The Nonmotor Symptoms of Parkinson’s Disease: Update on Diagnosis and Treatment
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ABSTRACT

- **Objective:** To review the prevalence, diagnosis, and treatment of the nonmotor symptoms (NMS) associated with Parkinson’s disease (PD).
- **Methods:** Narrative review of the literature.
- **Results:** The NMS of PD are becoming increasingly recognized as having a critical role in the impact of this neurodegenerative movement disorder. This has led to significant investigative efforts to identify new or better NMS therapies. The preponderance of PD patients will be diagnosed with 1 or multiple NMS during the course of their disease, with many of these symptoms occurring months or even years prior to receiving the PD diagnosis. Despite the high prevalence and impact on disease burden, NMS often go undetected due to a lack of reporting by patients or insufficient interrogation by physicians. Further complicating NMS management is that only a few therapies have the level of evidence needed to support their use in the treatment of NMS.
- **Conclusion:** The practitioner needs to be aware of NMS and conduct thorough patient questioning in order to recognize, diagnose, and address NMS in PD patients.

Parkinson’s disease (PD) is a neurodegenerative movement disorder with an estimated prevalence of 1% to 2% among the population over the age of 65 years [1]. Recognition and clinical diagnosis of PD is primarily made based on the cardinal motor features, including rigidity, tremor, bradykinesia, and postural instability. The motor symptoms are neuropathologically associated with accumulation of alpha-synuclein with Lewy body formation and neurodegeneration of the nigrostriatal dopamine system. Postmortem evaluation of the brains of PD patients has revealed more widespread degeneration in nondopaminergic systems, including several brainstem nuclei (raphe nucleus, locus ceruleus, dorsal vagal nucleus), limbic and neocortical structures, as well as the peripheral autonomic system [2,3].

The nonmotor symptoms (NMS) of PD are the clinical manifestations of this extensive degeneration, which suggests that NMS are intrinsic and fundamental features of PD. NMS are exceedingly common, and up to 90% of PD patients will experience nonmotor features, including depression, anxiety, sleep disturbances, cognitive impairment, and dysautonomia [4,5] (Table).

NMS have a greater impact on quality of life as compared to the motor symptoms [6,7], but are frequently underrecognized [8]. Evidence suggests that unless there is systematic and specific interrogation by practitioners, NMS will elude recognition [9–11]. Recognizing NMS as part of PD is complicated by the fact that these symptoms are common in the general population and not specific for PD [12,13]. NMS can occur at any stage of the disease and may predate diagnosis [12], although as PD progresses the NMS become more prevalent, with a greater impact on health care costs and institutionalization rates than motor features [14,15].

NEUROPSYCHIATRIC SYMPTOMS
Depression
**Epidemiology and Diagnosis**
Depression is one of the most common neuropsychiatric manifestations observed in PD patients, with prevalence reports between 4% and 72%, though likely to be closer to 30% to 45% [16–20]. The severity of depression in the PD population has been shown to be greater than in patients with matched chronic disabilities [21,22] and also greater than in the general population over the age...
The onset of depression can occur at any stage of the disease, even predating the diagnosis. Additionally, depression has more than twice the impact on health status than motor symptoms [24].

Though the mechanisms are not fully understood, it is suspected that psychosocial as well as neuropathological changes contribute to the pathogenesis of depression in PD. In a study comparing 104 PD patients and 61 patients with equivalent disability scores, functional disability was found to be responsible for only 9% of the variation of depression scores [22]. The increased prevalence of depression in PD patients can in part be explained...
by the neuropathological changes seen in post-mortem studies. Two neurotransmitters that are fundamental in the pathogenesis of depression are serotonin, from the raphe nuclei, and norepinepherine, from the locus ceruleus [20]. Both of these brainstem structures demonstrate alpha-synucleinopathy-associated degeneration and these changes can precede the development of motor dysfunction [3].

Diagnosing depression in PD is complicated by the fact that there is overlap between other PD symptoms and clinical features of depression (ie, amotivation, bradykinesia, fatigue, and sleep disturbances). However, many depressed PD patients are less likely to report feelings of guilt or failure and tend to have higher rates of anxiety [9,20,25]. Typically, PD patients are more likely to be diagnosed with minor depression or dysthymia rather than a major depressive disorder [19,20]. Formal testing through systematic questionnaires are diagnostically useful in the clinic, and serial testing can reveal changes over time to guide more effective treatment. Validated tools to evaluate depression in PD include the Beck Depression Inventory, Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, Geriatric DRS, and Hospital Anxiety and Depression scale [20].

