



AMERICAN PARKINSON DISEASE ASSOCIATION

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Medical Management of Parkinson's Disease

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EDUCATIONAL SUPPLEMENT 13

Parkinson's disease (PD) is a chronic, progressive neurological condition that affects the neurons located in the substantia nigra of the mid-brain. Gradual loss of these neurons causes a reduction in a neurotransmitter known as dopamine (DA) which is important for smooth, purposeful movement and balance. A decrease in dopamine produces one or more of the classic signs of Parkinson's disease:

1. **Resting tremor;**
2. **Slowness of movement (bradykinesia);**
3. **Stiffness of limbs (rigidity);**
4. **Gait or balance problems (postural dysfunction).**

As these symptoms become more pronounced, patients have difficulty walking, turning or completing activities of daily living.

The disruption of normal dopamine levels may trigger a cascade of other neurotransmitter imbalances that contribute further to PD disability. Imbalances in the ratio of acetylcholine and dopamine also may aggravate the disabling clinical

manifestations of PD. Decreased levels of norepinephrine, serotonin, and regional abnormalities in gamma-aminobutyric acid (GABA) result in secondary symptoms of PD such as depression, sleep difficulties, anxiety disorders, constipation, urinary frequency, decrease in blood pressure when standing, swelling in extremities and cold intolerance, to name a few.

While there is, as yet, no cure for this condition, advances in treatment allow many patients to maintain a high level of function throughout their lifetimes. Medications are the mainstay of treatment; they control the symptoms of PD caused by the imbalances in neurotransmitters.

There are essentially **six categories of drugs** used to treat the symptoms of Parkinson's disease.

LEVODOPA: CARBIDOPA-LEVODOPA
(Sinemet®, Sinemet CR®, Parcopa®)

Levodopa is the most effective treatment for the symptoms associated with PD. Levodopa is a short-

acting drug that enters the brain and is converted into dopamine, the neurotransmitter that is low in PD. The combination of levodopa with carbidopa (Sinemet) enhances levodopa's entry into the brain and minimizes side effects such as nausea. The main problem with levodopa therapy is the development of motor fluctuations and dyskinesias, which constitutes a major source of disability.

For example, with long-term use, some individuals notice a shorter duration of action from each dose (known as the "wearing off" phenomenon), and some can develop an "on-off" effect in which symptoms may come and go at unpredictable intervals. Dyskinesia (involuntary movements) which may occur in the face, limbs, neck, and/or trunk most commonly develop in people who have taken large doses of levodopa over an extended period of time. It is also common in individuals diagnosed at a younger age.

Motor fluctuations, once developed, are difficult to control with medical therapies and may require surgical intervention. PD treatment guidelines established in 2001 by a group of movement disorder specialists recommend initiating therapy with a dopamine agonist and supplementing with levodopa when symptoms are no longer adequately controlled. In addition, the 2006 American Academy of Neurology practice parameters support the use of dopamine agonists as initial monotherapy in treating PD symptoms and lessening motor complications. This approach may not be appropriate for all patients. Factors such as age, mental status, disease severity, presence of other diseases, and functional disability also need to be considered.

Sinemet CR (a controlled release formulation) slowly releases levodopa thereby prolonging the plasma and presumably brain levels. It has been found useful in the treatment of motor fluctuations, particularly the wearing-off effect. The bioavailability of levodopa in Sinemet CR relative to Sinemet is approximately 70-75%. Therefore, to produce a given clinical response with the controlled-release formulation, a higher levodopa dose is necessary.

Parcopa is an orally disintegrating tablet of

levodopa-carbidopa which can be taken any time, anywhere, with or without water. When a tablet is placed on the tongue it begins to dissolve within seconds. Parcopa is available in the same strengths as Sinemet tablets and allows the same dosing and administration schedules. Individuals who may benefit from this formulation are those who have trouble swallowing conventional tablets in addition to those who need help due to morning rigidity (the tablets can be taken in bed to initiate the "on" state).

