Parkinson’s Disease Treatment

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Program Overview:

To provide nurses and pharmacists with an understanding of Parkinson’s Disease treatment.

OBJECTIVES:

After completing this program, participants will be able to:

- Describe Parkinson’s Disease
- List drugs used in the treatment of Parkinson’s Disease
- Describe the pharmacological management of each drug used in the treatment of Parkinson’s Disease
- Describe the mechanism of action, toxicities, and pharmacokinetics of drugs used to treat Parkinson’s Disease
Introduction

While Alzheimer's disease is considered to be the most common neurodegenerative disease, Parkinson’s disease (PD) is regarded as number two.\textsuperscript{1,2,14} The clinical symptoms of PD include motor and nonmotor, with nonmotor symptoms starting 4 to 20 years before the motor symptoms are noticeable.\textsuperscript{2} The diagnosis, however, is based upon the classic motor symptoms of resting tremor, postural instability, bradykinesia and rigidity. The etiology is unknown for most cases, but it is theorized that toxic environmental factors and genetic predisposition are at play. For the minority of cases that have been found to be hereditary, gene mutations have been identified.\textsuperscript{44} No treatment that can stop the progression of PD is currently available; antiparkinson medication merely ameliorates the motor symptoms. This article focuses on the epidemiology, etiology and pathogenesis, pathophysiology, current medications and their side effects.

Epidemiology of Parkinson's Disease

The disease affects 1 million to 1.5 million, and both sexes are fairly equally affected.\textsuperscript{1,4,5} Although there are some PD patients who are in their 20’s, the average age of onset is approximately 60 years old. The risk of developing this disease rises with increased age, for while there are 16 cases of PD for every 100,000 Americans overall, there are 200 cases for every 100,000 in their 70’s and 80’s.\textsuperscript{1,3,4} Approximately 1 to 2% of people over 60 years old have PD.\textsuperscript{12} The lifetime risk to develop PD is estimated to be 2%, but a positive family history increases that risk to 4%.\textsuperscript{3}

Etiology and Pathogenesis of Parkinson's Disease
The etiology of PD is unknown for the approximately 85 to 90% of all cases where the disease occurs randomly. It is hypothesized, however, that sporadic PD may develop as a result of certain environmental factors that interact with specific genes in those who are genetically predisposed. The genetic predisposition and toxic environmental factor are both required in this hypothesis.

It was recently discovered that the first degree relatives of PD patients have an increased risk of developing the disease, and that monozygotic twins who develop PD before 50 years old have a higher rate of concordance than dizygotic twins who also develop PD early. Subsequently, several gene mutations and their specific chromosomal locations were identified for the 10 to 15% of PD cases now considered to be familial. The investigators of the Genetic Epidemiology of Parkinson's Disease Consortium conducted analyses from April 2004 to December 2005 involving 18 sites throughout the world, and concluded that the α-synuclein gene is associated with PD. Since that time, mutations in the α-synuclein gene located on chromosome 4q21-23 (loci 21 to 23 on the long arm of chromosome 4) have been found to cause the autosomal dominant familial form of PD. The function of α-synuclein is unknown, but it is located near the synaptic vesicles in a nerve cell, or the vesicles which store neurotransmitters until they are to be released across the synapse to the next nerve cell. Overexpression of the nonmutated gene also causes motor problems, decreased dopaminergic nerve cells and the creation of Lewy bodies, all characteristics of PD. A mutation in UCHL-1 (ubiquitin carboxyl terminal hydrolase L1) interferes with the normal disintegration of damaged and abnormal proteins. Found on chromosome 4p14 (locus 14 on the short arm of chromosome 4), a mutated UCHL-1 has been located in one family that has the autosomal dominant form of PD. The parkin gene on chromosome 6q25-27 is also
involved in the normal degradation of damaged and abnormal proteins. Mutations in this gene lead to autosomal recessive PD, although most patients will not have Lewy bodies.\(^1,^6\) A mutated LRRK2 has been associated with autosomal dominant PD.\(^{26,28,29}\) It has now been found on chromosome 12p11-q13, and has been identified in 1% of random cases and 4% of familial. The mutated LRRK2 is common in patients from southern Europe and the Mid East, with an increased risk of developing a benign form of PD between the ages of 69 years old to 79 years old.\(^6\) In one study, 37% of North African Arabs with the familial form of PD had the LRRK2 mutation.\(^{18}\)

Proteins fold in an orderly, stepwise manner to form a functional three-dimensional structure.\(^7\) All of the cells in the body have the ability to degrade proteins inside the cell which have not properly folded. If the cells lose this ability, proteins can accumulate and interfere with normal processes. This is the case in neurodegenerative diseases, including PD.\(^1,^13\) Lewy bodies are round, pink proteins which have not folded properly and have accumulated in the cytoplasm of neurons in the substantia nigra (area of the brain). Lewy bodies and the mutations of the UCHL-1 and parkin genes indicate that the abnormal accumulation of protein is at least partial explanation of the etiology and pathogenesis of PD.\(^1\)

