PARKINSON'S MEDICATIONS

What is Dopamine?

Delays in Parkinson's Treatment Due to Fear of Side Effects a Serious Problem, Neurologists Says

Parkinson's Related Medications

WebMD

"What Is Dopamine?"

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What Is Dopamine?

Dopamine is a type of neurotransmitter. Your body makes it, and your nervous system uses it to send messages between nerve cells. That's why it's sometimes called a chemical messenger.

Dopamine plays a role in how we feel pleasure. It's a big part of our unique human ability to think and plan. It helps us strive, focus, and find things interesting.

Your body spreads it along four major pathways in the brain. Like most other systems in the body, you don't notice it (or maybe even know about it) until there's a problem.

Too much or too little of it can lead to a vast range of health issues. Some are serious, like Parkinson's disease. Others are much less dire.

Dopamine Basics

It's made in the brain through a two-step process. First, it changes the amino acid tyrosine to a substance called dopa, and then into dopamine.

It affects many parts of your behavior and physical functions, such as:

- Learning
- Motivation
- Heart rate
- Blood vessel function
- Kidney function
- Lactation
- Sleep
- Mood
- Attention
- Control of nausea and vomiting

- Pain processing
- Movement

Role in Mental Health

It's hard to pinpoint a single cause of most mental health disorders and challenges. But they're often linked to too much or too little dopamine in different parts of the brain. Examples include:

Schizophrenia. Decades ago, researchers believed that symptoms stemmed from a hyperactive dopamine system. Now we know that some are due to too much of this chemical in certain parts of the brain. This includes hallucinations and delusions. A lack of it in other parts can cause different signs, such as lack of motivation and desire.

ADHD. No one knows for sure what causes attention deficit hyperactivity disorder (ADHD). Some research shows it may be due to a shortage of dopamine. This problem may be due to your genes. The ADHD drug methylphenidate (Ritalin) works by boosting dopamine.

Drug misuse and addiction. Drugs such as cocaine can cause a big, fast increase of dopamine in your brain. That satisfies your natural reward system in a big way. But repeated drug use also raises the threshold for this kind of pleasure. This means you need to take more to get the same high. Meanwhile, drugs make your body less able to produce dopamine naturally. This leads to emotional lows when you're sober.

Dopamine in Other Diseases

It also plays a role in diseases that aren't related to mental health. One of these is Parkinson's disease. Another is obesity, which the American Medical Association classified as a disease in 2013.

Parkinson's disease. Dopamine enables neurons in your brain to communicate and control movement. In Parkinson's, one type of neuron steadily degenerates. It doesn't have a signal to send anymore, so your body makes less dopamine. The chemical imbalance causes physical symptoms. These include tremor, stiffness, slowness of spontaneous movement, poor balance, and poor coordination. Doctors treat these symptoms with medications that raise levels of this chemical.

Obesity. Most of the time, if you take in more calories than you burn, you'll gain weight. So why can't obese people simply eat less and slim down? The answer isn't that simple. They may face obstacles that others don't. They could have problems with their natural reward systems. This can affect the amount of food they eat before they feel satisfied. Imaging studies suggest

that in people with this condition, the body may not release enough dopamine and another feel-good hormone, serotonin.

Dopamine Can Save Lives

This chemical usually plays a secondary role in the body, but in certain medical situations, it's literally a lifesaver. Doctors use prescription dopamine (Intropin) to treat:

- Low blood pressure
- Poor cardiac output (when the heart doesn't pump out enough blood)
- Poor blood flow to vital organs
- Some cases of septic shock

There are possible complications with any drug, even if taken under close supervision. The main ones associated with dopamine include:

- Irregular heartbeat
- Faster heart rate
- Trouble breathing
- Chest pain
- Nausea and vomiting
- Headache

Because many drugs interact with it, it's important that your doctor knows all the medications you take.

Delays in Parkinson's Treatment Due to Fear of Side Effects a Serious Problem, Neurologist Says

