Nonmotor Symptoms in Parkinson's Disease

Expanding the View of Parkinson's Disease Beyond a Pure Motor, Pure Dopaminergic Problem

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KEYWORDS

• Parkinson's disease • Nonmotor symptoms • Motor symptoms • Dopaminergic

KEY POINTS

- The pathology of Parkinson's disease (PD) extends far beyond the nigrostriatal dopamine pathway and results in nonmotor symptoms (NMS) in addition to the commonly accepted motor symptoms.
- NMS have a great impact on quality of life, but nonrecognition of NMS is an all too common problem, requiring a systematic approach to both recognizing and treating NMS.
- There are many useful questionnaires that might be used to detect and guide management of NMS.
- The number of evidence-based treatments for these problems remains limited.
- More work needs to be done in therapeutics, and it seems that future therapies for NMS should be developed specifically based on the pathogenesis of PD.
- Therapeutic strategies that use serotonin-based and noradrenaline-based approaches, in addition to dopamine therapy, may provide a more comprehensive control of the multitude of symptoms seen in most patients with PD.

INTRODUCTION

Ever since it was first recognized,[1] Parkinson's disease (PD) has been primarily identified by its cardinal motor symptoms: tremor, bradykinesia, muscle rigidity, and gait instability.[2] Current therapies act mainly on the dopaminergic system,[3] with the overall

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goal of improving motor symptoms and preserving independent function by enhancing dopamine tone.[2] However, intrinsic nonmotor symptoms (NMS) of PD are increasingly recognized as being critical to identify and treat because of their impact on quality of life in PD,[4–11] perhaps having an even greater impact than motor symptoms.[12] Despite increasing evidence of the importance of NMS on quality of life, studies clearly show that there are gaps in treatment of these issues.[11] Although physicians may be aware that NMS are common in PD, these gaps in treatment may be attributable to a need for increased information about and understanding of specific NMS, and clinical approaches for their assessment and management in the context of PD as a whole. This article discusses NMS of PD, how they may be related to the pathologic basis of PD, and how NMS can be best managed.

OVERVIEW OF NMS

The most commonly described primary NMS of PD (summarized in **Table 1**) are autonomic dysfunction, cognitive abnormalities, sleep disorders, mood disorders, pain, and sensory disorders.[7,9,10,13] These NMS are common in patients with PD, with the most common being autonomic dysfunction, mood disorders, and sleep problems.[13–15] There are also NMS in PD that are secondary to pharmacotherapy treatment, such as impulse control disorders and psychosis. In addition to being common, NMS have been reported by patient surveys to be more disabling than the motor symptoms of tremor and bradykinesia.[5]

Autonomic Dysfunction

Autonomic dysfunction associated with PD primarily consists of gastrointestinal (GI) dysfunction, genitourinary dysfunction, and cardiovascular dysfunction with orthostatic hypotension. Although it is a key feature of multiple system atrophy, autonomic dysfunction also commonly occurs in PD and is considered to be the most prevalent category of NMS, affecting more than 70% of patients in all stages of PD.[16]

Dysautonomia manifested as GI dysfunction, particularly constipation, is one of the most common NMS, with prevalence in the 50% to 70% range.[16,17] GI dysfunction was even described in James Parkinson's original monograph on PD[1] and often precedes the development of motor symptoms.[17] Another GI symptom includes drooling/sialorrhea, which is believed to be as much caused by decreased involuntary swallowing as it is to increased saliva production, and is believed to have a prevalence greater than 40%.[17] Incomplete bowel evacuation and bowel incontinence may also occur, but these are less common (30% and 8%, respectively) than constipation or drooling/sialorrhea.[17]

Genitourinary dysfunction is a frequent manifestation of dysautonomia in PD, mostly consisting of urinary urgency, frequency, and incontinence, and includes sexual dysfunction. Urinary dysfunction can be objectively assessed with urodynamic studies and is estimated to have a prevalence of 25% to 40%.[17–19] Sexual dysfunction in men with PD manifests primarily as erectile dysfunction; however, decreases in drive and orgasm have also been reported.[20]

