The Impact and Management of Nonmotor Symptoms of Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disorder diagnosed by the presence of bradykinesia and at least 1 of the symptoms of rigidity, resting tremor, or postural instability. It is increasingly recognized that nonmotor symptoms are common and can adversely affect quality of life, yet they often are not diagnosed and consequently are often untreated. Nonmotor symptoms include neuropsychiatric issues such as anxiety, depression, hallucinations, impulse control disorders, and cognitive impairment, as well as autonomic dysfunction, which may present as gastrointestinal, urinary, and sexual disturbances. Nonmotor symptoms also include excessive sweating, orthostatic hypotension, and sleep disturbances. Management of PD requires recognition of both motor and nonmotor symptoms as well as an understanding of the relationship between these symptoms and how they can be affected by treatments for PD. Therapy should be individualized for each patient, as treatments for the motor symptoms of PD can improve some nonmotor symptoms while they can worsen others. In many cases, symptom-specific treatments are necessary to control nonmotor symptoms of PD.

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For author information and disclosures, see end of text.

Parkinson's disease (PD) is a progressive, disabling neurodegenerative disorder of unknown cause, characterized by bradykinesia and at least 1 of the following: resting tremor, muscle rigidity, and postural instability.[1,2] In addition to the presence of these primary symptoms, which suggest parkinsonism according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria, the diagnosis of PD can be confirmed when other forms of parkinsonism and other diseases and causes are excluded and at least 3 of the following are present: unilateral onset, resting tremor present, progressive disorder, persistent asymmetry affecting side of onset most prominently, excellent response to levodopa, severe levodopa-induced chorea, levodopa response for 5 years or more, or clinical course of 10 years or more.[3]

Parkinson's disease is the second most common neurodegenerative disorder, after Alzheimer's disease.[4] The prevalence of PD is estimated to be 329 per 100,000 people, with an annual incidence ranging from 16 to 19 per 100,000 people.[1] The prevalence of PD increases with age, affecting about 1% to 2% of adults 60 years and older, and greater than 4% of adults 80 years and older.[5] As the elderly population grows, the incidence is expected to double by 2030 from the current estimates of 1 million patients in the United States and 5 million worldwide.[1,4] The annual economic impact of PD in the United States has been estimated at $10.8 billion, of which 58% is direct medical costs.[4] The annual direct medical cost per patient with PD is estimated to be between $10,000 and $12,500, more than double that of patients without the disease. Prescription drugs and long-term care account for approximately 14% to 22% and 41% of these costs, respectively. In addition, annual indirect costs, including lost productivity for patients and caregivers, are estimated at $9000 per patient.[4]

Although motor symptoms are diagnostic for PD, nonmotor symptoms are also prevalent and are often important determinants of quality of life (QOL) in PD.[5] Motor and nonmotor symptoms commonly associated with PD are summarized in the **Table**. The rising incidence of PD resultant from an aging US population will lead to clinicians increasingly encountering PD in their clinical practice. The high costs associated with PD, the expected rise in frequency, and the increasingly recognized importance of associated nonmotor symptoms highlight the necessity for increased understanding of all aspects of the disease and treatment options.

Table. Motor and Nonmotor Symptoms of Parkinson's Disease[1,3,4]

Cardinal Motor Symptoms
Bradykinesia (slowness of movement initiation with reduction of speed and amplitude of actions)
Muscular rigidity
Resting tremor
Postural instability
Nonmotor Symptoms
Neuropsychiatric disorders (depression, anxiety, psychosis/hallucinations, impulse control disorders)
Cognitive impairment (confusion; dementia; impairments in memory, executive function, and visuospatial skills)
Autonomic disorders (drooling, dysphagia, constipation, nausea, urinary dysfunction, orthostatic hypotension, excessive sweating, sexual dysfunction)
Sleep disturbances (fragmented sleep, insomnia, excessive daytime sleepiness, sleep disorders)

As such, this article will provide an overview of the nonmotor symptoms of PD and their treatment options.

