Parkinson's Disease and Its Management

Part 2: Introduction to the Pharmacotherapy of Parkinson's Disease, With a Focus on the Use of Dopaminergic Agents

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INTRODUCTION

Part 1 of this five-part series, published in the August 2015 issue of *P&T*, addressed the pathophysiology, diagnosis, and clinical presentation of Parkinson's disease (PD)—a chronic, progressive neurodegenerative disorder characterized by both motor and nonmotor features.[1–3] The key motor symptoms of PD are bradykinesia, resting tremor, and rigidity,[4–10] whereas nonmotor symptoms can include cognitive changes, sleep disorders, and depression.[11] Current PD therapies do not slow disease progression or provide a neuroprotective effect.[12,13] The main goal of treatment, therefore, is to improve patients' quality of life.[14,15]

In this installment, we review the pharmacotherapy of PD, with a focus on dopaminergic agents.

PHARMACOTHERAPY OF PARKINSON'S DISEASE

The use of medications in the management of PD can provide significant symptomatic improvement and allow improved mobility, functionality, and performance in the activities of daily living.[16–18] Current treatments focus on restoring dopaminergic activity through a variety of mechanisms. Although the short-term clinical effectiveness of pharmacotherapy in patients with PD is clear, treatment benefits wane as the disease progresses, and the use of medications in these patients becomes quite challenging.[16–18] The pharmacological management of PD requires careful implementation and monitoring to maintain a balance between clinical efficacy and the minimization of adverse events (AEs). Optimal control of the motor and nonmotor symptoms of PD with pharmacotherapy requires frequent dose adjustments and the appropriate use of combination therapies. Dopaminergic agents are considered to have beneficial effects on motor symptoms—referred to as improvements in "on time" or reduced "off time."[19–21]

Since PD medications can cause significant complications, such as dyskinesias, managing these adverse effects adds to the clinical challenge. The available pharmacotherapies increase levels of dopamine by preventing its breakdown or by activating dopaminergic receptors. An additional mechanism involves countering the imbalance that results from dopaminergic loss (e.g., a relative increase in acetylcholine function) through the use of anticholinergic medications.[21,22] Although most clinicians initiate pharmacotherapy when motor symptoms are evident, the question of which dopaminergic therapy should be used is debatable and will be discussed below. Regardless of the initial treatment choice, monotherapy is usually recommended, and as the disease progresses, various combinations and individual treatment plans will be required.[21–27] Pharmacotherapy is beneficial in all stages of the disease, but it is most useful during the first five or six years after the patient's diagnosis.[24–26] The complexity of PD and its pharmacotherapy requires knowledge of the medications used and consideration of multiple factors, such as the patient's age, the stage of the disease, comorbidities, safety, tolerability, and cost.[23–29]

DOPAMINERGIC AGENTS (LEVODOPA)

Pharmacology

Levodopa, a prodrug of dopamine, was introduced into clinical practice in the 1960s and has remained the mainstay in managing the motor symptoms of PD.[26,30] Although levodopa has no disease-modifying effects, its use has had a significant impact on mortality rates among patients with PD.[31,32] The neurotransmitter dopamine is predominantly ionized (protonated) at physiological pH and is unable to cross the blood–brain barrier (BBB). However, its prodrug, levodopa, when given exogenously, is able to cross the BBB via the large neutral amino acid transporter (LNAAT) and is then metabolized by L-aromatic amino acid decarboxylase (dopa decarboxylase) to dopamine. In addition, levodopa is extensively metabolized to dopamine in the gut, with approximately 30% of the dose reaching the systemic circulation. To counter this extensive peripheral metabolism, levodopa is administered in combination with carbidopa, a peripheral dopa decarboxylase inhibitor, which does not cross the BBB. The addition of carbidopa to levodopa results in an approximate tripling of levodopa's bioavailability, thereby reducing the dosage requirement, improving tolerability (e.g., fewer peripheral dopaminergic adverse effects), and allowing greater passage of levodopa across the BBB, enhancing striatal availability.[32–34] The marketed carbidopa/levodopa products include various formulations and dosing ratios (Table 1). Approximately 75 mg to 100 mg of daily carbidopa is required in these combinations for decarboxylase enzymatic inhibition to occur. These amounts are attainable with the available dosage forms.[26,32,33]

A concern regarding the concurrent use of dopa decarboxylase inhibitors and levodopa is the shift in levodopa metabolism via the catechol-O-methyltransferase (COMT) system, resulting in the formation of 3-O-methyldopa (3-OMD). This metabolite, an LNAA, competes with levodopa for passage from plasma to the brain, although the clinical significance of this competition is unclear.[35,36]

Once in the brain, levodopa is converted by dopa decarbox-

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Table 1 Carbidopa/Levodopa Products[22–24,26,30–34,40–48,50]