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Emma Yasinski

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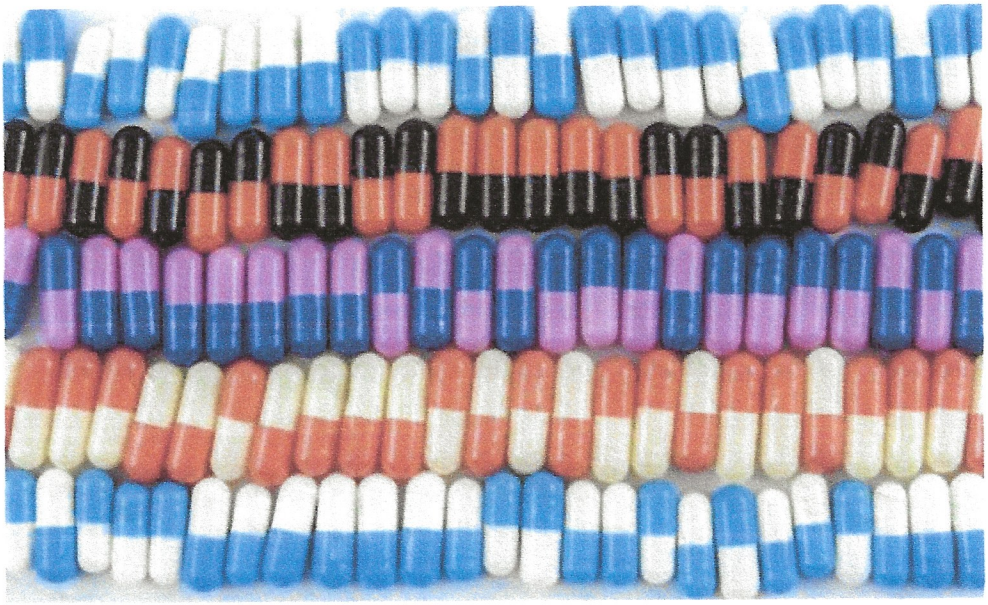

A fear of the potential side effects of Parkinson's disease treatments, dubbed "levodopa phobia," can cause patients and their doctors to delay the use of these therapies, a neurologist says.

However, evidence suggests that starting adequate levodopa therapy early is safe, particularly for patients with increased functional disability, according to a lecture by Joseph Jankovic, MD, a professor of neurology at Baylor College of Medicine, which was presented by the Parkinson Voice Project (PVP.)

Jankovic's lecture, "New and Emerging Treatments for Parkinson's Disease," was presented to patients and caregivers via Skype as part of the PVP's Parkinson's Lecture Series, from the Clark and Brigid Lund Parkinson's Education Center. A video of the presentation is available online.

Disease-modifying therapies

There are no therapies currently available that slow or prevent the progression of Parkinson's, though several are in clinical trials. A Phase 3 trial (NCT00256204), called ADAGIO, completed in 2011, suggested that early Azilect (rasagiline) treatment might be able to delay the progression of the disease. However, the study included two dosages, 1 mg and 2 mg, and while the benefits were true for the the lowest dose, they didn't hold up for the larger dose. Because the two doses were associated with different outcomes, the results needed careful interpretation, and the U.S. Food and Drug Administration (FDA) did not approve Azilect as a disease-modifying therapy.

Researchers are exploring several treatments with the potential to modify the disease, including inosine (which elevates urate levels), and isradipine (a calcium channel inhibitor). Both are in Phase 3 trials (NCT02642393 and NCT02168842).

However, Jankovic said, the "most important strategy in development" is reducing alpha-synuclein, the protein that doesn't work properly and accumulates in the brains of Parkinson's patients, leading to neuronal death.

Jankovic and his colleagueslast year published a study based on a Phase 2 trial (NCT03100149) of an antibody — prasinezumab (PRX002/RG7935) — that's designed to clear alpha-synuclein proteins. The 80-patient, ascending-dose study showed that the treatment was safe, and reduced alpha-synuclein concentrations in the blood over the course of 52 weeks, with no serious adverse events reported. The study supported the continuation of the Phase 2 trial.

Similar antibodies currently being tested in trials include Biogen's BIIB054 (NCT03318523), AstraZeneca's MEDI1341 (NCT03272165) — both currently recruiting — and AbbVie's ABBV-951 (NCT03781167), which is not yet enrolling participants.

Early symptomatic therapies

When patients first start to experience symptoms severe enough to require treatment, they and their doctors may be reluctant to start levodopa or levodopa-carbidopa — the most commonly used

treatment for Parkinson's symptoms — for fear they will develop motor complications such as dyskinesias.

Some patients may turn to natural supplements, such as bacopa extract or mucuna pruriens. Jankovic "strongly discouraged" the use of these products for "many, many reasons," chief among them that some supplements contain levodopa at inconsistent doses.

An alternative for patients and neurologists concerned about starting levodopa too early are dopamine agonists such as Mirapex (pramipexole), Requip (ropinirole), Dostinex (cabergoline), and Permax (pergolide). Instead of helping the brain produce more of the dopamine it lacks, these treatments directly stimulate the receptors that dopamine would normally act on.

A 2009 study, which compared pramipexole with levodopa in patients who had not yet been treated with levodopa, found that 50% of those on pramipexole experienced dyskinesia, compared with 68.4% of the levodopa patients.

