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Clinical Perspectives of Parkinson's Disease for Ophthalmologists, Otorhinolaryngologists, Cardiologists, Dentists, Gastroenterologists, Urologists, Physiatrists, and Psychiatrists

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ABSTRACT

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

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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.[1,2] In the Korean population, the prevalence of PD among individuals aged 65 and older has been reported to be 0.4%,[3] while that of essential tremor was 3.6%.[4] 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).[5,6] 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.[5,6] Although not yet confirmed, Braak's[7] 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).[7] The pathology also extends into the peripheral autonomic nervous system, thereby affecting cardiovascular and gastrointestinal functions.[8] 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.[6,9,10] 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.[9,11] 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,[12] 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.[6,13,14] 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.[6,13,14] 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.[15] 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.[15,16] Insomnia including difficulty falling asleep, sleep fragmentation, and frequent awakenings occurs in 40%–80% of patients with PD.[14,17] 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.[18] Upregulation of arousal

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 • Upregulation of arousal systems including serotoninergic, noradrenergic, and cholinergic neurons in the brainstem • 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)	• Improving sleep hygiene • Short-acting benzodiazepines • Non-benzodiazepine hypnotics ‣ Eszopiclone • Melatonin • Sustained dopaminergic medications ‣ Slow-release levodopa ‣ Rotigotine transdermal patch
EDS	• Hypothalamic hypocretin cell loss • Impaired serotonergic, noradrenergic, and cholinergic neurons in the brainstem • Some non-motor symptoms of PD (e.g., disrupted nighttime sleep, cognitive problems, and depression) • Anti-parkinsonian drugs, especially dopamine agonists and levodopa • Aging process	• Improving sleep hygiene (e.g., regular daytime exercise, reducing caffeine intake, and regular hours of sleep at night) • Central nervous system stimulants ‣ Modafinil, methylphenidate • Sodium oxybate
RBD	• Neurodegenerative changes in REM sleep generation in the brainstem • Dopaminergic deficit in the ventral tegmental area • Drugs ‣ Selective serotonin reuptake inhibitor ‣ Serotonin-norepinephrine reuptake inhibitor ‣ Tricyclic antidepressant	• Benzodiazepines ‣ Clonazepam • Melatonin
Non-REM parasomnias	• Cholinergic changes in the brainstem and subcortical circuits • Drugs ‣ Selective serotonin reuptake inhibitor ‣ Serotonin-norepinephrine reuptake inhibitor ‣ Tricyclic antidepressant	• Benzodiazepines ‣ Clonazepam
RLS	• Dysregulated circadian patterns in the dopaminergic system • Impaired central dopaminergic transmission	• Dopamine agonists ‣ Pramipexole, ropinirole • GABA analogues ‣ Gabapentin, pregabalin • Opioids ‣ Oxycodone, methadone
PLMS	• Dysregulated circadian patterns in the dopaminergic system • Impaired central dopaminergic transmission	• Dopamine agonists ‣ 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.

systems including serotonergic, noradrenergic, and cholinergic neurons in the brainstem nuclei is also suggested to contribute to insomnia.[19] In addition to this, motor disability and some NMS of PD, such as nocturnal akinesia, dystonia, pain, nocturia, depression or anxiety, RLS, and respiratory disorders can contribute to sleep maintenance problems in patients with PD.[20] On the other hand, excessive sleepiness during the daytime occurs in 20%–50% of patients with PD.[21,22] 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.[19] Furthermore, disrupted nighttime sleep, cognitive impairment, depression, and anti-parkinsonian drugs can contribute to the daytime somnolence.[21,23] In particular, dopamine agonists may have an important role in the development of EDS and sleep attacks.[24,25] 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.[26] In longitudinal studies, up to 50% of patients showed RBD heralding the motor symptoms of PD.[26-28] The pathogenesis of RBD in PD is thought to be caused by α-synuclein pathology involving REM sleep generation in the brainstem, especially the sublaterodorsal nucleus, magnocellular reticular formation, and peri-locus coeruleus area.[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.[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.[31,32] The cholinergic changes in the brainstem and brainstem-subcortical circuits have been implicated in the development of parasomnias in patients with PD.[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.[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.[35] Although it is debatable, dysregulated circadian patterns in the dopaminergic system may influence the development of RLS and PLMS.[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.[37-39] The prevalence of obstructive sleep apnea in patients with PD ranges 20%–60%.[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.[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**).[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.[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.[11,41] If these are not effective, wake-promoting agents (modafinil and methylphenidate) or sodium oxybate can be used.[11,41,44] For the treatment of RBD and parasomnias, clonazepam is usually used as the first-line therapy.[41] Melatonin, in combination with clonazepam can also be useful for symptoms of RBD.[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.[41] Both RLS and PLMS symptoms can be relieved by low doses of dopamine agonists (pramipexole and ropinirole).[41] Furthermore, gamma-aminobutyric acid (GABA) analogues (gabapentin and pregabalin) or opioids (oxycodone and methadone) can also be used as treatments for RLS.[41] The gold standard therapy for obstructive sleep apnea is continuous positive airway pressure, which can improve nighttime oxygenation and sleep maintenance.[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