Product *Manufacturer*	Dosing[a]	Mechanism/ Pharmacokinetics	Potential Adverse Events	Monitoring Parameters
Sinemet (carbidopa/ levodopa tablet)[b] *Merck* Parcopa ODT (carbidopa/ levodopa ODT)[c] *Mylan*	10/100 mg 25/100 mg 25/250 mg Starting dosage: usually 25/100 mg TID; weekly titration based on response	• Levodopa = dopamine prodrug; crosses BBB; converted to dopamine by dopa decarboxylase. • Adding carbidopa blocks peripheral conversion of levodopa to dopamine; more levodopa crosses into CNS, with fewer peripheral adverse events and less levodopa needed. • Absorption: proximal small intestine (food may delay); saturable; competes with LNAAs • Metabolism: GI tract, kidney, liver • Excretion: 70% in urine; half-life: approximately 1 hour	• CNS: confusion, sedation, vivid dreams, dizziness, hallucinations, psychosis, depression • GI: nausea, vomiting, changes in bowel habits • Other: orthostasis, leg edema, dyskinesia, dystonia, hemolytic anemia, leukopenia	• Blood pressure • Pulse • Changes in • mental status • Clinical response Note: May turn urine dark or brown/black.
Sinemet CR (carbidopa/ levodopa sustained-release tablet)[b] *Merck*	25/100 mg 50/200 mg Starting dosage: 50/200 mg BID			
Rytary ER (carbidopa/ levodopa ER tablet) *Impax Pharmaceuticals*	23.75/95 mg 36.25/145 mg 48.75/195 mg 61.25/245 mg Dosing is TID and may be increased to five times daily in advanced disease			
Duopa (carbidopa/ levodopa enteral suspension) *AbbVie*	4.63/20 mg/1 mL (100-mL cassettes); suspension delivered via infusion pump in small intestine[e] (PEG-J tube)			
Stalevo (carbidopa/ levodopa/entacapone)[b,d] *Novartis* Combines carbidopa/ levodopa with COMTI	12.5/50/200 mg 18.75/75/200 mg 25/100/200 mg 31.25/125/200 mg 37.5/150/200 mg 50/200/200 mg			

[a] A daily carbidopa dose of 75–100 mg is required to inhibit peripheral conversion of levodopa to dopamine. Dose reductions of 10% to 30% may be needed when carbidopa/levodopa is used with other agents, e.g., COMTIs/Stalevo, dopamine agonists, monamine oxidase B inhibitors.
[b] Generic available.
[c] Parcopa ODT contains phenylalanine; avoid in patients with phenylketonuria.
[d] Do not split tablets.
[e] Administered into the jejunum via a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) with an infusion pump.

BBB = blood–brain barrier; BID = twice daily; CNS = central nervous system; COMTI = catechol-O-methyltransferase inhibitor; GI = gastrointestinal; CR = controlled release; ER = extended release; LNAA = large neutral amino acid; ODT = orally disintegrating tablets; TID = three times daily.

ylase to dopamine in the substantia nigra pars compacta and is stored in presynaptic neurons. When needed, this dopamine is released into the synaptic cleft, where it binds to postsynaptic dopamine (D_1 and D_2) receptors. Levodopa's elimination half-life, even when given in combination with a dopa decarboxylase inhibitor, is short, ranging from 0.7 to 1.5 hours. In spite of this brief half-life, however, the duration of response to levodopa is relatively prolonged in patients with early PD. This may be due partly to the availability of endogenous dopamine in early stages of the disease. However, as the disease progresses, levodopa's clinical benefit diminishes. The reduced duration of response has been attributed to pharmacodynamic changes and the loss of endogenous dopamine, as well as to the drug's short half-life, all of which may contribute to dosing challenges.[32–34]

Although the use of carbidopa/levodopa combinations is effective for controlling motor symptoms in the early stages of PD, the therapeutic effectiveness of treatment is hampered by complex and variable pharmacokinetic and pharmacodynamic factors as the disease progresses. As a result, motor responses fluctuate; treatment responses are unpredictable; and complications, including dyskinesias, may occur in up to 80% of patients.[32–34]

As an LNAA, levodopa has properties that influence its kinetic profile, absorption, and response. Both intestinal and BBB absorption of levodopa occur via a saturable active transport system in the proximal duodenum and across the BBB, respectively. The significance of this process is that levodopa competes with other LNAAs, such as dietary proteins, for transport, which may affect its absorption.[33] To avoid this interaction, high-protein meals should be kept separate from levodopa administration and the daily dietary protein allowance should be reduced to approximately 0.8 g/kg of body weight.[34] The competition of levodopa with other LNAAs may have greater significance in patients with later-stage or advanced PD.[30–34]

Another factor that influences the bioavailability of levodopa

involves gastric emptying to the drug's primary site of absorption, the proximal small intestine. The delayed gastric emptying seen in patients with PD may be due to multiple factors, including impaired motility.[37] Reduced gastric emptying may affect the absorption of levodopa by slowing its movement into the proximal small intestine and by increasing its presystemic decarboxylation. This potential reduction in drug absorption may influence a patient's clinical response to treatment and contribute to response fluctuations, which are often seen in patients receiving long-term levodopa therapy. Food may delay gastric emptying, while some medications, such as antacids, may promote gastric emptying by increasing gastric pH.[33,37]

Although the pharmacokinetic profile of levodopa undergoes minimal changes during disease progression, aging is associated with increases in the drug's bioavailability, area under the curve (AUC), maximum plasma concentration (C_{max}), and plasma elimination half-life.[38,39] It is not clear how age influences these changes, but reduced systemic clearance is most likely involved. Pharmacodynamics may also play a role, with elderly patients being more sensitive to a given dose compared with younger patients (those under 65 years of age).[40] These age-related changes may be significant in some elderly patients and should be considered when dosing patients older than 65 years of age.[38,39]

