Parkinson’s Disease Treatment Update

New formulations for motor symptoms and new treatments for nonmotor symptoms provide more options.

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In recent years, there has been a groundswell of new treatment options for movement disorders. Therapies extend beyond motor symptoms of Parkinson’s disease (PD). Uniquely, recent therapies target nonmotor issues that have had limited treatment options and often been relegated to the sidelines in favor of motor symptoms of PD. New treatments can be broadly divided into 2 components. First is extended-release or other new formulations of existing medications. Second is newer products studied for specific indications in areas where no prior approved therapy was available.

Treating Motor Symptoms and Decreasing Off Time

The “off period” in PD has been a vexing and perpetual problem, despite adjuncts designed to extend duration of response and use of deep brain stimulation (DBS). Management of off periods requires understanding PD progression, causes of the off period, and pharmacologic limitations of existing therapy. As PD progresses there is loss of nigrostriatal dopaminergic neurons, and there is evidence for a vesicular storage deficiency, possibly preceding the loss of neurons.1 Presynaptic neurons lose their ability to store and release dopamine, and the response to levodopa becomes shorter with “off” symptoms. The pharmacologic response threshold becomes higher with progression of the disease, reducing the therapeutic window between a motor response and dyskinesia.2 Other factors contributing to the development of “off” symptoms include the pulsatile stimulation of dopamine receptors and impaired levodopa absorption in the small intestine.3 The first step is usually to avoid protein interaction at the time of drug administration and adjusting the levodopa dosing schedule (ie, increasing dose or frequency). However, this strategy can be challenging with progression of the disease because of unpredictable off-symptoms and risk of troublesome dyskinesia. Several therapies have been developed in the last 1 to 5 years with a goal of better addressing the motor fluctuations of levodopa treatment (Table 1).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Formulation</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbidopa/levodopa</td>
<td>Extended release</td>
<td>Titrate to a maximum daily dose of 2,450 mg/day given in 3 to 5 doses/day</td>
<td>When switching from immediate to extended release, double individual dose and take two-thirds less frequently</td>
</tr>
<tr>
<td>Carbidopa/levodopa</td>
<td>Enteral suspension</td>
<td>Titrate to a maximum daily dose of 2,000 mg/day given as 1 cassette</td>
<td>Ensure rescue dose available in case of pump failure or J tube migration</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Inhalation powder</td>
<td>84 mg up to 5 times daily, each delivered as 2 inhalations</td>
<td>Do not use within 2 weeks of taking a nonselective MAOI; not recommended for those with comorbid pulmonary disease</td>
</tr>
</tbody>
</table>

Abbreviation: MAOI, monoamine oxidase inhibitor.
ing C/L ER with C/L/E. C/L ER reduced off time and dose frequency compared with C/L/E. The single biggest challenge with switching treatment to C/L ER is dose conversion. Typically 75% of patients who switch to C/L ER require a dose adjustment, with the majority needing a dose increase. A switching strategy that may quickly bring an individual closer to the appropriate final C/L ER dose is to make the C/L ER dose approximately twice the total daily dose of C/L IR at two-thirds the frequency. For example, an individual taking C/L IR 500 mg/day in 5 doses would be switched to 1000 mg/day of C/L ER in 4 doses (61.25/245 mg/dose).

### Carbidopa/Levodopa Enteral Suspension

Over the course of PD, predictable response to oral levodopa/carbidopa replacement therapy is lost. This unpredictability manifests as delayed “on” dose failures and food interactions. Carbidopa/levodopa enteral suspension (CLES) allows for continuous delivery of levodopa to the jejunum via a percutaneous endoscopic transgastric jejunostomy (PEG-J) tube and an external programmable pump.

In the pivotal study of CLES, 66 participants with PD who had PEG-J were randomly assigned to receive oral placebo and CLES or oral C/L IR and placebo enteral gel. At baseline, participants’ mean off time was 6 to 7 hours and mean on time without troublesome dyskinesia was 8 to 9 hours. Titration to the optimal dose occurred over 4 weeks and was followed by an 8-week fixed dose maintenance phase. The primary end point was change in mean daily off time from baseline to week 12, and the secondary end point was change in mean daily on time without troublesome dyskinesia between baseline and 12 weeks. Participants who were treated with oral placebo and CLES had a 4 hour reduction in mean daily off time vs 2.1 hours for those treated with oral C/L IR and placebo enteral gel. A similar improvement in daily “on” time without troublesome dyskinesia was seen well. Peak plasma concentration of CLES occurs 2.5 hours after initiation and stays constant until the pump is turned off after 16 hours of infusion.

