How should I treat my Parkinson’s disease?

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Parkinson’s disease therapy

• Medical management

• Surgical management
Medications used in the treatment of Parkinson’s disease

<table>
<thead>
<tr>
<th><strong>Dopamine agonists</strong></th>
<th><strong>MAO-B inhibitors</strong></th>
<th><strong>COMT inhibitors</strong></th>
<th><strong>Anticholinergics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole (mirapex) Immediate and extended release</td>
<td>Selegiline</td>
<td>Entacapone (comtan)</td>
<td>Trihexyphenidyl (artane)</td>
</tr>
<tr>
<td>Ropinirole (requip) Immediate and extended release</td>
<td>Rasagiline (Azilect)</td>
<td>Tolcapone (tasmar)</td>
<td>Benztropine (Cogentin)</td>
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<tr>
<td>Rotigotine (Neupro) patch</td>
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<tr>
<td>Apomorphine (Apokyn) Subcutaneous injection</td>
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Levodopa

Levodopa remains the cornerstone of medical therapy for the last 50 years

Currently available formulations:

- carbidopa/levodopa Immediate Release (IR)
  - 10/100; 25/100; 25/250
- carbidopa/levodopa Controlled release (CR)
  - 50/200; 25/100
- carbidopa/levodopa Orally disintegrating (ODT) (Parcopa)
- carbidopa/levodopa with entacapone (Stalevo)
  - 50, 75, 100, 125, 150, 200
Non-motor manifestations of Parkinson’s disease

• Blood pressure fluctuations
  – Fludrocortisone
  – Midodrine
  – Droxidopa (recent FDA approval)

• Urinary incontinence
  – Oxybutynin (ditropan)
  – Solifenacin (vesicare)
  – Trospium (sanctura)
  – Darifenacin (enablex)
  – Tolterodine (Detrol LA)

• Sleep disturbances
  – Clonazepam
  – Long acting dopaminergic medications

• Smell loss
  – no treatment available
Non-motor manifestations of Parkinson’s disease

Anxiety and depression
• sertraline (zoloft)
• venlafaxine (effexor)
• escitalopram (lexapro)
• citalopram (celexa)

Cognitive abnormalities
• Rivastigmine (exelon)
• Memantine (namenda)
Behavioral manifestations

Hallucinations
Paranoid thinking
Agitation

• Clozapine (Clozaril)
  – Effective but requires weekly blood tests
• Quetiapine (Seroquel)
Medications **to be avoided** in Parkinson’s disease

Haloperidol (Haldol)
Risperidone (Risperidal)
Olanzapine (Zyprexa)
Metoclopramide (Reglan)
Compazine
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

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)
Surgical Treatments for Parkinson’s Disease

- Ablative procedures
  - thalamotomy
  - pallidotomy

- Electrical stimulation procedures (DBS)
  - globus pallidus internus
  - subthalamic nucleus
Deep Brain Stimulation (DBS)

- High frequency electrical stimulation
- Stimulating electrodes are stereotactically placed into target nucleus
- Can be activated and deactivated with an external magnet
- The patient has the option of adjusting stimulation parameters.
- Exact mechanism is unknown, but higher stimulation frequencies mimic ablation
DBS targets
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 depression
- Ability to tolerate surgical procedure
Contraindications to surgical treatment

Blood clotting disorders
Poorly controlled hypertension
Overall compromised health status
• pacemaker
Subthalamic nucleus DBS

- All cardinal features of PD noted to improve
- “Off” time improved 60%
- “On” time improved 10%
- Increased “on” time
- Reduced dyskinesias
- Reduced medication requirements
Subthalamic nucleus DBS

- Bilateral electrode placement is necessary
- Unilateral placement may be considered in select cases
- Indicated for control of rigidity, bradykinesia and dyskinesias
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
Timing of Surgery

• Are parkinsonian symptoms adequately treated?
• Is antiparkinsonian regimen optimized?
• Is DBS neuroprotective?
Effects of STN DBS

<table>
<thead>
<tr>
<th>STN</th>
<th>Tremor</th>
<th>+++</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bradykinesia</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Rigidity</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Gait</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Dyskinesias</td>
<td>- /+</td>
</tr>
<tr>
<td></td>
<td>Medication reduction</td>
<td>+++</td>
</tr>
</tbody>
</table>
## 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>
</tbody>
</table>

+ = improvement; -, worsening s, stable
MRI safety guidelines

- 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)
DBS-related Adverse Effects

Intracerebral hemorrhage
Seizures
Infection
Breaking of connection lead
Eyelid opening apraxia
Executive dysfunction
Confusion
Weight gain
DBS: how does it work?

• DBS mechanism continues to be a matter of debate
• Inhibition of the subthalamic nucleus
• Excitation of the subthalamic nucleus
• Combination of inhibition/excitation
• Modification of brain networks
Imaging of DBS effects

Kringelbach et al. Nat Rev Neurosci 2007
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.
Experimental therapies

• Gene therapy trials
  – Recently published clinical trial in 15 individuals with advanced Parkinson’s disease of gene therapy with genes involved in the processing of dopamine (Prosavin)
  – Treatment appears safe and well tolerated
  – Clinical improvement over a 12 month period was observed in all participants
Additional treatment options

- Continuous levodopa gel infusion in the gut (Duodopa)
- Currently in use in Europe
- Requires placement of a catheter in the duodenum
- Not enough information to compare its effectiveness with DBS therapy
Summary

• Parkinson’s disease treatment is multifaceted and complex.
• Frequent monitoring and adjustment of treatment is necessary
• Treatment is individualized as the disease has a varied presentation and course.