In patients with PD, carbidopa/levodopa products (i.e., Sinemet [Merck], Parcopa ODT [Mylan], generics) have recommended starting dosages of 25 mg/100 mg three times daily, a 1:4 ratio of carbidopa to levodopa (Table 1), but individual dose titration may be necessary according to the therapeutic response.[40,41] Patients whose motor symptoms are well controlled but who experience significant gastrointestinal (GI) AEs, such as nausea and vomiting, may be managed with the addition of separately dosed carbidopa (Lodosyn [Aton Pharma], generics).[42]

Controlled-release (CR) carbidopa/levodopa products (i.e., Sinemet CR [Merck], generics) have been available for decades,[43] although the advantage of these treatments over the regular-release products is debatable. The CR combinations were developed to enhance the duration of levodopa's clinical activity, but they are poorly and inconsistently absorbed and require a 10% to 30% dose increase when replacing regular-release formulations.[44] In January 2015, the Food and Drug Administration (FDA) approved an extended-release capsule formulation of carbidopa/levodopa (Rytary ER, Impax Pharmaceuticals)[45] and an enteral suspension product (Duopa, AbbVie).[46] Rytary ER will offer an additional advantage in patients requiring improved "on time," usually in more advanced disease. Duopa uses a portable infusion pump for direct delivery of carbidopa/levodopa into the small intestine via a surgically placed tube. Duopa will have a role in patients with advanced PD disease.

The maximum recommended daily doses of levodopa and carbidopa in the labeling for Sinemet are 2,000 mg and 200 mg, respectively.[40] Dose adjustments are recommended in patients with renal disease (i.e., creatinine clearance of less than 50 mL/min). In dialysis patients, clinicians should administer a dose post-session, with no supplemental doses. Caution is advised in patients with hepatic disease.[34,39,40]

Adverse Events

Commonly reported AEs associated with the use of carbidopa/levodopa products include nausea, vomiting, postural hypotension, sedation, vivid dreams, dizziness, dark urine, unusual sexual urges, and confusion. These effects are often problematic, especially in elderly patients, who comprise most of the PD population. PD patients are at risk for falls because of the motor features of the disease and because of levodopa-induced orthostatic hypotension, which may occur in up to 20% of patients.[40,47] Withdrawal from or abrupt discontinuation of treatment with carbidopa/levodopa can also be problematic because of the sudden loss of dopaminergic effects, which may result in the return of symptoms or cause parkinsonism–hyperpyrexia syndrome. The latter disorder is characterized by rigidity, akinesia, decreased consciousness, acute renal failure, coagulation disorders, fever, and other complications, and requires prompt clinical attention. Treatment consists of body cooling, fluid replacement, and the resumption of dopaminergic replacement.[28,29] It is important to educate patients about the risks of abruptly discontinuing carbidopa/levodopa therapy in order to avoid this serious AE.[29]

Dyskinesias and dystonias are also associated with carbidopa/levodopa therapy. These AEs occur in most PD patients within three to five years after the initiation of treatment.[40,47,48]

Drug Interactions

Numerous drug interactions are possible during carbidopa/levodopa therapy, and appropriate clinical monitoring and dose adjustments may be necessary—especially in patients with multiple comorbidities. For example, antihypertensive agents may potentiate the postural hypotension associated with levodopa.[26,49,50] Further, dopamine antagonists, including various antiemetics, phenothiazines, and antipsychotics (both first and second generation), should be avoided in PD patients receiving carbidopa/levodopa. If antipsychotic use is necessary, quetiapine or clozapine are viable treatment options. Metoclopramide may interact by increasing the bioavailability of levodopa through its influence on gastric emptying, in addition to its dopamine-antagonist properties.[40] Although selective monoamine oxidase inhibitors (MAOIs) can be used concurrently with carbidopa/levodopa, these agents should be administered with caution, and regular monitoring of blood pressure is recommended. Nonselective MAOIs (phenelzine and tranylcypromine) and other drugs with MAOI properties, such as linezolid, should be avoided because of their additive catecholamine influence and potential for hypertensive crisis.[49] Caution is also recommended with the use of drugs from the tricyclic antidepressant class, while concomitant use of inhaled halogenated general anesthetics should be avoided altogether because these agents can enhance the arrhythmogenic effect of dopaminergic agents.[40,49,51]

Contraindications and Precautions

Contraindications to carbidopa/levodopa therapy include documented hypersensitivity to the drug, narrow-angle glaucoma, and a history of melanoma, although there is no proven correlation with the latter. Other conditions in which caution is recommended include hepatic and renal impairment, psychiatric illness, severe pulmonary disease, and cardiovascular, hematologic, and endocrine disorders.[26,40,47,50,52]

Role in Therapy and Clinical Updates

As noted earlier, carbidopa/levodopa is the most effective therapy for the motor symptoms of PD. The combination is approved as monotherapy and is often the first-line treatment when patients present with motor symptoms, especially in late-onset disease. The first-line use of carbidopa/levodopa in patients with PD is supported by the observation that elderly individuals (i.e., those older than 65 years of age) have shown improved tolerability with levodopa compared with other dopaminergic drugs.[27,32,52] The carbidopa/levodopa combination effectively ameliorates bradykinesia and rigidity, and it is variably effective for tremor. Improvements in motor features are greater with carbidopa/levodopa compared with dopamine agonists.[52,53]