Table 2. Ocular disorders in PD

Manifestations	Suggestive causes	Treatment options
Dry eyes, blepharitis	• Decreased blink possibly due to dopamine deficiency • Parasympathetic autonomic dysfunction innervating the lacrimal gland • Drugs ‣ Anticholinergics	• Artificial tears • Eyelid hygiene with warm compression • Topical antibiotics for blepharitis • Optimal anti-parkinsonian medications
Diplopia	• Convergence insufficiency possibly due to dopamine deficiency	• Glasses with prism correction • Convergence exercises • Optimal anti-parkinsonian medications
Oculomotor impairment (e.g., saccade and smooth pursuit impairment, square wave jerks, and ocular oscillations)	• Possibly due to dopamine deficiency	• Optimal anti-parkinsonian medications
Blepharospasm	• Loss of inhibition within the sensorimotor cortico-basal ganglia • Ocular surface irritation with dry eyes	• Artificial tears • Botulinum toxin injections
Color vision impairment	• Deficiency of retinal dopamine • Deficits in the primary visual pathway	• Optimal anti-parkinsonian medications
Contrast sensitivity impairment	• Deficiency of retinal dopamine • Deficits in the primary visual pathway	• Optimal anti-parkinsonian medications
Stereopsis impairment	• Possibly related to non-dominant extrastriate cortical atrophy	• Unclear, possibly anti-parkinsonian medications
Visual hallucinations	• Decreased visual acuity • Cognitive impairment • Drugs ‣ Anticholinergics ‣ Dopaminergics (dopamine agonists more than levodopa) ‣ NMDA-receptor antagonist (amantadine) ‣ Monoamine oxidase inhibitors (selegiline and rasagiline)	• Dopaminergic medication adjustment (e.g., simplification or reduction in medications) • Anti-psychotic drugs ‣ Clozapine, quetiapine ‣ Pimavanserin

PD = Parkinson's disease, NMDA = N-methyl-D-aspartate.

(**Table 2**).[46] The estimated prevalence of dry eyes and blepharitis in patients with PD are approximately 60% and 20%, respectively.[46,47] This is attributed to decreased blink rates and considered as a form of hypokinesia in patients with PD.[48,49] Another contributor is decreased tear production in PD, caused by dysfunction of the parasympathetic nerves that innervate the lacrimal gland.[50] Diplopia has been reported in 10%–30% of patients with PD.[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.[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.[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,[52] square wave jerks, and ocular oscillations.[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).[51] In addition, an N-methyl-D-aspartate-receptor antagonist (amantadine) can cause blurry vision as a result of corneal endothelial edema.[51] Blepharospasm is usually found in patients with advanced PD, which has been reported in 1%–13% of patients with PD.[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.[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.[51,57] Deficiency of retinal dopamine or deficits in the primary visual pathway have been suggested as causes of diminished color discrimination and contrast sensitivity.[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.[60,61] The presence of visual hallucinations has been found in up to 60% of patients with PD,[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.[64,65] In addition, several anti-parkinsonian medications, such as anticholinergics, dopamine agonists, levodopa, amantadine, and monoamine oxidase inhibitors can exacerbate visual hallucinations.[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.[46] Diplopia due to convergence insufficiency can be corrected with base-in prisms or convergence exercises.[47,51] Improvements in smooth pursuit eye movements and convergence have been observed with the use of dopaminergic drugs.[66] Blepharospasm can be relieved by botulinum toxin injections if it is not relieved with artificial tears or if ocular surface irritation persists.[46,47,51] Impaired color discrimination, contrast sensitivity, and stereopsis may be improved with dopaminergic therapy although the improvements are variable.[59,61,67] Visual hallucinations do not always require dose reduction of dopaminergic drugs because of an unacceptable increase in motor disability.[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.[11,12]

