Parkinson's Disease and Its Management

Part 3: Nondopaminergic and Nonpharmacological Treatment Options

George DeMaagd, PharmD, BCPS; and Ashok Philip, PhD

INTRODUCTION

In part 2 of this five-part series, which appeared in the September 2015 issue of *P&T*, we discussed the dopaminergic combination carbidopa/levodopa and the available dopamine agonists, such as pramipexole and ropinirole, as treatment options for patients with Parkinson's disease (PD). Carbidopa/levodopa and the dopamine agonists are often used as first-line therapies in PD patients with motor features of the disease.

In this installment, we review the role of nondopaminergic pharmacotherapies and adjunctive options in the management of PD, as well as nonpharmacological treatment strategies.

MONOAMINE OXIDASE TYPE B INHIBITORS

Monoamine oxidase type B (MAO-B) inhibitors have a role in the treatment of PD as either early monotherapy or adjunctive therapy in patients with more-advanced disease.[1,2] However, controversy surrounds the use of these agents to achieve "neuroprotective" effects in early PD.[3–5]

Pharmacology

Selegiline—available as Eldepryl capsules (Somerset Pharmaceuticals), Zelapar orally disintegrating tablets (ODTs, Valeant Pharmaceuticals International), and numerous generic formulations—and rasagiline (Azilect, Teva Pharmaceuticals) are oral selective MAO-B inhibitors approved for the treatment of PD (Table 1). Their mechanism of action primarily involves selective, irreversible inhibition of MAO-B–catalyzed oxidation of dopamine in the brain, resulting in the increased availability of dopamine at central synapses and the subsequent prolongation of dopamine activity.[6,7] Both selegiline and rasagiline were initially developed as antidepressants; however, the low-to-moderate doses of seligiline needed to induce irreversible MAO-B inhibition did not provide antidepressant activity.[8] Recently, a transdermal-patch formulation of selegiline (Emsam, Somerset Pharmaceuticals) entered the market with an indication for the treatment of major depressive disorder.[9,10]

Selegiline and rasagiline have similar properties, although the two drugs differ in potency and pharmacokinetic characteristics (e.g., metabolism and half-life), which influence dosing and adverse effects (AEs). Both agents contain a propargylamine component, which is necessary for irreversible inhibition of MAO-B. Compared with older, nonselective MAO inhibitors (such as phenelzine), selegiline and rasagiline are more selective for MAO-B than for MAO-A at approved doses, although this selectivity may be lost with dose escalation. The selectivity for MAO-B reduces AEs and improves overall safety and tolerability.[6,7]

Dr. DeMaagd is the Associate Dean of Academic Administration and a Professor of Pharmacy Practice at the Union University School of Pharmacy in Jackson, Tennessee. Dr. Philip is an Associate Professor of Pharmaceutical Sciences at the Union University School of Pharmacy.

Selegiline, the older of the two agents, is dosed once daily (Zelapar) or twice daily (Eldepryl, generics), with twice-daily dosing administered no later than noon because of the drug's metabolism via the cytochrome P450 (CYP) system to amphetamine metabolites (L-amphetamine and methamphetamine). These metabolites may contribute to agitation and insomnia, which can affect a patient's sleep pattern.[6,11]

The bioavailability of the immediate-release selegiline capsules is poor (approximately 10%), which led to the development of ODTs such as Zelapar. These wafer tablets are administered once daily and the drug is absorbed through the oral mucosa, bypassing the liver and thus reducing the formation of amphetamine metabolites. This reduction in first-pass metabolism provides faster and more complete absorption, a faster onset of action, and improved bioavailability (80%) and tolerability.[12,13]

Rasagiline, administered once daily, differs from selegiline chemically and therefore is not metabolized to amphetamine-like metabolites, which improves its tolerability. Both the parent drug and its metabolites are excreted in urine. Similar to the dopaminergic therapies described previously, the abrupt cessation of treatment with either selegiline or rasagiline is not recommended, and a gradual tapering off is required to minimize the risk of withdrawal.[6,7]

Adverse Events

The gastrointestinal effects of the MAO-B inhibitors include nausea, abdominal pain, anorexia, dyspepsia, xerostomia, stomatitis, buccal mucosal irritation (from the ODT form of selegiline), constipation, and weight loss. Central nervous system (CNS) effects include confusion, hallucinations, compulsive behaviors, dizziness, fainting, abnormal dreams, depression, malaise, headache, paresthesia, insomnia, and nervousness (especially with late-day dosing of selegiline). Extrapyramidal reactions have been reported and include dyskinesias (especially with concurrent levodopa therapy), ataxia, and dystonia. Other AEs include orthostatic hypotension, rhinitis, conjunctivitis, rash, ecchymoses, flu-like symptoms (i.e., fever and arthralgia), sweating, and back or neck pain.[6,7]

The so-called "cheese reaction" is a serious AE that can occur when MAO inhibitors, primarily the nonselective types, are administered with certain foods and medications, such as cheese and decongestants. This reaction can result in a hypertensive crisis, palpitations, tachycardia, blurred vision, arrhythmias, and other sympathomimetic symptoms. It was often observed with the older, nonselective MAO inhibitors, such as phenelzine, isocarboxazid, and tranylcypromine, because of their ability to inhibit biogenic amine (norepinephrine) metabolism. The "cheese reaction" was especially prevalent when the older MAO inhibitors were administered in the presence of biogenic amine-like substances, such as decon-

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Table 1 Monoamine Oxidase Type B (MAO-B) Inhibitors[4–7,13–16,18,20,52]

Product *Manufacturer*	Dosing	Mechanism/ Pharmacokinetics	Potential Adverse Events	Monitoring Parameters
Selegiline (Eldepryl) *Somerset Pharmaceuticals*	• 10 mg/day as divided doses of 5 mg each taken at breakfast and lunch • Used as monotherapy or in combination with levodopa	• Blocks breakdown of dopamine via MAO-B inhibition • Metabolized via CYP 450 enzymes to amphetamines • Eliminated via urine • Half-life: 10 hours	• GI: nausea, weight loss, dyspepsia • CV: hypotension, decreased heart rate, hypertensive crisis (high doses) • CNS: headache, hallucinations, vivid dreams, dizziness, insomnia, flu syndrome • Neuromuscular: dyskinesias, dystonia • Dermatologic: rash, photosensitivity	• Blood pressure • Cardiac status • Changes in mental status (increased anxiety) • Rash • Drug interactions
Selegiline (Zelapar ODT) *Valeant Pharmaceuticals*	1.25 to 2.5 mg without liquid before breakfast	• Blocks breakdown of dopamine via MAO-B inhibition • Metabolism: bypasses liver; reduced formation of amphetamines • Eliminated via urine • Half-life: 10 hours	Same as Eldepryl, with less insomnia due to decreased formation of amphetamine metabolites	Same as above
Rasagiline (Azilect) *Teva Pharmaceuticals*	• 0.5 to 1.0 mg daily (0.5 mg if levodopa adjunct) • Slow titration of dose is necessary • Adjust dose in patients with hepatic disease	• Blocks breakdown of dopamine via MAO-B inhibition • Metabolized via CYP1A2 • Elimination: 7% feces, 70% urine (< 1% unchanged) • Half-life: 3 hours	Similar to Zelapar, but with less insomnia and no formation of amphetamine metabolites	Same as above

CNS = central nervous system; CV = cardiovascular; CYP = cytochrome P450; GI = gastrointestinal; ODT = orally disintegrating tablets

gestants or excessive dietary tyramine (more than 500 mg per day). Tyramine-containing foods and beverages include aged cheeses and fermented drinks, such as red wine and beer.[14,15]

Although rare, cases of the "cheese reaction" have been reported during treatment with selegiline. The labeling for both selegiline and rasagiline states that although normal dietary tyramine does not result in clinically relevant interactions, a tyramine intake of more than 150 mg per day may increase the risk. Appropriate monitoring is therefore recommended.[14,15]