Table. Nonmotor Features of Parkinson’s Disease, continued

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pathophysiology</th>
<th>Prevalence</th>
<th>Symptomatology</th>
<th>Pharmacologic Treatment</th>
<th>Nonpharmacologic Treatment</th>
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<tbody>
<tr>
<td>Orthostatic hypotension</td>
<td>Degeneration of autonomic centers: ventrolateral medulla, nucleus tractus solitarius, descending para/synaptic [3,183]</td>
<td>30%–60%</td>
<td>Dizziness, drowsiness, palpitations, nausea</td>
<td>Fludicortisone [141], midodrine[143], pyridostigmine [142], droxidopa [144]</td>
<td>Compression stockings, sleep w/ head elevated, ↑ salt and water intake, frequent small meals, ↓ carbohydrate [140,141]</td>
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<tr>
<td>Constipation/ gasroparesis</td>
<td>Loss of enteric DA cells, degeneration dorsal vagal nuclei [155]</td>
<td>60%</td>
<td>↓ # of BMs; early satiety</td>
<td>Macrogol [149], lubiprostone [150]</td>
<td>Dietary modification, mild exercise, ↑ fluid intake</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Hypothalamic dysfunction and dysregulation of DA-oxytocin pathway [166]</td>
<td>60%</td>
<td>Inability to maintain an erection</td>
<td>Phosphodiesterase inhibitors (sildenafil, vardenafil, tadalafil) [166,168], apomorphine [169]</td>
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Sensory

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<th>Feature</th>
<th>Pathophysiology</th>
<th>Prevalence</th>
<th>Symptomatology</th>
<th>Pharmacologic Treatment</th>
<th>Nonpharmacologic Treatment</th>
</tr>
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<tbody>
<tr>
<td>Pain</td>
<td>BG dysfunction in modulation of sensory input; altered 5-HT pathways [184]</td>
<td>30%–85%</td>
<td>Musculoskeletal/ shoulder pain, dystonic pain, vague discomfort</td>
<td>NSAIDs, adjust DA therapy or add CR formulation [173,174]</td>
<td>Physical therapy, exercise [173], DBS [174,175]</td>
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<tr>
<td>Hyposmia</td>
<td>Degeneration of olfactory structures and amygdala [3,185]</td>
<td>40%–100%</td>
<td>Inability to distinguish odors</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Visual disturbances</td>
<td>Retinal DA dysfunction, degeneration of visual cortex [186]</td>
<td>30%–40%</td>
<td>Impaired contrast sensitivity, blurred vision, diplopia</td>
<td>–</td>
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BG = basal ganglia; DA = dopamine; DDS = dopamine dysregulation syndrome; ICD = impulse control disorders; LB = Lewy bodies; LC = locus ceruleus; NA = nucleus accumbens; PPN = pedunculopontine nucleus; RAS = reticular activating system; SN = substantia nigra; VTA = ventral tegmental area.
Treatment Options

Treatment of depression in PD demonstrates generally poorer responses to typical antidepressants and side effects that may worsen other PD symptoms. Selective serotonin reuptake inhibitors (SSRIs) have been widely used as there are generally few drug-drug interactions and minimal effect on motor symptoms; however, several studies have demonstrated little benefit on depression in PD [26]. In a randomized, double-blind, placebo-controlled trial of the antidepressants paroxetine and venlafaxine, both were found to be effective and well tolerated [27]. Tricyclic antidepressants (TCAs) have also demonstrated efficacy. In randomized controlled trials comparing TCAs to SSRIs, a greater benefit on depression symptoms has been found with TCAs [28–30]. The use of TCAs, however, is limited by anticholinergic side effects that occasionally worsen orthostatic hypotension or cognitive impairment [15,31]. Dopamine agonists have also been studied in depressed PD patients. In a randomized, double-blind, placebo-controlled trial [32] and a prospective observational study [33], pramipexole demonstrated significant improvements in depression symptoms. Ropinirole also demonstrated significant symptomatic improvement [34]. These studies suggest that while SSRIs are commonly used, evidence is accumulating to support the role of TCAs, SNRIs, and dopamine agonists in the treatment of depression in PD.

Other therapies have also been tried in pharmacologic-resistant patients. Electroconvulsive therapy has been reported to improve both depression and motor symptoms [35,36]; however, this is a treatment reserved for patients with severe and drug-refractory depression. A randomized controlled trial investigating cognitive behavioral therapy has also demonstrated improvement of depression scores [37]. The role of physical activity as treatment for depression in PD patients is unclear. As described in a recent review by Loprinzi et al [38], the literature is contradictory, with one group experiencing reduced depression but with no significant effect in several other studies.

