Advanced Therapies in PD: DBS, DUOPA, Botulinum Toxin

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Parkinson Disease (PD) Generalities
Generalities

• Parkinsonism: is just a collection of signs and symptoms.
• Parkinsonism is diagnosed when at least 2 of the following features are seen in a patient: Resting tremor (shaking), stiffness, and slow movements.
• There are dozens of causes of parkinsonism. Parkinson Disease –PD- (AKA Idiopathic Parkinson Disease) is just one of the most common ones.
• The type of parkinsonism determines treatment responsiveness and prognosis.
Common Motor Symptoms of Parkinson’s

Early Symptoms
Resting tremors
Slow movement – bradykinesia
Stiff muscles – rigidity

Later Symptoms
Balance issues - Falls
Gait disturbances - Freezing
Motor Fluctuations
You are not alone:
Your PD management team

The most important team member is YOU!

Parkinsonism and Dystonia
Dystonia in PD

• Dystonia is characterized by excessive muscle contractions
• Therefore, dystonia can present as stiffness, jerking or abnormal postures
• Dystonia is associated with disability
• Dystonia is highly under-recognized and therefore under-treated
WHAT KINDS OF SYMPTOMS COULD BE DUE TO DYSTONIA?
Dystonia: excessive muscle activity
OTHER SYMPTOMS THAT COULD BE DUE TO DYSTONIA IN PD

- One foot dragging
- Tip-toe walking or foot turning
- Muscle spasms
- Severe stiffness (neck, arm, leg)
- Excessive eye closure (called blepharospasm)
- Uncontrollable movements (hand, face)
- Inability to use the hand
- Voice abnormality
- Some rare tremors.
What causes Dystonia in PD

Lack of medication

Medication Side Effect
Dystonia Treatment

- PT/OT
- Oral meds
- Injections
- Surgery
Week 1-2 versus week 6-7
Improvement of Anterocollis and Camptocormia in patients with PD
Fig. 1  (A, B) Patient with PD and severe anterocollis (before BoNT).

Joseph Jankovic

Disease-oriented approach to botulinum toxin use

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http://dx.doi.org/10.1016/j.toxicon.2008.11.013
Fig. 2  Patient's anterocollis markedly improved within 4 weeks after treatment with BoNT (Botox® 75 U in the right and 50 U in the left scalene).

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**Disease-oriented approach to botulinum toxin use**

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Fig. 3  Patient with PD and camptocormia.

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Fig. 4  Patient's camptocormia markedly improved after treatment with BoNT (Botox® 200 U in each rectus abdominus).

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MOTOR FLUCTUATIONS IN PD
LEVODOPA IS THE MOST EFFECTIVE TREATMENT FOR PD
More options...
Each Year There Are Few More...
And a Few More...
WHEN THE MEDICATIONS ARE WORKING, PATIENTS ARE "ON"
PD Medications Side Effects

• Dyskinesia (involuntary dancing-like movements)
• Motor fluctuations
• Other complications:
  – Loss of appetite, nausea or vomiting
  – Difficulty sleeping or excessive daytime sleepiness
  – Lightheadedness when standing up, near passing out
  – Loss of control issues (gambling), OCD-like.
A typical day

Symptoms controlled ('on' time)
- Symptoms go away
- Symptons return
- Medication starts to work

Symptoms not controlled ('off' time)
- PD medication
- Fading effect
- PD medication
- PD medication

Time
ON/OFF Fluctuations with Levodopa Treatment

EARLY PD  MODERATE PD  ADVANCED PD

OVER

ON time

OFF time

L-DOPA doses

Dyskinesia

Adapted from the Davies Phinney Foundation: https://www.davisphinneyfoundation.org/blog/life-before-after-deep-brain-stimulation-dbs/on-off/
We need to consider advance options, including surgery, once motor fluctuations or dyskinesias occur.
EXPECTED BENEFITS FROM SURGERY

To Stay “ON” LONGER, with less dyskinesias and medication side effects
DUOPA
# DUOPA: Pivotal Study PD Symptom Diary Analysis

Change From Baseline to Week 12 in “Off” time and in “On” Time Without Troublesome Dyskinesia in Patients With Advanced Parkinson’s Disease

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Baseline (hours)</th>
<th>LS Mean Change From Baseline at Week 12 (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Off” Time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUOPA</td>
<td>6.3</td>
<td>-4.0(^b)</td>
</tr>
<tr>
<td>Oral CL-IR</td>
<td>6.9</td>
<td>-2.1</td>
</tr>
<tr>
<td><strong>“On” Time Without Troublesome Dyskinesia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUOPA</td>
<td>8.7</td>
<td>4.1(^b)</td>
</tr>
<tr>
<td>Oral CL-IR</td>
<td>8.0</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Abbreviations: CL-IR, carbidopa/levodopa immediate-release; LS, least square

\(^a\) LS mean change from baseline based on Analysis of Covariance (ANCOVA).

