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REVIEW

Nonmotor symptoms in Parkinson's disease: classification and management

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Abstract: Despite the emphasis on the motor phenotype of Parkinson's disease (PD), it has been increasingly recognized that PD patients experience several nonmotor symptoms (NMS), which have even greater significance when assessed by quality-of-life measures and institutionalization rates. The burden of NMS tends to increase with age and disease severity and, in the very advanced stage of disease, NMS such as urinary problems, drooling, somnolence, psychosis, and dementia dominate the clinical phenotype. Moreover, the dopaminergic treatment used for the motor symptoms of PD can arise or worsen a number of NMS, including orthostatic hypotension, nausea, sleep disturbances, hallucinations, or impulsive compulsive behaviors. Here we review the most common NMS of PD with a focus on their pharmacological management.

Keywords: disease management, PD, NMS

Introduction

Despite the emphasis on the motor phenotype of Parkinson's disease (PD), it has been increasingly recognized that PD patients experience several nonmotor symptoms (NMS),[1–5] which have even greater significance when assessed by quality-of-life measures and institutionalization rates.[6–11]

Virtually all patients have at least one NMS at the time of diagnosis[12,13] and some NMS, such as hyposmia and rapid eye movement (REM) sleep behavioral disorder (RBD), can also predate the onset of motor symptoms by several years.[14] The burden of NMS tends to increase with age and disease severity and, in the very advanced stage of disease, such NMS as urinary problems, drooling, somnolence, psychosis, and dementia dominate the clinical phenotype.[15] However, there is a marked heterogeneity among patients[16] and, while the evolution of motor symptoms has been well characterized, little is yet known about the NMS progression.[17–19] This matter is also complicated by the fact that the dopaminergic treatment used for the motor symptoms of PD can cause or worsen a number of NMS, including orthostatic hypotension (OH), nausea, sleep disturbances, hallucinations, or impulsive compulsive behaviors (ICBs).[20–23]

A recent multicenter survey has shown that the large majority of NMS remain undeclared to health care professionals, probably because patients are either embarrassed or unaware that such NMS are due to PD.[24] Use of recently validated NMS screening questionnaire and/or rating scales[25,26] can facilitate their recognition and management in clinical practice.

NMS have been traditionally grouped into different domains on the basis of a seemingly common pathophysiology, yet not entirely proven. Four main domains are recognized (Table 1), and will be therefore covered accordingly: Autonomic

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Table 1 Overview of the nonmotor symptoms of PD

Nonmotor domain	Nonmotor symptoms
Autonomic	Dribbling
	Dysphagia
	Nausea
	Constipation
	Urinary frequency
	Urinary urgency
	Nocturia
	Urinary voiding symptoms
	Sexual dysfunction
	Orthostatic hypotension
	Supine (recumbent) hypertension
	Excessive sweating
Sleep	Excessive daytime sleepiness
	Vivid dreams/REM behavioral disorder
	Insomnia
	Restless legs syndrome
Neuropsychiatric	Cognitive impairment
	Mood disorder, apathy, anhedonia
	Psychosis
	Hallucinations
	Impulsive compulsive behaviors
Sensory and other NMS	Olfactory, visual, and auditory dysfunction
	Pain
	Fatigue

Abbreviations: PD, Parkinson's disease; REM, rapid eye movement; NMS, nonmotor symptoms.

(including gastrointestinal [GI], genitourinary, and cardiovascular symptoms), Sleep, Neuropsychiatric, and Sensory and other symptoms (including pain and fatigue). For each of these nonmotor domains, the most frequent symptoms will be described with a focus, when possible, on their pharmacological management. There is now evidence that nonpharmacological options, including deep brain stimulation,[27] can ameliorate certain NMS, but this is still a matter of ongoing research and hence will be not covered here.

