Deep Brain Stimulation for Parkinson’s Disease & Essential Tremor

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Current US Approvals

**Essential Tremor and Parkinsonian Tremor - 1997**
- Indicated for unilateral thalamic stimulation of the ventral intermediate nucleus (VIM) for the suppression of tremor in the upper extremity in patients diagnosed with essential tremor or parkinsonian tremor not adequately controlled by medications and where tremor constitutes a significant functional disability.

**Parkinson’s Disease - 2002**
- Indicated for bilateral stimulation of the internal globus pallidus (GPI) or the subthalamic nucleus (STN) as an adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson’s disease that are not adequately controlled with medication.

**Primary Dystonia - 2003 HDE**
- Indicated for unilateral or bilateral stimulation of the GPI or the STN as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age and older.

**Obsessive Compulsive Disorder - 2009 HDE**
- 120,000+ patients worldwide have received Medtronic DBS Therapy
Essential Tremor
Essential Tremor

Non-Life threatening disorder
Essential Tremor

- Non-Life threatening disorder
- Progressively worsens over time
Essential Tremor

Non-Life threatening disorder

Progressively worsens over time

Severe Effect on Quality of Life
Essential Tremor

Multidimensional Impacts are **Disabling**

- Social
- Professional
- Emotional

*frustration, embarrassment*
Why Surgery?
Why Surgery?

→ Tremor Refractory to Medicine
Why Surgery?

- Tremor Refractory to Medicine
- Side effects of Medication intolerable
Why Surgery?

- Tremor Refractory to Medicine
- Side effects of Medication intolerable
- Severe tremor jeopardizes job and quality of life
Outcome

Unilateral or Bilateral:

- Significant relief of upper / lower extremity tremor
Outcome

Unilateral or Bilateral:

Significant relief of upper / lower extremity tremor

→ Average Improvement 70%-90%
Outcome

Unilateral or Bilateral:

Significant relief of upper / lower extremity tremor

Average Improvement 70%-90%

stable - up to 5 yrs

stimulation parameters may increase

Hariz et al. (2008b); Limousin et al. (1999); Pahwa et al. (2006); Obwegeser et al. (2000); Zhang et al., (2009)
Parkinson’s Disease
Parkinson’s Disease

• Affects 1% to 3% of adults > 65 yrs
Parkinson’s Disease

• Affects 1% to 3% of adults > 65 yrs

Tremor, Bradykinesia, Rigidity

– Gait difficulties and postural instability
DBS for Who?

• Presence of symptoms of PD for ≥ 5 years
• No significant cognitive deficits or dementia
DBS for Who?

• Presence of symptoms of PD for $\geq 5$ years
• No significant cognitive deficits or dementia
• Prognostic indicator:
  $\uparrow$ Motor Response to levodopa challenge
  ($>33\%$ improvement in UPDRS III from off-state)
Parkinson’s Disease

Despite best Medical Therapy
Parkinson’s Disease

Despite best Medical Therapy

- 40% pts continue to have motor fluctuations
- 28% experience levodopa-induced dyskinesias

Schrag and Quinn (2000); Twelves et al. (2003); Schoenberg (1987)
Why Surgery?
Why Surgery?

Troubling Dyskinesias
Why Surgery?

- Troubling Dyskinesias
- On / Off Motor Fluctuations
Why Surgery?

- Troubling Dyskinesias
- On / Off Motor Fluctuations
- Tremor Refractory to Medicine
Why Surgery?

- Troubling Dyskinesias
- On / Off Motor Fluctuations
- Tremor Refractory to Medicine
- **Medication Side Effects intolerable**
Surgery? Parkinson’s Disease

Despite best Medical Therapy
Surgery? Parkinson’s Disease

Despite best Medical Therapy

Severe Dyskinesias ON meds
Surgery? Parkinson’s Disease

Despite best Medical Therapy

- Severe Dyskinesias ON meds
- Severe Motor Symptoms OFF meds
Window of Opportunity for **DBS** Therapy for Parkinson’s Disease

**Optimal Time for DBS Therapy**
- The best opportunity to control your motor symptoms is when the benefits of oral medications decrease

**Oral Medication**
- Medication works to control your motor symptoms

**DBS Therapy Window Closes**
- If you wait too long and your motor symptoms no longer respond to medications, DBS Therapy will no longer be effective

UTHealth
The University of Texas Health Science Center at Houston
Medical School

Memorial Hermann
Mischer Neuroscience Institute
Why DBS?
Why DBS?

Reversible, Not Permanent
Why DBS?

- Reversible, Not Permanent
- **Adjustable**
Why DBS?

- Reversible, Not Permanent
- Adjustable
- Relief of Motor Dysfunction
Why DBS?