**Pathophysiology**

In PD, there is a loss of dopaminergic neurons in the substantia nigra; decreased dopamine in the striatum (caudate and putamen); a loss of pigmentation in the neurons of the brainstem, but especially in the substantia nigra; and the development of gliosis and Lewy bodies. A decrease in dopaminergic neurons leads to increased firing of neurons in the globus pallidus and subthalamic nuclei. As a result, the thalamus is inhibited and there is less activation of
the motor cortex, which results in the clinical features of PD.\textsuperscript{1,5} Dopaminergic neurons in the substantia nigra project their axons to the striatum and regulate a balance between excitatory and inhibitory pathways.\textsuperscript{2,11,12,24} Dopamine is released in the striatum; thus, less dopaminergic neurons results in less dopamine in the striatum and the activation of the inhibitory pathway.\textsuperscript{5,24} The severity of the motor symptoms in PD is proportional to the deficiency of dopamine.\textsuperscript{11} The loss of pigmentation is such that the substantia nigra will look pale if it can be seen with the naked eye.\textsuperscript{4,5,8} The gliosis that develops involves the hyperplasia and hypertrophy of the astrocytes (the main cells responsible for repair in the brain). Gliosis also leads to the formation of scars.\textsuperscript{11} In almost all patients with sporadic PD, one or multiple Lewy bodies are discovered in the cytoplasm of some of the dopaminergic neurons that still remain.\textsuperscript{1,8,10,11}

**Pharmacological Management**

Currently, there is no treatment that can stop or reverse the loss of dopaminergic neurons in PD. The medications that are used are prescribed to give symptomatic relief. Treatment strategies involve increasing the amount of dopamine activity within the brain, decreasing the amount of muscarinic cholinergic brain activity or a combination of both. (Dopamine and acetylcholine need to be in balance for normal, balanced movement.)

**Levodopa**

Levodopa (larodopa, L-dopa, L-3,4-dihydroxyphenylalanine) was first introduced in the late 1960's.\textsuperscript{1,10} From that time until the present, it has been the most effective medication to treat the symptoms of PD and is considered the “gold standard,” even for those patients who are in an advanced stage.\textsuperscript{1,10,22} Administering dopamine will not alleviate the dopamine deficiency in
the striatum, because dopamine cannot cross the blood-brain barrier. The amino acid levodopa, however, is a precursor of dopamine and can cross the blood-brain barrier through an L-amino acid transporter. Once it has entered the brain, it is decarboxylated to dopamine by the enzyme L-amino acid decarboxylase.\textsuperscript{9,10} There are D1- and D2-type dopamine receptors in the substantia nigra, but symptomatic relief seems to primarily be the result of D2-receptor stimulation, although the stimulation of D1 receptors may be necessary to achieve the most benefit.\textsuperscript{9} To prevent levodopa from being converted in the peripheral body tissues to dopamine, since L-amino acid decarboxylase is also in many of the body tissues, the medication carbidopa is administered along with levodopa. Carbidopa does not cross the blood-brain barrier, and is a decarboxylase inhibitor in the peripheral body tissues. When it is administered with levodopa, the plasma half-life of levodopa is longer, the plasma level is higher and the daily requirement of levodopa is decreased by an estimated 75% when compared to the administration of levodopa alone.\textsuperscript{9,30}

Levodopa ameliorates the motor signs of PD in almost all patients; that is, the bradykinesia, rigidity, tremor at rest and postural instability. The ELLDOPA study conducted from 1998 to 2001 by the Parkinson Study Group demonstrated that levodopa does not increase the degeneration of the remaining dopaminergic neurons, nor increase the progression of PD, as was once thought.\textsuperscript{19} It improves the quality of life, lengthens independence and decreases the mortality rate.\textsuperscript{9,24} At first the amelioration of symptoms will last for several hours, but the response to levodopa will decrease over time; benefits from one dose last shorter and shorter, until the therapeutic response nears the half-life. This is referred to as the “wearing-off effect.”\textsuperscript{1,4}

Levodopa is quickly absorbed from the small intestines, but the amount and rate of absorption
depends upon how long the medication has been exposed to the gastric and intestinal enzymes, the pH of the gastric juice, the rate that the stomach empties and whether or not there is any competition for absorption from amino acids in the diet. Taking levodopa while consuming a high-protein meal will delay the absorption of levodopa and decrease its peak plasma concentration.\textsuperscript{9,10} Normally, the plasma concentration peaks between 0.5 to 2 hours, while the half-life is fairly short, lasting 1 to 3 hours. Within 8 hours, approximately 66% of levodopa will be in the urine as metabolic products, primarily as dihydroxyphenylacetic acid (DOPAC) and 3-methoxy-4-hydroxyphenyl acetic acid (HVA).\textsuperscript{41}

It is contraindicated to prescribe levodopa to psychotic patients. Patients with closed-angle glaucoma should not take levodopa; however, it can be taken by those with open-angle glaucoma, as long as the intraocular pressure is monitored and controlled.\textsuperscript{30,41} Someone with an active peptic ulcer should be carefully monitored, as gastrointestinal bleeding occasionally happens.\textsuperscript{9,30} It is contraindicated to take levodopa if a MAO inhibitor has been taken within 14 days prior because it can lead to a hypertensive crisis.\textsuperscript{9} Levodopa can be taken with MAO type B at the manufacturer’s recommended dose.\textsuperscript{30,41} A patient with a skin lesion that is undiagnosed or a history of melanoma should not take levodopa, for levodopa is a precursor of melanin. As such, it could activate melanoma. If prescribed, the patient should be carefully monitored by a dermatologist.\textsuperscript{9,30,41}

