

Update on Parkinson's Disease Therapy

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Since 2014, 11 new medications have been approved for the motor and non-motor symptoms of Parkinson's disease (PD), in addition to numerous advances in deep brain stimulation and the approval of focused ultrasound for certain PD indications. This article reviews these new options available for PD therapy and explains how best to utilize them in a treatment plan.

Keywords

Parkinson's disease, motor fluctuations, dyskinesias, non-motor symptoms

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Parkinson's disease (PD) is a progressive, neurodegenerative disorder that causes a range of motor and non-motor symptoms. The pathological hallmark of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain and the presence of Lewy bodies, abnormal accumulations of the protein alpha-synuclein. Loss of dopaminergic neurons causes the motor symptoms that are typical of PD, including tremor, typically at rest, stiffness or rigidity of the muscles, slowness of movement or bradykinesia, and postural instability. A person with PD may also have a characteristic decrease in facial expression, a soft and monotonous voice, difficulty swallowing and trouble with posture and coordination. A stooped posture, with decreased heel strike, which gives the gait a shuffling quality, is characteristic.¹

Of note, neuronal loss and Lewy bodies are features of many other brain regions in people with PD and are thought to be responsible for the non-motor symptoms of PD. Common non-motor symptoms of PD include cognitive dysfunction, hallucinations, orthostatic hypotension, sleep problems, constipation, anxiety, depression, fatigue and others.²

Medications available prior to 2014

Although first introduced in the 1960s, carbidopa/levodopa remains the most effective treatment for PD.³ Levodopa can cross the blood-brain barrier into the brain, where it is converted to dopamine. Levodopa reduces tremor, rigidity and bradykinesia in people with PD. The dopa-decarboxylase inhibitor carbidopa, prevents levodopa from being broken down in the bloodstream before it reaches the brain. Carbidopa/levodopa has traditionally been available in immediate-release and extended-release formulations. Side effects of carbidopa/levodopa include nausea, fatigue, orthostatic hypotension and hallucinations.

Other long-standing medications for PD include:⁴

- dopamine agonists, available in immediate-release, long-acting, patch form and injectable form (pramipexole, ropinirole, rotigotine, apomorphine)
- catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone)
- monoamine oxidase B (MAO-B) inhibitors (selegiline, rasagiline)
- anticholinergics (benztropine, trihexyphenidyl)
- amantadine.

Any discussion of PD therapies must highlight the important role that exercise, as well as physical, occupational and speech therapy, play in the management of PD motor and non-motor symptoms.⁵ Any treatment plan must incorporate exercise in order to maximize efficacy.

Continued challenges of Parkinson's disease treatment

Although the medications listed above brought substantial relief to motor symptoms of PD, additional therapies were necessary to address major impediments to quality of life as PD advances, including motor fluctuations,⁶ dyskinesias⁷ and non-motor symptoms.⁸

Motor fluctuations

Motor fluctuations refer to disease and treatment-related difficulties that typically develop after several years of receiving PD therapy. OFF time is defined as segments of the day when medications do not maintain adequate symptom control. For some, OFF time can be unpredictable and/or sudden in onset, and not clearly related to timing of doses.

Adjusting the amount and timing of baseline medications and adding supplemental medications were available strategies to reduce OFF time. However, OFF time remained a difficult problem for many, prompting the development of additional medications to improve this problem.

Dyskinesias

Levodopa treatment can lead to the development of dyskinesias, especially at the time of peak brain dopamine levels or when brain dopamine levels are in flux. Dyskinesias may not be troublesome, and many people with PD report they prefer some dyskinesia with good motor symptom control to no dyskinesia with less complete symptom control. Sometimes, however, dyskinesias can be socially distressing and/or disabling. New treatments were therefore necessary to address dyskinesias.

Non-motor symptoms

The established medications for PD almost exclusively sought to treat the motor symptoms of PD, despite the fact that as PD progresses, non-motor symptoms typically become more and more problematic, eclipsing the motor symptoms in their effect on quality of life. Typically, as motor symptoms worsen, non-motor symptoms worsen too. In addition, dopaminergic medications can worsen some non-motor symptoms such as hallucinations and orthostatic hypotension.⁹ Some studies, however, suggest that dopaminergic medications may improve non-motor symptoms.¹⁰

New treatments sought to treat non-motor symptoms that had not previously been the focus of PD-specific therapy. The remainder of this article highlights new medications approved in the USA since 2014. This author recognizes that some of these medications are not available in many countries, and other medications are available in some countries, but not in the USA. However, a comprehensive discussion of worldwide PD medications is beyond the scope of this article.

