Parkinson’s disease (PD): An update for medical and surgical treatment

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Physiology of Basal Ganglia

- Basal ganglia as a closed circuit of motor loop
- SNc (substantia nigra): direct output to putamen or indirect output to STN (subthalamus) and then to Globus (GPi)
Physiology of SN

• Rest: baseline tonic discharge with continuous dopamine stimulation (CDS)

• Planned Action: phasic discharges and bursting dopamine release
Pathology

- Degeneration of pigmented neuron, esp over the compact part of SN over mid-brain
- Pathological hallmark: appearance of Lewy body in substantia nigra

*Movement Disorder Society: teaching slide*
Pathogenesis of clinical features

• In physiology, tonic and continuous stimulation from SN to striatum

• In early disease, remaining SN as a buffer, maintaining basic dopamine over synapse, combining plasma levo-dopa providing nearly physiological stimulation

• In advanced disease, residual SN providing inadequate tonic stimulation to striatum and dependent on plasma L-dopa, causing motor complication

Obes et al. 2000
Motor features

• Bradykinesia with one of the other three features: 1) rigidity, 2) resting tremor, 3) postural instability

• Soft signs: 1) mask face, 2) a decrease of the associative movement, 3) monotonic and hypovolemic speech, 4) micrographia

Jankovic et al Parkinson’s disease and movement disorders 2002:4th ed
Non-Motor Symptoms of PD

Neuropsychiatric symptoms
- Depression, anxiety, panic attacks, hallucinations, psychosis, cognitive impairment

Sleep disorders
- REM sleep behaviour disorder (RBD), excessive daytime somnolence, sleep apnoea, restless legs syndrome (RLS) and periodic limb movements

Autonomic symptoms
- Bladder function, sweating, orthostatic hypotension, impotence

Digestive system symptoms
- Swallowing difficulties and constipation

Sensory Symptoms
- Pain and olfactory dysfunction
- Visual disturbances

Other symptoms
- Fatigue, gait and balance disturbances

<table>
<thead>
<tr>
<th>Differential diagnosis of parkinsonian syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Idiopathic Parkinson’s disease</td>
</tr>
<tr>
<td>- Monogenetically inherited forms of Parkinson’s disease</td>
</tr>
<tr>
<td>- Symptomatic parkinsonism</td>
</tr>
<tr>
<td>- Drug-induced</td>
</tr>
<tr>
<td>- Toxic</td>
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<tr>
<td>- Inflammatory</td>
</tr>
<tr>
<td>- Pseudoparkinsonism</td>
</tr>
<tr>
<td>- Vascular</td>
</tr>
<tr>
<td>- Normal pressure hydrocephalus</td>
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<tr>
<td>- Atypical parkinsonism</td>
</tr>
<tr>
<td>- Multiple system atrophy (MSA-P, MSA-C)</td>
</tr>
<tr>
<td>- Progressive supranuclear palsy, Steele-Richardson-Olszewski syndrome (PSP)</td>
</tr>
<tr>
<td>- Corticobasal degeneration (CBD)</td>
</tr>
<tr>
<td>- Dementia with Lewy bodies (DLB)</td>
</tr>
</tbody>
</table>
Atypical Parkinsonism

- Early manifestation of additional clinical features: falls, dysarthria, dysphagia, myoclonus, dystonia, autonomic dysfunction and dementia
- Poor levodopa response
- Dopaminergic drugs with potentially worsening atypical symptoms
- More rapid progression, for examples, falls and wheelchair-bound in less than 3 years
Fig. 1  Time course of parkinsonian syndrome. Atypical parkinsonism un masks within the first 4 years.
Imaging

• $^{18}$F-dopa PET scan: imaging of the striatum uptake of $^{18}$F-dopa
• Pre-synaptic and post-synaptic striatal imaging
• MRI: for atypical PD

Dopamine transporter (DAT)

D2 receptor
DAT scan available at our hospital

Tc99m TRODAT-1 Brain SPECT
11/26/2007

Dept. Nuclear Medicine, Veterans General Hospital, Tai-Chung
Wang Bao-Jhu 000778152E
Symptomatic Treatment of Motor Symptoms in PD

1. L-DOPA
2. Tyrosine
3. MAO-A
4. MAO-B
5. COMT
6. DDC
7. 3-OMD
8. Benzerazide
9. Carbidopa
10. Entacapone
11. Tolcapone
12. Selegiline
13. Rasagiline
14. Dopa
15. Dopamine transporter
16. Astrocyte
17. Blood-brain barrier
18. Postsynaptic terminal in the striatum
19. Synaptic vesicle
20. Presynaptic terminal from the substantia nigra

