medical therapy alone.
- Marked improvement in motor function is still evident at 5-year follow-up.
- Since both STN and GPi stimulation are effective in improving motor function, targets can be selected based on individual patients and symptoms.
- For motor fluctuations and dyskinesia, Medtronic DBS in the STN received the top recommendation (Level A) from the Movement Disorder Society European Section (MDS-ES) in collaboration with the EFNS.
- Improvement in motor functioning led to improvement in measurements of activities of daily living, emotional well-being, stigma, and bodily discomfort, cognition, mood, and overall psychiatric functioning were unchanged.
- Disease-related quality of life improves significantly from baseline to 24 months in patients receiving DBS therapy; there is a minor decline in quality of life in patients receiving medical therapy alone.
- Marked improvement in motor function is still evident at 5-year follow-up.
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PARKINSON’S DISEASE – SPECIFIC FINDINGS:

- Rates of serious adverse events in Level I studies are reported to range from 13% to 55% for DBS therapy in comparison to rates for best medical therapy of 4% to 44%.
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- Median 2-year follow-up mortality rates for DBS-treated patients ranged from 0% to 2%, and overall mortality rates observed for the BMT treated groups of 0% to 1.2%.

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

INDEX OF STUDY SUMMARIES

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Year</th>
<th>Abbreviated Title</th>
<th>Journal</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBS Study Group</td>
<td>2001</td>
<td>DBS of the STN or GPI in Parkinson’s disease</td>
<td><em>N Engl J Med</em></td>
<td>8</td>
</tr>
<tr>
<td>Weaver FM</td>
<td>2009</td>
<td>Bilateral DBS vs. BMT for advanced Parkinson’s disease</td>
<td><em>JAMA</em></td>
<td>12</td>
</tr>
<tr>
<td>Weaver FM</td>
<td>2012</td>
<td>Randomized trial of deep brain stimulation for Parkinson’s disease: 36-month outcomes</td>
<td><em>Neurology</em></td>
<td>16</td>
</tr>
<tr>
<td>Odekerken VJJ</td>
<td>2012</td>
<td>STN vs GPI DBS for advanced Parkinson’s disease (NSTAPS)</td>
<td><em>Lancet Neurol</em></td>
<td>20</td>
</tr>
<tr>
<td>Williams A</td>
<td>2010</td>
<td>DBS plus BMT vs. BMT alone for advanced Parkinson’s disease</td>
<td><em>Lancet Neurol</em></td>
<td>22</td>
</tr>
<tr>
<td>Deuschl</td>
<td>2013</td>
<td>Stimulation of the subthalamic nucleus at an earlier disease stage of Parkinson’s disease: concept and standards of the EARLYSTIM-study</td>
<td><em>Parkinsonism Relat Disord.</em></td>
<td>26</td>
</tr>
<tr>
<td>Witt K</td>
<td>2008</td>
<td>Neuropsychological and psychiatric changes after DBS for Parkinson’s disease</td>
<td><em>Lancet Neurol</em></td>
<td>32</td>
</tr>
<tr>
<td>Deuschl G</td>
<td>2006</td>
<td>A randomized trial of DBS for Parkinson’s disease</td>
<td><em>N Engl J Med</em></td>
<td>34</td>
</tr>
<tr>
<td>Oertel WH</td>
<td>2011</td>
<td>EFNS Guideline on Neurological Management Late (complicated) Parkinson’s disease</td>
<td><em>European Handbook of Neurological Management</em></td>
<td>36</td>
</tr>
</tbody>
</table>

BMT = best medical therapy. DBS = deep brain stimulation. GPI = pars interna of the globus pallidus. STN = subthalamic nucleus. EFNS = European Federation of Neurological Societies
Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson’s disease


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

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 37%, 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).

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Comparison of “On” Time with and without Deep Brain Stimulation (mean percentage of time during waking hours)

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

This study was sponsored by Medtronic.

PARS INTERNA OF THE GLOBUS PALLIDUS

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

ADVERSE EVENTS

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

KEY CONCLUSIONS

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


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).

Adverse Events

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

KEY CONCLUSIONS

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

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

- Motor function scores while off medication improved by 54% at 5 years compared with baseline (P < 0.001).
- Activities of daily living scores improved by 49% at 5 years (P < 0.001).
- 11 of 42 patients were no longer taking levodopa and 3 were not taking any dopaminergic drugs.