NOSE, MOUTH, AND THROAT DISORDERS

Olfactory dysfunction causing hyposmia or anosmia (**Table 3**) occurs in 70%–90% of patients with PD.[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.[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.[68,71] Ageusia (loss of taste) has also been reported in patients with PD at varying frequencies ranging 9%–54%,[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.[7] However, taste receptor genes have been found to be dysregulated in patients with PD.[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.[75] This results in angular cheilitis and foul odor.[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.[76,77] Xerostomia (dry mouth) due to decreased salivary production is also reported in up to 60% of patients with PD.[78] This is a likely autonomic symptom of patients with PD, with supportive evidence of salivary gland involvement by α-synuclein pathology.[79,80] Dysphagia can occur in patients with PD, especially in those with a late stage of the disease.[81] More than 80% of patients with PD develop dysphagia during the course of the disease,[81] and a study reported that around one-third of patients with PD aspirated silently.[75] This has been attributed to pharyngoesophageal motor abnormalities.[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,[83] and zinc supplementation provided some benefits in those with age-related taste dysfunction.[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.[10,85] Other options include chewing gum, and speech and language therapy.[10,85] Injection of botulinum toxin to the submandibular and parotid glands has been shown to improve drooling.[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.[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**).[87,88] Orthostatic hypotension, defined as at least a 20 mmHg decrease in systolic pressure and/or 10mmHg decrease in diastolic pressure within three minutes of standing, is the most well-known autonomic symptom, occurring in 20%–60% of patients with PD.[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.[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.[91] Furthermore, it can also be triggered by antiparkinsonian medications including levodopa, dopamine agonists, and monoamine oxidase inhibitors (selegiline and rasagiline).[92]

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Table 4. Cardiovascular disorders in PD

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

PD = Parkinson's disease.

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**).[93] In severe cases, medications such as fludrocortisone or midodrine may be needed to improve postural hypotension.[93] However, drugs acting on postsynaptic adrenoreceptors should be used in consideration of underlying cardiovascular diseases and supine arterial hypertension.[93] On the other hand, treatment for blood pressure variability and heart rate variability remains uncertain.[87,88]

SKIN DISORDERS

Sweating disorders consisting of hyperhidrosis, and to a lesser extent, hypohidrosis can be seen in patients with PD (**Table 5**).[94,95] The estimated prevalence of hyperhidrosis ranges 20%–60% in patients with PD, and that of hypohidrosis is less than 40%.[94,95] 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.[96,97] Moreover, fluctuating hyperhidrosis in patients with PD is often associated motor fluctuations, and modulating dopaminergic medication has been shown to be effective for the symptom.[96,97] 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.[95] In addition, the cutaneous autonomic nerves that innervate sweat glands have been found to be affected by α-synuclein pathology.[98,99]

Table 5. Skin disorders in PD

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

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**).[95] Sweating disorders related to motor complications can be managed by optimizing dopaminergic medications.[94,95] Anticholinergics are often considered for excessive sweating, but its effectiveness is limited and controversial.[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.[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.[100,101] Drugs with anticholinergic effects, such as anticholinergics, tricyclic antidepressants, and opiates, may secondarily worsen bowel hypomotility, manifesting as constipation.[10,85]

