INTRODUCTION

Parkinson’s disease (PD) is a progressive disorder in which the patient’s response to pharmacotherapy decreases over time, resulting in various motor complications. In addition, the occurrence of dyskinesias and dystonias in patients with advanced disease further complicates clinical management. Several factors, such as the dose and the duration of therapy, are associated with the development of motor complications in patients with PD. The prevalence of motor fluctuations, or movement problems, is reported to be as high as 60% to 90% in PD patients after five to 10 years of treatment. Movement problems are associated with the development of motor complications in patients with PD. The prevalence of motor fluctuations, or movement problems, is reported to be as high as 60% to 90% in PD patients after five to 10 years of treatment.

In part 3 of this five-part series, published in the October 2015 issue of P&T, we reviewed the role of nondopaminergic pharmacotherapies and adjunctive options in the management of PD, as well as nonpharmacological treatment strategies. In this installment, we focus on managing the motor complications of PD.

WEARING-OFF

In PD patients, motor fluctuations most commonly result from levodopa-related “wearing-off,” or the re-emergence of motor symptoms before the next scheduled levodopa dose. Although more subtle, wearing-off features may include nonmotor features, such as depression and anxiety. Wearing-off can have either an acute or gradual presentation. The suggested cause of this phenomenon is postjunctional alterations of striatal dopaminceptive systems, in addition to reduced dopamine levels in the striatum due to the degeneration of presynaptic dopaminergic terminals.

Management

The management of wearing-off usually involves increasing or manipulating dopaminergic stimulation. In addition, addressing potential dietary issues, such as the avoidance of protein consumption during dosing, may improve levodopa absorption and provide benefit in some patients.

Levodopa dose adjustments for the management of wearing-off may involve fractionating the dose or increasing individual doses. Responses to the fractionation of levodopa can be variable because peaks and troughs are not eliminated, whereas increasing individual doses of the drug may put patients at increased risk of peak-dose dyskinesias.

Researchers continue to evaluate alternative delivery forms of levodopa to provide more constant and sustainable levels of the drug.

Although the controlled-release carbidopa/levodopa product Sinemet (Merck) was designed to treat PD patients who are experiencing wearing-off, it has not demonstrated significant benefits compared with regular-release carbidopa/levodopa products. In addition, delayed and often unpredictable responses resulting from erratic absorption have been reported with Sinemet, along with dyskinesias. Tolerability is similar between the controlled-release and regular-release carbidopa/levodopa products. Anecdotal reports have suggested a potential role for the bedtime administration of controlled-release carbidopa/levodopa for the treatment of nocturnal akinesia.

A controlled study of Rytary (Impax Pharmaceuticals), a new extended-release carbidopa/levodopa product, reported a reduction in “off” time of 1.2 hours daily compared with an immediate-release product. This new formulation contains beads that release the two drugs at different rates compared with the polymeric-based erosion-tablet delivery system used in current controlled-release products.

Rytary was approved for the treatment of PD in January 2015. In that same month, the Food and Drug Administration (FDA) also approved a carbidopa/levodopa enteral suspension (Duopa, AbbVie) for the treatment of motor fluctuations in patients with advanced PD. The product is administered using a small, portable infusion pump that delivers carbidopa and levodopa directly into the small intestine for 16 continuous hours via a procedurally placed tube. In a 12-week, phase 3, double-blind, double-placebo, active-control, parallel-group trial, Duopa significantly reduced daily mean “off” time (per 16 waking hours) at 12 weeks by four hours, which resulted in an average of 1.9 fewer hours of “off” time compared with immediate-release carbidopa/levodopa tablets.

The addition of adjunctive pharmacotherapies is usually necessary to manage wearing-off in patients with advanced PD who are receiving carbidopa/levodopa products. Adjuvants include dopamine agonists and levodopa potentiators, such as catechol-O-methyltransferase (COMT) and monoamine oxidase type B (MAO-B) inhibitors. When added to carbidopa/levodopa, dopamine agonists have demonstrated the greatest improvements in “off” time and in PD assessment scores compared with the addition of COMT or MAO-B inhibitors. In the presence of adjunctive therapies, it is recommended that the levodopa dose be reduced to minimize the incidence of dyskinesias and other adverse effects.