\(^b\) Statistically significant.
DUOPA: Most Common Adverse Reactions for DUOPA (At Least 7% Greater than Oral Immediate-Release Carbidopa-Levodopa)

- Complication of device insertion
- Nausea
- Depression
- Peripheral edema
- Hypertension
- Upper respiratory tract infection
- Oropharyngeal pain
- Incision site erythema
- Atelectasis

https://www.parkinsons.va.gov/Consortium/Presentations/Audio_Conference/DuopaSlides03_10_2016.pdf
Adverse events are most seen during the first week of treatment

https://www.parkinsons.va.gov/Consortium/Presentations/Audio_Conference/DuopaSlides03_10_2016.pdf
DEEP BRAIN STIMULATION (DBS)
Indications for DBS surgery

- When increasing medications dosage is needed, but by increasing the meds you cause unwanted severe side effects.
Examples

• Patient with 15 years of disease, taking levodopa 3 tablets every 3 hours. Levodopa improves a disabling tremor and gait, but is causing embarrassing dyskinesias at this dose.

• Patient with 10 years of disease, freezing goes away with levodopa, but can’t walk due to dyskinesias and leg cramps caused by the treatment.

• Patient with 6 years of disease, taking 4 tablets of levodopa every 4 hours, which improves Tremor partially. Patient has limiting somnolence, and tremor continues to be disabling when awake.
DBS Evaluation Protocol at UNMC

Mov Dis
- What type of PD? Rule out curable causes
- Can the issue be improved with DBS?

Neurosurg
- After DBS candidacy evaluation, refer to Neurosurgery
- Lots of education. If appropriate → DBS surgery

Programming
- Programming of the device
- Continuous monitoring, added drug options.
Bilateral STN DBS in PD

• Effective & Safe:
  – Improves Parkinson’s scores
  – Improves motor fluctuations:
    • Decreases OFF time, Increases ON Time
    • Improves dyskinesia
  – Decreases daily dose of levodopa and other PD medications
  – Improves sleep
  – Improves Quality of Life.
Risks of the procedure

• Surgical complications:
  – Bleeding
  – Seizure
  – Stroke
  – Mild transient confusion
  – Infections
  – Death.

• Others:
  – Malfunction of the stimulator
  – Lead-cables
Pallidal versus Subthalamic Deep-Brain Stimulation for Parkinson’s Disease

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ABSTRACT

BACKGROUND

Deep-brain stimulation is the surgical procedure of choice for patients with advanced Parkinson’s disease. The globus pallidus interna and the subthalamic nucleus are accepted targets for this procedure. We compared 24-month outcomes for patients who had undergone bilateral stimulation of the globus pallidus interna (pallidum stimulation) or subthalamic nucleus (subthalamic stimulation).

METHODS

At seven Veterans Affairs and six university hospitals, we randomly assigned 299 patients with idiopathic Parkinson’s disease to undergo either pallidal stimulation (152 patients) or subthalamic stimulation (147 patients). The primary outcome was the change in motor function, as blindly assessed on the Unified Parkinson’s Disease Rating Scale, Part III (UPDRS-III), while patients were receiving stimulation but not receiving antiparkinsonian medication. Secondary outcomes included self-reported function, quality of life, neurocognitive function, and adverse events.

RESULTS

Mean changes in the primary outcome did not differ significantly between the two study groups (P = 0.50). There was also no significant difference in self-reported function. Patients undergoing subthalamic stimulation required a lower dose of dopaminergic agents than did those undergoing pallidal stimulation (P = 0.02). One component of processing speed (visuomotor) declined more after subthalamic stimulation than after pallidal stimulation (P = 0.03). The level of depression worsened after subthalamic stimulation and improved after pallidal stimulation (P = 0.02). Serious adverse events occurred in 56% of patients undergoing pallidal stimulation and in 56% of those undergoing subthalamic stimulation, with no significant between-group differences at 24 months.

CONCLUSIONS

Patients with Parkinson’s disease had similar improvement in motor function after either pallidal or subthalamic stimulation. Nonmotor factors may reasonably be included in the selection of surgical target for deep-brain stimulation.

(ClinicalTrials.gov numbers, NCT00056563 and NCT01076452.)