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Parkinson's Disease Medications For Medical Professionals

How is Parkinson's Disease Treated?

At this time no treatment has been shown to slow or stop the progression of Parkinson's disease. Treatment is therefore symptomatic. There is no standard or "best" treatment for Parkinson's disease. A number of treatment approaches help patients with Parkinson's disease. These approaches include:

- general lifestyle modifications (rest and exercise)
- dietary considerations
- physical therapy
- speech therapy
- medication therapy
- surgical therapy

Medications for Parkinson's disease

A number of medications are available for treating the motor symptoms of Parkinson's disease. Because individuals with Parkinson's disease experience various motor symptoms of differing severity, the optimal medication (and whether to treat with medication) varies between individuals. With time and progression of disease, the dose of medication(s) may need to be increased or new medications added.

No drug has been shown with confidence to slow the progression of Parkinson's disease (i.e., exert a 'protective' effect). In some cases a protective effect has been suggested but the evidence for benefit is incomplete and debatable. Early symptomatic treatment has been advocated by some in the belief that it may support basal ganglia compensatory mechanisms and restore normal dopaminergic transmission (Schapira, 2009).

Levodopa (carbidopa/levodopa; Sinemet®, Atamet®, and Parcopa®)

The introduction of levodopa (L-dopa) more than 40 years ago revolutionized the treatment of Parkinson's disease. Although Parkinson's disease is characterized by a loss of neurons that contain and release dopamine, oral or intravenous dopamine is not effective because like other charged amino acids, it does not pass the blood/brain barrier. However, levodopa (a precursor of dopamine) is transported to the brain and is then metabolized to dopamine.

For most individuals, treatment with levodopa reduces the symptoms of slowness, stiffness, and tremor. To **prevent blood amino acid decarboxylases from metabolizing most of an administered does of levodopa** before it reaches the brain, levodopa is always **combined with an inhibitor of this enzyme**. In the US, the dopa decarboxylase inhibitor is carbidopa, whereas in Europe benserazide is used. Many patients need a minimum of 75 mg/d of carbidopa to avoid the nausea that occurs if levodopa is converted to dopamine systemically.

Although levodopa remains the single most effective treatment for Parkinson's disease, treatment over a number of years may lead to variability in an individual's response to treatment—so-called “motor fluctuations.” The fluctuating response to levodopa can be broadly divided into **"on" and "off" periods**. During an "on" period, a person can move with relative ease often with reduced tremor and stiffness. “Off” periods describe those times when a person has greater difficulty with movement. A common time for a person with Parkinson's disease to experience an "off period" is just prior to taking the next dose of levodopa, and this experience is called "wearing off." The “off periods” may also occur unpredicatably without a consistent relation to the timing of medication. Another form of motor fluctuation is **uncontrolled abnormal movements, called “dyskinesias.”** These may take a variety of forms and may be localized or generalized. About 40% of patients treated with levodopa will develop motor fluctuations within six years of treatment.

Levodopa is rapidly absorbed from the small intestine. Most patients experience improvement in symptoms about 30 minutes after a dose, and the benefit lasts for about 3-5 hours. However, the duration of benefit may range from as long as a day to as short as an hour. **Food (in particular, protein-rich food) delays absorption of levodopa** by the gastrointestinal tract and delivery into the bloodstream and diminishes transport across the blood-brain barrier. Thus, patients should be instructed to take levodopa 30-45 minutes before meals or 2 hours after meals to maximize the benefit of an individual dose.

Over the past decade, there has been increasing concern that treatment with levodopa might hasten the rate of neurodegeneration. The Early versus later Levodopa Study was designed to address this concern. About 360 patients with early Parkinson's disease were assigned to receive carbidopa/levodopa at daily doses of 37.5/150, 75/300 , 150/600 versus placebo over a period of 40 weeks and then undergo a withdrawal of treatment for 2 weeks. After the 2-week withdrawal, the severity of parkinsonism was greater in the placebo group than in those undergoing treatment. These data were interpreted as **suggesting that levodopa either slows the progression of PD or has a prolonged effect on the symptoms of the disease** (Fahn et al, 2004).

