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Parkinson's Disease Medications: Patient Edition

How is Parkinson's disease treated?

At this time no treatment has been proven to slow or stop the progression of Parkinson's disease. Instead, therapy is directed at treating the symptoms that are most bothersome to an individual. For this reason, 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 the treatment of Parkinson's disease. Because individuals with Parkinson's disease have a range of symptoms, the choice of medication (and whether to treat with medication) varies considerably between individuals. Moreover, over time, the dose of medication(s) may need to be increased or new medications added.

Doctors recommend a number of medications for the symptoms of Parkinson's disease. The following paragraphs describe the commonly prescribed medications for slowness of movement, tremor and stiffness—the so-called motor symptoms of the disease.

Levodopa (carbidopa/levodopa)

Although Parkinson's disease is characterized by a **loss of brain cells** that contain and release the brain chemical (or neurotransmitter) **dopamine**, simple replacement of dopamine by pill or intravenously is not effective because dopamine is not transported to the brain. However, **levodopa** (a chemical precursor of dopamine) is transported to the brain and is then transformed into dopamine. The introduction of levodopa (or L-dopa) more than 40 years ago revolutionized treatment of Parkinson's disease. For most individuals, treatment with levodopa reduces the motor symptoms. It remains the most effective treatment for Parkinson's disease.

After being absorbed in the gastrointestinal tract, levodopa is transported to brain cells, where it is transformed into dopamine. It is subsequently released by brain cells and activates dopamine receptors, allowing for improved function of the movement control centers of the brain. Since blood enzymes, called "amino acid decarboxylases," would break down most levodopa before it reached the brain, levodopa is always combined with an enzyme inhibitor called **carbidopa** (or benserazide in Europe). The trade names of this combination are called Sinemet® or Atamet®. Parcopa® is a formulation that easily dissolves in the mouth.

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, 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**." Another form of motor fluctuation is uncontrolled writhing or other abnormal movement of the body or a limb, which is called "**dyskinesia**." About 40% of people treated with levodopa will develop motor fluctuations within six years of treatment.

Levodopa is rapidly absorbed from the small intestine. Food (in particular, protein-rich food) delays its absorption by the gastrointestinal tract and delivery into the bloodstream. When levodopa is taken 30-60 minutes before a meal, many people notice an improvement beginning after about 30 minutes. Most people with Parkinson's disease note that benefit of levodopa lasts about 3-5 hours, but the duration of benefit may range from as long as a day to as short as an hour.

Levodopa is also available as a long acting or "controlled-release" (**CR**, **ER**, or **SR**) formulation. Controlled release levodopa provides a longer duration of action by increasing the time it takes for the gastrointestinal tract to absorb levodopa. However, because the controlled release formulation only allows 70% of the levodopa to be absorbed by the gastrointestinal tract, in order to obtain the same benefit, it may be necessary to increase the levodopa (measured in mg) when a person is switched from standard (or immediate-release) levodopa to controlled-release levodopa.

Levodopa preparations

Standard release preparations:

levodopa/carbidopa (Sinemet®, 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

Extended release preparations:

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

Side effects

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 people treated for 4-6 years.

Catechol-*O*-methyl transferase (COMT) inhibitors

A different class of enzyme inhibitors, called **COMT inhibitors**, has been developed for Parkinson's disease. Like carbidopa, COMT inhibitors prevent the breakdown of levodopa. Their main effect is to prolong the duration of action of a dose of levodopa. Since COMT inhibitors do not contain levodopa, they must be taken with levodopa in order to have any benefit. COMT inhibitors may be prescribed when an individual experiences "wearing off," particularly when dopamine agonists (see below) are not tolerated. If involuntary movements (dyskinesias) develop after starting a COMT inhibitor, the dose of levodopa may need to be reduced.

COMT inhibitors

-Entacapone (Comtan®)--available in the U.S. and many other countries.

200 mg tablets usually given with each dose of levodopa

-Tolcapone (Tasmar®)--available in the United States, but not Canada or Europe.

100 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). People taking tolcapone must have blood drawn periodically to monitor liver function.

