Nonmotor Manifestations in Parkinson Disease

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**Background:** Although the diagnosis of Parkinson disease (PD) still relies mainly on the appearance of its classical motor features of resting tremor, rigidity, bradykinesia, and postural instability, nonmotor manifestations in PD are now recognized as an integral component of this multisystem disorder.

**Review Summary:** Nonmotor complications in PD occur commonly. The current understanding of cognitive dysfunction; neuropsychiatric manifestations including psychosis, impulsive control, and compulsive disorders; depression, anxiety and apathy; autonomic complications such as hypotension, erectile dysfunction, and urinary complications; sleep disorders and other nonmotor manifestations are summarized in this review.

**Conclusion:** Nonmotor complications often carry a greater impact than motor features in PD. Therefore, heightened awareness and proper recognition of these features are critical in improving a Parkinson patient’s quality of life.

**Key Words:** nonmotor symptom, Parkinson, dementia, behavioral, psychiatric, sleep disorders, autonomic dysfunction

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To date, the diagnosis of Parkinson disease (PD) is made primarily by the presence of its cardinal motor manifestations: bradykinesia; rigidity; resting tremor; and later on, gait dysfunction and postural instability. Moreover, during the course of the illness, motor complications such as dyskinesias and dystonic postures can appear to be the most prominent clinical manifestation of the illness. However, nonmotor features of PD have risen to the forefront of research and clinical care in the past 2 decades, and in some way, has helped elucidate the current emerging pathogenesis of the disorder. Neuropsychiatric, cognitive, sleep, dysautonomic, and even skin changes and sensorial manifestations are among the long list of nonmotor symptoms experienced by most PD sufferers. In most cases, nonmotor symptoms contribute to a greater source of disability and poorer quality of life (QOL) than motor complications. Moreover, nonmotor symptoms can be prominent in the “off” medication state; they may be an intrinsic feature and pervade regardless of the medication state; or, they can be an iatrogenic complication of pharmacologic and surgical intervention for the treatment of motor symptoms of PD.

**COGNITIVE DYSFUNCTION**

**Dementia**

Although cognitive dysfunction can be appreciated early on, especially with detailed neuropsychological testing, it is still often labeled as a late-onset feature of PD. One study has shown that cognitive decline appeared early in most PD patients and paralleled motor progression independent of disease duration. The authors hypothesized that early cognitive impairment was a less tangible feature (compared with the more visible signs of tremor and bradykinesia, albeit mild), therefore, cognitive impairment often was appreciated much later and its progression is not as tracked as the evolution of motor symptoms. Most cross-sectional studies find significant cognitive impairment in about 40% of the PD population. However, in longitudinal studies, when PD cohorts are followed long enough, cognitive decline can affect up to 80% or more of patients. Reported risk factors for PD dementia include patients with advanced age, predominantly akinetic-rigid forms of PD, presence of psychosis, and less robust response to levodopa.

The etiology of dementia in PD is not yet perfectly understood. Among the implicated etiologies that may play a role is the existence of α-synuclein, β-amyloid plaque, Lewy body inclusions, and deficits in cholinergic connections. Functional and cognitive studies have shown that both frontal and temporal lobes are preferentially atrophic in patients with advanced stages of PD. Earlier in the illness, subtle cognitive dysfunction and behavioral changes may seem in part because of the involvement of the ventromedial prefrontal area, limbic circuit, and amygdala. This impairment of cognitive function and emotional processing often translates into riskier decisions and loss of opportunities, or unawareness of gains in comparison with normal controls. Disorders of attention, praxis, and executive function, amnesia, and visual and verbal recognition...
may follow as the disease progresses. As mentioned, these behavioral and cognitive changes often run in parallel with changes in motor aspects of the disease. Nonmotor symptoms such as delusions, hallucinations, sleep disorders, and behavioral dyscontrol often become comorbid conditions.

Dementia is an important cause of mortality and loss of independence, and a significant contributor of patient and caregiver burden. Moreover, cognitive impairment in PD can be caused or worsened by medications (including all PD medications). In addition, metabolic, infectious, and vascular disorders can occur in the elderly PD patient and worsen their cognitive status. Cognitive dysfunction is, perhaps, the single greatest limiting factor for the optimal treatment of motor symptoms in PD. When dementia ensues, often PD medications need to be simplified. Adjunctive PD medications may need to be eliminated, typically leaving only levodopa to control motor symptoms.

Medications commonly used for dementia in PD include donepezil, rivastigmine, and galantamine (cholinesterase inhibitors), and memantine (N-methyl-D-aspartate receptor antagonist). However, rivastigmine is the only Food and Drug Administration-approved drug for PD dementia in the United States.

In a large multicenter, multinational placebo-controlled trial, rivastigmine was shown to be safe and well tolerated, with a modest improvement in cognitive performance based on the Alzheimer Disease Assessment Scale-Cognitive subscale and the Clinician’s Interview-Based Impression of Change. The most common motor adverse event noted was a transient increase in tremor. Rarely was significant worsening of motor impairment seen. It also has the advantage of having transdermal application, which has been shown to provide better tolerance and fewer side effects than the oral formulation. In addition, rivastigmine has also been shown to possibly improve hallucinations and other behavioral dysfunction in PD.

Other studies have also shown donepezil to provide a modest effect in cognitive function. Similarly, it is well tolerated, although gastrointestinal side effects and tremor exacerbation may be experienced. Galantamine has also been studied in small groups reporting modest benefit in cognitive scales, including improvement in hallucinations, anxiety, and sleep disorders. Nausea and gastrointestinal side effects can sometimes limit its use.

Memantine, an NMDA receptor antagonist, also acts like a weak dopamine type 2 receptor agonist. Improvement in cognition and good tolerability has been reported. Because of its prodopaminergic activity, it may theoretically produce additional motoric benefit; although encouraging results have recently been reported, double-blind, randomized trials are lacking.