Motor Symptoms

Motor symptoms are the hallmark of PD and there are multiple treatment options available. It is important to adequately treat motor symptoms, as many nonmotor symptoms are increased during "off" periods when PD medications are not controlling symptoms.[6] In other cases, PD medications can exacerbate some nonmotor symptoms, particularly neuropsychiatric and cognitive symptoms. Early treatment options include monoamine oxidase type B (MAO-B) inhibitors (rasagiline and selegiline), dopamine agonists (pramipexole and ropinirole), and the mainstay of PD treatment, carbidopa/levodopa. Less commonly, amantadine is used for mild symptoms; anticholinergics, particularly benztropine and trihexyphenidyl, have limited use due to a poor side effect profile.[7] Levodopa is generally used earlier in older patients, as dopamine agonists result in more neuropsychiatric and cognitive side effects, while dopamine agonists are often used in younger patients in an attempt to delay levodopa-induced side effects.[7] As symptoms progress, nearly all patients with PD will require levodopa therapy. However, motor complications such as dyskinesia (characterized by abnormal involuntary movements) and motor fluctuations (characterized by wearing-off, on-off, or unpredictable-off effects) are common side effects of levodopa.[8] These motor complications occur in up to 90% of patients with PD within 5 to 10 years after the initiation of levodopa.[9] Motor fluctuations may be managed by altering the frequency or dosage of levodopa, adding a catechol-O-methyltransferase (COMT) inhibitor (eg, entacapone, tolcapone) to decrease metabolism of levodopa and extend the levodopa effect, adding an MAO-B inhibitor (selegiline, rasagiline), or using a dopamine agonist (pramipexole, ropinirole).[10] Other than altering the frequency or dosage of levodopa and other PD medications, amantadine is currently the only pharmacological treatment option that has been shown to reduce dyskinesia.[11] In a recent review, complications of levodopa therapy and gait disturbances were the most important motor symptoms affecting QOL in patients with PD.[5]

Nonmotor Symptoms

Nonmotor symptoms are often not recognized and therefore remain untreated in many patients with PD. In 1 report, patients with PD reported an average of 11 nonmotor symptoms; however, on average, only 5 nonmotor symptoms were recorded in their medical charts.[12] A partial list of nonmotor symptoms related to PD is provided in the Table. The American Academy of Neurology has recommended that in addition to the regular assessment of PD motor symptoms, nonmotor symptoms should also be regularly assessed. Specifically, it was recommended that neuropsychiatric and cognitive assessments be performed annually, and that patients also be asked about autonomic and sleep disturbances annually.[13] Formal assessment of the nonmotor dimensions of PD can be accomplished clinically with a 30-item scale called the Nonmotor Symptoms Scale (NMSS). The NMSS has 9 dimensions, including cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal tract abnormalities, urinary tract abnormalities, sexual dysfunction, and miscellaneous symptoms.[14] The NMSS is a validated tool for rating frequency and severity of nonmotor symptoms in PD.[14,15] The Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) has also been validated in PD and includes an assessment of nonmotor symptoms of PD.[16] Although nonmotor symptoms of PD may be categorized in

many ways, for purposes of this review, nonmotor symptoms will be categorized as follows: neuropsychiatric, cognitive, autonomic, and sleep dysfunction.

Since PD frequently occurs in an older population, the question of whether nonmotor symptoms of PD differ from normal aging has been raised. A recent case-control study addressed this issue by studying 174 patients with PD and 128 age-matched controls.[17] In that study, the frequency of nonmotor symptoms and the NMSS scores were significantly greater among patients with PD in all domains, including cardiovascular disease, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal tract abnormalities, urinary tract abnormalities, urinary dysfunction, sexual dysfunction, and miscellaneous symptoms. Additionally, the group of patients with PD demonstrated no effect of age and minimal effect of sex on nonmotor symptoms, while in controls, symptoms increased with age, and sex failed to demonstrate an effect. These results suggest that nonmotor symptoms of PD are disease-specific and not purely a result of normal aging.[1,7,17] In addition, nonmotor symptoms significantly impact QOL.[5,12]

