Parkinson’s disease (PD) is a multisystemic disorder characterized by various non-motor symptoms (NMS) in addition to motor dysfunction. NMS include sleep, ocular, olfactory, throat, cardiovascular, gastrointestinal, genitourinary, or musculoskeletal disorders. A range of NMS, particularly hyposmia, sleep disturbances, constipation, and depression, can even appear prior to the motor symptoms of PD. Because NMS can affect multiple organs and result in major disabilities, the recognition and multidisciplinary and collaborative management of NMS by physicians is essential for patients with PD. Therefore, the aim of this review article is to provide an overview of the organs that are affected by NMS in PD together with a brief review of pathophysiology and treatment options.

Keywords: Parkinson’s Disease; Non-motor Symptoms
INTRODUCTION

Parkinson’s disease (PD) and essential tremor are common neurological disorders associated with tremors. The estimated prevalence of the disorders, with a lower frequency in PD, has ranged from 0.4% to 5% of the global population. In the Korean population, the prevalence of PD among individuals aged 65 and older has been reported to be 0.4%, while that of essential tremor was 3.6%. Unlike patients with essential tremor, those with PD present with asymmetric rest tremor, and nearly all of them have one or more non-motor symptoms (NMS). Certain NMS, such as olfactory dysfunction, rapid eye movement (REM) sleep behavior disorder (RBD), depression, constipation, and pain can even antedate the development of motor symptoms of PD. Although not yet confirmed, Braak’s hypothesis illustrates NMS preceding the motor signs of PD; α-synuclein and its aggregates called Lewy bodies, the principle pathology of PD, form in the olfactory bulbs and the lower brainstem involving the dorsal motor nucleus of the vagus, nucleus ambiguous, raphe nucleus, and locus coeruleus, thereby affecting olfactory and autonomic functions as well as sleep. These structures correspond to Braak stages I–II and may precede the motor manifestations that are resulted from ascending pathology reaching the midbrain (Braak stage III). The pathology also extends into the peripheral autonomic nervous system, thereby affecting cardiovascular and gastrointestinal functions. In terms of neurotransmitters, degeneration of dopaminergic, serotonergic, and cholinergic neurons in the central, peripheral, and autonomous nervous systems are implicated in the mechanism of NMS in PD. This evidence suggesting multisystem involvement may account for various non-motor phenomena of PD. Moreover, the multifactorial causes may be responsible for non-responsiveness to levodopa in the treatment of NMS, unlike motor symptoms of PD.

This article reviews diverse NMS of PD manifesting as multiple organ dysfunction aside from typical neurological or neuropsychological presentations. For neuropsychological presentations, such as cognitive dysfunction, dementia, depression, anxiety, and psychosis, we have published a review article in the previous issue of this journal, and the current article concentrates on NMS in other fields than cognitive and psychiatric problems. This article will be useful for physicians to recognize the necessity of a multidisciplinary and collaborative approach for the management of patients with PD.

SLEEP DISORDERS

Sleep disturbances are one of the most common NMS in PD, affecting 60%–90% of the patients. The spectrum of sleep disorders in PD varies (Table 1); insomnia, excessive daytime somnolence (EDS), RBD, non-REM parasomnias, restless legs syndrome (RLS), and periodic leg movements in sleep (PLMS) are sleep disorders causing sleep disturbances in patients with PD. The pathophysiology of sleep disturbances in PD is attributed to neurodegenerative changes (α-synuclein and Lewy body formation) in the brainstem areas, such as the raphe nucleus and locus coeruleus. The degeneration of these nuclei that play a significant role in thalamocortical arousal and the sleep-wake cycle can lead to the disruption of sleep architecture, thereby manifesting insomnia, EDS, and parasomnias in patients with PD. Insomnia including difficulty falling asleep, sleep fragmentation, and frequent awakenings occurs in 40%–80% of patients with PD. In the sleep structures, underactivity of the ventrolateral preoptic area (sleep-promoter) and overactivity of the hypocretin neurons in the hypothalamus (wake-promotor) have been implicated in the development of insomnia in patients with PD. Upregulation of arousal...
systems including serotonergic, noradrenergic, and cholinergic neurons in the brainstem nuclei is also suggested to contribute to insomnia. In addition to this, motor disability and some NMS of PD, such as nocturnal akinesia, dystonia, pain, nocturia, depression or anxiety, restless legs syndrome, and respiratory disorders can contribute to sleep maintenance problems in patients with PD. On the other hand, excessive sleepiness during the daytime occurs in 20%–50% of patients with PD. EDS and involuntary dozing result from damage to the arousal system, presumably due to hypothalamic hypocretin cell loss and impairment in the above-mentioned brainstem nuclei that serve to maintain wakefulness. Furthermore, disrupted nighttime sleep, cognitive impairment, depression, and anti-parkinsonian drugs can contribute to the daytime somnolence. In particular, dopamine agonists may have an important role in the development of EDS and sleep attacks, RBD, characterized by vocalizations and/or dream-enactment behavior (e.g., talking, shouting, punching, or kicking) during REM sleep occurs in about a third of patients with PD.