NEUROPSYCHIATRIC MANIFESTATIONS

Psychosis

Psychosis in PD has been aggressively investigated in the past few decades. A number of recent studies have documented the wide prevalence of psychotic symptoms in PD. The lifetime prevalence of psychosis in PD can range from 25% to nearly 50% in a community-based and clinic-based studies, respectively. Goetz and Stebbins previously reported on the strong association between hallucinations and nursing home placement, including its unfortunate consequence of increased mortality. Although cognitive decline is the consistent major risk factor for development of psychosis; other reported associated factors include older age, longer duration of illness, severe motor impairment, presence of depression and rapid eye movement (REM) sleep disorder, significant autonomic impairment, and poor visual acuity. Visual hallucination is the most common psychotic feature, occurring in approximately 30% to 40% of PD patients, and is typically experienced late in the disease, often being reported 10 or more years after the initial diagnosis. Initially, the term “benign hallucination” is often used, describing nonthreatening visual hallucinations, manifesting within a context of a clear sensorium and preserved insight. Insight may be lost as the disease progresses or when cognitive dysfunction ensues, and symptoms may become more threatening. In general, visual hallucinations are well-formed, often consisting of people, animals, and, less frequently, inanimate objects. Hallucinations generally occur in dim lighting conditions or at the end of the day, lasting only for seconds or minutes, occurring intermittently at least once a week but often much more frequently. “Minor hallucinations” can occur in up to 40% of patients. Examples include “presence hallucinations” characterized by a vivid feeling that a person or animal is closely present, and “passage hallucinations” described as a sensation of a person or animal (typically a rodent or an insect such as a cockroach) quickly passing in the peripheral vision. Other hallucinations can also be experienced, such as auditory and tactile hallucinations, but are less likely to be seen in isolation. Approximately 8% to 13% of the patients describe auditory hallucinations occurring together with visual hallucinations. These are often simple in nature such as whispering or ringing but some studies have described complex phenomena with threatening voices. Tactile hallucinations are often characterized by the feeling of close contact with small animals or being touched by someone else.

Delusions are often more clinically significant, necessitating urgency in treatment and affect about 8% of treated patients with PD. Delusions are commonly paranoid, typically consisting of beliefs of abandonment or spousal infidelity. Grandiose, somatic, persecutory, and religious delusions, which are typical of schizophrenia, also have been reported, but are less likely to occur as a theme in PD delusions. Interestingly, the occurrence of delusions as opposed to hallucinations have been associated with younger age at onset of PD.

Behavioral manifestations, hallucinations in particular, and sleep disorders are common conditions of chronic PD and its treatment; however, the relationship remains controversial. In 1 study, severe sleep disorders were found to be the main factor predicting the onset of hallucinations, and the presence of REM behavior disorder (RBD) was found to be at 2.7 higher risk of manifesting hallucinations and delusions. “A continuum hypothesis” proposed by Moskowitz and colleagues suggested that medication-induced psychotic symptoms in PD patients usually progress from sleep alterations to frank hallucinations. The authors found that 61.3% of all hallucinations were associated with preexistent or concurrent vivid dream phenomena. To investigate this relationship, another study consisting of 174 patients evaluated 3 behavioral abnormalities including sleep fragmentation, altered dream phenomena (including vivid dreams, nightmares, and reports suggestive of RBD or night terrors) and hallucinations/ illusions. In this study, the authors found that altered dream phenomena were the core relationship and were significantly associated with sleep fragmentation and hallucinations, whereas as a significant relationship was not seen with the others. Thus, the authors proposed that altered dream phenomena are of importance, whereas the others may be part of the sleep-hallucination behavioral continuum.
In contrast, a 6-year prospective longitudinal study by Goetz et al revealed that hallucinations and sleep disorders are different in their patterns of progression. Hallucinations appeared to be chronic and progressive over time, whereas sleep disorders fluctuated widely among the patients and time points without evidence of progression in severity. Thus, sleep alterations were not necessarily a strong predictor of the occurrence of hallucinations. Similarly, a recent study by Lavault et al demonstrated that the presence of RBD is neither a marker of severe PD nor a predictor of increased propensity for progression. Still another study by Postuma and colleagues also did not support a strong relationship between RBD and psychosis in PD once strict criteria measuring hallucinations were applied. The results showed no significant increase in hallucinations between PD patients with or without RBD.

Management of hallucinations and psychosis in PD should be balanced between controlling the psychosis without worsening motor symptoms. Psychosis can improve by decreasing or eliminating anti-PD medications or instituting antipsychotic medications. However, the antipsychotic medications may be at the risk of worsening parkinsonism. Despite the lack of well-designed comparative studies on determining which and how anti-PD agents should be eliminated in the setting of PD psychosis, most authorities “peel off” anti-PD medications in the following order, based on their motor efficacy and their propensity to cause psychosis: anticholinergics, amantadine, MAO-inhibitors, dopamine agonists, COMT-inhibitors, and then, finally, levodopa.

Dopamine has been implicated as the principal neurotransmitter in the development of PD psychosis. Thus, atypical antipsychotic (AA) agents, with “milder” dopamine blocking action (thereby minimizing extrapyramidal side effects), have played a central role in the treatment of psychosis in PD. A meta-analysis of the Quality Standards Subcommittee of the American Academy of Neurology concluded that among the AAs available, clozapine was determined “efficacious without the risk of worsening parkinsonism”; quetiapine was “probably efficacious and would probably not worsen parkinsonism”; clozapine was “probably efficacious and would probably not worsen parkinsonism,” but olanzapine was determined as “ineffective with a higher likelihood of worsening motor symptoms.” Fewer reports on other AAs such as risperidone, ziprasidone, and aripiprazole prevent definitive conclusions about their use in this population.

In addition to dopamine, the role of acetylcholine has also been investigated. Previous studies, with improvement of psychosis as a secondary or tertiary outcome measure, have suggested that rivastigmine, donepezil, and memantine may be an alternative to AA for the treatment of psychosis in PD, with perhaps a better tolerability profile, especially among the cognitively impaired PD population.