Approximately 80% of the patients who take levodopa without carbidopa will have the gastrointestinal toxicities of nausea, vomiting and anorexia. These side effects can be decreased if the medication is gradually titrated by slowly increasing the daily dose, by taking levodopa with or immediately after meals, dividing the doses, or taking an antacid 30 to 60 minutes before taking the medication. However, tolerance to nausea usually does develop
after a period of several months.\textsuperscript{1,9} Cardiovascular toxicities include postural hypotension, which is common but decreases with time. Levodopa can cause hypertension if concurrently taking a sympathomimetic or nonselective MAO inhibitor.\textsuperscript{41} Some patients experience ventricular extrasystoles and tachycardias, but the reported percentage is low, even in those who have heart disease.\textsuperscript{9} Various behavioral effects have been noted; these toxicities are more common in those taking levodopa without carbidopa. It is hypothesized that this is the result of increased dopamine in the brain due to carbidopa, but behavioral effects may also be precipitated by surgical operations and illness.\textsuperscript{9} Some patients report nightmares, confusion, agitation, euphoria, delusions, insomnia, depression, hallucinations, somnolence and anxiety. Atypical antipsychotics may be of help.\textsuperscript{9, 41}

Many who take levodopa develop choreiform movement disorders, myoclonus, or dystonia when the medication is at its peak plasma concentration. This dyskinesia is not disabling if it is mild, but it can be disabling if the abnormal movements are severe.\textsuperscript{9,27} In advanced PD, levodopa can cause an “on-off phenomenon,” which takes place in a time span of a few hours, in which the patient will have disabling dyskinesias but improved mobility in the “on” period, and akinesia and hypomobility in the “off” period. The mechanism of action for this pharmacological effect is unknown, but usually happens in those who initially respond favorably to levodopa.\textsuperscript{9,24} Precautions should be taken not to falsely diagnose a pheochromocytoma when interpreting catecholamine levels in the urine and plasma. Caution should be taken in patients with a respiratory disease, impaired kidney or liver.\textsuperscript{30,41}

Oral iron salts can interact with levodopa and decrease its absorption, with the exception of iron sucrose, ferumoxytol, iron dextran complex and ferric gluconate.\textsuperscript{41} Sapropterin, metoclopramide, phenytoin and large doses of methionine can all lower the therapeutic
effects. Pyridoxine can lower the effects because it increases the metabolism of levodopa; taking carbidopa along with levodopa and pyridoxine eliminates this negative interaction.\textsuperscript{9} Kava kava should not be taken with levodopa as it can decrease the effects as well. Methylphenidate can raise the toxicity of levodopa.\textsuperscript{41}

Rare reports of adverse reactions include various hematologic disorders; gout; priapism; hot flushes; brown-colored vaginal secretions, urine or saliva; abnormalities of taste and smell; mild, temporary increases in bilirubin, BUN, alkaline phosphatase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST); and mydriasis which precipitates acute glaucoma.\textsuperscript{9,30,41}

Levodopa is usually prescribed with carbidopa. The immediate release (IR) tablet initially prescribed is carbidopa 25 mg/levodopa 100 mg, at 3 tablets a day. If necessary, the dosage can be increased by one tablet every other day. If the prescription is for the IR tablet of carbidopa 25 mg/levodopa 250 mg, the dosage can be increased one-half tablet to one tablet every 1 to 2 days. At either strength, the maximum number of tablets per day is 8 tablets or 200 mg of carbidopa and 2000 mg of levodopa. The initially prescribed sustained release tablet is carbidopa 50 mg/levodopa 200 mg, taken 2 times a day, at least 6 hours apart. The dosage can be adjusted every 3 days, with 8 tablets as the maximum number of tablets per day. The initial dosage for the elderly is carbidopa 25 mg/levodopa 100 mg, 2 tablets a day.\textsuperscript{9,41}

The pregnancy risk factor is C; that is, the safety is uncertain. Teratogenic effects have been seen in studies involving animals. There are reports that levodopa crosses the placenta, but it is not known if it is excreted in breast milk.\textsuperscript{41}
Dopamine Agonists

The dopamine agonists include the various medications that work directly on dopamine receptors. The first dopamine agonists developed were bromocriptine and pergolide, both ergot derivatives. Pergolide caused regurgitation of one or more of the cardiac valves.\textsuperscript{17} It was then pulled from the market in 2007 because it led to fibrosis of the cardiac valves.\textsuperscript{1,9} Ergot alkaloids are made by the fungus Claviceps purpurea, which is a fungus that affects spoiled or wet grain and synthesizes tyramine, acetylcholine and histamine. There are over 20 ergot alkaloids, but just a few are used for synthetic therapeutic medications. Some are partial agonists at serotonin receptors and alpha adrenoreceptors, while bromocriptine and pergolide stimulate the D2 receptors in the neurons of the brain, which increases the activity of the dopaminergic pathways.\textsuperscript{1,8,9,10} The newer dopamine agonists are represented by pramipexole and ropinirole, which stimulate the D3 and D2 receptors respectively, but are non-ergot dopamine agonists. Dopamine agonists usually last therapeutically longer than levodopa.\textsuperscript{10}

Bromocriptine

Bromocriptine is rarely prescribed, for the current medications of choice are the newer, non-ergot dopamine agonists, which have less troublesome side effects. As a dopamine agonist, it improves motor functions and its therapeutic effects last longer than levodopa, but it also decreases the amount of “off” time in the “on-off phenomenon.” \textsuperscript{1,9,10} Bromocriptine is absorbed from the gastrointestinal tract; the plasma concentration peaks in 1 to 2 hours, while its half-life lasts 8 to 20 hours. It is metabolized in the liver via the
cytochrome P450 enzymes, and excreted in the urine and feces with 2 to 6% as either metabolites or unchanged.\textsuperscript{42}