Drug–Drug Interactions

In addition to the AEs described above, another concern with the use of MAO-B inhibitors is the potential for an additive serotonergic effect when these drugs are used in combination with other serotonergic medications. The MAO-B inhibitors can increase serotonin levels through their ability to inhibit its metabolism and subsequent activation of 5-hydroxytryptamine (5HT) receptors. This can increase the risk of serotonin syndrome when used at higher doses and in various combinations.[6,7] Serotonin syndrome is a rare iatrogenic disorder caused by overstimulation of 5HT receptor systems. It can result in severe CNS toxicity leading to hyperpyrexia, myoclonus, hyperreflexia, diaphoresis, tremor, shivering, rigidity, agitation, and hallucinations, and can be fatal if not identified and treated promptly. Some commonly used drugs with serotonergic properties are listed in Table 2. The use of certain serotonergic agents (e.g., meperidine) is considered to be an absolute contraindication that should be avoided.[16]

Additional drug interactions can occur when the MAO-B inhibitors are used concurrently with CYP1A2 inhibitors, such as ciprofloxacin. Both selegiline and rasagiline may exacerbate the AEs associated with levodopa, such as peak-dose dyskinesias. Therefore, it may be necessary to adjust the levodopa dose when an MAO-B inhibitor is added to therapy. Monitoring for potential drug–drug interactions should be a major component of clinical care when MAO-B inhibitors are used.[6,7]

Table 2 Drugs with Serotonergic Properties (Additive Risk of Serotonin Syndrome)[6,7,16]

Antidepressants	
• Nefazodone	• Tranylcypromine
• Phenelzine	• Trazodone
• St. John's wort*	
Other	
• Bromocriptine	• Lithium
• Buspirone	• Meperidine*
• Cocaine	• Methadone*
• Cyclobenzaprine*	• Rasagiline
• Dextromethorphan*	• Selegiline
• Levodopa	• Tramadol*
• Linezolid	

* Contraindicated with MAO inhibitors.

Precautions and Contraindications

In the past, the use of nonselective MAO inhibitors in surgical settings raised concerns about the potential for hemodynamic events, such as reduced sympathetic stability.[8,17] More recent data with the selective MAO-B inhibitors suggest a lower risk of such events during surgery.[8] Rasagiline has the potential to cause or potentiate psychiatric AEs. In addition, caution is advised when MAO-B inhibitors are used in patients with multiple comorbidities, including hypertension, seizure disorders, diabetes, psychiatric illness, and cardiovascular or cerebrovascular disease.[4,18]

Contraindications to the use of MAO-B inhibitors include documented hypersensitivity to these drugs, severely elevated blood pressure (e.g., pheochromocytoma), and the concomitant use of serotonergic agents (Table 2). Rasagiline is contraindicated in patients with moderate-to-severe hepatic disease (i.e., those with a Child-Pugh score of less than 6).[6,7,18] An increased risk of melanoma has been observed in patients treated with MAO-B inhibitors, but current evidence does not support a causal relationship.[19]

Role in Therapy and Clinical Update

Both selegiline and rasagiline may be used as monotherapy in patients with PD, although only rasagiline is FDA-approved for this indication.[7] As monotherapy, selegiline was reported to provide modest improvements in the motor features of PD.[5] Rasagiline has shown some clinical efficacy when used as monotherapy in patients with mild-to-moderate PD.[20–22] Thus, the use of MAO-B inhibitors may be considered for the treatment of patients with early PD accompanied by mild-to-moderate motor features before initiating carbidopa/levodopa or a dopamine agonist.[7,18,21] A recent study comparing initial therapies of PD reported similar efficacy with MAO-B inhibitors and dopamine agonists in the management of motor symptoms.[23]

Much of the discussion regarding the use of MAO-B inhibitors in early PD has focused on a potential "neuroprotective" or "disease-modifying" benefit. Advocates of a neuroprotective effect have suggested that MAO-B inhibitors reduce the formation of neurotoxins through their ability to inhibit dopamine breakdown. This potential benefit was first reported in 1989 in the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) trial of selegiline. This National Institutes of Health–sponsored study reported neuroprotective benefits with selegiline, although this benefit was confounded by the observation that the pharmacological effect exceeded the study's drug washout period.[24–26]

In addition to their use as monotherapy in patients with early PD, the MAO-B inhibitors have a role in more advanced disease as adjunctive treatment for motor fluctuations in combination with carbidopa/levodopa and dopamine agonists. The evidence in this regard is primarily for rasagiline,[27–31] with limited data available for selegiline.[24,32] Patients who are started on carbidopa/levodopa and develop motor fluctuations may be given rasagiline as adjunctive therapy, which can increase "on" time by approximately one hour.[27–31] Selegiline has also been reported to improve the wearing-off effect of carbidopa/levodopa, although its limited efficacy, poor bioavailability, and amphetamine metabolites make it a less desirable option.[32] When the MAO-B inhibitors are administered in combination with carbidopa/levodopa, lower doses of carbidopa/levodopa should be used initially and adjusted according to the patient's response and tolerability. Some patients with advanced PD may receive triple regimens, such as carbidopa/levodopa, an MAO-inhibitor, and a dopamine agonist.[27–31]

CATECHOL-O-METHYLTRANSFERASE INHIBITORS

Catechol-O-methyltransferase (COMT) plays a key role in the metabolism of various neurotransmitters, both in the periphery and in the CNS. The disruption of levodopa breakdown by COMT inhibitors led to research into the use of these agents in patients with PD. The result was the development and marketing of two COMT inhibitors: entacapone (Comtan, Novartis) and tolcapone (Tasmar, Valeant Pharmaceuticals).[33,34] Entacapone is also available in a fixed-dose combination with carbidopa/levodopa as Stalevo (Novartis).[35] The use of a COMT inhibitor with carbidopa and levodopa helps prevent the metabolism of levodopa to inactive 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD).[33–35]

The COMT inhibitors (Table 3) were introduced as potentiators of levodopa and offer an additional option for managing the motor symptoms of PD. These agents are used only as adjunctive treatments in patients who are experiencing "wearing off" or other motor complications during treatment with carbidopa/levodopa.[36,37]

Pharmacology

The mechanism of action of these medications involves inhibition of the COMT enzyme either in the periphery (entacapone) or in both the periphery and the CNS (tolcapone), thus providing another target for increasing the central availability of levodopa and its subsequent conversion to dopamine.[33]

Studies have reported a 30% to 50% increase in the area under the curve for levodopa during concomitant treatment with entacapone. Moreover, the half-life of levodopa and "on" time with the drug were increased by approximately half an hour to two hours.[38,39] Another potential benefit in using COMT inhibitors is their ability to reduce the formation of 3-OMD metabolite. Since 3-OMD is a large, neutral amino acid, it competes with levodopa for absorption both in the stomach and at the blood–brain barrier. The use of COMT

Table 3 Catechol-O-Methyltransferase (COMT) Inhibitors[33–41]

Product *Manufacturer*	Dosing	Mechanism/ Pharmacokinetics	Potential Adverse Events	Monitoring Parameters
Entacapone (Comtan) *Novartis*	• 200 mg with each dose of carbidopa/levodopa • Maximum dosage: 1,600 mg daily	• Inhibits peripheral metabolism of levodopa (COMT inhibitor) • Use only with levodopa • Metabolized to active *cis*-isomer; undergoes glucuronidation to inactive metabolites • Eliminated in feces (90%) • Half-life: 2 hours	• Exacerbation of levodopa adverse effects • Brown/orange urine • Diarrhea	• Blood pressure • Changes in mental status
Tolcapone (Tasmar) *Valeant Pharmaceuticals*	• 100 mg three times daily • Maximum dosage: 600 mg daily	• Inhibits peripheral and central metabolism of levodopa (COMT inhibitor) • Use only with levodopa • Metabolized via glucuronidation and CYP2A6 and CYP3A4 enzymes • Elimination in urine (60%) and feces (40%) • Half-life: 3 hours	Same as above, plus: • Transient elevations in liver enzymes • Fulminant liver failure	• Blood pressure • Changes in mental status • Liver enzymes • Liver-function tests
Carbidopa/levodopa/ entacapone (Stalevo) *Novartis*	• Various tablet formulations: ◦ 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 • Optimal daily dose determined by titration • Do not split tablets	• Carbidopa: ◦ Decarboxylated to dopamine in extracerebral tissues ◦ Inhibits decarboxylation of peripheral levodopa ◦ Primarily eliminated in urine unchanged ◦ Half-life: 1.6 to 2.0 hours • Levodopa: ◦ Selective and reversible COMT inhibitor ◦ Extensively metabolized to various metabolites ◦ Half-life: 1.7 hours • Entacapone: ◦ Excreted in feces (90%) and urine (10%) ◦ Half-life: 0.8 to 1.0 hour	Same as above	• Blood pressure • Pulse • Changes in mental status