Impulsive and Compulsive Disorders

Impulse control disorders (ICDs) are characterized by the inability to resist the drive to act; a desire or an irrational want to produce self-gratification but at the same time producing suffering to relatives thereby compromising their relationships and impairing social and work-related functioning.

ICDs include hypersexuality, gambling, compulsive shopping, binge eating, and, recently, impulsive smoking have been reported. Across different studies with thousands of patients, ICDs have been associated with the use of dopamine agonist medications. However, nowadays we find new evidence that ICD is not seen exclusively with dopamine agonist use. It is more prevalent in males, patients with early onset of the disease and right-sided onset of motor manifestations, with past or actual medical history of depression or bipolar disorder, disinhibition, irritability, and appetite disorders. Dopaminergic activity in the ventral and dorsal striatum, nucleus accumbens, and mesolimbic network may play a role in the development of impulsivity and compulsive disorders. Although dopamine agonists are involved in ICD, higher doses of levodopa are implicated in compulsive disorders.

Compulsive eating or binge eating disorder is defined as the intake of larger amounts of food than normal to relieve hunger or fulfill metabolic requirements. This disorder has been reported to be associated with decarboxylase inhibitor and dopamine agonist intake. Zahodne and colleagues, in a survey of 96 consecutive PD patients seen at a Movement Disorders Center, found that 9.6% met criteria for “overeaters” but only 1% for true binge eaters. The authors concluded that binge eating disorder was not highly prevalent in PD, but subclinical binge eating was as common (8.3%) as other impulsive-compulsive spectrum behaviors. They also found that binge eating often co-occurred with other ICDs, as 67% of overeaters met psychometric criteria for another ICD, compared with only 29% of nonovereaters; and that overeating may also be associated with subthalamic deep brain stimulation (DBS). They recommended that future studies should examine whether binge eating is related to post-DBS weight gain.

The true prevalence of hypersexuality is difficult to ascertain. One study found that 4.3% of PD patients met criteria for hypersexuality. Hypersexuality can be so severe as to result in sexual abuse of close persons including spouses and children. Examples include compulsive masturbation, prostitution, internet pornography, and even zoophilia (ie, sex involving animals). Hypersexuality has been reported with dopamine agonist use such as pramipexole or ropinirole, but is not limited to these classes of drugs. MAO-B inhibitors also can produce hypersexuality. Treatment consists of reduction of the dopamine agonist, MAO-B inhibitor and sometimes the addition of antipsychotics, antidepressants, or hormonal inhibitors.

Compulsive disorders have been described as a class distinct from impulse control disorders, and involve repetitive, stereotyped and well-ordered acts to decrease inner anxiety and avoid harm. These traditionally include punding and also dopamine dysregulation syndrome (DDS). Punding is a stereotyped, repetitive, and generally nonproductive manipulation.
of things such as examination of mechanical, electrical or electronic devices, or grooming, hoarding, writing, lining up of pebbles or rocks, etc., without purpose or producing pleasure. However, if the activity is interrupted it leads to severe annoyance and irritability.69 Perhaps hobbyism can be considered as a milder, more productive form in the same class of disorders. The prevalence of punding varies from 1.4% to 14% depending on the cohort and the diagnostic criteria used.69 Although the total “levodopa daily burden” has been traditionally implicated in punding, 1 survey has reported the use of dopamine agonists as associated with this condition.91 Moreover, punders are often sleep deprived, perhaps because of the repetitive activity lasting through the night. Decreasing the amount of PD medication can alleviate this disorder but in severe or refractory cases adjunctive medication may be needed. Selective serotonin reuptake inhibitor (SSRI) medications92 and AAs93 have been reported to be helpful. However, there are similar reports showing that quetiapine may worsen punding in patients with PD.94 DDS is an iatrogenic disorder defined by an excess use of dopaminergic medication, in particular with levodopa, or an addictive pattern to treat parkinsonian manifestations with excessive medication. The term DDS has also been used as an umbrella term to include all types of ICD and compulsive disorders seen in PD.95 In DDS, patients usually ignore the “on” state and dyskinesias and request more medications. They are reluctant to reduce medications despite good control of motor symptoms. They are often demanding, depressed, anxious, and irritable if the medication is not provided, often impairing their family, social, or work environment.96 The recognition (or admission of its presence) and the treatment of impulsive and compulsive disorders may require the combined expertise of a psychiatrist and a clinical psychologist.

Depression

Depression can affect up to 72% of patients with PD in the first 10 years of the disease, and is perhaps the most frequent psychiatric manifestation.97 Usually depression is mild to moderate, and can be present years before motor symptoms are manifested.98 Studies have also shown depression to be correlated with the severity of motor symptoms, stage of the disease, cognitive dysfunction, anxiety, psychosis, and level of functioning.99–101 Occasionally, depressive symptoms can be a nonmotor symptom of an “off” medication state.

Diagnosis of depression in PD is not always straightforward. The core and associated features of depression, such as cognitive decline, psychomotor retardation, lack of facial expression, apathy, sleep dysfunction, loss of appetite, loss of weight, lack of energy, and fatigue are intrinsic features of PD and can also be seen in nondepressed PD patients.102–104 Patients with depression and PD experience less sorrow and self-blame, and more anxiety, irritability, cognitive compromise, and suicidal ideation compared with depressed non-PD patients. One survey has shown that clinicians often fail to recognize depression and other behavioral dysfunctions in PD, and may benefit from the use of patient/self-administered behavioral scales to assist in their recognition.105

Treatment must be individualized in every patient according to the severity of symptoms and potential side effects of the medication. In some cases, proper adjustment of dopaminergic therapy may be enough to treat the symptoms. Currently, SSRI such as sertraline,106 escitalopram, citalopram, and paroxetine are widely used. Because of better tolerance and lesser side effects, the SSRIs are usually preferred as the first-line treatment. Mirtazapine (a noradrenergic and serotonergic antidepressant) can be useful in depression, and in low doses can also alleviate insomnia and anxiety. Escitalopram, paroxetine, bupropion (norepinephrine reuptake inhibitor), and buspirone (a serotonin 5-HT1A receptor partial agonist) can be helpful in patients with concomitant anxiety. Duloxetine and venlafaxine, dual serotonin and noradrenaline reuptake inhibitors, have also been widely used in depression. Duloxetine can also be helpful in chronic pain, and in Europe is approved for stress urinary incontinence.107 Tricyclic antidepressants (TCAs) are also effective, although they may produce anticholinergic side effects such as cognitive decline, delirium, visual and bladder disturbances, and hypotension.108 However, alternatively, tryclic agents can be helpful in sleep problems, drooling, and bladder hyperactivity, commonly seen in PD.