In PD patients, a favorable response to carbidopa/levodopa usually equates to an improvement in motor symptoms, often referred to as increased "on time" or reduced "off time."[19,52,53] The results of the PD MED Collaborative Group Trial, published online in June 2014, support the use of carbidopa/levodopa as initial therapy for the motor symptoms of PD, especially in patients who are older (more than 60 years of age) at disease onset. This trial compared outcomes for up to seven years in patients managed with initial MAO type-B inhibitors, dopamine agonists, or carbidopa/levodopa. The results showed a small but persistent benefit from initial therapy with carbidopa/levodopa; similar efficacy was reported with initial MAO-B inhibitor therapy or dopamine agonist therapy. Treatment options for PD patients younger than 60 years of age are not clear and require further study. The PD MED study demonstrated that, in older-onset PD, the available early treatments result in similar outcomes, although carbidopa/levodopa may provide slightly improved mobility scores.[27]

Although treatment with carbidopa/levodopa can significantly improve quality of life in patients with PD, the disease is progressive, and the beneficial effects of therapy will diminish over time. The initial response to carbidopa/levodopa is usually positive because of the presence of a sufficient number of intact dopaminergic systems.[54,55] In patients with early PD, these systems provide enough endogenous dopamine to act as a "buffer" for exogenous carbidopa/levodopa. However, as the disease progresses, the loss of dopaminergic neurons, receptor changes, modifications in circuitry, and desensitization of receptors result in inconsistent and unpredictable responses.[54,56] The development of motor fluctuations—including wearing off, delayed onset, dyskinesias, and dystonias—will occur in most PD patients at some point in their disease.[54,56] These changes will require carbidopa/levodopa dose adjustments and the use of adjunctive therapies to control fluctuations in the patient's motor response.[23,27,57–59]

While carbidopa/levodopa is effective for symptomatic management, the treatment cannot prevent or delay the clinical progression of PD. An important clinical diagnostic "pearl" is that the lack of a response to levodopa in a suspected PD patient may suggest an alternative diagnosis. A somewhat controversial issue that confronts the practitioner is the choice of first-line therapy in a newly diagnosed PD patient with motor features of the disease. Clinical studies have shown that patients started on carbidopa/levodopa may develop motor complications and/or dyskinesias sooner than patients who have been started on levodopa-sparing therapies.[48,58–61] As mentioned previously, the PD MED Collaborative Group Trial reported a small advantage for carbidopa/levodopa in terms of mobility scores compared with levodopa-sparing therapies (i.e., dopamine agonists or MAO-B inhibitors).[27]

In addition to its use as monotherapy, carbidopa/levodopa may be administered in combination with dopamine agonists and other adjunctive agents, including COMT inhibitors, MAO-B inhibitors, and amantadine. In patients initially started on carbidopa/levodopa, adjunctive treatments may be added prior to maximization of the carbidopa/levodopa dose. Patients with advanced PD will usually require various combinations to manage the progression of motor disability. Patients initially started on amantadine or an MAO-B inhibitor for mild-to-moderate symptoms usually require the addition of carbidopa/levodopa or a dopamine agonist as the disease progresses.[27,62–65] Patients who were initially treated with carbidopa/levodopa may benefit from a COMT inhibitor or an MAO-B inhibitor. In general, the addition of agents that extend the duration of action of levodopa, especially the COMT inhibitors, usually requires a reduction in the levodopa dose of approximately 20% to 30% to avoid additive AEs and complications.[35,36] Patients who initially receive dopamine agonist monotherapy will eventually require carbidopa/levodopa as an adjunctive treatment.[65]

In summary, although various combinations of PD medications can be used with carbidopa/levodopa and can help improve motor responses, they all require dose adjustments in the event of AEs or complications.[66,67]

DOPAMINE RECEPTOR AGONISTS

Overview

An alternative first-line pharmacotherapeutic option for PD patients with motor symptoms is the use of dopamine receptor agonists (Table 2). These drugs may be administered as monotherapy in patients with early disease or in combination with carbidopa/levodopa in those with advanced disease.[23,27] Dopamine receptor agonists compensate for hypodopaminergic function through their direct activation of central post-synaptic dopamine receptors in the caudate-putamen region, thereby enhancing dopaminergic effects.[68,69]

Pharmacology

The dopamine agonists are classified as ergot or nonergot types, with the differences primarily related to receptor affinities. The ergot derivatives include bromocriptine (Parlodel, Validus Pharmaceuticals)[70] and cabergoline (Dostinex, Pharmacia & Upjohn)[71]—compounds rarely used for the treatment of PD, although they are beneficial in patients with acromegaly, hyperprolactinemia, neuroleptic malignant syndrome, and other conditions. Bromocriptine is approved for the treatment of patients with PD, but cabergoline is not.[70,71] The ergot class of dopamine agonists are non–receptor-specific (nonselective) and interact with both inhibitory D_2 and excitatory D_1 receptors, as well as with serotonin and adrenergic receptors. Dopamine agonists in the ergot class, however, have the potential to cause fibrosis as a result of their high affinity for serotonin ($5\text{-}HT_{2B}$) receptors, which are expressed in heart valves and other organ systems.[68,69,72,73]