CYP = cytochrome P450

inhibitors reduces this competition. The resulting increased availability of levodopa usually requires that the carbidopa/levodopa dose be reduced by approximately 15% to 30% to avoid additive dopaminergic-related AEs. Patients receiving low doses of carbidopa/levodopa (e.g., 25 mg/100 mg three times daily) may not require dose reductions, but monitoring will still be necessary.[37,38]

The two currently available COMT inhibitors—entacapone and tolcapone—have different pharmacology and toxicity profiles. Tolcapone is a reversible inhibitor of both peripheral and central COMT and has a longer half-life than that of entacapone. The drug is metabolized by the liver via glucuronidation and by CYP2A6 and CYP3A4 enzymes, with elimination in both urine (60%) and feces (40%). Less than 1% of the parent drug is excreted unchanged in the urine. The elimination half-life of tolcapone is three hours. The drug is administered three times daily, with a maximum daily dose of 600 mg.[34]

Entacapone—the COMT inhibitor primarily used in clinical practice—is reversible and peripherally acting. The drug is initially metabolized via isomerization to its *cis*-isomer (active). This process is followed by glucuronidation of both the *cis*-isomer and the parent molecule to inactive metabolites, with most of the active drug (90%) eliminated in feces. The elimination half-life of entacapone is two hours. As mentioned above, the drug is marketed both alone (Comtan) and in a fixed-dose combination with carbidopa/levodopa (Stalevo), which reduces the number of tablets needed for treatment and potentially improves compliance (see Table 3). When used separately, entacapone is coadministered with carbidopa/levodopa in 200-mg increments up to a maximum daily dose of 1,600 mg.[33,35]

Adverse Events

The most common AEs associated with the addition of COMT inhibitors to carbidopa/levodopa therapy are related to the drugs' dopaminergic potentiation (e.g., nausea and vomiting). In addition, delayed-onset diarrhea may occur with both agents and may be severe enough to warrant the discontinuation of therapy.[33,34]

Because tolcapone may cause hepatotoxicity (boxed warning), entacopone is considered to be the first-line treatment option for patients with PD.[36,39] Darkened urine during tolcapone therapy could indicate liver problems and should be addressed immediately.[34] If tolcapone is used to treat patients with PD, appropriate monitoring of liver function and liver enzymes is necessary, especially during the first six to eight months of therapy.[34]

Study data have indicated that dyskinesias occur earlier in PD patients receiving adjunctive therapy with entacapone.[38,40]

Drug Interactions

The COMT inhibitors' ability to potentiate the effects of levodopa may be additive in the presence of adjunctive PD therapies, and monitoring and dose adjustments may be necessary.[33,34]

Precautions and Contraindications

The FDA has issued a safety notification with regard to the increased number of prostate cancer cases and cardiovascular events (e.g., myocardial infarction) observed in clinical studies of entacopone. Therefore, appropriate monitoring is recommended.[41–43] In addition, as mentioned previously, the use of tolcapone requires appropriate clinical monitoring of liver function and liver enzymes because of its potential to cause hepatotoxicity.[34]

Role in Therapy and Clinical Updates

Clinical studies that evaluated the role of entacapone as adjunctive therapy in PD patients experiencing motor fluctuations while receiving carbidopa/levodopa have reported improvements in end-of-dose "wearing off" of approximately 1.5 hours daily, as well as approximately one hour of additional daily "on time." Other benefits included improvements in motor function and reductions of approximately 15% to 30% in levodopa total daily doses, especially in patients receiving daily doses of less than 600 mg.[44–49]

Although tolcapone and entacapone are similarly effective in patients with PD, the association of tolcapone with hepatic toxicity limits its clinical utility.[46] Tolcapone may be considered in PD patients who have failed other therapies, with appropriate monitoring for liver toxicity.[50]

Clinical trials do not support the use of COMT inhibitors as adjuncts to carbidopa/levodopa in patients who are not experiencing motor complications, nor are these drugs used to prevent or delay motor fluctuations or dyskinesias.[38,40,51]

ANTICHOLINERGIC AGENTS

Overview and Pharmacology

Before 1969, anticholinergics were the only agents available to treat PD. However, their use has declined significantly since the introduction of carbidopa/levodopa and other therapies. Anticholinergics were first proposed as PD treatments in the 1960s, when it was determined that dopaminergic deficiency resulted in increased striatal cholinergic activity and a subsequent imbalance between these neurotransmitter systems. This imbalance was thought to contribute to the symptoms of PD, and the use of anticholinergics was proposed to correct it.[52–55]

Anticholinergic agents currently used to treat PD include benztropine (Cogentin, Akorn, Inc.) and trihexyphenidyl (generics).[56,57] A major concern with drugs in this class is their adverse effects secondary to nonselective blockade of cholinergic receptors throughout the body.[58] Studies of selective cholinergic receptor antagonists have failed to show significant benefits in PD patients. This finding suggests that multiple receptor subtypes may have a role in the circuitry of the basal ganglia.[52,55]

Adverse Effects

The biggest drawback to the use of anticholinergics is their safety profile, especially in elderly patients. CNS-related AEs may include confusion, exacerbation of dementia, delirium, sedation, blurred vision, and hallucinations. Other body-system AEs include constipation, xerostomia, and urinary retention, and higher doses may contribute to postural hypotension and palpitations.[58,59]

Drug Interactions

Additive anticholinergic effects are a concern when these agents are coadministered with antidepressants, antihistamines, antipsychotics, and numerous other drugs. Additive CNS-

related AEs, such as sedation and confusion, are also a potential problem when anticholinergics are coadministered with other centrally acting drugs.[20,52,60]

Precautions and Contraindications

Contraindications to the use of anticholinergic agents include documented hypersensitivity to these drugs, narrow closed-angle glaucoma, dementia, and benign prostatic hypertrophy. Precautions should be taken during activities that require concentration, such as operating a motor vehicle.[52,58,59]

Role in Therapy and Clinical Updates

In general, anticholinergic therapies appear to be most effective in younger patients (less than 60 years of age) with tremor-predominant PD and preserved cognitive status, although they may also have beneficial effects on rigidity and complications of dystonia.[54,55] These drugs provide minimal benefit when used to treat advanced motor symptoms. Their use may be considered in younger PD patients with tremor who require dexterity because of their work.[53,54,61]

AMANTADINE

Amantadine (Symmetrel, Endo Pharmaceuticals, and generics) is an antiviral agent that was identified as having anti-parkinsonism properties secondary to its effects on dopamine. In the early 1960s, the drug was found to inhibit several strains of influenza virus, and it was approved by the FDA in 1966 for prophylactic use against influenza A. In 1968, a 58-year-old woman with PD reported improvement of her motor features after treatment with amantadine, and a subsequent case series in 10 patients supported this benefit.[62,63]

Pharmacology

Amantadine's mechanism of action in PD is not fully understood. The drug shows antagonist activity on N-methyl-D-aspartate (NMDA) receptors and enhances the release of dopamine from presynaptic terminals, in addition to having anticholinergic properties. The beneficial effects of amantadine on dyskinesias may be related to its ability to inhibit excitatory neurotransmission through the blockade of NMDA receptors. Amantadine is eliminated via the kidneys and therefore requires dose adjustments in patients with renal impairment. [64–66]