"There is no doubt that delaying levodopa therapy by using dopamine agonists early may delay the onset of levodopa-related motor complications," Jankovic said.

Although levodopa has some potential for side effects *in vitro* (or in the laboratory), Jankovic said there is no evidence that this translates to patients. Therefore, delaying the use of the therapy, particularly for patients with increased functional disability, is not backed by currently available scientific data, he said.

However, he believes that because every patient is different, the timing, choice, and dosage of therapy must be individualized according to the needs of each particular patient.

Emerging and experimental therapeutics

Almost all patients with severe Parkinson's who take levodopa or levodopa-carbidopa will, over time, experience motor fluctuations and dyskinesias. Thus, many emerging therapies are designed to make the treatment more effective and reduce the side effects.

There are three therapies work to extend the effectiveness of levodopa by maintaining increased dopamine concentrations in the brain. Xadago (safinamide) inhibits monoamine oxidase, an enzyme that normally breaks down dopamine. Opicapone works by preventing a different enzyme, catechol-O-methyltransferase (COMT), from breaking down dopamine. Gocovri (amandine) prevents cells from recycling dopamine.

Several new formulations of levodopa are intended to stretch the effects of a single dose, or act almost immediately to help patients recover from "off" episodes between doses.

Rytary, a capsule that can be taken orally, contains beads of carbidopa-levodopa that dissolve and release the medicine at different times. Since the treatment needs to be taken more than once a day, patients end up ingesting a higher dose of levodopa than they would otherwise. But the effects start sooner and last longer than the common formulation of carbidopa-levodopa.

Researchers have experimented with administering the treatment continuously for 24 hours using an intestinal gel, which is surgically implanted into the small intestine and programmed to consistently administer the treatment at the appropriate dose.

But choosing this surgery "cannot be taken lightly," Jankovic said. While patients did increase their "on" time without dyskinesia (by 4.11 hours for those who used the intestinal gel compared with 2.24 hours for those who used oral levodopa), almost all of the 66 patients in a 2014 study experienced gastrointestinal side effects as a result of the device insertion.

Jankovic also described the "accordion" pill currently being tested in a Phase 3 trial (NCT02605434). The pill, developed by Intec Pharma, is a multilayer film that unfolds in the stomach and stays there for 12 hours, releasing a combination of levodopa and carbidopa.

Rather than extending the life of a dose of levodopa, some companies develop "rescue therapies" that can be taken during "off" periods, or when treatment wears off. These therapies take effect

almost immediately, and help the patient make it until their next scheduled dose of levodopa. Several forms — both approved and in trials — are dopamine agonists injected under the skin.

Other companies are developing treatments they hope will be delivered through less invasive methods, such as under the tongue, in the case of APL-130277, or through inhalation, like Inbrija, a levodopa powder approved in December 2018.

Surgical therapies are gaining more attention, with scientists testing focused ultrasound, which was approved by the FDA at the end of 2018. However, it is available in very few centers, and costs more than $4 million.

Also during 2018, researchers conducted a pilot study of five patients suggesting that spinal cord stimulation may be able to help patients improve gait.

Jankovic says it is too early to meaningfully discuss several other experimental therapies, such as gene therapies or stem cell treatments. “Ask me in 10 years,” he said.

Different agents are being investigated to treat non-motor symptoms, including Exelon (rivastigmine) and memantine (sold under the brand name Namenda, among others) for cognitive impairment, paroxetine and venlafaxine for depression, and SEP-363856 for psychosis. Nuplazid (pimavanserin) is the only therapy currently approved by the FDA for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis.

In addition to all the therapies on the market, Jankovic said, he “couldn’t emphasize enough the importance of physiotherapy,” and high-intensity exercise — “something that really makes you huff and puff.”

PD - Related Medications

Dopamine Replacement Therapy: levodopa/carbidopa

Examples: **Sinemet, Sinemet CR, Stalevo (levodopa/carbidopa and entacapone), Parcopa, Rytary,* Duopa***

Levodopa was approved for Parkinson's in the late 1960s and is the most widely prescribed drug for Parkinson's. It is absorbed in the intestine and the brain converts it to dopamine, which is the brain chemical that powers normal movement but decreases in Parkinson's disease (PD).

Carbidopa prevents levodopa from turning into dopamine before it gets to the brain and limits levodopa's side effects, such as nausea and vomiting. In the United States, the combination of immediate-release levodopa and carbidopa is commonly referred to by the brand name Sinemet. A controlled-release form — Sinemet CR — also is available, as is a capsule (Rytary) that combines both immediate and extended-release levodopa in one.

