Advances in Parkinson’s Disease Treatment

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Disclosure

Ryan J. Uitti, MD

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Treatment of Parkinsonism

Summary:

- Education
- Focus on Quality of Life
- Medications
- Surgery
“Parkinson’s disease” … is actually a syndrome

- Probably many causes
- Probably many unique progression courses
- Progression may be influenced (inadvertently) by a variety of factors (treatment, others)
- Probably will have many cures
Potentially Neuroprotective Agents for Parkinson’s

- **Bioenergetic agents**
  - Coenzyme Q10, creatine

- **Antioxidants**
  - Vitamin E, C, iron chelators

- **MAO-B inhibitors**
  - Selegiline, rasagiline

- **Anti-apoptotic agents**
  - Mixed lineage kinase inhibitors (CEP-1347, TCH346, rapamycin, selegiline, rasagiline); caspase inhibitors

- **NMDA-receptor antagonists**
  - Amantadine, memantine

- **Surgery – STN-DBS**

- **Hormones**
  - Estrogen

- **Dopaminergic agents**
  - Nicotine, dopamine agonists, levodopa

- **A2A (adenosine receptor) antagonists**
  - Istradefylline, caffeine

- **Anti-inflammatory agents**
  - Minocycline, aspirin, COX-2 inhibitors, NSAIDs, tetracycline

- **Growth/Neurotrophic factors**
  - Neuroimmunophilins -GPI-1485, GDNF, GM-1 ganglioside, SR57667, proprarygylamines TCH346
Studies – all “negative”

• DATATOP
• CoQ10
• SINDEPAR (Sinemet-Deprenyl-Parlodel)
• CALM-PD
• Ropinirole 056 Study
• ELLDOPA (Early vs Late L-Dopa)
• Riluzole/CEP-1347 study – no substantial benefit
• Rasagiline (PRESTO) – MAO-B inhibitor and propargylamine – used delay start study design: possibly disorder-modifying
Conclusions:

- LRRK2 can cause Parkinson’s disease
- Causes 1-2% of all PD in North America
- Causes 30% of all PD in Tunisia

- “23 ‘n Me”
  - Sergey Brin has LRRK2 G2019S mutation
Genetic causes of Parkinson’s Disease

- LRRK2 – PARK8 – most common genetic cause
- SNCA – PARK 1 / 4
- VPS35 – PARK17
- DNAJC13 – PARK 21
- PRKN – PARK 2
- PINK1 – PARK 6
- DJ-1 – PARK 7
- ATP13A2 – PARK 9
- GIGYF2 – PARK 11
- PLA2G6 – PARK 14
- DNAJC6 – PARK 19
- SYNJ1 – PARK 20
Genetic contributors to Parkinson’s Disease

Susceptibility variants

- LRRK2
- SNCA
- MAPT H1
- GBA

- Alpha-synuclein
- Tauopathy
Survival Curves for Ability to Work and Live Independently
# Parkinson’s disease and Ability to Work

(Jasinska-Myga et al Parkinsonism & Rel Disord 2011)

<table>
<thead>
<tr>
<th>Age at baseline &amp; symptomatic duration</th>
<th>capable of working 5 yrs after baseline</th>
<th>capable of working 10 yrs after baseline</th>
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<tbody>
<tr>
<td>≤70 &amp; ≤4 yrs</td>
<td>88%</td>
<td>44%</td>
</tr>
<tr>
<td>≤70 &amp; &gt;4 yrs</td>
<td>66%</td>
<td>26%</td>
</tr>
<tr>
<td>&gt;70 &amp; &lt;4 yrs</td>
<td>58%</td>
<td>8%</td>
</tr>
<tr>
<td>&gt;70 &amp; &gt;4 yrs</td>
<td>43%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>
Parkinson’s disease and Ability to Live Independently (Jasinska-Myga et al Parkinsonism & Rel Disord 2011)

<table>
<thead>
<tr>
<th>Age at baseline &amp; symptomatic duration</th>
<th>capable of indpt living 5 yrs after baseline</th>
<th>capable of indpt living 10 yrs after baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤70 &amp; ≤4 yrs</td>
<td>90%</td>
<td>64%</td>
</tr>
<tr>
<td>≤70 &amp; &gt;4 yrs</td>
<td>68%</td>
<td>31%</td>
</tr>
<tr>
<td>&gt;70 &amp; &lt;4 yrs</td>
<td>80%</td>
<td>23%</td>
</tr>
<tr>
<td>&gt;70 &amp; &gt;4 yrs</td>
<td>57%</td>
<td>5%</td>
</tr>
</tbody>
</table>
General Guidelines

• Well balanced diet, vitamin D and calcium supplementation for strong bones

• Good mood, sleep hygiene

• Stay Active
  • Mental gymnastics
  • Physical activity
Exercise Trial

- Moderate exercise (150 minutes/week)
  - +9000 steps per week

- Cognitive Scale benefit:
  - + 1.3 points
  - (+0.5 points with donepezil)
Conclusions

- Moderate exercise (150 minutes/week) resulted in improved cognitive function at 6 months and increased size of hippocampus.