Heartburn, nausea, or vomiting can be improved by prokinetics having peripheral dopamine (D_2) receptor antagonizing or serotonin (5-HT_4) receptor agonizing effects, such as domperidone and mosapride (**Table 6**).[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.[103] In contrast, certain prokinetics, such as levosulpiride, metoclopramide, and clebopride, which act on the central D_2 receptor, can worsen motor symptoms of PD.[104] Constipation can be improved by diet with high fiber foods and fluids along with regular exercise.[11,105] The use of probiotics and prebiotic fibers can be helpful for bowel mobility.[11,105] If these are ineffective, laxatives such as osmotic agents or peristaltic agents (e.g., macrogol, lactulose, or magnesium hydroxide) can be used.[11,105]

Table 6. Gastrointestinal disorders in PD

Manifestations	Suggestive causes	Treatment options
Heartburn, nausea, vomiting	• Central preganglionic autonomic dysfunction • Peripheral postganglionic parasympathetic dysfunction • Neurodegenerative changes in the peripheral autonomic ganglia and enteric nervous system	• Prokinetics with peripheral dopamine (D_2) receptor antagonizing or serotonin (5-HT_4) receptor agonizing effects ‣ DA-9701 ‣ Domperidone ‣ Mosapride
Constipation	• Central preganglionic autonomic dysfunction • Peripheral postganglionic parasympathetic dysfunction • Neurodegenerative changes in the peripheral autonomic ganglia and enteric nervous system • Drugs with anticholinergic effect ‣ Anticholinergics ‣ Tricyclic antidepressant (e.g., amitriptyline) ‣ Opiates	• Diet of high fiber foods and fluids • Regular exercise • Probiotics and prebiotic fiber • Osmotic agents ‣ Macrogol known as polyethylene glycol ‣ Lactulose ‣ Magnesium hydroxide • Peristaltic agents ‣ Psyllium/senna

PD = Parkinson's disease.

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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**).[106-108] 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.[109-111] 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.[112] 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.[111,113-116] 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.[111,117] Symptoms of depression also play a role in sexual dysfunction in patients with PD.[118] In contrast, hypersexuality or aberrant sexual behaviors can be present in susceptible patients with PD, which is linked to dopaminergic drugs, especially dopamine agonists.[118]

Despite the dopaminergic pathophysiology above, overactive bladder symptoms do not respond to levodopa therapy (**Table 7**).[11,111] 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.[11,111] For these patients who have an overactive bladder, mirabegron, which is a β_3 adrenergic agonist, is an alternative therapeutic option.[11,111] α-Adrenergic blockers (tamsulosin, doxazosin, or terazosin) can be used for the sensation of incomplete bladder emptying and an intermittent urinary stream.[111,119] 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.[11,111]

Table 7. Genitourinary disorders in PD

Manifestations	Suggestive causes	Treatment options
Urinary frequency, nocturia	· Detrusor hyperactivity due to altered dopamine-basal ganglia circuit	· Anticholinergic agents ‣ Solifenacin, trospium, fesoterodine · β_3 adrenergic agonist ‣ Mirabegron
Urinary urgency	· Detrusor hyperactivity due to altered dopamine-basal ganglia circuit	· Anticholinergic agents ‣ Solifenacin, trospium, fesoterodine · β_3 adrenergic agonist ‣ Mirabegron
Urinary incontinence	· Detrusor hyperactivity due to altered dopamine-basal ganglia circuit	· Anticholinergic agents ‣ Solifenacin, trospium, fesoterodine · β_3 adrenergic agonist ‣ Mirabegron · 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 ‣ Solifenacin, trospium, fesoterodine · α-Adrenergic blockers for incomplete bladder emptying ‣ Tamsulosin, doxazosin, terazosin · Pelvic floor muscle therapy
Erectile dysfunction, decrease of lubrication	· Hypothalamic dysfunction due to altered dopamine-oxytocin circuit · Depression	· Phosphodiesterase inhibitors ‣ 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 postual 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 quadrartus lumborum muscles in patients with Pisa syndrome,[132-134] and to hyperactive rectus abnominis 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 realinment 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 thoraco-pelvic anterior distraction orthosis ‣ Rehabilitation programs (e.g., proprioceptive and tactile stimulation, postural reduction, and stretching to improve flexibility and mobility of the trunk) · Botulinum toxin injections for camptocormia or Pisa syndrome · Spinal realinment surgery · Anti-parkinsonian medications · Deep brain stimulation
Striatal hand and foot	· Central dopamine deficiency · Dopaminergic-cholinergic imbalance	· Anti-parkinsonian medications · Deep brain stimulation

PD = Parkinson's disease.

