

# Parkinson's disease: A Quick Update

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## ABSTRACT

Parkinson's disease is a neurodegenerative disorder characterized by motor and non-motor symptoms. Although the diagnosis still relies on the presence of motor signs, new diagnostic criteria have been proposed to incorporate recent observations in order to improve accuracy. The cornerstone of therapy remains dopamine replacement with L-Dopa. However, new therapies, with different modes of action, or administration have become available to improve management.

**KEYWORDS:** Parkinson's disease, movement disorder, extrapyramidal, tremor, deep brain stimulation

## BACKGROUND

Parkinson's disease (PD) is a neurodegenerative disease, characterized by motor and non-motor symptoms. The prevalence of the disease ranges from 100 to 200 per 100,000 people and its annual incidence is approximately 15 per 100,000. Men are more frequently affected than women and age of onset is variable, usually after age 50. Onset earlier than 40 years is observed in less than 5% of the cases. Aging increases the risk of developing the disease. Monogenetic forms are responsible for less than 10% of the cases, and the majority of cases are considered idiopathic. (1) In this paper, we will discuss the most recent published diagnostic criteria for PD as well as the most recent clinically available treatments.

## CLINICAL DESCRIPTION

The diagnosis of PD relies mostly on clinical expertise. Recently the International Movement Disorders Society published a proposed new set of criteria (2). In summary, the first step is to diagnose the presence of Parkinsonism defined by bradykinesia (slowness of movement, and decrement in amplitude or speed on continuous movement), in combination with either rest tremor, rigidity (velocity-independent resistance to passive movement), or both.

The second step in diagnosing "clinically established PD" requires the absence of absolute exclusion criteria; the presence of at least two supportive criteria; and no "red flags."

The diagnosis of clinically probable PD can be made in the absence of absolute exclusion criteria and the presence of red flags counter balanced by supportive criteria. Exclusion criteria include findings on the neurological examination suggestive of signs not seen in PD such as cerebellar, pyramidal or eye movement abnormalities. The most important red flags are rapid progression of gait and balance impairment, lack of progression of disease not attributable to treatment, and absence of any of the common non-motor features of the disease.

## IMAGING STUDIES

Imaging is not helpful in diagnosing PD and is used only for atypical cases. 123I-ioflupane SPECT (DatSCAN) is approved for distinguishing essential tremor from PD and is probably also helpful, although not approved, for distinguishing drug-induced parkinsonism from PD. DaT is normal in ET and DIP. However, DaTSCAN is also abnormal in patients with other forms of primary Parkinsonism which attack the dopaminergic cells in the basal ganglia (3) Therefore DaT, if normal, excludes the diagnosis of PD but a positive scan does not make the diagnosis.

## TREATMENT

PD treatment involves a combination of life style measures, medication and, in some cases, surgery. In the following section, we will discuss newer therapeutic interventions.

### Exercise

Exercise improves motor and non-motor symptoms, such as pain, sleep and mood. Most experts agree that exercise should be encouraged as part of the treatment (4). There are no data to suggest an optimal exercise strategy, so that common sense dictates that the regimen chosen should: (a) take into consideration safety, motor and cognitive constraints and other medical comorbidities; (b) be an activity the patient is comfortable with; (c) be one the patient will likely adhere to.

### Medication

The choice of the initial therapy of patients with PD takes into account age, employment status, presence of comorbidities, cognitive status, active psychiatric issues, and patient

preference. There are no therapies known to slow disease progression. Even though there is no consensus on the best time for therapy to be initiated, there is also no reason to withhold therapy in those with clear symptoms in order to prevent future treatment-related complications.

#### *Motor symptoms*

**1) Levodopa:** A precursor in dopamine synthesis remains the superior drug in symptom control. A new formulation of carbidopa/levodopa is available. Rytary ( Impax Laboratories, Hayward, CA, USA) is an oral, extended-release capsule that contains beads of levodopa and carbidopa with differing rates of absorption, allowing for a decreased dosing frequency. Rytary is FDA approved for both drug naive patients and those with motor complications by increasing "on" times, without worsening troublesome dyskinesias. Its side effect profile and tolerability are similar to other levodopa preparations. (5, 6) There are no long-term data on starting patients directly on Rytary compared to immediate release (IR) levodopa. The major indication to switch a patient from the IR formulation to Rytary is the presence of wearing off, especially if the patient is already receiving IR at a frequency of over 4 doses a day. The ratio for conversion is approximately 2:1 (Rytary: IR levodopa), and it can be done overnight. Since part of the formulation contains IR granules, patients should be advised to avoid taking medication with food (at least 30- minute interval). Rytary can take up to 8 weeks for the full benefit to be observed after the switch, and dose adjustments are usually required (7).

**2) Dopaminergic agonists (DA):** DA bind to post-synaptic dopamine receptors. They can be used as monotherapy in patients with early disease or as adjunctive therapy in later disease stages. The main adverse effects are nausea, vomiting, edema, hypotension, excessive daytime sleepiness and sleep attacks, impulse control disorders and hallucinations, especially in elderly patients. The most commonly used are pramipexol, ropinirole and rotigotine. Apomorphine has a different profile from other agonists with potent D1 and D2 agonist action. Apomorphine is available as an intermittent injection and in other countries as a continuous infusion. It has poor bioavailability after oral ingestion. The ideal subjects are on an optimized oral schedule, are able to both recognize their "off" state and to inject themselves (or have a caregiver to do it). Indications are the need for rescue medication (early morning "off", delayed "on", unpredictable "offs") or gastroparesis. Subcutaneous apomorphine is rapidly absorbed and peak plasma concentration is achieved in 10 to 20 minutes, with a clinical effect lasting from 45 to 60 minutes. First apomorphine injection should be monitored particularly for hypotension and nausea. Side effects include nausea, injection site reactions, postural hypotension, confusion, psychosis, impulse control disorders, and rarely hemolytic anemia and eosinophilic syndrome. (8) Nausea is so common that an antiemetic is always started before

the first dose, and is required for ongoing treatment in about half the cases.