Adverse Events

AEs associated with amantadine include "jitteriness," hallucinations, insomnia, confusion, gastrointestinal symptoms, urinary retention, and edema.[64,65] Visual impairment associated with corneal edema has also been reported.[67] In addition, some patients experience a reddish mottling of the skin (livedo reticularis). This is believed to result from the local release of catecholamines, from vasoconstriction, and from permeability changes in surface blood vessels. Although the disorder is benign, it may require clinical intervention, such as a dose reduction, because of cosmetic concerns and a potential association with peripheral edema.[52,64,65]

Drug Interactions

Additive anticholinergic effects may occur when amantadine is used in combination with drugs that have a similar AE profile, especially in terms of constipation and CNS effects, such as confusion and hallucinations. Amantadine can be antagonistic when used concomitantly with a live, attenuated influenza vaccine; therefore, its use should be avoided within two weeks of administering such a vaccine. In addition, a live vaccine should not be administered within 48 hours of discontinuing amantadine.[52,64,65]

Precautions and Contraindications

Amantadine should not be used in patients with known hypersensitivity to the drug. In addition, treatment with amantadine may exacerbate certain comorbidities, such as depression, peripheral edema, angle-closure glaucoma, congestive heart failure, and seizure disorders. The abrupt withdrawal of treatment should be avoided to reduce the potential for motor-symptom rebound.[52,64,65]

Role in Therapy and Clinical Updates

Amantadine has demonstrated beneficial effects in the early symptomatic management of PD and may improve motor symptoms, including tremor, akinesia, and rigidity, as well as overall functional ability.[54,63] The total daily dose of amantadine is 300 mg, administered in divided doses, with dose adjustments in patients with renal impairment. The long-term use of amantadine is limited in PD patients because of tachyphylaxis, which occurs within a few months after the initiation of treatment.[1,52,64,65] In addition to its potential role in early PD, amantadine's ability to block NMDA receptors and, consequently, excitatory neurotransmission may support its role in the management of carbidopa/levodopa-induced dyskinesias. Clinical studies of amantadine have reported a reduction of approximately 50% in the severity and duration of dyskinesias.[1,66–68] In addition, a recent study reported the worsening of dyskinesias when amantadine was discontinued and the patients were switched to placebo.[69]

ALTERNATIVE THERAPIES

A variety of alternative treatments have been evaluated in patients with PD, although evidence supporting their use in this setting is limited.[70] A placebo-controlled trial comparing alpha-tocopherol (vitamin E) with placebo in PD patients measured the time required for the initiation of carbidopa/levodopa and reported no significant difference between the two treatment groups.[24] A recent long-term, randomized, controlled study (with a minimum treatment period of five years) found no benefit in treating PD patients with creatine monohydrate.[71] Similarly, high-dose coenzyme Q10 failed to improve early PD in another randomized, controlled trial.[72] Curcumin has been evaluated for its potential neuroprotective effects in PD,[73] but the compound's low bioavailability and metabolic instability have proved problematic.[74]

INVESTIGATIONAL AGENTS

The National Institute of Neurological Disorders is evaluating various compounds for their potential disease-modifying or neuroprotective effects in patients with PD.[75–79] One class of agents being studied comprises the adenosine A_{2A} receptor antagonists. The A_{2A} receptors are co-localized on dopamine D_2 receptors and may be overactivated in PD; therefore, blockage of these receptors may alleviate the motor symptoms of the

disease.[80] In this regard, it is interesting to note that caffeine, a nonselective adenosine receptor antagonist, may have neuroprotective effects on dopaminergic neurons.[81] Istradefylline, the first of the adenosine A_{2A} receptor antagonists to be studied in PD, received a "not approvable" letter from the FDA because of its lack of clinical benefit and its association with the development of dyskinesias.[82] A meta-analysis concluded that istradefylline 50 mg had clinical potential as augmentation for levodopa therapy in PD patients.[83] Ongoing clinical trials are evaluating A_{2A}-receptor antagonists with greater selectivity, potency, and improved tolerability.[84]

The finding that PD is linked to overactivation of glutamate activity in basal ganglia circuits, resulting in oxidative stress and cell death, has led to the development of glutamate receptor antagonists for use in this setting.[85] One such compound is riluzole, an NMDA receptor antagonist approved for the treatment of amyotrophic lateral sclerosis. This drug, however, had no significant effects on survival or disease progression in patients with PD.[86]

Other investigational agents for PD include mixed dopamine agonist/antagonist agents with additional serotonergic properties. These treatments are being studied in PD patients based on their proposed potential to reduce overstimulation of dopamine receptors, in addition to their antidepressant benefits.[87]

Safinamide, an alpha-aminoamide, is currently being developed as an add-on therapy to dopamine agonists or levodopa in patients with early or mid-to-late-stage PD. It exhibits both dopaminergic and nondopaminergic activity, including selective and reversible MAO-B inhibition, activity-dependent sodium-channel antagonism, and inhibition of glutamate release *in vitro*.[88] The drug (at a dosage of 100 mg per day) significantly improved motor symptoms compared with placebo in patients with early PD when combined with a dopamine agonist.[89] A post-hoc analysis of safinamide in PD patients confirmed that the 100-mg dose may be effective when added to dopamine agonist therapy.[90] The FDA accepted safinamide (under the tentative trade name Xadago) for review in March 2015.[88]

Research with uric acid suggests that an inverse relationship exists between PD and serum urate levels, with low levels associated with more rapid disease progression. This finding prompted research into agents that could elevate uric acid levels.[91]

Several established drugs have been studied for their potential therapeutic and/or neuroprotective role in patients with PD. For example, a cohort study conducted in Denmark reported a reduced risk of PD in patients 65 years of age or older treated with the calcium-channel blocker isradipine.[92] Evidence supporting the role of neuroinflammation in the pathogenesis of PD has led to trials of various anti-inflammatory agents in this setting.[79] Wahner and colleagues, for instance, reported that nonsteroidal anti-inflammatory drugs (NSAIDs) may be protective against PD.[93] Overall, evidence to support the role of aspirin and nonaspirin NSAIDs in PD is inconsistent, with some trials reporting a possible neuroprotective effect and others reporting little or no benefit.[93–97] A prospective study reported that the regular use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) was associated with a modest reduction in the risk of PD.[98]

The stimulant methylphenidate, used to treat attention-deficit/hyperactivity disorder and narcolepsy, was reported to improve gait hypokinesia and freezing in PD patients undergoing stimulation of the subthalamic nucleus.[99]

Aviles-Olmos and colleagues evaluated subcutaneous exenatide in 45 patients with moderate PD. Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist commonly used to treat patients with type-2 diabetes. The study results suggested clinically relevant improvements in PD across motor and cognitive measures compared with untreated controls. Exenatide-treated patients had a mean improvement at 12 months on the Unified Parkinson's Disease Rating Scale of 2.7 points, compared with a mean decline of 2.2 points in the control patients ($P = 0.037$).[100] However, because of the lack of a placebo control, it is possible that the observed differences between patients receiving exenatide and nontreated controls were due to a placebo effect.[101]

Zonisamide, an anticonvulsant with neurotransmitter effects, including effects on dopamine synthesis, has been approved in Japan for the treatment of PD patients. Murata and colleagues evaluated the drug as an adjunct to levodopa in patients free of motor complications and reported improvements in "off time" with a 50-mg dose.[102]

Beta blockers have been considered as a therapeutic option for PD tremor, although some patients may not benefit from or be able to tolerate these agents.[103]