Contraindications to the use of bromocriptine include ischemic heart disease, pregnancy, hypersensitivity to bromocriptine or its ingredients, vascular disorders and uncontrolled hypertension. The toxic effects include postural hypotension, nausea, vomiting and anorexia.\textsuperscript{42} Similar to levodopa, there can be delusions, hallucinations and confusion as a result of increased dopamine in the brain. Long-term use can lead to fibrosis of the cardiac valves. Patients should be warned that this medication can cause somnolence and the sudden onset of sleep, as there have been reports of patients falling asleep while driving.\textsuperscript{1,21,31,42} Those taking bromocriptine need regular monitoring by a dermatologist, due to an increased risk for the development of melanoma.\textsuperscript{41}

With the exception of the alpha agonist dipivefrin, alpha agonists and beta agonists can increase the toxicity of bromocriptine, potentially causing seizure, ventricular arrhythmias and increased blood pressure. Methylphenidate and macrolide antibiotics, with the exception of spiramycin and azithromycin, can increase the toxic effects. Metoclopramide and St. John's wort lower the therapeutic effects. MAO inhibitors can raise the risk of hypotension, while taking cyclosporine concomitantly with bromocriptine can increase the concentration of cyclosporine in the serum. The following medications should not be used concomitantly: sibutramine, protease inhibitors, efarirenz, serotonin receptor agonists, antipsychotics, posaconazole, voriconazole and itraconazole. The use of bromocriptine with sibutramine can cause serotonin syndrome, there can be vasoconstriction with the concomitant use of serotonin receptor agonists, while combining efarirenz can lead to ischemia. Antipsychotics either increase the toxic effects or lower the therapeutic effects. Protease inhibitors,
posaconazole, voriconazole and itraconazole can increase the serum concentration of bromocriptine. ⁴²

Bromocriptine is initially prescribed at 1.25 mg twice a day, to be increased every 2 to 4 weeks by 2.5 mg a day over a period of 2 to 3 months, to minimize any adverse reactions. The maximum dosage is 100 mg/day. Elderly patients are usually prescribed lower doses.⁹,⁴² Women not planning to become pregnant should be advised to take contraception. There is no evidence of bromocriptine being teratogenic based on animal studies; thus, the pregnancy risk factor is B. There are no reports of an increase in birth defects, but most women stopped using bromocriptine by the eighth week of pregnancy. It is not recommended to take bromocriptine while breastfeeding, because the medication is excreted in breast milk. ⁴²

**Pramipexole**

Pramipexole is a non-ergot dopamine agonist which stimulates the D₃ receptors. It may be prescribed for mild cases of PD, but when used in advanced stages, the levodopa dosage can be decreased by an estimated 50% and it is especially effective treating patients who are experiencing the “on-off phenomenon.”⁸,⁹,¹⁰ It is quickly absorbed from gastrointestinal tract. The plasma concentration peaks in approximately 2 hours for the IR form, but peaks in 6 hours for the extended release (ER) form. The half-life is 8.5 hours, but 12 hours for the elderly. It is excreted in the urine, 90% unchanged.⁹,⁴³

It is contraindicated to prescribe pramipexole for a patient who is hypersensitive to pramipexole or any of its ingredients. The toxic effects include postural hypotension, fatigue, sleepiness, nausea, confusion and hallucinations. Hallucinations may especially be seen in
older patients.\textsuperscript{10,32,43} Pramipexole can either cause or exacerbate any existing dyskinesia and should, therefore, be used with caution in any patient who is already exhibiting this effect. Patients should be monitored on a regular basis by a dermatologist due to the increased risk for developing melanoma.\textsuperscript{32,43} There are reports of pulmonary infiltrates, pleural thickening and retroperitoneal fibrosis, which warrants close monitoring. The dosage will need to be adjusted for any patient who has renal impairment.\textsuperscript{43}

Antipsychotics either increase the toxic effects or decrease the therapeutic effects and should not be taken concomitantly. MAO inhibitors can raise the risk of hypotension, methylphenidate can raise the toxicity, metoclopramide can lower the therapeutic effects, and cimetidine can raise the serum concentration of pramipexole. Kava kava, valerian, SAMe and St. John’s wort should not be taken while taking pramipexole, as their interaction can cause excessive sedation and/or the serotonin syndrome.\textsuperscript{43}

The initial dosage for the IR form is 0.375 mg a day, which should be divided into 3 doses. The dosage should be gradually increased every 5 to 7 days, to minimize any adverse effects, with the maximum dose as 4.5 mg a day. The initial dosage for the ER form is also 0.375 mg a day, but there is just 1 dose a day. The dosage can be gradually increased by 0.75 mg a day, every 5 to 7 days. The maximum dose is 4.5 mg a day.\textsuperscript{43} If pramipexole is going to be discontinued, it must be gradually tapered over one week, otherwise there is a risk of developing a disorder that resembles neuroleptic malignant syndrome.\textsuperscript{9,32,43} The pregnancy risk factor is C, as there have not been any controlled studies involving pregnant women, but animal studies showed embryo demise and impaired postnatal growth. It is not recommended to take pramipexole while breastfeeding; it is not known whether or not the medication is excreted in breast milk.\textsuperscript{43}
Ropinirole

Ropinirole is a non-ergot dopamine agonist. It stimulates the D2 receptor and is effective in mild cases. It is also effective in those patients in an advanced stage who have “on-off phenomenon.” 9,10 It is absorbed in the gastrointestinal tract, but its absorption is unaffected by the consumption of food. Ropinirole is metabolized in the liver by the cytochrome P450 enzymes to inactive metabolites. The plasma concentration peaks at approximately 1 to 2 hours for the IR form, and at 6 to 10 hours for the ER form. The half-life elimination is estimated at 6 hours. It is excreted in the urine, 60% as metabolites and less than 10% as unchanged. For patients over 65 years old, its clearance is decreased from 15 to 30%.44