Neuropsychiatric Disturbances

Depression can occur in up to 80% of patients with PD and, according to a recent systematic review, is the most consistently identified determinant of adverse health-related quality of life (HRQOL) in patients with PD.[5,18] The review of included studies determined that depression was a significant predictor of QOL.[5] Depression is often untreated, as symptoms can be mistaken for symptoms of PD such as loss of appetite, lack of motivation, slowed movement, slowed thinking or confusion, and sleep disturbances.[9] It is important to also interview the family/caregiver, as patients often do not recognize that they are depressed. Counseling or other forms of psychotherapy can be helpful but it is generally believed that depression is both psychological and organic in PD; therefore, treatment with medication is often required.[9] Depression can be worsened during "off" time, so it is important to make sure that PD symptoms are well controlled. Early randomized studies of antidepressants for the treatment of depression in PD included the tricyclic antidepressants (TCAs) amitriptyline and nortriptyline, and the selective serotonin reuptake inhibitors (SSRIs) citalopram and fluvoxamine. A Cochrane review summarized these randomized studies, and found insufficient data to determine efficacy and safety of these antidepressants.[19] Adverse effects were minimal in the trials; however, visual hallucinations and confusion were noted.[19] These are currently the most common treatments for depression in PD; however, in some cases other antidepressants such as bupropion, mirtazapine, and venlafaxine (recently evaluated in the Study of Antidepressants in Parkinson's Disease [SAD-PD] trial,[20] sponsored by the National Institute of Neurological Disorders and Stroke) can be beneficial. Finally, studies have shown that the dopamine agonist pramipexole may also improve depression in some patients.[21]

In a systematic review of HRQOL in PD, anxiety and fatigue predicted adverse QOL in 83% and 80% of studies, respectively.[5] Anxiety often occurs in combination with depression and can manifest as excessive nervousness or worrying, generalized anxiety disorder, panic attacks, or obsessive compulsive disorder. Anxiety can be increased during "off" periods. In 1 study, 66% of patients with PD experienced anxiety and 88% of the time the anxiety occurred during a medication "off" period.[6] Optimizing dopaminergic therapy to limit "off" time may be beneficial, but the use of benzodiazepines in low doses or SSRIs may also be helpful.[10] Benzodiazepines may cause fatigue or drowsiness, especially in higher doses.

Hallucinations, which are most commonly visual, and psychosis occur in 25% to 30% of patients with PD, and may be related directly to the disease or to anti-PD medications.[11,22,23] It is important to initially assess the patient for other potential causes of hallucinations such as urinary tract or other infections and dehydration, as well as non-PD medications known to cause neuropsychiatric symptoms, such as psychotropics and anticholinergics. Anticholinergic agents, amantadine, dopamine agonists, and COMT inhibitors may worsen hallucinations, and if there are no obvious causes for the psychotic symptoms, these medications should be reduced or eliminated if possible.[11,23] The atypical antipsychotics clozapine and quetiapine are preferred for use in PD due to their predominant affinity for D_1, D_4, and serotonergic receptors, with low affinity for D_2 receptors.[10,23] Despite promising results from open-label studies, a systemic review of randomized controlled trials involving quetiapine demonstrated disappointing results.[24,25] In practice, however, clinicians still prefer quetiapine, since it does not appear to worsen motor function and has a favorable safety profile compared with clozapine, which is associated with agranulocytosis and requires monitoring.[24,25] Other atypical antipsychotic agents as well as the typical antipsychotics such as haloperidol and similar medications should be avoided due to worsening of motor function.[10] Finally, in some cases, cholinesterase inhibitors or antidepressants may be beneficial.