Motor Symptoms in PD
Symptomatic Treatment

**Levodopa**
- Decarboxylase inhibitors: benserazide, carbidopa
- Cathechol-\(O\)-methyltransferase (COMT) inhibitors: entacapone, tolcapone

**Dopamine agonists**
- Non-ergots: pramipexole, ropinirole, rotigotine, apomorphine
- Ergots: bromocriptine, cabergoline, lisuride, pergolide

**Monoamine oxidase (MAO)-B inhibitors**
- selegiline, rasagiline

**Non-dopaminergic drugs**
- Anticholinergics: benzhexol, trihexyphenidyl
- Glutamate antagonist: amantadine
Treatment with L-dopa

• L-dopa: gold standard treatment for PD since the introduction in 1960’s

• Motor fluctuation occurring after long-term treatment with L-dopa

• Major motor fluctuation including, 1) wearing off, 2) inter-dose dyskinesia, 3) on-off

Jankovic et al Parkinson’s disease and movement disorders 2002:4th ed
<table>
<thead>
<tr>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most efficacious antiparkinsonian drug</td>
</tr>
<tr>
<td>Virtually all PD patients respond</td>
</tr>
<tr>
<td>Improves disability, and prolongs capacity to maintain employment and independent activities of daily living</td>
</tr>
<tr>
<td>Reduces mortality rate</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>Motor complications</td>
</tr>
<tr>
<td>Dyskinesias: choreiform movements, dystonia</td>
</tr>
<tr>
<td>Motor fluctuations</td>
</tr>
<tr>
<td>Neuropsychiatric problems: confusion, psychosis, punding</td>
</tr>
<tr>
<td>Sedation</td>
</tr>
<tr>
<td>Does not treat the so-called nondopaminergic features of PD (e.g., freezing, postural instability, autonomic dysfunction, dementia)</td>
</tr>
</tbody>
</table>

PD = Parkinson disease.
Adapted with permission from Olanow and Koller.¹⁴
Types of Motor Complications in PD

Motor fluctuations
- Wearing-off
- Delayed “on”
- No “on”
- “On/off”

Dyskinesias
- Diphasic
- Peak-dose
- “Off”-period dystonia

Parkinsonian Disorders in Clinical Practice; 2008.
Putative Pathophysiology of Motor Complications in PD

- Striatal dopaminergic denervation
- Priming of striatal dopamine receptors (esp with L-dopa, less with DAs)
- Pulsatility of drug administration and subsequent receptor stimulation

Dyskinesia occurrence:

- **Priming:** by dopamine agonists and L-dopa
- **Induction:** by L-dopa
<table>
<thead>
<tr>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiparkinsonian effects when used as monotherapy or as an adjunct to levodopa</td>
</tr>
<tr>
<td>Reduced risk of developing levodopa-related motor complications</td>
</tr>
<tr>
<td>Do not generate oxidative metabolites</td>
</tr>
<tr>
<td>Levodopa sparing effect</td>
</tr>
<tr>
<td>Potential neuroprotective benefits</td>
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</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>Dopaminergic side effects (nausea, vomiting, orthostatic hypotension)</td>
</tr>
<tr>
<td>Neuropsychiatric side effects (hallucinations, psychosis, and ICDs)</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
</tr>
<tr>
<td>Ergot-related side effects with some ergot-derived agonists (erythromelalgia, pulmonary fibrosis, cardiac valve fibrosis)</td>
</tr>
<tr>
<td>Swelling of legs and weight gain</td>
</tr>
<tr>
<td>Do not eliminate the need for levodopa</td>
</tr>
<tr>
<td>Do not treat nondopaminergic features of PD, such as freezing, postural instability, autonomic dysfunction, and dementia</td>
</tr>
</tbody>
</table>

PD = Parkinson disease; ICD = impulse control disorder.
Adapted with permission from Olanow et al.\textsuperscript{15}
Rasagiline

- Irreversible inhibitor of MAO-B
- Effective in early PD with monotherapy
- Adjunct with L-dopa for advanced PD
Tests of the neuroprotection

Diagram: Delayed-Start Design

Implying symptomatic treatment effect
MAO-B inhibitors (Rasagiline)