Table 2 Dopamine Receptor Agonist Products[3,20,22–24,27,50,64,68–89,92–103]

Product *Manufacturer*	Dosing	Mechanism/ Pharmacokinetics	Potential Adverse Events	Monitoring Parameters
Parlodel (bromocriptine mesylate)* *Validus Pharmaceuticals* Approved for PD, but rarely used. Other indications: hyperprolactinemic states, acromegaly	• Strengths: 2.5-mg tablet; 5-mg capsule • Initial dose in PD: one-half of 2.5-mg tablet (1.25 mg) BID with meals • Dosage may be increased every 14 to 28 days by 2.5 mg/day with meals • Safety has not been demonstrated in dosages exceeding 100 mg/day	• Hepatic metabolism; CYP3A4 substrate • Excretion: 82% in feces; 6% in urine • 90% to 96% bound to serum albumin • Half-life: 5–15 hours	• Pulmonary: pleural thickening (fibrosis) after long-term treatment • GI: nausea, vomiting, abdominal discomfort • CNS: abnormal involuntary movements, ataxia, hallucinations, confusion, "on-off" phenomenon, dizziness, syncope, drowsiness, insomnia, depression • Other: visual disturbance, hypotension, shortness of breath, constipation, vertigo, asthenia	• Pulmonary function • Blood pressure • Daytime alertness • Weight • Heart rate
Requip, Requip XL (ropinirole)* *GlaxoSmithKline* Approved for PD and restless legs syndrome (IR) or for idiopathic PD (XL)	• IR strengths: 0.25-mg, 0.5-mg, 1-mg, 2-mg, 3-mg, 4-mg, 5-mg tablets • XL strengths: 2-mg, 4-mg, 8-mg, 12-mg tablets • IR starting dose: 0.25 mg TID; titrate weekly to maximum of 24 mg/day • XL starting dose: 2 mg QD for 1–2 weeks; titrate weekly to maximum of 24 mg/day	• Hepatic metabolism; CYP1A2 substrate (inactive metabolites) • Excretion: > 88% of radiolabeled dose in urine (IR); < 10% in urine as unchanged drug (XL) • Half-life: about 6 hours (IR/XL)	• GI: nausea, vomiting, dyspepsia, abdominal pain, constipation • CNS: dizziness, somnolence, headache, syncope, confusion, hallucinations, impulse control disorders, sleep attacks • Other: fatigue, asthenia, dependent/leg edema, viral infection, pain, increased sweating, orthostatic symptoms, pharyngitis, abnormal vision, UTIs	• Blood pressure • Daytime alertness • Weight • Heart rate
Mirapex, Mirapex ER (pramipexole)* *Boehringer Ingelheim* Approved for PD and restless legs syndrome (IR) or for PD (ER). Overnight switch from IR to ER successful in 80% of patients	• IR strengths: 0.125-mg, 0.25-mg, 0.5-mg, 0.75-mg, 1-mg, 1.5-mg tablets • ER strengths: 0.375-mg, 0.75-mg, 1.5-mg, 2.25-mg, 3.0-mg, 3.75-mg, 4.5-mg tablets • IR starting dose: 0.125 mg TID; titrate weekly to 0.25–1.5 mg TID; BID dosing not approved • ER starting dose: 0.375 mg QD; titrate weekly to maximum of 4.5 mg QD	• Negligible metabolism (< 10%) • Excretion: 90% in urine as unchanged drug (via renal tubules) • Half-life: about 8 hours in young, healthy subjects; about 12 hours in elderly subjects (IR) • Dose adjustment required in renal impairment	• GI: nausea, abdominal pain/discomfort, constipation • CNS: dizziness, somnolence, headache, hallucinations, impulse control disorders, sleep attacks • Other: dyskinesia, orthostatic hypotension, xerostomia, peripheral edema, muscle spasms	• Blood pressure • Daytime alertness • Weight • Heart rate

The nonergot class of dopamine agonists consists of ropinirole (Requip and Requip XL, GlaxoSmithKline)[74,75] and pramipexole (Mirapex and Mirapex ER, Boehringer Ingelheim),[76,77] along with the rotigotine transdermal patch (Neupro, UCB, Inc.).[78] These products have demonstrated clinical efficacy as well as improved safety and tolerability in patients with PD as a result of their selective D_2 and D_3 receptor profiles. The low affinity of these drugs for 5-HT_{2B} receptors is clinically important and contributes to their positive safety profile compared with that of the ergot agents. The clinically advantageous pharmacokinetic properties of the nonergot oral formulations include good GI absorption and effective passage across the BBB. Since no conversion to active drug is required for these agents to become active, they have a longer half-life compared with that of levodopa and, therefore, an extended duration of action.[68,72]

The dopamine agonists have a variety of dosing regimens

Table 2 Dopamine Receptor Agonist Products[3,20,22–24,27,50,64,68–89,92–103] (continued)