A patient hypersensitive to ropinirole or any of its ingredients should not take this medication. Ropinirole can cause somnolence, fatigue, hallucinations, nausea, confusion, dyskinesia and postural hypotension, although the dyskinesias are less frequent than those seen with patients taking levodopa.8,10 The elderly are at a higher risk of developing hallucinations.44 Ropinirole can cause low blood pressure when the dose is greater than 0.25 mg.44 It is hypothesized that this happens due to a decreased noradrenergic reaction to standing and decreased resistance in the peripheral veins. Patients should be carefully monitored for postural hypotension, especially when the dosage is being increased. Some patients have syncope with or without bradycardia.44 There should be regular monitoring by a dermatologist because of the increased risk of melanoma. Patients should be monitored for signs and symptoms of pulmonary infiltrates, retroperitoneal fibrosis and pleural thickening.33,44

MAO inhibitors increase the risk of postural hypotension, metoclopramide lowers the
therapeutic effects of ropinirole, methylphenidate raises its toxicity, ciprofloxacin lowers its metabolism, and estrogen derivatives raise the serum concentration. Antipsychotics lower the therapeutic effects or raise the toxicity; the recommendation is not to take antipsychotics concomitantly with ropinirole. It is also advised not to take valerian, kava kava, St. John's wort and gotu kola, for they can increase central nervous system (CNS) depression.44

The initial dosage for the IR tablet for the first week is 0.25 mg 3 times a day. The dosage is then slowly increased to minimize any toxic effects. The dosage for the second week is 0.5 mg 3 times a day, week 3 is increased to 0.75 mg 3 times a day and the dosage for week 4 is 1 mg 3 times a day. If the patient still needs an increase in dosage, it can be increased by 1.5 mg a day on a weekly basis, up to a total daily dose of 9 mg a day.9 If needed, it can then be raised by 3 mg a day on a weekly basis until the total daily dose is 24 mg a day. If ropinirole is going to be discontinued, it must be gradually tapered over a 7 day period; the frequency should be decreased to 2 times a day for the first 4 days, and then lowered to one time a day for the remaining 3 days. The initial dosage for the ER tablet is 2 mg once a day for the first 1 or 2 weeks. The dose can be increased by 2 mg a day on a weekly basis, with the maximum dosage as 24 mg a day. Ropinirole ER tablet is tapered in the same manner as the IR tablet.44 The pregnancy risk factor is C; no controlled studies have been done involving pregnant women. Animal studies show teratogenesis. It is not known whether ropinirole is excreted in breast milk and is, therefore, not recommended to take it while breastfeeding.44

**Apomorphine**

Apomorphine is a dopamine agonist which stimulates D2, D3, D4 and D5 receptors.10 It is used as “rescue therapy” for a patient who has a severe “off” period (of the “on-off
Apomorphine is subcutaneously injected and rapidly goes from the bloodstream to the D2 receptors in the striatum. Therapeutic benefit starts in approximately 10 minutes and lasts for up to 2 hours. The plasma concentration peaks in 20 minutes; the half-life is 40 minutes. It is not known how apomorphine is metabolized, but it is primarily excreted in the urine.

A patient hypersensitive to apomorphine or any of its ingredients should not take it. It is contraindicated to administer it via an IV or for it to be used concomitantly with serotonin (5HT3) antagonists. The toxic effects include hypotension, chest pain, dyskinesia, sweating, drowsiness, falls, abnormal EKG (QT prolongation), nausea and vomiting. Vomiting can be such that taking apomorphine necessitates pre and post anti-emetics. Trimethobenzamide at 300 mg 3 times a day should be started 3 days before the patient receives the first dose of apomorphine. This anti-emetic should continue to be administered for at least the first 2 months of receiving apomorphine. It may need to be administered indefinitely.

Ondansetron is an anti-emetic, but a serotonin (5HT3) antagonist. If used, it can cause loss of consciousness and extreme hypotension; thus, its use is contraindicated with apomorphine.

The patient should be monitored for pleural thickening, pulmonary infiltrates and retroperitoneal fibrosis, and see a dermatologist on a regular basis because of the increased risk for melanoma. Apomorphine should be used with great caution in patients who have cardiovascular disease, for hypotension can lead to ischemia in the coronary arteries. Hypotension can lead to ischemia in the cerebral arteries, so caution is advised for patients with cerebrovascular disease. Apomorphine can exacerbate dyskinesias in those with the preexisting condition. Caution is advised for patients who have renal and hepatic impairment,
and for those who are at risk for developing torsade de pointes. These risk factors include bradycardia, hypomagnesemia, hypokalemia, genetics and medications that prolong the QT on an EKG.\textsuperscript{10, 45}

Antipsychotics increase the toxicity of apomorphine or decrease its therapeutic effects; as such, it is recommended not to take any antipsychotics while taking apomorphine. Methylphenidate raises the toxic effects of apomorphine, while metoclopramide lowers its therapeutic effects, and MAO inhibitors raise the risk of becoming hypotensive. Alfuzosin, chloroquine, ciprofloxacin, and gadobutrol can increase the QT effects of QT-prolonging agents. Taking these medications requires careful monitoring.\textsuperscript{45}