- Benefits maintained at 18 & 24 months.
What Can I do NOW?

Two main problems without good treatment: balance and cognition

• Response:
  • Exercise
  • Exercise
  • Exercise
Treatment of Parkinson’s Disease

Issues:

- Motor
- Behavioral & psychological
- Non-motor

Modalities:

- Education
- Psychiatric
- Physical Medicine
- Pharmacological
- Surgical
Treatment of Parkinson’s Disease

Quality of Life:

- Depression is the greatest determinant early in course

- Falls/Injury & Dementia greatest determinants later in course
Treatment for Parkinson’s Disease

1965:
- Trihexyphenidyl
- Thalamotomy (?)

2016:
- 25 medications
- 12 surgeries
  - Multiple targets
  - Multiple modalities
Pharmacological Agents for Parkinson’s Disease

- anticholinergics (trihexyphenidyl, benztropine)
- amantadine (Symmetrel)
- carbidopa/levodopa (Sinemet, Sinemet-CR, Parcopa)
- pramipexole (Mirapex)
- ropinirole (Requip)
- selegiline (Zelapar, Emsam, Eldepryl, Deprenyl)
- tolcapone (Tasmar)
- entacapone (Comtan)
- carbidopa/levodopa/entacapone (Stalevo)
- apomorphine (Apokyn)
- rasagiline (Azilect)
- rotigotine (Neupro)
- carbidopa/levodopa IR/ER (Rytary)
- duodopa (Duopa)
Levodopa - Dopamine Agonists

Levodopa:
- most potent
- more likely to cause dyskinesia (usually chorea)
- Multiple forms (IR, ER, pump)

DA Agonists:
- less potent
- longer half-life
- more likely to cause confusion, hallucinations, hypotension, sleep disturbance, impulse control behavior disorder (~20%)
Levodopa

**SURVIVAL**

Use of L-dopa is associated with sustained, improved survival

L-dopa and amantadine are the only drugs for which this statement can be made (with data).

*Figure 2. The isolated effect of levodopa on mortality in PD over time developed from the mathematical model. The relative risk of death for the levodopa-untreated patients was set at “1” (dashed line).*


PD and Treatment-induced dyskinesia

Drugs that can **produce** dyskinesia:
- Levodopa
- Dopamine agonists

Drugs that can **exacerbate** dyskinesia:
- L-dopa/dopamine agonists
- COMT inhibitors
- MAO-B inhibitors

Drugs that can **ameliorate** dyskinesia:
- Amantadine
Medication Costs

Cost-pharmacychecker.com, 100 tablets (October, 2016):

- Generic carbidopa/levodopa 25/100: $39
- Sinemet 25/100: $54
- Pramipexole (Mirapex) 1.5 mg: $251
  - Pramipexole (generic) 1.5 mg: $87
  - Mirapex ER 4.5: $321
- Ropinirole (Requip) 5 mg: $437
  - Ropinirole (generic) 5 mg: $135
  - Requip XL 2 - 8 mg: $572
- Stalevo 100 (carbidopa/levodopa & entacapone): $200
- Rytary 23.75/95: $311
- Azilect 1 mg: $380
“Advanced” Parkinson’s Disease

No single definition:

• Disabling/Problematic

• Unpredictable motor fluctuations
  • Wearing off
  • Painful dystonia
  • Problematic dyskinesia
  • Severe tremor

• Problematic postural instability

• Non-motor: Dementia, Depression, Sleep Disturbance
Are motor complications inevitable?

... Can some treatment approaches prevent ADVANCED PD?
Are motor complications inevitable?

- Not everyone always develops dyskinesia/postural instability/falls
- With treatment, more common
  - … but not inevitable
    - With 5 treatment years: 30%
    - With 10 treatment years: 59%

Are motor complications harmful?

Severity?

- Rating scales - limitations
- Practice implications:
  - 17% require medication Δ after 5 yrs
    - 30% had dyskinesia of any severity
  - 43% require medication Δ after 10 yrs
    - 59% had dyskinesia of any severity
  - Only 12% can expect dyskinesia that cannot be adequately controlled with medication Δ

- ALL reversible with reduction in medications (save for graft-surgery)

Are there treatment protocols/treatments that mitigate or avoid motor complications?