Levodopa/carbidopa can be taken alone or with other Parkinson's medications. It comes in a pill, a dissolvable tablet (Parcopa) and a gel (Duopa). The gel is infused directly into the small intestine, where levodopa is absorbed.

Pros

In the majority of patients, especially people with mild symptoms, levodopa significantly improves motor symptoms. Typically, the medication remains effective as long as you need it, but since Parkinson's symptoms gradually progress over time, you may need to increase your dose or change how often you take it.

Cons and Complications

When first starting levodopa, the most common potential side effects are nausea and vomiting. If these occur, doctors usually recommend taking the medication with a small carbohydrate snack, such as crackers or toast, or adding extra carbidopa (Lodosyn). Other possible side effects include drowsiness, low blood pressure (which can cause lightheadedness or dizziness) or hallucinations.

With long-term use of levodopa (as well as longer duration of Parkinson's disease), complications may develop. These can include dyskinesia or motor fluctuations. Dyskinesia is uncontrolled, involuntary writhing or wriggling movement. It most often occurs when symptoms are otherwise well controlled (known as "on" times). Motor fluctuations are when medication effect wears off and symptoms return before your next medication dose is scheduled. These "off" times alternate with "on" times during the course of a day. "Off" periods often come on gradually but also can occur suddenly or unpredictably.

Certain dietary factors, particularly the amount of protein you eat and when, can affect how well levodopa works. This is often most noticeable in people who are experiencing dyskinesia or "off" times. Levodopa and dietary protein, found in meat and fish, for example, are absorbed in the same place in the intestine. So, taking the medication with a high-protein meal could decrease the amount of levodopa that is absorbed and the effect you get from that dose. (Read more about Parkinson's medications and diet.

- **Decarboxylase Inhibitor: Lodosyn (carbidopa)**

This medication is taken with levodopa. It prevents the body from converting levodopa to dopamine, so more levodopa can get to the brain and convert to dopamine there. Carbidopa also helps prevent or lessen levodopa side effects, such as nausea and vomiting. Carbidopa is usually combined with levodopa in one pill (or gel, as in Duopa), but if these medications cause significant nausea or vomiting, doctors may prescribe extra carbidopa to ease those side effects.

- **Dopamine Agonists**

Examples: **Mirapex, Mirapex ER (pramipexole); Requip, Requip XL (ropinirole); Neupro (rotigotine), Apokyn (apomorphine)**

Dopamine agonists mimic the effect of dopamine, the chemical that decreases in PD, in the brain. You can take these drugs alone or combine them with other PD medications, including levodopa/carbidopa. They come in immediate or extended-release forms and can be taken as pills, through a skin patch or by injection. (The injectable form — apomorphine — is used as needed for sudden and unpredictable "off" periods, which may occur as the disease progresses.) Some people benefit equally from all of the available dopamine agonists; others might get side effects from one and not another. There is no way to predict your response until you try the medication. If you and your doctor decide dopamine agonists are the right medication for your symptoms, your doctor will choose one to start at a low dose and then gradually increase until your symptoms are controlled, side effects occur or you reach the maximum dosage.

Pros

Compared to levodopa, long-term use of dopamine agonists may be less likely to lead to dyskinesia or "off" times. And if these complications do develop, they may be less severe. Dopamine agonists do not compete with dietary protein for absorption like levodopa, so there are no specific dietary restrictions. Doctors may recommend taking dopamine agonists with or without food, depending on an individual's response to medication or side effects. If a person's symptoms are not well controlled, it may be best to try the medication on an empty stomach. On the other hand, if the medication causes nausea, you might want to take it with food.

Cons and Complications

Dopamine agonists work well for many people. In general, though, they may be less effective than levodopa for treating motor symptoms. They have similar potential side effects to levodopa, and the most common are nausea and low blood pressure (which may result in lightheadedness or dizziness). Dopamine agonists also can cause leg swelling, drowsiness, "sleep attacks" (sudden, unanticipated onset of sleep) or hallucinations. In some people, these drugs can lead to impulse control disorders, such as compulsive gambling, hypersexuality (increased interest in sex or sexual activity) and excessive shopping.

- **Monoamine Oxidase (MAO) B Inhibitors**

Examples: **Azilect (rasagiline); Eldepryl, Zelapar (selegiline); Xadago (safinamide)***

Monoamine oxidase (MAO) B inhibitors block an enzyme in the brain that breaks down dopamine after it does its work. They allow the available dopamine (made by remaining dopamine-producing brain cells and/or given through other medications, such as levodopa) to function for a longer period of time.