Three days before the initial dose of apomorphine, the anti-emetic trimethobenzamide should be administered at 300 mg 3 times a day, and continued for a minimum of 2 months. At that time, an assessment should be made to determine if trimethobenzamide is still needed.\textsuperscript{9} The initial dose of apomorphine is a test dose of 2 mg, given during an “off” period. If the patient tolerates the test dose and is therapeutically benefiting, the start dose is 2 mg. The dose may be increased by 1 mg every few days. Maximum dosage is 6 mg. For a patient who tolerates the test dose but is not therapeutically responding, a second test dose of 4 mg may be administered. If there is a response to 4 mg, the starting dose is 3 mg, the dose can be increased by 1 mg every few days, with the maximum dose as 6 mg. For the patient who does not tolerate a test dose of 4 mg, a third test dose of 3 mg can be given. If this dosage is tolerated, the start dosage is 2 mg. The 2 mg dosage may be increased by 1 mg to a maximum dose of 3 mg. If apomorphine is not administered for more than 1 week, the start dose is 2 mg; the dosage must gradually be increased. The standing and supine blood pressure must be checked before administering a test dose. Both blood pressures must then
be checked 20 minutes, 40 minutes and 60 minutes after administering the test dose. If additional test doses are needed, there must be a 2-hour wait before the next test dose, which should only be given during an “off” period. Apomorphine should be used cautiously in patients with mild to moderate impairment of the liver. For those with mild to moderate renal impairment, both the test dose and starting dose should be 1 mg.

No controlled studies with pregnant women have been done; thus, the risk factor is C. It is contraindicated to take apomorphine while breastfeeding, for it is unknown whether or not it is excreted in breast milk.

MAO-B Inhibitors

Monoamine oxidase type B is an enzyme which metabolizes dopamine to homovanillic acid in the striatum. Selegiline and rasagiline are MAO-B inhibitors which, by interfering with dopamine metabolism, increase the concentration of dopamine at the neuronal synapse. They both provide some therapeutic benefit when used as monotherapy in early or mild PD. They may decrease the effects of the “off” period of “on-off phenomenon” when administered with levodopa and prolong the therapeutic effects of levodopa, allowing the dosage of levodopa to be reduced. These results are substantiated by a meta-analysis of data from 17 trials, as well as one of the largest adjuvant therapy clinical trials.

Selegiline starts to take effect within 1 hour, and lasts for 24 hours to 72 hours. The half-life elimination is 10 hours for the tablet, but 18 to 25 hours for the transdermal form. It is metabolized in the liver by cytochrome P450 enzymes to inactive and active metabolites, and excreted in the urine and feces, primarily in the urine. Rasagiline also starts its effect within...
1 hour, but it lasts for approximately 1 week. Its half-life is 1.3 to 3 hours. Metabolized in the liver, it is primarily excreted in the urine, with some excretion via the feces.\textsuperscript{47}

It is contraindicated to take selegiline if the patient is hypersensitive to the medication or any of its ingredients. The oral disintegrating tablet should not be taken concomitantly with tramadol, methadone, meperidine, propoxyphene, and dextromethorphan. The transdermal formulation should not be taken along with SSRIs, propoxyphene, St. John's wort, bupropion, tramadol, dextromethorphan, cyclobenzaprine, oxcarbazepine, bupropion, TCAs, methadone, mirtazapine, and carbamazepine. If a patient has a pheochromocytoma, it is contraindicated to use the transdermal form. For patients who need surgery that involves general anesthesia or a local anesthesia that has vasoconstrictors, the transdermal patch should be discontinued at least 10 days before surgery. Supplements that have tryptophan, phenylalanine, caffeine, tyrosine, and food high in tyramine should be avoided while using transdermal selegiline.\textsuperscript{46} It is recommended not to concomitantly take tramadol, propoxyphene, dextromethorphan, St. John's wort, methadone or cyclobenzaprine while taking rasagiline. Meperidine cannot be taken within 14 days of taking rasagiline.\textsuperscript{47}

The toxic effects of selegiline and rasagiline include headache, dizziness, nausea and hypotension. Dyskinesias may increase if administered with levodopa, but this can be controlled by lowering the levodopa dose.\textsuperscript{1} It is recommended that patients taking selegiline or rasagiline have regular checkups with a dermatologist due to increased risk of melanoma. The selegiline transdermal patch may contain metal; the patch must be removed before taking a MRI. Selegiline and rasagiline can raise the blood pressure if used with direct-acting alpha or beta agonists, with the exception of dipivefrin. Antihypertensives and altretamine can increase postural hypotension. Hydromorphone, bezafibrate, pizotifen, opioids,
amphetamine, tapentadol, tetrahydrozoline, buprenorphine, atomoxetine, and indirect-acting alpha and beta agonists should not be used along with selegiline and rasagiline.46,47

Selegiline tablets are prescribed at 5 mg 2 times a day, to be taken at breakfast and lunch. It can cause insomnia if the medication is taken much later on in the day.9 The initial dose of the oral disintegrating tablet is 1.25 mg every day for 6 weeks. It may be increased if needed to the maximum dose of 2.5 mg daily.46 Rasagiline is prescribed for 1 mg once a day if used as monotherapy. If prescribed with levodopa, the initial dose is 0.5 mg once a day, which can be increased to 1 mg per day if needed and tolerated. The levodopa dose may need to be lowered by 9 to 13% to avoid dyskinesias. If the patient has mild hepatic impairment, the rasagiline dose should be 0.5 mg once a day. Rasagiline should not be administered if the hepatic impairment is moderate to severe.47

No controlled studies have been conducted with pregnant women and the use of selegiline and rasagiline, but there was teratogenesis in animal studies, which gives a risk factor of C. It is not known whether these medications are excreted in breast milk.46,47