Do treatments/Rx plans make dyskinesia:

- more likely? – some do
- “priming” – no
- “forestall development” – not really, only in an indirect manner

Once present:

- What can be done? – modify Rx; add amantadine, consider surgery; DBS/L-dopa pump (Duopa)
Evolution of Surgery for Parkinson’s Disease

Thalamotomy
Pallidotomy

L-DOPA

Subthalamotomy

Pallidotomy - reintroduction

GPI DBS

STN DBS

DBS technique, Vim DBS

Asleep DBS

Who? - Patient Selection

Parkinson’s Disease:

- disability despite optimal medical therapy: levodopa + dopamine agonist
- levodopa-responsive; persistent motor fluctuations: “off” and dyskinetic states
- contraindications: dementia, severe postural instability, atypical parkinsonism, uncontrolled psychiatric disorder
Selection Criteria

- **age**: no restriction (30s-90s)
- **prior surgery**: lesioning operations not contraindicated for DBS
- **bilateral surgery**: stimulation safer than “-otomies”
## Effectiveness of DBS

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>VIM-DBS</th>
<th>GPI-DBS</th>
<th>STN-DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>–</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Rigidity</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Levodopa dose reduction</td>
<td>±</td>
<td>±</td>
<td>+++</td>
</tr>
<tr>
<td>Electricity consumption</td>
<td>Low</td>
<td>Significant</td>
<td>Low</td>
</tr>
</tbody>
</table>

Ząbek M, Sobstyl M. *Neurol Neurochir Pol* 2006; 40: 203
WHAT?: Stimulation vs. Lesioning Therapy

**Pros:**
- Nondestructive
- Reversible
- Adjustable
- May be performed bilaterally

**Cons:**
- Requires labor intensive follow-up
- Need for battery replacement
- Potential implantable device problems (infection, lead breakage, scalp erosions)
- Expensive
What?

DBS versus Lesioning

- **Bilateral** lesioning – unacceptable risk for permanent AEs

- **Unilateral** pallidotomy produces an equivalent outcome to **unilateral** STN-DBS or unilateral Gpi-DBS
  - 30-40% reduction in UPDRS motor score
  - reduced dykinesia
  - long-lasting
When? - Surgical Treatment

Parkinson’s disease

• at time of disability: excessively slow, unpredictable “off” and dyskinesias

• usually >>3 years of symptoms;

Tremor

• when difficulties with hand function occur: eating, drinking, writing, working

• age not a primary consideration
Surgical Treatment for Movement Disorders

Where?

- Experienced Centers:
  - Need Neurosurgical and Neurological Expertise
  - Treatment is ongoing in contrast to most surgery
  - Surgical Placement
  - Stimulation Programming
HOW? - Surgical Treatment

varies significantly between institutions

- MR-guided anatomic stereotactic targeting: usually yes
- Electrophysiologic guidance – microelectrode recordings: yes vs. no
- Clinical guidance intraoperatively: yes vs. no
- Radiofrequency vs. gamma-knife for lesioning: most centers only advise RF lesioning
RESULTS – DBS Surgery

- **Tremor**: >90% receive functional improvement; return in ADLs
- **PD**: >80% enjoy increased functional “on” time; elimination of off/excessive dyskinesia; STN-DBS + meds is better than meds alone
- **Dystonia**: 30-60% have significant improvement
DBS Complications – Mayo Series

Consecutive series of >3000 procedures

• 0 mortality

• 4 symptomatic hemorrhages (0.13%)
  • 2-8% reported in the literature

• Infection rate –
  • 0% short term (90 days)
  • 4% long term (average time to infection 11 months)
  • 2-15% reported in the literature, 6% in Lozano’s series

• Hardware failure-
  • 10% overall but 2% since 2003
  • 8-26% reported in the literature

Clinical Research project by Michael Sobystl, MD – Movement Disorder fellow from Poland
• RESULTS
  • No difference in primary outcome
  • Patients with STN required lower dose of dopaminergic agents (p=0.02)
  • Visuomotor processing speed declined more after STN than Gpi DBS (p=0.03)
  • Level of depression worsened after STN and improved after Gpi DBS (p=0.02)
  • No difference in adverse effects between groups
Emerging Evidence – Unilateral DBS

Unilateral vs. bilateral STN DBS effects on working memory and motor function in Parkinson disease

T. Hershey a,b,d,e, J. Wu a, P.M. Weaver a, D.C. Perantie a, M. Karimi b, S.D. Tabbal b, J.S. Perlmutter b,c,d,e

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Commentary

Are two leads always better than one: An emerging case for unilateral subthalamic deep brain stimulation in Parkinson’s disease

Jay L. Alberts a,b,c,* Christopher J. Hass d, Jerrod L. Vitek b,e, Michael S. Okun f,g

Unilateral stimulation of the subthalamic nucleus in Parkinson disease: a double-blind 12-month evaluation study

Isabelle M. Germain, M.D., Jean-Michel Gracies, M.D., Ph.D., Donald J. Weinz, Ph.D., Winona Tse, M.D., William C. Koller, M.D., and C. Warren Olanow, M.D.