Levodopa preparations

Levodopa is available in a standard and a "controlled-release" (CR or SR) formulation. Controlled-release levodopa has a longer duration of action because the time taken for the gastrointestinal tract to absorb levodopa is increased. However, because the **controlled-release formulation only allows 70% of the levodopa to be absorbed** by the gastrointestinal tract, it is often necessary to increase the amount of levodopa taken when a person is switched from standard (or immediate-release) levodopa to controlled-release levodopa, in order to obtain the same benefit.

Standard release preparations

carbidopa/levodopa (Sinemet® or Atamet®) available in 10/100, 25/100, or 25/250 tablets

Parcopa® is an accelerated-release preparation available in 10/100, 25/100, or 25/250 tablets

Controlled-release preparations

levodopa/carbiopa (Sinemet CR®) 25/100 or 50/200 tablets

Side effects include nausea, vomiting, dry mouth, dyskinesias, and dizziness. In some individuals, levodopa may cause confusion, hallucinations, or psychosis. Motor fluctuations develop in about 40% of individuals treated for 4-6 years.

Catechol-O-methyl transferase (COMT) inhibitors

Another class of enzyme inhibitors, called COMT inhibitors, also prevent the metabolic breakdown of levodopa. Their **main effect is to prolong the duration of action of levodopa**. COMT inhibitors do not contain levodopa, and they must therefore be taken with levodopa for benefit. They may be prescribed when an individual experiences "wearing off," particularly when dopamine agonists (see below) are not tolerated. If dyskinesias develop after starting a COMT inhibitor, the dose of levodopa may need to be reduced. A recent study has shows that entacapone, when used as an adjunct to levodopa in parkinsonian patients without motor fluctuations, does not improve performance on standard rating scales but does improve a variety of quality-of-life measures (Olanow et al, 2004).

COMT inhibitors:

- Entacapone (Comtan®)—200 mg tablets are usually given with each dose of levodopa.
- Tolcapone (Tasmar®)—100 mg and 200 mg tablets; generally given three times a day.

Because **liver toxicity** has occurred in patients taking tolcapone, it is only indicated for patients whose symptoms are not adequately controlled by other medications (including entacapone). **Patients taking tolcapone must have blood drawn before initiating treatment and then periodically to monitor liver function** (every 2-4 weeks for the first 6 months of treatment and thereafter when clinically relevant).

Side effects for both of these medications include **urine discoloration, diarrhea, vivid dreams, visual hallucinations, drowsiness, and dyskinesias**.

Combined carbidopa, levodopa and entacapone

This preparation combines all 3 medications in one pill, which may be more convenient but may not be as flexible as taking the medications individually.

Doses:

Stalevo® 50: 50 mg levodopa, 12.5 mg carbidopa, and 200 mg entacapone

Stalevo® 75: 75 mg levodopa, 18.75 mg carbidopa, and 200 mg entacapone

Stalevo® 100: 100 mg levodopa, 25 mg carbidopa and 200 mg entacapone

Stalevo® 125: 125 mg levodopa, 31.25 mg carbidopa, and 200 mg entacapone

Stalevo® 150: 150 mg levodopa, 37.5 mg carbidopa, and 200 mg entacapone

Stalevo® 200: 200 mg levodopa, 50 mg carbidopa, and 200 mg entacapone

Side effects of this combined preparation are the same as for levodopa and entacapone and include: **urine discoloration, diarrhea, vivid dreams, visual hallucinations, drowsiness, and dyskinesias**.

Dopamine agonists

Dopamine agonists differ from levodopa, since they **do not have to be modified by brain enzymes in order to activate dopamine receptors**. They may be used in place of levodopa or in combination with it. Although treatment with dopamine agonists **causes motor fluctuations less frequently** than levodopa, dopamine agonists are **more likely to cause a number of other side effects** (such as nausea, somnolence, postural hypotension, hallucinations, and lower extremity edema), particularly in patients over 70 and those with baseline cognitive deficits. Thus, in prescribing dopamine agonists, the treating physician must weigh the potential benefits and adverse effects.

There are two commonly prescribed oral dopamine agonists in the United States:

- pramipexole
- ropinirole.