One of the most debilitating NMS is the subcategory of dysautonomia categorized as cardiovascular dysfunction. Cardiac sympathetic denervation is known to occur in PD and is at least partially responsible for contributing to an array of symptoms ranging from orthostatic lightheadedness and hypotension to dyspnea on exertion and fatigue.[21] Although generally occurring later in the disease course and less severe than in multiple system atrophy, orthostatic hypotension can be particularly problematic, resulting in cerebral hypoperfusion, which may impair cognition. When severe,

Table 1
NMS of PD

Category	Subcategory	Examples
Autonomic dysfunction	Gastrointestinal dysfunction	Constipation Sialorrhea/drooling Fecal incontinence
	Genitourinary dysfunction	Urinary urgency/frequency Urinary incontinence Sexual dysfunction
	Cardiovascular dysfunction	Orthostatic lightheadedness/ hypotension Dyspnea on exertion Fatigue
Cognitive dysfunction		Bradyphrenia Executive dysfunction PD dementia
Sleep disorders		REM sleep behavior disorder Restless legs syndrome Periodic limb movements of sleep Excessive daytime somnolence Insomnia
Mood disorders		Depression Anxiety/panic attacks
Pain and sensory disorders	Pain	Paresthesias Limb pain Joint pain Visceral pain
	Olfactory dysfunction	Loss of sense of smell
NMS secondary to pharmacotherapy	Impulse control disorders	Obsessive-compulsive behaviors
	Psychosis	Visual hallucinations Delusions Illusions

Abbreviation: REM, rapid eye movement.

orthostatic hypotension may also lead to syncope and falls. In a survey of more than 1100 patients with PD, the prevalence of symptomatic orthostatic hypotension was 18%,[22] whereas in another study, it was as high as 32%.[17] Compounding this problem is that pharmacotherapy with levodopa or the dopamine agonists is known to worsen orthostatic hypotension, wherein the patient symptoms are dually caused by the PD process itself and by treatment of motor symptoms. Although fatigue in patients with PD is common, with prevalence of fatigue ranging from 33% to 58%, and has multiple contributors and is poorly understood, autonomic dysfunction may play a role in its occurrence.[10,13,23]

Cognitive Dysfunction

Cognitive dysfunction in PD may present in varying degrees. Occurrence is common even among patients with mild PD, and includes difficulties such as bradyphrenia, or slowing of thinking, and executive dysfunction, such as impairment of planning and goal-directed behaviors.[24] When cognitive dysfunction reaches a level of impairment in activities of daily living, it is classified as PD dementia, with its prevalence in the 20%

to 44% range.[17,21] Although the impairments on neuropsychological testing are similar between PD dementia and dementia with Lewy bodies, the dementia in PD, if it occurs, appears years after the onset of motor symptoms. In contrast to dementia seen in Alzheimer disease, PD dementia has relative sparing of encoding of short-term memories, and other cortical features such as aphasia and apraxia are usually absent.

Sleep Disorders

Sleep disorders associated with PD include rapid eye movement (REM) sleep behavior disorder, restless legs syndrome, periodic limb movements of sleep, insomnia, and excessive daytime somnolence (EDS).[25] In a study by Tandberg and colleagues,[26] two-thirds of all patients with PD reported a sleep disorder, and an international study[17] found that 37% of patients reported a sleep disorder. In milder forms, problems may be restricted to fragmentation of nocturnal sleep. However, when combined with restless legs syndrome and periodic limb movements of sleep, these problems can be compounded and lead to insomnia and subsequent EDS. Similar to constipation, REM sleep behavior disorder often precedes the motor onset of the disease and has been evaluated as a predictor for the development of PD.[27–29] Sleep behavior disorder is characterized by recurrent dream enactment behavior during characteristic REM sleep, but without atonia on polysomnography.[27] Although the effect of sleep behavior disorder may be greater on the patient's bedmate than on the patients with PD, perhaps the greatest importance of sleep behavior disorder is early recognition and surveillance for the onset of PD.