Depending on the specific MAO-B inhibitor and a person's symptoms, these drugs can be taken alone or combined with levodopa and other Parkinson's therapies. Azilect (rasagiline) is the only MAO-B inhibitor FDA-approved to be taken by itself for PD. When prescribed in this manner, it's most often for mild symptoms and in earlier stages of disease. In mid to later stages, MAO-B inhibitors are typically coupled with levodopa or dopamine agonists to boost the effects of these drugs. When combined with levodopa, MAO-B inhibitors may allow you to take less levodopa while still increasing the amount of time that symptoms are controlled ("on" time) and decreasing the amount of time that symptoms return ("off" time).

Pros

In the early Parkinson's stage, Azilect may lessen mild symptoms when taken alone and, therefore, could be an option for those who wish to delay or avoid levodopa or dopamine agonists for any reason. In some people, certain MAO-B inhibitors can lessen fatigue and even depression, although antidepressant effects usually come at higher dosages than what are prescribed in Parkinson's disease.

Cons and Complications

Potential side effects of Azilect and Eldepryl/Zelapar (selegiline) include flu-like symptoms, joint pain and blood pressure changes. Selegiline also may cause insomnia or hallucinations, both of which are more likely to occur in older people or those with more advancing Parkinson's. Xadago (safinamide) may cause dyskinesia (uncontrolled, involuntary movement), falls, nausea or insomnia.

When taken with certain drugs, all MAO-B inhibitors pose a risk for a rare, but potentially severe, reaction called serotonin syndrome. These drugs include, but are not limited to, specific antidepressants, muscle relaxants and pain medications, as well as herbal supplements (St. John's Wort, for example) and some over-the-counter sinus, cough or cold therapies. Serotonin syndrome causes muscle stiffness, increased tremor, high blood pressure and heart rate, sweating, diarrhea, fever, shivering, confusion and agitation.

When taken in high doses (often more than what is prescribed for Parkinson's) and combined with large amounts of foods that contain tyramine, such as aged cheeses and cured meats, MAO-B inhibitors could significantly elevate blood pressure. This potential side effect, known as hypertensive crisis, is rare. You do not need to eliminate foods high in tyramine from your diet, but you probably should eat them in moderation.

Learn more about MAO-B inhibitors and diet

- **Catechol-O-methyltransferase (COMT) Inhibitors**

Examples: **Comtan (entacapone), Stalevo (levodopa/carbidopa and entacapone), Tasmar (tolcapone)**

Catechol-O-methyltransferase (COMT) inhibitors block an enzyme in the body that breaks down levodopa. This allows more levodopa to reach the brain, where it is converted to dopamine. COMT inhibitors are not effective on their own and must be combined with levodopa. Comtan (entacapone) typically is taken with each dose of levodopa, whereas Tasmar (tolcapone) is prescribed three times daily, regardless of how often levodopa is taken. Stalevo contains levodopa/carbidopa and entacapone in one pill.

COMT inhibitors help levodopa last longer. When levodopa does not last until the next scheduled dose and symptoms return — in other words, you have "off" periods — COMT inhibitors can prolong the duration of levodopa's effect.

Pros

COMT inhibitors extend the benefit of each levodopa dose. When "off" time occurs, they may be used, at least as a first step, instead of taking levodopa more frequently.

Cons and Complications

Potential side effects of COMT inhibitors include diarrhea and harmless urine discoloration. Tasmar (tolcapone) also can cause liver damage, so your doctor will monitor your liver function through regular blood tests. Since COMT inhibitors work with levodopa, side effects or complications may include those associated with levodopa, including dyskinesia.

• • Anticholinergic Medications

Examples: **Artane (trihexyphenidyl), Cogentin (benztropine)**

Anticholinergic drugs decrease the activity of the brain chemical acetylcholine to restore balance between acetylcholine and dopamine, the brain chemical that decreases in Parkinson's. This balance is important for normal movement. Anticholinergics can be used alone or taken with other Parkinson's therapies.

Pros

These medications typically work best to treat tremor, especially in younger people. They sometimes are prescribed for dystonia (prolonged muscle contractions), as well. In some cases, doctors use anticholinergics to treat drooling, which can occur in advancing Parkinson's disease.

Cons and Complications

Possible side effects include blurred vision, dry eyes and mouth, constipation, cognitive problems (short-term memory loss or confusion) and hallucinations. Because older people are most susceptible to side effects, these drugs typically are used in people younger than age 70.

• • Amantadine

Examples: **Symmetrel (immediate-release amantadine), Osmolex ER (amantadine extended release),* Gocovri (amantadine extended release)***

There are three amantadine-based medications, which work on the dopamine and glutamate brain chemical pathways.