Product *Manufacturer*	Dosing	Mechanism/ Pharmacokinetics	Potential Adverse Events	Monitoring Parameters
Neupro (rotigotine) *UCB, Inc.* Transdermal patch; indicated for PD and restless legs syndrome	• Strengths: 1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, 8 mg/24 hours • Initial dose: 2 mg/24 hours (early PD) or 4 mg/24 hours (advanced PD); may be increased at weekly intervals to maximum of 6 mg/24 hours or 8 mg/24 hours, respectively • Apply QD to healthy skin; do not use same site more than once every 2 weeks	• Extensive metabolism • Excretion: 71% in urine (inactive conjugates); about 23% in feces • Initial half-life: 3 hours • Terminal half-life: 5 to 7 hours after patch removal	• GI: nausea, vomiting • CNS: somnolence, dizziness • Other: application-site reactions, dyskinesia, anorexia, hyperhidrosis, visual disturbance, peripheral edema • Avoid in patients with sulfa allergy • Remove patch prior to MRI (burn risk): patch contains aluminum	• Blood pressure • Daytime alertness • Weight • Heart rate • Skin reactions
Apokyn (apomorphine) *US MedWorlds* Subcutaneous injection into abdominal wall, upper arm, or upper leg (rotate sites); indicated for hypomobility, "off" episodes associated with PD	• Strength: 30 mg/3 mL (10 mg/mL) glass cartridge • Initial dose: 0.2 mL (2 mg) under medical supervision; can be titrated to maximum dose of 0.6 mL • Reduce starting dose in patients with renal impairment • Treatment with concomitant antiemetic (e.g., trimethobenzamide) is recommended, starting 3 days before first Apokyn dose and continuing for at least first 2 months of therapy	• Extensive first-pass metabolism • Terminal half-life: about 40 min	• GI: nausea, vomiting • CNS: drowsiness, somnolence, dizziness, postural hypotension, hallucinations, confusion • Other: dyskinesia, rhinorrhea, edema/ swelling of extremities • Avoid use with serotonin blockers (may cause profound hypotension)	• Blood pressure (supine/standing) • Drowsiness

* Generic version available

BID = twice daily; CNS = central nervous system; CYP = cytochrome P450; ER = extended release; GI = gastrointestinal; IR = immediate release; MRI = magnetic resonance imaging; PD = Parkinson's disease; PO = by mouth; QD = once daily; SC = subcutaneous; TID = three times daily; UTI = urinary tract infection.

(Table 2). As PD progresses, dose adjustments require careful monitoring with individualized approaches. Doses should be titrated slowly to minimize AEs and to maximize the clinical response.[20,68] The extended-release (ER) and transdermal formulations offer convenience and improved compliance.[79,80] In addition, the ER products may avoid the pulsatile receptor stimulation associated with dyskinesias, although this potential benefit requires further research.[80,81]

The rotigotine transdermal patch is an ER dosing system that releases active drug for 24 hours after application to intact skin. This product has a role in PD patients with dysphagia or in other situations where oral therapy is restricted.[79,80,82] The absolute bioavailability of rotigotine is approximately 37%, which may vary among application sites, although the differences do not appear to affect the treatment's clinical efficacy. When the patch is applied to the trunk, rotigotine is detected in plasma after approximately three hours, with maximum levels reached at 15 to 27 hours. Daily application of the patch provides predictable release and absorption of rotigotine, with steady-state concentrations reached within one to two days.[80]

Rotigotine has a large volume of distribution (84 L/kg), along with 92% binding to plasma proteins. The drug is extensively metabolized via conjugation and N-dealkylation by CYP 450 isozymes and other enzyme systems. The multiple pathways involved in the metabolism of rotigotine make it unlikely that the inhibition of any one pathway would alter drug concentrations. Metabolites are primarily eliminated in the urine, with an elimination half-life of three to seven hours. Although dosage adjustments of rotigotine appear to be necessary in PD patients with renal impairment, it is not known whether such adjustments are necessary in patients with hepatic disease.[80] The safety and tolerability of subcutaneous rotigotine appear to be similar to that of the oral nonergot dopamine agonists.[83,84] When dispensing the rotigotine transdermal patch, pharmacists should educate patients regarding the patch's proper use. This includes the application process, application-site location and rotation, and contraindications, such as magnetic resonance imaging (MRI) procedures.[84,85]

Apomorphine (Apokyn, US WorldMeds) is another nonergot dopamine agonist. It is administered as a subcutaneous injec-

tion for the treatment of acute, intermittent hypomobility in PD patients, including use in rescue situations (e.g., severe freezing episodes or related immobility crises).[86] As PD progresses, nonresponders to other medications (about 10% of patients) may be candidates for the intermittent administration of apomorphine. The beneficial effects of this agent are limited, however, by its short duration of action, by extensive first-pass metabolism (which precludes oral formulations), and by potential tolerance. Clinical studies of apomorphine infusions have been fraught with technical difficulties and cutaneous AEs, which limit its clinical use.[87–89] If the drug is used for the acute management of PD, test doses and careful monitoring are recommended. In addition, the severe nausea associated with apomorphine requires pretreatment with an antiemetic, typically trimethobenzamide. It is important that apomorphine not be administered in the presence of a 5-HT_3 receptor antagonist because of the potential for profound hypotension and loss of consciousness.[80,90,91]

