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An update on Pathophysiology, Epidemiology, Diagnosis and Management Part 7: Medical Treatment of Early and Advanced Parkinson's Disease: Use of Dopamine Agonist

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ABSTRACT

Dopamine agonists are useful first-line medications that may cause less dyskinesia than levodopa/dopa-decarboxylase inhibitors. They are accessible in a once-daily form. Long-term data indicate that there is no statistically significant difference in outcomes between patients initiated on levodopa/dopa-decarboxylase inhibitors and those initiated on dopamine agonists (6). As time passes, it is becoming more common to utilize a mix of these medications. The drugs available to manage Parkinson's disease include the following: 1-Levodopa & Carbidopa/Levodopa 2- Agonists of Dopamine Receptors Inhibitors of Catechol-O-Methyltransferase (Tolcapone and Entacapone) 4-MAO 5-Anticholinergic 6-Puatative. In this review we present the latest on the use of Dopamine-receptors Agonists.

Key words: Medical Treatment of Early and Advanced Parkinson's Disease, Use of Dopamine Agonist

Dopamine agonists

Dopamine agonists stimulate the postsynaptic dopamine D1–3 receptors in the striatum directly, without requiring further metabolism within dopaminergic neurons. Dopamine agonists are not as efficient as levodopa at reversing motor symptoms but are associated with a decreased risk of dyskinesia; they may be taken alone or in combination with levodopa in the early stages of the disease. Similar to levodopa, the adverse effects include leg oedema, increased impulse control difficulties, and excessive daytime sleepiness. Ropinirole and pramipexole are taken orally and come in immediate and extended release forms. Rotigotine is delivered once daily via transdermal patch. Apomorphine, which has a brief duration of action, can be given subcutaneously as an injection for acute OFF episodes or as a continuous infusion to minimize motor fluctuations in advanced Parkinson's disease (1). Other formulations of apomorphine are also being explored, including inhaled (VR040) (2) and sublingual (APL-130277) (3) forms.

Numerous dopamine agonists have been developed with variable degrees of affinity for various dopamine receptors. In the United States, historical and current DAs include the following:

- **Bromocriptine (Parlodel®)**
- **Pergolide (Permax®)**
- **Pramipexole (Mirapex®, Mirapex ER**
- **Ropinirole (Requip®, Requip XL®)**
- **Rotigotine (Neupro® patch)**
- **Apomorphine (Apokyn® injection)**

These dopamine agonists exist in three forms including oral, transdermal and injection (Table 1).

Table 1. Dopamine Agonists for the Treatment of Parkinson's Disease

Medication	Available Doses	Initial Dosing	Target Maintenance Dose
Apomorphine HCl (Apokyn injection)	0.02-0.06 mL	0.02 mL during "off" periods	3-6 mg three times per day
Rotigotine transdermal system (Neupro)	2 mg every 24 hours 4 mg every 24 hours 6 mg every 24 hours	One 2-mg patch per day	4-6 mg every 24 hours
Bromocriptine	2.5mg 5mg	1.25 mg q12h initially may increase dose by 2.5 mg/day q2-4Weeks until optimal therapeutic response achieved	Up to maximum of 15 mg/day
Pramipexole (Mirapex)	0.125 mg 0.25 mg 0.5 mg 1 mg 1.5 mg	0.125 mg three times per day	1.5-4.5 mg/day
Ropinirole (Requip)	0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	0.25 mg twice daily	5 mg twice daily

Oral Agents

Three oral dopamine-receptor agonists are available for the treatment of PD: an older agent, bromocriptine (Parlodel, Novartis), and two newer, more selective compounds, ropinirole (Requip, GlaxoSmithKline) and pramipexole (Mirapex, Pfizer). Another agent, pergolide (Permax, Valeant; Par, Teva), was removed from the market in 2007.

Bromocriptine (Parlodel®) and Pergolide (Permax®) were created in the 1970s and were both produced from the ergot plant (fungus). When it was established that pergolide can induce faulty heart valves in a significant minority of users, the FDA judged that the danger outweighed the benefit and pulled it from the market in the United States for treatment in PD in March 2007. Bromocriptine, the first DA to achieve commercial success, is still accessible for various medicinal purposes.