Impulse control disorders (ICDs) occur in up to 17% of patients with PD,[26] especially in those taking dopamine agonists. ICDs include a group of disorders resulting from

a failure to resist an urge, drive, or temptation to perform an act considered to be harmful to the patient or others. Hypersexuality, compulsive buying, binge eating, pathological gambling, and punding (a complex behavior involving repetitive meaningless activities) have all been reported.[21] Pathological gambling, which occurs in up to 6% of patients with PD, is the most well-studied form of ICD.[25] Indirect evidence suggests that pathological gambling is more common with dopamine agonists than with levodopa.[27] Gambling, which usually occurs in patients who have not previously had a gambling problem, appears within a few months of initiating therapy, and may occur at any dose of dopamine agonists, but is more likely at higher doses.[27] When ICDs are present, dose reduction or discontinuation of the dopamine agonist may be required; however, with a dose reduction or discontinuation of the dopamine agonist, a dose increase or initiation of levodopa or another PD medication may be necessary to treat motor symptoms.[22,27] In 1 study, dopamine agonists were significantly reduced or discontinued in 15 patients with PD who experienced ICDs; an MAO-B inhibitor was added, and 84% of patients reported a reduction or complete resolution of the ICD.[28] In some cases, a TCA or norepinephrine reuptake inhibitor (eg, mirtazapine, venlafaxine) may be required when mood changes occur.[23]

Cognitive Impairment

According to a systematic literature review published by the Movement Disorder Society, mild cognitive impairment is present in 19% to 38% of patients with PD who do not have dementia.[29] It is estimated that dementia will eventually develop in 75% of patients within about 10 years. Cognitive deficits appear to be more prevalent in executive functions (eg, information processing speed, impaired planning, working memory) than in episodic memory storage and language. Visuospatial and attentional deficits have also been associated with PD.[29] As in other forms of dementia, even mild cognitive defects in PD are associated with poor QOL.[5] Furthermore, there is a strong relationship between PD-related cognitive impairment and neuropsychiatric issues such as depression, hallucinations, and psychosis.

Treatment of cognitive dysfunction generally begins with an evaluation to rule out other potential causes of cognitive impairment or confusion including depression, infection, dehydration, and sleep disturbances. All medications should be reviewed and non-PD medications known to cause cognitive disturbances should be reduced or eliminated if possible. PD medications may actually worsen cognitive function, so it is important to tailor therapy to achieve motor control while minimizing cognitive decline.[10] Therefore, if no other potential causes of cognitive impairment are present, PD medications should be slowly reduced and eliminated in the following order: anticholinergics, amantadine, dopamine agonists, COMT inhibitors, and finally, MAO-B inhibitors. Cholinesterase inhibitors as well as memantine may provide improvement in cognitive function in patients with PD.

In a 2008 Cochrane review evaluating randomized, double-blind, placebo-controlled trials of cholinesterase inhibitors (ie, tacrine, donepezil, galantamine, rivastigmine) in PD dementia, 1 study of rivastigmine was identified for inclusion. The study included 541 patients, and the main outcome measure, the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog), improved by 2.5 points relative to placebo. Rivastigmine is the only cholinesterase inhibitor approved by the Food and Drug Administration (FDA) for the treatment of cognitive dysfunction in PD. However, in the trial, rivastigmine was associated with a 3.25-fold increase in nausea, 2.8-fold increase in tremor, and 11.66-fold increase in vomiting.[30] A smaller study evaluated donepezil and noted improvement in memory; however, 4 of the 7 patients treated with donepezil (57%) withdrew due to adverse effects.[31] Adverse effects of cholinesterase inhibitors, such as diplopia, constipation, nausea, urinary frequency, increased tremor, gait impairment, and falls, appear to be due to peripheral cholinergic effects.[31] In a meta-analysis of 54 randomized controlled trials of cholinesterase inhibitors and memantine, cholinesterase inhibitors were associated with a greater risk of syncope than placebo, but not falls, fracture, or accidental injury. In contrast, memantine was associated with fewer fractures, without effect on other events.[32] A recent study of more than 13,000 participants documented that medications with definite or possible anticholinergic properties were associated with greater cognitive decline and mortality, after adjusting for sex, education level, social class, number of nonanticholinergic medications, number of comorbid conditions, and cognitive performance at baseline.[33] These results suggest that cholinesterase inhibitors may be associated with improved cognition; however, anticholinergic medications are associated with cognition impairment and are rarely used in the treatment of PD.