Adverse Events

Dopamine agonists are associated with a number of potential AEs that may be particularly troublesome in elderly patients. Overall, the adverse drug reaction (ADR) profile of the dopamine agonists is similar to that of carbidopa/levodopa and is related to their dopaminergic effects, although clinical data suggest that carbidopa/levodopa is better tolerated. The ergot derivatives, such as bromocriptine, are rarely used in PD patients because of their vasoconstrictive properties and are associated with serious fibrotic complications. Retroperitoneal fibrosis, Raynaud's phenomenon, pulmonary infiltrates, pleural thickening and effusions, cardiac valvulopathy, pericarditis, myocardial infarction, arrhythmias, heart failure, and hypertension have been reported. Although these complications usually resolve when the ergot derivatives are discontinued, they can cause permanent damage. Fibrotic complications are usually not associated with the nonergot dopamine agonists, but close monitoring is still necessary.[92–94]

AEs commonly associated with dopamine agonists include somnolence, sleep attacks, dizziness, vivid dreams, nausea, constipation, edema of the lower extremities, chest pain, sweating, flushing, pallor, dyskinesia, rhinorrhea, and orthostatic hypotension. The latter disorder is concerning because of its association with falls and fractures, especially in elderly patients. Sudden sleep attacks are another AE that may affect patients during waking activities (e.g., during driving), resulting in potentially harmful consequences. Sleep attacks have been reported primarily with the newer dopamine agonists, such as ropinirole, pramipexole, and rotigotine.[50,68,69,72]

Psychiatric AEs reported with the dopamine agonists include confusion, cognitive changes, hallucinations, delusions, and impulse-control disorders (ICDs). The challenge in identifying these effects is that they need to be differentiated from the nonmotor symptoms of PD. The management of severe delusions and hallucinations may require the use of second-generation antipsychotic agents.[50,68,69,72]

As with sleep attacks, ICDs are more common with the newer dopamine agonists (nonergot agents). These disorders may be related to a phenomenon known as dopamine dysregulation syndrome. The association of ICDs with dopamine agonists in the treatment of PD is supported by reports of this AE in patients receiving dopamine agonists for other indications, such as restless legs syndrome.[95–97] ICDs include hypersexuality, binge eating, excessive gambling or shopping, and pathological collecting. Risk factors for ICDs include higher drug doses, single marital status, and being younger than 65 years of age.[98–102] Reduced doses are recommended in high-risk patients.[76] ICDs are burdensome for both the family and caregivers, especially when they must deal with embarrassing and socially unacceptable behaviors. Although ICDs have been reported with carbidopa/levodopa, they are more common in patients taking dopamine agonists.[97] The mechanism of ICDs is thought to be related to dopaminergic transmission along the mesocorticolimbic pathway.[98,99]

The management of ICDs related to dopamine agonist therapy usually involves reducing the dose of the drug or discontinuing it, which may require the adjustment of adjunctive therapies as well. In addition, nonpharmacological interventions for patients with ICDs include caregiver support and education, behavioral therapy, and self-help groups. The use of adjunctive pharmacotherapy in severe cases may include antidepressants for compulsive behaviors and antipsychotic agents, such as quetiapine or clozapine, for behavioral problems.[100–102]

The rotigotine transdermal patch has a systemic ADR profile similar to that of the oral dopamine agonists, and clinical trials in patients with both early and advanced PD have reported good tolerability.[83] Application-site reactions have been observed, however, with approximately 3% described as severe (e.g., anaphylactic). These reactions may be related to the patch's sodium metabisulfite component; therefore, use of the patch should be avoided in patients with a sulfite allergy.[78,84] Serious AEs were more common in asthmatic patients. In addition, the patch contains aluminum, which can cause skin burns if the patient is exposed to magnetic imaging or cardioversion procedures. Both patients and health care professionals should understand the importance of removing the patch before these procedures are performed.[78,84]

Drug Interactions

The dopamine agonists are prone to numerous drug interactions, and it is essential that all concurrent medications be evaluated. Ropinirole is metabolized by CYP1A2; therefore, inhibitors of this enzyme, such as ciprofloxacin, may increase plasma levels of ropinirole, and adjustments may be necessary. Pramipexole, on the other hand, is not significantly metabolized by the liver and is devoid of CYP-related drug interactions. Inhibitors of renal tubular secretion, specifically the cationic transport system (e.g., cimetidine, ranitidine, diltiazem, triamterene, verapamil, cisplatin, and quinidine), may decrease the clearance of pramipexole by approximately 20%, although the clinical relevance of this interaction is unclear.[76] In addition, drugs with dopamine-antagonist properties, phenothiazines, butyrophenones (e.g., haloperidol), thioxanthenes, and other antipsychotics should be avoided in PD patients treated with dopamine agonists. The antiemetic agent metoclopramide may decrease the effectiveness of dopamine agonists and should be avoided as well.[74,76,78,86]

Treatment with apomorphine may cause severe nausea. In addition, severe hypotension may occur if the drug is administered concurrently with 5-HT_3 receptor antagonists,

including ondansetron, dolasetron, granisetron, palonosetron, and alosetron. If the patient requires an antiemetic during treatment with apomorphine, an alternative agent, such as trimethobenzamide, is recommended. Arrhythmias may occur when apomorphine is coadministered with thioridazine, quinidine, sotalol, erythromycin, or dofetilide. In addition, since apomorphine is metabolized by COMT, the concurrent use of entacapone may reduce its elimination.[86,88]

Precautions and Contraindications

Postural hypotension requires evaluation in PD patients treated with dopamine agonists, especially if the patients report symptoms of dizziness when going from a supine position to standing, which can increase their risk of falls. Caution is also advised for patients who drive while being treated with these drugs. GI bleeding and ulceration have also been reported and require subsequent monitoring.[74,76,78,86]