NONPHARMACOLOGICAL TREATMENT OPTIONS

Numerous nonpharmacological strategies have been used to treat patients with PD, including exercise programs and occupational, physical, and speech therapy.[104–110] Although clinical studies of these approaches have been fraught with design and control problems, the data suggest that they may provide a clinical benefit when used as adjunctive treatment.[104–107] The Chinese meditative exercise tai chi was reported to improve balance impairments in patients with mild PD,[106] and another study demonstrated the benefit of exercise in reducing falls in this patient group.[108] Physical and occupational therapy appear to be useful as adjunctive treatments in PD patients, but more studies are needed.[107,110] Speech therapy may help PD patients with hypokinetic dysarthria,[111] and cognitive training may be beneficial in other PD patients as well.[109] Evidence does not support the use of acupuncture as an adjunct to levodopa therapy in patients with PD.[112,113] Education of the patient and family members is a key element of PD management, along with the use of support groups.[109]

Ablative Surgery

Before the introduction of deep-brain stimulation (DBS) in the mid-1990s, the main surgical treatment for PD was lesioning,[114] which consists of inserting a heated probe into a precisely targeted region of the brain to destroy tissue.[115] Pallidotomy (involving the globus pallidus internus), thalamotomy (involving the thalamus), and subthalamotomy (involving the subthalamic nucleus) are types of surgical lesioning. Of these three procedures, pallidotomy has been the most widely used surgical approach for relieving the motor symptoms of PD.[115]

Deep-Brain Stimulation

DBS involves the delivery of electrical impulses to the brain by way of a tiny implanted electrode. Unlike lesioning, it does

not permanently destroy brain tissue.[115–118] Two DBS devices are currently available. The first device, the Activa Deep Brain Stimulation Therapy System (Medtronic), was approved in 1997 for the treatment of tremor associated with essential tremor and PD. In 2002, the indications were expanded to include the symptoms of PD. The second device, the Brio Neurostimulation System (St. Jude Medical), was approved in June 2015 to help reduce the symptoms of PD and essential tremor.[119]

PD patients who have significant clinical features of the disease (such as intractable motor fluctuations, tremor, or dyskinesias) despite optimal dopaminergic pharmacotherapy may be candidates for DBS. Patients undergoing the procedure must be free of comorbidities, including psychiatric problems, dementia, or signs of atypical parkinsonism. Medications are usually stopped 12 hours before surgery, and computed tomography or magnetic resonance imaging is used to establish target locations in the brain before the electrode is positioned.[120–122] Although the precise mechanism by which DBS influences PD motor features and complications is unclear, it may involve the modulation of thalamic signals and/or the local release of glutamate and adenosine within the targeted brain region.[123,124]

Several areas of the brain are targeted in DBS.[125–128] For example, studies using DBS to treat PD symptoms as an adjunct to levodopa and to manage motor complications have targeted the subthalamic nucleus, the globus pallidus, and the thalamus. These investigations reported improvements in PD assessment scores, including motor features, and reductions in dyskinesias, as well as reductions in the levodopa dosage and improvements in patients' quality of life.[117,125–131] Moreover, data from a cohort of 309 patients with PD who underwent DBS of the subthalamic nucleus found this area of the brain to be an excellent target for the procedure.[125]

AEs associated with DBS include surgical-site infections, falls, intracerebral hematoma, cognitive decline, emotional lability, suicide (rarely), impulsive behaviors, mania, apathy, social maladjustment, and hypersexuality.[132–135]

DBS has been compared with lesioning in clinical trials. In one study, for instance, thalamotomy was associated with a higher incidence of AEs, including cognitive, gait, and balance disturbances, compared with thalamic DBS. However, a procedure-related death from cerebral hemorrhage was reported in the DBS group.[136] In another study, subthalamic DBS resulted in greater improvements in PD motor scores compared with pallidotomy.[137]

Transplantation, Stem Cell Research, and Gene Therapy

The transplantation of dopaminergic neurons has been studied for more than 20 years. The results have been variable, with some patients developing graft-induced dykinesias.[138,139] Stem-cell transplantation in PD patients appears to be more promising, but it, too, has caused some concern regarding cell survival, tumor formation, tissue rejection, and purification.[140]

Other areas of research include the use of neurorestorative proteins, physiologic delivery of deficient neurotransmitters, and gene-replacement procedures.[141–143] A dose-escalation study of ProSavin, an experimental gene-based therapy, reported positive changes in motor outcomes, but these effects were inferior to the preoperative response to levodopa.[144]

CONCLUSION

The MAO-B inhibitors selegiline and rasagiline are effective as either monotherapy or adjunctive therapy in PD patients with advanced disease.[1,2] The COMT inhibitors entacapone and tolcapone were introduced as potentiators of levodopa and provide an additional option for managing the motor symptoms of PD. These agents, however, are used only as adjunctive treatments in patients who are experiencing "wearing off" or other motor complications during therapy with carbidopa/levodopa.[36,37] Anticholinergic agents currently used to treat PD include benztropine and trihexyphenidyl.[56,57] The antiviral agent amantadine has demonstrated beneficial effects in the symptomatic management of early PD and may improve motor symptoms, including tremor, akinesia, and rigidity, as well as overall functional ability.[54,63]

Numerous investigational compounds are being evaluated for their potential disease-modifying or neuroprotective effects in patients with PD.[75–79] These treatments include the adenosine A_{2A} receptor antagonist istradefylline;[82] the glutamate receptor antagonist riluzole;[86] and the alpha-aminoamide agent safinamide.[88,89]

A variety of nonpharmacological strategies have been used to treat PD patients, including exercise programs and occupational, physical, and speech therapy.[104–110] Lesioning, once the main surgical treatment for PD,[114] has been superceded by deep-brain stimulation.[115–118]

In the next issue of *P&T*, part 4 of this five-part article will discuss the management of motor complications in patients with PD.

REFERENCES

1. Fox SH, Katzenschlager R, Lim SY, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 2011;26(suppl 3):S2–S41.
2. Gárdián G, Vécsei L. Medical treatment of Parkinson's disease: today and the future. *Int J Clin Pharmacol Ther* 2010;48:633–642.
3. De la Fuente-Fernández R, Schulzer M, Mak E, Sossi V. Trials of neuroprotective therapies for Parkinson's disease: problems and limitations. *Parkinsonism Relat Disord* 2010;16:365–369.
4. Keating GM, Lyseng-Williamson KA, Hoy SM. Rasagiline: a guide to its use in Parkinson's disease. *CNS Drugs* 2012;26:781–785.
5. Fabbrini G, Abbruzzese G, Marconi S, et al. Selegiline: a reappraisal of its role in Parkinson disease. *Clin Neuropharmacol* 2012;35:134–140.
6. Eldepryl (selegiline hydrochloride capsules) prescribing information. Morgantown, West Virginia: Somerset Pharmaceuticals, Inc.; June 2012. Available at: http://medlibrary.org/lib/rx/meds/eldepryl-2. Accessed May 29, 2015.
7. Azilect (rasagiline mesylate tablets) prescribing information. North Wales, Pennsylvania: Teva Pharmaceuticals USA, Inc.; May 2014. Available at: https://www.azilect.com/Resources/pdf/AZI-40850-Azilect-Electronic-PI.pdf. Accessed May 29, 2015.
8. Van Haelst IM, van Klei WA, Doodeman HJ, et al. Antidepressive treatment with monoamine oxidase inhibitors and the occurrence of intraoperative hemodynamic events: a retrospective observational cohort study. *J Clin Psychiatry* 2012;73:1103–1109.
9. Feiger AD, Rickels K, Rynn MA, et al. Selegiline transdermal system for the treatment of major depressive disorder: an 8-week, double-blind, placebo-controlled, flexible-dose titration trial. *J Clin Psychiatry* 2006;67:1354–1361.
10. Emsam (selegiline transdermal system) prescribing information. Morgantown, West Virginia: Somerset Pharmaceuticals, September 2014. Available at: http://www.emsam.com/includes/pdf/EMSAM-PIR12_Exhibit.pdf . Accessed May 29, 2015.