DOPAMINE AGONISTS:

Bromocriptine (Parlodel®), Pramipexole (Mirapex®), Ropinirole (Requip®), Ropinirole Extended-Release (Requip XL®), Apomorphine (Apokyn®), Rotigotine (Neupro®)

Dopamine agonists help control symptoms by copying the action of dopamine in the brain. They work directly on the postsynaptic dopamine receptors without the need for metabolic transformation, neuronal presynaptic storage, or active transport across the blood brain barrier. Dopamine agonists are utilized for the treatment of symptoms associated with early and late stage Parkinson's disease with the exceptions of apomorphine, which is specifically indicated for the treatment of motor symptoms associated with late stage PD, and rotigotine, which is indicated for early stage PD. Dopamine agonists were originally used in advanced patients to help improve therapeutic response and minimize dyskinesias and motor fluctuations. Research, particularly with pramipexole, ropinirole and rotigotine has demonstrated they may be as beneficial as levodopa in early disease and provide an effective treatment strategy, delaying the need for levodopa for a number of years. Initiation of treatment with a dopamine agonist is also associated with a reduced risk for development of motor complications compared with levodopa. Furthermore, preliminary data suggests dopamine agonists may possibly have neuroprotective effects slowing the progression of PD.

The adverse effect profile of the dopamine agonists,

as a class, includes nausea, vomiting, lightheadedness, dizziness, postural hypotension, sedation/somnolence and hallucinations. All dopamine agonists have the potential to cause compulsive behaviors. There have been reports of an increase in gambling, sexuality, eating and shopping. These behaviors decrease when the medication is modified and should be reported to the patient's physician.

Apomorphine is used as needed for the acute, intermittent treatment of "off" (poor motor function) episodes associated with advanced Parkinson's disease, as supplemental therapy to standard PD therapy. Apomorphine is poorly absorbed when given orally, therefore is given subcutaneously (under the skin) delivered via metered injector pen. The drug is rapidly transported into the brain and can trigger an "on" response within 10 minutes of injection with effects lasting up to 2 hours. A wealth of experience, mostly from Europe and more recently in the United States, supports its ability to acutely treat "off" episodes. The drug is also useful in patients who are temporarily unable to swallow their usual PD medication or who are to undergo surgery and cannot take oral medication. Injections can be repeated up to five times per day and may be given regardless of the timing of other anti-parkinsonian medications. Adverse events associated with apomorphine include (but are not limited to): nausea, vomiting, dizziness, drowsiness, dyskinesias, yawning, injection site reactions and hallucinations. The frequency of hallucinations in patients receiving intermittent subcutaneous apomorphine has been shown to be lower than with other dopamine agonists. Patients with a tendency to develop hallucinations on oral dopamine agents have often been able to tolerate apomorphine injections without recurrence. Patients using apomorphine are prescribed the medication trimethobenzamide hydrochloride (Tigan®) to decrease nausea and vomiting.

Rotigotine was approved by the FDA in May 2007 to treat the signs and symptoms of early stage Parkinson's disease. It is the first transdermal (skin) patch for PD. The patch is applied once a day and

releases rotigotine continuously through the skin into the body over 24 hours. The effectiveness of rotigotine was evaluated in three randomized, double-blind, placebo controlled studies conducted in the US and abroad. The patients who participated in these studies all had early stage PD and were not receiving dopaminergic medications. The most common side effects for rotigotine include skin reactions at the patch site, dizziness, nausea, vomiting, drowsiness and insomnia. Other potential safety concerns include sudden onset of sleep while engaged in routine activities such as driving, hallucinations, and decreased blood pressure on standing up. The patch can be an alternative for multiple daily oral doses of medication, and it may be more tolerable for patients who have adverse reactions, such as involuntary movements. In addition, the patch avoids problems with absorption of oral drugs in the stomach and other parts of the gastrointestinal tract.

At the end of April 2008, it was temporarily withdrawn from the US Market because of problems related to crystallization of the drug, which caused unreliable drug delivery. These problems have since been solved by the company. The FDA reapproved its use and Neupro was made available in the US market in July 2012.

Ropinirole extended-release was FDA approved in June 2008. It is the only oral once-daily dopamine agonist for the treatment of the signs and symptoms of PD. It may be taken alone or in combination with levodopa. The tablets are composed of an innovative tri-layer formulation that allows a steady rate of absorption with fewer fluctuations in ropinirole concentration over 24 hours compared to immediate-release ropinirole given three times daily. Switching from the previous ropinirole immediate-release formulation can take place overnight. The initial switching dose of ropinirole extended-release should most closely match the total daily dose of immediate-release ropinirole. In general, similar types of adverse reactions are seen with ropinirole extended-release and immediate-release ropinirole. Individuals with Parkinson's disease often require multiple doses of one or more medications to control their symptoms, which

makes taking medicines correctly and at the right time challenging. Ropinirole extended-release is an important once daily treatment option.