- Reduce “off” time about 1-1.2 hours

<table>
<thead>
<tr>
<th>Advantages</th>
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</thead>
<tbody>
<tr>
<td>Antiparkinsonian effects as monotherapy (selegiline and rasagiline)</td>
</tr>
<tr>
<td>Reduced motor fluctuations and increased “on” time as adjuncts to levodopa</td>
</tr>
<tr>
<td>Levodopa-sparing effect</td>
</tr>
<tr>
<td>Neuroprotective in laboratory models</td>
</tr>
<tr>
<td>Once-daily dosing (rasagiline and Zydus selegiline)</td>
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<tr>
<td>Well tolerated and good adverse event profile</td>
</tr>
<tr>
<td>Early start provides benefits not achieved with delayed start (rasagiline)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modest antiparkinsonian effect</td>
</tr>
<tr>
<td>Neuroprotection not established</td>
</tr>
<tr>
<td>Amphetamine and methamphetamine metabolites may cause side effects (selegiline)</td>
</tr>
<tr>
<td>Theoretical risk of “cheese effect” and “serotonin syndrome”</td>
</tr>
</tbody>
</table>

MAO-B = monoamine oxidase-B.
The Management of Parkinson’s Disease, 2001

Parkinson’s Disease

Pharmacologic Therapy

Neuroprotection (Selegiline?)

Functional impairment

No

Continue to Monitor

Yes

Dopamine Agonists

Levodopa (+/- COMT inhibitor)

Dopamine Agonist + Levodopa (+/- COMT inhibitor)

Add COMT inhibitor if not on

Motor complications See section on management of motor complication

Unacceptable control with medical therapy See section on surgical treatment
Continuous Drug Delivery (CDD)

- Physiological stimulation of striatal dopamine receptors is generally continuous and tonic
- Dopaminergic tone is lost in PD
- Pulsatile stimulation by short-acting drugs such as levodopa may contribute to motor complications
- Longer-acting dopamine agonists contribute to more continuous dopaminergic stimulation and lower the incidence of motor complications compared to levodopa

Continuous Drug Delivery and PD

- Levodopa plus catechol-\(O\)-methyltransferase (COMT) inhibitor (failed)
- **Intrajejunal administration** – levodopa
- Transdermal administration – rotigotine, lisuride (failed)
- **Subcutaneous infusion** – apomorphine
- **Extended-release preparations** – pramipexole, ropinirole (no data)

Continuous Drug Delivery Almost Abolishes Dyskinesia

Primate # 1, 2, 3, 4

PULSATILE delivery dyskinesias within 7–10 days

CONTINUOUS delivery NO dyskinesias up to 6 months

Abnormal Involuntary Movement Scale

Intermittent vs Continuous Levodopa Administration in Patients With Advanced Parkinson Disease

A Clinical and Pharmacokinetic Study

Fabrizio Stocchi, MD, PhD; Laura Vacca, MD, PhD; Stefano Ruggieri, MD; C. Warren Olanow, MD

Figure 1. Number of off hours per day (A) and the dyskinesia score based on answers to questions 32 through 34 on the Unified Parkinson's Disease Rating Scale (B) for each patient at baseline, when patients were receiving a standard oral formulation of levodopa/carbidopa, and at 6 months, when patients were treated with continuous intraintestinal infusion of levodopa methyl ester. There was improvement in both the number of off hours and in the dyskinesia scores for each patient with the levodopa infusion.
Tests of CDD theory with oral Extended Release of dopamine agonists in Advanced PD

Conclusion Efficacy

- In summary, ER providing effective treatment for the early and advanced stages of PD
- ER is as effective and well tolerated as IR
- In principle, by its ER formulation, possibly providing more continuous drug delivery than IR, but clinical benefit?
Non-motor complication with medication

- **impulse control disorders**
- Psychosis: delusion and hallucination
- **Orthostatic dizziness**
Definition: Impulse in DSM-IV

- A failure to resist an impulse, drive or temptation to perform a typical pleasurable activity (avoiding harm)
- Harmful to the person or others because of its excessive nature
PD: impulse control disorders in DSM-IV

- Pathological gambling (PG)
- Compulsive sexual behavior
- Compulsive buying
- Binge eating disorder
Other impulse control–related disorders in PD

- Dopamine dysregulation syndrome (DDS)
- Punding
DDS

• An addiction-like state marked by excessive dopaminergic medication usage beyond the dose needed to optimally control motor disability, particularly L-dopa or short acting dopamine agonists (DAs)

• Usually defined as compulsive use of dopamine replacement therapy (DRT)
Punding

• Intense fascination with meaningless movement or activities (collecting, arranging or taking apart objects)
Pathophysiology of ICD

- VTA (ventral tegmental area) with less cell loss of dopamine neuron than SN
- Involving the dopamine mesocorticolimbic pathways (reward behavior)
- Affected brain regions: ventromedial and orbitofrontal regions of pre-frontal cortex, ventral striatum (nucleus accumbens) and amygdala
Dopaminergic projection fields in the human brain, in which the caudate and putamen form the striatum.
Principle of management

