Long-Term Care Updates

March 2025

Apomorphine subcutaneous infusion for Parkinson's disease

PharMerica®

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that affects predominately the dopamine-producing neurons in the substantia nigra. The cause of PD is largely unknown, but it is believed to be caused by a combination of genetic and environmental factors. PD itself is non-fatal, but disease complications can be serious. The CDC rates complications from PD as the 14th cause of death in the United States. Symptoms of PD generally develop slowly over many years and the progression of symptoms varies from person to person. Common symptoms of PD include tremors at rest, bradykinesia, rigidity, and postural instability. Motor symptoms become evident later in the course of the disease, after 60 to 80% of the substantia nigra neurons have been lost or impaired. With majority of symptoms being motor-related, patients with PD can also be impacted by non-motor symptoms. Examples of non-motor symptoms include depression, anxiety, apathy, hallucinations, among others. Currently, there is no cure for PD, but there are options to help manage disease complications. These options include medications, lifestyle adjustments, and surgery.[1]

To relieve the motor symptoms of PD, medication options include dopaminergic medications that promote dopamine activity in the brain. Current treatment guidelines recommend initial therapy of the following three treatment options: levodopa, dopamine agonists, or monoamine oxidase B (MAO-B) inhibitors. Levodopa is converted into dopamine in the brain, dopamine agonists mimic the effects of dopamine while MAO-B inhibitors prevent the enzyme MAO-B from breaking down dopamine. Among these three medications, treatment with levodopa provides superior benefit at reducing motor symptoms when compared to the other treatment options. Despite the benefits of these medications, there are still risks with their use. Risks of levodopa include dyskinesia during the first years of treatment and treatment guidelines recommend prescribing the lowest effective dose to optimize benefit and minimize risk of dyskinesia. Dopamine agonists are more likely to cause impulse-control disorders and are associated with a greater risk of excessive daytime sleepiness.[2] Oral medication options for PD can be less effective at delivering consistent motor control due to GI dysmotility in patients and variable absorption of the oral medication. Patients have reported alternating states of "on", when their medication is working, and "off", when the medication is not working with their oral PD medication. These changes can be disruptive and happen at any time; therefore, managing the "off" time of PD treatment is key to improving patients' quality of life and a more continuous treatment option would be beneficial for patients.[3]

Novel Drug Approvals (February and March 2025)

Brand	Generic	Indication	Mechanism of Action	Dosage Form
Blujepa	Gepotidacin	Uncomplicated UTI (females)	Triazaacenaphthylene bacterial type II topoisomerase inhibitor	Oral tablets
Emblaveo	Aztreonam and avibactam	Complicated intra-abdominal infection	Monobactam antibacterial (aztreonam) and beta-lactamase inhibitor (avibactam)	Intravenous injection
Qfitlia	Fitusiran	Hemophilia A or B	Antithrombin-directed small interfering ribonucleic acid	Subcutaneous injection

Apomorphine (ONAPGO)

In 2025, the U.S. Food and Drug Administration (FDA) approved apomorphine hydrochloride (ONAPGO) injection, formerly known as PSN-830, as the first and only subcutaneous apomorphine infusion device for the treatment of motor fluctuations in adults with advanced PD. Apomorphine directly stimulates postsynaptic dopamine receptors with no metabolic conversion, unlike levodopa. The subcutaneous delivery of apomorphine bypasses the GI tract and enters the brain, which can allow for more predictable symptoms improvement. Continuous subcutaneous apomorphine infusion has proven benefit in Europe where it was showed to help deliver more consistent control of motor fluctuations in thousands of patients. Patients experiencing unpredictable "on" time from their oral medications can benefit from the consistent daily control of the "off" time that apomorphine provides, making the symptoms of the disease more predictable. The approval of this formulation indicates that patients not responding to their current treatment regimen will have the option of using a wearable device to deliver a continuous infusion without the need for an invasive procedure.[3]

Apomorphine is contraindicated with concomitant use with selective serotonin receptor (5-HT_3) antagonists due to antiemetics enhancing the hypotensive effect of apomorphine and loss of consciousness has been attributed to the concomitant use of the two medications. Common side effects of the apomorphine infusion include yawning, nausea, vomiting, injection site reactions, dyskinesia, orthostatic hypotension, drowsiness, and hallucinations. Pretreatment with an antiemetic may be necessary to avoid nausea and vomiting side effects and should be started 3 days prior to initiation of apomorphine infusion therapy and continued only as long as necessary to control nausea and vomiting. Trimethobenzamide may be used as a pretreatment antiemetic with