11. Zelapar (selegiline hydrochloride orally disintegrating tablets) prescribing information. Bridgewater, New Jersey: Valeant Pharmaceuticals North America LLC; July 2014. Available at: http://www.valeant.com/Portals/25/Pdf/PI/Zelapar-PI.pdf. Accessed May 29, 2015.
12. Waters CH, Sethi KD, Hauser RA, et al. Zydis selegiline reduces off time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. *Mov Disord* 2004;19:426–432.
13. Ondo WG, Hunter C, Isaacson SH. Tolerability and efficacy of switching from oral selegiline to Zydis selegiline in patients with Parkinson's disease. *Parkinsonism Relat Disord* 2011;17:117–118.
14. Chen JJ, Wilkinson JR. The monoamine oxidase type B inhibitor rasagiline in the treatment of Parkinson disease: Is tyramine a challenge? *J Clin Pharmacol* 2012;52:620–628.
15. Finberg JP, Gillman K. Selective inhibitors of monoamine oxidase type B and the "cheese effect." *Int Rev Neurobiol* 2011;100:169–190.
16. Dunkley EJ, Isbister GK, Sibbritt D, et al. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnosis decision rules for serotonin toxicity. *QJM* 2003;96:635–642.
17. Krings-Ernst I, Ulrich S, Adli M. Antidepressant treatment with MAO inhibitors during general and regional anesthesia: a review and case report of spinal anesthesia for lower-extremity surgery without discontinuation of tranylcypromine. *Int J Clin Pharmacol Ther* 2013;51:763–770.
18. Hoy SM, Keating GM. Rasagiline: a review of its use in the treatment of idiopathic Parkinson's disease. *Drugs* 2012;72:643–669.
19. Strupp M. Parkinson's disease I: glucocerebrosidase mutations, family history of melanoma, and questionable effects of rasagiline. *J Neurol* 2009;256:2111–2114.
20. National Institute for Health and Clinical Excellence. *Parkinson's Disease: Diagnosis and Management in Primary and Secondary Care*. NICE Clinical Guidelines, No. 35. London: Royal College of Physicians; 2006. Available at: http://www.ncbi.nlm.nih.gov/books/NBK48513. Accessed June 24, 2015.
21. Viallet F, Pitel S, Lancrenon S, et al. Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson's disease. *Curr Med Res Opin* 2013;29:23–31.
22. Stern MB, Marek KL, Friedman J, et al. Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. *Mov Disord* 2004;19:916–923.
23. PD MED Collaborative Group. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. *Lancet* 2014;384:1196–1205.
24. Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1989;321:1364–1371.
25. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. *Ann Neurol* 1996;39:37–45.
26. Shoulson I, Oakes D, Fahn S, et al. Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: a randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of parkinsonism trial. *Ann Neurol* 2002;51:604–612.
27. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Arch Neurol* 2005;62:241–248.
28. Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily) study: a randomised, double-blind, parallel-group trial. *Lancet* 2005;365:947–954.
29. Leegwater-Kim J, Bortan E. The role of rasagiline in the treatment of Parkinson's disease. *Clin Interv Aging* 2010;5:149–156.
30. Elmer L, Schwid S, Eberly S. Rasagiline-associated motor improvement in PD occurs without worsening of cognitive and behavioral symptoms. *J Neurol Sci* 2006;248:78–83.
31. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO study. *Arch Neurol* 2002;59:1937–1943.
32. Cedarbaum JM, Toy LH, Green-Parsons A. L-deprenyl (selegiline) added to Sinemet CR in the management of Parkinson's disease patients with motor response fluctuations. *Clin Neuropharmacol* 1991;14:228–234.
33. Comtan (entacapone tablets) prescribing information. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation, July 2014. Available at: https://www.pharma.us.novartis.com/product/pi/pdf/comtan.pdf. Accessed June 3, 2015.
34. Tasmar (tolcapone tablets) prescribing information. Bridgewater, New Jersey: Valeant Pharmaceuticals North America LLC; May 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020697s004lbl.pdf. Accessed June 3, 2015.
35. Stalevo (carbidopa, levodopa, and entacapone tablets) prescribing information. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation, July 2014. Available at: https://www.pharma.us.novartis.com/product/pi/pdf/stalevo.pdf. Accessed June 3 2015.
36. Espinoza S, Manago F, Leo D, et al. Role of catechol-O-methyltransferase (COMT)-dependent processes in Parkinson's disease and L-DOPA treatment. *CNS Neurol Disord Drug Targets* 2012;11:251–263.
37. Widnell KL, Comella C. Role of COMT inhibitors in the treatment of motor fluctuations. *Mov Disord* 2005;20(suppl 11):S30–S37.
38. Stocchi F, Rascol O, Kieburtz K. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. *Ann Neurol* 2010;68:18–27.
39. Reichmann H, Emre M. Optimizing levodopa therapy to treat wearing-off symptoms in Parkinson's disease: focus on levodopa/carbidopa/entacapone. *Expert Rev Neurother* 2012;12:119–131.
40. Fung VS, Herawati L, Wan Y. Quality of life in early Parkinson's disease treated with levodopa/carbidopa/entacapone. *Mov Disord* 2009;24:25–31.
41. Muller T. Entacopone. *Expert Opin Drug Metab Toxicol* 2010;6:983–993.
42. Food and Drug Administration. FDA drug safety communication: ongoing safety review of Stalevo (entacapone/carbidopa/levodopa) and possible development of prostate cancer. March 31, 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm206363.htm. Accessed June 25, 2015.
43. Food and Drug Administration. Stalevo (carbidopa/levodopa and entacapone): ongoing safety review: possible increased cardiovascular risk. September 6, 2013. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm223423.htm. Accessed June 25, 2015.
44. Iansek R, Danoudis M. A single-blind cross over study investigating the efficacy of standard and controlled release levodopa in combination with entacapone in the treatment of end-of-dose effect in people with Parkinson's disease. *Parkinsonism Relat Disord* 2011;17:533–536.
45. Jankovic J, Stacy M. Medical management of levodopa-associated motor complications in patients with Parkinson's disease. *CNS Drugs* 2007;21:677–692.
46. Ries V, Selzer R, Eichorn T, et al. Replacing a dopamine agonist by the COMT-inhibitor tolcapone as an adjunct to L-dopa in the treatment of Parkinson's disease: a randomized, multicenter, open-label, parallel-group study. *Clin Neuropharmacol* 2010;33:142–150.
47. Mizuno Y, Kanazawa I, Kuno S, et al. Placebo-controlled, double-blind dose-finding study of entacapone in fluctuating parkinsonian patients. *Mov Disord* 2007;22:75–80.
48. Olanow CW, Kieburtz K, Stern M, et al. Double-blind, placebo-controlled study of entacapone in levodopa-treated patients with stable Parkinson disease. *Arch Neurol* 2004;61:1563–1568.
49. Hauser RA, Panisset M, Abbruzzese G, et al. Double-blind trial of levodopa/carbidopa/entacapone versus levodopa/carbidopa in early Parkinson's disease. *Mov Disord* 2009;24:541–550.
50. Lees AJ, Ratziu V, Tolosa E, Oertel WH. Safety and tolerability of adjunctive tolcapone treatment in patients with early Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007;78:944–948.
51. Reichmann H, Boas J, Macmahon D, et al. Efficacy of combining levodopa with entacapone on quality of life and activities of daily living in patients experiencing wearing-off type fluctuations. *Acta Neurol Scand* 2005;111:21–28.