Autonomic domain

Autonomic symptoms in PD may be due to the abnormal deposition of α-synuclein aggregates in a number of key autonomic regulatory areas (namely, the hypothalamus, parabrachial nucleus, intermediate reticular zone of the medulla, locus coeruleus, and raphe), preganglionic parasympathetic (ie, Edinger–Westphal nucleus and dorsal vagal motor nuclei) and sympathetic regions (ie, intermediolateral cell column), and also in the paravertebral and paravertebral autonomic gangli.[28] The deposition of α-synuclein in such areas can directly cause autonomic symptoms, but it should be noted that antiparkinsonian medications might also play a role. Dopaminergic receptors are widely distributed throughout both the central and peripheral autonomic nervous systems; dopamine lowers systemic blood pressure through vasodilation and decreased catecholamine release and reduces gastric migrating motor complex and gastric motility, whereas it may increase colonic motor activity.[28] Table 2 provides an overview of the useful investigations to assess the autonomic symptoms.

Gastrointestinal symptoms

GI symptoms can be very common in PD, with prevalence estimates of 75% in advanced PD patients.[29] However, such NMS are very common also in the elderly; therefore, in PD patients they can be due to a combination of the pathological process and normal aging. In PD, they can be classified into upper GI symptoms, among which the most common are sialorrhea, dysphagia, and nausea, and lower GI symptoms, including constipation.[30]

Although excessive drooling has been classically considered an NMS, there is no increased production of saliva as such in PD. Excessive drooling in fact results from inefficient swallowing in PD, and it should be therefore considered more as a motor rather than an autonomic symptom.[30] A great percentage of patients experience dysphagia and show abnormalities on X-ray tests of swallowing.[30] Although management of dysphagia can be difficult, speech/swallowing therapy can improve symptoms.[30] Changes in food consistency that reduce the risk of aspiration are sometimes needed. As to excessive drooling, botulinum toxin injections into the salivary glands can ameliorate the sialorrhea, and are relatively free from side effects.[31,32] Anticholinergic drugs can be tried,[30] remembering that their side effects, including memory problems, confusion, or blurred vision, are not uncommon with increasing dosage and age of the patients.

Table 2 Overview of the useful investigations to assess autonomic symptoms in PD

Nonmotor symptoms	Investigations
Gastrointestinal symptoms	Swallowing and esophageal motility (modified barium swallow test)
	Gastric emptying studies
	Electrogastrogram
	Colon transit time and anorectal manometry
Urinary symptoms	Urodynamic study and sphincter electromyography
Cardiovascular symptoms	Head-up tilting
	Valsalva maneuver and pressor stimuli tests
	24-hour blood pressure recording
	Meal challenge and exercise test
	Heart rate variability
	Skin vasomotor reflex
Others	Thermoregulatory sweating test
	Skin biopsy

Abbreviation: PD, Parkinson's disease.

Nausea has been reported in drug-naïve PD patients, but is much more common as a side effect of the dopaminergic treatment, especially of dopamine agonists.[30] In the majority of patients, it is usually transitory, and it can be prevented with domperidone, a peripheral antidopaminergic drug, which increases GI peristalsis and relieves nausea and vomiting.

Constipation is probably the most common GI symptom, with about half of PD patients experiencing it.[29,30] Constipation can predate the motor onset of PD,[33] and some evidence has shown that men who have bowel movements less than once daily compared with two or more times daily have a four times higher risk of PD after a mean time of 10 years.[34] Severity of constipation increases with advancing disease severity and duration, and can produce complications such as pseudo-obstruction and megacolon.[30] Drugs used for PD, including the anticholinergics, can exacerbate constipation.[30] Apart from a well-balanced diet with plenty of fiber (in the range of 20–35 grams daily) and fluid intake, macrogol can be used to treat constipation.[30]

Genitourinary symptoms

Urinary symptoms (US) are common in PD, with a prevalence of more than 50% according to screening questionnaires.[25,26,29] Once again, benign prostate hyperplasia and idiopathic detrusor overactivity often occur in the elderly and can contribute to the US seen in PD.[28] Interestingly, US likely reflect a combination of underactive D1 receptors activity with possible exacerbation by D2 receptor stimulation.[35]

US can be categorized into storage symptoms (ie, frequency, urgency, and nocturia) and voiding symptoms (eg, delays in initiating urination, poor or prolonged urine stream). Storage symptoms are common even in the early stage of the disease; troublesome incontinence is usually observed in more advanced PD patients.[25,26,29] On the other hand, severe voiding symptoms are quite uncommon in PD, at least in the early/middle stages.[17,29] Medications that work to block or reduce bladder overactivity can be useful in treating storage symptoms.[36] A number of medications are available for this aim, including older drugs such as oxybutynin and tolterodine, and newer medications such as solifenacin and darifenacin.[36] Such drugs are obviously not useful to treat voiding symptoms.[37] In such cases, bethanechol or botulinum toxin injections may be helpful, but intermittent self-catheterization is sometimes necessary.