Acute episodes of “off” time may be managed with subcutaneous (SC) injections of the dopamine agonist apomorphine. Apomorphine is indicated only for acute “off” episodes in advanced PD in patients when other therapies have been optimized. The antiemetic trimethobenzamide should be given as premedication due to apomorphine’s side effect of severe nausea and vomiting. An evidence-based review of several long-term, open-label studies found that SC apomorphine is superior to placebo for the management of symptoms associated with Parkinson’s disease. More recently, Duopa was approved for the management of motor fluctuations in patients with advanced PD who are experiencing wearing-off.

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infusions were successful in aborting “off” periods in a total of 233 PD patients. In an early study, 24 patients treated with SC apomorphine were followed for a median period of 22 months. “Off” time was reduced significantly (P < 0.001) in these subjects from 50.0% before treatment to 29.5% with apomorphine. Investigators in Spain evaluated long-term (at least three months) continuous SC apomorphine in 82 patients with advanced PD. The mean follow-up period was 19.9 months. The authors found a statistically significant reduction in “off” hours compared with baseline values, based on self-scoring diaries (6.64 hours per day at baseline versus 1.36 hours per day after treatment) and on Unified Parkinson’s Disease Rating Scale (UPDRS) total and motor scores (both P < 0.0001).

**DELAYED OR ABSENT RESPONSE TO CARBIDOPA/LEVODOPA**

Patients with advanced PD may experience a delayed response or no response to carbidopa/levodopa therapy. The causes of these phenomena include absorption problems related to delayed gastric emptying and changes in receptor dynamics.

**Management**

The management of a delayed response or the lack of a response to carbidopa/levodopa generally consists of interventions to improve the duodenal absorption of levodopa, such as reducing tablet disintegration in the stomach or facilitating the gastric-emptying time. Practical suggestions have included avoiding protein meals with levodopa doses; drinking a full glass of water after chewing or crushing a tablet; or using the oral-disintegration tablet formulation. The use of SC apomorphine may be necessary in some patients who fail to respond to carbidopa/levodopa.

**FREEZING OF GAIT**

Another complication that occurs in the later stages of PD is “freezing of gait” (FOG). FOG occurs in up to 60% of PD patients and is more common in males than in females. It is also more common in patients with akinetic–rigid PD than in those with tremor-dominant forms of the disease. Patients describe FOG as being unable to move or feeling “stuck to the floor.” The occurrence of FOG can confer a significant risk of falls and subsequent fractures. Several factors can trigger FOG in PD patients, including anxiety and obstacles to walking. FOG may occur in older individuals with PD when they are turning, initiating a step, crossing a busy road, or dueling-tasking, or when they are confronted with spatial restrictions. The pathophysiology of FOG is unclear, but imaging studies have implicated the presence of dysfunctional parietal–lateral right-sided premotor circuits or the loss of norepinephrine associated with degeneration of the locus coeruleus.

**Management**

Limited data suggest that dopaminergic agents may improve “on” time in PD patients with FOG, although PD symptoms related to gait generally show a poor response to these drugs. The MAO-B inhibitor selegiline has been effective in reducing the development of FOG in patients with early PD as well as in those with advanced disease. Rasagiline, another MAO-B inhibitor, has also been shown to have a positive effect on FOG. In the large-scale LARGO and PRESTO trials, the drug demonstrated a significant effect on the UPDRS subscores of FOG and postural instability and gait disorder (PIGD) in patients with advanced PD. Moreover, in a LARGO ancillary study, rasagiline significantly reduced FOG in comparison with placebo. More recently, in a case report, treatment with rasagiline provided a rapid and sustained reduction in the frequency and duration of FOG in an 84-year-old man with a four-year history of the disorder.

Alternative treatments, such as the selective norepinephrine reuptake inhibitor (SNRI) atomoxetine, botulinum toxin injections, and methylphenidate, have been studied in PD patients with FOG, but there is little evidence to support their use in this setting. Atomoxetine (Strattera, Lilly) is currently indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD), but since it enhances noradrenergic transmission, it may not be effective in managing FOG. In a recent study, low-frequency (60 Hz) bilateral subthalamic-nucleus DBS significantly reduced FOG in seven patients with PD. The therapeutic benefits persisted over the study’s six-week assessment period.