With bilateral STN stimulation in the off medication state, UPDRS III scores for rigidity, tremor, and akinesia improved compared with baseline (n = 49) at 1, 3, and 5 years. (P < 0.001) (5 years post implant vs. baseline.) STN = subthalamic nucleus UPDRS = Unified Parkinson’s Disease Rating Scale.
Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson’s disease


OBJECTIVE

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

Study Type – Prospective, randomized, controlled, multicenter

Design – 256 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Best Medical Therapy (n = 134)</th>
<th>Deep Brain Stimulation (n = 121)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor function improvement without medication (UPDRS III)</td>
<td>4%</td>
<td>29%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Medication (levodopa equivalents) Change in mg over baseline (1,281 mg)</td>
<td>+15</td>
<td>-296</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Quality of life improvement PDQ-39 single index</td>
<td>-0.02%</td>
<td>17.1%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

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

ADVERSE EVENTS

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

KEY CONCLUSIONS

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

Patient Motor Diary Outcomes

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


OBJECTIVE

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


Study Type – Prospective, multicenter, randomized, double-blind

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

RESULTS

AVERAGE MEDICATION USE DECREASED 408 MG (32%) IN PATIENTS RECEIVING STN STIMULATION (FROM 1,295 MG TO 887 MG) AND DECREASED 243 MG (18%) IN PATIENTS RECEIVING GPI STIMULATION (FROM 1,361 MG TO 1,118 MG) (P = 0.02)

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

Quality of life as measured by the PDQ-39 improved for both groups

STN

Levodopa equivalents (mg)

Baseline 1,295
24 Months 887

GPI

Levodopa equivalents (mg)

Baseline 1,361
24 Months 1,118

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).

ADVERSE EVENTS

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

KEY CONCLUSIONS

- Deep brain stimulation improved motor function in patients with Parkinson’s disease who underwent either GPI or STN stimulation.
- Benefits observed at 6 months were sustained through 24 months of follow-up in both study groups.
- The choice of surgical target can take into consideration non-motor symptoms and the level of dopaminergic medications, both of which contribute to quality of life.
- There was no significant difference between the study groups in the type or frequency of adverse events at 24 months.

Decrease in Medication at 24 Months with Deep Brain Stimulation
Randomized trial of deep brain stimulation for Parkinson’s disease: 36-month outcomes


OBJECTIVE

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


Study Type – Prospective, multicenter, randomized, 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 (GPI vs. STN, trend over time: P = 0.07)

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)

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

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.

ADVERSE EVENTS

▼ Authors did not comment on adverse events.

Medication Usage: GPI vs. STN – Baseline, 6 Mo, 36 Mo

<table>
<thead>
<tr>
<th>DBS Target</th>
<th>Baseline (mg*)</th>
<th>6-mo post-DBS (mg*)</th>
<th>36-mo post-DBS (mg*)</th>
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<tbody>
<tr>
<td>GPI (n = 89)</td>
<td>1356</td>
<td>1106</td>
<td>1115</td>
</tr>
<tr>
<td>STN (n = 70)</td>
<td>1270</td>
<td>831</td>
<td>817</td>
</tr>
</tbody>
</table>

*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 significantly lower (improved) than baseline.

▼ There was no difference in the PDQ-39 trends over time between STN and GPI DBS (P < 0.38).

The Department of Veterans Affairs Cooperative Studies Program and the National Institute of Neurological Disorders and Stroke contributed to the study design. The sponsors were not involved in the conduct, collection, management, analysis, and/or interpretation of the study results and preparation, review, or approval of the manuscript. Medtronic provided financial support for monitoring and collecting data at 3 years of patient follow-up.
OUTCOMES OF GPI VS. STN DBS – BASELINE TO 3 YEARS ON STIMULATION/OFF MEDICATION

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.