Symmetrel (immediate-release amantadine) is approved to treat Parkinson's symptoms, such as slowness, stiffness and tremor. Doctors may prescribe it alone to treat mild symptoms in early Parkinson's, but often use it for dyskinesia, which are involuntary, uncontrolled movements. (This is an example of "off-label" use, because the drug is not specifically FDA-approved for dyskinesia.) Symmetrel typically is taken two or three times per day. In 2018, Osmolex ER, an extended-release formulation of Symmetrel, was approved. Like Symmetrel, it is meant to treat Parkinson's symptoms and has the same potential benefits and side effects. It differs in that it is taken once a day, in the morning.

Gocovri (amantadine extended release) was approved in 2017 as the first medication specifically for dyskinesia in Parkinson's. It is taken once daily at bedtime so that the medication levels are highest during the day, when dyskinesia typically is most bothersome.

Pros

In early and mild Parkinson's, Symmetrel or Osmolex ER may be options to lessen motor symptoms. Some people notice a decrease in fatigue, particularly with Symmetrel, but both of these medications can cause insomnia.

Gocovri decreases dyskinesia, but it also may help prevent symptoms from returning because other medications aren't working well ("off" time).

Some find the once-daily dosing of Osmolex ER or Gocovri to be convenient and advantageous, as well. For people with swallowing problems, Symmetrel is available as a liquid (as well as a tablet).

Cons and Complications

For Symmetrel and Osmolex ER, the most common potential side effects include insomnia, nausea, dizziness and purple-red blotchy spots on the skin. Gocovri could cause hallucinations (seeing things that aren't there), dizziness, dry mouth, swelling of the legs and feet, constipation and falls. With any of these medications, people with kidney problems may need to decrease their dosage.

Read more about these three amantadine-based medications

Inbrija (levodopa)

About

In 2018, the U.S. Food and Drug Administration (FDA) approved Inbrija (inhaled levodopa) for the treatment of Parkinson's "off" times — when symptoms return between medication doses. Inbrija in inhaled and absorbed through the lungs. In the brain, levodopa turns into dopamine, the chemical that decreases in Parkinson's, causing movement problems. Levodopa is the most effective and most commonly prescribed Parkinson's medication, and many people take levodopa pills (Sinemet, for example) to control symptoms. Inbrija typically works quicker than pills taken by mouth. It can be taken as needed when symptoms return, up to five times per day, in addition to regularly scheduled Parkinson's medications. (Similar to an asthma rescue inhaler for breathing problems, you'd keep it on hand to use when necessary.)

Pros

Inbrija is the first inhalable formulation of levodopa and can quickly relieve Parkinson's symptoms. It's an option to treat "off" time that occurs between medication doses, first thing in the morning, or suddenly and unpredictably. In clinical trials, Inbrija started working, in some people, within 10 minutes and lasted, on average, an hour.

Cons and Complications

Inbrija is not a replacement for daily scheduled Parkinson's treatments. It is an add-on, on-demand medication for "off" time. While most may find the inhaler easy to use, some might experience challenges or discomfort with this method of drug delivery. Trials did not test Inbrija in people with asthma or COPD (chronic obstructive pulmonary disease), so safety and benefits in those who live with these conditions is unclear.

The most common potential side effects of Inbrija include nausea, cough, upper respiratory infection, or changes in saliva or spit color.

- **Constipation**

Constipation decreases how often a person has bowel movements or makes them difficult to pass. Exercise and diet, as well as lifestyle changes, typically are the first steps in the treatment of constipation. Read more about these recommendations. Today, there are **no prescription drugs specifically for Parkinson's-related constipation**. But if exercise and lifestyle changes aren't enough, your doctor may recommend over-the-counter or prescription medications, including:

- **Fiber supplements**: Metamucil(psyllium)
- **Stool softeners**: Colace (docusate)
  These are used if stools are hard and difficult to pass. They can be taken daily for short periods.
- **Laxatives**: Miralax (polyethylene glycol), Dulcolax (bisacodyl), Senokot (senna)
  There are different types of laxatives. Miralax pulls water into the colon to ease constipation; it is fairly

gentle. Dulcolax and Senokot, "stimulant" laxatives, cause gut muscle contractions. They can be harsher so are not recommended for daily use.

- **Enemas**: Fleet enema
  These are sometimes recommended for significant constipation. You should use them cautiously and only under the advice of your health care provider.
- **Drugs for severe constipation**: Linzess (linaclotide), Amitiza (lubiprostone), Trulance (plecanatide)
  The FDA has approved several drugs for severe constipation with no known medical cause. When exercise, diet and lifestyle changes, and the above over-the-counter therapies fail, these (and even others) may be considered.