Pharmacotherapeutic dose adjustments have little effect in patients with FOG; therefore, supportive care, walking devices, and other aids are often used. The treatment of FOG may also focus on attention strategies, such as walking on a path with a pattern (zebra lines) and visual or auditory cueing. An interesting method for managing FOG consists of using a stimulus, such as stepping over an object, sounding an alarm bell, or walking to music, to paradoxically relieve the patient’s “freezing.” A case report described a PD patient with freezing episodes who was able to ride a bicycle without difficulty.

Researchers in Europe and Israel have developed a smartphone app aimed at preventing FOG in PD patients. The app combines wearable sensors, audio biofeedback, and external cueing to provide motivational training tailored to each patient. The results are monitored remotely by medical professionals.

**DYSKINESIAS**

Dyskinesias are commonly associated with dopaminergic (levodopa) therapy in PD patients. They usually occur within three to six years after the initiation of treatment and affect 30% to 80% of PD patients. The clinical presentation of dyskinesias can vary from unilateral or generalized symptoms to more-specific manifestations (e.g., athetotic or oculogyric). Some patients will tolerate mild treatment-associated dyskine-
sias in exchange for improved motor control, whereas others experience presentations that are incapacitating. There are two types of dyskinesias: peak-dose (or “on”-period) and diphasic dyskinesia. Peak-dose dyskinesias are associated with high plasma levels of levodopa, paralleling the drug’s maximal benefits, and present with choreic features involving the upper extremities, trunk, and neck. Diphasic dyskinesias appear at the onset and offset of levodopa’s clinical effects, coinciding with the increase and decrease in levodopa levels. Diphasic dyskinesias often occur when walking and may interfere with a patient’s gait. In general, dyskinesias initially affect the legs, but they can spread to the arms, torso, head, and neck, and may involve the muscles used in respiration and speech. Some patients experience dyskinesias soon after their first dose of carbidopa/levodopa, while others may develop these disorders over the course of several years.

A retrospective evaluation of 109 patients with PD reported that their age at the time of diagnosis was a predictor for the development of levodopa-induced dyskinesias. According to this study, after five years of levodopa dosing, the risk of developing dyskinesias was higher in younger patients (ages 40 to 49 years; 70%) than in older patients (ages 70 to 79 years; 24%). Other risk factors for developing dyskinesias include genetic factors, the severity of PD, and being female. The pathophysiology of levodopa-induced dyskinesias is complex, and these movement complications can originate in multiple regions of the brain. Levodopa-induced dyskinesias have been linked to nigrostriatal dopaminergic loss, pulsatile stimulation of receptors, changes in striatal transmission, and circuit alterations associated with synaptic abnormalities. Research has also implicated nondopaminergic receptor systems, including glutamatergic, opioid, and serotonergic systems.

Levodopa-related dyskinesias may be precipitated by adjustments in PD medications, such as increasing the carbidopa/levodopa dose or adding dopamine agonists or levodopa potentiators (e.g., COMT or MAO-B inhibitors). Severe dyskinesias may result in rhabdomyolysis and dehydration, and they can be life-threatening. The onset of dyskinesias may be delayed by starting patients on dopamine agonists rather than on carbidopa/levodopa.

**Management**

Several therapeutic strategies are used to manage dyskinesias, including adjusting existing PD medications, conducting trials of adjunctive pharmacotherapies, and performing DBS. Initial interventions may involve lowering the dose of existing carbidopa/levodopa therapy and discontinuing or adjusting the dose of a levodopa potentiator, such as entacapone. If carbidopa/levodopa doses are reduced, the addition of a dopamine agonist or other adjunctive therapies may be required. All dose-adjustment options and drug discontinuations require careful titration and monitoring to avoid the re-emergence of motor symptoms.

The randomized, controlled Comparison of the Agonist Pramipexole Versus Levodopa on Motor Complications of Parkinson’s Disease (CALM-PD) trial evaluated the risk of developing dyskinesias in patients with early PD initially treated with either the dopamine agonist pramipexole or levodopa. After a median follow-up period of six years, the patients receiving levodopa experienced significantly more dyskinesias compared with the pramipexole-treated patients (36.8% versus 20.4%, respectively), but there was no difference between the two groups in the incidence of disabling or painful dyskinesias.