Bromocriptine, an ergot derivative, is a strong agonist of dopamine D2 receptors and a partial antagonist of D1 receptors. It is available in 2.5 mg tablet and 5 mg capsule dosage forms. It has been used in combination with carbidopa/levodopa (Sinemet) to alleviate symptoms and mitigate the deleterious effects of long-term levodopa medication. Bromocriptine is still accessible, however it is less efficient than other dopamine agonists in the early stages of Parkinson's disease and is ineffective at reducing motor fluctuations generated by levodopa in late-stage PD.

Ropinirole and pramipexole. These two agents have selective activity at D2 class sites (specifically at the D2 and D3 receptor proteins) and little or no activity at D1 class sites.
The FDA approved pramipexole (Mirapex®) and ropinirole (Requip®) in 1997 and are currently the most commonly used DAs. Neither of these dopamine agonists is ergot-derived, and neither has been linked to heart valve problems. They are both effective in the early stages of Parkinson's disease (PD) and serve a critical role in reducing motor fluctuations, despite the fact that they have a higher rate of adverse effects than levodopa.

These medications, like bromocriptine, are readily absorbed when taken orally and have similar therapeutic effects. They, like levodopa, can alleviate PD's clinical symptoms. Dopamine agonists have a longer duration of action (8 to 24 hours) than levodopa (6 to 8 hours), making them particularly effective in treating on/off phenomena. All three medications may also cause hallucinations or confusion, similar to those seen with levodopa, and may exacerbate orthostatic hypotension (5).

While these agents' therapeutic effects are mediated by their actions on postsynaptic dopamine receptors, they can also activate presynaptic autoreceptors found on dopamine terminals, the majority of which are of the D2 class. Pramipexole and ropinirole may reduce endogenous dopamine production and release it by stimulating presynaptic receptors, thereby alleviating oxidative stress.

To achieve clinically significant maintenance doses of ropinirole and pramipexole, several weeks are required (5). While these agents generally cause less GI disturbance than bromocriptine, they can cause nausea and somnolence. The somnolence may be severe, and sudden attacks of irresistible sleepiness have been reported to result in motor vehicle accidents (6).

The introduction of pramipexole and ropinirole significantly altered the clinical use of dopamine agonists in Parkinson's disease. Due to their tolerability, these selective agonists are increasingly used as first-line therapy for Parkinson's disease rather than as adjuncts to levodopa. This change was prompted by two factors: (1) dopamine agonists have a longer duration of action and are therefore less likely than levodopa to cause on/off effects and dyskinesias; and (2) levodopa may contribute to oxidative stress, thereby accelerating the loss of dopaminergic neurons.

In two large controlled clinical trials comparing levodopa to pramipexole or ropinirole as an initial therapy for Parkinson's disease, it was observed that patients receiving these agonists had a lower rate of motor fluctuation (7,8). However, in both studies, this benefit was associated with an increased rate of adverse events, most notably somnolence and hallucinations (7,8). Numerous specialists now recommend dopamine agonists as first-line treatment in patients with early Parkinson's disease and in younger patients to alleviate motor fluctuations and dyskinesia. Levodopa should be used first in older patients, who may be more susceptible to the dopamine agonists' adverse cognitive effects.

Adverse effects (ropinirole). In early PD trials, the most frequently observed adverse events were nausea, dizziness, somnolence, headache, vomiting, syncope, fatigue, dyspepsia, viral infection, constipation, pain, increased sweating, asthenia, dependent or leg edema, orthostatic symptoms, abdominal pain, pharyngitis, confusion, hallucinations, urinary tract infections, and abnormal viscosity (9).

In advanced PD trials, the most frequently observed adverse events in more than 5% of patients were dyskinesias, nausea, dizziness, aggravated parkinsonism, somnolence, headache, insomnia, injury, hallucinations, falls, abdominal pain, upper respiratory infection, confusion, increased sweating, vomiting, viral infection, an elevated drug level, arthralgia, tremor, and an elevated drug level (9).

