Parkinson’s Disease and Its Management
Part 5: Treatment of Nonmotor Complications

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INTRODUCTION
Although Parkinson’s disease (PD) is considered to be a neurological disorder that affects motor function, most patients also experience nonmotor complications. The nonmotor features of PD may be broadly classified under two categories: neuropsychiatric presentations (such as psychosis and depression) and autonomic disorders (including gastrointestinal, cardiovascular, and urogenital complications). Many of these features are not generally recognized as being associated with PD and may be missed by clinicians during diagnosis.1–3

The nonmotor features of PD result from neurodegeneration extending beyond the dopaminergic system and involving brainstem nuclei in the serotonergic, noradrenergic, and cholinergic systems.4–6 Nonmotor features may also correlate with the presence of Lewy bodies (abnormal protein deposits) in the brain.7

The nonmotor complications of PD may present early in the disease process (before the onset of motor features) or as a component of disease progression. Neurodegeneration has been observed as early as 10 to 20 years before the onset of motor features in PD patients.8 Researchers continue to explore ways to identify the early nonmotor symptoms of PD to allow earlier diagnosis and management.1,2,9,10 Despite the high prevalence of nonmotor features in PD, treatment options are limited.3,11–16

While part 4 of this five-part series, published in the November 2015 issue of P&T, discussed the management of PD’s motor complications, this final installment will focus on the nonmotor features of the disorder.

NEUROPSYCHIATRIC PRESENTATIONS
Neuropsychiatric complications, including psychosis, depression, anxiety, and sleep-related disorders, are associated with PD. Impulse-control disorders in PD patients usually result from the use of dopamine agonists.17–19

Psychosis
Features of psychosis occur in up to 40% of PD patients, with hallucinations being the most common presentation.17 Although benign in some PD patients, psychosis may progress to delusional thinking in others and may have a significant effect on the patient as well as on his or her family and caregivers.16,17

The management of hallucinations and other psychotic complications of PD is challenging because of the potential for dopaminergic medications to contribute to psychiatric symptoms. Nonpharmacological therapies and medication adjustments are often used for first-line management in this setting. These approaches include behavioral interventions and treatment adjustments, especially the avoidance of unnecessary medications. The challenge for clinicians is to achieve a dopaminergic dosage that will maintain motor control without exacerbating the psychotic features of PD.16,17

PD patients with features of psychosis who are unresponsive to nonpharmacological therapies may require management with antipsychotic drugs. If antipsychotics are used, it is important to avoid agents that may worsen the motor features of PD, such as haloperidol.19 Since clozapine and quetiapine do not aggravate the motor complications of PD, both agents have been studied as treatments for PD-related psychosis.20–22 Clozapine, however, may cause severe blood dyscrasias, such as agranulocytosis, and requires close monitoring.22 While quetiapine has a safety profile that supports its use in PD patients, the data supporting its efficacy in managing PD-related psychosis are contradictory.23–26 Other antipsychotics in this class, such as olanzapine, have a high risk for exacerbating the motor symptoms of PD and have not been studied in PD patients with psychosis.3 A further concern with both conventional and atypical antipsychotics is their association with cerebrovascular events and mortality in elderly patients with dementia.27

If antipsychotic therapy is necessary in PD patients with psychosis, clozapine or quetiapine should be administered with caution and at the lowest doses to achieve a clinical benefit.13,19

Depression
Many PD patients (up to 90%) experience depression, which can occur in both early and advanced disease, leading to significant disability.16,19,28,29 The disorder may be underdiagnosed in PD.10 The development of depression in patients with PD appears to involve disturbances in neurotransmitters.30–32

The initial management of depression in PD patients should include nonpharmacological interventions, including counseling for both patients and caregivers.33,19 The use of PD medications with potential antidepressant activity should also be considered. The monoamine oxidase type B (MAO-B) inhibitor selegiline (Emsam, Somerset Pharmaceuticals, Inc.) is used as a transdermal formulation to treat atypical depression, but it has not been well studied in PD patients.33

Evidence indicates that dopaminergic losses may be associated with PD-related depression, based on the observation that depressive features can occur during “off” time. Several trials have evaluated the dopamine agonist pramipexole in patients with PD-associated depression. In a randomized study, pramipexole was compared with sertraline in 67 PD patients with depression. Scores on the Hamilton Depression Rating Scale (HAM-D) decreased throughout 12 weeks of treatment with both drugs, but in the pramipexole group the proportion of patients who recovered, as defined by a final HAM-D...
score of 8 or less, was significantly higher (61% versus 27%; \( P = 0.006 \)).