Mood Disorders

Mood disorders in PD consist primarily of depression and anxiety, but can also include psychosis and apathy.[30] Anxiety disorders, including generalized anxiety disorder, agoraphobia, panic disorder, and social phobia, have all been reported in PD, with a prevalence of 20% to 40%.[6,17,31] The prevalence of depression in PD is estimated to be 40%, although only a few (4%–6%) meet the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for major depression.[21] In contrast to primary depression, patients with PD show more dysphoria and irritability, but less guilt and a lower incidence of suicide.[32] As a result, the depression in PD is believed to be related more to primary neuropathology selective to the disease state, rather than a secondary reaction to motor deficits in PD.[21,32]

NMS Secondary to Pharmacotherapy

As mentioned earlier, certain NMS may occur as a result of pharmacotherapy for PD. Impulse control disorders are complex behavioral problems and may include pathologic gambling, hypersexuality, compulsive shopping, and compulsive eating. With a reported prevalence up to 13.6%, these impulse control disorders occur more frequently in patients with PD than in the general population, and are critical to recognize because of the known link to treatment, especially dopamine agonists.[33]

In addition, vivid dreams and frank psychosis may occur as a result of dopamine-replacement therapy. Psychosis may occur in up to one-third of all patients with PD.[17,21,34] The most commonly described psychotic symptoms are hallucinations, delusions, and illusions. Hallucinations are usually nonthreatening and visual, as opposed to the auditory hallucinations more frequently seen in primary psychiatric disorders. The most commonly described visual hallucinations include seeing crawling bugs, as well as small animals or people (Lilliputian figures), including children.[34] In a medical illness setting, psychosis such as from dehydration or infection may also

occur in patients with PD. Therefore, an initial medical evaluation should be performed in any patient with PD who develops acute psychosis in the absence of changes to dopamine therapy.

Because PD is primarily regarded as a movement disorder, the natural focus on motor symptoms often leads to underrecognition of NMS by patients and clinicians.[23,35] The importance of recognizing NMS in PD is highlighted by the expanding evidence that NMS cause significant morbidity for patients with PD, perhaps equal to the morbidity caused by the motor symptoms themselves, and this is particularly true in patients with advanced disease.[6,23] In addition, the wearing-off phenomenon most often accompanying motor symptoms has also been described with NMS for more than 20 years and continues to be difficult to identify and treat.[36,37]

PATHOPHYSIOLOGY OF PD MOTOR SYMPTOMS AND NMS

Although the precise pathophysiology of most NMS is not known, the traditional viewpoint that PD is caused by a pure dopamine deficiency beginning in the substantia nigra (SN) is insufficient to explain the asis of NMS. The pathology of PD reflects abnormalities in multiple neurotransmitters, from the cortex to the brainstem and even outside the central nervous system (CNS) altogether. Historically, PD has been linked to depigmentation of the midbrain SN, with surviving neurons in this nucleus containing cytoplasmic inclusions called Lewy bodies.[38,39] These cells were known for providing dopamine to the striatum, and when this catecholamine was measured in patients with PD who had never been treated, it was decreased by approximately 90% in that area of the brain.[40] As a result, most of the pharmacologic therapies for PD have focused on replenishing the CNS dopamine deficiency in these patients,[3] with generally good recovery of motor deficits.[2]

However, the hypothesis that PD is primarily a dopamine deficiency in the brain caused by degeneration of the nigrostriatal pathway was seriously challenged when Braak and Braak[41] introduced their pathologic staging system, which denoted stage 1 with initial degeneration in the caudal brainstem or olfactory bulbs. This degeneration manifests clinically as the NMS of olfactory loss that has been implicated in the preclinical stages of PD.[28] Although not accounted for in the Braak staging system, the PD premotor symptom of GI dysfunction may be explained by the discovery that Lewy bodies, also immunoreactive for α synuclein, were increased in the myenteric plexus of the GI tract in patients with PD.[42–44] This finding has been applied to suggest that the pathology of PD extends beyond the brain and may even preclude CNS involvement.[43]