- Reducing the dose of DAs
- Switching to a different DAs
- Discontinuing DAs treatment, esp with short-half life DAs
DBS (deep brain stimulation): targeting on STN and GPi

Topography of sub-thalamus:
- **Motor:** dorsolateral part
- **Mood:** medial
- **Cognition:** ventrolateral

**FIG. 2.** Main functional division of the cortico-basal ganglia connections. A, The motor loop, which involves the cortical motor areas (Areas 4 and 6 and supplementary motor area), the posterolateral putamen, posterolateral globus pallidus pars externa and pars interna, the dorsolateral subthalamic nucleus and the ventrolateral thalamus. B, The associative loop. C, The limbic loop. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
Fig. 2. Schematic diagram of basal ganglia in the normal state (A) and in Parkinson’s disease patients (B). This is a simplified version of Figure 1 showing the “standard box model” of the proposed major pathophysiological changes. The increase or decrease of the arrows in part B compared to A indicates the increases or decreases in neuronal activity in the various pathways, and the red and blue lettering and boxes represents the increase or decrease in neuronal activity within each of the nuclei. Abbreviations as in Figure 1.
Disabling motor symptoms for medical treatment

- Peak dose dyskinesia
- Wearing off
- Intractable resting tremor
Patient selection

- Presence of dopaminergic responsive symptoms, not effective for freezing and gait disturbance
- Still L-dopa response
- Good cognitive function
- No significant psychotic symptoms, for example, hallucination
<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of idiopathic PD</td>
<td>Dementia (MMSE&lt;24, MDRS≤ 130)</td>
</tr>
<tr>
<td>Disabling or troubling motor symptoms despite optimized medical treatment: <strong>Motor fluctuation</strong> <strong>Dyskinesia</strong> <strong>Tremor</strong></td>
<td>Serious surgical co-morbidities: Poor general health Coagulopathy Anticoagulation therapy Immunosupression</td>
</tr>
<tr>
<td>Robust motor response (other than tremor) to levodopa: &gt; 30% improvement of UPDRS motor part</td>
<td>Uncontrolled psychiatric illness: Anxiety and mood disorder (BDI&gt;15)</td>
</tr>
<tr>
<td><strong>H&amp;Y stage ≤ 3 in best on condition</strong></td>
<td>Pre-operative MRI: Extensive white matter change Severe brain atrophy</td>
</tr>
<tr>
<td>Clear understanding of risk and realistic expectation from surgery</td>
<td></td>
</tr>
</tbody>
</table>

*Kindly from Dr. Kuo*
Stereotactic localization of STN

- **Subthalamic nucleus; like peanut**
  - Small (5 x 7 mm)
  - Anterior Commissure (AC) and Posterior Commissure (PC)
    - 11-13 mm lateral to midline
    - 4-5 mm posterior to mid AC/PC point
    - 4-6 mm inferior to AC/PC plane
  - Combination of MRI and CT imaging to minimize error
Frame settings
Microelectrode recording for locating STN

SNr: Regular firing pattern
Macrostimulation

<table>
<thead>
<tr>
<th>Typical STN effects</th>
<th>Time course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of rigidity</td>
<td>After seconds to minutes</td>
</tr>
<tr>
<td>Improvement of akinesia</td>
<td>After seconds to hours/days</td>
</tr>
<tr>
<td>Improvement of tremor</td>
<td>After seconds to hours</td>
</tr>
<tr>
<td>Improvement of off-dystonia</td>
<td>After seconds to minutes</td>
</tr>
<tr>
<td>Dyskinesias</td>
<td>After minutes to hours</td>
</tr>
</tbody>
</table>
Fig. 5. Sketch of patient with bilateral deep brain stimulation electrodes. Reprinted with permission from Lozano (2001).
Post-op programming

- Adjusting the electric stimulation parameters
- Starting when it is more convenient for the patient and the physician (during admission or as out-patient)
- One month later in our hospital to avoid lesion effect interruption
## Clinical approved indication for DBS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>GPI</th>
<th>STN</th>
<th>Vim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Rigidity</td>
<td>++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>+++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Primary dystonia</td>
<td>+++</td>
<td>?</td>
<td>-/?</td>
</tr>
</tbody>
</table>