Side effects for both of these medications include diarrhea, vivid dreams, visual hallucinations, drowsiness, urine discoloration (orange) and dyskinesias. Tolcapone has been associated with liver toxicity.

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: diarrhea, vivid dreams, visual hallucinations, drowsiness, urine discoloration and dyskinesias.

Dopamine agonists

Over the years, a number of substitutes for levodopa have been developed. Unlike levodopa, these medications do not have to be modified by brain enzymes in order to activate dopamine receptors. As a class, these medications are called **dopamine agonists** and they act like dopamine. They may be used in place of levodopa or in combination with it. Although treatment with dopamine agonists appear to cause motor fluctuations less frequently than levodopa, dopamine agonists are more likely to cause certain other side effects than levodopa, so doctors must consider a number of factors in deciding whether to prescribe dopamine agonist or levodopa.

There are two commonly prescribed dopamine agonists in the United States which are taken by mouth:

- pramipexole
- ropinirole

A third dopamine agonist, **rotigotine** comes in a patch form and is absorbed through the skin. A 4th agent, **apomorphine**, is an injectable drug that is used to treat "off periods." The dopamine agonists differ in several respects, including:

- chemical structure
- duration of action
- side effects

Bromocriptine

Bromocriptine, originally popular, is now rarely used. Bromocriptine (and the recently withdrawn pergolide) are similar in chemical structure to a chemical called "ergot." Like other ergot medications, bromocriptine may rarely cause fibrosis (or scarring) of the tissues that surrounds the lung, heart, and kidney. Bromocriptine, pramipexole, and ropinirole provide benefit for 6-12 hours so they are usually given 2-4 times daily.

Pramipexole and ropinirole

Pramipexole and ropinirole were developed more recently than bromocriptine. They are not ergot compounds. Large trials comparing use of these medications show that they can be used in early or advanced Parkinson's disease and can reduce the severity of symptoms. One side effect which occurs with all dopamine agonists is daytime sleepiness and "sleep attacks." Some patients

manage this symptom by taking the dopamine agonist once they have arrived at a destination instead of just before beginning a monotonous activity like highway driving.

Rotigotine skin patch

Rotigotine is not an ergot compound either. The patch, which contains rotigotine and releases it over 24 hours, 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

Apomorphine is not an ergot compound. It **is given as an injection into the skin**, and for this reason has a **rapid effect**, usually within 10-20 minutes. Its effects last for only about an hour. Because of these properties, apomorphine is frequently used as a rescue treatment (given occasionally or several times a day) for those individuals who experience a profound "off state," that does not respond to other medication adjustments. Apomorphine is only available from specialty pharmacies. Because nausea occurs in the vast majority of patients, pretreatment with an anti-nausea medication (trimethobenzamide (Tygan®) is required. Moreover, because use of this medication is more complex and side effects (such as a drop in blood pressure) are more profound, patient training and the initial dosing of apomorphine must occur in the physician's office.

Starting treatment with dopamine agonists

The response to a particular dopamine agonist varies considerably between individuals, so that if one dopamine agonist does not help or causes bothersome side effects, another agonist may be tried. Most dopamine agonists are given 2-4 times a day. Treatment with dopamine agonists often begins at a very low dose. The dose is increased every 5-7 days until benefit is appreciated.

Two recent clinical studies observed patients with early Parkinson's disease randomly assigned to treatment either with a dopamine agonist (pramipexole or ropinirole) or with levodopa. Over the course of both trials, about half of the participants assigned to dopamine agonist treatment received supplemental levodopa because of worsening symptoms. In the final analysis of these studies, dyskinesias developed at a higher rate in the levodopa groups than the dopamine agonist groups. These findings are balanced by two other findings: those patients treated with levodopa alone had slightly better control of movement and other side effects were more common in the dopamine agonist group than the levodopa groups.

The ropinirole study followed participants for 5 years. In that study, dyskinesias developed in about 20% of people initially treated with ropinirole compared to about 45% of participants treated with levodopa alone. Drowsiness, hallucinations and swelling of the legs were more common in the ropinirole group than the levodopa group.