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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**).[141-143] Musculoskeletal pain, a common type of pain, can result from multiple factors such as parkinsonian rigidity, stiffness, immobility, and the above-mentioned musculoskeletal deformities.[141-143] 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.[141,144] 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.[141-143] Patients with PD may have central pain, characterized as persistent pain or paresthesia (e.g., burning or tingling sensations) without other causative etiologies.[145] 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.[141,146] 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.[141-143] Fatigue has been reported in about one-third of patients with PD,[147-149] occurring even in those with an early stage of PD.[150] Dopaminergic deficiency has been suggested to play a role in the development of fatigue,[151,152] 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) • Musculoskeletal deformities	• Physical therapy • Analgesics • Muscle relaxants ‣ GABA agonist (baclofen) • Opioids ‣ Oxycodone, methadone
Dystonia-related pain	• Central dopamine deficiency • Fluctuated with levodopa-related motor fluctuations	• Dopaminergic medication adjustment • 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 • Serotonergic deficiency in the basal ganglia and limbic systems • Some non-motor symptoms of PD (e.g., depression and sleep disturbance)	• Selective serotonin reuptake inhibitors • Dopaminergic medication ‣ Levodopa ‣ Methylphenidate

PD = Parkinson's disease, NMDA = N-methyl-D-aspartate, GABA = gamma-aminobutyric acid.

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serotonergic deficiency in the basal ganglia and limbic systems has been proposed as a reason for chronic fatigue syndrome in patients with PD.[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.[155,156]

Musculoskeletal pain can be treated with physical therapy, analgesics, muscle relaxants, or opioids (**Table 9**).[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.[141-143] For neuropathic pain, avoidance of overusing the affected body part or poor posture with physical therapy may alleviate the pain.[141-143] Otherwise, neuropathic pain agents that include GABA analogues, tricyclic antidepressants, and opioids, or decompressive surgery as indicated may be beneficial.[141-143] Central pain is often not alleviated by dopaminergic treatment, but analgesics, opiates, tricyclic antidepressants, and atypical neuroleptics (clozapine) may help.[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.[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.[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,[158] and NMS are often unresponsive to conventional dopaminergic therapy,[9,11] recognition and proper management of NMS by physicians cannot be overemphasized.

REFERENCES

1. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord* 2010;25(5):534-41.
PUBMED | CROSSREF
2. Tanner CM, Goldman SM. Epidemiology of Parkinson's disease. *Neurol Clin* 1996;14(2):317-35.
PUBMED | CROSSREF
3. Kim JM, Kim JS, Kim KW, Lee SB, Park JH, Lee JJ, et al. Study of the prevalence of Parkinson's disease using dopamine transporter imaging. *Neurol Res* 2010;32(8):845-51.
PUBMED | CROSSREF
4. Oh ES, Kim JM, Kim YE, Yun JY, Kim JS, Kim SE, et al. The prevalence of essential tremor in elderly Koreans. *J Korean Med Sci* 2014;29(12):1694-8.
PUBMED | CROSSREF
5. Postuma RB, Aarsland D, Barone P, Burn DJ, Hawkes CH, Oertel W, et al. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. *Mov Disord* 2012;27(5):617-26.
PUBMED | CROSSREF