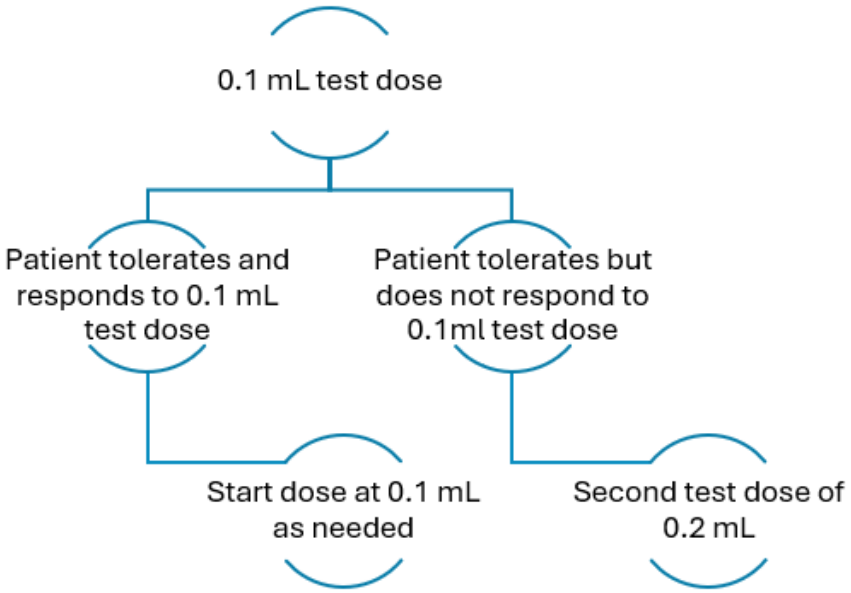
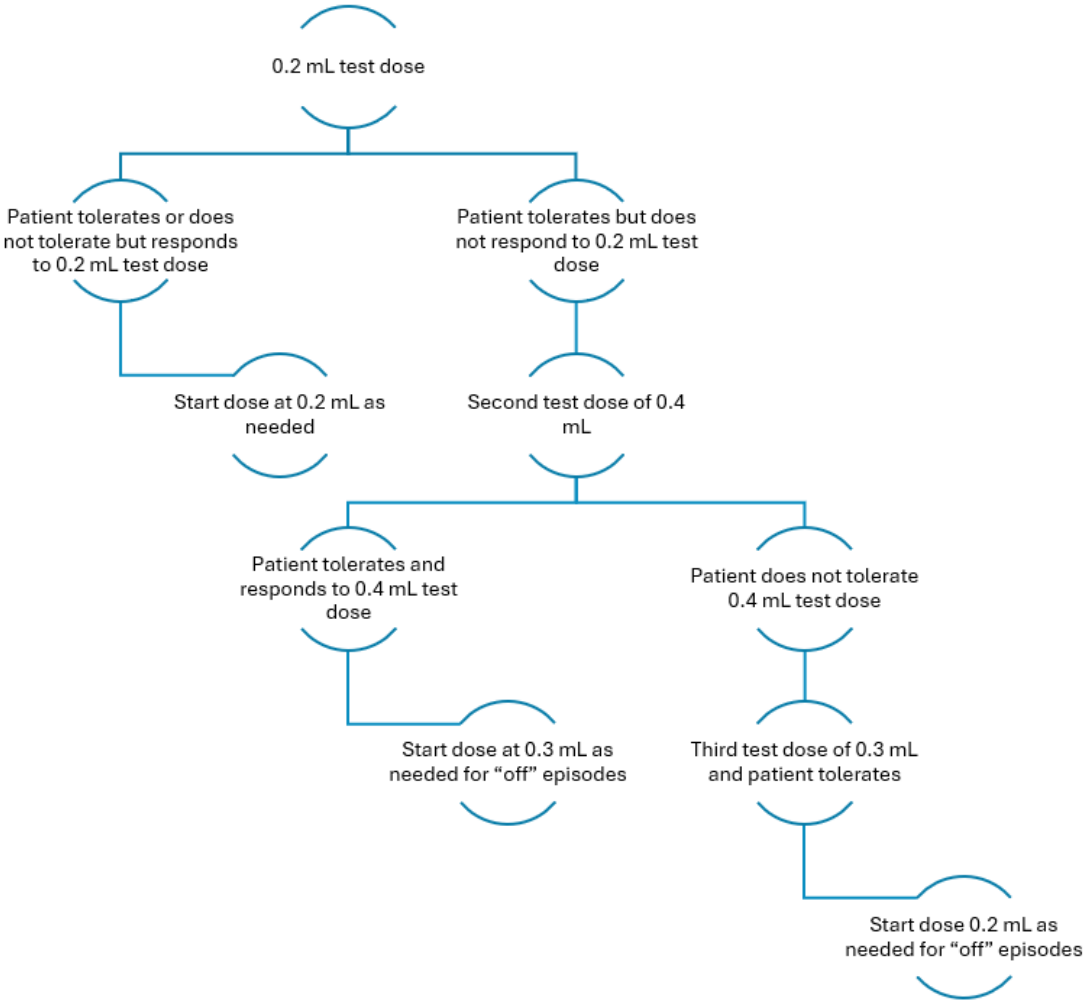