### Table 1. Sleep disorders in PD

| Manifestations | Suggestive causes | Treatment options |
|----------------|-------------------|-------------------|
| **Insomnia**   |                   |                   |
|                | Underactivity of the ventrolateral preoptic area and overactivity of the hypocretin neurons in the hypothalamus | Improving sleep hygiene |
|                | Upregulation of arousal systems including serotoninergic, noradrenergic, and cholinergic neurons in the brainstem | Short-acting benzodiazepines |
|                | Motor and non-motor symptoms of PD (e.g., nocturnal akinesia, off-period dystonia, pain, nocturia, depression or anxiety, restless legs syndrome, and respiratory disorders) | Non-benzodiazepine hypnotics |
|                |                   | Eszopiclone |
|                |                   | Melatonin |
|                |                   | Sustained dopaminergic medications |
|                |                   | Slow-release levodopa |
|                |                   | Rotigotine transdermal patch |
| **EDS**        |                   |                   |
|                | Hypothalamic hypocretin cell loss | Improving sleep hygiene (e.g., regular daytime exercise, reducing caffeine intake, and regular hours of sleep at night) |
|                | Impaired serotoninergic, noradrenergic, and cholinergic neurons in the brainstem | Central nervous system stimulants |
|                | Some non-motor symptoms of PD (e.g., disrupted nighttime sleep, cognitive problems, and depression) | Modafinil, methylphenidate |
|                | Anti-parkinsonian drugs, especially dopamine agonists and levodopa | Sodium oxybate |
|                | Aging process |                   |
| **RBD**        |                   |                   |
|                | Neurodegenerative changes in REM sleep generation in the brainstem | Benzodiazepines |
|                | Dopaminergic deficit in the ventral tegmental area | Clonazepam |
|                | Drugs | Melatonin |
|                | Selective serotonin reuptake inhibitor |                   |
|                | Serotonin-norepinephrine reuptake inhibitor |                   |
|                | Tricyclic antidepressant |                   |
| **Non-REM parasomnias** | Cholinergic changes in the brainstem and subcortical circuits | Benzodiazepines |
|                | Drugs | Clonazepam |
|                | Selective serotonin reuptake inhibitor |                   |
|                | Serotonin-norepinephrine reuptake inhibitor |                   |
|                | Tricyclic antidepressant |                   |
| **RLS**        | Dysregulated circadian patterns in the dopaminergic system | Dopamine agonists |
|                | Impaired central dopaminergic transmission | Pramipexole, ropinirole |
|                | | GABA analogues |
|                | | Gabapentin, pregabalin |
|                | | Opioids |
|                | | Oxycodone, methadone |
| **PLMS**       | Dysregulated circadian patterns in the dopaminergic system | Dopamine agonists |
|                | Impaired central dopaminergic transmission | Pramipexole, ropinirole |
| **Obstructive sleep apnea** | Incoordination of respiratory muscle, autonomic dysfunction, and reduced respiratory drive | Continuous positive airway pressure |

PD = Parkinson’s disease, REM = rapid eye movement, RBD = rapid eye movement sleep behavior disorder, GABA = gamma-aminobutyric acid, EDS = excessive daytime somnolence, RLS = restless legs syndrome, PLMS = periodic leg movements in sleep.
studies, up to 50% of patients showed RBD heralding the motor symptoms of PD.\textsuperscript{26-28} The pathogenesis of RBD in PD is thought to be caused by $\alpha$-synuclein pathology involving REM sleep generation in the brainstem, especially the sublaterodorsal nucleus, magnocellular reticular formation, and peri-locus coeruleus area.\textsuperscript{29,30} Because these REM sleep structures are connected to dopamine neurons in the ventral tegmental area, a dopaminergic deficit has also been suggested to be related to RBD in patients with PD.\textsuperscript{15} Non-REM parasomnias, such as vivid dreams, nightmares, night terrors, nocturnal hallucinations, confusional arousals or arousal-related episodes mimicking RBD can also occur in patients with PD.\textsuperscript{31,32} The cholinergic changes in the brainstem and brainstem-subcortical circuits have been implicated in the development of parasomnias in patients with PD.\textsuperscript{31,33} Certain drugs that include selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, and tricyclic antidepressant can trigger both RBD and non-REM parasomnias.\textsuperscript{34} RLS, characterized by uncomfortable sensations in the legs, an urge to move, and a transitory decrease after moving, as well as PLMS, rhythmical extension of the big toe and dorsiflexion of the ankle, have been reported in 15\%-20\% of patients with PD.\textsuperscript{35} Although it is debatable, dysregulated circadian patterns in the dopaminergic system may influence the development of RLS and PLMS.\textsuperscript{15,36} Impaired central dopaminergic transmission has also been suggested to be involved, with evidence of the efficacy of dopaminergic drugs in the treatment of RLS and PLMS.\textsuperscript{37-39} The prevalence of obstructive sleep apnea in patients with PD ranges 20\%-60\%.\textsuperscript{20,40,41} Although a few studies have demonstrated that its prevalence in patients with PD is similar to that of the general population, incoordination of respiratory muscle, autonomic dysfunction, and reduced respiratory drive in PD have been suggested to contribute to the obstructive sleep apnea.\textsuperscript{20,40,41} Before initiating pharmacological treatment, the above-mentioned potential contributors that have a secondary effect on sleep, such as comorbid NMS or drug-induced sleep disorders should be ruled out. Then, insomnia may be improved with good sleep hygiene, administration of short-acting benzodiazepines, non-benzodiazepine hypnotics (eszopiclone), and melatonin (Table 1).\textsuperscript{11,41,42} Sustained dopaminergic stimulation by using slow-release levodopa or long-acting dopaminergic agonists (rotigotine patch) may also improve insomnia as well as nighttime motor symptoms of PD.\textsuperscript{11,41,43} EDS may be managed by improving sleep hygiene, for example, regular daytime exercise, reducing caffeine intake, and regular hours of sleep at night.\textsuperscript{11,41} If these are not effective, wake-promoting agents (modafinil and methylphenidate) or sodium oxybate can be used.\textsuperscript{11,41,44} For the treatment of RBD and parasomnias, clonazepam is usually used as the first-line therapy.\textsuperscript{41} Melatonin, in combination with clonazepam can also be useful for symptoms of RBD.\textsuperscript{11,41} Additionally, it is important to maintain a safe bedroom and to remove potentially dangerous objects that might injure the patients during dream enactment.\textsuperscript{41} Both RLS and PLMS symptoms can be relieved by low doses of dopamine agonists (pramipexole and ropinirole).\textsuperscript{41} Furthermore, gamma-aminobutyric acid (GABA) analogues (gabapentin and pregabalin) or opioids (oxycodone and methadone) can also be used as treatments for RLS.\textsuperscript{41} The gold standard therapy for obstructive sleep apnea is continuous positive airway pressure, which can improve nighttime oxygenation and sleep maintenance.\textsuperscript{45}