There have been few recently reported randomized trials on PD depression. One study showed that amitriptyline (a TCA) was as beneficial as sertraline (an SSRI).109 Another double-blind randomized-controlled study on PD depression showed an initial faster response using desipramine compared with citalopram, although after 30 days the efficacy was similar in both groups compared with placebo. The authors did recognize the side effects of desipramine.110 In contrast, Menza et al also found a better response to depression in patients with PD using nortriptyline compared to paroxetine or placebo which was sustained throughout the study.111 However, this study had a high dropout rate. This raised the possibility that in an intention-to-treat study with high dropout rates for both treatment arms, the cohort randomized to the treatment arm known to produce earlier symptomatic benefit (such as the TCAs) might show superiority (because the earlier improvement of the TCA would have been recorded and “carried forward” despite some subjects dropping out, whereas similar patients on the SSRI would not have experienced this effect if they had dropped out at a similar point in the study).112 Recently, dopamine receptors type 2/3 agonists including pramipexole have been reported to alleviate depressive symptoms in a randomized, placebo-controlled, double-blinded fashion, over and above the motor improvement they provided to PD patients.113 Previous studies reported the superiority of pramipexole compared with sertraline in patients with PD and without motor complications.114 Similarly, ropinirole has been reported to have antidepressant and anxiolytic properties in patients with PD.115

In patients with a refractory response to pharmacological options, cognitive behavioral therapy, transcranial magnetic stimulation116,117 or electroconvulsive therapy may be alternative treatments.118 In patients with major depression and persistence of symptoms, patients may need the combination of pharmacotherapy and psychotherapy.119 DBS is a promising tool for treatment of patients with resistant and persistent depression.120

Anxiety

On the basis of epidemiological studies that utilized the DSM-IV criteria, anxiety disorders were highly prevalent in patients with PD, affecting about 40% of the population.121 Anxiety includes a wide range of disorders according to the DSM-IV-TR. These include panic attacks with or without agoraphobia, specific phobias, social phobia, obsessive compulsive disorder, posttraumatic stress disorder, anxiety disorder secondary to general medical conditions, substance-induced anxiety disorder, other anxiety disorders, and generalized anxiety disorder, all of which can affect a person with PD.
Anxiety, depression, fatigue, and apathy are prevalent features in PD that impair QOL; however, anxiety may be the behavioral dysfunction that causes the greatest impact.122 Scales such as the Beck Anxiety Inventory, the Hospital Anxiety and Depression Scale, the Zung Self-Rating Anxiety scale, the Spielberger State Trait Anxiety Inventory and the Hamilton Anxiety Rating Scale have been used to screen for and evaluate progression of anxiety.

In PD, anxiety is often not simply a reaction to the motor disability. Changes in neurotransmitters such as noradrenalin, serotonin, γ-aminobutyric acid and some peptides related to dopaminergic, noradrenergic, and serotonominergic pathways in the striatal motor system, nucleus acumbens, amygdala, locus ceruleus, and limbic structures seem to play an important role.123 Moreover, anxiety can be manifested as a premotor symptom in PD.124 However, anxiety is much more frequent in patients in the “off” state and those with motor fluctuations and dyskinesia, reaching a prevalence up to 66%.125 Sweating, flushing, and panic attacks can be present at the same time with anxiety in the “off” medication state.

Unfortunately, double-blind placebo-controlled randomized trials on anxiety in PD are wanting. Adjustments in the levodopa and dopamine agonist doses may be helpful in relieving anxiety associated to PD, but not in every case.126 In 1 study, 92% of PD patients with anxiety had concomitant depression. Therefore, medications such as SSRIs may be effective and helpful for both conditions. Benzodiazepines such as clonazepam or alprazolam can be added when panic attacks are present. Recent studies show contradicting evidence on the benefit of DBS surgery in relieving anxiety symptoms.127,128

Apathy
Apathy is characterized by a primary loss of motivation, loss of interest, and loss of effortful behavior that translate to a lack of productivity and reliance on others for activities of daily living. Apathy impacts behavioral, cognitive, and affective domains. This condition has a high prevalence in patients with PD, reported between 38% and 51%, compared with other movement disorders such as dystonia and other chronic disorders.129

Apathy can be misinterpreted as depression due to common symptoms such as lack of interest and alexythimia (ie, difficulty identifying or describing feelings) that are seen in both conditions. However, patients can experience apathy without having depression. Overall, a solid and consistent relationship between depression and apathy has not been supported.130 In 1 study, comparing the prevalence of apathy and depression among PD patients and patients with dystonia, whereas the prevalence of pure depression and apathy with depression was similar in both conditions, more PD patients were found to experience pure apathy compared with the patients with dystonia.130 From the physiological standpoint, Kulisevsky and colleagues also hypothesized that apathy is independent from depression. Apathy is commonly reported in patients with mesial frontal-anterior cingulate cortex connections and dopaminergic pathways, whereas depression has been implicated in alterations in the orbitofrontal-subcortical connections and serotonergic and noradrenergic pathways.131