Pramipexole was also evaluated in a 12-week, placebo-controlled study involving 287 PD patients with depression. The study’s primary endpoint was the change in the Beck Depression Inventory (BDI) score. This score decreased by a mean of 5.9 points in the pramipexole group compared with a mean of 4.0 points in the placebo group \( (P = 0.01) \). An analysis showed that the direct effect of pramipexole on depressive symptoms accounted for 80% of the total treatment effect \( (P = 0.04) \).

A study conducted in 2003 compared pramipexole with the dopamine agonist pergolide (subsequently removed from the U.S. market in 2007\(^{38} \)) in 41 patients with advanced PD and mild or moderate depression. After eight months of open-label therapy, the average score on the Montgomery–Åsberg Depression Rating Scale (MADRS) was significantly reduced in the pramipexole group but not in the pergolide group.\(^{37} \)

In view of these and other similar results, clinicians might consider a trial of pramipexole in PD patients with depression as a component of their treatment regimen.

Traditional antidepressant agents, including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), have also been studied in PD patients with depression.\(^{3,28,38} \) Specifically, the TCAs nortriptyline, desipramine, and amitriptyline have been compared with paroxetine controlled release (CR), citalopram, and sertraline, respectively.\(^{39–43} \) Although these small trials reported antidepressant efficacy with both TCAs and SSRIs in PD patients with depression, differences between these two drug classes were also reported. For example, desipramine was associated with more adverse events compared with citalopram in one study, and paroxetine CR was reported to be less effective and less well tolerated compared with nortriptyline in another study.\(^{39,43} \)

SSRIs are used more commonly than TCAs in clinical practice. They have the potential, however, to contribute to tremor or to increase the risk of anticholinergic effects when antidepressant drugs and MAO-B inhibitors are used concomitantly.\(^{45,46} \) TCAs increase the risk of anticholinergic adverse effects and require careful monitoring as well.\(^{47} \)

Other classes of antidepressants have also been studied in PD patients. Nefazodone and venlafaxine were reported to be similarly effective compared with fluoxetine and paroxetine, respectively.\(^{48,49} \) Atomoxetine was found to be ineffective in PD patients,\(^{50} \) but bupropion appears to have a role in the treatment of PD-associated depression.\(^{51} \)

Although the use of antidepressants may have a positive effect on outcomes in PD patients,\(^{52} \) individuals with severe or resistant depression may present a clinical challenge to practitioners. As an alternative, psychosocial interventions have been tried in patients with PD-related depression, but more study is needed in this area.\(^{3,53} \) The role of electroconvulsive therapy in PD patients with depression has not been embraced by the neurology community, nor is it supported by current guidelines.\(^{54} \) Repetitive transcranial magnetic stimulation was shown to be as effective as the SSRI fluoxetine for the treatment of depression in PD patients.\(^{55} \)

### Anxiety

In addition to depression, PD patients may experience anxiety, which can range in severity from mild to full-blown panic attacks. As in PD patients with depression, the use of nonpharmacological interventions, including counseling and cognitive and behavioral therapy, should be given first consideration in PD patients with anxiety.\(^{56} \)

Although benzodiazepines have been used in PD patients with anxiety, these drugs carry a risk of confusion, falls, and fractures. No controlled studies have evaluated antidepressants in PD patients with anxiety.\(^{17,29,38} \)

### Impulse-Control Disorders

Impulse-control disorders (ICDs) have been associated with the use of dopamine agonists. In some patients, these disorders will continue after the treatment has been stopped.\(^{57} \) A study with amantadine, using a crossover design, evaluated its role in the management of pathological gambling that continued after discontinuation of dopamine agonists and suggested some benefits.\(^{59} \) Although amantadine is used to manage dyskinesias in PD patients, this drug has a minor role in the control of motor symptoms and is not well tolerated.\(^{60} \) Concerns regarding corneal edema and the risk for continued ICDs after treatment do not support the routine use of amantadine in patients with PD-related ICDs.\(^{60} \)