**OCULAR DISORDERS**

Patients with PD may experience ocular surface irritation such as burning or gritty sensation, intermittent tearing, blurred vision or red eyes caused by dry eye syndrome, and blepharitis.
The estimated prevalence of dry eyes and blepharitis in patients with PD are approximately 60% and 20%, respectively.\textsuperscript{46,47} This is attributed to decreased blink rates and considered as a form of hypokinesia in patients with PD.\textsuperscript{48,49} Another contributor is decreased tear production in PD, caused by dysfunction of the parasympathetic nerves that innervate the lacrimal gland.\textsuperscript{50} Diplopia has been reported in 10%–30% of patients with PD.\textsuperscript{46,51} This is caused mainly due to convergence insufficiency, characterized by failure of convergence and exotropia while fixating on a near object, and blurred vision during reading and near tasks.\textsuperscript{47,51} Diplopia might be associated with levodopa-related motor fluctuations, which has been observed during end-of-dose “off” period and has been improved with dopaminergic medication, albeit with unclear etiology.\textsuperscript{47,51}

Other oculomotor abnormalities, occurring in patients with PD are impairment of saccadic and smooth pursuit eye movements, which has been reported in up to 75% of patients with PD,\textsuperscript{52} square wave jerks, and ocular oscillations.\textsuperscript{53,54} Patients with PD could exhibit blurred vision due to dry eyes, accommodation disorders, or medications that include anticholinergics and monoamine oxidase inhibitors (selegiline and rasagiline).\textsuperscript{51} In addition, an N-methyl-D-aspartate-receptor antagonist (amantadine) can cause blurry vision as a result of corneal endothelial edema.\textsuperscript{51} Blepharospasm is usually found in patients with advanced PD, which has been reported in 1%–13% of patients with PD.\textsuperscript{55,56} While blepharospasm is believed to be related to a loss of inhibition within the sensorimotor cortico-basal ganglia, ocular surface irritation with dry eyes may partly contribute to paradoxical excessive blinking.\textsuperscript{46,55,56}

Contrast sensitivity, the ability to distinguish subtle differences of an object from its background at low contrast, and color discrimination are both commonly impaired early in the course of the disease, although the exact prevalence is not known.\textsuperscript{51,57} Deficiency of retinal dopamine or deficits in the primary visual pathway have been suggested as causes

\begin{table}
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\begin{tabular}{|l|l|l|}
\hline
\textbf{Manifestations} & \textbf{Suggestive causes} & \textbf{Treatment options} \\
\hline
Dry eyes, blepharitis & Decreased blink possibly due to dopamine deficiency & Artificial tears \\
& Parasympathetic autonomic dysfunction innervating the lacrimal gland & Eyelid hygiene with warm compression \\
& Drugs & Topical antibiotics for blepharitis \\
& • Anticholinergics & Optimal anti-parkinsonian medications \\
\hline
Diplopia & Convergence insufficiency possibly due to dopamine deficiency & Glasses with prism correction \\
& & Convergence exercises \\
& & Optimal anti-parkinsonian medications \\
\hline
Oculomotor impairment (e.g., saccade and smooth pursuit impairment, square wave jerks, and ocular oscillations) & Possibly due to dopamine deficiency & Optimal anti-parkinsonian medications \\
\hline
Blepharospasm & Loss of inhibition within the sensorimotor cortico-basal ganglia & Artificial tears \\
& Ocular surface irritation with dry eyes & Botulinum toxin injections \\
& & Optimal anti-parkinsonian medications \\
\hline
Color vision impairment & Deficiency of retinal dopamine & Optimal anti-parkinsonian medications \\
& Deficits in the primary visual pathway & \\
\hline
Contrast sensitivity impairment & Deficiency of retinal dopamine & Optimal anti-parkinsonian medications \\
& Deficits in the primary visual pathway & \\
\hline
Stereopsis impairment & Possibly related to non-dominant extrastriate cortical atrophy & Unclear, possibly anti-parkinsonian medications \\
\hline
Visual hallucinations & Decreased visual acuity & Dopaminergic medication adjustment (e.g., simplification or reduction in medications) \\
& Cognitive impairment & Anti-psychotic drugs \\
& Drugs & Clozapine, quetiapine \\
& • Anticholinergics & Pimavanserin \\
& • Dopaminergics (dopamine agonists more than levodopa) & \\
& • NMDA-receptor antagonist (amantadine) & \\
& • Monoamine oxidase inhibitors (selegiline and rasagiline) & \\
\hline
\end{tabular}
\caption{Ocular disorders in PD}
\end{table}
of diminished color discrimination and contrast sensitivity.\cite{57,59} Stereopsis, the ability to perceive a three-dimensional image by both eyes, is also impaired early in the disease and is associated with visuospatial impairments in patients with PD, of which pathophysiology might be related to non-dominant extrastriate cortical atrophy.\cite{60,61} The presence of visual hallucinations has been found in up to 60% of patients with PD,\cite{62,63} and may occur spontaneously with multifactorial contributors, being associated with decreased visual acuity as in Charles Bonnet syndrome, impaired color discrimination and contrast sensitivity, and cognitive impairment.\cite{64,65} In addition, several anti-parkinsonian medications, such as anticholinergics, dopamine agonists, levodopa, amantadine, and monoamine oxidase inhibitors can exacerbate visual hallucinations.\cite{51}