Departments of Neurosurgery and Neurology, The Mount Sinai School of Medicine, New York, New York, USA and The New York Presbyterian Hospital, New York, New York, USA

Unilateral deep brain stimulation of the subthalamic nucleus for Parkinson disease

Jerzy L. Słowski, Ph.D., John D. Puttek, Ph.D., Ryan J. Uitti, M.D.,* John A. Lucas, Ph.D., Margaret F. Turk, M.D., Bruce A. Kall, M.S., M.D., and Robert E. Whalen, M.D.

Unilateral subthalamic nucleus stimulation has a measurable ipsilateral effect on rigidity and bradykinesia in parkinson disease

Samer D. Tabbal a, Mwiza Ushe a,e, Jonathan W. Mink e,f,d, Fredy J. Revilla h, Angie R. Wernle a, Minna Hong a,d, Movarid Karimi a, Joel S. Perlmutter b,c,d,e

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Available online 14 February 2008

Unilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) in patients with medically intractable parkinson disease (PD) who were unilaterally operated and underwent a 12-month follow-up was performed using a randomized, double-blind, sham-controlled, crossover study. PD patients with median UPDRS PART III score of 31, the motor component (79%), and a disease duration of 9.5 years with a Disease Rating Scale (dyskinesia score of 15%) showed improvement by approximately 15% or less. A post hoc analysis found that bilateral stimulation lead to a greater improvement than unilateral stimulation. These findings are consistent with previous reports of bilateral STN DBS benefit so that a bilateral STN DBS may be considered in patients with PD who are not candidates for bilateral DBS.
Emerging Evidence – Unilateral DBS

**Pros**

- Unilateral DBS provides 15-20% improvement in ipsilateral motor function on UPDRS III ratings
- Decrease in the daily dose of levodopa ranging between 15-36% after unilateral DBS
- Marked improvement in bimanual functional dexterity
- Unilateral stimulation provides improvement in gait parameters (speed, cadence, step length)
- Reduced surgical time
  - More patient cooperation/less confusion
- Improved safety in older patients

**Cons**

- Majority of PD patients have bilateral disease – may need second operation
- Extrapolated data from lesioning literature suggests synergistic effect on appendicular symptoms with bilateral stimulation
- Variable control with medication impacting both hemispheres
What?
Type of Surgery

- Lesioning
  - Radiofrequency
  - Gamma-knife
  - MR focused Ultrasound
- Deep Brain Stimulation
- Combinations
Current Surgery Scenario

Initial & Staged

- **Unilateral pallidotomy or Gpi-DBS or STN-DBS +/- VIM-DBS**
- **Tandem DBS** (unilateral Gpi&fornix DBS)
- **Bilateral DBS**

- **3 months or more later ...**
  - Contralateral Gpi-DBS or STN-DBS (or VIM-DBS)
Surgery for Parkinson’s

**SUMMARY**

- Multiple Options
- Unilateral lesion and unilateral DBS are bioequivalent
- Unilateral vs. Bilateral equally used
- STN & GPi equivalent (?) Gpi becoming favored

Jacksonville Mayo Clinic
Stereotactic Surgery for Parkinson’s Disease

CHALLENGES:

• Unresponsive symptomatic targets:
  • **postural instability** resistant to medical therapy
  • dementia
Surgical Treatment Trial for Parkinson’s disease

“Tandem DBS“:

• **Gpi** or **STN** → motor
• **Hypothalamus/fornix** → cognitive improvement
Future? …

Surgical Treatment to address:

• cognitive decline:
  • Executive dysfunction
  • Attention deficits
  • “Sub-cortical dementia”
  • Fluctuations/variability

• REM sleep behavior disorder

• → Dementia with Lewy Bodies
Looking Forward: Future Surgical Treatments for PD

- “Smart” Electrodes - DBS
- Directional Electrodes – DBS
- +/- Spinal Cord Stimulation
- Gene Therapy
Treatment of Parkinsonism

Summary:

• No cure today – participate in research

• Most treatable neurodegenerative disease
  
  • Education

  • Focus on Quality of Life

  • Medications

• Surgery
Questions?  uitti.ryan@mayo.edu