Rotigotine transdermal is not an ergot compound either. The patch, which contains rotigotine and releases it gradually, is applied to the skin once daily. It has similar side effects to the other dopamine agonist. Some patients also experience a skin reaction to it. **Apomorphine**, a subcutaneously administered dopamine agonist, was approved for use in the United States in 2004. The dopamine agonists differ in several respects, including:

- chemical structure
- duration of action
- side effects

Bromocriptine and the recently withdrawn pergolide are **ergot derivatives** and may rarely cause **retroperitoneal, pulmonary, and pericardial fibrosis, and cardiac valvulopathies**. Pramipexole and ropinirole have half-lives 6-12 hours and are therefore taken 2-3 times daily.

Pramipexole, ropinirole and rotigotine transdermal

Pramipexole, ropinirole **and rotigotine transdermal** are not ergot compounds. Large clinical trials comparing these medications to levodopa showed that they can be used in early Parkinson's disease and reduce the severity of symptoms. Over the years, differences in the effects of the dopamine agonists have emerged. One side effect is daytime sleepiness and "sleep attacks."

Although this may occur with all of the dopamine agonists (and levodopa), it was first appreciated in people treated with pramipexole.

Apomorphine

Apomorphine is indicated in patients who experience **"off states"** refractory to modifications of oral medications such as increasing the dose or frequency of dopaminergic medications or introducting a COMT inhibitor. It has a rapid onset of action, usually within 10-20 minutes but the duration of action is short, lasting for only about an hour. Apomorphine is only available from specialty pharmacies. Because nausea occurs in the vast majority of patients, pretreatment with trimethobenzamide (Tygan®) is required. Initial titration and observation for side effects (syncope, hypotension) must occur in the physician's office.

Prescribing dopamine agonists

The response to a particular dopamine agonist is idiosyncratic**.** If one dopamine agonists does not offer benefit or causes bothersome side effects, another agonist may be tried. Treatment with dopamine agonists should begin at a low dose, which is increased at intervals (depending on the agent) until benefit occurs.

In two recent clinical studies, patients with early Parkinson's disease were randomly assigned to treatment with either a dopamine agonist (pramipexole or ropinirole) or levodopa. In both trials, about half of the participants assigned to dopamine agonist treatment required supplemental levodopa because of worsening symptoms. **Dyskinesias developed more frequently with levodopa than the dopamine agonist**. However, other side effects were more common in the dopamine agonist group, and **patients treated with levodopa alone had slightly better control of movement**.

Dopamine agonists:

- Bromocriptine (Parlodel®): 2.5 mg tablet and 5 mg capsule
  Common therapeutic dose: 5-10 mg tid

- Pramipexole (Mirapex®): 0.125 mg, 0.25 mg, 0.5 mg, .75mg, 1 mg, and 1.5 mg tablets
  Common therapeutic dose: 0.5-1.5mg tid

- Pramipexole (ER) (Mirapex®): 0.375mg, 0.75mg, 1.5 mg, 3mg, 4mg, 5 mg
  This extended-release formulation of pramipexole allows for a single daily dose that is chosen to match the total daily dose of standard-release pramipexole.

- Ropinirole (Requip®): 0.25 mg, 0.5, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg tablets
  Common therapeutic dose: 3-8 mg tid

- Ropinirole XL (Requip XL®): 2mg, 4mg, 6mg, 8mg, 12mg
  Common therapeutic dose: 4-20mg daily.

The extended-release formulation of ropinirole allows one single daily dose to be taken. The dose of ropinirole XL is chosen to match the total daily dose of standard ropinirole

- Rotigotine (Neupro®): 1mg, 2 mg, 3mg 4 mg, 6 mg and 8 mg patches

Common therapeutic dose: 3-8 mg daily

- Apomorphine (Apokyn®): 2 ml vials or 3 ml cartridges. The cartridges are used with a reusable, multiple dose injector. Typical doses vary from 1-8 mg (0.1-.8 ml). The starter kit includes trimethobenzamide (Tygan®) which patients should start 3 days prior to dose titration.