The treatment of ocular disorders depends on symptomatology (Table 2). Artificial tears to provide corneal lubrication for dry eyes as well as eyelid hygiene with warm compression and topical antibiotics for blepharitis can be helpful.\cite{46} Diplopia due to convergence insufficiency can be corrected with base-in prisms or convergence exercises.\cite{47,51} Improvements in smooth pursuit eye movements and convergence have been observed with the use of dopaminergic drugs.\cite{66} Blepharospasm can be relieved by botulinum toxin injections if it is not relieved with artificial tears or if ocular surface irritation persists.\cite{46,47,51} Impaired color discrimination, contrast sensitivity, and stereopsis may be improved with dopaminergic therapy although the improvements are variable.\cite{59,61,67} Visual hallucinations do not always require dose reduction of dopaminergic drugs because of an unacceptable increase in motor disability.\cite{46} However, in cases of distressing visual hallucinations, a simplification or reduction in antiparkinsonian medications may be effective, and further treatments with anti-psychotic drugs (clozapine and quetiapine) or recently developed serotonergic drug (pimavanserin) may need to be considered.\cite{11,12}

**NOSE, MOUTH, AND THROAT DISORDERS**

Olfactory dysfunction causing hyposmia or anosmia (Table 3) occurs in 70%–90% of patients with PD.\cite{68,69} This has been shown to be associated with α-synuclein pathology in the olfactory bulbs, olfactory tract, and olfactory nuclei, as previously discussed in Braak’s hypothesis.\cite{7,70} A decrease in dopaminergic input from the ventral tegmentum to

| Table 3. Nose, mouth, and throat disorders in PD |
|-----------------------------------------------|
| Manifestations                           | Suggestive causes                                                                 | Treatment options                      |
| Hyposmia, anosmia                        | - Neurodegenerative changes in the olfactory bulb, olfactory tract, and olfactory nuclei  
- Dopamine deficiency in the olfactory bulb and olfactory tubercle | - Some benefit with olfactory training |
| Ageusia (loss of taste)                  | - Dysregulation of taste receptor genes                                                 | - Some benefit with zinc supplement |
| Dribbling of saliva                      | - Infrequent swallowing due to reduced activity of the epiglottis and decreased motor coordination for swallowing | - Anticholinergic agent               |
|                                          |                                                                                      | - Trihexyphenidyl                      |
|                                          |                                                                                      | - Drugs with anticholinergic effect |
|                                          |                                                                                      | - Amitriptyline                       |
|                                          |                                                                                      | - Chewing gum                         |
|                                          |                                                                                      | - Speech and language therapy         |
|                                          |                                                                                      | - Botulinum toxin injections to the submandibular and parotid glands |
| Xerostomia (dry mouth)                   | - Neurodegenerative changes in the salivary gland                                      | - Improving oral hygiene              |
|                                          |                                                                                      | - Saliva substitutes and chewing gum  |
| Dysphagia                                | - Pharyngoesophageal motor abnormalities                                                | - Softening solid food and thickening liquids |
|                                          |                                                                                      | - Tube feeding or gastrostomy          |

PD = Parkinson’s disease.
the olfactory tubercle and a decrease of dopaminergic neurons in the olfactory bulb are also related to olfactory dysfunction in PD.\textsuperscript{68,71} Ageusia (loss of taste) has also been reported in patients with PD at varying frequencies ranging 9\%–54\%,\textsuperscript{72,73} but its pathophysiology remains unclear. Unlike the pathogenesis of olfactory dysfunction, the gustatory nucleus in the brainstem of patients with PD showed an absence of α-synuclein pathology, even in those with late-stage PD.\textsuperscript{7} However, taste receptor genes have been found to be dysregulated in patients with PD.\textsuperscript{74} Dribbling of saliva from the corner of the mouth occurs in 35\%–75\% of patients with PD, which is caused by infrequent swallowing, as a result of reduced activity of the epiglottis and decreased motor coordination for swallowing.\textsuperscript{75} This results in angular cheilitis and foul odor.\textsuperscript{76,77} Furthermore, difficulties in maintaining oral hygiene due to motor disability and neurocognitive or affective symptoms (e.g., dementia, apathy, or depression) increase the chances of periodontal diseases.\textsuperscript{76,77} Xerostomia (dry mouth) due to decreased salivary production is also reported in up to 60\% of patients with PD.\textsuperscript{78} This is a likely autonomic symptom of patients with PD, with supportive evidence of salivary gland involvement by α-synuclein pathology.\textsuperscript{79,80} Dysphagia can occur in patients with PD, especially in those with a late stage of the disease.\textsuperscript{81} More than 80\% of patients with PD develop dysphagia during the course of the disease,\textsuperscript{81} and a study reported that around one-third of patients with PD aspirated silently.\textsuperscript{75} This has been attributed to pharyngoesophageal motor abnormalities.\textsuperscript{81,82}

Unlike other NMS, olfactory dysfunction and ageusia do not respond to anti-parkinsonian or other medications (Table 3). Olfactory training has been shown to improve olfactory dysfunction,\textsuperscript{83} and zinc supplementation provided some benefits in those with age-related taste dysfunction.\textsuperscript{84} However, there are currently no cures for patients with PD who have olfactory dysfunction and ageusia. For symptoms of excessive drooling, there are several treatment options including anticholinergics (trihexyphenidyl) or drugs with anticholinergic effects (e.g., amitriptyline); however, these drugs may cause xerostomia or other adverse effects such as constipation, urinary retention, memory impairment, and hallucinations.\textsuperscript{10,85} Other options include chewing gum, and speech and language therapy.\textsuperscript{10,85} Injection of botulinum toxin to the submandibular and parotid glands has been shown to improve drooling.\textsuperscript{85} To manage dysphagia, softening solid foods and thickening liquids before consumption may help, but in patients with advanced stages of the disease, tube feeding or gastrostomy may be needed.\textsuperscript{86}