The pramipexole study followed participants for 2 years. Dyskinesias developed in about 10% of participants in the pramipexole group compared to 31% of the levodopa group. Wearing off occurred in 24% of the pramipexole group and 38% of the levodopa group. Drowsiness, hallucinations, generalized swelling and leg swelling occurred more frequently in the pramipexole group.

Preliminary controlled trials with pramipexole and ropinirole, although encouraging, did not provide conclusive proof that either agent slowed the progression of PD.

Preparations of Dopamine Agonists

- Bromocriptine (Parlodel®): 2.5 mg tablet and 5 mg capsule
- Pramipexole (Mirapex®): 0.125 mg, 0.25 mg, 0.5 mg, .75mg, 1 mg, and 1.5 mg tablets
- Pramipexole (ER) (Mirapex®): 0.375mg, 0.75mg, 1.5 mg, 2.25mg, 3mg., 3.75, & 4.5mg
- Ropinirole (Requip®): 0.25 mg, 0.5 mg, 1 mg, 2mg, 3mg 4 mg, 5 mg tablets
- Ropinirole XL (Requip XL®): 2mg, 4mg, 6mg, 8mg, 12mg
- Rotigotine (Neupro®): 1mg, 2 mg, 3mg 4 mg, 6 mg and 8 mg patches
- 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 (.1-.8ml).

Side effects

Side effects for all the dopamine agonists include drowsiness, nausea, vomiting, dry mouth, dizziness, leg swelling, and feeling faint upon standing. Although these symptoms are common when starting a dopamine agonist, they typically resolve over several days. In some individuals, dopamine agonists may cause confusion, hallucinations, or psychosis. Sleepiness, drowsiness, or sedation may be a significant side effect of some dopamine agonists in some people, and may interfere with driving or other activities.

A number of **behavioral side effects** also occur. These behavioral changes are often called “impulse control disorders” because 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, binge eating**, as well as increased **sexual behaviors**. They occur in 5-10 percent of patients on these medications and may occur more frequently in patients with depression. These behavioral changes typically resolve once the dose of the dopamine agonist is reduced or discontinued.

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

Monoamine Oxidase B Inhibitors (MAO-B inhibitors)

Selegiline

Selegiline is an inhibitor of the enzyme MAO-B (monoamine oxidase B). Since MAO-B breaks down dopamine, inhibiting it prolongs the action of dopamine in the brain, and improves the

symptoms of Parkinson's disease. Selegiline also has a mild antidepressant effect. Early studies of selegiline initially led doctors to believe that it may delay the progression of Parkinson's disease, but currently there is no firm evidence that this is so.

Patients taking selegiline **should avoid** treatment with **meperidine (Demerol)**, a pain medication.

Selegiline preparations include:

- Eldepryl®: 5 mg capsule
- Zelapar®: 1.25 mg orally disintegrating tablets

Usually it is taken once in the morning and at midday. Zelapar® is an orally disintegrating form of selegiline which comes in 1.25 mg tablets; it is usually taken once daily.

Side effects may include heartburn, nausea, dry mouth, insomnia, and dizziness. Confusion, nightmares, hallucinations, and headache occur less frequently and should be reported to your doctor.

Rasagiline

Rasagiline is a more recent MAO-B inhibitor which has been approved for use as a single medication to treat symptoms in early Parkinson's disease or in addition to other agents such as dopamine agonists or levodopa when the symptoms of Parkinson's disease are more prominent. 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 effect (i.e., slowing the disease) whereas treatment with 2 mg daily did not. Because the two doses were not associated with different outcomes, the study is difficult to interpret.

Rasagiline (Azilect®) is available as 0.5 and 1 mg tablets.

Side effects include abnormal movements, headache, and fatigue.

Precautions: Patients taking rasagiline **should avoid meperidine (Demerol), dextromethorphan, and ephedrine**. Treatment with **ciprofloxacin** may **increase the blood level of rasagiline** so it should be avoided or only be used with caution.

Other medications

A number of other medications can be used alone or in combination with levodopa or a dopamine agonist to improve movement for people with Parkinson's disease. These medications do not stimulate dopamine receptors but affect the movement control center by other means. Although a number of medications are used by doctors, the most commonly used medications are

- amantadine
- anticholinergic medications.