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 mos</th>
<th>12 mos</th>
<th>18 mos</th>
<th>24 mos</th>
<th>36 mos</th>
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<tbody>
<tr>
<td>GPI (n = 89)</td>
<td>45</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
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<tr>
<td>STN (n = 70)</td>
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<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>15</td>
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</table>

*lower scores indicate better function

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 mos</th>
<th>12 mos</th>
<th>24 mos</th>
<th>36 mos</th>
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<tbody>
<tr>
<td>GPI (n = 89)</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>STN (n = 70)</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
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</table>

*Based on Diaries

Medication Usage (levodopa equivalents)

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>6 mos</th>
<th>24 mos</th>
<th>36 mos</th>
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<tr>
<td>GPI (n = 89)</td>
<td>1600</td>
<td>1400</td>
<td>1200</td>
<td>1000</td>
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<tr>
<td>STN (n = 70)</td>
<td>1500</td>
<td>1300</td>
<td>1100</td>
<td>900</td>
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Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson’s disease (NSTAPS study): a randomised controlled trial


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

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).

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.

ADVERSE EVENTS

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

KEY CONCLUSIONS

No difference was found between GPI and STN targets in the primary outcomes: weighted ALDS and composite score for cognition, mood, and behavioural effects.

No difference occurred between groups in the number of patients with cognitive, mood, and behavioural side effects.

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.
Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson’s disease (PD SURG trial): a randomized, open-label trial


OBJECTIVE

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

Study Type – Prospective, randomized, open label, multicenter

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

RESULTS

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Best Medical Therapy</th>
<th>Deep Brain Stimulation + Best Medical Therapy</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDQ-39 Summary index</td>
<td>-0.3</td>
<td>-5.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Mobility</td>
<td>0.7</td>
<td>-8.2</td>
<td>0.0004</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>0.1</td>
<td>-12.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Bodily discomfort</td>
<td>-2.4</td>
<td>-9.8</td>
<td>0.004</td>
</tr>
</tbody>
</table>

UPDRS Parts I-IV

| Total score: On medication | 1.6 | -6.6 | < 0.0001 |
| Total score: Off medication | -0.9 | -27.4 | < 0.0001 |

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

ADVERSE EVENTS

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

KEY CONCLUSIONS

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

AT 1 YEAR, PATIENTS RECEIVING DBS WERE ON A MEAN LEVODOPA EQUIVALENT DOSE OF 894 MG/DAY. THOSE IN THE MEDICAL THERAPY GROUP WERE ON 1,347 MG/DAY. THE DIFFERENCE REPRESENTS A 34% REDUCTION IN MEAN DRUG DOSE IN THE SURGERY GROUP COMPARED TO BEST MEDICAL THERAPY ALONE.

THE IMPROVEMENT WAS ALSO SIGNIFICANTLY GREATER FOR THE UPDRS PARTS I-IV SCORES, ON AND OFF MEDICATION, IN THE DBS + BMT GROUP (SEE TABLE ON LEFT FOR DETAIL).
At 1 year, 75 patients in the surgery group, and 21 in the medical therapy group, reported no waking day dyskinesia ($P < 0.0001$). DBS = deep brain stimulation, BMT = best medical therapy.

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

At 1 year, 45 patients in the surgery group and 5 in the medical therapy group reported no waking day “off time” ($P < 0.0001$).
Stimulation of the subthalamic nucleus at an earlier disease stage of Parkinson’s disease: concept and standards of the EARLYSTIM-study


OBJECTIVE

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

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

Design of EARLYSTIM – Enrolled patients (n = 251) were 60 years or younger with levodopa-induced motor complications of no more than 3 years, and preserved social and occupational functioning. The criteria excluded patients with advanced PD (Hoehn and Yahr stage was ≥ 2.5 in the best condition). Disease duration was ≥ 4 years to likely exclude atypical disease. Various assessments were compared in patients randomized to deep brain stimulation (DBS) or to best medical treatment (BMT) only. Patients were followed for 24 months.

OVERVIEW

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

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

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

  ▪ Blinded video assessments – The UPDRS-III, except rigidity, was assessed by two independent, blinded raters based on standardized video recording

  ▪ Standardized neurosurgery – Neurosurgical standards were defined by the involved neurosurgeons to assure an optimal approach

  ▪ Defined stimulator programming – Stimulation parameter settings were defined based on expert consensus, in the absence of evidence-based recommendations

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

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

*Duration of dopaminergic treatment

DISCUSSION POINTS

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

▪ Thorough attention and effort were given to quality of care and standardized algorithms for patients receiving best medical treatment and for those receiving neurostimulation. This will improve the ability to compare outcomes between treatment groups and to provide the best clinical outcomes for both groups.

▪ The rigorous methodological framework applied in this study may be a solution for critical aspects in future clinical research of DBS in Parkinson’s disease, as well as in routine care of patients.