**CARDIOVASCULAR DISORDERS**

Cardiovascular autonomic dysfunction, specifically orthostatic hypotension, blood pressure variability, and heart rate variability, is commonly observed in patients with PD (Table 4).\textsuperscript{87,88} Orthostatic hypotension, defined as at least a 20 mmHg decrease in systolic pressure and/or 10 mmHg decrease in diastolic pressure within three minutes of standing, is the most well-known autonomic symptom, occurring in 20\%–60\% of patients with PD.\textsuperscript{89} Those symptoms of dysautonomia are likely due to dysfunction of the central nuclei (dorsal motor nucleus of the vagus, nucleus ambiguous, and other medullary nuclei) located at the lower brainstem, which controls the sympathetic preganglionic neurons.\textsuperscript{90} Dysfunction of the peripheral, postganglionic sympathetic nerves also contributes to cardiac and extra-cardiac noradrenergic denervation as well as failure of the arterial baroreflex.\textsuperscript{91} Furthermore, it can also be triggered by antiparkinsonian medications including levodopa, dopamine agonists, and monoamine oxidase inhibitors (selegiline and rasagiline).\textsuperscript{92}
Recommendations for patients with orthostatic hypotension include standing up gradually in order to decrease sudden blood pressure changes, sleep with head-up position, wearing elastic stockings, fragmentation of meals, avoidance of high-carbohydrate foods, cautious use of volume-depleting drugs (e.g., diuretics or antihypertensives), and increasing salt and water intake (Table 4). In severe cases, medications such as fludrocortisone or midodrine may be needed to improve postural hypotension. However, drugs acting on postsynaptic adrenoreceptors should be used in consideration of underlying cardiovascular diseases and supine arterial hypertension. On the other hand, treatment for blood pressure variability and heart rate variability remains uncertain.

**SKIN DISORDERS**

Sweating disorders consisting of hyperhidrosis, and to a lesser extent, hypohidrosis can be seen in patients with PD (Table 5). The estimated prevalence of hyperhidrosis ranges 20%–60% in patients with PD, and that of hypohidrosis is less than 40%. Dopamine deficiency has been suggested as a mechanism of sweating disorders in patients with PD based on the fact that dopamine is one of the neurotransmitters in hypothalamus-driven thermoregulation. Moreover, fluctuating hyperhidrosis in patients with PD is often associated with motor fluctuations, and modulating dopaminergic medication has been shown to be effective for the symptom. Axial hyperhidrosis, which can be observed in patients with PD is explained as compensatory mechanism for reduced sympathetic function in the extremities, leading to hypohidrosis in the hands and feet. In addition, the cutaneous autonomic nerves that innervate sweat glands have been found to be affected by α-synuclein pathology.

**Table 4. Cardiovascular disorders in PD**

| Manifestations         | Suggestive causes                                                                 | Treatment options                                                                 |
|------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Orthostatic hypotension| - Central preganglionic autonomic dysfunction                                     | - Getting up slowly from supine and sitting position                            |
|                        | • Peripheral postganglionic sympathetic dysfunction                              | • Elevating the head of the bed while sleeping                                   |
|                        | • Drugs                                                                          | • Wearing elastic stockings                                                     |
|                        | • Levodopa                                                                       | • Fragmentation of meals                                                        |
|                        | • Dopamine agonists                                                              | • Avoiding high carbohydrates or low sodium diet, and volume depleting drugs     |
|                        | • Monoamine oxidase inhibitors (selegiline and rasagiline)                       | (e.g., diuretics and antihypertensives)                                         |
|                        | ▶ Levodopa                                                                       | • Increasing salt and water intake                                              |
|                        | ▶ Dopamine agonists                                                              | ▶ Fludrocortisone or midodrine                                                  |
| Blood pressure variability| - Central preganglionic autonomic dysfunction                                       | - Unclear                                                                        |
| Heart rate variability  | - Central preganglionic autonomic dysfunction                                       | - Unclear                                                                        |

PD = Parkinson's disease.

**Table 5. Skin disorders in PD**

| Manifestations | Suggestive causes                                                                 | Treatment options                                                                 |
|----------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Hyperhidrosis  | - Central dopamine deficiency                                                    | - Avoiding hot and humid environments and food that can trigger sweating       |
|                | • Axial hyperhidrosis, compensatory for reduced sympathetic function (hypohidrosis) in the extremities | • Wearing well-ventilated clothes and keeping well hydrated                     |
|                | • Neurodegenerative changes in the cutaneous autonomic nerves                    | • Optimal anti-parkinsonian medications                                         |
| Hypohidrosis   | - Central dopamine deficiency                                                    |                                                                                  |
|                | • Neurodegenerative changes in the cutaneous autonomic nerves                    |                                                                                  |

PD = Parkinson’s disease.
For hyperhidrosis, non-pharmacological interventions, such as avoiding hot and humid environments and foods that may trigger sweating, wearing well-ventilated clothes, and staying well-hydrated can be beneficial (Table 5).\textsuperscript{95} Sweating disorders related to motor complications can be managed by optimizing dopaminergic medications.\textsuperscript{94,95} Anticholinergics are often considered for excessive sweating, but its effectiveness is limited and controversial.\textsuperscript{95}