Autonomic Dysfunction

Autonomic symptoms include gastrointestinal dysfunction such as drooling, dysphagia, nausea, constipation, urinary dysfunction, orthostatic hypotension, sexual dysfunction, and thermodysregulation.[9] A recent cross-sectional study reported that drooling was among the most important determinants of HRQOL in patients with PD.[34] Drooling, also known as sialorrhea, is a symptom of PD observed in a majority of patients

and is a byproduct of dysphagia, rather than an overproduction of saliva.[35] The forward head posture and open mouth often observed in more advanced PD also contribute to drooling. Speech and swallowing therapy can be beneficial in helping to improve posture and teach good swallowing techniques. Chewing gum or sucking on hard candy can increase swallowing and consequently reduce drooling. If drooling occurs primarily during the medication "off" state, increasing PD medications can be beneficial. Traditionally, anticholinergic agents or antihistamines have been used; however, their effectiveness is uncertain. A study of botulinum toxin B for sialorrhea demonstrated effectiveness in reducing drooling severity and frequency, without worsening dysphagia, although dry mouth and gait disturbances were noted.[35] Dysphagia is linked to aspiration, malnutrition, weight loss, and dehydration, and thus may increase the risk of mortality.[10]

Other frequently experienced gastrointestinal complications include nausea and constipation.[22] Nausea and vomiting may be related to dopaminergic therapy. If nausea results from impaired gastric motility, then levodopa absorption is likely to be impaired. Since levodopa is absorbed in the intestines, a prokinetic agent (eg, domperidone; although not currently available in the United States) or addition of carbidopa will improve nausea and levodopa absorption.[8] Nausea may also be minimized by slow dose titration when initiating a new dopaminergic medication. In some cases, PD medications may need to be reduced, particularly dopamine agonists. It is important to note that dopamine antagonists such as metoclopramide and prochlorperazine should not be used, as they can worsen PD symptoms. Constipation, which is experienced by up to 60% of patients, may also result from impaired gastrointestinal motility or dehydration, and may be treated with standard therapies. The most common therapies include increased dietary fiber and fluid intake, increased exercise, and laxatives or stool softeners, if needed.[10,22]

Nocturia is often the initial urinary problem, and is a common complaint, occurring in over 60% of patients with PD. Patients should be advised to eliminate liquids in the evening. Urinary urgency, frequency, and incontinence become more common as the disease progresses. The most common reason for urinary frequency and urgency is detrusor overactivity.[36] When urinary problems are reported, it is important to rule out urinary tract infections and prostate issues. If they occur primarily during the "off" state it may be beneficial to adjust PD medications to reduce "off" time. Anticholinergic agents (eg, tolterodine, trospium chloride, oxybutynin) may be beneficial.[36]

The most common cardiovascular feature of PD is orthostatic hypotension, a drop in systolic blood pressure of at least 20 mm Hg and diastolic blood pressure of at least 10 mm Hg within 3 minutes of standing up. Orthostatic hypotension is most common in more advanced disease. Symptomatic orthostatic hypotension presents with dizziness, lightheadedness, cloudy thinking, generalized weakness, or syncope.[37] Adequate hydration is mandatory; an intake of at least 2 liters of water and 8 grams of salt daily should be ensured.[10] Waist-high support hose and elevation of the head of the bed can be helpful. If orthostasis becomes problematic, antihypertensive therapy and diuretics should be limited or eliminated if possible. The mineralocorticoid fludrocortisone or the alpha-adrenergic agent midodrine may be used if orthostatic hypertension is severe. If response to treatment is poor, a reduction in dopaminergic medications may be warranted.[7,22] Amantadine should also be avoided to limit the risk of orthostatic hypotension.[7] In addition, a recent study, which evaluated the effect of carbidopa/levodopa with or without entacapone, demonstrated an increased risk of myocardial infarction with entacapone, suggesting the potential for an increased risk of cardiovascular events in patients taking COMT inhibitors.[38]