Anxiety

Epidemiology and Diagnosis

The prevalence of anxiety in PD patients is about 40% [39], which is 2 times greater than in the general population [9]. Anxiety may worsen PD symptoms, especially tremor and cognition. Risk factors for anxiety include the female gender, greater motor fluctuations, prior history of anxiety, and younger age of PD onset [40]. As with depression, some patients also report worsening of anxious symptoms during “off” states [41]. Screening tools that have been validated to help practitioners identify anxiety in PD include the Hospital Anxiety and Depression Scale, Beck Anxiety Inventory, Zung Self-rating Anxiety Scale, Spielberger State Trait Anxiety Inventory, and Hamilton Anxiety Rating Scale [15].

Treatment Options

The treatment of diagnosed anxiety in PD is primarily with benzodiazepines, which are particularly beneficial in patients whose tremors are exacerbated by anxiety or stress. The use of benzodiazepines has not been evaluated by a randomized controlled trial and use should be limited given the potential risks of sedation, cognitive effects, and psychomotor agitation. Other case studies have found benefit with serotoninergic medications like fluoxetine or citalopram (especially with concomitant depression) or with optimization of levodopa therapy [42,43].

Hallucinations, Delusions, and Psychosis

Epidemiology

The prevalence of visual hallucinations in PD patients is about 20% to 40% [44,45]. Risk factors for psychotic symptoms include cognitive impairment, advanced age, prolonged duration of disease, depression, severe dysautonomia, and sleep disorders [46–48]. Early recognition of hallucinations is critical because of a strong correlation between the manifestation of psychosis and the need for nursing home placement or hospitalization. With early and effective treatment there is a decreased need for placement and a reduction on caregiver burden [44,49].

Treatment Options

Hallucinations can occur in delirium and it is important to first rule out an underlying infection or an offending medication, especially if there is a sudden onset or worsening of symptoms. Psychotic symptoms have been reported in drug-naïve patients, though they are often iatrogenically induced with dopaminergic agents. All antiparkinsonian medications are capable of inducing or exacerbating hallucinations [9,50]. Additionally, psychotic symptoms tend to improve when dopaminergic agonists are reduced or eliminated. However, there is no clear relationship between the dose of dopaminergic agents and manifestation of hallucinations [48,51,52]. If hallucinations persist or there are motor complications
that arise from reduction of dopaminergic agents, initiation of clozapine has been demonstrated to be efficacious in a rater-blinded prospective study and in a retrospective analysis [53–55]; however, regular monitoring for neutropenia is required. Quetiapine has demonstrated similar benefit without significant effects on motor symptoms in a randomized, rater-blinded study and in an evidence-based review [56,57]. It is also important to review or eliminate other medications that may contribute to hallucinations.

**Cognitive Impairment**

**Epidemiology**

The prevalence of dementia in the PD population is 20% to 40% [58], though almost 80% of PD patients ultimately develop cognitive decline [59]. Overall, a PD patient is 6 times more likely to develop dementia than someone in the general population [60]. There may be parallel progression of cognitive impairment and motor symptoms, but there is no correlation with overall duration of disease [60,61]. Risk factors linked with the presence of dementia include older age at onset of PD, presence of hallucinations, and male gender [62,63].

Cognitive dysfunction can be detected early in PD through neuropsychological testing; however, impairment of cognition is often insidious and may not be appreciated until symptoms become severe. Several screening tools have been used to evaluate for cognitive impairment in PD including the Mini-Mental State Exam (MMSE), Montreal Cognitive Assessment (MoCA), Mini-Mental Parkinson, Scales for Outcomes of Parkinson's disease–Cognition, and others. Accumulating evidence, however, is suggestive of the superiority of the MoCA in the detection of cognitive deficits associated with PD [64].

Dementia is a substantial burden for the caregiver and is a significant contributor to mortality in PD patients [65]. Cognitive impairment often presents with other behavioral symptoms, which further hastens placement outside the home and increases cost of caring for PD patients [49,66].

Cognitive impairment in Parkinson’s disease is typically associated with degeneration of primarily subcortical structures. PD patients with mild cognitive impairment were found to have deficits most significantly in memory, executive function, memory, and language abilities [67]. A recent study by Mak et al evaluated grey matter volumes by structural MRI in PD patients with evidence of mild cognitive impairment by MMSE and MoCA as compared with findings in cognitively intact patients. This demonstrated decreased brain volumes in areas that correlate with affected cognitive domains including the left insula, left superior frontal and left middle temporal areas [68].