### GASTROINTESTINAL DISORDERS

Gastrointestinal symptoms, including heartburn, nausea, vomiting, and constipation, are common NMS of PD (Table 6). Among them, constipation is the most frequently encountered problem, occurring in 50\%–60\% of patients with PD.\textsuperscript{10} These gastrointestinal hypomotility symptoms are thought to be derived from parasympathetic autonomic dysfunction due to damaged dorsal motor nucleus of the vagus nerve in the brainstem along with α-synuclein pathology in the peripheral autonomic ganglia and enteric nervous system.\textsuperscript{100,101} Drugs with anticholinergic effects, such as anticholinergics, tricyclic antidepressants, and opiates, may secondarily worsen bowel hypomotility, manifesting as constipation.\textsuperscript{10,85}

Heartburn, nausea, or vomiting can be improved by prokinetics having peripheral dopamine (D\textsubscript{2}) receptor antagonizing or serotonin (5-HT\textsubscript{4}) receptor agonizing effects, such as domperidone and mosapride (Table 6).\textsuperscript{102} A recent study has shown that DA-9701, a novel prokinetic drug, can be useful in patients with PD by enhancing gastric motility without aggravating PD symptoms.\textsuperscript{103} In contrast, certain prokinetics, such as levosulpiride, metoclopramide, and clebopride, which act on the central D\textsubscript{2} receptor, can worsen motor symptoms of PD.\textsuperscript{104} Constipation can be improved by diet with high fiber foods and fluids along with regular exercise.\textsuperscript{11,105} The use of probiotics and prebiotic fibers can be helpful for bowel mobility.\textsuperscript{11,105} If these are ineffective, laxatives such as osmotic agents or peristaltic agents (e.g., macrogol, lactulose, or magnesium hydroxide) can be used.\textsuperscript{11,105}

| Table 6. Gastrointestinal disorders in PD |
|-----------------------------------------|
| Manifestations                      | Suggestive causes                                                                 | Treatment options                                                                 |
| Heartburn, nausea, vomiting          | • Central preganglionic autonomic dysfunction                                        | • Prokinetics with peripheral dopamine (D\textsubscript{2}) receptor antagonizing or serotonin (5-HT\textsubscript{4}) receptor agonizing effects |
|                                       | • Peripheral postganglionic parasympathetic dysfunction                               | • DA-9701                                                                          |
|                                       | • Neurodegenerative changes in the peripheral autonomic ganglia and enteric nervous system | • Domperidone                                                                       |
| Constipation                          | • Central preganglionic autonomic dysfunction                                        | • Mosapride                                                                        |
|                                       | • Peripheral postganglionic parasympathetic dysfunction                               | • Diet of high fiber foods and fluids                                              |
|                                       | • Neurodegenerative changes in the peripheral autonomic ganglia and enteric nervous system | • Regular exercise                                                                  |
|                                       | • Drugs with anticholinergic effect                                                 | • Probiotics and prebiotic fiber                                                   |
|                                       | • Anticholinergics                                                                 | • Osmotic agents                                                                   |
|                                       | • Tricyclic antidepressant (e.g., amitriptyline)                                    | • Macrogol known as polyethylene glycol                                            |
|                                       | • Opiates                                                                           | • Lactulose                                                                         |
|                                       |                                                                                   | • Magnesium hydroxide                                                              |
|                                       |                                                                                   | • Peristaltic agents                                                                |
|                                       |                                                                                   | • Psyllium/senna                                                                   |

PD = Parkinson’s disease.
GENITOURINARY DISORDERS

Lower urinary tract symptoms including urinary frequency, nocturia, urgency, and incontinence have been reported in approximately one-half of patients with PD (Table 7). These overactive bladder symptoms in patients with PD are thought to be caused by an altered dopamine-basal ganglia circuit in the urinary system since basal ganglia has an inhibitory effect on micturition. Additionally, about two-thirds of patients with PD who exhibit urinary symptoms have urodynamically defined impaired detrusor contractility, resulting in voiding phase symptoms such as weak stream, hesitancy, and feelings of incomplete voiding. Symptoms of sexual dysfunction including decrease in libido, erectile dysfunction in males, and decrease in lubrication in females are also frequent NMS, occurring in one-half to two-thirds of patients with PD. Hypothalamic dysfunction due to altered dopamine-oxytocin circuit is thought to be responsible for the sexual dysfunction in PD because oxytocinergic neurons in the hypothalamus inhibit prolactinergic neurons that have an inhibitory effect on sexual function. Symptoms of depression also play a role in sexual dysfunction in patients with PD. In contrast, hypersexuality or aberrant sexual behaviors can be present in susceptible patients with PD, which is linked to dopaminergic drugs, especially dopamine agonists.

Despite the dopaminergic pathophysiology above, overactive bladder symptoms do not respond to levodopa therapy (Table 7). Anticholinergics (solifenacin, trospium, or fesoterodine) are generally used as a first-line treatment, but they should be cautiously used particularly among elderly patients with psychiatric symptoms or cognitive decline. For these patients who have an overactive bladder, mirabegron, which is a β3 adrenergic agonist, is an alternative therapeutic option. α-Adrenergic blockers (tamsulosin, doxazosin, or terazosin) can be used for the sensation of incomplete bladder emptying and an intermittent urinary stream. Phosphodiesterase inhibitors (sildenafil, tadalafil, or vardenafil) are used to treat sexual dysfunction in patients with PD, but they are not generally recommended for patients with cardiovascular disease.