Braak stage 2 involves progression of neurodegeneration to the lower brainstem, where key nondopamine nuclei are found. For example, noradrenaline (NA)-producing cells in the locus coeruleus (LC) of the dorsal pons[45,46] and in the reticular formation of the medulla oblongata[46,47] have long been shown to be degenerated in patients with PD. These nuclei play an important role in central autonomic control and are thus implicated in the pathogenesis of the NMS of autonomic dysfunction.[4,48,49] Also potentially degenerated at this stage are the raphe nuclei, which produce serotonin (5-HT). This observation is supported by the findings that 5-HT levels in the brains of patients with PD have been shown to be decreased by 56% in the striatum[50] and by 50% in the frontal cortex of nontreated patients.[45] As a result, the degeneration of these NA and 5-HT systems has been implicated in the cause of the mood symptoms of PD.[30]

Braak stages 3 and 4 describe progression of degeneration to the midbrain, especially to the SN, where loss of dopamine cells has long been linked to the cardinal motor symptoms of tremor, rigidity, and bradykinesia.[40] It is at this stage that PD crosses

from a premotor disorder to a motor disorder and is usually clinically diagnosed. However, there are also some implications that dopamine loss influences NMS as well. For example, the role of dopamine in sleep disorders of patients with PD has been suggested because of its function as a modulator of the sleep-wake cycle and its control of periodic limb movements and REM sleep atonia.[51,52]

In the final stages of PD (ie, Braak stages 5 and 6), there is progression to the limbic structures and cortex. The presence of cortical Lewy bodies has been suggested as a primary cause of the cognitive dysfunction found in patients with PD in these stages of disease.[53] Also, decreased activity of choline acetyltransferase, the key synthetic enzyme for acetylcholine production (which, in the PD brain, is at 40%–50% of normal levels), has been noted, which also contributes to the cognitive dysfunction seen in patients with PD.[45] The spread to the limbic system has been implicated in contributing to mood disorders and psychosis.[9]

Complicating the deficiencies of other monoamines in the brains of patients with PD is the use of levodopa, a precursor molecule that still remains the gold-standard pharmacologic therapy. After passing through the blood-brain barrier, levodopa was theorized to be taken up by surviving SN neurons and converted to dopamine by the enzyme aromatic acid decarboxylase (AADC). However, the striking improvements seen in motor functioning seemed unlikely if most dopamine neurons in the SN were already degenerated.[38,39] As a result, it has long been suspected that the efficacy of levodopa in most patients with PD depends in part on surviving striatal 5-HT pathways originating from the raphe nuclei, which also contain AADC needed for the synthesis of 5-HT. Because there was less degeneration in the raphe in patients with PD compared with the SN, it was theorized that much of the conversion from exogenous levodopa into dopamine happens in striatal 5-HT terminals. If this theory is true, then it could further be deduced that increased amounts of exogenous levodopa taken by patients with PD would overwhelm the AADC in raphe terminals, causing them to begin producing dopamine at the expense of 5-HT. This hypothesis has been supported by numerous in vivo experiments,[54–59] implying that the use of levodopa in patients with PD further exacerbates CNS 5-HT deficiency.

Another group of brainstem nuclei also containing AADC are NA-producing neurons of the LC and medullary reticular formation, which are also directly affected by PD.[45–47] As a result, the use of levodopa may also influence NA utilization in these cells, with potential clinical significance, which has rarely been acknowledged in the study of this disease.[60] For example, mounting evidence suggests that the LC provides direct input to the SN and influences dopamine release in the striatum.[60] In addition, the NA produced in the LC influences activity in both the caudate and nucleus accumbens, which are involved in numerous behaviors, such as the proclivity for addiction,[61] and may explain the impulse control disorders that can be seen with dopamine-replacement therapy.[33] In addition, evidence for abundant α_2-noradrenergic receptors of unknown significance have been documented in the striatum and cerebral cortex.[62] Theoretically, these receptors may be involved with motor as well as nonmotor behavioral functions, perhaps even playing a role in neuroprotection.[60]

NMS may also arise as a manifestation of pharmacotherapy. Treatment with dopamine agonists has been linked to the development of impulse control disorders, and treatment with levodopa can cause wearing off of NMS in addition to the more commonly recognized wearing off of motor symptoms.[8,37] This finding belies the need for both a better understanding of the wearing-off phenomenon and of improved treatments that cause neither the development nor fluctuations of NMS.