**Treatment Options**

Prior to initiation of therapy, it is important to evaluate the patient for depression and to rule out pseudodementia. Bradyphrenia, or slowness of thought, should also be considered, as this symptom may also lead to an incorrect dementia diagnosis. Lastly, a thorough review of medications should be performed and offending agents including anticholinergics, TCAs, dopamine agonists, and amantadine should be discontinued as these can worsen cognition.

Rivastigmine has demonstrated modest improvement in cognitive performance in PD patients with dementia in a large multicenter, placebo-controlled study [69]. Other cholinesterase inhibitors (ie, donepezil or galantamine) are not recommended at this time due to limited studies or contradictory results in the literature [31,54]. Caution is advised with use of cholinesterase inhibitors as they may worsen tremor or autonomic dysfunction; also, use is limited by nausea or other gastrointestinal symptoms. Memantine, an NMDA receptor antagonist, has also been investigated in randomized, double-blind, placebo-controlled trials and demonstrated modest improvement of cognition and is generally well tolerated [70,71].

Nonpharmacologic therapy includes physical exercise, which has demonstrated improvement in memory tasks and processing speed [72]. Cognitive training has been less rigorously studied; however, a recent single-blinded controlled study demonstrated significant improvement of learning and memory in PD patients who completed computer-based cognitive training [73].

**Compulsive Disorders**

**Impulse Control Disorders**

Impulse control disorders (ICDs) are inappropriate behaviors resulting from a failure to resist an impulse, which leads to pleasure-seeking activities at the expense of relationships and ability to function socially. In PD, ICDs are expressed as pathologic gambling, hypersexuality, binge eating, compulsive shopping, and excessive spending [9,66]. The prevalence of all ICDs in PD is 15% to 20% and a patient may be diagnosed with multiple
ICDs [74]. Dopamine agonist use has been implicated in the development of ICDs and this risk is further increased with the addition of levodopa [75,76]. Clinical features associated with ICDs include young age of onset, male gender, family history of addiction, depression or anxiety, and disinhibition or impulsive traits [77,78].

Traditionally, treatment consists of reduction or elimination of dopamine agonists, though adjustment of levodopa therapy may also be necessary. Amantadine as an adjunct therapy has been shown in a randomized, double-blind crossover study to reduce impulsivity in a few patients with pathologic gambling [79].

**Dopamine Dysregulation Syndrome**

Dopamine dysregulation syndrome (DDS) is characterized by compulsive use of dopaminergic medications beyond what is needed to treat parkinsonian symptoms, and is associated with social impairment. Patients describe addictive symptoms like craving or intense desire to obtain more dopaminergic medication [9,74]. Like ICDs, treatment of DDS consists of modification to dopaminergic medications, though patients with DDS may also require psychiatric evaluation and treatment.

**Punding**

Punding is another compulsive disorder that is defined as an intense fascination with objects and is associated with repetitive handling, manipulation, sorting, or arrangement of the items [80]. Occurrence of punding has been associated with higher total daily levels of levodopa, although one study has also implicated dopamine agonists [15,81]. As with the other compulsive disorders, punding also tends to respond well to reduction or discontinuation of levodopa. Studies have demonstrated modest benefit with SSRIs or atypical antipsychotics in long-term follow-up [82,83], though one study reported worsening of punding with quetiapine [84].

**Apathy**

**Epidemiology and Treatment**

Apathy is often characterized by a loss of motivation or inability to initiate goal-directed behavior, which results in dependence on others for activities of daily living and increases caregiver burden [85]. Patients demonstrate indifference, lack of interest, or inability to express or describe emotion. The apathetic patient may lack spontaneous and voluntary activity, and their affect display is often flattened [86].

With a prevalence of 30% to 50% [87], apathy is as common as depression in PD patients [66,88]. Risk factors associated with apathy include advanced age, severity of depression, severity of motor dysfunction, and dementia [89]. Apathy is frequently mistaken for depression given the significant overlap in symptoms; however, the patient with pure apathy will deny sadness or depressed feelings. It is also important to distinguish apathy from motor impairment or cognitive dysfunction that could explain the behavioral changes. No medications have reliably been shown to improve apathy, though it may be improved with initiation of dopaminergic therapy, especially early in the course [86,90].