- Reversible, Not Permanent
- Adjustable
- Relief of Motor Dysfunction

140,000 Cases Worldwide to Date
DBS Surgery: beginning

1987 Vim thalamus for PD (France)
DBS procedure

Occurs as 2 Stages
DBS procedure: Stage I

Local Anesthesia only

Patient is Awake
DBS procedure: Stage I

Local Anesthesia only

- Patient is Awake
- Overnight stay for monitoring
DBS procedure: Stage I

- Placement of the stereotactic frame
DBS procedure: Stage I

- Placement of the stereotactic frame
Surgical Technique: Targeting

- Sophisticated imaging and software enables precise targeting for optimal outcomes and minimal risk

- Microelectrode recording (MER) offers additional levels of verification of lead location
STN Target: MER in PD

DBS for Parkinson’s Disease

• STN (Subthalamic Nucleus)
  – Bilateral implant
  – FDA approval 2002

• GPi (Globus Pallidus Interna)
  – Bilateral implant
  – FDA approval 2002
DBS: Gpi Target
DBS procedure: Stage I

- Implantation of DBS electrode spanning target

- Testing of DBS electrode for efficacy/side effects
  - Contractions, paresthesias, gaze deviation

- Final placement and securement
DBS Procedure: Stage II

- Performed as a separate surgery
  - General Anesthesia
  - Short, Outpatient procedure
- Infraclavicular or subcostal placement
- Single or Dual-channel IPG
- New Rechargeable IPG available
DBS Procedure: Stage II

- Unilateral vs. Bilateral Implantation
- Staged IPG implantation
Outcomes

• Multi-center Studies evaluating DBS efficacy compared to pre-op baseline or best medical treatment
Long-Term Results of a Multicenter Study on Subthalamic and Pallidal Stimulation in Parkinson’s Disease

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Additional Supporting Information may be found in the online version of this article.
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Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease
A Randomized Controlled Trial

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Context Deep brain stimulation is an accepted treatment for advanced Parkinson disease (PD), although there are few randomized trials comparing treatments, and most studies exclude older patients.

Objective To compare 6-month outcomes for patients with PD who received deep brain stimulation or best medical therapy.

Design, Setting, and Patients Randomized controlled trial of patients who received either deep brain stimulation or best medical therapy, stratified by study site and patient age (<70 years vs ≥70 years) at 7 Veterans Affairs and 6 university hospitals between May 2002 and October 2005. A total of 256 patients with PD (Hoehn and Yahr stage ≥2 while not taking medications) were enrolled; 25% were aged 70 years or older. The final 6-month follow-up visit occurred in May 2006.

Intervention Bilateral deep brain stimulation of the subthalamic nucleus (n = 60) or globus pallidus (n = 61). Patients receiving best medical therapy (n = 134) were actively managed by movement disorder neurologists.

Main Outcome Measures The primary outcome was time spent in the “on” state (good motor control with unimpaired motor function) without troubling dyskinesia, using motor diaries. Other outcomes included motor function, quality of life, neurocognitive function, and adverse events.

Results Patients who received deep brain stimulation gained a mean of 4.6 h/d of on time without troubling dyskinesia compared with 0 h/d for patients who received best medical therapy (between-group mean difference, 4.6 h/d [95% CI, 3.7–5.4 h/d]; P < .001). Motor function improved significantly (P < .001) with deep brain stimulation vs best medical therapy, such that 71% of deep brain stimulation patients and 52% of best medical therapy patients experienced clinically meaningful motor function improvements (>5 points). Compared with the best medical therapy group, the deep brain stimulation group experienced significant improvements in the summary measure of quality of life and on 7 of 8 PD quality-of-life scores (P < .001). Neurocognitive testing revealed small decrements in some areas of information processing for patients receiving deep brain stimulation vs best medical therapy. At least 1 serious adverse event occurred in 49 deep brain stimulation patients and 15 best medical therapy patients (P < .001), including 39 adverse events related to the surgical procedure and 1 death secondary to cerebral hemorrhage.

Conclusion In this randomized controlled trial of patients with advanced PD, deep brain stimulation was more effective than best medical therapy in improving time on without troubling dyskinesia, motor function, and quality of life at 6 months, but was associated with an increased risk of serious adverse events.

Trial Registration clinicaltrials.gov Identifier: NCT00056563
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www.jama.com

For editorial comment see p 104.
A Randomized Trial of Deep-Brain Stimulation for Parkinson’s Disease

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ABSTRACT

BACKGROUND
Neurostimulation of the subthalamic nucleus reduces levodopa-related motor complications in advanced Parkinson’s disease. We compared this treatment plus medication with medical management.