Figure 1. Apomorphine dosing algorithm: 0.1 mL test dose

Figure 2. Apomorphine dosing algorithm: 0.2 mL test dose



apomorphine because it is not a 5-HT_3 antagonist or antidopaminergic antiemetic agent that would worsen Parkinson's disease symptoms. It is recommended to avoid apomorphine in patients with major psychotic disorders to prevent the hallucination side effect. Apomorphine can cause orthostatic hypotension and syncope, especially during dose escalations. These hypotensive effects can be exacerbated by concomitant alcohol consumption and sublingual nitroglycerin use. Other risk factors for hypotension include the concomitant use of other antihypertensive medications. It is extremely important to monitor for signs and symptoms of postural hypotension and avoid alcohol consumption during therapy.[4]

For apomorphine subcutaneous infusion dosing, it is recommended to perform an initial test dose of 0.1 mL (1 mg) or 0.2 mL (2 mg). Medical supervision is required for all test doses with standing and supine blood pressure monitored before the initial dose and 20-, 40-, and 60-minutes post-dose. Monitoring may be continued after 60 minutes if there is significant hypotension at 60 minutes. It is recommended to initiate therapy at 0.1 mL as an alternative to antiemetic therapy to reduce the adverse effect of nausea and vomiting. If a patient responds to the 0.1 mL test dose, start the dose at 0.1 mL as needed and increase the dose in 0.1 mL increments every few days to a maximum dose of 0.6 mL. If additional test doses are required, it must be at least 2 hours after the last test dose was given. The next test dose should be timed with an "off" episode and if a single dose is ineffective for an "off" episode, then a second dose should not be given. If therapy is interrupted for greater than 1 week, restart the dose at 0.2 mL and gradually titrate dose.[4]

Clinical Evidence

Apomorphine subcutaneous infusion was approved on the basis of the TOLEDO study, a phase 3, double-blind, randomized, controlled trial of 106 patients with at least 3 years' history of PD and motor fluctuations inadequately controlled by conventional medications. This trial included a 12-week double-blind phase, where patients were randomized 1:1 to receive apomorphine subcutaneous infusion or placebo (saline) infusion. Apomorphine dose was individualized based on response and tolerability, with flow rates between 3-8 mg/hr and infusion occurring for roughly 16 hours daily. Upon completion of the 12-week trial, or upon discontinuation due to a lack of clinical effect, patients in the placebo group could switch to apomorphine and enter the 52-week open-label phase of the trial.[5]

After 12 weeks of treatment, apomorphine reduced "off" time by around 1.9 hours/day, increased "on" time without troublesome dyskinesia by around 2.0 hours/day, and reduced oral levodopa doses and levodopa-equivalent doses when compared with placebo. Further, response to therapy, defined as "off" time reduction of 2 hours/day or more, was observed in 62% and 29% of patients receiving apomorphine and placebo, respectively. These results suggest that, for every 3 patients treated with apomorphine subcutaneous infusion over placebo, 1 additional patient will respond to therapy. Improvements in motor (MDS-UPDRS Part III) and quality of life (PDQ-8) scores were not observed; however, the study was not powered to detect differences for these outcomes. Apomorphine-treated patients were, however, more likely to report an overall improvement in their state of general health compared with placebo-treated patients (79% vs 24%; $p < 0.0001$).[5] The open-label phase of this trial found the pooled change in "off" time and "on" time (without troublesome dyskinesia) from baseline to week 64 was -3.7 hours and +3.3 hours, respectively, with apomorphine vs. placebo.[6] The most common adverse effects noted were infusion-site reactions, nausea, somnolence, dyskinesia, headaches, and insomnia.[5]

Research is continuing to study the long-term safety of apomorphine in a current ongoing clinical trial, INFUS-ON. INFUS-ON is a phase 3 multicenter, open-label, safety and tolerability study that will assess the long-term safety, tolerability, and clinical effectiveness of continuous subcutaneous infusion of apomorphine. It will be studied in advanced PD patients whose motor fluctuations remain unsatisfactory with levodopa and at least one other class of drug or mode of therapy for PD. INFUS-ON will measure the percent daily "off" time during the waking day from baseline to week 12. It will also measure the occurrence of adverse events and adverse events of special interest screening through week 52. Results of the INFUS-ON trial are not available currently.[6]

Conclusion

Despite not having a cure for PD, there are options available to help manage the motor complications associated with the disease and allow patients to manage their everyday activities with the disease, such as levodopa among other oral medications. As PD progresses, treatment often becomes less effective at delivering consistent motor control and the symptoms of the disease can worsen over time. This is when patients report alternating states between the "on" and "off" time of the medication working. A continuous treatment option like apomorphine can control the "off" time of medications in patients with advanced PD. This formulation is the first and only subcutaneous apomorphine infusion device for the treatment of motor fluctuations in adults with advanced PD. The efficacy and safety data of apomorphine infusion is promising and has led to the medication's FDA approval this year and is expected to be available in the U.S. in the second quarter of 2025. Advancements in PD therapy like apomorphine are a promising solution to help manage motor fluctuations and improve quality of life for patients with advance stages of the disease.

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