Risk factors for apathy include age, male gender, higher depression scores, worsening of speech, motor skills with axial involvement, higher scores in the motor UPDRS, and dementia.132,133 Apathy, in general, is a syndrome that does not affect intellectual, emotional or conscious functions; however, some studies show that patients with apathy have associated impairments in specific cognitive functions such as executive functioning and verbal fluency.134 Thus far, there is no medication consistently shown to improve apathy. Amantadine, bromocriptine, dopamine agonists, levodopa, galantamine, donepezil, modafinil, and methylphenidate have been used in different studies without conclusive results.135–138

AUTONOMIC COMPLICATIONS

Hypotension
Orthostatic hypotension (OH) is a dysautonomic facet in PD that can also be aggravated by medications or activities. OH affects around 35% of patients139 but its prevalence can be as high as 58%, with an increased risk of mortality (OR, 1.64).140 It can be manifested with nausea, dizziness, lightheadedness, drowsiness, tiredness, loss of concentration, palpitations, and loss of consciousness. More importantly, OH increases the risk of falling.141 Hypotension tends to be aggravated with advancing age, increased temperatures, postprandial, or post-exercise states, and the intake of certain medications such as vasodilators, levodopa, TCAs, and alcoholic beverages. Currently, first-line measures in the treatment of hypotension include the correction of treatable causes and avoidance of situations that can lower the blood pressure. Other nonpharmacological actions include increasing intake of fluids and caffeine, adding salt in the diet, elevation of the head of the bed, and using an abdominal ring binder and/or compressive socks. Advising patients to slowly shift position from supine to sitting or standing is often beneficial. Medications such as midodrine, fluodrocortizone, pyridostigmine, and droxidopa have been used.142

Sweating
Abnormal sweating affects roughly 45% of the patients with PD. In advanced stages of the disease, prevalence may reach up to 75% of patients. Sweating is more frequent during “wearing off” phenomena, dyskinesias, motor fluctuations, and in the overnight hours.143 Hyperhydrosis usually involves the head, face, and trunk—areas where the sympathetic response is diminished. Apart from the sweating disturbance itself, patients can experience behavioral dysfunction such as depression and anxiety that may interfere with social interaction.144 Dysregulation of body temperature, facial flushing, dilation of blood vessels, and changes in skin color can be present with changes in sweating, but can also be an isolated feature.145

There is no clear pharmacological treatment for this bothersome symptom; however, control of motor fluctuations, and avoiding “wearing off” are proven to be the most helpful. If the “wearing off” phenomenon occurs at night, sustained release levodopa can be part of the solution. Other options include the use of cool, comfortable clothing, maintaining low room temperature, and increasing intake of fluids.

Nausea
Nausea is a common symptom in PD, and is more frequently related to medications rather than as an intrinsic feature.146,147 The use of metoclopramide is not recommended in patients with PD due to its potential to cause extrapyramidal side effects. Often times, very slow upward titration of PD medications (especially levodopa and dopamine agonists) and instructing patients to take them with meals can alleviate nausea. Lodosyn (pure carbidopa) is available for patients who
develop nausea with levodopa. Antiemetic medications that are generally free of extrapyramidal side effects include domperidone (not available in the United States), trimethobenzamide, and ondasentron.

Drooling, Sialorrhea, and Dysphagia

Disproportionate increase of saliva in the mouth cavity and sometimes in the pharynx, consequently impairing the ability to control oral secretions, can occur in up to 75% of PD patients; becoming more frequent in the late stages of the disease.\textsuperscript{48} The dorsal motor nucleus of the vagus and the peripheral autonomic nervous system have been implicated in drooling in PD.\textsuperscript{149} Sialorrhea can also be secondary to dysphagia and, rarely, due to the stooped posture of the patient, or hypersalivation produced by excessive activity of salivary glands.\textsuperscript{150} Drooling and dysphagia can be embarrassing, producing emotional and social consequences in up to 77% of patients affected.\textsuperscript{151} But drooling also affects speech, eating, and comfort in social situations.\textsuperscript{152}

Botulinum toxin types A\textsuperscript{153} and B\textsuperscript{154} have been demonstrated to be viable options for treatment of sialorrhea. A recent study with glycopyrrolate\textsuperscript{155} provides evidence that it is better than placebo in alleviating this condition; however, long-term side effects of this anticholinergic medication were not available, and xerostomia, a common side effect present in most patients, also predisposes patients to develop swallowing impairment. Saliva is essential for the lubrication of oropharynx; it prevents dental caries, aids in digestion and prevents the overpopulation of bacteria in the mouth.\textsuperscript{156} Ipratropium bromide has been used in some studies reporting some advantage;\textsuperscript{157} irradiation and neuroectomy are also available although with less definitive evidence.\textsuperscript{158,159} Gum chewing can be helpful not only with drooling but also with dysphagia.\textsuperscript{160} Dysphagia can be ameliorated with some maneuvers and requires a thorough evaluation by the speech and swallowing specialists.

With loss of neurons also appears gastroparesis. It is characterized by a sensation of fullness, satiety, and sometimes nausea. Moreover, prolonged retention of food and medications in the gastric pouch can slow intestinal absorption of levodopa and dopa medications, losing effectiveness and worsening motor and non motor symptoms. The treatment for gastroparesis includes use of domperidone\textsuperscript{172} (not available in the United States) and in extreme cases, application of botulinum toxin in the pyloric sphincter, electric stimulation, or surgery may be necessary.\textsuperscript{173} Exercise, diet with high intake of liquids and dietary fiber, symbiotic yogurt, and medications such as macrogol\textsuperscript{174} and application of botulinum toxin\textsuperscript{175} in the anal sphincter have also been reported to alleviate constipation. Constipation can respond in some cases to dopaminergic therapy. Studies using apomorphine\textsuperscript{176} and duodopa\textsuperscript{177} have shown improvement in bowel transit time.

Urinary Symptoms

Urinary retention secondary to overactivity of the detrusor muscle is an important cause of urge incontinence, urinary urgency, and high frequency of micturition, especially at night. The prevalence of these symptoms is between 37% and 70%.\textsuperscript{178} They may also occur before the onset of motor symptoms, although this is less consistently reported compared with hyposmia, depression, and constipation. Its frequency increases proportional to the stage of the disease; when nocturia is the predominant symptom, it can affect the sleep pattern producing insomnia.