METHODS
In this randomized-pairs trial, we enrolled 156 patients with advanced Parkinson’s disease and severe motor symptoms. The primary end points were the changes from baseline to six months in the quality of life, as assessed by the Parkinson’s Disease Questionnaire (PDQ-39), and the severity of symptoms without medication, according to the Unified Parkinson’s Disease Rating Scale, part III (UPDRS-III).

RESULTS
Pairwise comparisons showed that neurostimulation, as compared with medication alone, caused greater improvements from baseline to six months in the PDQ-39 (50 of 78 pairs, P<0.02) and the UPDRS-III (55 of 78, P<0.001), with mean improvements of 9.5 and 19.6 points, respectively. Neurostimulation resulted in improvements in 24 to 38 percent in the PDQ-39 subscales for mobility, activities of daily living, emotional well-being, stigma, and bodily discomfort. Serious adverse events were more common with neurostimulation than with medication alone (13 percent vs. 4 percent, P=0.04) and included a fatal intracerebral hemorrhage. The overall frequency of adverse events was higher in the medication group (64 percent vs. 50 percent, P=0.08).

CONCLUSIONS
In this six-month study of patients under 75 years of age with severe motor complications of Parkinson’s disease, neurostimulation of the subthalamic nucleus was more effective than medical management alone. (ClinicalTrials.gov number, NCT00196911.)
Best Medical Therapy vs. DBS
Best Medical Therapy vs. DBS

DBS found to be more effective in treating symptoms of PD
Best Medical Therapy vs. DBS

GPI / STN DBS: PD pts received

5.2 hours of additional ON time

without dyskinesias

104 more days ON per year!
Best Medical Therapy vs. DBS

Dyskinesias were significantly reduced (>75%) compared to preoperative baseline and to those receiving best medical therapy sustained over 5 years.
Early DBS for PD

Neurostimulation for Parkinson’s Disease with Early Motor Complications

Early DBS for PD

- 251 PD patients with early motor complications
- mean age, 52 years; mean duration of disease, 7.5 years
- randomized to DBS + meds OR medical therapy alone
Early DBS for PD

• The primary end point was quality of life, as assessed with the use of the Parkinson’s Disease Questionnaire (PDQ-39) summary index
Early DBS for PD

• The primary end point was quality of life, as assessed with the use of the Parkinson’s Disease Questionnaire (PDQ-39) summary index
Early DBS for PD
Quality of Life
Early DBS for PD
Quality of Life

A

PDQ-39 Summary Index Score

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<tr>
<th>Months since Randomization</th>
<th>Medical therapy</th>
<th>Neurostimulation</th>
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<tr>
<td>0</td>
<td>30.2</td>
<td>30.2</td>
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<tr>
<td>5</td>
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<td>20.3</td>
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<tr>
<td>24</td>
<td>30.4</td>
<td>22.4</td>
</tr>
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P = 0.002
Early DBS for PD: Quality of Life

![Graph showing change from baseline for various aspects of quality of life compared to neurostimulation and medical therapy.](image)
Motor Symptoms Improvements Maintained Up to 5 Years

In a 5-year study, DBS Therapy significantly improved OFF-medication assessments of tremor, rigidity, and akinesia Bradykinesia.

*Results for STN

Medication Reduction
Change in Levodopa Use Over Time

Reduction in Medication
6 month, DBS vs. BMT

+1.3%  -22.7%

1318  1335  1336  1032

LED (mg/day)

BMT (n=116)  DBS+BMT (n=111, pooled data)
DBS Procedure: Risks
DBS Procedure: Risks

• Risk of hemorrhage for bilateral lead placement
DBS Procedure: Risks

- Risk of hemorrhage for bilateral lead placement
  
  $1 - 4\%$ worldwide

Limousin et al., 2008; Krack et al., 2003; Kumar et al., 2000; Wider et al., 2007; Lyons et al., 2002; Rezai et al; 2006
DBS Procedure: Risks

• Risk of hemorrhage for bilateral lead placement

1 – 4 % worldwide

Most unlikely to be symptomatic

Limousin et al., 2008; Krack et al., 2003; Kumar et al., 2000; Wider et al., 2007; Lyons et al., 2002; Rezai et al; 2006
DBS Procedure: Risks

• Risk of Infection
  very low
DBS Procedure: Risks

- Risk of Infection: **very low**

- Hardware problems (lead fracture / IPG failure)

Rezai et al; 2006
DBS Procedure: Risks

- Risk of Infection
  very low

- Hardware problems (lead fracture / IPG failure)
  4.3% per electrode

Rezai et al; 2006
These risks are lower compared to other cranial neurosurgical procedures
PATIENT ADVOCATES

• JULIE ANDERSON
  – Parkinson’s Disease
  – DBS Patient since May 2015

• FRANCES RABURN
  – Essential Tremor
  – DBS Patient since November 2015