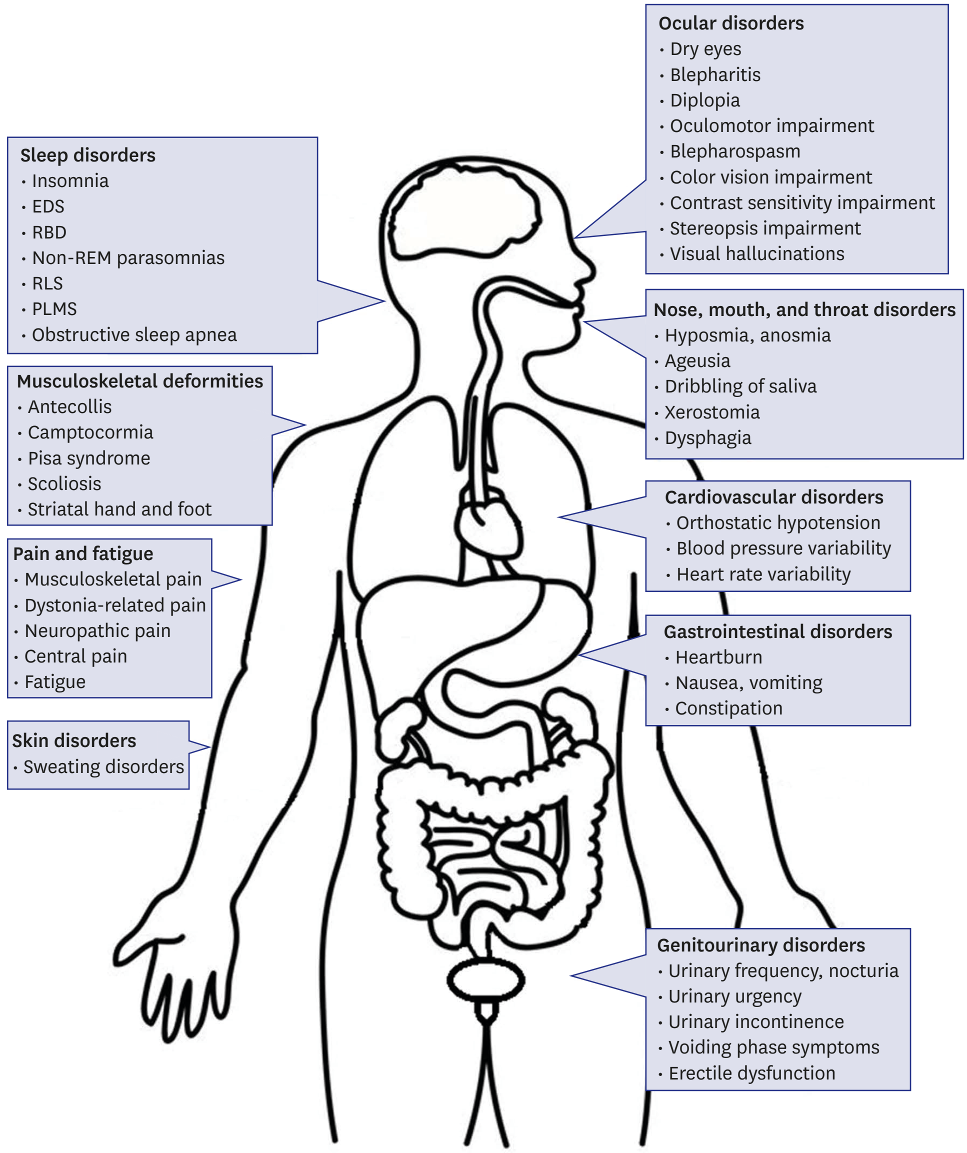

Fig. 1. Summary of multi-organ involvements in PD. In addition to motor symptoms, various NMS manifest in patients with PD. These NMS may pose a diagnostic and therapeutic challenge for physicians and surgeons in many different fields.
PD = Parkinson's disease, NMS = non-motor symptoms, EDS = excessive daytime somnolence, REM = rapid eye movement, RBD = rapid eye movement sleep behavior disorder, RLS = restless legs syndrome, PLMS = periodic leg movements in sleep.

6. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord* 2009;24(11):1641-9.
PUBMED | CROSSREF
7. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24(2):197-211.
PUBMED | CROSSREF
8. Forno LS. Neuropathology of Parkinson's disease. *J Neuropathol Exp Neurol* 1996;55(3):259-72.
PUBMED | CROSSREF

9. Chaudhuri KR, Healy DG, Schapira AH; National Institute for Clinical Excellence. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol* 2006;5(3):235-45.
PUBMED | CROSSREF

10. Rana AQ, Ahmed US, Chaudry ZM, Vasan S. Parkinson's disease: a review of non-motor symptoms. *Expert Rev Neurother* 2015;15(5):549-62.
PUBMED | CROSSREF

11. Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, et al. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. *Mov Disord* 2019;34(2):180-98.
PUBMED | CROSSREF