▪ Strict safety assessments and documentation of all adverse events were implemented in both treatment groups to improve the ability of comparison to published literature.

References


This physician-initiated study received financial support from Medtronic.
Neurostimulation for Parkinson’s disease with early motor complications 

**EARLYSTIM Study**


**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).

**SERIOUS ADVERSE EVENTS**

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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DBS therapy</th>
<th>Medical therapy</th>
<th>P Value – Difference Between Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in quality of life PDQ-39 summary index</td>
<td>+26%*</td>
<td>-1</td>
<td>0.002</td>
</tr>
<tr>
<td>Improvement in motor score UPDRS-III (off medication)</td>
<td>+53%*</td>
<td>+4%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Improvement in activities of daily living (ADL)</td>
<td>+30%*</td>
<td>-12%*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Improvement in UPDRSIV (levodopa-induced complications)</td>
<td>+61%*</td>
<td>-13%*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Increased hours of good mobility without troublesome dyskinesia (Patient diary)</td>
<td>+20%*</td>
<td>+2%</td>
<td>0.01</td>
</tr>
<tr>
<td>Improved SCOPA-PS (SCales for Outcomes in Parkinson’s disease – PsychoSocial questionnaire)</td>
<td>+28%*</td>
<td>+3%</td>
<td>0.02</td>
</tr>
<tr>
<td>Within group change in daily levodopa-equivalent dosage</td>
<td>-39%*</td>
<td>+21%*</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Within group change from baseline to 24 months - P < 0.05
The EARLYSTIM study is a large randomized controlled trial of DBS therapy for Parkinson’s disease that confirms the impact of the therapy earlier in the progression of the disease. It is also the first comparison of DBS therapy to medical therapy at 24 months.

This study showed consistent, significant findings that DBS therapy for patients with early motor complications is superior to medical therapy in the evaluation of multiple outcomes, including the primary and major secondary objectives.

Disease-related quality of life improves significantly from baseline to 24 months in patients receiving DBS therapy; there is no change in quality of life in patients receiving medical therapy alone.

Safety outcomes were similar in both treatment groups.

This study provides additional insights into patient selection criteria for successful DBS therapy outcomes.

Reference
Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson’s disease: a randomized, multicentre study


Objective

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

Study Type – Prospective ancillary protocol to a controlled, multicenter, randomized trial

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

RESULTS

Anxiety was significantly reduced in the DBS group (P < 0.0001) but remained unchanged in the BMT group.

Changes in dysarthria score (P = 0.24) and other neuropsychological tests after DBS were not significantly different compared with BMT.

Overall cognition did not differ significantly between DBS and BMT groups.

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.

The DBS group experienced significantly greater negative changes in semantic (P = 0.03) and phonemic (P = 0.02) fluency scores of the verbal fluency test; this was not associated with changes in scores in quality of life or psychiatric scales.

ADVERSE EVENTS

Serious Adverse Events in the Psychiatric Domain

<table>
<thead>
<tr>
<th>Event</th>
<th>DBS (n = 78)</th>
<th>BMT (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death in a psychotic episode</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Psychosis</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Severe loss of affect (apathy)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Suicide</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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.
A randomized trial of deep-brain stimulation for Parkinson’s disease


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

NEUROSTIMULATION WAS ASSOCIATED WITH A 25% IMPROVEMENT IN THE QUALITY OF LIFE SUMMARY (PDQ-39): CHANGE IN THE MEDICATION GROUP WAS INSIGNIFICANT

Patients’ diaries revealed profound and significant changes, only in the neurostimulation group, with longer periods of mobility, shorter periods of immobility, shorter periods with troubling dyskinesia, and longer periods of sleep.

41% IMPROVEMENT IN SEVERITY OF SYMPTOMS INDEX (UPDRS-III) WAS FOUND IN THE NEUROSTIMULATION GROUP BUT REMAINED UNCHANGED IN THE MEDICATION GROUP

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.

Neurostimulation resulted in a 41% improvement in motor symptom scores in patients when off medication (P < 0.001).

Scores remained unchanged in the best medical management group.

UPDRS III= Unified Parkinson’s Disease Rating Scale, part III.

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

ADVERSE EVENTS

<table>
<thead>
<tr>
<th></th>
<th>Neurostimulation</th>
<th>Medical Management</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Events</td>
<td>10 (12.8%)</td>
<td>3 (3.8%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>39 (50%)</td>
<td>50 (64.1%)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

▼ 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 severity and duration of periods of immobility and dyskinesia.