PPN: gait and balance?
<table>
<thead>
<tr>
<th></th>
<th><strong>GPI</strong></th>
<th><strong>STN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>Less frequent</td>
<td>More frequent (?)</td>
</tr>
<tr>
<td>Off-symptoms</td>
<td>Reduction</td>
<td>Marked reduction</td>
</tr>
<tr>
<td>Fluctuations</td>
<td>Reduction</td>
<td>Marked reduction</td>
</tr>
<tr>
<td>Dyskinesias</td>
<td>Marked reduction</td>
<td>Marked reduction</td>
</tr>
<tr>
<td>Energy consumption</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Medication</td>
<td>Unchanged</td>
<td>Reduced (40-60%)</td>
</tr>
<tr>
<td>Adjustment period</td>
<td>Short</td>
<td>Long</td>
</tr>
</tbody>
</table>
Effect of deep brain stimulation of subthalamus

- Improvement of off-medication score by 30-60%
- 40-80% reduction of L-dopa dosage
- Long term improvement of dyskinesia and motor fluctuation
- Minimal to mild improvement of on-medication score

Jankovic et al Parkinson’s disease and movement disorders 2002:4th ed
Beyond Nine Years of Continuous Subthalamic Nucleus Deep Brain Stimulation in Parkinson’s Disease

Maurizio Zibetti, MD, PhD, Aristide Merola, MD, Laura Rizzi, PhD, Valeria Ricchi, MD, Serena Angrisano, MD, Corrado Azzaro, MD, Carlo Alberto Artusi, Nichy Arduino, Alice Marchisio, Michele Lanotte, MD, Mario Rizzone, MD, and Leonardo Lopiano, MD, PhD
Department of Neuroscience, University of Torino, Torino, Italy

ABSTRACT: Deep brain stimulation of the subthalamic nucleus is an effective treatment for advanced Parkinson’s disease. The benefits of bilateral subthalamic stimulation are well documented, and some studies reported outcomes with a follow-up of 5 to 6 years; nevertheless, few data are available beyond 5 years. We report a long-term prospective evaluation of 14 consecutive parkinsonian patients, treated by bilateral subthalamic stimulation for at least 9 years. Motor symptoms, activity of daily living, and motor complications were evaluated by means of the Unified Parkinson’s Disease Rating Scale, while cognition and mood were assessed with a specific neuropsychological test battery; medication intake, stimulation parameters, comorbidity, and adverse events were also recorded. Patients were evaluated before surgery and at 1, 5, and ≥9 years after surgery. At last follow-up, deep brain stimulation significantly improved the motor score by 42% compared to baseline, whereas activities of daily living were no longer improved; there was a 39% reduction in the dosage of dopaminergic drugs and a 59% improvement of L-dopa–related motor complications. The neuropsychological assessment showed that 4 patients (29%) developed a significant cognitive decline over the follow-up period. These results indicate a persistent effect of deep brain stimulation of the subthalamic nucleus on the cardinal motor symptoms in advanced Parkinson’s disease patients in the long-term; however, a worsening of patients’ disability, mainly due to disease progression, was observed. © 2011 Movement Disorder Society

Key Words: Parkinson’s disease; deep brain stimulation; subthalamic nucleus; long-term follow-up
ADL scores
L-dopa could be reduced to 67-50% of pre-operative state

### TABLE 3. Stimulation parameters and LEDD

<table>
<thead>
<tr>
<th>Stimulation parameters</th>
<th>Baseline&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1 y&lt;sup&gt;b&lt;/sup&gt;</th>
<th>5 y&lt;sup&gt;c&lt;/sup&gt;</th>
<th>≥9 y&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltage (V)</td>
<td>n/a</td>
<td>3.2 (0.4)</td>
<td>3.4 (0.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.4 (0.3)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
<td>n/a</td>
<td>145.4 (21.4)</td>
<td>145.3 (21.4)</td>
<td>141.8 (19.7)</td>
</tr>
<tr>
<td>Impulse duration (μsec)</td>
<td>n/a</td>
<td>63.7 (11.2)</td>
<td>62.8 (7.9)</td>
<td>63.1 (8.1)</td>
</tr>
<tr>
<td>LEDD</td>
<td>955 (406)</td>
<td>412 (265)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>569 (288)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>579 (295)&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD).

<sup>a,b,c</sup>The letters a, b, and c indicate a significant difference (P < 0.05) between 2 time-points (Friedman test and Wilcoxon post hoc test). n/a, not applicable; y, years; LEDD, L-dopa equivalent daily dose.
Take home message

• No neuroprotective medication available to stop disease progression
• L-dopa is the gold standard medication; however with more motor complication
• Dopamine agonist (DAs) with rare association with motor complication, but less effective in symptomatic control
• Impulse control diseases commonly with DAs
• DBS for patients with dopaminergic responses, intractable tremor, marked wearing off and dyskinesia
Thank you for your attention

Comments and queries