Parkinson’s disease: Current and Future treatments

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Summary

- Dopaminergic drugs
- Deep brain stimulation surgery
- Non-motor symptoms
- Future directions
Clinical and pathological

Motor symptoms

- Tremor
- Rigidity
- Bradykinesia
- Shuffling gait
- Loss of facial expression
Subtypes of PD

Tremor dominant
• Tremor predominant
• Less stiffness
• Balance often good
• Less cognitive dysfunction

Postural instability gait dominant (PIDG)
• More gait difficult
• More stiffness
• More balance trouble
• More cognitive symptoms
Dopaminergic medicines

• Mild (amantadine, selegilene, rasagiline, anticholinergics)

• Dopamine agonists
  – Ropinirole
  – Pramipexole
  – Rotigotine

• Carbidopa/levodopa (sinemet)
Motor fluctuations

- 50% of patients by 5-10 years levodopa treatment
- Wearing OFF
- Peak dose dyskinesia
- Often improved by medicine adjustments
Motor Fluctuations
Deep brain stimulation surgery

- Very effective in correct patients
- Treats motor fluctuations
- Not a cure
Motor fluctuations

Without DBS Therapy

With DBS Therapy

Dyskinesias

“On” time without dyskinesias

“Off” time

Time (daily)
Who is a candidate for DBS?

- Motor fluctuations with good response to levodopa *
  - or
- Medicine resistant disabling tremor
- >5 years disease duration
Severe early symptoms or rapid progression may not be PD

**Dementia with lewy bodies**
- dementia in first few years

**Progressive supranuclear palsy**
- frequent falls in first few years

**Multiple system atrophy**
- significant autonomic dysfunction early
Who is a poor candidate?

- Atypical forms of parkinsonism
- Unstable psychiatric disease
- Dementia
- Major medical co-morbidities
- Unrealistic expectations
DBS targets - Basal Ganglia Nuclei

- Tremor
- Dystonia
- Parkinson’s
Electrical changes in PD

- **Normal**

- **PD**

Diagram showing the brain structures:
- Cortex cerebri
- PUT
- GPe
- GPI
- STN
- SN
- THA

Abbreviations:
- GPe: Globus pallidus externus
- GPI: Globus pallidus internus
- PUT: Putamen
- SN: Substantia nigra
- STN: Nucleus subthalamicus
- THA: Thalamus
- Mesencephalon
# DBS - What to expect

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Improves</th>
<th>Generally does not Improve</th>
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<tbody>
<tr>
<td>Tremor</td>
<td>X</td>
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<tr>
<td>Bradykinesia</td>
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<td>Rigidity</td>
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<tr>
<td>Dyskinesia</td>
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<tr>
<td>Motor fluctuations</td>
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<tr>
<td>Hypophonic speech</td>
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<tr>
<td>Dysphagia</td>
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<td>Freezing of gait, esp in ON state</td>
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<tr>
<td>Significant Balance problems</td>
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<tr>
<td>Cognitive dysfunction</td>
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<tr>
<td>Dysautonomia</td>
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The Parkinson’s Complex

- Pons
- Basal Forebrain
- Medulla
- Amygdala
- Hypothalamus
- Olfactory Bulb
- Spinal Cord (intermediolateral column)
- Peripheral Autonomic Nervous System (heart, intestinal track, bladder)
- Neocortex
- Olfactory Cortex
- Temporal Cortex

Langston, Ann Neurol. 2006
Non-motor symptoms include

- Depression - anxiety
- Insomnia - daytime sleepiness
- Bowel and bladder dysfunction
- Cognitive and behavior changes
20 year prodrome followed by 20 year course
Spread of pathology accounts for disease progression

Future directions

• Better ways to deliver medicines (pump)

• Slow/stop disease progression (neurotrophic factors, gene therapy)

• Prevent disease (vaccines)
Conclusions

• Dopaminergic medicines are effective but complicated by motor fluctuations

• Some patients with severe motor fluctuations will benefit from DBS

• Need for disease modifying treatments to prevent disability due to disease progression