EMERGING TREATMENTS FOR PARKINSON’S DISEASE

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Complications of Levodopa Therapy

- Motor fluctuations
  - Delayed “ON” response
  - Dose failure
  - End-of-dose wearing-Off
  - Unpredictable “OFF” time
  - Freezing episodes
Complications of Levodopa Therapy

• Dyskinesias (involuntary “wiggly” movements)
  • Peak dose (30-60 minutes after a dose)
  • Biphasic (occur twice in a dosing interval)
  • Continuous (30 minutes after dose and lasting until next dose)
Response to Levodopa and Progression of Parkinson’s Disease

Early PD
- Long duration motor response
- Low incidence of dyskinesias

Moderate PD
- Shorter duration motor response
- Increased incidence of dyskinesias

Advanced PD
- Short duration motor response
- “On” time consistently associated with dyskinesias

Surgical Treatments for Parkinson’s Disease

- Ablative procedures
  - thalamotomy
  - pallidotomy

- Electrical stimulation procedures

- Deep brain stimulation
  - subthalamic nucleus (STN)
  - globus pallidus internus (Gpi)
Deep Brain Stimulation (DBS)

- High frequency, pulsatile electrical stimulation
- Stimulating electrodes are stereotactically placed into the target region
- It can be activated and deactivated with an external device
- The patient has the option of adjusting stimulation parameters
Surgical Candidate Selection

- Disease duration > 5 years
- Confirmed diagnosis of Parkinson’s Disease
- Complications of optimal medical therapy
- Continued good response to levodopa
- Absence of dementia
- Absence of severe depression
- Ability to tolerate the surgical procedure
Contraindications to Surgical Treatment

- Blood clotting disorders
- Blood malignancies
- Poorly controlled hypertension
- Overall compromised health status

- Cardiac pacemaker is not a contraindication for DBS surgery
FDA Approved DBS Target Structures
Which is the Optimal Surgical Target?

- Both STN and GPi placement have shown efficacy in treating symptoms of Parkinson’s.
- STN placement allows for more reduction of medications than GPi.
- STN placement is more widely performed and is more effective.
Subthalamic Nucleus DBS

- All cardinal features of PD improve
- “OFF” time improved 60%
- “ON” time improved 10%
- Increased “ON” time
- Reduced dyskinesias
- Reduced medication requirements <50%
Subthalamic Nucleus DBS

- Bilateral electrode placement is necessary
- Unilateral placement may be considered in select cases
- Indicated for control of rigidity, bradykinesia and dyskinesias
Globus Pallidus Internus (GPI) DBS

- All cardinal features of PD improve
- Reduced dyskinesia
- Moderate improvement in “OFF” signs
- No medication reduction
Globus Pallidus Internus (GPI) DBS

- Similar benefits to the STN DBS
- Significant improvement in dyskinesia
- Moderate improvement in bradykinesia and rigidity
- Bilateral DBS may be better tolerated than bilateral pallidotomy
# Effects of STN, GPi DBS

<table>
<thead>
<tr>
<th></th>
<th>STN</th>
<th>GPi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Rigidity</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Gait</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Dyskinesias</td>
<td>-/+</td>
<td>+++</td>
</tr>
<tr>
<td>L-dopa dose decrease</td>
<td>+++</td>
<td>+/-0</td>
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### Symptom Change After Turning on Stimulation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sec.</th>
<th>Min.</th>
<th>Days</th>
<th>Wk/Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigidity</td>
<td>+++</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Tremor</td>
<td>+++</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Bradykinesia/akinesia</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>S</td>
</tr>
<tr>
<td>Off-phase dystonias</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>S</td>
</tr>
<tr>
<td>Diphasic dyskinesias</td>
<td>(-)</td>
<td>-, (+)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>On-period dyskinesia</td>
<td>(-)</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
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+ = improvement;  - = worsening  s = stable
Timing of Surgery

- Are parkinsonian symptoms adequately treated?
- Is the antiparkinsonian regimen optimized?
- Is DBS neuroprotective?
DBS Surgery Timing

- DBS has been an established treatment for advanced Parkinson’s disease
- A recent large clinical trial published in 2013 (EARLYSTIM trial) supports surgery earlier in the disease process
- Study participants with levodopa-induced complications had better quality of life and less motor disability than those that received medical therapy only
# Post-Operative Medication Requirements

<table>
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<tr>
<th>Procedure</th>
<th>Requirements</th>
</tr>
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<tbody>
<tr>
<td>GPI DBS</td>
<td>Usually no change. Occasional patients with severe preoperative dyskinesias may tolerate higher levodopa doses.</td>
</tr>
<tr>
<td>STN DBS</td>
<td>Reduction in drug dosage by 50% (range 0-100%)</td>
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</table>
DBS-Related Adverse Effects

- Intracerebral hemorrhage
- Seizures
- Infection
- Breaking of connection lead
- Eyelid opening apraxia
- Executive dysfunction
- Confusion
- Weight gain
MRI Safety Guidelines (Medtronic)

- MRI field strength: 1.5 Tesla
- MRI type: horizontal bore, not open-sided systems
- DBS leads and extensions should be intact and functional (needs to be checked prior to scan)

MRI scan parameters:
- Radio frequency (RF) Specific absorption rate (SAR)
- Gradient dB/dt parameters
DBS: Mechanisms of Action

- DBS mechanism continues to be a matter of debate
- Inhibition of stimulated region
- Excitation of stimulated region
- Combination of inhibition/excitation
- Modification of brain networks
Imaging of DBS Effects
Summary

- DBS is effective in treating moderate to advanced PD
- Recent studies demonstrate that DBS is effective also early in the disease process
- Stimulation parameter adjustment can be useful to control symptoms effectively.
- DBS effects reflect changes at a systems level rather than an effect on a single brain structure
Regenerative Therapies in Parkinson’s Disease

- Infusion of trophic factors (GDNF)
- Infusion of genes involved in dopamine processing
- Stem cells
  - Fetal cell derived
  - Induced pluripotent stem cells (iPSC)
  - Adipose tissue-derived stem cells
Intracerebral Trophic factor infusion

- Glial-derived neurotrophic factor (GDNF) has been shown to be effective in animal models of Parkinson’s disease.

- Its use in double-blind, placebo controlled human clinical trials however has been associated with significant side effects and lack of efficacy.
Gene Therapy Trials

• Recently published phase ½ open label clinical trial in 15 individuals with advanced Parkinson’s disease in which genes involved in the processing of dopamine were infused into the putamen, a brain structure severely affected in Parkinson’s disease (Prosavin)
• The treatment appears safe and well tolerated
• Clinical improvement over a 12 month period was observed in all participants
Vaccines in Parkinson’s Disease

- Clinical trial of a vaccine against alpha-synuclein (AFF011)
- It assesses the safety and tolerability of two doses of a vaccine against alpha-synuclein
- Trial is ongoing in Europe
Stem cell therapies

- Stem cells derived from fetal tissue have been tried with limited success and conflicting effects.
- iPSC are still in the development phase and have not been yet tried in humans.
- Stem cells derived from adipose (fat) tissue are being developed to be infused by intravenous injection.
- It is doubtful however, that these cells can reach the nerve cells in the brain, as the brain is protected from the circulation by the “blood-brain barrier”
Information on Clinical Trials

• www.clinicaltrials.gov