52. Chen JJ, Swope DM. Parkinson's disease. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 9th ed. New York: McGraw-Hill, 2014; chapter 43.
53. Fox SH. Non-dopaminergic treatments for motor control in Parkinson's disease. *Drugs* 2013;73:1405–1415.
54. Miyasaki JM, Martin W, Suchowersky O, et al. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review. *Neurology* 2002;58:11–17.
55. Xiang Z, Thompson AD, Jones CK, et al. Roles of the M1 muscarinic acetylcholine receptor subtype in the regulation of basal ganglia function and implications for the treatment of Parkinson's disease. *Pharmacol Exp Ther* 2012;340:595–603.
56. Cogentin (benztropine mesylate injection) prescribing information. Lake Forest, Illinois: Akorn, Inc.; April 2014. Available at: http://www.akorn.com/documents/catalog/package_inserts/76478-611-02.pdf. Accessed June 5 2015.
57. Trihexyphenidyl hydrochloride tablets, USP, prescribing information. Buffalo Grove, Illinois: Pack Pharmaceuticals, LLC; December 2010.Available at: http://www.packpharma.com/Files/Prescribing-Info/Package%20Insert%20-%20Trihexyphenidyl%20Hydrochloride%20Tablets%20-%202mg%20and%205mg.pdf. Accessed June 5, 2015.
58. Ehrt U, Broich K, Larsen JP, et al. Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study. *J Neurol Neurosurg Psychiatry* 2010;81:160–165.
59. Nishtala PS, Fois RA, McLachlan AJ, et al. Anticholinergic activity of commonly prescribed medications and neuropsychiatric adverse events in older people. *J Clin Pharmacol* 2009;49:1176–1184.
60. Schrag A, Horsfall L, Walters K, et al. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol* 2015;1:57–64.
61. National Parkinson Foundation. Anticholinergic drugs: What are the facts? Available at: http://www.parkinson.org/Parkinson-s-Disease/Treatment/Medications-for-Motor-Symptoms-of-PD/Anticholinergic-Drugs. Accessed June 5, 2015.
62. Symmetrel (amantadine hydrochloride) prescribing information. Chadds Ford, Pennsylvania: Endo Pharmaceuticals; January 2009. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016023s041,018101s016lbl.pdf. Accessed June 5, 2015.
63. Hubsher G, Haider M, Okun MS. Amantadine: the journey from fighting flu to treating Parkinson disease. *Neurology* 2012;78:1096–1099.
64. Schwab RS, England AC Jr, Poskanzer DC, et al. Amantadine in the treatment of Parkinson's disease. *JAMA* 1969;208:1168–1170.
65. Schwab RS, England AC Jr. Amantadine HCL (Symmetrel) and its relation to Levo-Dopa in the treatment of Parkinson's disease. *Trans Am Neurol Assoc* 1969;94:85–90.
66. Sawada H, Oeda T, Kuno S, et al. Amantadine for dyskinesias in Parkinson's disease: a randomized controlled trial. *PLoS One* 2010;5:e15298.
67. Kubo S, Iwatake A, Ebihara N, et al. Visual impairment in Parkinson's disease treated with amantadine: case report and review of the literature. *Parkinsonism Relat Disord* 2008;14:166–169.
68. Wolf E, Seppi K, Katzenschlager R, et al. Long-term antidyskinetic efficacy of amantadine in Parkinson's disease. *Mov Disord* 2010;25:1357–1363.
69. Ory-Magne F, Corvol JC, Azulay JP, et al. Withdrawing amantadine in dyskinetic patients with Parkinson's disease: the AMANDYSK trial. *Neurology* 2014;82:300–307.
70. Suchowersky O, Gronseth G, Perlmutter J, et al. Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;66:976–982.
71. Kieburtz K, Tilley BC, Elm JJ, et al. Effect of creatine monohydrate on clinical progression in patients with Parkinson disease: a randomized clinical trial. *JAMA* 2015;313:584–593.
72. Parkinson Study Group QE3 Investigators. A randomized clinical trial of high-dosage coenzyme Q10 in early Parkinson disease: no evidence of benefit. *JAMA Neurol* 2014;71:543–552.
73. Mythri RB, Bharath MM. Curcumin: a potential neuroprotective agent in Parkinson's disease. *Curr Pharm Des* 2012;18:91–99.
74. Anand P, Kunnamakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm* 2007;4:807–818.
75. Montgomery EB Jr. Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. [Author reply] *Neurology* 2007;68:164.
76. Sozio P, Cerasa LS, Abbadessa A, et al. Designing prodrugs for the treatment of Parkinson's disease. *Expert Opin Drug Discov* 2012;7:385–406.
77. Rákóczi K, Klivényi P, Vécsei L, et al. Neuroprotection in Parkinson's disease and other neurodegenerative disorders: preclinical and clinical findings. *Ideggyogy Sz* 2009;62:25–34.
78. Calabresi P, Di Filippo M, Gallina A, et al. New synaptic and molecular targets for neuroprotection in Parkinson's disease. *Mov Disord* 2013;28:51–60.
79. Hirch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? *Lancet Neurol* 2009;8:382–397.
80. Hauser RA, Olanow CW, Kieburtz KD, et al. Tozadenant (SYN115) in patients with Parkinson's disease who have motor fluctuations on levodopa: a phase 2b, double-blind, randomised trial. *Lancet Neurol* 2014;13:767–776.
81. Palacios N, Gao X, McCullough ML, et al. Caffeine and risk of Parkinson's disease in a large cohort of men and women. *Mov Disord* 2012;27:1276–1282.
82. Park A, Stacy M. Istradefylline for the treatment of Parkinson's disease. *Expert Opin Pharmacother* 2012;13:111–114.
83. Zhu C, Wang G, Li J, et al. Adenosine A2A receptor antagonist istradefylline 20 versus 40 mg/day as augmentation for Parkinson's disease: a meta-analysis. *Neurol Res* 2014;36:1028–1034.
84. Hickey P, Stacy M. Adenosine A2A antagonists in Parkinson's disease: What's next? *Curr Neurol Neurosci Rep* 2012;12:376–385.
85. Johnson KA, Conn PJ, Niswender CM. Glutamate receptors as therapeutic targets for Parkinson's disease. *CNS Neurol Disord Drug Targets* 2009;8:475–491.
86. Bensimon G, Ludolph A, Agid Y, et al. Riluzole treatment, survival, and diagnostic criteria in Parkinson disorders: the NNIPPS study. *Brain* 2009;132(Pt 1):156–171.
87. Hauser RA. Future treatments for Parkinson's disease: surfing the PD pipeline. *Int J Neurosci* 2011;121(suppl 2):53–62.
88. Zambon Pharma. Xadago (safinamide) new drug application (NDA) accepted for filing by the U.S. Food and Drug Administration (FDA). March 2, 2015. Available at: http://www.zambonpharma.com/en/zspa-newsspa/zc-zcnews/entry/0/1228/2823/la-food-and-drug-administration-fda-statunitense-ha-accettato.html. Accessed June 15, 2015.
89. Stocchi F, Borgohain R, Onofrj M, et al. A randomized, double-blind, placebo-controlled trial of safinamide as add-on therapy in early Parkinson's disease patients. *Mov Disord* 2012;27:106–112.
90. Schapira AH, Stocchi F, Borgohain R, et al. Long-term efficacy and safety of safinamide as add-on therapy in early Parkinson's disease. *Eur J Neurol* 2013;20:271–280.
91. Shen C, Guo Y, Luo W, et al. Serum urate and the risk of Parkinson's disease: results from a meta-analysis. *Can J Neurol Sci* 2013;40:73–79.
92. Pasternak B, Svanström H, Nielsen NM, et al. Use of calcium channel blockers and Parkinson's disease. *Am J Epidemiol* 2012;175:627–635.
93. Wahner AD, Bronstein JM, Bordelon YM, Ritz B. Nonsteroidal anti-inflammatory drugs may protect against Parkinson disease. *Neurology* 2007;69:1836–1842.
94. Samii A, Etminan M, Wiens MO. NSAID use and the risk of Parkinson's disease: systematic review and meta-analysis of observational studies. *Drugs Aging* 2009;26:769–779.
95. Manthripragada AD, Schernhammer ES, Qiu J, et al. Non-steroidal anti-inflammatory drug use and the risk of Parkinson's disease. *Neuroepidemiology* 2011;36:155–161.
96. Hancock DB, Martin ER, Stajich JM, et al. Smoking, caffeine, and nonsteroidal anti-inflammatory drugs in families with Parkinson disease. *Arch Neurol* 2007;64:576–580.
97. Powers KM, Kay DM, Factor SA, et al. Combined effects of smoking, coffee, and NSAIDs on Parkinson's disease risk. *Mov Disord* 2007;23:88–95.