**COMT Inhibitors**

The enzyme catechol-o-methyltransferase (COMT) metabolizes dopamine to homovanillic acid, which is excreted in the urine. When a PD patient is administered carbidopa with levodopa, carbidopa inhibits dopa decarboxylase and levodopa is mainly metabolized by COMT.1,9,10 Thus, COMT inhibitors increase the levodopa half-life and allow more levodopa to cross the blood-brain barrier to enter the brain.1,10,22 Administering a COMT inhibitor with levodopa decreases the “off” period and increases the “on” period of the “on-off
phenomenon," while improving motor function and allowing the possibility of lowering the levodopa dosage.²²

The entacapone COMT inhibitor is quickly absorbed and has a quick onset of action, with peak effect at 1 hour. The half-life elimination is 2 hours,⁹ with plasma concentration peaking in 1 hour. Entacapone is primarily excreted in the feces, with 10% excretion in the urine.⁴⁸ The tolcapone COMT inhibitor is also rapidly absorbed. Its half-life elimination is 2 to 3 hours, with peak plasma concentration in 2 hours. Tolcapone has 60% excretion in the urine, and the remainder in the feces.⁴⁹

It is contraindicated to use entacapone if the patient is hypersensitive to the medication or any ingredient in its formulation. The same contraindication applies to tolcapone, but it is also advised not to administer tolcapone if the patient has tolcapone-induced liver injury, liver disease, or is experiencing confusion, hyperpyrexia or rhabdomyolysis not associated with trauma.

Entacapone can cause diarrhea, a brown-orange colored urine from the accumulation of metabolites, dyskinesia, nausea and vomiting.³⁸,⁴⁸ The dyskinesia and nausea can be decreased or avoided by lowering the dose of levodopa by 20 to 30% in the first 48 hours of administering entacapone.¹,⁹ Tolcapone can also cause diarrhea, brown-orange urine, dyskinesia, nausea and vomiting. Similar to entacapone, the dyskinesia and nausea is decreased by lowering the levodopa dose, but the diarrhea can be so severe that 5 to 10% of patients have to stop taking the medication.¹ Tolcapone can also cause dizziness, hallucinations, somnolence, and postural hypotension. It is associated with hepatic toxicity, including some fatal cases. As a result, it should only be administered if no other treatment is
available or responsive. Patients must sign a consent form before taking it and the liver enzymes (ALT and AST), which increase in liver damage, must be monitored every 2 weeks for the first year. Patients taking entacapone or tolcapone should have regular monitoring by a dermatologist because of the increased risk of melanoma. Physicians must monitor for pleural thickening, pulmonary effusion, pulmonary infiltrates and retroperitoneal fibrosis.\textsuperscript{38,39,48,49}

SSRIs, hydroxyzine, methotrimeprazine and droperidol interact with entacapone and tolcapone and increase CNS depression. Pimozide should not be concurrently used with entacapone.\textsuperscript{48,49}

With every dose of levodopa/carbidopa, 200 mg of entacapone is prescribed. The maximum frequency is 8 times a day, maximum daily dosage at 1,600 mg a day.\textsuperscript{48} The initial tolcapone dosage is 100 mg 3 times a day, which can be increased to 200 mg 3 times a day. If there is no improvement by 3 weeks' time, no matter what the dosage, the patient should stop using this medication. If hepatic impairment develops, tolcapone use should be stopped immediately.\textsuperscript{49} It is not recommended to take entacapone while pregnant; the risk factor is C. It is unknown if it is excreted in breast milk. There have not been any controlled studies on the use of tolcapone in pregnant women, but teratogenesis was found in animal studies, giving the risk factor of C. It is not recommended to take it while breastfeeding and not known if it is excreted in breast milk.\textsuperscript{48,49}

\textbf{Anticholinergics}

Antimuscarinic anticholinergic medications, like trihexyphenidyl and benztropine, lower the
actions of the cholinergic neurons in the striatum, but the basis for their therapeutic effects is not totally understood.\textsuperscript{1,10} Due to the toxicity of other PD medications, if a patient is in the early stage of PD, is not elderly and the main symptom is tremor, some neurologists will prescribe anticholinergics and the patient may be on only anticholinergics for several years if no other symptoms develop. Anticholinergics do not have much of an effect on the other symptoms of the disease and are not tolerated well by the elderly.\textsuperscript{1,8,10}

Trihexyphenidyl has a half-life of 33 hours, the plasma concentration peaks in 1.3 hours, and it is excreted in bile and urine.\textsuperscript{50} Benztropine starts to take effect in 1 hour, and it lasts for 6 to 48 hours.\textsuperscript{51} There are no contraindications listed in the labeling from the manufacturer for trihexyphenidyl. However, it is contraindicated to take benztropine if the patient is hypersensitive to benztropine or any of its ingredients; has myasthenia gravis; has obstructions in the duodenum, pylorus, or neck of the bladder; achalasia; or stenosing peptic ulcers.\textsuperscript{50,51}

Trihexyphenidyl and benztropine can cause constipation, urinary retention, mydriasis, blurred vision, tachycardia, confusion, hallucinations, nausea and vomiting. They can cause hyperthermia and anhidrosis and should, therefore, be used with great caution while exercising in hot weather or doing manual labor in the heat. These medications should be used with caution in patients with cardiovascular disease, renal impairment, hepatic impairment, glaucoma and prostatic hyperplasia. Potassium chloride can interact with trihexyphenidyl and benztropine and may lead to ulcers. These medications can lower the stimulatory effect of secretin; pramlintide can interact and raise their anticholinergic effects.\textsuperscript{40,50}
The initial dose of trihexyphenidyl is 1 mg a day, which is increased by 2 mg every 3 to 5 days. The usual dose is 6 to 10 mg a day divided into 3 to 4 doses. Some patients may need 12 to 15 mg a day. If trihexyphenidyl is prescribed concomitantly with levodopa, the usual dose is 3 to 6 mg a day divided into doses.\textsuperscript{50} Benztropine is initially prescribed at 1 to 2 mg a day, divided into 2 to 4 doses. The dose may be increased by 0.5 mg each week; the maximum dose at 6 mg/day. Avoid the use of anticholinergics with patients older than 60 years old.\textsuperscript{51} It is unknown whether trihexyphenidyl or benztropine are excreted in breast milk; pregnancy risk factor is C.\textsuperscript{50,51}