Side effects were primarily related to the PEG-J procedure or device and occurred in 57% of individuals who received CLES vs 44% of those who received placebo enteral gel. Most device-related adverse events occurred in the immediate postoperative period, (eg, nausea, constipation, and incision site erythema). Neuropathy because of a vitamin B6 deficiency also occurred. A potential complication is withdrawal hyperpyrexia and confusion due to the sudden reduction of CLES delivery from pump failure or J-tube migration. It is important to provide patients with a rescue supply of oral levodopa.

For individuals with motor fluctuations (wearing off and/or dyskinesias) that cannot be managed with medical therapy, CLES is a valuable tool. It provides an attractive alternative to DBS for some and opens the window for surgical management of PD for those with mild cognitive impairment or early dementia. There is potential for combination therapy in individuals who have significant residual dyskinesia after DBS.

### Levodopa Inhalation Powder

Levodopa inhalation powder was recently approved by the Food and Drug Administration (FDA) for treating off periods of PD in people being treated with carbidopa/levodopa. Used with a proprietary oral inhaler, the central mechanism of action is similar to other levodopa-containing medications, but unique in that absorption occurs rapidly in the lung rather than the gastrointestinal tract. This rapid delivery allows management of off episodes caused by erratic gastrointestinal levodopa absorption. In a 12-week clinical trial, treatment with levodopa inhalation powder improved symptoms as measured by lower Unified Parkinson’s Disease Rating Scale (UPDRS) motor scores (mean decrease of 9.8 points at 30 min after dose) during off periods. A dose is comprised of 2 capsules containing 42 mg levodopa each for a total of 84 mg to be taken when off symptoms begin up to 5 times per day (maximum daily dose 420 mg/day).

The most common adverse reactions seen in the clinical trial of levodopa inhalation powder were cough (15% of those treated vs 2% of those who received placebo) and, much less frequently, upper respiratory infection, nausea, and discolored sputum. Of note, there was no difference in lung function between the active-treatment and placebo groups based on forced expiratory volume in 1 second (FEV1) in a second trial. Levodopa inhalation powder should not be used by people taking a nonselective monoamine oxidase inhibitor (MAOI) or who have taken an MAOI in the last 2 weeks. Levodopa inhalation powder is not recommended for individuals with asthma, chronic obstructive pulmonary disease (COPD) or other chronic lung diseases. General precautions similar to those used for other levodopa-containing medications should be considered before starting levodopa inhalation powder. People should be counseled not to drive until they are aware of their tolerability to levodopa inhalation powder.

### Extended-Release Amantadine

Dyskinesia in PD is frequently bothersome, affecting daily activity and causing social embarrassment, and possibly reducing functional status and quality of life. Treatment options for PD dyskinesia are limited. Reducing the levodopa dose may help, but often at the cost of increased off time and symptoms. The levodopa dose can be given in smaller more frequent doses; however, this can increase the burden of treatment and make it more difficult to adhere to treatment. Adjunctive medications may be used to provide steadier dopaminergic stimulation. Dyskinesia limits the addition of other medications for PD despite the presence of off symptoms. For dyskinesia that does not respond to medication, DBS is effective in appropriate candidates for improving PD dyskinesia.
The N-methyl-D-aspartate (NMDA) receptor has been implicated in the pathogenesis of dyskinesia. Amantadine was additionally developed as a drug to treat PD and has antidyskinetic effects attributed to its function as an NMDA receptor antagonist. The use of amantadine, however, has been limited by loss of antidyskinesia benefit several months into treatment due to tachyphylaxis. The American Academy of Neurology has given a level C recommendation for amantadine as being “possibly effective in reducing dyskinesia.”

Extended-release formulation of amantadine taken once daily at bedtime, was the first and only treatment for PD dyskinesia approved by the FDA in 2017. This formulation provides a slow, steady release of the medication during sleep, providing plasma drug levels of the drug during day-time active hours that are approximately twice that of immediate-release amantadine.

In pivotal studies for extended-release amantadine, dyskinesia reduction was measured with the standardized Unified Dyskinesia Rating Scale (UDysRS). Participants with PD dyskinesia treated with extended-release amantadine had a 37% to 46% reduction in dyskinesia from the pretreatment baseline. The most common adverse effects were hallucinations, orthostatic hypotension, and livedo reticularis, and classified as mild. Visual hallucinations were the most common reason for discontinuation (8%) of extended-release amantadine.