MAO-B Inhibitors: Selegiline (Eldepryl®), Selegiline ODT (Zelapar®), Rasagiline (Azilect®)

Selegiline and rasagiline slow the metabolism of dopamine through the blockade of monoamine oxidase (MAO)-B. MAO-B is an enzyme located in the brain which metabolizes dopamine to an inactive product. By inhibiting dopamine degradation in the brain selegiline and rasagiline may prolong the duration of the dopamine effect. They are used as monotherapy in the early phase of the disease or in combination with levodopa, or in the later stages of the disease (in fluctuating patients). Rasagiline is approximately five to ten times more potent than selegiline. Selegiline orally disintegrating tablets (ODT), are a once-daily adjunct therapy for Parkinson's disease patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. The formulation is a fast-dissolving dosage form in a unique freeze-dried tablet that does not require water to aid swallowing. When the tablet is put into the mouth, the freeze-dried structure disintegrates instantaneously and releases selegiline, which dissolves in the saliva and is absorbed directly into the systemic circulation through the oral mucosa. More active drug is delivered at a lower dose compared to conventional selegiline. The once daily tablet should be taken in the morning before breakfast and without liquid; food or liquids should be avoided for five minutes before and after the ODT. Both selegiline ODT and rasagiline do not produce similar metabolites as conventional selegiline and may have fewer side effects.

COMT Inhibitors: Tolcapone (Tasmar®), Entacapone (Comtan®)

Tolcapone and entacapone are selective and reversible inhibitors of the enzyme catechol-O-

methyltransferase (COMT). This enzyme is responsible for the metabolism of levodopa, dopamine, other catecholamines (adrenaline and noradrenaline), and their metabolites. When administered with levodopa and carbidopa, these agents increase the availability of levodopa for delivery to the brain. In addition, COMT inhibitors decrease levodopa clearance, prolonging the half-life and increasing levodopa bioavailability without affecting peak levodopa plasma concentration. Tolcapone and entacapone are indicated as adjunct to levodopa and carbidopa for the treatment of the signs and symptoms of idiopathic Parkinson's disease. Both tolcapone and entacapone have no antiparkinsonian effect when administered in the absence of levodopa. Because of the risk of potentially fatal, acute fulminant liver failure, tolcapone should ordinarily be used in patients with Parkinson's disease on levodopa/carbidopa who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies. Because of the risk of liver injury and because tolcapone, when it is effective, provides an observable symptomatic benefit, the patient who fails to show substantial clinical benefit within 3 weeks of initiation of treatment, should be withdrawn from tolcapone. Liver function must be monitored closely especially for the first six months. The drug must be discontinued if liver enzyme levels are twice the upper level or if clinical signs and symptoms suggest the onset of liver failure.

There is no evidence of liver dysfunction in patients treated with entacapone. Entacapone is recommended for PD patients experiencing the signs and symptoms of "wearing-off," i.e., slowness, tremor, rigidity that begin to reappear between levodopa doses, usually near the end of the dosing cycle. Because entacapone is almost completely metabolized prior to excretion, it should be used with caution in patients with hepatic impairment. The most common side effects observed with the COMT inhibitors are dopaminergic in nature, for example, dyskinesias, nausea, hallucinations and hypotension. These side effects can usually be reduced or eliminated by decreasing the levodopa dose. They

can also cause diarrhea and urine discoloration.

COMT Inhibitor and Levodopa:
Carbidopa-Levodopa-Entacapone (Stalevo®)

A combination tablet of carbidopa, levodopa and entacapone is available and marketed as Stalevo. Stalevo is indicated for treatment of idiopathic PD to substitute for immediate-release (IR) carbidopa-levodopa and entacapone previously administered as individual products and to replace IR carbidopa-levodopa when patients experience the signs and symptoms of end-of-dose “wearing-off.” Stalevo simplifies treatment by providing three medications in one tablet, which reduces the number of tablets patients need to take daily. An additional advantage is Stalevo 50 and 100mg tablets are smaller for patients with swallowing difficulties. The most common side effects of the combination product are nausea and dyskinesia which can often be managed with alteration in the drug dosing schedule. Other common side effects include diarrhea, urine discoloration, abdominal pain, dizziness, constipation, fatigue, pain and hallucinations.