A recent drug safety communication from the FDA reported a possible increased risk of heart failure with pramipexole. Although the data are not conclusive, monitoring for this complication is recommended, along with educating patients to report any signs of heart failure.[103] Other precautions include use in patients with renal and/or hepatic impairment and a history of ulcers or GI bleeds, psychosis, or dementia.[74,76,78] The potential for pro-arrhythymic effects secondary to QT prolongation has been reported with apomorphine, and caution in this regard is recommended in high-risk patients.[86]

Contraindications to the use of dopamine agonists include patients with documented hypersensitivity or a sulfite allergy.[78] The use of ergot derivatives is contraindicated in patients with cardiovascular disease because of the fibrotic changes described earlier.[73,74,76] Epidemiological studies have reported that patients with PD have a sixfold greater risk of developing melanoma.[104] Therefore, both patients and clinicians are advised to monitor for signs of melanoma on a regular basis, including periodic evaluation by a dermatologist. The abrupt withdrawal of any dopaminergic agent, or a rapid dosage reduction, may precipitate hyperpyrexia syndrome, a condition that resembles neuroleptic malignant syndrome. In addition to emergent hyperpyrexia, hyperpyrexia syndrome is characterized by confusion, muscular rigidity, rhabdomyolysis, and akinetic crises. Appropriate drug tapering is therefore required in patients who develop this disorder.[74,76,78,86]

Role in Therapy and Clinical Updates

The dopamine agonists, both oral and transdermal formulations (Table 2), are approved for monotherapy in patients with early PD and may offer an initial treatment option for younger patients (under 65 years of age) with mild-to-moderate motor symptoms. A dopamine agonist should be initiated at low doses with slow titration to minimize AEs.[105–108] Clinical studies also support once-daily extended-release products as options for monotherapy in some patients.[80,109] The use of dopamine agonists as first-line therapy rather than carbidopa/levodopa in patients with PD is controversial, and experts in the field have differing opinions. Those who advocate delaying carbidopa/levodopa and starting a dopamine agonist as first-line treatment have expressed concern with the earlier onset of motor complications, such as "wearing off" and dyskinesias, related to carbidopa/levodopa use. Although this concern may be valid in younger patients (those under 65 years of age), most PD patients will develop these complications within five to 10 years regardless of the drug therapy that is used.[67,110–115] A recent study (discussed in the carbidopa/levodopa section) reported a small but persistent benefit in mobility scores with the initial use of carbidopa/levodopa compared with dopamine agonists or MAO-B inhibitors.[27] A concern that levodopa might be toxic to neurons was not supported by data from recent clinical studies.[116,117]

Those who advocate the early use of carbidopa/levodopa focus on the progressive nature of PD and on the importance of early treatment for maintaining activities of daily living and employment. Practice parameters support carbidopa/levodopa as being more effective than dopamine agonists in treating the motor features of PD.[61,65,118,119] In addition, the more-tolerable ADR profile of carbidopa/levodopa compared with that of the dopamine agonists supports its earlier use in PD, especially in elderly patients.[120] Elderly PD patients started on dopamine agonists have an increased risk of serious AEs, including orthostatic hypotension, hallucinations, and confusion.[120,121]

Clinical trials also support the role of dopamine agonists in combination with carbidopa/levodopa or other adjunctive therapies in patients with advanced PD and motor complications. Dopamine agonists, when added to carbidopa/levodopa, reduce the frequency of "off periods" and may allow a reduction in carbidopa/levodopa dosing. Dopamine agonists may also be used in combination with MAO-B inhibitors in PD patients with advanced disease, which can result in some patients receiving triple therapy. PD patients receiving multiple therapies must be closely monitored for efficacy, additive AEs, and the need for dose adjustments.[122–126]

SUMMARY

The use of medications in the management of PD can alleviate symptoms in addition to improving mobility, functionality, and performance in the activities of daily living.[16–18] Levodopa, a prodrug of dopamine, is the mainstay in managing the motor symptoms of PD.[26,30] The addition of carbidopa to levodopa triples levodopa's bioavailability, thereby allowing greater passage of levodopa into the brain.[32–34] Carbidopa/levodopa is approved as monotherapy in PD and is often the first-line treatment when patients present with motor symptoms.[27,32,52] Controlled-release carbidopa/levodopa products have been available for decades,[43] although the advantage of these treatments over the regular-release formulations is unclear. The newer ER product Rytary, released this year, may offer advantages over the previous CR product.

The dopamine agonists are classified as ergot or nonergot types. The ergot derivatives include bromocriptine and cabergoline (compounds rarely used for the treatment of PD), and the nonergot derivatives include oral ropinirole and pramipexole, along with the rotigotine transdermal patch.[69,72] Both the oral and transdermal forms of the nonergot derivatives are approved for monotherapy in patients with early PD and may offer an initial treatment option for younger patients (under 65 years of age) with mild-to-moderate motor symptoms.[105–108] Dopamine agonists are also used in combination with carbidopa/levodopa and other PD agents in more advanced disease.[122–126]

In the next issue of *P&T*, part 3 of this five-part series will discuss additional therapeutic options and the management of motor complications in patients with PD.

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