**SLEEP DISORDERS**

The original report of PD by James Parkinson describes sleep disturbances and daytime somnolence [91], which suggests that sleep disorders may be an intrinsic feature of the neurodegenerative process of PD itself.

**REM Behavioral Disorder**

**Epidemiology and Diagnosis**

Rapid eye movement behavioral disorder (RBD) is a parasomnia characterized by vocalizations and motor activity during dreaming due to loss of normal atonia associated with rapid eye movement (REM) sleep. Patients enact their dreams, which may lead to violent behaviors that can injure the patient or their bed partner. RBD is seen in 25% to 50% of PD patients [92,93], with variability depending on diagnostic technique and patient selection. Polysomnography is the most important diagnostic tool and demonstrates increased chin tone and limb movements during REM sleep in RBD [94,95]. Diagnosis can also be made clinically with patient and bed partner reports, though sensitivity is only approximately 30% [15].

Interestingly, many studies are now investigating the relationship between presence of RBD and later onset of neurodegenerative disorders. Multiple studies have shown that 40% to 65% of patients diagnosed with idiopathic RBD later develop an alpha-synucleinopathy, which includes PD, dementia with Lewy bodies, or multiple system atrophy within 10 years [92,95]. Prior studies report that as many as 90% of patients with idiopathic RBD develop neurodegenerative synucleinopathy when followed over 14 years [96]. Idiopathic RBD is currently being investigated as a potential clinical marker of presymptomatic PD in a multicenter observational study. If RBD is an early marker for neurodegenerative disease, it
may be used to identify patients for neuroprotective trials as treatments are developed.

**Treatment Options**

Low-dose clonazepam (0.25–1 mg) is the mainstay of therapy, especially for patients that injure themselves or bed partners [97]; however, the use of benzodiazepines is historical and there remain no randomized controlled double-blind studies to evaluate the efficacy of clonazepam. Use of clonazepam may be limited by daytime sedation, confusion, or psychomotor agitation [31,97,98]. Melatonin (doses between 3–12 mg at bedtime) has also demonstrated benefit in RBD in a double-blind, placebo-controlled trial and in a small case series, with fewer side effects and no addiction potential as compared to clonazepam [99,100]. Case reports also support the use of several other effective medications, including cholinesterase inhibitors (rivastigmine and donepezil) and dopaminergic agents (pramipexole and levodopa) [15,20].

**Restless Leg Syndrome and Periodic Limb Movements in Sleep**

**Epidemiology**

Restless leg syndrome (RLS) and periodic limb movements in sleep (PLMS) cause disruptions of sleep and have an important impact on quality of sleep in PD patients. RLS is described as a strong urge to move the legs, accompanied by an uncomfortable sensation that is exacerbated at rest and relieved by movement. RLS is more frequently diagnosed in patients with PD, though prevalence reports vary widely [15]. Secondary causes for RLS should be investigated including iron deficiency, uremia and polyneuropathy. Several case reports demonstrate onset or worsening of RLS with use of antidepressants [101,102] or antipsychotics like risperidone, aripiprazole, and quetiapine [103,104].

PLMS occurs in approximately 80% to 90% of patients with RLS, though may be present independently, and when seen on polysomnography is supportive of RLS [105]. PLMS is characterized by repetitive dorsiflexion of the foot, extension of the great toe, and may be accompanied by flexion of the knee and hip. The prevalence of PLMS in PD is approximately 60% and correlates with severity of PD motor features [106].

**Treatment Options**

Treatment of RLS should be initiated with nonpharmacologic therapies including good sleep hygiene, exercise, leg massage, and heat or ice packs [105,107]. Dopamine (DA) agonists are the primary treatment for RLS; however, even modest adjustments in levodopa can be helpful. One drawback to levodopa therapy is augmentation (a worsening or reappearance of symptoms) when serum levels fall due to the short half-life of levodopa [107,108]. DA agonists are less likely to cause augmentation. Both pramipexole and ropinirole have been extensively investigated in controlled, randomized, double-blind studies with benefits in 70% to 90% of patients with RLS and PLMS; however, there is a risk of developing compulsive behaviors [109–112]. Another option for PD patients is rotigotine, which has demonstrated improvement of RLS symptoms in a randomized, double-blind, placebo-controlled trial and has the added benefit that it may also help with motor symptoms [113,114].

More recently, gabapentin enacarbil has demonstrated improvement of moderate to severe RLS and was well tolerated in multiple randomized, double-blind, placebo-controlled trials [107,115,116]. Lastly, opioids (tramadol, oxycodone, codeine) have been shown to be effective, especially in the treatment of RLS that is refractory to other treatments [105,107].