98. Gao X, Simon KC, Schwarzschild MA, et al. Prospective study of statin use and risk of Parkinson disease. *Arch Neurol* 2012;69:380–384.
99. Moreau C, Delval A, Defebvre L, et al. Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial. *Lancet Neurol* 2012;11:589–596.
100. Aviles-Olmos I, Dickson J, Kefalopoulou Z, et al. Exenatide and the treatment of patients with Parkinson's disease. *J Clin Invest* 2013;123:2730–2736.
101. Simuni T, Brundin P. Is exenatide the next big thing in Parkinson's disease? *J Parkinsons Dis* 2014;4:345–347.
102. Murata M, Hasegawa K, Kanazawa I. Zonisamide improves motor function in Parkinson disease: a randomized, double-blind study. *Neurology* 2007;68:45–50.
103. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. *JAMA* 2014;311:1670–1683.
104. Tomlinson CL, Patel S, Meek C. Physiotherapy intervention in Parkinson's disease: systematic review and meta-analysis. *BMJ* 2012;345:e5004.
105. Rosenthal LS, Dorsey ER. The benefits of exercise in Parkinson disease. *JAMA Neurol* 2013;70:156–157.
106. Corcos DM, Comella CL, Goetz CG. Tai chi for patients with Parkinson's disease. *N Engl J Med* 2012;366:1737–1738.
107. Shulman LM, Katzel LI, Ivey FM, et al. Randomized clinical trial of 3 types of physical exercise for patients with Parkinson disease. *Arch Neurol* 2012;5:1–8.
108. Canning CG, Sherrington C, Lord SR, et al. Exercise for falls prevention in Parkinson disease: a randomized controlled trial. *Neurology* 2014;84:304–312.
109. París AP, Saleta HG, de la Cruz Crespo Maraver M, et al. Blind randomized controlled study of the efficacy of cognitive training in Parkinson's disease. *Mov Disord* 2011;26:1251–1258.
110. Sturkenboom IH, Graff MJ, Hendriks JC, et al. Efficacy of occupational therapy for Parkinson's disease: a randomized controlled trial. *Lancet Neurol* 2014;13:557–566.
111. Halpern AE, Ramig LO, Matos CE. Innovative technology for the assisted delivery of intensive voice treatment (LSVT Loud) for Parkinson disease. *Am J Speech Lang Pathol* 2012;21:354–367.
112. Huang W-Y, Xi G-F, Hua X-G. Clinical observation of combined acupuncture and herbs in treating Parkinson's disease. *J Acupunct Tuina Sci* 2009;7:33–36.
113. Lee MS, Shin BC, Kong JC, Ernst E. Effectiveness of acupuncture for Parkinson's disease: a systematic review. *Mov Disord* 2008;23:1505–1515.
114. Yu H, Slavin KV. *Parkinson's Disease.* San Francisco, California: International Neuromodulation Society; December 2011. Available at: http://www.neuromodulation.com/assets/documents/Fact_Sheets/fact_sheet_parkinsons.pdf . Accessed July 8, 2015.
115. Okun MS, Zeilman PR. *Parkinson's Disease: Guide to Deep Brain Stimulation Therapy*, 2nd ed. Hagerstown, Maryland: National Parkinson Foundation; 2014. Available at: http://www3.parkinson.org/site/DocServer/Guide_to_DBS_Stimulation_Therapy.pdf?docID=189. Accessed July 8, 2015.
116. Fasano A, Daniele A, Albanese A, et al. Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. *Lancet Neurol* 2012;11:429–442.
117. Okun MS. Deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2012;367:1529–1538.
118. Williams A, Gill S, Varma T, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol* 2010;9:581–591.
119. Food and Drug Administration. FDA approves brain implant to help reduce Parkinson's disease and essential tremor symptoms. June 12, 2015. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm451152.htm. Accessed July 6, 2015.
120. Okun MS, Fernandez HH, Rodriguez RL, et al. Identifying candidates for deep brain stimulation in Parkinson's disease: the role of the primary care physician. *Geriatrics* 2007;62:18–24.
121. Okun MS, Foote KD. Parkinson's disease DBS: what, when, who and why? The time has come to tailor DBS targets. *Expert Rev Neurother* 2010;10:1847–1857.
122. Terzic D, Abosch A. Update on deep brain stimulation for Parkinson's disease. *J Neursurg Sci* 2012;56:267–277.
123. Lee KH, Hitti FL, Chang SY, et al. High frequency stimulation abolishes thalamic network oscillations: an electrophysiological and computational analysis. *J Neural Eng* 2011;8:046001.
124. Tawfik VL, Chang SY, Hitti FL, et al. Deep brain stimulation results in local glutamate and adenosine release: investigation into the role of astrocytes. *Neurosurgery* 2010;67:367–375.
125. Welter ML, Schupbach M, Czernecki V, et al. Optimal target localization for subthalamic stimulation in patients with Parkinson disease. *Neurology* 2014;82:1352–1361
126. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2010;362:2077–2091.
127. Weaver FM, Follett KA, Stern M, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes; turning tables: should GPi become the preferred DBS target for Parkinson disease? *Neurology* 2012;79:55–65.
128. Taba HA, Wu SS, Foote KD, et al. A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort. *J Neurosurg* 2010;113:1224–1229.
129. Alberts JL, Hass CJ, Vitek JL, Okun MS. Are two leads always better than one? An emerging case for unilateral subthalamic deep brain stimulation in Parkinson's disease. *Exp Neurol* 2008;214:1–5.
130. Odekerken VJ, van Laar T, Staal MJ, et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. *Lancet Neurol* 2013;12:37–44.
131. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med* 2013;368:610–622.
132. Okun MS, Fernandez HH, Wu SS, et al. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. *Ann Neurol* 2009;65:586–595.
133. Voges J, Waerzeggers Y, Maarouf M, et al. Deep-brain stimulation: long-term analysis of complications caused by hardware and surgery: experiences from a single centre. *J Neurol Neurosurg Psychiatry* 2006;77:868–872.
134. Sillay KA, Larson PS, Starr PA. Deep brain stimulator hardware-related infections: incidence and management in a large series. *Neurosurgery* 2008;62:360–366.
135. Fenoy AJ, Simpson RK. Management of device-related wound complications in deep-brain stimulation surgery. *J Neurosurg* 2012;116:1324–1332.
136. Schuurman PR, Bosch DA, Merkus MP, Speelman JD. Long-term follow-up of thalamic stimulation versus thalamotomy for tremor suppression. *Mov Disord* 2008;23:1146–1153.
137. Esselink RA, de Bie RM, de Haan RJ, et al. Long-term superiority of subthalamic nucleus stimulation over pallidotomy in Parkinson disease. *Neurology* 2009;73:151–153.
138. Barker RA, Barrett J, Mason SL. Fetal dopaminergic transplantation trials and the future of neural grafting in Parkinson's disease. *Lancet Neurol* 2013;12:84–91.
139. Kefalopoulou Z, Politis M, Piccini P, et al. Long-term clinical outcome of fetal cell transplantation for Parkinson disease: two case reports. *JAMA Neurol* 2014;71:83–87.
140. Arenas E. Toward stem cell replacement therapies for Parkinson's disease. *Biochem Biophys Res Commun* 2010;396:152–156.
141. Douglas MR. Gene therapy for Parkinson's disease: state-of-the-art treatments for neurodegenerative disease. *Expert Rev Neurother* 2013;13:695–705.
142. Aron L, Klein R. Repairing the parkinsonian brain with neurotrophic factors. *Trends Neurosci* 2011;34:88–100.
143. Marks WJ, Bartus RT, Siffert J, et al. Gene delivery of AAV2 neurturin for Parkinson's disease: a double-blind, randomized, controlled trial. *Lancet Neurol* 2010;9:1164–1172.
144. Palfi S, Gurruchaga JM, Ralph GS, et al. Long-term safety and tolerability of ProSavin, a lentiviral vector-based gene therapy for Parkinson's disease: a dose escalation, open-label, phase 1/2 trial. *Lancet* 2014;383:1138–1146. ■