Sexual dysfunction is common in PD, but most data are available only in male patients.[19,38] Erectile dysfunction is very frequent, with prevalence up to 75%.[18,25,29] In a recent epidemiological study, erectile dysfunction was also associated with a 2.7 to four-times higher risk of developing PD later in life.[39] Sexual dysfunction in PD might be caused by multiple factors, including the disease itself or other associated features, such as depression and anxiety. Testosterone deficiency has been implicated.[40] If sexual drive is normal, both injectable (ie, papaverine, phentolamine, alprostadil) and oral preparations (ie, sildenafil, vardenafil, tadalafil, yohimbine) are available.[41,42]

Cardiovascular symptoms

Among cardiovascular symptoms, OH is the most common. Postural hypotensive symptoms in PD have been reported in about half of the patients, but their prevalence increases in the advanced stages.[28] Symptoms related to OH can be very heterogeneous. Patients can experience posturally induced dizziness, visual disturbances, transient cognitive impairment, and syncope. OH may also cause fatigue, chest pain, dyspnea, and falls. Food ingestion, exercise, heat, or drugs with hypotensive properties, including some antiparkinsonian agents, can aggravate OH. The management of OH in patients with PD should start with patient education and nonpharmacological treatment.[28,41,42] Drug therapy is required for symptomatic patients who do not improve from nonpharmacological management, and consists of alpha1-adrenergic agonists (mainly midodrine) or plasma volume expanders (mainly fludrocortisone).[28,41,42]

PD patients with OH may also have supine (recumbent) hypertension, especially at night if they lie entirely supine, with a reversal of the circadian change in blood pressure.[28] Recumbent hypertension may contribute to ventricular hypertrophy, renal dysfunction and intracerebral hemorrhage.[28] Antihypertensive drugs can be taken at night, and patients need to be instructed to sleep in a semi-supine position.[28]

Sleep domain

Sleep symptoms including excessive daytime sleepiness (EDS), vivid dreams, and RBD are very common in PD and affect more than two-thirds of patients.[12,17,43] Patients can also have restless legs syndrome or sleep disorder breathing, which in turn can affect sleep quality.[43] Of note, RBD can antedate motor onset by several decades and has been associated with development of cognitive dysfunction in PD.[12] The pathophysiology of RBD is supposed to involve neuronal degeneration/dysfunction in the brainstem, in particular in the cholinergic regions that regulate muscle atonia during REM sleep.[12,20,43] Symptoms of RBD are in fact due to a lack of atonia during REM sleep and result in

dream-enacting behaviors, with possible secondary injuries. There are no clear differences in the frequency of RBD among male and female patients (about 30% in both), but significant sex differences are associated with its clinical expression, with female PD patients reporting significantly less aggressive behaviors during dreams but more disturbed sleep than male PD patients.[44] Some medications, including tricyclic antidepressants and serotonin reuptake inhibitors, can worsen RBD symptoms and should be discontinued.[45] Clonazepam (0.5–1.0 mg, once at night) is the first choice for RBD. It is well tolerated and efficacious in the majority of cases.[45] If clonazepam is proven ineffective or poorly tolerated, melatonin (3–6 mg, at night) is recommended as second-line therapy.[46,47] In individual cases, melatonin could be tried first given its favorable side effect profile, but it should be acknowledged that it is far less effective than clonazepam for the treatment of RBD.[46,47]

EDS is likely more frequent than RBD, affecting about 50% of patients. A combination of the disease process, nocturnal sleep fragmentation, and dopaminergic medications (particularly dopamine agonists) likely determines EDS.[48] Patients can experience involuntary dozing, with abnormal periods of sleep latency (less than 5 minutes), or sudden sleep attacks.[48] Improvement of nocturnal sleep can in turn improve EDS, but in some patients specific treatments for EDS are required. Modafinil improves EDS in PD patients, at least on a subjective or behavioral level, and can be therefore considered in PD patients in whom otherwise treatable causes of EDS are absent.[46]