Medications for treatment of motor fluctuations

A number of new medications approved since 2014 have been designed to treat motor fluctuations and reduce OFF time. These medications fall into four major categories:

- new formulations of carbidopa/levodopa that last longer than an immediate-release carbidopa/levodopa dose
- other medications that lengthen the effect of a carbidopa/levodopa dose
- new formulations of carbidopa/levodopa that are used as needed if medication effects wear off
- other medications that are used as needed if medication effects wear off.

In general, new medications that extend the length of a carbidopa/levodopa dose are used if OFF time is somewhat predictable and occurs prior to next dose. New medications that are used as needed are most beneficial when OFF time is not predictable.

New formulations of levodopa that last longer than immediate release

Carbidopa/levodopa extended-release capsules (Rytary®)

Carbidopa/levodopa extended-release capsules (Rytary®; Amneal Pharmaceuticals, Inc., Bridgewater, NJ, USA) was approved in 2015, and is a formulation of carbidopa/levodopa that is designed to prolong the effects of carbidopa/levodopa. The capsules contain both immediate-release and extended-release beads, which are of different sizes and dissolve at different rates. Capsules can be opened and added to food without losing their extended-release properties.

Multiple clinical trials were conducted with carbidopa/levodopa before approval.¹¹ The APEX-PD trial compared three doses of carbidopa/levodopa extended-release capsules and demonstrated its efficacy over placebo in early PD.¹² Advance-PD was a phase III randomized, double-blind trial, which demonstrated improvement in OFF time by an average of 1.17 hours with extended-release capsules compared with immediate release.¹³

Transitioning from immediate-release carbidopa/levodopa to extended-release capsules can be challenging but rewarding. In this author's clinical experience, if insufficient extended-release capsules are prescribed, patients may stop the medication because they find it is not helpful. This observation is supported by a published expert discussion suggesting that patients be switched to a total daily dose of extended-release carbidopa/levodopa capsules equivalent to 1.5–2 times the total daily dose of immediate-release carbidopa/levodopa divided into three to four doses.¹⁴ Modifications of this dose may be necessary over subsequent weeks. Four strengths of the carbidopa/levodopa extended-release capsules are available: 23.75/95, 36.25/145, 48.75/195, 61.25/245, which allows the dose to be refined.

Carbidopa/levodopa enteral suspension (Duopa™)

Carbidopa/levodopa enteral suspension (Duopa™; AbbVie Inc., North Chicago, IL, USA) was approved by the US Food and Drug Administration (FDA) in 2015. It is infused directly into the gut through a percutaneous endoscopic transgastric jejunostomy (PEG-J) tube. This allows levodopa to be delivered continuously into the jejunum, smoothing out its blood and brain levels. A double-blind, randomized clinical trial demonstrated that mean OFF time decreased by 2 hours, and mean ON time without troublesome dyskinesias increased by almost 2 hours in patients receiving the enteral suspension compared with those receiving oral doses.¹⁵ Two other randomized controlled trials support these findings.^{16,17}

The levodopa suspension is stored in a cartridge that is attached to a wearable pump. The pump can fit in a vest or waist bag and can be programmed to deliver a wide range of infusion rates as well as boluses of medication as needed. The medication is delivered up to 16 hours a day. Complications, including infection of the PEG-J insertion site, are possible. Additionally, the tube may clog, kink or become dislodged.

The side effects of the carbidopa/levodopa infusion are similar to those of oral carbidopa/levodopa, but may be associated with a higher incidence of peripheral neuropathy.¹⁸

New medications that lengthen the effect of a dose of carbidopa/levodopa

Istradefylline (Nourianz®)

Istradefylline (Nourianz®; Kyowa Kirin Inc., Bedminster, NJ, USA) is an adenosine A2A receptor antagonist, which was approved in the USA in 2019 as an add-on therapy to levodopa for treatment of OFF time in PD. It has a novel mechanism of action, acting on the adenosine receptor, which modulates the dopaminergic system, but is not directly dopaminergic. It is the first medication in its class to be approved for PD. The drug was developed in Japan and underwent clinical trials in both Japan and the USA. The initial clinical trials conducted in the USA,^{19–21} collectively showed a reduction in OFF time of about 0.7 hours per day. These trials were evaluated by the FDA in 2008, which did not approve its use due to concern that the motor improvement shown in the trials was too small and not clinically significant. Further trials were then conducted,²² and based on the newer data, the FDA did approve its use in 2019.