Although dopamine and nondopamine-producing nuclei and their influences on motor symptoms and NMS have been discussed, these nuclei have complex

interconnections and are subject to higher cortical regulation, meaning that the true pathophysiology of NMS is likely more multifactorial than based on single lesions. Even although Braak staging[41] does not provide an overall explanation for all NMS and premotor findings, it is still helpful in understanding the pathogenesis of NMS when combined with a broader view of PD as being more than merely a disorder of dopamine deficiency in the brain. This is an important consideration when choosing PD treatments for motor complaints and NMS, because therapies addressing beyond just a striatal dopamine deficiency may be needed to treat PD in its entirety.

ASSESSMENT OF NMS

Successful management of PD requires careful and early assessment and monitoring that is specific for NMS, over and above the usual careful management of motor symptoms.[7,63] The importance of this requirement is highlighted by the recent American Academy of Neurology Parkinson's Disease Quality Measures, in which half of the questions specifically address NMS.[64] However, although these measures state that NMS should be recognized and managed, they do not provide direction on how this should be accomplished.

Given the complexity of NMS, successful identification of these symptoms requires a comprehensive approach. One common method is through the use of established, validated questionnaires. Questionnaires that assess NMS range from those that attempt to address aspects of individual symptoms to those that address the entire NMS complex (see **Table 2** for a summary). Although designed to augment routine clinical assessment, questionnaires may be superior in some ways. It has been shown that questionnaires may detect NMS undeclared during clinical assessment[35] and may be better at detecting wearing off of motor problems as well as NMS.[65] Therefore, use of such patient-administered questionnaires can be a useful clinical tool for NMS assessment in the office setting.

The most commonly used patient-administered NMS questionnaire is the Non-Motor Symptoms Questionnaire (NMS-Q),[66] which was designed as a screening tool. This 30-item questionnaire in yes/no format is used to determine whether or not particular NMS are present and shows a sensitivity of 63.4% and specificity of 88.5% for all NMS.[67] After the creation of the NMS-Q, a clinician-administered Non-Motor Symptoms Scale (NMS-S) for PD was created to assess the frequency and severity of these problems in patients with PD.[68] The NMS-S is also 30 items in length, but instead of simple yes/no responses, the clinician administering the questionnaire is asked to rate the frequency and severity of each item. Frequency is rated from 1 (less than once per week) to 4 (daily or more often), and severity is rated from 0 (none) to 3 (severe). For each item, the frequency rating is multiplied by the severity rating, and these values are summed to obtain the total NMS-S score. When compared against other existing scales used in assessing PD, the NMS-S was found to be free of floor or ceiling effects and to be valid and precise overall.[69] Comparing the NMS-Q with the NMS-S, the frequency of NMS reported varied between the 2 instruments, with a higher correlation between patient and caregiver report using the NMS-Q.[13]

In addition to the NMS-S and NMS-Q, there are broader questionnaires that assess general quality of life as well as more specific questionnaires that may address 1 particular symptom. For example, quality-of-life questionnaires can be PD-specific, such as in the Parkinson's Disease Questionnaire (PDQ-39), or more general. A recent task force assessed these quality-of-life questionnaires and reported that the PDQ-39 had the strongest significance and recommends its use in addition to other