In an open-label extension study, extended-release amantadine provided sustained reduction of dyskinesia and was well-tolerated with 80% of participants continuing the drug for up to 88 weeks. This trial included 61 people treated with DBS and individuals on immediate release amantadine who experienced dyskinesia. Extended-release amantadine addresses an unmet need in the management of dyskinesia and medical optimization of PD.

Treating Nonmotor Symptoms

Neurogenic Orthostatic Hypotension

Neurogenic orthostatic hypotension (nOH) is common in PD and a key feature of multiple system atrophy (MSA). A major source of disability, nOH increases the risk of falls and health care utilization. Droxidopa is a synthetic amino acid that is converted to norepinephrine (NE) in cells that express the enzyme L-aromatic-amino acid decarboxylase (LAAAD). In the US, droxidopa is approved to treat nOH in PD, MSA, pure autonomic failure (PAF), dopamine β-hydroxylase deficiency, and nondiabetic autonomic neuropathy. The mechanism of action of droxidopa is unknown as yet but is thought to be secondary to conversion to NE. A small study found substantial renal conversion of droxidopa to NE in individuals who were not taking carbidopa suggesting a possible intrarenal paracrine mechanism.

In a clinical trial, droxidopa treatment of people with nOH improved symptoms of nOH and the effects of symptoms on daily activities, with an associated increase in standing systolic blood pressure. The primary outcome measured was the Orthostatic Hypotension Questionnaire (OHQ) composite score, and secondary outcomes included changes in symptoms (eg, lightheadedness), individual OHQ items, and changes in standing systolic blood pressure from baseline at randomization to end of study. Only participants with PAF, who were not taking levodopa/carbidopa, had significant improvement on the OHQ composite score with droxidopa treatment vs placebo (−2.63 ± 1.89 vs −0.96 ± 2.02, P = .001). Participants with PAF also had a significant increase in their standing systolic blood pressure with droxidopa treatment vs placebo (11.6 ± 18.6 mm Hg vs 4.9 ± 12.6, P = .009). Neither primary nor secondary outcomes differed significantly between droxidopa and placebo treatment for individuals with PD, MSA, or non-diabetic autonomic neuropathy. Approximately 30% of people taking droxidopa had no increase in blood pressure. The reason there was no pressor effect in some individuals is unclear and may be explained by inhibition of LAAAD by carbidopa or by higher supine resting plasma NE levels. Another clinical trial that included people with PD who were taking carbidopa/levodopa showed benefit from droxidopa treatment with a short-term pressor effect, improvement in dizziness/lightheadedness, and reduction in falls with an increase in standing systolic blood pressure at 1 week for those given droxidopa vs placebo (6.4 ± 18.85 mm Hg vs 0.7 ± 20.18 mm Hg, P = .032).

In clinical practice, droxidopa improves nOH symptoms in people with PD or MSA. A subgroup of people, however, may not respond to the standard doses. The most common side effects encountered in the clinic are headaches, dizziness, nausea, and hypertension. Droxidopa is available in 100-mg, 200-mg and 300-mg capsules, and the dose should be titrated by monitoring symptoms and changes in standing blood pressure over a 2- to 4-week period with variable dosing frequency (1-3 doses/day). It is always recommended to add conservative measures (eg, increasing fluid and salt intake, avoiding getting up too quickly or standing motionless, maximizing the use of leg muscles, and raising head of bed by 5 to 10 inches at night) to prevent supine hypertension and pressure natriuresis.

Parkinson’s Disease Psychosis

Parkinson’s disease psychosis (PDP) may affect more than 50% of people with PD over the course of the disease. Psychosis in PD is progressive and manifests as hallucinations, illusions, and delusions. Diagnostic criteria have been proposed by the National Institute of Neurological Disorders and Stroke and the National Institute of Mental Health (NINDS/NIMH). Effects of PDP are negative for both individuals with PD and their caregivers and has been independently correlated with increased mortality risk and reduced quality of life. After evaluation for concomitant medications and exclusion of metabolic and systemic illnesses, management of PDP has tradition-
ally included atypical antipsychotics such as clozapine or quetiapine that act through an inverse agonism of serotonergic type 2A (5-HT2A) receptors.43 However, atypical antipsychotics may worsen motor symptoms by their action on dopamine type 2 (D2) receptors and are associated with potential side effects such as sedation or orthostatic hypotension.38