| Manifestations | Suggestive causes | Treatment options |
|----------------|-------------------|-------------------|
| Urinary frequency, nocturia | Detrusor hyperactivity due to altered dopamine-basal ganglia circuit | Anticholinergic agents<br>• Solifenacin, trospium, fesoterodine<br>• β3 adrenergic agonist<br>• Mirabegron |
| Urinary urgency | Detrusor hyperactivity due to altered dopamine-basal ganglia circuit | Anticholinergic agents<br>• Solifenacin, trospium, fesoterodine<br>• β3 adrenergic agonist<br>• Mirabegron |
| Urinary incontinence | Detrusor hyperactivity due to altered dopamine-basal ganglia circuit | Anticholinergic agents<br>• Solifenacin, trospium, fesoterodine<br>• β3 adrenergic agonist<br>• Mirabegron<br>Pelvic floor muscle therapy |
| Voiding phase symptoms (e.g., weak stream, hesitancy, and feeling of incomplete voiding) | Detrusor contractility impairment | Anticholinergic agents for overactive symptom<br>• Solifenacin, trospium, fesoterodine<br>α-Adrenergic blockers for incomplete bladder emptying<br>• Tamsulosin, doxazosin, terazosin<br>Pelvic floor muscle therapy |
| Erectile dysfunction, decrease of lubrication | Hypothalamic dysfunction due to altered dopamine-oxytocin circuit | Phosphodiesterase inhibitors<br>• Sildenafil, tadalafil, vardenafil |

PD = Parkinson's disease.
MUSCULOSKELETAL DEFORMITIES

Musculoskeletal deformities, especially posture and spinal deformities, and striatal hand and foot, are common manifestations in PD (Table 8).120-122 Health-related quality of life is significantly affected by musculoskeletal problems in PD.123 Among them, striatal hand or foot, characterized by ulnar deviation of the hand, flexion of the metacarpophalangeal joints, extension of the interphalangeal joints, and extension of the great toe, have been reported as the most common deformities, which has been estimated to occur in 10%–40% of patients with PD.120-122 Postural deformities that include antecollis, camptocormia (forward flexion of the thoracolumbar spine), Pisa syndrome (dystonia leading to lateral flexion of the spine), and scoliosis have also been described in patients with PD, and patients with an advanced stage of PD have more postural abnormalities.120-122 The pathophysiology for these musculoskeletal deformities in PD is not well-understood, but dopaminergic deficiency or dopaminergic-cholinergic imbalance might contribute to these deformities.120-122 In addition, sensorimotor dysfunction, alterations in the perception of postural alignment, and imbalances in the muscles in the trunk have been suggested as a mechanism of the dynamic postural deformities for camptocormia and Pisa syndrome.124,125

Although the evidence level is low, non-pharmacological approaches can be considered for the treatment of postural deformity (camptocormia and Pisa syndrome) (Table 8). To correct the sagittal malalignment in the camptocormia, a plaster corset, low-slung backpack with weight, high-frame walker with forearm support, or thoracopelvic anterior distraction orthosis can help.126-129 Rehabilitation programs with proprioceptive and tactile stimulation, postural reduction, and stretching to improve flexibility and mobility of the trunk can reduce malalignment.130,131 Botulinum toxin injections to hyperactive paraspinal or quadratus lumborum muscles in patients with Pisa syndrome,132-134 and to hyperactive rectus abdominis and iliopsoas muscles in patients with camptocormia have resulted in beneficial effects.135-137 However, the efficacy of botulinum toxin injection is inconclusive due to the small sample sizes and lack of standard clinical outcome assessments. Spinal realignment surgery might be considered in severe cases of camptocormia or Pisa syndrome, but possible common postoperative complications should be considered.138 Treatment with dopaminergic medication has been attempted for patients with PD who have these deformities, but the treatment resulted in variable responses.120-122,139 Neurosurgical interventions, such as deep brain stimulation, have also been attempted to treat postural deformities; the results have been limited but promising.140

Table 8. Musculoskeletal deformities in PD

| Manifestations                              | Suggestive causes                                      | Treatment options                                              |
|---------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------|
| Posture and spinal deformities (e.g., antecollis, camptocormia, Pisa syndrome, and scoliosis) | - Central dopamine deficiency  
- Dopaminergic-cholinergic imbalance  
- Sensorimotor dysfunction  
- Alteration in the perception of postural alignment  
- Imbalance in the muscles in the trunk | - Non-pharmacological interventions  
- For camptocormia, plaster corset, low-slung backpack with weight, high-frame walker with forearm support, or thoracopelvic anterior distraction orthosis  
- Rehabilitation programs (e.g., proprioceptive and tactile stimulation, postural reduction, and stretching to improve flexibility and mobility of the trunk) |
| Striatal hand and foot                      | - Central dopamine deficiency  
- Dopaminergic-cholinergic imbalance | - Anti-parkinsonian medications  
- Deep brain stimulation |

PD = Parkinson’s disease.
PAIN AND FATIGUE

The various forms of pain that can be categorized as musculoskeletal pain, dystonia-related pain, neuropathic pain, and central pain have been reported in approximately 40%–60% of patients with PD (Table 9). Musculoskeletal pain, a common type of pain, can result from multiple factors such as parkinsonian rigidity, stiffness, immobility, and the above-mentioned musculoskeletal deformities. Dystonia-related pain has been reported in 40% of patients with PD and may fluctuate with levodopa-related motor fluctuations, featuring as end-of-dose, diphasic, or early morning painful dystonia. Radicular or neuropathic pain that is well localized to the territory of a nerve or nerve root has been attributed to a nerve or root entrapment. Patients with PD may have central pain, characterized as persistent pain or paresthesia (e.g., burning or tingling sensations) without other causative etiologies. This primary pain has been suggested to be related to disrupted pain perception as a result of dopaminergic deficits, based on that the nociceptive threshold is decreased in patients with PD, but levodopa treatment has been shown to increase the threshold and relieve the pain. However, this finding is not consistently observed, and other neurotransmitters such as noradrenalin, serotonin, and glutamate could also contribute to pain in patients with PD. Fatigue has been reported in about one-third of patients with PD, occurring even in those with an early stage of PD. Dopaminergic deficiency has been suggested to play a role in the development of fatigue, but