AMANTADINE
(Symmetrel®)

This antiviral agent has mild antiparkinson effects and is thought to act by causing a release of dopamine from intact dopamine neurons remaining in the substantia nigra. It may also inhibit dopamine reuptake, stimulate dopamine receptors, exert an anticholinergic effect and block NMDA (N-methyl-D-aspartate) receptors. Amantadine is used mainly in the early stages of the disease (first 6 to 12 months) as a means of controlling the symptoms of PD, thereby lengthening the amount of time the patient can remain functional without the addition of levodopa. It seems to have only a minimal effect on tremor and modest effect on rigidity and bradykinesia which may not be long lasting. Amantadine is also utilized in later stages of the disease for symptoms of “wearing off” or to possibly reduce dyskinesias (abnormal involuntary move-

ments).

ANTICHOLINERGIC AGENTS
(Artane®, Cogentin®)

These drugs include trihexyphenidyl (Artane) and benztropine (Cogentin). Anticholinergic agents exert their effect in PD by correcting the imbalance created from decreased dopamine and unabated cholinergic input. In addition to suppressing central cholinergic activity, these agents may also inhibit the reuptake and storage of dopamine at the central dopamine receptors, thereby prolonging the action of dopamine. They were the standard antiparkinsonian treatment until the late 1960's, when newer drugs were developed. Anticholinergics are most effective for reducing tremor, and usually provide minimal benefit with regard to bradykinesia and rigidity. In addition, tremor may or may not improve with anticholinergic agents and a given patient may respond to one anticholinergic but not others. Their use is often limited by side effects such as dry mouth, constipation, memory impairment, confusion and hallucinations and they are less well tolerated by older patients and those with dementia. Therefore, the prescribing of anticholinergics is often confined to younger patients with tremor as the primary symptom.

Medication Dosing and Administration

All medication used in the treatment of Parkinson's disease should be introduced slowly to minimize the appearance of adverse effects. They must also be administered on time. Fluctuations of 30 minutes to an hour might be acceptable for other agents but not Parkinson's medications.

Even a slight fluctuation in schedule can result in an exacerbation of symptoms and diminished quality of life for some patients. Worse yet, the appearance of these symptoms could mistakenly convince caregivers that a patient needs more medication and that could lead to unwarranted increases in dosage.

Research has shown that dietary protein antagonizes the clinical effectiveness of the levodopa-carbidopa combination. Dietary protein causes a large peak in the concentration of certain amino acids; when the blood amino acid levels are high, levodopa uptake into the brain is slow and inadequate.

Meals high in fat can also be a problem. A high-fat meal can take as long as two hours to clear the stomach. If Sinemet is in the stomach too, it will also take two hours to clear, shortening its useful lifespan. Therefore, it is best to take Sinemet 30 to 60 minutes before eating a meal or 45 minutes after the meal to decrease interference between absorption of Sinemet and off proteins in the food.

Studies have further demonstrated that patients who experience "on-off" fluctuations or who don't respond to levodopa-carbidopa therapy can benefit by adjusting their protein intake. Specifically, high-protein foods should be eaten only in the evening; this allows better mobility during the day. Another suggestion is to eat meals that consist of a ratio of seven parts of carbohydrate to one part protein. A high ratio of carbohydrate to protein causes a large amount of insulin to be released into the blood. Insulin removes some of the amino acids

from the blood and may help lower the competition between amino acids and levodopa thereby increasing Sinemet's effectiveness.

SUMMARY

The pharmacological management of Parkinson's disease is complex and dynamic; there is no one right strategy for what drugs to use at what stage of the disease. However, it has been shown in various studies that starting medications early will give better long-term motor results. The current trend is to initiate symptomatic therapy with a dopamine agonist or other levodopa sparing agent such as rasagiline or selegiline and supplement with levodopa when clinical features are no longer satisfactory. As PD progresses a combination of levodopa therapy, dopamine agonists, MAO-B and/or COMT inhibitors are often used. Amantadine and anticholinergic agents are also occasionally used. The optimal effect of medication is further obtained when used in conjunction with exercise, speech therapy, counseling, diet, support groups and other nonpharmacologic therapies.

The enclosed pamphlet "Medications Approved for the Treatment of Parkinson's Disease in the USA" provides a summation of the PD medications, along with their mode of action and common side effects.



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