The overactivity of the detrusor muscle is attributed to the loss of inhibition of D1 receptors. These D1 receptors are present in the micturition center located in the pons and are responsible for the reflexive part of micturition. Patients with PD and urinary symptoms often need a complete urologic evaluation to rule out prostate pathology in men or pelvic floor weakness in women before treatment. Newer tools, such as the overactive bladder questionnaire, have been used to detect urinary problems in patients with PD.\textsuperscript{179}

Pharmacological treatment includes anticholinergic drugs such as oxybutynin, solifenacin, and tolterodine. Well-known anticholinergic side effects of these medications include cognitive impairment,\textsuperscript{180} somnolence, blurred vision, hallucinations, confusion, and arrhythmias, among others. Diarrheacin is a selective M2 to M3 muscarinic receptor that can also be used.\textsuperscript{181} Periodic injection of botulinum toxin in the muscle improves hyperactivity of the bladder.\textsuperscript{182} Apomorphine has been used with some benefit, but randomized studies are lacking.\textsuperscript{183,184}

Erectile Dysfunction (ED)

ED and loss of libido are also frequent in PD, reaching about 65% of patients with loss of interest in sexual desire, and 42% with erectile dysfunction. Loss of libido is correlated with depression, increasing age, and female gender.\textsuperscript{178} Factors such as stage of the illness, autonomic symptoms, left-side predominance of motor symptoms, educational level, cognitive impairment, fatigue, apathy, and low testosterone levels have been associated with ED and must be taken into account in a patient with PD and ED.\textsuperscript{185} Medications reported to alleviate ED include apomorphine,\textsuperscript{186} sildenafil, and other phosphodiesterase inhibitors.\textsuperscript{187,188}

SLEEP DISORDERS

Sleep problem are seen in 60% to 98% of PD patients at some point during their disease and often negatively impact the patient’s QOL.\textsuperscript{189,190} Dysregulation of REM and NREM
architecture in the brainstem, particularly in 3 major nuclei—the raphe nucleus (serotonin), locus ceruleus (norepinephrine), and pedunculopontine nucleus (PPN), have been most implicated in sleep disorders as these structures play a key role in the sleep-wake cycle and arousal.\(^{191}\) However, the specific neuronal networks responsible for sleep disorders in PD remain unclear due to its complex etiology.

**Excessive Daytime Sleepiness (EDA)**

EDS occurs frequently in patients with PD. Several studies show that it can be found up to 50% of the patients.\(^{192}\) In a community-based study by Tanberg et al,\(^{193}\) EDS was seen in 15.5% of PD patients compared with 1% of the control group. A 4-year longitudinal study in PD patients reported a 6% yearly incidence of EDS.\(^{194}\) A large Honolulu-Asian Aging longitudinal study showed that EDS was associated with an increased risk of developing PD later in life, up to 3-fold compared with the elderly population who did not have EDS.\(^{195}\)

Several studies using polysomnography and multiple sleep latency tests have suggested that EDS may be a primary feature of PD, unrelated to PD treatment or nocturnal sleep disturbance.\(^{196,197}\) Nonetheless, the etiology of EDS in PD is probably multifactorial. It could be caused by drug side effects, the disease process itself, the effect of nocturnal sleep disturbance, or other unrelated or loosely associated comorbidities such as obstructive sleep apnea (OSA). Previous studies have shown that EDS correlated with advanced disease,\(^{198}\) male gender, the total load of levodopa, the use of dopamine agonists,\(^{192,199,200}\) a longer duration of levodopa therapy, greater PD-related disability, cognitive decline, more rapid progression of parkinsonism, and more frequent hallucinations.\(^{194}\)

Sleep disturbance may also be aggravated or caused by motor symptoms or other comorbid conditions such as restless legs syndrome (RLS), autonomic dysfunction, and OSA. These conditions affect the sleep quality at night causing frequent arousals resulting in EDS. Although EDS can be an intrinsic pathologic change in advanced PD, it is also strongly associated with dopaminergic treatment. This is of particular interest especially among PD patients experiencing “sleep attacks” (ie, falling asleep suddenly, without warning, even during an active state), which have been found to have a clear association with dopamine agonists. Patients on a dopamine agonist have a twice-higher risk of sleep attacks than those using levodopa alone.\(^{201}\) Recent trials of prolonged-release dopamine agonists (ie, transdermal rotigotine and 24 h once daily ropinoreline) as adjunctive therapy have shown more frequent sleepiness in the treated group than in the placebo group, but with a lesser likelihood of developing sleep attacks.\(^{202,203}\)

PD patients who experience sleep attacks are clearly at risk for motor vehicle accidents; thus driving should be avoided, particularly when starting or adjusting the dose of the medications.\(^{204}\)

The etiology of nocturnal sleep disturbance should be ascertained whenever possible. Sleep habits, the presence of nocturnal sleep disruption, and drug history should all be determined. If no identifying cause for EDS seems apparent, polysomnography and multiple sleep latency test can help in the diagnosis of primary sleep disorder and in ruling out other comorbid conditions.