Four randomized controlled studies (two 24-week phase 3 trials and two four-week phase 2 trials) compared pramipexole with placebo in a total of 669 patients with idiopathic PD and long-term complications of levodopa therapy. Although the reduction in “off” time was significantly greater with pramipexole in all four investigations, no significant changes were noted in dyskinesia scales. Moreover, dyskinesia as an adverse event was reported more often in the pramipexole group.

In a randomized, open-label study conducted in Japan, 34 PD patients with levodopa-induced dyskinesias were randomly assigned either to an add-on group (n = 18), in which pramipexole was added to the existing drug regimen for the treatment of PD without changing the dose or the administration of the other drugs, or to a “switch” group (n = 16), in which the current dopamine agonist was switched to pramipexole. After 24 weeks of treatment, the overall study population showed no changes in UPDRS subscores for dyskinesia.

Researchers have also treated PD patients with dyskinesias using dopaminergic stimulation via continuous intrajejunal infusions. For example, in a randomized, double-blind, double-dummy, double-titration trial, Olanow and colleagues compared levodopa/carbidopa intestinal gel infusions with immediate-release oral levodopa/carbidopa in 66 adults with advanced PD. After 12 weeks of treatment, mean “on” time without troublesome dyskinesia was significantly greater with the intestinal gel than with oral therapy (4.11 hours versus 2.24 hours, respectively; \( P = 0.0059 \)).

In a prospective study, Zibetti et al. observed the safety and efficacy of continuous levodopa/carbidopa intestinal gel in 59 adults with advanced PD and dyskinesias treated for seven years. The duration of dyskinesias was reduced from 1.7 hours at baseline to 1.2 hours at follow-up (\( P = 0.002 \)), and dyskinesia disability was reduced from 1.0 to 0.5 hours (\( P < 0.001 \)).

Although continuous intrajejunal infusions of levodopa/carbidopa gel have been shown to reduce dyskinesias and improve motor fluctuations in PD patients, the surgical procedure involved and the discomfort of tubing protruding from the abdomen may be contraindications in some patients.

Currently, this form of levodopa administration remains investigational in the U.S.

In an early study, Colzì et al. investigated continuous waking-day dopaminergic stimulation with SC apomorphine in 19 patients with PD and disabling levodopa-induced dyskinesias. The patients were treated for a minimum period of 2.7 years. SC apomorphine achieved a mean 65% reduction in dyskinetic severity and a mean 85% reduction in frequency and duration.

Katzschlager and colleagues retrospectively assessed the effects of a continuous SC infusion of apomorphine in 12 PD patients with disabling dyskinesias. The mean apomorphine dose was 75.2 mg per day. After six months, the treatment had provided a marked reduction in dyskinesias.

The efficacy of intermittent SC apomorphine injections as an add-on to levodopa therapy in patients with advanced PD...
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was investigated in one short-term, randomized, double-blind, placebo-controlled trial and in one short-term and six long-term, open-label, uncontrolled studies that involved a total of 195 patients. Although SC apomorphine, as an add-on to levodopa, helped prevent “off” periods and improve PD motor scores, the combination treatment also tended to increase dyskinesias.31

While it appears that SC apomorphine can reduce the potential for dyskinesias in some PD patients, administration problems, tolerance, and psychiatric side effects may limit the use of this approach.79

The role of glutamate N-methyl-D-aspartate (NMDA) receptors in the pathophysiology of dyskinesias led to the use of NMDA receptor antagonists in PD patients.80,86 One such drug, amantadine (1-aminoadamantane), has been effective in managing dyskinesias in PD patients, with treatment benefits extending beyond one year.80-82 In a double-blind, randomized, placebo-controlled, cross-over trial, Sawada and colleagues assigned 36 PD patients with dyskinesias to treatment with amantadine (300 mg per day) or placebo for 27 days. At 15 days after washout, the treatments were crossed over. Secondary outcome measures included the UPDRS-IVa, which is related to dyskinesias. This measure showed significant improvement in the amantadine-treated patients compared with the placebo-treated patients (mean: 1.83 versus 0.03, respectively).89