Pimavanserin is the most highly selective 5-HT2A inverse agonist, has no affinity for dopaminergic, muscarinic, adrenergic, or histaminergic receptors, and is the only FDA-approved treatment of hallucinations and delusions associated with PDP. In a clinical trial, participants with PDP were randomly assigned to receive pimavanserin (n = 105; 40 mg daily) or placebo (n = 94), for 6 weeks.44 The primary efficacy measure was the Scale for the Assessment of Positive Symptoms for Parkinson’s Disease Psychosis (SAPS-PD) which includes questions covering specific types of hallucinations and delusions. At 6 weeks, individuals treated with pimavanserin had improvement on the SAPS-PD compared with those treated with placebo. Secondary outcomes were also significantly improved with pimavanserin treatment compared with placebo (Table 2).45 The most common side effects included nausea, constipation, peripheral edema, gait disturbance, and hallucinations. Pimavanserin did not worsen motor function in individuals with PDP.46

There is a risk of QT prolongation and serious arrhythmia associated with pimavanserin noted in the warnings and precautions section of the drug label. Risk factors for QT prolongation include age more than 65, preexisting cardiovascular abnormalities, female sex, and electrolyte abnormalities. Pimavanserin increases the QTc interval by 5 to 8 msec; whereas, quetiapine increases QTc interval by 6 to 15 msec, and clozapine increase it by 10 msec.46 Given the efficacy data and tolerability and safety profile, pimavanserin may be started at symptom onset as a first-line agent for the treatment of PDP. Treatment of PDP should always be individualized, but the use of concurrent antipsychotics should be strongly discouraged because this has been associated with increased incidence of antipsychotic drug-related events, stroke, falls, infections, and worsening of PD motor symptoms.38

**Future Directions**

New treatments for PD provide clinicians and patients with new options and improved ability to manage the off period that occurs with prolonged levodopa treatment. Novel indications provide robust data for conditions that previously lacked appropriate treatment, such as PDP and nOH. New formulations and novel delivery mechanisms provide clinical benefit with better efficacy, tolerability, and reduction of disability.

We remain hopeful about future therapeutic options that potentially include long acting catechol-O-methyl transferase (COMT) inhibitors, subcutaneous apomorphine, and subcutaneous levodopa infusions aimed at reducing off time. Nondopaminergic medications such as idrasidefylline (a selective antagonist at the adenosine A2A receptor) provide novel and intriguing targets in the management of PD. Finally, we remain optimistic for the “holy grail” of movement disorders—medications that provide true disease modification and halt or slow the progression of neurodegeneration.

**TABLE 2. PRIMARY AND SECONDARY OUTCOMES OF PIMAVANSERIN FOR PARKINSON’S DISEASE PSYCHOSIS**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pimavanserin</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS-PD score</td>
<td>−5.79</td>
<td>−2.73</td>
<td>.001</td>
</tr>
<tr>
<td>UPDRS score</td>
<td>−2.47</td>
<td>−5.35</td>
<td>.22</td>
</tr>
<tr>
<td>CGI illness severity</td>
<td>−1.02</td>
<td>−0.44</td>
<td>.0007</td>
</tr>
<tr>
<td>CGI symptom improvement</td>
<td>3.45</td>
<td>2.78</td>
<td>.001</td>
</tr>
<tr>
<td>CGI caregiver burden</td>
<td>−4.34</td>
<td>−3.94</td>
<td>.0016</td>
</tr>
<tr>
<td>SCOPA night</td>
<td>−1.42</td>
<td>−0.49</td>
<td>.0466</td>
</tr>
<tr>
<td>SCOPA day-wake</td>
<td>−2.21</td>
<td>−0.99</td>
<td>.12</td>
</tr>
</tbody>
</table>

Abbreviations: CGI, clinical global impression; SAPS-PD, scale for the Assessment of Positive Symptoms for Parkinson’s disease psychosis; SCOPA, scale for outcomes of Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

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11. Buopu (Carbidopa Levodopa Enteral Suspension 4.8mg/20mg per mL) [package insert]. North Chicago, IL; AbbVie Inc; 2019.
21. Snow BJ, MacDonald A, McAlary O, Wals W. The effect of amantadine on levodopa-induced dyskinesias in Parkinson’s