▼ Improvement in motor functioning led to improvement in measurements of activities of daily living, emotional well-being, stigma, and bodily discomfort; cognition, mood, and overall psychiatric functioning were unchanged.

▼ The prospect of improved quality of life resulting from deep brain stimulation must be weighed against the risks of surgical intervention.
EFNS guideline on neurological management late (complicated) Parkinson’s disease


OBJECTIVE

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

Study Type – Guidance paper developed using unified criteria for standards of reporting within the framework established by an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). Refer to Table 1 on page 35 for rating of recommendations and evidence classification scheme.

RESULTS

Recommendations:

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

Symptomatic Control of Severe Motor Fluctuations

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

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

Symptomatic Control of Unpredictable ON-OFF

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

Symptomatic Control of Peak-Dose Dyskinesia

- Reduce individual levodopa dose size
  - May increase OFF time
  - Compensate by increasing the number of doses of levodopa or dopamine agonist (Level C)
- Discontinue or reduce dose of MAO-B inhibitors or COMT inhibitors (good practice point [GPP])
  - May worsen wearing-off (end-of-dose) akinesia
- Add amantadine (Level A)
  - Benefit may last < 8 months
  - Other antiglutamatergic drug use is investigational
- Discontinue or reduce dose of MAO-B inhibitors or COMT inhibitors (GPP)
  - May worsen wearing-off (end-of-dose) akinesia
- Add amantadine (Level A)
  - Benefit may last < 8 months
  - Other antiglutamatergic drug use is investigational
- Deep brain stimulation
  - Allows reduction of dopaminergic treatment (Level A)
  - GPi (globus pallidus interna) stimulation may also inhibit severe dyskinesia (Level C)
- Add atypical antipsychotics, clozapine, or quetiapine (Level C)
  - Clozapine is associated with serious adverse events including agranulocytosis and myocarditis, limiting its use (GPP)
- Apomorphine continuous subcutaneous infusion allows reduction of levodopa therapy (Level C)
- Intrajejunal levodopa infusion in patients with marked peak dose dyskinesia and motor fluctuations (Level C)

Symptomatic Control of Off-Period and Early Morning Dystonias

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

Treatment of Sleep Problems

- Levodopa, standard or prolonged-release dose, at bedtime (Level B)
- Transdermal rotigotine, pramipexole, and prolonged-release ropinirole for patients with motor fluctuations (Level A)
- Deep brain stimulation of the STN except for nocturnal motor phenomena of sleep disorders (Level B)

KEY CONCLUSIONS

- Recommendations for the therapeutic management of patients with advanced PD are systematically graded according to the strength of available scientific evidence.
- Deep brain stimulation of the STN is among the highest recommendations for treatment and control of symptoms associated with late (complicated) Parkinson’s disease.
**Table 1. EFNS Evidence Classification Scheme for a Therapeutic Intervention**

<table>
<thead>
<tr>
<th>Rating of Recommendation</th>
<th>Level A</th>
<th>Established as effective, ineffective, or harmful. Requires ≥ 1 convincing class I study or ≥ 2 consistent, convincing class II studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level B</td>
<td>Probably effective, ineffective, or harmful. Requires ≥ 1 convincing class II study or overwhelming class III evidence.</td>
</tr>
<tr>
<td></td>
<td>Level C</td>
<td>Possibly effective, ineffective, or harmful. Requires ≥ 2 convincing class III studies.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class of Evidence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td>▼ An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population, or ▼ An adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations</td>
</tr>
</tbody>
</table>
|                   | ▼ The following are required:  
|                   |   a. randomization concealment  
|                   |   b. primary outcome(s) is/are clearly defined  
|                   |   c. exclusion/inclusion criteria are clearly defined  
|                   |   d. adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias  
|                   |   e. relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences |
| **Class II**       | ▼ Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above, or ▼ A randomized, controlled trial in a representative population that lacks one criteria a–e |
| **Class III**      | ▼ All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment |
| **Class IV**       | ▼ Evidence from uncontrolled studies, case series, case reports, or expert opinion |
| **GPP** (good practice point) | ▼ Used in exceptional clinical areas for which no high class evidence is available or likely to become available in the near future  
| | ▼ Not grounded on more than class IV evidence, implying large clinical uncertainty  
| | ▼ Based on the experience and consensus of the guideline development group |

**Reference**

Selected articles about DBS therapy

Parkinson’s disease


Medtronic evidence compendium – glossary

Adverse event – Side effects to a medication that are unintended, generally of a harmful or unpleasant nature.