Wolf and colleagues provided evidence supporting the long-term use of amantadine in PD patients with dyskinesias. They conducted a randomized, double-blind, placebo-controlled, parallel-group study to assess the antidyskinetic effect of amantadine in 32 PD patients who were switched to amantadine or placebo after having been on stable amantadine therapy for levodopa-induced dyskinesias for at least one year. The study’s primary outcome was the score change in UPDRS-IV items 32 and 33 (severity and duration, respectively) between baseline and three weeks after the treatment switch. The authors reported a significant increase in the two UPDRS-IV items from 3.06 to 4.28 (P = 0.02) at the three-week follow-up in the patients switched to placebo compared with no significant change between baseline and follow-up values (3.2 to 3.6) in the patients who remained on amantadine.90

The three-month AMANDYSK trial evaluated the long-term efficacy of chronic treatment with amantadine in 57 PD patients with levodopa-induced dyskinesias. Like the study by Wolfe and colleagues, the primary outcome measure of this randomized, double-blind, placebo-controlled, parallel-group, wash-out trial was the change from baseline in UPDRS-IV items 32 and 33. These parameters deteriorated more in patients switched to placebo compared with those maintained on amantadine (+1.7 units versus +0.2 units, respectively; P = 0.003). Moreover, the authors found that withdrawing amantadine significantly aggravated patients’ dyskinesias within a median period of seven days.91

Monitoring amantadine and adjusting the dosage according to the patient’s renal function are important, especially in elderly patients. Adverse events related to the central nervous system, including hallucinations and confusion, may occur with this drug, and patients should be monitored for vision changes due to corneal edema.92,93

Another NMDA antagonist, memantine (1-amino 3,5-dimethyl-adamantane hydrochloride), has been used to manage levodopa-induced dyskinesias in PD patients with varying results. In an early study, Merello et al. evaluated the effect of memantine on dyskinesias in 12 PD patients who were randomly assigned to active treatment or placebo in a cross-over design. The authors reported that although memantine improved UPDRS motor scores, it had no effect on drug-induced dyskinesias in these patients.94 Similarly, in a recent randomized, double-blind, placebo-controlled, crossover study, the primary outcome measure—a change in observed dyskinesias ratings—did not reach statistical significance in 15 PD patients treated with memantine. Seven of these patients showed 32% reductions in their dyskinesias, whereas dyskinesias increased by 33% in three others. The remaining five patients showed no change.95 In a Swedish report, two out of three cognitively impaired PD patients “seemed to benefit” from treatment with memantine in terms of their dyskinesias.96 In view of the results from these and similar studies, further research is needed to validate the use of memantine as an antidyskinetic agent in PD patients.94,72

Riluzole (Rilutek, Sanofi), another NMDA receptor inhibitor, has been studied as a dyskinesia treatment in PD patients with little success. Rilutel is approved for the treatment of amyotrophic lateral sclerosis.97 Braz and colleagues reported that riluzole could extend the duration of the “on” state in 16 PD patients but was unable to reduce apomorphine-induced dyskinesias.98 In another study, Bara-Jimenez et al. evaluated the antidyskinetic effect of riluzole in 15 patients with moderately advanced PD. Again, the treatment failed to lessen the severity of levodopa-induced motor complications.99

Other medications evaluated for the management of dyskinesias in PD include the atypical antipsychotic clozapine and the anticonvulsant levetiracetam. Durif and colleagues treated 50 PD patients with clozapine or placebo for 10 weeks in a double-blind, parallel-group study. The clozapine group showed a significant reduction in the duration of “on” periods with levodopa-induced dyskinesias compared with the placebo group at the end of the study (clozapine, 5.68 hours on day 0 and 3.98 hours at study end; placebo, 4.54 hours on day 0 and 5.28 hours at study end; P = 0.003).100 The mechanism behind this effect is not fully understood, although it may involve interactions with dopaminergic and serotonergic receptor systems.101 Safety concerns with clozapine include its association with rare but serious blood dyscrasias.100