Opicapone (Ongentys®)

Opicapone (Ongentys®; Bial Pharma UK Ltd., Windsor, UK; licensed in the USA by Neurocrine Biosciences Inc, San Diego, CA, USA) is a COMT inhibitor that is taken once a day. It was approved in the USA in 2020 as an add-on therapy to levodopa for motor fluctuations. Its approval was **based on two randomized, placebo-controlled phase III trials**, BI-PARK 1²³ and BI-PARK 2.²⁴ Both studies demonstrated similar results. Opicapone 25 mg and 50 mg significantly reduced OFF time compared with placebo. BI-PARK 1 included an arm of patients taking entacapone 200 mg, an FDA-approved COMT inhibitor that is taken with each dose of levodopa, and demonstrated that opicapone was not worse than entacapone, and in fact showed a greater magnitude of reduction in OFF time. While the placebo group demonstrated a change in OFF time of 56 minutes, and entacapone demonstrated a change in OFF time of 96 minutes, opicapone 50 mg demonstrated a change in OFF time of 117 minutes. Long-term efficacy data were recently published²⁵ and demonstrated maintenance of good effect without an increase in troublesome dyskinesias.

Safinamide (Xadago®)

Safinamide (Xadago®; Newron Pharmaceuticals, Milan, Italy, manufactured in the USA by Supernus, Rockville, MD) was approved in 2017 as an add-on therapy to carbidopa/levodopa for the treatment of OFF time.²⁶ It is a selective MAO-B inhibitor but has other mechanisms of action such as inhibition of glutamate release. Clinical trials demonstrated increased ON time in PD patients with motor fluctuations, with the placebo group demonstrating an improvement of 0.57 hours and safinamide demonstrating an improvement of 1.42 hours.²⁷⁻²⁹

New formulations of levodopa designed to be used as needed

Levodopa inhalation powder (Inbrija®)

Levodopa inhalation powder (Inbrija®; Acorda Therapeutics, Inc., Ardsley, NY, USA) was approved in 2018 to be used as needed if medication effects wear off between oral doses of carbidopa/levodopa.³⁰ A phase III trial showed that the treatment improved United Parkinson's Disease Rating Scale (UPDRS) motor scores during OFF periods, with few serious adverse effects. The change in UPDRS from pre-dose to 30 minutes post-dose was 5.91 for the placebo group and 9.83 for the inhaled Levodopa group.³¹

A breath-activated inhalation device, is provided with the medication into which capsules of 42 mg of levodopa are inserted. One dose consists of two capsules. Absorption of the medication is through the pulmonary tree, which bypasses the gastrointestinal tract. The capsules only contain levodopa without a dopa-decarboxylase inhibitor, which means that the inhalation powder needs to be added to a regimen of carbidopa/levodopa.

In this author's clinical experience, a potential limitation of the system is that the device cannot be pre-loaded. Therefore, the capsules need to be unwrapped and inserted into the inhalation device when the patient is OFF and has decreased dexterity.

Other medications used as needed if medication effects wear off

Apomorphine HCl sublingual film (Kynmobi®)

Apomorphine is a dopamine agonist with rapid onset of effect. It can be used as a rescue medication for someone whose dose of levodopa wears off unexpectedly before the next dose is due. Previously, apomorphine was dispensed as an under-the-skin injection. In 2020, a sublingual film was approved (Kynmobi®; Sunovion, Marlborough, MA, USA, a wholly-owned subsidiary of Sumitomo Dainippon Pharma Co.), which can be

used as needed during the day if medication effects wear off. Clinical trials demonstrated that sublingual apomorphine was an effective treatment for OFF episodes.^{32,33} The change in UPDRS from pre-dose to 30 minutes post-dose was 3.5 for the placebo group and 11.1 for the sublingual apomorphine group.³⁴

This new route of delivery is associated with oropharyngeal side effects, including dry mouth, oral mucosal irritation and swelling, and throat irritation, which can lead to discontinuation of treatment.³⁵ In addition, apomorphine (both injectable and sublingual) can induce nausea, leading to the recommendation that it be taken with an antiemetic, typically trimethobenzamide.