• • Dementia

Parkinson's disease dementia (PDD) is when memory or thinking (cognitive) changes interfere with a person's job, daily activities or social interactions.

- **Exelon (rivastigmine)** is FDA-approved to treat mild to moderate PDD. It increases the amount of the brain chemical acetylcholine, which supports memory and thinking. Exelon is available as a pill, liquid or skin patch.
- **Aricept (donepezil)** or **Razadyne (galantamine)** work in the same way but were developed for Alzheimer's.

Potential benefits of these drugs may include improved memory and thinking; decreased behavioral changes, such as agitation; and delayed need for long-term care facilities. Common side effects may include nausea, vomiting, diarrhea, decreased appetite, weight loss and increased tremor.

• • Depression and Anxiety

Anxiety and depression can occur in up to half of people with Parkinson's, at any time during the course of their disease. Talk therapy instead of or in addition to medications can be beneficial. Your doctor also may prescribe an antidepressant and/or anti-anxiety medication:

- **Antidepressants**:
  These medications, such as Paxil (paroxetine) and Effexor XR (venlafaxine XR), work on the brain chemicals serotonin and norepinephrine, which regulate mood. They are called **selective serotonin reuptake inhibitors (SSRIs)** or **selective serotonin norepinephrine reuptake inhibitors (SNRIs)**. In studies of people with PD who had depression, Paxil and Effexor XR improved depression without worsening motor symptoms.
- **Anti-anxiety medications**
  Antidepressants, especially SSRIs, also may help with anxiety. If anxiety comes on only occasionally or in panic attacks, your doctor may prescribe as-needed medications, such as Ativan (lorazepam) or Xanax (alprazolam). These types of drugs can cause confusion, sleepiness and imbalance.

• • Drooling

People with Parkinson's swallow their saliva less often. In later years with PD, this could lead to drooling, which can be embarrassing and isolating. In these situations, doctors may prescribe therapies to treat drooling:

- **Injections of Botox or Myobloc** (botulinum toxin) into the glands that make saliva
- **Artane (trihexyphenidyl):** Parkinson's medication that can cause dry mouth as a side effect; might help drooling as well as Parkinson's symptoms (it works best for tremor)
- **Robinul (glycopyrrolate):** a medication that decreases secretions, such as saliva

Because the medications can cause many possible side effects, such as constipation, memory problems and sleepiness, especially in older people, their potential benefits must be carefully weighed against the risks.

• • Fatigue

People with Parkinson's who experience fatigue often find it difficult to describe, but it's more than drowsiness or extreme tiredness. Fatigue is difficult to treat with medication, so the **first steps are behavioral strategies**, such as regular exercise and short naps in the early afternoon. Doctors make sure other conditions, such as sleep problems and depression, aren't contributing to the fatigue. If behavioral strategies don't work and fatigue is significant, drugs might be tried:

- **Stimulants: Ritalin (methylphenidate)**
- **Wakefulness-promoting agents: Provigil (modafinil)**
  Common medication side effects include nausea, anxiety and insomnia.
- Parkinson's medications: **Symmetrel (amantadine)**, **Azilect (rasagiline)**, **Eldepryl (selegiline)**
  Some people report a decrease in daytime fatigue in addition to PD motor symptoms on these drugs.

• • Low Blood Pressure (Orthostatic Hypotension)

Low blood pressure when changing positions, such as standing from sitting, is called orthostatic hypotension. **Dietary and behavioral changes are the first steps to treating orthostatic hypotension**. When these aren't enough, your doctor may recommend medication to raise blood pressure.

- **Northera (droxidopa)**
  This drug converts to the chemical norepinephrine, which regulates blood pressure. Side effects may include headache, dizziness and nausea, as well as high blood pressure, especially when lying down at night. Your doctor will have you measure your blood pressure, especially when increasing the dose, to monitor for side effects.
- **Florinef (fludrocortisone)** or **ProAmatine (midodrine)**
  For some people, doctors may recommend other medications to raise blood pressure. Potential side effects include high blood pressure, especially when lying down at night. Florinef also can cause leg swelling and decrease potassium, so blood levels need to be checked periodically.

• • Pain

Pain is common in Parkinson's. But it can have many different causes (everything from cramping with dystonia to discomfort with constipation) and therefore treatments. Treatment starts with finding the cause of the pain and making sure motor symptoms are as best controlled as they can be. At the same time, you might use exercise and other non-medication strategies, such as massage, hot or cold therapy, or meditation, to ease your pain. When medication therapy is necessary, it may include:

- **Botox (botulinum toxin) injections** into cramping muscles for dystonia
- **Anti-inflammatory medications**: ibuprofen
- **Pain relievers**: Tylenol (acetaminophen) or opioids (narcotics)
  Doctors typically recommend opioids only in cases of severe pain because they can cause constipation, confusion and sleepiness.