If antiparkinsonian medication side effect is suspected, either a reduction in dose or a switch to another drug may be necessary.\(^{205}\) Adding a stimulant medication may be considered in patients who do not have an identifiable sleep pathology or when reducing sedating medications (such as benzodiazipines, sedative antidepressants, or dopaminergic drugs) result in worsening of motor symptoms. Stimulant medications include modafinil, sodium oxybate,\(^{206}\) methylphenidate,\(^{207}\) and anti-H3 drugs.\(^{208,209}\) Modafinil is a stimulant drug used in primary narcolepsy that has been shown in 2 controlled studies in a small number of PD patients to alleviate EDS.\(^{210,211}\) Interestingly, modafinil has been reported to have neuroprotective effects in animal models of dopamine depletion.\(^{212}\) Finally, the recent use of PPN DBS has provided unexpected insights into the sleep and alertness mechanisms in humans. Patients report feeling more alert during the daytime with low frequency stimulation of the PPN.\(^{211}\)

**RLS and Periodic Limb Movements During Sleep (PLMS)**

RLS and PLMS can cause sleep disruption in PD. The reported prevalence of RLS is wide, from 7.9% to nearly 50%.\(^{214-216}\) In 1 study, only 1 of 125 PD outpatients (0.8%) had RLS-like symptoms.\(^{217}\) RLS is marked by a desire to move accompanied by unpleasant sensations in the limbs that occurs or worsens during period of rest, and is alleviated by movement. The symptoms usually appear in a circadian pattern with onset in the evening or at night. RLS is overrepresented in PD compared with the general population and both disorders are efficiently treated by dopaminergic medication. RLS can precede or come on after PD onset. Peralta et al\(^{218}\) reported that the RLS symptoms onset was 4.5 ± 3.7 years after PD onset.

Given that both diseases are efficiently treated by dopaminergic medications, it has been hypothesized that RLS and PD may have the same pathologic basis. Dopaminergic deficiency has been proposed as the main pathologic substrate. However, it should be noted that not all RLS patients require dopaminergic therapy, but eventually all PD patients will require dopaminergic treatment. RLS may therefore involve dopaminergic pathways other than the nigrostriatal dopaminergic pathways.

The role of dopamine has been elucidated further by imaging studies. Eisensehr et al\(^{219}\) found no differences in dopamine transporter (DAT) and DA receptor binding between RLS patients and controls in a SPECT study using the DAT. Another study showed a reduction in D2 receptor binding but no difference in β-CIT binding between the RLS and control groups was seen.\(^{220}\) Interestingly, RLS patients seem to display normal nigrostriatal terminal function.

Iron deficiency itself can be a risk factor for RLS. Iron deficiency is commonly seen in the elderly, perhaps contributing to its higher incidence in the PD population.

PLMS may occur independently or in association with RLS. PLMS is the key supportive polysomnographic finding for RLS. Similar to RLS, PLMS has also been reported to be more prevalent in PD compared with controls, seen in approximately 30% to 80% in PD patients.\(^{221,222}\) The typical PLMS manifestations consist of a dorsal flexion of the foot and great toe that may go along with flexion of the knee and hip. One study using striatal β-CIT binding SPECT found a correlation between dopaminergic cell loss and PD patients with PLMS.\(^{223}\) However, there have been too few studies to clearly establish the increased incidence of PLMS in PD patients.

Dopaminergic agents are considered as the first-line drug for RLS. Several studies have shown the long-term benefit of l-dopa in RLS patients with varying responsiveness of the treatment ranging from 85% after 2 years to 31% after a mean
duration of treatment of 31 months. However, a “rebound” and an “augmentation” are the common side effects from L-dopa therapy in RLS as well as PLMS. The reappearance of symptoms in rebound phenomena is caused by withdrawal due to the short plasma half-life of L-dopa. The prevalence rates of augmentation in open-label trials with L-dopa in RLS patients varied from 18.6% to 72%. In severe cases of augmentation, the medications should be discontinued. Dopamine agonists have been shown to improve RLS and PLMS symptoms in 70% to 90%. These drugs are generally preferred over L-dopa as they are less likely to cause rebound or augmentation. Pramipexole and ropinirole have been extensively studied for RLS and PLMS treatments and have been approved for the treatment of moderate to severe RLS in the United States. In several studies, pramipexole has been very effective in treating RLS and PLMS and it has also been shown to have a sustained efficacy in >80% of RLS patients. Augmentation from pramipexole has been reported in open trials to occur between 8.5% and 39%. Similarly, randomized placebo-controlled trials have shown the effectiveness of ropinirole in suppressing RLS. For PLMS, in 1 study using polysomnography, a mean dose of 1.8 mg ropinirole significantly reduced episodes of PLM and improved sleep parameters. The long-term study showed ropinirole maintained the therapeutic efficacy in 82% without augmentation. A newer nonergotamine derivative, rotigotine, can be administered transdermally and it has been shown to improve RLS and PLMS symptoms in >80% without augmentation. A newer nonergotamine derivative, rotigotine, can be administered transdermally with a continuous release over 24 hours. Several studies have reported the efficacy of the rotigotine patch in reducing the severity of RLS symptoms. Recently, a large randomized double-blind controlled study demonstrated that rotigotine transdermal patches at 2 to 3 mg per day significantly improved RLS symptoms.

In double-blinded, placebo-controlled trials of RLS patients with iron deficiency, iron supplementation has been shown to significantly improve RLS symptoms. Several studies have shown that having idiopathic RBD carries a substantial risk of developing PD or DLB, ranging from 20% to 45% within 5 years and ranging from 40% to 65% within 10 years. Patients with primary RBD have also been noted to have olfactory deficits, visual changes, and motor symptoms, similar to those seen in PD. As RBD may predate the onset of parkinsonism or dementia in patients with an underlying synucleinopathy such as MSA, PD, and DLB by years or decades, some authors suggest that RBD may be a selective marker of a synucleinopathy.

The pathophysiology of RBD is thought to be a degeneration of lower brainstem nuclei involving of laterodorsal tegmentum, PPN, periolus cereuleus, medial medulla, and the ventrolateral reticulospinal tracts, consistent with Braak stages 1 and 2. Of note, RBD preceding parkinsonism might reflect early involvement of nondopaminergic medullary and pontine REM sleep-related structures before the impairment of dopaminergic neurons in the substantia nigra pars compacta. A greater disease severity involving a younger age onset and more polysomnography abnormalities in MSA rather than PD suggests more extensive pathologic changes in the brainstem modulating REM sleep. However, brainstem spectroscopy does not show differences between PD patients with and without RBD.