### Cognitive Impairment and Dementia

Cognitive impairment and dementia occur in up to 75% of patients with PD and have a significant effect on social and occupational activities, as well as adding to the caregiver’s burden.\(^{61–63} \) Research indicates that the dementia of PD is heterogeneous, presenting with a wide range of cognitive deficits.\(^{64} \) The pathology of PD-related dementia involves the degeneration of cortical and subcortical regions, resulting in dopamine and cholinergic dysmodulation along with the formation of Lewy bodies.\(^{65,66} \) Most PD patients with cognitive impairment experience cognitive symptoms during advanced stages of their disease.\(^{64,65,66} \) Clinical presentations of PD-related dementia include problems with working memory, learning, and planning.\(^{65} \) Typically, the onset of dementia in PD patients occurs after motor symptoms have been present for at least one year.\(^{68} \)

Nonpharmacological interventions in PD patients with cognitive impairment or dementia can include cognitive therapy, music, and art therapy, along with physical activity. Noninvasive brain-stimulation techniques have shown some promise as future treatments.\(^{19,69,70} \)

Pharmacological treatment may include the use of acetylcholinesterase inhibitors (AChEIs). Both open-label and controlled studies of these agents have demonstrated improvements in cognitive measures, although the efficacy data varied among agents.\(^{71–79} \) Rivastigmine (Exelon, Novartis) showed the most promise, which resulted in the Food and Drug Administration (FDA) approving it for use in PD patients with mild-to-moderate dementia.\(^{71–74} \) Because AChEIs potentiate acetylcholine, there is the possibility that these agents may exacerbate tremor. This concern is related to the increase in acetylcholine associated with dopaminergic loss in PD patients. Although motor scores did not worsen in studies of rivastigmine and donepezil in PD
patients.74-77 Tremor was exacerbated in galantamine-treated patients.78 Careful monitoring for adverse events and for the worsening of motor symptoms is recommended during treatment with AChEIs in PD patients with dementia.

The N-methyl-D-aspartate (NMDA) receptor antagonist memantine (Namenda, Forest Laboratories) may be considered for the treatment of dementia in PD patients with Lewy bodies, although the data have been contradictory.79-84 One open-label study suggested that memantine may offer some symptomatic benefits in PD patients, but these benefits were lost when treatment was withdrawn.82

Sleep Disorders
PD patients often experience sleep problems, such as rapid-eye-movement sleep behavior disorders (RSBDs), vivid dreams, restless legs syndrome, insomnia, and excessive daytime somnolence.3,11,13 RSBDs involve abnormal behavior or other features that occur during the rapid-eye-movement phase of sleep, such as atonia, twitches, ocular movements, and the acting out of dreams. Brain pathologies appear to be related to RSBDs, which have been studied as possible early markers of PD.85,86

Numerous pharmacological therapies have been evaluated for the management of insomnia in PD patients. In a comparison of controlled-release carbidopa/levodopa and placebo, both administered at bedtime, the authors reported a trend toward increased sleep time with the active treatment, along with improvements in nocturnal akinesia.87 Another study reported a nonsignificant increase in sleep time with the hypnotic agent eszopiclone (Lunesta, Sunovion) compared with placebo. This investigation also found that the number of awakenings and the quality of sleep were improved in the eszopiclone group.88

Two placebo-controlled studies evaluated melatonin supplementation for the treatment of sleep disturbances in PD patients. One study reported an improvement in nocturnal sleep time with a 50-mg dose and improved overall sleep quality with a 5-mg dose.89 The second study reported improved sleep quality with a 3-mg dose.90

Eliminating caffeine from afternoon and evening menus, avoiding excessive daytime napping, and participating in an exercise program may also benefit PD patients with insomnia.13,16

Excessive daytime sleepiness (EDS) and sudden-onset sleep can occur in PD patients and can have a significant negative effect on quality of life. The presence of these disorders is further complicated by “sleep attacks” associated with the use of dopamine agonists.91

Three studies evaluated the use of modafinil (Provigil, Teva Pharmaceuticals), a narcolepsy agent, in PD patients with EDS.92-94 Of these studies, two reported a reduction in daytime sleepiness with active treatment. Modafinil, however, has been associated with life-threatening cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. In addition, there have been reports of psychiatric adverse events, including mania, delusions, hallucinations, and suicidal ideation.95 In view of these findings, modafinil cannot be recommended for the treatment of EDS in PD patients.