About 20% of PD patients can also manifest restless legs syndrome, which can cause trouble falling asleep and disrupt sleep quality, if there are associated sleep periodic limbs movements in sleep stages 1 and 2. Low doses of dopamine agonists at bedtime might relieve these symptoms.[46]

Neuropsychiatric domain

Cognitive impairment

Cognitive dysfunction is quite common in PD, and it can occur from the early stages.[12,49] It has a negative impact on the daily lives of patients and their caregivers[6–8] and may be associated with subtle functional impairments.[50] Patients may show executive dysfunctions (planning, concept formation, problem solving), impaired attention and memory, and/or visuospatial dysfunctions.[51] Whether specific cognitive disturbances are related to different underlying mechanisms is not entirely known, but altered naming or visuospatial functions are considered the strongest predictors of subsequent dementia in PD.[52] More recently, the construct of Mild Cognitive Impairment (MCI) has been applied also in PD research. The prevalence of MCI in a meta-analysis of 1346 PD patients was 26%,[53] a figure similar to that obtained by the task force commissioned by Movement Disorders Society.[54] Many risk factors for MCI in PD have been reported, including advanced age, disease duration, and disease severity,[54] while other features such as side of motor onset have been discarded.[55] Further NMS, including hallucinations, sleep, and mood disturbances, have been also associated with the development of MCI.[56] Moreover, subjective memory complaints have been found to be a predictor of MCI.[57] Since patients with MCI, arguably with posterior cortical profiles, may be at high risk for developing dementia, early identification of patients with MCI is crucial for future neuroprotective trials. To this aim, specific diagnostic criteria for MCI have been recently proposed.[58]

Rivastigmine is effective for the treatment of dementia in PD, whereas there is not enough evidence as far as donepezil, galantamine, and memantine are concerned.[46] Atomoxetine, a noradrenergic reuptake inhibitor, was reported to improve cognitive function in depressed PD patients.[59] Rasagiline has shown positive effects on attention and executive functions in nondemented PD patients.[60] Finally, amantadine has been reported to delay cognitive decline in PD.[61]

Mood disorder, apathy, and anhedonia

Depressive disorders in PD include major depression, minor depression, dysthymic disorders, and subthreshold depression.[62] Anxiety can co-occur in some patients[62] and has been supposed to share, at least in part, the same pathophysiology.[63] Depression is associated with severe motor symptoms, greater disability, more advanced disease stage, longer disease duration, higher levodopa equivalent dosages, hallucinations, sleep disorders, and dysautonomia.[64,65] The combination of apathy, anhedonia, and frontal lobe dysfunctions might contribute to the overdiagnosis of depression in PD.[66] The hypothesis that apathy and depression are in fact two independent NMS of PD was confirmed recently.[67] Depressive symptoms in PD can be effectively treated by means of dopamine agonists.[68] There is some evidence for efficacy of selective serotonin and norepinephrine reuptake inhibitors (paroxetine and venlafaxine, respectively) for depression in PD,[69] while nonpharmacological interventions, including cognitive behavior therapy and repetitive transcranial magnetic stimulation, have been suggested.[70–73]

Apathy is one of the most common NMS of PD, with prevalence rates ranging from 13.9% to 70%.[74] Apathy is associated with altered ability of processing inferences about

other people's emotions and feelings[75] and with cognitive impairment, particularly dysexecutive syndromes.[76,77] There are no approved drugs for managing apathy, but since apathy is related to depression and cognitive impairment, pharmacologic agents most frequently administered to apathetic patients include dopaminergic drugs and acetylcholinesterase inhibitors (for a recent review, see reference 74).