Postuma et al postulated that a striking the degree of orthostatic blood pressure change in patients with RBD might be associated with degeneration of sympathetic but not parasympathetic ganglia. To date, there have been no randomized, double-blinded, controlled, studies evaluating the efficacy of RBD treatment. Most previous studies were case reports and small case series, which had limitations in methodology.

In cases where behaviors are mild and intermittent, treatment may not be necessary. If the symptoms are more violent, providing a safe environment and a pharmacological...
treatment are indicated. Low-dose clonazepam is currently regarded as the treatment of choice. There have been 2 large reported case series showing substantial improvement (55% to 79% complete benefit and 11% to 32% partial benefit) in the majority of patients treated with clonazepam in terms of a suppression of troublesome sleep behaviors and nightmares. Only a minority of patients reported significant side effects, such as increased confusion or falls, or worsening of OSA. Melatonin has been also reported to be beneficial in some studies and has fewer side effects. One study, by Boeve et al,261 has shown that 3 to 12 mg of bedtime melatonin improved symptoms in 12 of 14 patients with coexisting neurological disorders (DLB, MSA, PD), mild cognitive impairment with parkinsonism, and narcolepsy). Drugs with controversial effects on RBD symptoms are anticholinesterases inhibitors (donepezil and rivastigmine) and dopaminergic drugs (pramipexole and levodopa). Novel treatments such as DBS targeting the subthalamic nucleus have been reported to provide subjective improvement in sleep quality, probably through improved nocturnal mobility and also reduction of antiparkinsonian medications.

OTHER NONMOTOR SYMPTOMS

Hypomimia

Hypomimia, or lack of emotional expression, can be one of the initial manifestations of the disease that prompts neurological consultation. The physiopathology of masked facies seems to be associated with the loss of speed of movements, secondary to the basal ganglia pathology, and similar to other motor symptoms.262 Although PD patients report emotional changes as well as in normal controls,263 peers of patients with PD can misinterpret their facial expression as angry, sad, introverted, anxious, or somber, affecting their relationships and social interactions.264 Interestingly, patients with PD may also have impaired recognition of emotions and facial expressions of their peers. Consequently PD patients may experience more difficulties sustaining good relationships.265 In 1 study, the hypomimia seemed to be more pronounced in men than in women; men were less likely to begin a relationship with women counterparts.267

Speech Changes

Speech disorders are present in 100% of patients with PD. Disturbances in respiratory, articulatory, mouth, pharyngeal, and laryngeal muscles translates into clinical disorders distinguished by changes in tone, volume, rate, prosody, respiration, and pronunciation.268 The etiology of speech disorders in PD is not clear. Although levodopa therapy can be helpful,269 suggesting the importance of the dopaminergic pathways in the expression of the speech, this is far from consistent. Another study suggested somatosensory deficits in the laryngeal sensory input as an important feature,270 and new pathways in the expression of the speech, this is far from consistent.270 Some studies have reported benefit with medications such as amantadine, methylphenidate,271 modafinil,272,273 duodopa,274 selegline, sodium oxybate,275 and levodopa. Changes in daily routines such as pattern of sleep and exercise can be helpful; however, studies with class I evidence are lacking.276

Fatigue

Fatigue has been described in several ways, such as lack of energy, sensation of tiredness, and sometimes exhaustion, heaviness, and sleepiness, with loss of productivity in daily function and labor; despite the desire to do it. Fatigue is not exclusively a bodily sensation, it can also be a conscious awareness that some patients express as the loss of the ability to concentrate on a given task.277 Around 44% of patients with PD experience fatigue. Probable causes for the occurrence of fatigue in PD include mood disorders, changes in neurotransmitters, hormonal imbalance such as testosterone deficiency, expression of cytokines, and other inflammatory factors, changes in life patterns, sleep disturbances, apathy, and dysautonomia.

Fatigue has not been found to correlate with the stage or duration of the disease. However, a relationship with depression, anxiety, response to medications, and sleep pattern has been reported. Some studies suggest a relation between cognitive function and fatigue, especially the mental sensation of tiredness.279 Fatigue and similar symptoms in PD result in loss of interest, decreased QOL, and poorer emotional well-being and self-development.280

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Weight Changes

Weight loss can be present in 65% of PD patients. The origin of loss of weight may be due to the imbalance between the intake and consumption of energy. Loss of appetite, taste, olfaction and motility of bowels, low levels of leptins, dysphagia, drooling, gastroesophageal reflux, nausea, vomiting, constipation, depression, side effects of medications, loss of income, muscle wasting, rigidity, and excess of movement (dyskinesias) have been associated with weight loss.280 The usual approach to loss of weight is multidirectional: behavioral therapies; treatment of other nonmotor and motor manifestations and side effects; and the right food at the right time with supplements must be considered.272 Mirtazapine, a medication used in the treatment of depression may also increase appetite as a side effect.

Dyspnea

This symptom is usually underrecognized because patients with PD tend to be noncomplainers and the motor complaints often overshadow respiratory symptoms. However, respiratory effort may be proportionally increased with the degree of rigidity or wearing “off” phenomenon, becoming more difficult in patients with advanced stages of the disease. Moreover, sympathetic and dysautonomic changes in the respiratory system may result in a restrictive airway pattern. The thoracic cage is less capable of expansion due to abnormal contraction of muscles and abnormal contraction of vocal cords.288 Levodopa, medication optimization, and adequate respiratory exercise may alleviate some of the symptoms.289

CONCLUSIONS

Clearly, PD is a multisystem disorder. Nonmotor symptoms are prevalent throughout the course of the illness and included cognitive dysfunction; neuropsychiatric manifestations
such as psychosis, impulsive control and compulsive disorders, depression, anxiety, and apathy; autonomic complications such as hypotension, erectile dysfunction, and urinary complications; sleep disorders and other nonmotor manifestations. They can be intrinsic to the illness and/or iatrogenic complications of treatments used to alleviate the motor symptoms of PD. Because nonmotor complications often carry a greater impact than motor features in PD, their recognition is often the key to the successful treatment of a Parkinson patient.

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