12. Han JW, Ahn YD, Kim WS, Shin CM, Jeong SJ, Song YS, et al. Psychiatric manifestation in patients with Parkinson's disease. *J Korean Med Sci* 2018;33(47):e300.
PUBMED | CROSSREF

13. Garcia-Borreguero D, Larrosa O, Bravo M. Parkinson's disease and sleep. *Sleep Med Rev* 2003;7(2):115-29.
PUBMED | CROSSREF

14. Bonnet AM, Jutras MF, Czernecki V, Corvol JC, Vidailhet M. Nonmotor symptoms in Parkinson's disease in 2012: relevant clinical aspects. *Parkinsons Dis* 2012;2012:198316.
PUBMED | CROSSREF

15. French IT, Muthusamy KA. A review of sleep and its disorders in patients with Parkinson's disease in relation to various brain structures. *Front Aging Neurosci* 2016;8:114.
PUBMED | CROSSREF

16. Salawu F, Olokoba A. Excessive daytime sleepiness and unintended sleep episodes associated with Parkinson's disease. *Oman Med J* 2015;30(1):3-10.
PUBMED | CROSSREF

17. Gjerstad MD, Wentzel-Larsen T, Aarsland D, Larsen JP. Insomnia in Parkinson's disease: frequency and progression over time. *J Neurol Neurosurg Psychiatry* 2007;78(5):476-9.
PUBMED | CROSSREF

18. Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev* 2010;14(1):19-31.
PUBMED | CROSSREF

19. Suzuki K, Miyamoto M, Miyamoto T, Iwanami M, Hirata K. Sleep disturbances associated with Parkinson's disease. *Parkinsons Dis* 2011;2011:219056.
PUBMED | CROSSREF

20. Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML, et al. Parkinson's disease and sleepiness: an integral part of PD. *Neurology* 2002;58(7):1019-24.
PUBMED | CROSSREF

21. Tandberg E, Larsen JP, Karlsen K. Excessive daytime sleepiness and sleep benefit in Parkinson's disease: a community-based study. *Mov Disord* 1999;14(6):922-7.
PUBMED | CROSSREF

22. Abbott RD, Ross GW, White L. Excessive daytime sleepiness and the future risk of Parkinson's disease. *Mov Disord* 2005;20:S101.

23. Pirker W, Happe S. Sleep attacks in Parkinson's disease. *Lancet* 2000;356(9229):597-8.
PUBMED | CROSSREF

24. Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? *Neurology* 2006;67(5):853-8.
PUBMED | CROSSREF

25. Ferreira JJ, Galitzky M, Thalamas C, Tiberge M, Montastruc JL, Sampaio C, et al. Effect of ropinirole on sleep onset: a randomized, placebo-controlled study in healthy volunteers. *Neurology* 2002;58(3):460-2.
PUBMED | CROSSREF

26. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. *Brain* 2000;123(Pt 2):331-9.
PUBMED | CROSSREF

27. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med* 2013;14(8):744-8.
PUBMED | CROSSREF

28. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. *Neurology* 1996;46(2):388-93.
PUBMED | CROSSREF

29. Shouse MN, Siegel JM. Pontine regulation of REM sleep components in cats: integrity of the pedunculopontine tegmentum (PPT) is important for phasic events but unnecessary for atonia during REM sleep. *Brain Res* 1992;571(1):50-63.
PUBMED | CROSSREF

30. Lai YY, Siegel JM. Muscle tone suppression and stepping produced by stimulation of midbrain and rostral pontine reticular formation. *J Neurosci* 1990;10(8):2727-34.
PUBMED | CROSSREF

31. Ratti PL, Sierra-Peña M, Manni R, Simonetta-Moreau M, Bastin J, Mace H, et al. Distinctive features of NREM parasomnia behaviors in Parkinson's disease and multiple system atrophy. *PLoS One* 2015;10(3):e0120973.
PUBMED | CROSSREF

32. Liu Y, Zhu XY, Zhang XJ, Kuo SH, Ondo WG, Wu YC. Clinical features of Parkinson's disease with and without rapid eye movement sleep behavior disorder. *Transl Neurodegener* 2017;6:35.
PUBMED | CROSSREF

33. Bohnen NI, Kanel P, Müller ML. Chapter seven - molecular imaging of the cholinergic system in Parkinson's disease. In: Politis M, editor. *International Review of Neurobiology*. Boston, MA: Academic Press; 2018, 211-50.