Cabergoline (Dostinex®) : not approved in the United States for the treatment of PD

Lisuride (Dopergine®) : not currently available in the United States

Side effects

Side effects include drowsiness, **nausea, vomiting, dry mouth, dizziness, leg swelling, and orthostatic hypotension**. Although these symptoms are common when starting a dopamine agonist, they typically resolve over several days. In some individuals, dopamine agonists cause confusion, hallucinations, or psychosis. Sleepiness, drowsiness, or sedation is sometimes a significant side effect of certain dopamine agonists, and may interfere with driving or other activities.

Behavioral side effects occur in 5-10 percent of patients taking dopamine agonists. The behaviors often reflect a **disorder of "impulse control"** in which the patient fails to resist the behavior even when it may be distressing or may impair function socially or occupationally These behavioral changes are often compulsive and include **gambling**, **shopping**, and **binge eating**, as well as increased **sexual behaviors**. These behavioral changes typically resolve once the dose of the dopamine agonist is reduced or discontinued.

The nausea associated with apomorphine may be profound. In the United States, pretreatment with trimethobenzamine (Tygan®) 250 mg 3 times daily for 3 days prior to initial apomorphine dosing is required. Some patients are able to discontinue trimethobenzamine after several weeks of treatment with apomorphine.

Monoamine oxidase B inhibitors

Selegiline

Selegiline is an inhibitor of the enzyme MAO-B (monoamine oxidase B). MAO-B breaks down dopamine. When it is inhibited, the action of dopamine is prolonged in the brain, and the symptoms of Parkinson's disease are improved. MAO-B inhibitors also have a mild antidepressant effect. Early studies of selegiline suggested that it may delay the progression of Parkinson's disease but this appears to have been confounded by a mild symptomatic effect. Currently there is no firm evidence that selegiline slows disease progression. It is effective as monotherapy for symptomatic relief or as an adjunctive agent.

Selegiline preparations include:

- Eldepryl®: 5 mg capsule usually taken twice daily (morning and noon)

- Atapryl®: 5 mg tablets usually taken twice daily (morning and noon)
- Carbex®: 5 mg tablets usually taken twice daily (morning and noon)
- Zelapar (an orally disintegrating form of selegiline): 1.25 mg tablets taken once daily (morning).

Side effects include heartburn, nausea, dry mouth, insomnia and dizziness. Confusion, nightmares, hallucinations, and headache occur less frequently.

Rasagiline

Rasagiline is another MAO-B inhibitor that has been approved for monotherapy and adjunct therapy in Parkinson's disease. It is taken once daily and is less likely to cause insomnia than selegiline. A recent study showed that treatment with 1 mg rasagiline provided benefits that were consistent with a possible disease-modifying (or neuroprotective) effect whereas treatment with 2 mg daily did not (Olanow et al, 2009)

- Rasagiline (Azilect®) is available as 0.5 and 1 mg tablets, usually taken once daily

Side effects include abnormal movements and hallucinations (when taken with levodopa), headache, and fatigue.

Precautions when using MAO-B inhibitors

Meperidine (Demerol®) and tramadol are contraindicated. Dextromethorphan and ephedrine should also be avoided, as should over-the-counter cold remedies. Treatment with **ciprofloxacin** may increase the blood level of rasagiline and so concomitant use should be avoided.

Other medications

A number of other antiparkinsonian medications can be used alone or in combination with levodopa or a dopamine agonist in patients with Parkinson's disease. These medications do not stimulate dopamine receptors but alter basal ganglia neurotransmission by affecting other receptors. The most commonly used medications are amantadine and anticholinergic medications.

Amantadine

Amantadine may be used alone or in combination with levodopa or dopamine agonists. It reduces symptoms of fatigue and tremor in certain patients with early Parkinson's disease, but benefit may be short-lived. More recently, amantadine has been found helpful for people with advanced Parkinson's disease who experience levodopa-induced dyskinesias.

- Amantadine (Symmetrel®) as 100 mg **capsules, tablets, or in liquid form** that may be convenient for an individual who does not tolerate a full 100-mg dose or has dysphagia

Side effects include difficulty concentrating, confusion, insomnia, nightmares, agitation, headache, hallucinations, edema and livedo reticularis.