Table 2
NMS questionnaires

NMS Addressed	Scale Name	Features	Use
Entire NMS complex	Non-Motor Symptoms Questionnaire (NMS-Q)	30-item, self-completed Yes/no responses	Screening for NMS
	Non-Motor Symptoms Scale (NMS-S)	30-item, clinician-administered 9 domains Requires rating of frequency/severity of NMS	Quantitating NMS
PD quality of life	Parkinson's Disease Questionnaire (PDQ-39)	39-item, clinician-administered NMS only 1 aspect of PD covered by questionnaire	Assesses overall quality of life in PD
Autonomic dysfunction	Scales for Outcomes in Parkinson's Disease (SCOPA)–Autonomic subscale	25-item, self-completed Domains: gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual dysfunction	Screens and measures severity of overall autonomic problems
Cognitive dysfunction	Parkinson's Disease-Cognitive Rating Scale (PD-CRS)	7 tasks, clinician-administered More sensitive/specific for PD-related cognitive problems than MMSE Takes 15–30 min to administer	Screening for early PD-related cognitive deficits and onset of PD dementia
	SCOPA-Cognitive subscale	10 tasks, clinician-administered More sensitive/specific for PD-related cognitive problems than MMSE Takes 10–15 min to administer	Screening for early PD-related cognitive deficits
Depression	Hamilton Depression Index (Ham-D)	Has self-completed, clinician-administered, and semistructured versions 17-item is most commonly used Most widely used of all depression scales Very high sensitivity/specificity	Screening and measuring severity of depression
	Beck Depression Inventory (BDI)	21-item, self-completed, multiple choice responses Moderate sensitivity/specificity Most widely used self-completed depression scale	Screening and measuring severity of depression
	Montgomery-Asberg Depression Rating Scale (MADRS)	10-item, clinician-administered Only 1 study in patients with PD Very high sensitivity/specificity	Measuring change in severity of depression, primarily for use in studies; not designed for clinical screening

Sleep	Parkinson's Disease Sleep Scale (PDSS)	15-item, self-completed, Likert scale Designed for PD-related sleep problems Looks at symptoms over the previous week	Screening and measuring severity of overall sleep problems
	SCOPA-Sleep subscale	12-item, self-completed Looks at symptoms over the previous month	Screening and measuring severity of overall sleep problems and daytime sleepiness
	Pittsburgh Sleep Quality Index (PSQI)	19-item, self-completed Looks at symptoms over the previous month	Screening and measuring severity of overall sleep problems
	Epworth Sleepiness Scale (ESS)	8-item, self-completed 0–3 scoring for each item, cutoff of 10/11 for pathologic sleepiness	Screening and measuring severity of daytime sleepiness
	Inappropriate Sleep Composite Score (ISCS)	6-item, clinician-administered	Screening and measuring of severe daytime sleepiness or sleep attacks
	Stanford Sleepiness Scale (SSS)	1-item, self-completed, yes/no responses	Screening daytime sleepiness and measuring severity at a specific moment only
Apathy	Apathy Evaluation Scale (AES)	Likert scale with 18 items; 4 items scored by patient alone, 1 item by rater alone	Screening for apathy in treatment studies
	Apathy Scale (AS) – Modified	Abridged AES developed for PD 4-point Likert scale with 14 items, scored by patient (items are read to patient)	Screening for apathy in treatment studies
	Lille Apathy Rating Scale (LARS)	33-item, structured interview with yes/no or Likert scale responses	Screening for apathy in treatment studies
Anhedonia	Snaith-Hamilton Pleasure Scale	14-item, self-completed, Likert scales	Screening for anhedonia in treatment studies

Abbreviation: MMSE, Mini-Mental State Examination.

disease-specific instruments (Parkinson's Disease Questionnaire Short Form, Parkinson's Disease Quality of Life Questionnaire, Parkinson's Impact Scale, and Scales for Outcomes in Parkinson's Disease-Psychosocial) and general questionnaires (EuroQoL-5, Nottingham Health Profile, 36-Item Short-Form Health Survey, and Sickness Impact Profile).[70] Another commonly used tool is the Scales for Outcomes in Parkinson's Disease (SCOPA), which has multiple subscales, including measurement of motor, cognitive, sleep, autonomic, and psychiatric complications (SCOPA-PC).[71] The SCOPA provides outcome measures for both motor problems and NMS and, in several recent reviews, the different SCOPA subscales have been compared with various other symptom-specific scales.[72–75]