Amantadine

Amantadine was initially developed as an antiviral medication for treatment of influenza. By coincidence it was found to help with symptoms of early and advanced Parkinson's disease. It may be used alone or in combination with levodopa or dopamine agonists. Amantadine reduces symptoms of fatigue and tremor in some people with early Parkinson's disease. However, for some, this benefit is short-lived. More recently, amantadine has been found helpful for people with advanced Parkinson's disease who experience dyskinesias.

Formulation: Amantadine (Symmetrel®) as 100 mg capsules or in liquid form that may be convenient for treating an individual who does not tolerate a full 100 mg dose or a person with swallowing problems.

Side effects may include difficulty concentrating, confusion, insomnia, nightmares, agitation, headache, and hallucinations. Amantadine may cause leg swelling as well mottled skin (livedo reticularis), often on the legs.

Anticholinergic medications

Anticholinergic medications are the oldest class of medications available for Parkinson's disease. They may reduce tremor or rigidity but appear to have little effect on slowness of movement and imbalance. They can be taken alone or in combination with levodopa. These drugs are rarely used in elderly patients or those with cognitive problems, because increased confusion can be one of their side effects. Specific anticholinergic medications include:

- 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.

Which medications are right for me?

Medications that are effective for one person with Parkinson's disease, may not work well for another person. The best way for a person to identify the right medications is through an evaluation by a doctor or nurse practitioner who is knowledgeable about Parkinson's disease. Several general comments may be helpful in providing general background.

For an individual with the **first symptoms of Parkinson's disease** (for example, a mild 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.

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 people 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 and/or leg, monamine oxidase type B inhibitor, a dopamine agonist, or carbidopa/levodopa may be used. As discussed in the section describing [dopamine agonists](#), many doctors favor dopamine agonists over levodopa, so long as the dopamine agonist is effective and does not cause troubling side effects. If a cramp-like contraction of a limb develops during exercise, an anticholinergic may be helpful. Symptoms of fatigue are occasionally helped by treatment with amantadine, rasagiline, or selegiline.

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 your doctor recommends. For example, many experts recommend levodopa as a first line of therapy for individuals older than 70. For individuals younger than 70, dopamine agonists are often used as first-line therapy while levodopa is reserved for those people who either do not respond adequately to a number of 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 they had previously. Increasing the dose or frequency of 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 dopamine agonists may be indicated. Alternatively, adding levodopa to treatment with a dopamine agonist may be appropriate.

Treatment of moderate to advanced Parkinson's disease may be challenging. It is extremely helpful to your doctor for you to provide details regarding the type(s) of problem that are most disabling and the time of day that the problem typically occurs. Observations by a spouse, family member, or other caretaker are often helpful to doctors because they often provide additional information of which the person with Parkinson's disease may be unaware.

One of the most frustrating symptoms of advanced Parkinson's disease is longer periods of time spent when movement is poor, and is known as the "**off state**" or "**off period.**" A number of interventions that may reduce the period of time spent in the off state includes:

- increasing the dose or frequency of a dopamine agonist

- increasing the dose or frequency of levodopa
- beginning treatment with a COMT inhibitor (either as an additional agent or the combination of carbidopa/levodopa/entacapone (Stalevo®))
- addition of either selegiline or rasagiline

Because protein-rich foods interfere with the absorption of levodopa, many who experience response fluctuations choose to eat the majority of their daily protein during the evening meal, when they are less active. Apomorphine may be used as a rescue for patients who experience intermittent disabling "off states." For some people who do not respond to these adjustments and who still experience benefit from levodopa treatment, [surgical treatments](#) of Parkinson's disease may be considered.

Dyskinesia refers to unwilled abnormal movements such as facial grimacing, writhing or twisting movements of a limb, or rocking in a chair and is typically a symptom of too much levodopa or dopamine agonist. This problem may be helped by reducing the dose of these medications or by increasing the time period between doses. If this strategy results in prolonged "off periods," then an alternative would be 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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