**Amantadine**

Amantadine is an antiviral medication, used in the treatment of influenza A. By chance, it was discovered to have antiparkinson activity, although how it does this is not clear. It seems to release stored dopamine and inhibit the NMDA glutamate receptor; glutamate excites most of the neurons in the brain.\textsuperscript{1,8-10} Some physicians may prescribe amantadine for the early stages of PD, but it is primarily prescribed to decrease the dyskinesia, tremor and rigidity of the advanced stage. It may only be beneficial for a few weeks or months, however.\textsuperscript{1,8-10,22}

Amantadine is well absorbed, being able to take effect within 48 hours. Its half-life elimination is from 9 to 31 hours, its plasma concentration peaks in 2 to 4 hours, and it is excreted in the urine.\textsuperscript{52} A patient who is hypersensitive to amantadine or any of its ingredients should not take this medication. Amantadine can cause several toxic effects including confusion, hallucinations, insomnia, peripheral edema, postural hypotension, weight gain, aggravation of congestive heart failure and glaucoma, impaired cognition, urinary retention, headache, constipation and nausea.\textsuperscript{52} The dermatological disorder livedo reticularis may occur, but
usually clears up within one month after the patient stops taking amantadine.\textsuperscript{8,9,10} A dermatologist needs to regularly monitor for melanoma.

Antipsychotics may increase or decrease the therapeutic effects of amantadine; concomitant use should be avoided if possible. Taking MAO inhibitors with amantadine can increase postural hypotension; taking trimethoprim can raise the risk of delirium and myoclonus, and raise the concentration of amantadine in the serum. Methylphenidate can raise the toxic effects of amantadine, while metoclopramide lowers the therapeutic effects.\textsuperscript{52}

The standard dose for monotherapy is 100 mg 2 times a day, which may be increased to 400 mg a day divided into doses. For patients who are taking high doses of other medications for PD, the initial dose of amantadine should be 100 mg a day. After 1 or more weeks, this dosage can be raised to 100 mg 2 times a day. The pregnancy risk factor is C, for there are reports of teratogenesis in animals and humans. It is not recommended to breastfeed while taking this medication, because it is excreted in breast milk.\textsuperscript{52}

Parkinson's disease is a common, slowly progressive neurodegenerative disease which includes motor and nonmotor symptoms. For most cases of PD, the etiology is unknown, but a minority of people with this disorder have it because of gene mutations. The diagnosis of PD is made by a clinical evaluation of the symptoms. Currently, there is no treatment available that can cure this disease or even stop the neurodegeneration. The antiparkinson medications ameliorate the motor symptoms.
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TABLE 1. SYMPTOMS OF PARKINSON'S DISEASE

<table>
<thead>
<tr>
<th>Motor Symptoms</th>
<th>Nonmotor Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural instability</td>
<td>Motor Symptoms</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>Resistance to passive movement</td>
</tr>
<tr>
<td>Rigidity</td>
<td>“Lead-pipe” rigidity</td>
</tr>
<tr>
<td>“Cogwheel” movement</td>
<td>Resting tremor</td>
</tr>
<tr>
<td>“Pill-rolling” movement</td>
<td>Micrographia</td>
</tr>
<tr>
<td>4-6 Hz</td>
<td>Abnormal gait</td>
</tr>
<tr>
<td></td>
<td>Small, shuffling steps</td>
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<tr>
<td></td>
<td>Decreased arm swing</td>
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<tr>
<td>Difficulty swallowing</td>
<td>Dysautonomia</td>
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<tr>
<td>Mask-like face</td>
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<tr>
<td></td>
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<tr>
<td>Neurological abnormalities</td>
<td></td>
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<td>Cognitive abnormalities</td>
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<tr>
<td>Hyposmia</td>
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</tr>
<tr>
<td>Name</td>
<td>Mechanism of Action</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Carried into the CNS where converted to dopamine. Also converted to dopamine in peripheral tissues.</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Releases stored dopamine and inhibits NMDA glutamate receptor.</td>
</tr>
<tr>
<td><strong>Dopamine Agonists:</strong></td>
<td></td>
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<tr>
<td>Pramipexole</td>
<td>Non-ergot derivative. Stimulates D3 receptors.</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Non-ergot derivative. Stimulates D2 receptors.</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Stimulates D2, D3, D4 and D5 receptors.</td>
</tr>
<tr>
<td><strong>MAO-B Inhibitors:</strong></td>
<td></td>
</tr>
<tr>
<td>Selegiline and Rasagiline</td>
<td>Inhibit MAO-B enzyme, which increases dopamine at neuronal synapse.</td>
</tr>
<tr>
<td><strong>COMT Inhibitors:</strong></td>
<td></td>
</tr>
<tr>
<td>Entacapone and Tolcapone</td>
<td>Inhibit COMT enzyme.</td>
</tr>
<tr>
<td><strong>Anticholinergics:</strong></td>
<td></td>
</tr>
<tr>
<td>Trihexyphenidyl and Benztropine</td>
<td>Lower action of cholinergic neurons in striatum.</td>
</tr>
</tbody>
</table>