AUTONOMIC DISORDERS
Gastrointestinal Complications
Patients with PD may develop gastrointestinal disorders resulting from parasympathetic innervation of the vagus nerve, dopamine loss, or pathological involvement of the enteric nervous system.96-98

Nausea and vomiting in PD patients may be due to impaired gastric emptying and may be exacerbated by concurrent dopaminergic therapy.98 The management of nausea and vomiting in this setting is complicated by the fact that many antiemetic drugs are dopaminergic antagonists contraindicated in PD patients.99 The use of 5-HT3 (serotonin) receptor antagonists is contraindicated in PD patients receiving the dopamine agonist apomorphine.100 The antiemetic drug trimethobenzamide may be an option in these patients.101

Impaired gastric emptying (gastroparesis) may occur in PD patients as a result of reduced colon transit or reduced intestinal motility. The latter, in turn, may cause constipation, nausea and vomiting, and incomplete drug absorption.96,98

Initial management should include increased water intake, the use of dietary fiber or supplements, and in some cases stool softeners and laxatives.13 If laxatives are necessary, osmotic agents are recommended; these treatments include sorbitol, polyethylene glycol solutions, and the chloride channel activator lubiprostone.102,103

PD patients may also experience dysfunctional defecation, such as fecal incontinence or incomplete defecation. In these disorders, the lack of anal sphincter control, puborectalis relaxation, or the lack of intra-abdominal pressure prevents complete defecation.104-106 Dysfunctions in defecation have been associated with “off” time in PD patients, and dopaminergic therapy may also play a role.105,106

Sialorrhea occurs in at least 70% of PD patients and may have significant social consequences in some individuals. The disorder is due to a reduced ability to swallow (dysphagia), not to an overproduction of saliva, resulting in bothersome drooling. Nonpharmacological interventions include sucking on hard candies or chewing on gum, both of which can reduce drooling in social settings.107,108 Adjusting dopaminergic therapies may also benefit some patients.108

Pharmacotherapy for severe sialorrhea includes the inhibition of saliva production with muscarinic receptor antagonists. Two such agents, sublingual ipratropium spray and oral glycopyrrolate, have been studied in this setting.109-111 A major concern with the use of anticholinergic agents is their adverse-event profiles, especially in elderly patients.112

Treatment with botulinum toxin (BTX) has provided symptomatic benefits in PD patients with sialorrhea. BTX should be administered only by clinicians trained in dosing and monitoring the drug.113-115

Dysphagia in PD patients can lead to choking or more-serious events, including aspiration. This disorder appears to be secondary to oral, pharyngeal, and/or esophageal dysfunction.105,116 Management approaches to dysphagia include adjusting dopaminergic therapies, having the patient perform swallowing exercises, and (in severe cases) placing a gastrostomy tube.107,116-118
Cardiovascular Disorders
Orthostatic hypotension (OH) is defined as a sudden drop in systolic blood pressure of 20 mm Hg or more and in diastolic blood pressure of 10 mm Hg or more within minutes of standing from a supine position.96,119 OH is likely related to autonomic dysfunction, although dopaminergic drug therapy may be a contributing factor.120,121 In PD patients, the disorder is commonly referred to as neurogenic OH.122

OH affects an estimated 30% of PD patients, although this rate may be substantially higher in patients with advanced disease.119,121,122 The primary symptoms include dizziness and lightheadedness resulting in postural instability, falls, and potential fractures. Dopaminergic therapies, such as levodopa and dopamine agonists, have been associated with the disorder.121,122