Agranulocytosis – A failure of the bone marrow to make enough white blood cells.

Akinesia – Lack of movement.

Baseline – A set of critical observations or data used for comparison or as a control.

Blinded – In a blinded clinical trial information about the test that might lead to bias in the results is concealed from the tester, the subject or from both.

BMT – Best medical therapy.

COMT inhibitor – A class of medication used to prolong the duration of the effects of levodopa by blocking an enzyme called catechol-O-methyl transferase (COMT). This enzyme breaks down levodopa so blocking it slows the destruction of levodopa in the body.

Cross-over – A study method in which participants receive a sequence of different treatments.

Dopaminergic – Related to dopamine or dopamine-producing cells.

Double-blind – In a double-blind trial neither the participants nor the researchers know who is receiving the active treatment and who is receiving placebo.

Dysautonomia – A motor speech disorder which makes articulation difficult.

Dyskinesia – Any abnormal, involuntary movement (often in response to Parkinson’s medication).

Dystonia – Involuntary sustained muscle contractions causing abnormal movements and postures.

Endpoint – Something that is measured in a clinical trial or study. Measurement of selected endpoints is the goal of a trial.

Enteric – Relating to the intestines.

Gait – The posture or positioning of the body during walking.

Gastrostomy – The creation of an artificial opening into the stomach, usually for the administration of nutrition or medication.

Glaucoma pallidus (GPi) – The Globus Pallidus (GPi) is a part of the basal ganglia, the brain that is one of the target sites for deep brain stimulation.

GPi – See Globus pallidus.

Intracranial – Within the cranial, that is the upper bony section of the skull.

Intracerebral – Within the cerebrum, the principal part of the brain located in the front area of the skull.

Intrajejunum – Within the jejunum, that is the middle section of the small intestine.

Kinetic – Relating to motion.

MAO–B inhibitor – A class of medication that is used to treat the symptoms of early Parkinson’s, as well as to treat levodopa-induced motor fluctuations in the more advanced stages of the disease.

Motor – Referring to movement or motion of a part of the body.

Myocardial infarction – Heart attack.

Myocarditis – Inflammation of the myocardium, the muscular middle layer of the heart wall.

Non-motor – Not relating to movement.

“Off” time – When medication is not working and Parkinson’s symptoms return.

“On” time – When medication is working and there is good symptom control.

Palidal – Relating to or involving the Globus pallidus.

Paraesthesia – A tingling, prickling or numb sensation of the skin, sometimes described as “pins and needles”.

Pars interna – A part of the Globus pallidus.

Percutaneous – Performed through the skin.

Pharmacological – Relating to drugs.

Phonemic – Relating to the smallest units of sound that combine to form meaningful units such as words.

Prospective – A study that starts with the present condition of subjects and follows them into the future.

Psychosis – Any form of severe mental disorder in which the individual’s contact with reality becomes highly distorted. People experiencing psychosis often exhibit personality changes, inappropriate behaviour and a deterioration in normal social functioning.

Randomized (clinical trial) – A clinical trial in which participants are randomly assigned to receive a test medication/placebo, or a control medication/placebo.

Schwab and England scale – A means of assessing a person’s ability to perform daily activities in terms of speed and independence through a percentage figure.

Semen – Relating to the meaning of words or phrases that relate to the male reproductive system.

SN – See Subthalamic (nucleus).

Subcutaneous – Into tissue directly beneath the skin.

Subthalamic (nucleus) – To do with the subthalamic nucleus, a part of the basal ganglia area of the brain and one of the target sites for deep brain stimulation.

Transdermal – Relating to the application of a medication through the skin, typically using an adhesive patch, so that it is absorbed slowly into the body.


Wearing-off – The gradual return of symptoms that occurs at the end of a dose of levodopa. This pattern appears when a person with Parkinson’s disease has been using levodopa for many years.
Medtronic deep brain stimulation (DBS) therapy is not for everyone. Not everyone will receive the same results. For further information please consult with your physician.