Adverse effects (pramipexole): In placebo-controlled trials of early Parkinson's disease, the most frequently observed adverse events were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations. The most frequently reported adverse events that resulted in treatment discontinuation were nervous system-related (hallucinations, dizziness, somnolence, extrapyramidal syndrome, headache, and confusion) and gastrointestinal symptoms (e.g., nausea) (10).

Postural hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, and urinary frequency were the most frequently observed adverse events in patients with advanced PD who received pramipexole and concomitant levodopa (10).

Transdermal Patch

Rotigotine (Neupro®), the most recently approved dopamine agonist, was approved by the FDA in 2007 for use as a once-daily transdermal (skin) patch that is changed every 24 hours (11). It is just as effective as the oral DAs pramipexole and ropinirole, according to clinical research. Neupro is the first once-daily dopamine agonist patch that is non-ergolinic and provides stable, continuous drug delivery 24 hours a day (12). The therapeutic benefits are age, sex, and race insensitive. The patch is available in three strengths: 2 mg every 24 hours, 4 mg every 24 hours, and 6 mg every 24 hours.

Adverse effects. In clinical trials, nausea, application-site reactions, somnolence, dizziness, headache, vomiting, and insomnia were frequently reported adverse events. Additionally, peripheral edema, fluid retention, hallucinations, symptomatic orthostatic hypotension, weight gain, elevated heart rate, elevated blood pressure, and syncope were reported as adverse effects (13). Despite the agent's benefits, the manufacturer informed health providers and patients that the patch would be unavailable in pharmacies in the United States by the end of April 2008. The recall was initiated in response to reports of possible decreased clinical performance due to the formation of rotigotine crystals in the patches, resulting in decreased drug absorption through the skin and the possibility of decreased efficacy. Neupro® was revamped and reintroduced in 2012, with daily doses of 1, 2, 3, 4, 6, and 8 mg.

An Injectable Medication

Apomorphine (Apokyn®) was first tried to treat Parkinson's disease in 1950, but it was accompanied with a number of adverse effects, most notably nausea and vomiting. It was reintroduced in the 1990s in a more palatable formulation and has found a special niche as a self-injectable "rescue" medication for persons with advanced Parkinson's disease and severe "off" episodes (14). Its short half-life (about 40 minutes) and chemical structure make oral administration problematic, if not impossible. In individuals experiencing severe "off" reactions, in which crippling bradykinesia and rigidity impair function, a self-injected dose of Apokyn® can reverse the "off" period within minutes and bridge the gap of one to two hours between levodopa doses. In the early phase of treatment, an anti-nausea medicine (often trimethobenzamide or Tigan®) is required prior to injection but can be withdrawn after the first week or two. Apokyn® can be administered as a rescue agent up to five times per day. Each person's response to Apokyn® is unique.

Apomorphine HCl (Mylan/Bertek) is a subcutaneously injected dopaminergic agonist with a rapid onset of action. It has a high affinity for D4 receptors, a moderate affinity for D2, D3, and D5 receptors, and a low affinity for adrenergic 1D, 2B, and 2C receptors. It is approved as a rescue therapy for the acute intermittent treatment of "off" episodes in patients receiving dopaminergic therapy who have a fluctuating response. Apomorphine can be injected into the muscles if they become frozen and the patient is unable to rise from a chair or perform routine tasks. As-needed injections may allow for dose reductions of other anti-PD medications. This may help to reduce the risk of experiencing adverse effects such as twitching and other uncontrollable movements.

Adverse consequences. Apart from the other potential side effects associated with dopamine receptor agonists, apomorphine is extremely emetic and can result in QT prolongation, injection site reactions, hallucinations, dyskinesia, and abnormal behavior (15). Trimethobenzamide (Tigan, King), an oral antinausea and antiemetic, is recommended to be started three days before the initial apomorphine dose and continued for at least the first two months of therapy. Apomorphine should not be used in conjunction with serotonin (5-HT3) antagonist antiemetic medications due to reports of profound hypotension and loss of consciousness when ondansetron (Zofran, GlaxoSmithKline) and apomorphine are combined (16).

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