Mixed results have been reported with levetiracetam in the management of dyskinesias. For example, Wolz and colleagues conducted a randomized, double-blind, placebo-controlled, parallel-group study of levetiracetam in 32 PD patients with moderate-to-severe levodopa-induced dyskinesias. After 11 weeks of treatment, mean changes in UPDRS item 32 and 33 scores from baseline showed significant improvement in dyskinesias in the levetiracetam group (–20%; P = 0.012), but not in the placebo group (–8%; P = 0.306). Levetiracetam and placebo were not significantly different, however, in terms of mean changes from baseline in the modified abnormal involuntary movement scale (AIMS).102

Stathis et al. investigated the efficacy of levetiracetam in 38 PD patients with dyskinesias using a double-blind, placebo-controlled, parallel-group design. The two dosages of levetiracetam (500 mg per day and 1,000 mg per day) signifi-
cantly increased “on” time without dyskinesias by 46 minutes ($P = 0.004$) and 55 minutes ($P = 0.018$), respectively. Moreover, UPDRS item 32 showed a decreased duration of dyskinesia at the higher dosage ($P = 0.009$).

Adenosine A2A receptor (A2AR) antagonists are being investigated as another treatment option for levodopa-associated dyskinesias. Studies have shown that expression of the A2AR receptor is increased in PD patients with dyskinesias.

In two placebo-controlled studies, the A2Ar antagonist istradefylline (Kyowa Pharmaceutical) improved “off” time without increasing dyskinesias in levodopa-treated PD patients. Another A2Ar antagonist, preladenant (Mercck), was ineffective at treating PD patients in three separate phase 3 trials, and its development was discontinued. A phase 3, placebo-controlled study of tozadenant (Biotie Therapies) began in July 2015; the drug was effective at reducing “off” time in a phase 2b study. Other A2Ar antagonists are in development at the preclinical and early clinical levels.

Various surgical procedures, including DBS, have also been used to manage dyskinesias in PD patients. DBS is considered a surgical treatment alternative for PD patients with motor fluctuations and severe dyskinesias.

Dystonias

Dystonias are another complication that may occur in PD patients, usually in those at more-advanced stages of the disease. Dystonias are primarily characterized by involuntary, sustained muscle contractions resulting in twisting or squeezing movements. These muscle contractions may be viewed as another form of “off” time, presenting as abnormal postures in fixed and painful positions. Dystonias can affect many parts of the body but are most common in the feet. Although they can occur at any time during treatment, they are usually experienced in the morning upon rising. Painful morning dystonias occur in approximately 40% of PD patients and appear to be secondary to the rigidity and akinesia associated with reduced dopaminergic stimulation.

Management

Dystonias are difficult to manage, although they may respond to adjustments in dopaminergic therapy if they occur during the “off” state. A small study reported that controlled-release levodopa products were beneficial in treating early-morning dystonia. Additional therapies for dystonias, although not well studied in this setting, include muscle relaxants, botulinum toxin, and DBS.

Dystonias have been associated with serious complications, such as choking (resulting from involvement of the laryngeal area) and fixed postural changes that result in kyphosis and a restricted pulmonary capacity. The management of these complications may include breathing and trunk exercises, general conditioning, and postural re-education. Pulmonary function may be improved with coughing techniques, incentive spirometry, and respiratory therapy. Aggressive management, such as ventilator support, laryngeal adductor botulinum injections, or tracheostomy, may be required in some patients.

CONCLUSION

The occurrence of motor complications is a key component of PD and presents a clinical challenge to practitioners. Such features include wearing-off, a delayed or absent response to carbidopa/levodopa therapy, FOgs, dyskinesias, and dystonias.

The management of wearing-off usually involves increasing dopaminergic stimulation as well as manipulating doses. Interventions to improve the duodenal absorption of levodopa, such as reducing tablet disintegration in the stomach, are the primary methods for managing a delayed or absent response to carbidopa/levodopa. Limited data support the use of dopaminergic agents in PD patients with FOgs. Current approaches used to manage dyskinesias include adjusting existing PD medications and the use of DBS. Other investigational therapies continue to be evaluated.

Dystonias may respond to adjustments in dopaminergic therapy if they occur during the “off” state. Researchers continue to seek improved management options for PD patients with motor complications.

In the next issue of P&T, the final installment of this five-part article will discuss the management of nonmotor complications of PD.

REFERENCES