**3) MAO-B inhibitors** increase dopamine availability by inhibition of monoamine oxidase B, which metabolizes dopamine. They can be used as monotherapy in mildly symptomatic young subjects or as adjunctive therapy. Side effects include nausea, vomiting and insomnia (selegiline). Safinamide (XADAGO), the newest agent, has dopaminergic action, by selective and reversible inhibition of MAO-B, and nondopaminergic properties due to voltage-gated sodium and N-type calcium channels inhibition, modulating glutamate release. It is indicated as adjunctive treatment in patients with PD experiencing "off" episodes, as it increases "on-time" with no increase in bothersome dyskinesias. Efficacy as monotherapy has not been established. Common adverse events (AEs) include dyskinesia, insomnia, somnolence, dizziness, headache, cataract, orthostatic hypotension, nausea and falls. (9, 10) Relative efficacy of MAO-b inhibitors is unknown. Safinamide is a reversible MAO-b inhibitor, unlike selegiline and rasagiline. Thus the effects of safinamide begin much sooner than the older drugs, and resolve much sooner if discontinued.

**4) Amantadine:** amantadine extended release capsules (GOCOVRI) is the first and only FDA-approved medicine for treatment of dyskinesia in patients with Parkinson's disease receiving levodopa therapy, with or without concomitant dopaminergic agents. It reduces both off times and well as levodopa-induced dyskinesias in PD patients with dyskinesias (11). There are no data to determine if this formulation is more effective than the generic form of the drug, which is usually given 2 or 3 times daily.

#### *Non-motor symptoms*

**1) Pimavanserin:** is a selective 5-HT<sub>2A</sub> inverse agonist with a lower affinity for 5-HT<sub>2C</sub> and sigma-1 receptors. It lacks dopaminergic, muscarinic, adrenergic, and histaminergic activity. (12) Data suggests a high benefit/risk profile with number need to treat (NNT) <10 (using a very conservative definition of improvement), number needed to harm (NNH) was ≥ 10 (although not statistically different from placebo) and the likelihood to be helped by taking the medication was consistently over 1 (13). Pimavanserin is the only drug with FDA approval for the treatment of hallucinations and delusions associated with PD psychosis. (12)

**2) Droxidopa:** is an oral norepinephrine precursor approved for the treatment of neurogenic orthostatic hypotension caused by primary autonomic failure. Studies show a good safety profile with NNT <10, NNH from 23-302. Droxidopa is 7.8 times more likely than placebo to provide clinical benefit than drug discontinuation due to an adverse event. (14) Droxidopa has been studied in patients with PD showing similar results, leading to decreased number of falls and increased standing systolic blood pressure. (15, 16)

### Device-aided treatments

Response to levodopa is a prerequisite for all therapies below as neither is helpful in patients not responsive to the drug. Patients with drug-resistant tremor may respond well to DBS, though, when L-Dopa is not helpful.

**1) Levodopa-carbidopa intestinal gel (LCIG)** is an aqueous gel containing a combination of levodopa and carbidopa (20 mg and 5 mg respectively per milliliter) delivered directly to the proximal jejunum *via* a percutaneous endoscopic gastrostomy tube with a jejunal extension connected to a portable, programmable infusion pump. By bypassing gastric emptying, levodopa is steadily absorbed producing stable plasma concentrations, thus decreasing motor complications (dyskinesia and motor fluctuations). Dose is individually titrated, and after a morning bolus a continuous infusion is administered over 16 hours, with further bolus if necessary. LCIG may be administered as monotherapy, or with adjunctive therapies. The treatment may be continued for as long as it is beneficial. Procedure/device related adverse events are reported in 76% of subjects; 17% of those are considered serious. Most frequent non-procedure/device adverse events are dyskinesias, chronic polyneuropathy (due to vitamin B deficiencies), stoma infection and weight loss. (17, 18)

**2) DBS:** The two main sites of DBS placement are the subthalamic nucleus (STN) and the globus pallidus (GPi). STN-DBS improves off-drug score compared with preoperative off-drug condition; decreases off-time during the day; improves quality of life; and allows the decrease in levodopa equivalent daily dose resulting in the reduction in levodopa-induced dyskinesia. (19) A recent analysis in the German health care system suggested that STN-DBS at earlier stages of the disease is cost effective in patients younger than 61 years when compared with the best medical treatment (20). GPi-DBS also provides improvement in motor scores associated with reductions in dyskinesias with modest or no decrease in dopaminergic therapy. Complications of DBS are either related to surgery, implanted material or by stimulation itself. Severe adverse events such as death or permanent disability are rare, and occur in less than 2% of the cases, while hardware-related adverse events are observed in 9% of the cases. Much more common are reversible adverse effects of stimulation, which may happen in up to 20% of patients. Long-term follow-up demonstrates sustained benefits of STN-DBS and GPi-DBS despite disease progression. Practitioners should be aware that DBS does not slow disease progression and should be considered another symptomatic therapy. It is considered a stand-of-care treatment, covered by all insurers.

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### Disclosures

None

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