The management of symptomatic OH includes adjusting existing dopaminergic therapies; avoiding exacerbating factors, such as alcohol consumption; implementing frequent small meals; wearing support socks; increasing fluid and sodium intake (if not contraindicated); and elevating the head of the bed.122,123 Pharmacotherapy may be considered as a secondary option. Agents that have been used to treat OH in general practice include fludrocortisone (a mineralocorticoid that retains sodium), desmopressin (to promote the reabsorption of water), and midodrine (an alpha agonist that increases peripheral vascular resistance). There is insufficient evidence, however, to recommend these agents for the management of PD patients with OH.3,119 Droxidopa (Northera, Lundbeck), a synthetic amino acid precursor of norepinephrine, was recently approved for the treatment of PD-associated OH, but it has shown limited efficacy in short-term studies.123

Cardiac sympathetic denervation (CSD) has been linked to PD and is considered a marker for the disease.125,126 Symptoms include OH, fatigue, shortness of breath, and changes in cardiac electrical activity.127 In addition to standard autonomic testing, cardiac scintigraphy may be useful in detecting silent CSD in PD patients.129,129

Urogenital Disorders
Bladder dysfunction, including urgency, frequency, nocturia, and obstructive features, may occur in PD patients. Urge incontinence (“overactive bladder”) is the most common feature and may have a significant negative effect on a patient’s quality of life.130 The obstructive features of bladder dysfunction, such as hesitancy and poor stream, are believed to result from detrusor underactivity and may be complicated by concurrent prostatic hypertrophy. In general, urinary dysfunction in PD patients appears to be associated with disinhibition of the micturition center secondary to the loss of dopaminergic cells.130,131

Anticholinergic medications may be used to treat urgency, although the potential for urinary retention and other adverse effects calls for low doses and careful monitoring. The obstructive features of bladder dysfunction are commonly treated with alpha-adrenergic blockers, but 5-alpha reductase inhibitors may also be useful. In severe cases of urinary obstruction, intermittent catheterization may be necessary.123,131

Sexual Disorders
Sexual disorders in PD patients include erectile dysfunction (ED) and impaired ejaculation in men, and reduced libido and vaginal sensitivity in women. Dopaminergic therapy may be a contributing factor.96,119 In the general population, treatment approaches to male sexual dysfunction have included prostaglandin injections, testosterone therapy, and prosthetic devices, but there is insufficient evidence for the use of these treatments in PD patients.3,12,13 Treatment with phosphodiesterase inhibitors (PDIs) may be appropriate in men with ED. If PDIs are used, however, careful monitoring is recommended because of the potential for hypotension.3,12,13,132

OTHER NONMOTOR FEATURES OF PARKINSON’S DISEASE
PD patients commonly experience nociceptive (i.e., musculoskeletal or dystonia-related) and/or neuropathic pain, which is believed to result from basal ganglia dysfunction. Pharmacological approaches to PD-related pain include adjusting PD medications, administering antineuropathic and antinociceptive drugs, and performing deep brain stimulation.3,13,133 Chronic fatigue is also a common feature of PD. Currently, there is no recognized treatment. Methylphenidate and modafinil have been studied as potential fatigue therapies in PD patients, with varying results.134–136 In a six-week comparison of methylphenidate and placebo in PD patients, the active treatment significantly reduced scores on the Fatigue Severity Scale (FSS) as well as general fatigue on the Multidimensional Fatigue Inventory (MFI).134 An eight-week study of modafinil, however, showed no differences from placebo on any dimension of the MFI in PD patients with significant fatigue.135 Similarly, in a nine-week comparison of modafinil and placebo, no significant changes were seen on the FSS.136

Most PD patients (up to 96%) present with loss of smell (anosmia).137 In fact, some experts consider anosmia to be an early marker for PD, although it is important to rule out other causes.138,139 In PD patients, anosmia has been associated with an increased risk for neuropsychiatric complications, including dementia.140,141 PD is one of many disorders that can damage or destroy the olfactory pathway, resulting in anosmia; the others include Alzheimer’s disease, brain aneurysm, diabetic hypoglycemia, multiple sclerosis, and Sjögren’s syndrome.142 There are no treatments for anosmia.143

CONCLUSION
The importance of managing the nonmotor features of PD cannot be overemphasized, as these symptoms may have significant effects on patients’ quality of life. Clinical challenges in managing the nonmotor features of PD include identifying the appropriate pharmacological and nonpharmacological therapies, and determining the patient’s responsiveness or exacerbations from existing dopaminergic treatments.3,13

REFERENCES


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