**Insomnia**

**Epidemiology**

The most common sleep disorder in PD is insomnia, with a prevalence between 37% to 88% [14,117]. Insomnia is associated with difficulty in initiation or maintenance of sleep. Disruption of sleep typically leads to daytime somnolence and patient reports of a strong impact on motor disability and overall quality of life. There are several contributors to insomnia in PD patients including nocturia, depression, RLS, dystonia, and akinesia/rigidity/difficulty turning in bed [118].

**Treatment Options**

The use of carbidopa/levodopa controlled-release formulations at bedtime is associated with improved sleep duration and nocturnal akinesia, although it does not demonstrate a significant improvement in overall sleep ratings [54]. Hypnotics like eszopiclone and zolpidem have also demonstrated improved quality of sleep in limited controlled trials and a meta-analysis, but use is limited by sedation, dizziness, and falls [54,119]. Benzodiazepines improve sleep latency, but there is a risk of cognitive impairment, tolerance, and falls [117,120]. Melatonin at 3 to 5 mg and 50 mg doses have been investigated in
2 randomized, double-blind, placebo-controlled trials; however, there was a modest benefit and it was concluded that there is insufficient evidence to support the use of melatonin [54]. Nevertheless, melatonin is well tolerated and may be tried with minimal risk [54]. More recently, a randomized controlled trial using doxepin has demonstrated improvement of insomnia scores and was generally well tolerated [121].

**Excessive Daytime Sleepiness and Abrupt Sleep Onset**

**EDS and Fatigue: Epidemiology and Treatment**

A common complaint by PD patients is excessive daytime sleepiness (EDS), which can be verified with multiple sleep latency testing. EDS frequency varies in the literature, but is seen in approximately 15% to 50% of PD patients [4,122]. The etiology is usually multifactorial, with insomnia, dysautonomia, and depression as contributing factors [117]. A longer duration of symptoms, greater total load of levodopa, cognitive decline, and male gender are all risk factors for EDS [122,123]. It has been proposed that EDS is an intrinsic feature of PD; however, there is also an association with the use of antiparkinsonian medications. A randomized controlled trial demonstrated that use of the dopamine agonist pramipexole was associated with greater somnolence as compared to levodopa therapy (35% vs. 13%); however, this difference was only seen during the initial escalation phase [124]. Additionally, the combined use of dopamine agonists and levodopa has shown an even greater risk of EDS [125]. The evidence for the use of stimulants for EDS is lacking. The few studies conducted with modafinil have not demonstrated a robust improvement of EDS [126–128]. Other stimulants like methylphenidate have been studied with improvement of Epworth Sleepiness Score, though no randomized control trials have been undertaken [129].

It is important to distinguish EDS, a propensity for daytime sleep, from fatigue or excessive tiredness associated with mental or physical exertion [117]. Fatigue is often multifactorial and may be related to insomnia, sleep apnea, sedating effects of medications, frequent awakenings from nocturia, and degeneration of brain areas regulating sleep/wake cycles related to the underlying disease process [20, 117]. It is also important to consider depression and dementia in the differential, as these disorders may be erroneously be diagnosed as fatigue. Treatment of fatigue should include regular mild exercise, maintenance of a stimulating environment, removal of sedating medications, and management of intrinsic sleep disorders if present [117]. The use of stimulants for fatigue is controversial. A small randomized controlled trial (n = 48) using modafinil demonstrated improvement on the global clinical impression scale for fatigue but no significant change on the Fatigue Severity Scale; this study was limited by the power and points to the need for a larger study [130].

**Sleep Attacks: Epidemiology and Treatment**

Abrupt sleep onset, or “sleep attacks,” occurs when transition from wake to sleep is unavoidable and may occur without warning. Sleep attacks are threefold more likely to occur in patients using DA agonists, with an associated dose-related increase in risk [131]. Adjustment or elimination of DA agonists often improves sleep attacks, though it is important to address concurrent EDS if present. Nonpharmacologic treatments to consider include mild exercise, early morning bright light exposure, and a stimulating environment [117].