Thermodysregulation has been reported in up to 64% of patients with PD and involves intolerance to cold and heat, as well as excessive sweating.[39] Excessive sweating occurs most commonly either during the "off" state or when the patient is experiencing dyskinesia, and can also be associated with other autonomic symptoms, particularly constipation. Adjustments to PD medications to reduce motor complications can be beneficial. Botulinum toxin injections may reduce sweating. Deep brain stimulation has also been shown to be beneficial, but likely due to a reduction in levodopa-induced motor complications.[40]

Sexual dysfunction is common in PD, affects both men and women, and can include diminished arousal, drive, or orgasm. However, the most common sexual problem is erectile dysfunction.[41] In addition to PD, neuropsychological issues as well as medications for depression and cardiac problems can cause sexual dysfunction. Therefore, all medications should be reviewed, potentially offending agents should be reduced or eliminated if possible, and neuropsychiatric assessments should be completed. In some cases, sexual dysfunction can be worsened during "off" periods, so adjustments of PD medications may be helpful. Finally, phosphodiesterase-5 inhibitors (eg, sildenafil, vardenafil, tadalafil) can be prescribed.

Sleep Disturbances

Sleep disturbances, seen in up to 98% of patients with PD, may manifest as sleep fragmentation, insomnia, exces-

sive daytime sleepiness, altered sleep-wake cycle or rapid eye movement (REM) sleep behavior disorder (RBD), and other sleep disorders.[10,22] These sleep problems may be linked to PD symptoms, PD medications, or an actual sleep disorder.[42] All patients should be educated on good sleep hygiene and should try to maintain a regular sleep schedule. In addition, neuropsychiatric issues should be evaluated, as depression, anxiety, and dementia can result in sleep disturbances. Fragmented sleep may be a result of "off" symptoms during the night, and therefore a trial of extended-release carbidopa/levodopa or a long-acting dopamine agonist may be considered; however, in some patients, dopamine agonists can cause insomnia.[43] If these adjustments are not beneficial, the patient should undergo a formal sleep evaluation to rule out a sleep disorder such as sleep apnea, RBD, periodic limb movements of sleep, or restless legs syndrome. If sleep is interrupted by nocturnal urinary frequency, reduction of liquid intake prior to bedtime may be helpful, or anticholinergic medications may be used (unless patients have memory problems or other contraindications).[10] In addition, sleep aids such as hypnotics (eg, zolpidem, zaleplon, eszopiclone, ramelteon, etc) or other sedating medications (mirtazapine, trazodone, nortriptyline, etc) may be helpful.

Higher doses of dopaminergic agents are known to be associated with excessive daytime somnolence, which may be more pronounced with dopamine agonists than with levodopa.[7,43] In fact, sudden onset of sleep (sudden sleep during the day without a prodrome) has been reported with pramipexole and ropinirole, and may be especially problematic in younger patients who drive.[43] Dopaminergic agents may need to be reduced or discontinued if this occurs.[43] In 1 randomized, placebo-controlled trial, modafinil (200 mg daily) improved daytime sleepiness in 35% of evaluated patients with PD without worsening UPDRS scores.[44] Methylphenidate may also be considered for daytime sleepiness.[43]

Summary

Nonmotor symptoms of PD may occur early in the disease process. The impact of nonmotor symptoms on HRQOL can be significant, suggesting that early recognition, diagnosis, and management of PD is critical to improving patient outcomes. It is also important to recognize that the treatments for motor and nonmotor symptoms may impact the disease process, and vice versa. Clinicians must understand the symptoms of PD, the benefits and adverse effects of management strategies, and the impact of regimen changes on symptoms in order to fully contribute to improving patient outcomes.

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