Table 9. Pain and fatigue in PD

| Manifestations            | Suggestive causes                                                                 | Treatment options                                                                 |
|---------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Musculoskeletal pain      | • Motor symptoms of PD (e.g., rigidity, stiffness, and immobility)                | • Physical therapy                                                                |
|                           | • Musculoskeletal deformities                                                     | • Analgesics                                                                       |
|                           |                                                                                  | • Muscle relaxants                                                                 |
|                           |                                                                                  | • GABA agonist (baclofen)                                                          |
|                           |                                                                                  | • Opioids                                                                          |
|                           |                                                                                  | • Oxycodone, methadone                                                            |
| Dystonia-related pain     | • Central dopamine deficiency                                                    | • Dopaminergic medication adjustment                                               |
|                           | • Fluctuated with levodopa-related motor fluctuations                            | • Anticholinergics                                                                 |
|                           |                                                                                  | • NMDA-receptor antagonist (amantadine)                                            |
|                           |                                                                                  | • GABA agonist (baclofen)                                                          |
|                           |                                                                                  | • Deep brain stimulation                                                           |
|                           |                                                                                  | • Botulinum toxin injections for focal dystonia                                      |
| Neuropathic pain          | • Nerve or root entrapment                                                       | • Avoidance of overusing the affected body part or poor posture                    |
|                           |                                                                                  | • Physical therapy                                                                 |
|                           |                                                                                  | • Neuropathic pain agents                                                           |
|                           |                                                                                  | • GABA analogues (gabapentin and pregabalin)                                        |
|                           |                                                                                  | • Tricyclic antidepressants                                                         |
|                           |                                                                                  | • Opioids                                                                          |
|                           |                                                                                  | • Decompressive surgery as indicated                                                |
| Central pain              | • Disrupted pain perception due to dopamine deficiency                            | • Analgesics                                                                       |
|                           |                                                                                  | • Opioids                                                                          |
|                           |                                                                                  | • Tricyclic antidepressants                                                         |
|                           |                                                                                  | • Atypical neuroleptics                                                            |
|                           |                                                                                  | • Clozapine                                                                        |
|                           |                                                                                  | • Dopaminergic medication adjustment                                               |
| Fatigue                   | • Central dopamine deficiency                                                    | • Selective serotonin reuptake inhibitors                                           |
|                           | • Serotonergic deficiency in the basal ganglia and limbic systems                | • Dopaminergic medication                                                           |
|                           | • Some non-motor symptoms of PD (e.g., depression and sleep disturbance)         | • Levodopa                                                                         |
|                           |                                                                                  | • Methylphenidate                                                                  |

PD = Parkinson’s disease, NMDA = N-methyl-D-aspartate, GABA = gamma-aminobutyric acid.
serotonergic deficiency in the basal ganglia and limbic systems has been proposed as a reason for chronic fatigue syndrome in patients with PD.\textsuperscript{153,154} Indeed, severity of fatigue correlated with the presence of depression and sleep disturbances rather than disease duration or severity of motor disability, suggesting the role of the serotonergic system.\textsuperscript{155,156}

Musculoskeletal pain can be treated with physical therapy, analgesics, muscle relaxants, or opioids (Table 9).\textsuperscript{141-143} Dystonia-related pain can be relieved by adjustment of dopaminergic drugs, administration of anticholinergics, amantadine, or muscle relaxants, deep brain stimulation, and with botulinum toxin for focal dystonia.\textsuperscript{141-143} For neuropathic pain, avoidance of overusing the affected body part or poor posture with physical therapy may alleviate the pain.\textsuperscript{141-143} Otherwise, neuropathic pain agents that include GABA analogues, tricyclic antidepressants, and opioids, or decompressive surgery as indicated may be beneficial.\textsuperscript{141-143} Central pain is often not alleviated by dopaminergic treatment, but analgesics, opiates, tricyclic antidepressants, and atypical neuroleptics (clozapine) may help.\textsuperscript{141-143} In case of pain as a non-motor fluctuating symptom during wearing-off, anti-parkinsonian medication, rather than analgesics, may alleviate the pain during the “off” period.\textsuperscript{141,142} Chronic fatigue in patients with PD is commonly treated with selective serotonin reuptake inhibitors, whereas studies have indicated a beneficial effect of dopaminergic agents on fatigue, including levodopa and methylphenidate, which is a dopamine transporter blocker.\textsuperscript{157}

CONCLUSION

We reviewed the clinical features of NMS in patients with PD, characterized by multi-organ involvement, as summarized in Fig. 1, and briefly reviewed the pathophysiology and treatment options for NMS. Although more studies are needed to determine the exact mechanism and to manage NMS more effectively in clinical practice, our review emphasized the importance of a multidisciplinary approach for the care of patients with PD. In consideration of the fact that many NMS greatly impact the quality of life of patients with PD,\textsuperscript{158} and NMS are often unresponsive to conventional dopaminergic therapy,\textsuperscript{9,11} recognition and proper management of NMS by physicians cannot be overemphasized.

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**Fig. 1.** Summary of multi-organ involvements in PD. In addition to motor symptoms, various NMS manifest in patients with PD. These NMS may pose a diagnostic and therapeutic challenge for physicians and surgeons in many different fields.

PD = Parkinson’s disease, NMS = non-motor symptoms, EDS = excessive daytime somnolence, REM = rapid eye movement, RBD = rapid eye movement sleep behavior disorder, RLS = restless legs syndrome, PLMS = periodic leg movements in sleep.
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