**Sleep-Disordered Breathing/Obstructive Sleep Apnea**

**Epidemiology and Treatment**

Sleep-disordered breathing (SDB) consists of either a deficit in the drive to breathe as in central sleep apnea, or may be due to an blockage of the airway as seen in obstructive sleep apnea (OSA). Apnea leads to oxygen desaturations that consequently trigger awakenings throughout the night, which in turn is experienced by the patient as daytime somnolence [117]. The prevalence of SDB and OSA is variable in the literature, ranging from no increased risk in PD patients [132,133] to 50% prevalence in PD patients [134,135]. Discussions with bed partners, history of snoring, and clinical reports of EDS or daytime fatigue are important indicators of SDB. Polysomnography confirms the diagnosis and can direct treatment, which frequently includes application of CPAP devices during sleep.

**AUTONOMIC DYSFUNCTION**

**Orthostatic Hypotension**

**Epidemiology and Diagnosis**

Orthostatic hypotension (OH) is defined as a 20-mm Hg fall in systolic blood pressure or 10-mm Hg drop in diastolic blood pressure within 3 minutes of a change in position. The prevalence of OH in PD patients is 30% to
60% [136,137]. Symptoms of OH can occur early in the disease and may precede diagnosis of PD [137]. Patients experience OH as dizziness, drowsiness, palpitations, nausea, or loss of consciousness. Additionally, falls and supine hypertension that accompany OH are associated with increased risk of morbidity and mortality in PD patients [138]. Several medications used in the treatment of PD can exacerbate OH, including levodopa, DA agonists, MAO-B inhibitors, and TCAs [139].

**Treatment Options**

First-line therapies for OH include nonpharmacologic methods such as compression stockings, sleeping with head elevated to 30 degrees, increased water and salt intake, more frequent small meals, and slowly changing position [140]. Additionally, it is important to discuss the removal or reduction of all antihypertensives with the patient’s PCP. Fludrocortisone (a mineralocorticoid) and domperidone (a peripheral dopamine antagonist not currently approved for use in the United States) modestly improved OH in a 2-phase, randomized, controlled, double-blind, crossover trial [141]. Pyridostigmine has also demonstrated improvement of standing blood pressure and OH symptoms in a double-blind, randomized cross-over study and has the additional benefit of not worsening supine hypertension [142]. Other effective treatments include midodrine, per a randomized, double-blind multicenter study [143], as well as droxidopa in a double-blind, crossover, placebo-controlled study [144]. Currently there is insufficient evidence to support the preferential use of any specific agent in the treatment of OH in PD.

**Gastrointestinal Dysmotility**

**Constipation: Epidemiology and Treatment**

Constipation is reported by nearly 60% of PD patients [145]. Constipation can precede the development of motor symptoms of PD, and the prevalence of GI disturbances increases with age and longer duration of disease. Nearly one third of patients will have been diagnosed with a GI disturbance within the year prior to PD diagnosis [146], which is associated with an increased risk for the development PD [147]. People with constipation (defined as < 1 bowel movement per day) but without a PD diagnosis had more nigral Lewy body degeneration postmortem [148] compared with people without constipation.

Treatments for constipation include dietary modification, increased fluid intake, and mild exercise. Macrogol significantly improved constipation in PD patients and was very well tolerated in a randomized placebo-controlled study [149]. Lubiprostone, a GI active prostaglandin, is also effective in the short-term treatment of constipation in a placebo-controlled trial [150].

**Gastroparesis: Epidemiology and Treatment**

Gastroparesis, like constipation, is related to enteric dopaminergic cell loss and degeneration of the dorsal motor nucleus of the vagus [151]. Patients experience gastroparesis as early satiety, full sensation, and nausea. Decreased gastric motility leads to retention of food as well as medications, which can slow absorption and delay onset of action for many medications including levodopa. Domperidone has both prokinetic and antiemetic properties, which have been beneficial in the treatment of gastroparesis [152], but its use is not currently approved in the United States.

**Dysphagia: Epidemiology and Treatment**

Dysphagia is associated with more advanced stages of PD as well as a significant increase in morbidity. Swallow exercises have demonstrated improvement of dysphagia [153]. The impact of levodopa therapy on dysphagia in the literature is controversial. Videofluoroscopic examination is the most common method for evaluation of swallowing disorders and provides important information for speech-language pathologists regarding recommendations for dietary modifications [154]. Adjustment of medication regimens to avoid an oral route is also helpful. This includes Parcopa, orally disintegrating carbidopa/levodopa tablets, and transdermal approaches like the rotigotine patch. For some patients, enteral nutrition is needed and placement of nasogastric tubes or percutaneous endoscopic gastrostomy tubes are an option.