Anhedonia is defined as a low ability to experience physical and social pleasure, and its prevalence ranges from 15% up to 79.7% in PD patients with depression.[78,79] It is associated with apathetic or depressive syndromes in PD patients, indicating that reduced hedonic tone may be considered a feature of apathy[80] and of depression.[81,82] Conversely, Isella et al[78] did not find a relationship between anhedonia, depression, and apathy. Increasing age, apathy, and cognitive dysfunctions were found contributing factors to anhedonia severity.[83] Anhedonia might be related to cognitive dysfunctions as well. On one hand, no correlations have been found;[78] on the other hand, we reported that patients with anhedonia performed worse than nondepressed patients without apathy or anhedonia on cognitive tasks tapping visual-constructional and frontal functions.[66,82] The relationship between anhedonia and frontal dysfunctions might support the idea that anhedonia may depend on frontal lobe dysfunctions arising from alteration of prefrontal dopamine circuits. In this regard, pramipexole and rotigotine have been found to improve anhedonia.[83,84]

Impulsive compulsive behaviors

A heterogeneous spectrum of ICBs can be seen in PD, ranging from subsyndromal disturbances to frank impulse control disorders (ICDs).[85,86] They are characterized by the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others, and are likely under-reported.[85,86] The most common ICDs include pathological gambling, compulsive buying, hypersexuality, compulsive eating, and medication overuse. Male sex, younger age or younger age at PD onset, personal or family history of substance abuse or ICD, a personality profile characterized by impulsiveness,[87,88] and cognitive dysfunction, mainly alteration of executive functions, are factors strongly associated with ICDs.[89,90] Beside these risk factors, treatment with dopamine agonists more than with levodopa has been strongly associated with ICBs/ICDs.[85,86,89,91–93] Management of ICDs consists of dose reduction or drug discontinuation;[94,95] results pertaining to the efficacy of amantadine are conflicting.[96,97] Studies on small samples of PD patients reported reduction of ICDs and impulsivity scores after treatment with selective serotonin reuptake inhibitors,[98] atypical antipsychotics,[99–103] and antiepileptic drugs.[104–107]

Sensory domain

Olfactory, visual, and auditory dysfunction

Olfactory dysfunction has been long recognized to be associated with PD, occurring in up to 90% of cases[107] and often appearing years prior to the motor symptom onset.[108] Early onset of anosmia in PD strongly correlates with Braak's findings showing α-synuclein deposits in the olfactory structures at the earliest stages of development of PD pathology.[109–111] Such early involvement of olfactory circuits together with a high prevalence of anosmia in the PD population render smell test a useful and easy-to-administer tool for screening of at-risk subjects.[112] Smell loss has been also demonstrated in first-degree relatives of patients with inherited forms of PD[113] and findings from longitudinal studies showed that smell test may predict future development of PD in asymptomatic family members.[108,114] Hence, olfactory testing combined with dopamine transporter imaging or other indicators of PD may offer a useful tool to predict risk of PD. Finally, olfactory dysfunction is not stationary in PD patients and deteriorates over time, so hyposmia has been suggested as a marker to assess the disease's progression and the effects of disease-modifying drugs.[115]

Patients with PD may develop a range of visual problems during the course of the disease resulting from abnormalities in visual acuity, color perception, and visual contrast sensitivity. Color and contrast discrimination disturbances have been also suggested as early premotor signs of PD.[116,117] Furthermore, the severity of these deficits fluctuates throughout the day in association with the dosing schedule of dopaminergic medications.[118] As the disease progresses, poor visual acuity becomes a common complaint of PD patients, resulting in part from natural aging,[119] with low contrast acuity being especially affected.[120,121] Impaired visual acuity also appears to be caused by retinal dopamine deficiency, abnormal eye movements, or poor blinking[121] and seems to be a risk factor for the development of chronic hallucinations in PD.[122] Visual deficits in PD are important in influencing global mobility[123] and are important in influencing quality of life.[124] Although early in the course of the illness these changes are subtle, as the disease progresses they become clinically evident.