Medications for treatment of dyskinesia

Amantadine

Originally used to prevent or treat influenza, amantadine was observed to ease the tremor of PD as well as muscle rigidity. It has therefore been used as an adjunct medication to other therapies for PD. In addition, it was also observed to be effective at decreasing dyskinesias caused by levodopa and is typically prescribed two to three times a day.³⁶

In 2017, an extended-release formulation of amantadine (Gocovri®; formerly owned by Adamas Pharmaceuticals, Inc., Emeryville, CA, USA, now Supernus, Rockville, MD, USA), was approved. It is taken once daily at night, and is indicated for both the treatment of levodopa-induced dyskinesias and for reduction of OFF time. It is designed to provide an initial lag, followed by a slow rise in amantadine concentration during the night, and a high concentration in the morning and through the waking day. Results of two phase III clinical trials demonstrated improvement in both dyskinesias and OFF time.^{37,38} In 2018, a second extended-release formulation of amantadine (Osmolex ER™; formerly owned by Osmotica Pharmaceuticals, Bridgewater, NJ, USA, now Supernus, Rockville, MD, USA)³⁹ was approved. It is taken once daily in the morning and is indicated for the treatment of PD motor symptoms as well as drug-induced parkinsonism.

Medications for treatment of non-motor symptoms

Treatment of neurogenic orthostatic hypotension

Neurogenic orthostatic hypotension (NOH) is a common non-motor symptom in PD and can be a major driver of disability, causing chronic dizziness and contributing to falls. Other symptoms that can be correlated to NOH include weakness, fatigue and cognitive slowing.⁴⁰ NOH can be a symptom of PD itself as well as a side effect of many PD medications, including levodopa. Although first steps in management involve implementing lifestyle changes (such as increasing dietary fluids and salts) and removing exacerbating medications, prescription medication may be necessary to maintain blood pressure. Midodrine is approved for orthostatic hypotension and is often used in clinical practice. Fludrocortisone is also often used, although not specifically approved for this indication.⁴¹

Droxidopa (Northera™)

Droxidopa (Northera™; formerly owned by Chelsea Therapeutics, Charlotte, NC, USA, now Lundbeck, Deerfield IL, USA) was approved in 2014 for the treatment of NOH caused by the autonomic failure of PD and other diseases.

Droxidopa is a synthetic amino acid analogue that is metabolized to norepinephrine by amino acid decarboxylase. Once metabolized into norepinephrine, it increases blood pressure by inducing peripheral

arterial and venous vasoconstriction. Results of four phase III trials were contradictory, with two meeting their primary outcomes of improved symptom control and raised blood pressure.⁴²⁻⁴⁵ Studies also utilized the Orthostatic Hypotension Questionnaire, a validated symptom assessment scale.⁴⁵ Despite mixed results, the studies led to FDA approval.⁴⁷ Approval was granted under the Accelerated Approval Program, provided that further studies would be conducted to verify the clinical effects.

Supine hypertension is a concern for all medications given for NOH and doses should not be given close to bedtime.

Treatment of psychosis

Psychosis (encompassing hallucinations and delusions) is another common non-motor symptom of PD and can significantly affect quality of life. The first step in management is to review all medications and lower or stop any potential offenders. Most PD medications can contribute to hallucinations, so lowering these medications must be considered, but must also be balanced with its impact on motor symptoms.⁴⁸

Most antipsychotic medications act by blocking postsynaptic dopamine receptors and can therefore cause parkinsonism. Two antipsychotics, quetiapine and clozapine, can be used safely, but off-label, for Parkinson's disease psychosis (PDP). Clinical trial data for quetiapine are lacking, but there are clinical trial data for the use of clozapine.⁴⁹ However, because clozapine carries a known risk of agranulocytosis and requires regular blood monitoring, it is difficult to use in practice.⁴⁹

Pimavanserin (Nuplazid®)

Pimavanserin (Nuplazid®; Acadia Pharmaceuticals Inc., San Diego, CA, USA) is a selective serotonin inverse agonist, which was approved in 2016 as a treatment for PDP. A randomized placebo-controlled phase III trial demonstrated modest clinical improvement on a novel PDP scale called the Scale for the Assessment of Positive Symptoms for Parkinson's Disease Psychosis.⁵⁰ Because the scale had not been widely used previously, the decision of the FDA engendered some controversy.⁵¹ Pimavanserin remains the only medication specifically approved for PDP. Recently published real-world clinical data demonstrated clinical improvement in 76% of patients, with adverse effects reported in 22%.⁵²

Of note, pimavanserin, as well as other antipsychotic medications, carry a black-box warning of increased risk of death in elderly patients with dementia-related psychosis associated with the use of these drugs. After approval, concern was raised that the risk of death with pimavanserin exceeded that of other antipsychotics, but a review by the FDA concluded in 2018 that post-marketing data were consistent with safety data obtained during clinical trials.⁵³

Procedures for Parkinson's disease: Deep brain stimulation and high-intensity focused ultrasound

Despite the multiple medication options available, motor fluctuations and dyskinesias can remain difficult problems. In addition, certain patients with PD do not gain adequate control of their tremor with medications. When medication management does not achieve sufficient symptom control, a neurosurgical procedure such as deep brain stimulation (DBS) or high-intensity focused ultrasound (HIFU) may be indicated.