• • Psychosis (Hallucinations or Delusions)

Parkinson's disease psychosis causes **visual hallucinations** (seeing things that aren't there) and **delusions** (false, often paranoid, beliefs). Hallucinations and delusions are **more common in later stages of Parkinson's.** When hallucinations and delusions are frightening or upsetting, doctors may recommend medication treatments.

- **Nuplazid (pimavanserin)** was approved in 2016 by the U.S. Food and Drug Administration (FDA) for hallucinations and delusions associated with Parkinson's disease. It works on the brain chemical serotonin. Nuplazid may improve nighttime sleep and daytime wakefulness as well as lessen a care partner's stress. Side effects may include leg swelling, nausea and confusion.
- **Clozaril (clozapine)** or **Seroquel (quetiapine)**
  These drugs work on the dopamine and serotonin brain chemical systems. They are approved for mood and thought disorders, such as schizophrenia. Before Nuplazid, these were among the only options for PD psychosis. Because these drugs work on the dopamine system, they can worsen motor symptoms of Parkinson's. Other side effects include sleepiness, weight gain and associated diabetes. Clozaril also can decrease infection-fighting white blood cells, so it requires regular blood monitoring.

All psychosis medications carry a "black box" warning of increased risk of death in elderly people who have dementia. As with any medication, this and all possible side effects need to be carefully considered. Medications to treat psychosis are considered only when symptoms are significant and the potential benefits of treatment outweigh the risks.

• • Sexual Problems

Sexual problems are common among people with Parkinson's. They can be complex, involving both physical and emotional issues. Sexual problems also vary from person to person and between men and women.

In men with PD, the most common sexual problem is erectile dysfunction. Many treatments, including medications, are available, but all have a possible side effect of low blood pressure:

- **Viagra (sildenafil)**
- **Cialis (tadalafil)**
- **Levitra (vardenafil)**

In women with Parkinson's, sexual problems can range from decreased sex drive to pain with sexual intercourse. If problems stem from hormonal changes, treatments may include hormone replacement therapy or estrogen cream. Other times, doctors may recommend lubrication for vaginal dryness or medication to boost sex drive.

Read more on the Sexual Health webpage.

• • Sleep Problems

For insomnia, your doctor will make sure your symptoms and medications aren't contributing to sleep trouble. Behavioral strategies, such as exercising regularly and avoiding naps and caffeine late in the day, are often the first steps in combating insomnia. See the Sleep and Parkinson's Guide for more. When these aren't enough, doctors may recommend sleep medications:

- **Sedatives**: Lunesta (eszopiclone), Ambien (zolpidem), Sonata (zaleplon)
- **Melatonin**: an over-the-counter hormonal supplement
- **Antidepressants** that help with sleep: Silenor (doxepin), Desyrel (trazodone)

When medication is needed for **excessive daytime sleepiness** (extreme tiredness that makes it difficult to stay awake during the day), doctors may look to:

- **Wakefulness-promoting agents**: Provigil (modafinil), Nuvigil (armodafinil)
- **Stimulants**: Ritalin (methylphenidate)

Restless legs syndrome causes an uncomfortable urge to move the legs that goes away only with moving them. Motor symptoms, such as tremor, slowness and stiffness, at or around bedtime might interfere with sleep. Adjustments to Parkinson's medications may help.

Acting out dreams in **REM sleep behavior disorder** (RBD) may be disruptive or dangerous. A person may, for example, punch, kick and get out of bed unknowingly. Treatment may be necessary:

- **Klonopin (clonazepam)**
- **Melatonin:** an over-the-counter hormonal supplement

Sleep medications could potentially worsen Parkinson's symptoms or interact with other medications. Take them only on the advice of your doctor.

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Urinary Problems

People with PD may need to urinate more often and may feel the urge to go almost immediately, which can lead to accidental loss of urine or incontinence. Doctors may recommend a variety of treatments to relax the bladder:

- **Botox (botulinum toxin injections)** into the bladder muscles
- **Ditropan (oxybutynin)** or **Detrol (tolterodine)**
  Possible side effects, which may be more likely in older people, are dry eyes and mouth, constipation, sleepiness and confusion.
- **Myrbetriq (mirabegron)**
  Possible side effects include high blood pressure.

Some people with Parkinson's experience the opposite problem, which is not urinating enough. In these situations, a person may need to periodically empty their bladder with a catheter to prevent infection or kidney problems.