Hearing impairment in the general population increases with age, with 62% of people having some degree of hearing loss by age 85.[124] Despite this high prevalence, there is preliminary evidence that hearing impairment can be intrinsic to the NMS spectrum in PD.[125,126] We have previously showed that

there is an age-dependent peripheral, unilateral, or bilateral hearing impairment in PD patients, but we could not rule out whether hearing loss is intrinsic to PD or secondary to more complex causative factors.[127] We hypothesized that natural aging in combination with widespread neuropathologic changes associated with the disease might affect cochlear transmission thus promoting hearing impairment.[127] More recently, Lai et al investigated in a large retrospective population-based study whether hearing loss was associated with PD and found that the incidence of PD in the hearing loss group was 1.77-fold higher than that in the nonhearing loss group.[128] Furthermore, they also suggested that auditory dysfunction might antedate the clinical diagnosis of PD.[128] Overall, these results support an association between PD and hearing loss, thereby expanding the nonmotor PD phenotype.

Other NMS

Fatigue

Fatigue occurs in every stage of PD, with a prevalence ranging from 28% to 77.6%.[129] It may also antecede the onset of motor symptoms in some patients.[129] Female sex, postural instability/gait difficulties phenotype, depression, anxiety, apathy, sleep disturbances, and autonomic impairment have been associated with fatigue.[28,129,130] As such, there is a debate on whether fatigue should be considered either a sensory or a neuropsychiatric problem. In view of the fact that clear neuropsychiatric issues can be lacking in PD patients complaining about fatigue, we thought it reasonable to consider fatigue (and pain, as outlined ahead) on their own. The pathophysiology of fatigue in PD is in fact still poorly understood. Several findings suggest that fatigue in PD might have a minor peripheral contribution and a major component due to central mechanisms.[131] However, it is worth noting that central fatigue may overlap with a number of NMS such as depression, apathy, and sleep problems, thus complicating the understanding of its pathophysiology. Data from neuroimaging studies have suggested that fatigue can be associated with nondopaminergic neural circuits.[132] However, most studies investigated the effect of dopaminergic drugs on fatigue. There is a suggestion of a beneficial effect of levodopa and pergolide.[133,134] Moreover, a post hoc analysis of the RECOVER study[84] found significant improvement on the fatigue item of the Non-Motor Symptoms Scale (NMSS) in the rotigotine group compared with the placebo group, though such benefit was also associated with improvement in depression, apathy, and anhedonia. Finally, a substudy of the ADAGIO study has shown that rasagiline was associated with significantly less progression of fatigue compared with placebo over a 9-month period.[135] More recently, methylphenidate, a dopamine transporter blocker, at a dose of 10 mg three times a day has been found to improve fatigue in a randomized, placebo-controlled study.[136]

Pain

Pain is one of the most common NMS in PD. O'Sullivan et al reported that pain was the most frequent NMS reported by PD patients as a first complaint.[137] Quite intuitively, pain correlates with poorer quality of life; it can also be treatment resistant. The mechanisms underlying pain in PD are not totally clear. Pain process in PD might be affected at multiple levels, from the transmission of the pain from peripheral structures to the higher centers; in fact, authors have identified four different types of pain in PD. Musculoskeletal pain, determined by rigidity/skeletal deformity, and radicular or neuropathic pain are differentiated by whether or not the pain is described as radiating.[138] Dystonic pain (often as a complication of dopaminergic medications) and central neuropathic pain are also seen in PD.[139] As such, the management of pain in PD follows its proper recognition and distinction into these four main types. Peripheral causes of pain can be managed according to the specific situation and with conventional analgesics. Pain associated with dystonia can be related to both ON and OFF phases, and can be best managed with botulinum toxin injections if rearrangement of dopaminergic therapy cannot be pursued. Central pain can be effectively treated by increasing the dopaminergic load.[140] Conventional analgesics, opiates, and tricyclic antidepressants are second-line options.[140]

Conclusion

Poor recognition of NMS in PD affects patients' quality of life and also costs of care; therefore, routine screening for NMS is recommended. The decision as to when to start treatment for NMS and which therapy to use must be taken on an individual basis and depends on several factors, including patient preference, age, the degree of disability, and comorbidities. Future studies are warranted to fully understand the pathophysiology of NMS in PD; this will allow designing specific trials focused on their management.

Author contribution

RE, GS, PB, and CV made substantial contributions to the conception and design, acquisition of data, and analysis and interpretation of data, drafted the article and revised it critically for intellectual content, and had final approval of the version to be published.

Disclosure

The authors report no conflicts of interest in this work.

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