For the NMS of sleep dysfunction, a review by Hogl and colleagues[73] recommends the Parkinson's Disease Sleep Scale (PDSS), SCOPA-sleep, and the Pittsburgh Sleep Quality Index for both screening and measuring severity of overall sleep problems. For scales to screen and measure daytime sleepiness, the same investigators recommend the Epworth Sleepiness Scale (ESS), whereas the Inappropriate Sleep Composite Score and the Stanford Sleepiness Scale were suggested only for use as alternatives to the ESS.[73]

For the NMS of dysautonomia, Evatt and colleagues[72] recommends the SCOPA-Autonomic and NMS-Q, based on the specific use of these instruments in PD clinical studies, which was beyond the group that developed it, thereby verifying its validity, reliability, and sensitivity.

For the NMS of cognitive dysfunction, the Parkinson's Disease–Cognitive Rating Scale (PD-CRS) and the SCOPA-Cognitive subscale were most recommended, according to Kulisevsky and Pagonabarraga,[74] because of their strongest validation scores. Both tools were designed specifically to detect cognitive deficits in patients with PD, as opposed to other forms of dementia, and both were deemed superior to the more commonly used Mini-Mental State Examination (MMSE) in sensitivity for PD-related cognitive dysfunction. The MMSE has never been validated in populations with PD.

For the NMS of depression, the Beck Depression Inventory (BDI), Hamilton Depression Scale (Ham-D), and Montgomery-Asberg Depression Rating Scale (MADRS) were found to be the most useful scales for both screening and measurement of severity of depression related to PD.[75] The MADRS was not designed for clinical screening, although it was applied as such in 1 study in patients with PD. The BDI and Ham-D have both been used extensively in patients with PD. The BDI is completed by the patient, whereas the Ham-D has both clinician-administered and patient-completed components. Apathy and anhedonia are related to depression, which can also be signs of depression in patients with PD but can also be separately related to PD itself. Although there are scales that have been developed for apathy (Apathy Evaluation Scale, Lille Apathy Rating Scale) and anhedonia (Snaith-Hamilton Pleasure Scale), their use has been primarily limited to treatment studies and not to clinical screening.

In addition to screening for the presence of NMS, many of these questionnaires also measure severity of NMS complaints, providing a helpful tool for the clinician to help guide treatment. However, other efforts are still needed to raise awareness about the meaning of NMS in the cause and progression of PD. As alluded to previously, NMS are being evaluated as potential core features of the premotor stage of PD,[76] which has significant implications in predicting the manifestation of motor problems in PD, as well as defining an at-risk population for developing PD. NMS may also have value as biomarkers for the progression of PD, because the number of NMS reported by patients correlate significantly with advancing disease.[5]

EVIDENCE-BASED TREATMENT OF NMS

Of existing treatments, several options may be considered for management of NMS. **Table 3** summarizes conclusions of the 2010 American Academy of Neurology (AAN) Practice Parameters for NMS in PD[11] and the Movement Disorder Society (MDS) recommendations for treatment of NMS from 2011,[77] as well as a clinical review by Wood and colleagues[78] from 2010. The AAN and MDS recommendations applied rigorous criteria and only recommend therapies that have shown robust evidence-based support for their use, whereas the Wood and colleagues review evaluated expert opinions in addition to clinical studies and provides clinically based recommendations.