Anticholinergic Agents

Anticholinergic medications may reduce tremor or rigidity but have little effect on bradykinesia and imbalance. They can be taken alone or in combination with levodopa. They are rarely used in elderly patients or those with cognitive problems, because increased confusion is a side effect. Specific anticholinergic medications include:

- Biperiden HCL (Akineton®): 2 mg tablets
- Benztropine mesylate (Cogentin®): 0.5 mg, 1 mg, 2 mg tablets
- Trihexyphenidyl (Artane®): 2 mg and 5 mg tablets as well as liquid form

Side effects may include dry mouth, blurred vision, sedation, delirium, hallucination, constipation, and difficulty urinating.

What medications are appropriate for my patient?

The best way to identify the right medications for some-one with Parkinson's disease is to identify the **most disabling symptom**.

For some-one with mild symptoms of Parkinson's disease (for example, a slight tremor in an arm or stiffness in a leg), **no medication may be necessary**. Mild intermittent symptoms (particularly when it involves the non-dominant arm) may not limit activity. At this early stage, adequate rest, a balanced diet, and an exercise program that emphasizes range of motion may be the most appropriate treatments. Because monamine oxidase inhibitors, in particular, possibly have disease-modifying effects (as yet, unproven), treatment with these agents is sometimes started soon after diagnosis.

Over time, people with Parkinson's disease note worsening of symptoms. Common symptoms that may limit activity include: tremor, slowness, and stiffness. The threshold for beginning treatment varies considerably between individuals. When starting medical treatment for Parkinson's disease, it is important for patients to have a realistic expectation about the degree of improvement to expect from medical treatment. For most, an improvement of 20-40% is typical.

If **tremor of a limb becomes a troubling symptom**, **treatment with an anticholinergic or amantadine** may be tried. If the main symptom is slowness or stiffness of an arm or leg, a MAO-B inhibitor, dopamine agonist, or carbidopa/levedopa may be used. As discussed earlier, treatment is often initiated with a dopamine agonist, so long as it is effective and does not cause troubling side effects. **For exercise-induced dystonia**, **an anticholinergic may be helpful**. Symptoms of fatigue are occasionally helped by treatment with amantadine or a MAO-B inhibitor. Because side effects of dopamine agonists are more common in older individuals, the age of a person with Parkinson's disease may influence which medication is prescribed. Thus, many experts recommend levodopa as first-line therapy for individuals older than 70. For younger patients, dopamine agonists are often recommended as first-line therapy while levodopa is reserved for those individuals who either do not respond adequately to dopamine agonists or experience intolerable side effects.

The progression of Parkinson's disease varies considerably between individuals. Over time, many people find that they do not obtain the same degree or duration of relief from a dopamine agonist or levodopa as previously. Increasing the dose or frequency may resolve this problem. If raising the dose of a dopamine agonist results in side effects (drowsiness, confusion, or nausea), a trial with one of the other agonists may be indicated. Alternatively, adding levodopa to treatment with a dopamine agonist may be useful.

For patients who have not started dopaminergic therapy, the development of postural instability may signal an appropriate time to begin or adjust therapy, since falls may cause significant morbidity.

One of the most frustrating symptoms of advanced Parkinson's disease is **longer periods of time during which movement is poor (the "off state").** A number of interventions that may reduce the period of time spent in the off state include:

- increasing the dose or frequency of a dopamine agonist
- increasing the dose or frequency of levodopa
- beginning treatment with a COMT inhibitor (for patients on levodopa)
- beginning treatment with a MAO-B (for patients on levodopa)

Because protein-rich foods interfere with the absorption of levodopa and its transport into the brain, many who experience response fluctuations choose to eat the majority of their **daily protein during the evening meal**, when they are less active. If the individual continues to experience disabling "off states," treatment with **apomophine may be considered**. If these adjustments are unhelpful (and the patient still experiences benefit from levodopa treatment), surgical treatments of Parkinson's disease may be considered.

Dyskinesia is typically a dose-related side effect of levodopa. They may be helped by reducing the dose of levodopa or by increasing the interval between doses. If this strategy results in prolonged "off periods," then an alternative is to start **amantadine**. For some people who do not respond to these adjustments, surgical treatments**)** of Parkinson's disease may be considered.

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