Deep brain stimulation

DBS is a neurosurgical procedure for people with PD who retain a good response to levodopa, but who have developed significant motor

fluctuations including dyskinesias. DBS may also be used to treat medication-resistant tremor. DBS involves the implantation of permanent, thin electrodes into selected deep parts of the brain. Contacts along the electrodes deliver electricity to very targeted areas of the brain. A battery-operated pulse generator is implanted under the skin of the chest or abdomen.

DBS technology is constantly evolving with many new developments in recent years.⁵⁴ Certain systems offer rechargeable batteries. The newer DBS systems are magnetic resonance imaging (MRI) conditional and can be placed in MRI mode or turned off for the duration of an MRI.

In the past, the surgery was only performed when a patient was awake (albeit under mild sedation and with appropriate pain control), allowing the surgeon to monitor symptoms as the electrode was advanced. Certain surgeons will now perform the surgery in the bore of a computed tomography scanner or MRI machine, allowing for visualization of the electrode. When performed this way, the patient can be completely asleep during the procedure.

Although DBS is typically performed at more advanced stages of disease, the FDA has also approved DBS for earlier-stage PD of at least 4 years' duration with motor symptoms that are not adequately controlled with medication, including recent-onset motor complications.

The available DBS systems for PD are all slightly different. Each offers its own technology in programming the stimulation variables, with the goal of maximizing symptom control and minimizing the side effects of stimulation. All the systems can utilize directional leads, in which the contacts on the electrodes are subdivided into sections around the circumference of the electrode and stimulation can be applied to different sections. This allows for the field of stimulation to be steered in a particular direction, with the goal of reducing side effects of stimulation.⁵⁵ Clinical trials have demonstrated the clinical benefit of this approach.^{56,57}

Abbott

The Infinity™ system (Abbott Laboratories, Abbott Park, IL, USA) uses directional leads. Abbott also offers Neurosphere™, a remote programming option that allows clinicians to connect with patients through a wireless network and perform DBS programming through a telemedicine appointment.

Boston Scientific

The Vercise™ system (Boston Scientific, Marlborough, MA, USA) offers two different electrodes, one with eight contacts, more than other leads, and one that offers directional stimulation. The electrodes use multiple independent current control, which means that each contact has its own energy source and allows for a more customizable field of stimulation.

Medtronic

The SenSight™ system (Medtronic, Minneapolis, MN, USA) uses directional leads, allowing for a customized field of stimulation. The SenSight™ system is compatible with the Percept™ PC Neurostimulator with Brainsense™ system (Medtronic), which captures local field potentials (LFPs) from the neurons that are in contact with the DBS electrode. DBS adjustments can be made based on LFP patterns of an individual patient as they correlate with reported symptoms and medication ingestion. Clinical studies are under way to determine whether adjustment based on LFP patterns improves outcomes.

High-intensity focused ultrasound

HIFU is a procedure that uses targeted ultrasound waves to create lesions in a deep brain structure. HIFU of the ventral intermediate nucleus of the thalamus was approved in 2018 for the treatment of tremor in PD based on a randomized clinical trial,⁵⁸ which demonstrated a 62% improvement of on-medication tremor score after HIFU of the ventral intermediate nucleus compared with a 22% improvement in the group that received the sham procedure. Side effects included mild and reversible hemiparesis, as well as parasthesias and one case of ataxia. Exablate Neuro[®] is the focused ultrasound platform designed for brain treatments (Insightec, Miami, FL, USA).

HIFU of the globus pallidus interna has very recently (November 2021) been approved for the treatment of bradykinesia, rigidity and dyskinesias associated with PD. Data from the pivotal trial that led to its approval

have not yet been published, but published data from an open-label clinical trial demonstrated improvements in dyskinesia scores and UPDRS scores from baseline.⁵⁹

Conclusions

With multiple new medications and procedures available for the treatment of PD, there is more hope than ever that symptoms can be successfully managed for many years of PD. However, even with the new treatments discussed above, PD presents significant challenges for many people, especially as the disease advances. Research focused on improvement of motor and non-motor symptoms continues. In addition, discovering treatments that will slow down or halt disease progression is a major emphasis of current PD research, with the hope that soon medications will be available not only to treat symptoms, but also to improve the course of PD. □

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