For constipation, all 3 groups agree that evidence supports the use of isosmotic macrogol (polyethylene glycol).[11,77,78] Wood and colleagues[78] also note that, when treating GI dysfunction in patients with PD, the practitioner must take special care

Table 3
Summary of evidence-based treatment guidelines for NMS in PD

NMS	American Academy of Neurology Practice Parameter	Movement Disorder Society Recommendations	Clinical Review Recommendations
Constipation	Polyethylene glycol	Polyethylene glycol	Polyethylene glycol; avoid dopamine-blocking antiemetics
Orthostatic hypotension	Insufficient evidence	Insufficient evidence	Begin with nonpharmacologic interventions (increased fluid/salt intake, compressive stockings) If fails, add fludrocortisone and/or midodrine
Depression	Insufficient evidence	Evidence supports use of nortriptyline, desipramine, and pramipexole; avoid nefazodone	Although no evidence, expert opinion favors use of selective serotonin reuptake inhibitors as first-line treatment
Psychosis	Reduce dopaminergic medication where possible	Reduce dopaminergic medication where possible Evidence supports use of clozapine; avoid olanzapine	Reduce dopaminergic medication where possible Quetiapine or, if ineffective, clozapine
Dementia	Not mentioned	Rivastigmine	All cholinesterase inhibitors
Sleep-related dysfunction	Consider modafinil for excessive daytime somnolence Consider methylphenidate for fatigue	No mention	Tailor treatment to individual patient's predominant symptoms

to avoid antiemetics with dopamine receptor-blocking properties (eg, metoclopramide, prochlorperazine).

For autonomic dysfunction manifested as orthostasis, the most common treatment plan is to begin with nonpharmacologic interventions such as increased fluid/salt intake and compressive stockings, followed by pharmacologic treatments such as fludrocortisone, midodrine, or indomethacin. Both the AAN and MDS reviews state that there is insufficient evidence to strongly support or refute these treatments.[11,77]

Regarding mood disorders in PD, expert opinion favors the use of selective serotonin reuptake inhibitors as first-line therapy, although all 3 reviews report that there is little evidence to support this. For depression, the strongest evidence supports the use of nortriptyline, desipramine, and pramipexole.[77] In addition, the MDS review states that nefazodone should be avoided for safety reasons.[77] For psychosis occurring in patients with PD, the general recommendation is to start by reducing dopamine therapy for motor symptoms, when possible.[78] If this strategy fails, then there is, in general, common use of quetiapine or clozapine.[78] However, although there is good evidence to support the use of clozapine,[77] there is still insufficient evidence to recommend the use of quetiapine.[11,77] The MDS review makes specific mention that olanzapine should be avoided because of safety concerns.[77]

For cognitive abnormalities, specifically dementia occurring in PD, the strongest evidence supports the use of rivastigmine[77]; however, there is wide use of all of the central cholinesterase inhibitors.[78]

Regarding sleep-related dysfunction, Wood and colleagues[78] noted that, from insomnia to daytime hypersomnolence to REM sleep behavioral disorder to restless legs syndrome, sleep disorders of PD can vary among individual patients; therefore, therapies should be tailored for each patient's most prominent symptoms. The AAN review recommends consideration of modafinil in the treatment of EDS and methylphenidate in the treatment of fatigue in patients with PD.[11] The MDS review also reported that there are several ongoing randomized controlled trials; therefore, the data need to be continuously monitored so that recommendations for treatment remain up to date. Overall, all 3 reviews[11,77,78] agree that there is still much work to be done to improve evidence-based treatment of NMS in PD and many more clinical data are needed to develop more robust treatment guidelines for NMS.

SUMMARY

The pathology of PD extends beyond the nigrostriatal dopamine pathway and results in NMS in addition to the commonly accepted motor symptoms. NMS have a great impact on quality of life, but nonrecognition of NMS is an all too common problem, requiring a systematic approach to both recognizing and treating NMS. There are many useful questionnaires that might be used to detect and guide management of NMS. However, as reported here, the number of evidence-based treatments for these problems remains limited. Most work needs to be done in therapeutics, and it seems that future therapies for NMS should be developed specifically based on the pathogenesis of PD. Therapeutic strategies that use 5-HT-based and NA-based approaches, in addition to dopamine therapy, may provide a more comprehensive control of the multitude of symptoms seen in most patients with PD.

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