**Sialorrhea (Drooling)**

**Epidemiology**

Difficulty handling oral secretions due to impaired or infrequent swallowing results in sialorrhea in up to 75% of PD patients [155], which is a significant embarrassment for most patients [156]. PD patients with drooling have difficulty speaking, eating, and engaging in social interactions, which significantly impacts perceived quality of life [157].

**Treatment Options**

Botulinum toxin (A and B) injections into the submandibular or parotid glands have demonstrated efficacy in
multiple double-blind, randomized, placebo-controlled studies for the treatment of sialorrhea in PD patients; however, injections are associated with greater invasiveness and cost [158–160]. Glycopyrrolate, an anticholinergic drug, was also efficacious in the treatment of sialorrhea in the short term in a double-blind, randomized, placebo-controlled study [161]. Alternatively, gum chewing increases swallow frequency, improves drooling, and also shows a benefit with dysphagia [162].

**Genitourinary Disturbances**

**Bladder Dysfunction: Epidemiology and Treatment**

Bladder dysfunction in PD is often secondary to hyperactivity of the detrusor muscle leading to urinary urgency, increased urinary frequency, and nocturia. Less commonly, hypoactive detrusor muscle causes difficulty with initiation of urination, delayed bladder emptying, and recurrent infections. Urinary disturbances may occur before the onset of motor symptoms or early on in the disease course [12]. Disease severity is associated with greater urinary disturbances, and more than 50% of advanced PD patients report severe bladder symptoms [163].

Anticholinergic medications such as oxybutynin, solifenacin, and tolterodine are commonly used in the treatment of detrusor hyperactivity and demonstrate significant improvement in detrusor pressure in a recent systematic review and meta-analysis [164]. PD patients on these agents should be closely monitored for side effects including cognitive impairment, somnolence, hallucinations, confusion, and blurred vision. Other treatments include botulinum toxin injections into the detrusor muscle, which has demonstrated safety and efficacy in a recent systematic review [165].

**Erectile dysfunction: Epidemiology and Treatment**

Erectile dysfunction (ED) is reported by more than 60% of male PD patients [145] and is thought to be related to hypothalamic dysfunction and modification of the dopamine-oxytocin pathway [166]. Effects of PD medications, cognitive impairment, fatigue, apathy, and low testosterone contribute to loss of libido and ED [20,167]. Phosphodiesterase inhibitors such as sildenafil, vardenafl, and tadafalfl are possibly useful in the treatment of ED in PD patients, though randomized trials have been limited [166,168]. Apomorphine sublingually is another medication that has demonstrated improvement of ED in a double-blind, crossover study and can be considered for patients with contraindications to phosphodiesterase inhibitors [169].

**SENSORY SYMPTOMS**

**Pain**

**Epidemiology**

Sensory disturbances in PD include diminished ability to identify odors, visual abnormalities (blurred vision, abnormal color perception, double vision), and pain. Pain is the most disabling sensory disturbance, though frequently underreported. Nearly two thirds of PD patients report pain, [170], though only half of patients receive any treatment [171]. Pain may also be a presenting symptom that precedes the clinical diagnosis of PD [172,173].

**Treatment Options**

There are several types of pain described by PD patients, the most common of which is musculoskeletal, typically involving the shoulder. Other types include dystonic, radicular, and central pain [174]. First-line treatment of musculoskeletal complaints includes nonsteroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. Modification of levodopa regimen (including altering timing and frequency or adding controlled release formulations) can often provide relief for dystonic pain, and also for central pain for some patients [173, 174]. Deep brain stimulation, with subthalamic nucleus or globus pallidus targets, has demonstrated improvement with dystonic, central, and musculoskeletal pain in a small clinical study [175].

**CONCLUSION**

NMS are an intrinsic part of PD, may predate diagnosis, and substantially affect the majority of patients with PD. For many of these patients, NMS have a greater impact on quality of life and health care costs than the cardinal motor symptoms that define the disease. Many of these symptoms are not recognized by practitioners and often are not volunteered by PD patients, making it important for practitioners to routinely and directly inquire about NMS. Treatment of NMS in PD is challenging, and only a few therapies have the level of evidence needed to support their use in the treatment of these problems. Nevertheless, proper recognition and addressing of these symptoms afford the clinician an opportunity to make a positive and potentially significant impact on the PD patient’s quality of life.
**REFERENCES**

75. Voon V, Reynolds B, Brezing C, et al. Impulsive choice and...
91. Parkinson J. An essay on the shaking palsy. Sherwood, Neely, and Jones; 1817.
NONMOTOR SYMPTOMS OF PARKINSON’S DISEASE