34. Mahowald MW, Schenck CH, Bornemann MA. Pathophysiologic mechanisms in REM sleep behavior disorder. *Curr Neurol Neurosci Rep* 2007;7(2):167-72.
PUBMED | CROSSREF

35. Garcia-Borreguero D, Odin P, Serrano C. Restless legs syndrome and PD: a review of the evidence for a possible association. *Neurology* 2003;61(6 Suppl 3):S49-55.
PUBMED | CROSSREF

36. Winkelman JW. Considering the causes of RLS. *Eur J Neurol* 2006;13 Suppl 3:8-14.
PUBMED

37. Rye DB. Parkinson's disease and RLS: the dopaminergic bridge. *Sleep Med* 2004;5(3):317-28.
PUBMED | CROSSREF

38. Ferini-Strambi L, Carli G, Casoni F, Galbiati A. Restless legs syndrome and Parkinson disease: a causal relationship between the two disorders? *Front Neurol* 2018;9:551.
PUBMED | CROSSREF

39. Happe S, Pirker W, Klösch G, Sauter C, Zeitlhofer J. Periodic leg movements in patients with Parkinson's disease are associated with reduced striatal dopamine transporter binding. *J Neurol* 2003;250(1):83-6.
PUBMED | CROSSREF

40. Cochen De Cock V, Abouda M, Leu S, Oudiette D, Roze E, Vidailhet M, et al. Is obstructive sleep apnea a problem in Parkinson's disease? *Sleep Med* 2010;11(3):247-52.
PUBMED | CROSSREF

41. Loddo G, Calandra-Buonaura G, Sambati L, Giannini G, Cecere A, Cortelli P, et al. The treatment of sleep disorders in Parkinson's disease: from research to clinical practice. *Front Neurol* 2017;8:42.
PUBMED | CROSSREF

42. Todorova A, Jenner P, Ray Chaudhuri K. Non-motor Parkinson's: integral to motor Parkinson's, yet often neglected. *Pract Neurol* 2014;14(5):310-22.
PUBMED | CROSSREF

43. Diederich NJ, McIntyre DJ. Sleep disorders in Parkinson's disease: many causes, few therapeutic options. *J Neurol Sci* 2012;314(1-2):12-9.
PUBMED | CROSSREF

44. Büchele F, Hackius M, Schreglmann SR, Omlor W, Werth E, Maric A, et al. Sodium oxybate for excessive daytime sleepiness and sleep disturbance in Parkinson disease: a randomized clinical trial. *JAMA Neurol* 2018;75(1):114-8.
PUBMED | CROSSREF

45. Neikrug AB, Liu L, Avanzino JA, Maglione JE, Natarajan L, Bradley L, et al. Continuous positive airway pressure improves sleep and daytime sleepiness in patients with Parkinson disease and sleep apnea. *Sleep (Basel)* 2014;37(1):177-85.
PUBMED | CROSSREF

46. Biousse V, Skibell BC, Watts RL, Loupe DN, Drews-Botsch C, Newman NJ. Ophthalmologic features of Parkinson's disease. *Neurology* 2004;62(2):177-80.
PUBMED | CROSSREF

47. Borm CD, Smilowska K, de Vries NM, Bloem BR, Theelen T. How I do it: the neuro-ophthalmological assessment in Parkinson's disease. *J Parkinsons Dis* 2019;9(2):427-35.
PUBMED | CROSSREF

48. Karson CN, LeWitt PA, Calne DB, Wyatt RJ. Blink rates in parkinsonism. *Ann Neurol* 1982;12(6):580-3.
PUBMED | CROSSREF

49. Taylor JR, Elsworth JD, Lawrence MS, Sladek JR Jr, Roth RH, Redmond DE Jr. Spontaneous blink rates correlate with dopamine levels in the caudate nucleus of MPTP-treated monkeys. *Exp Neurol* 1999;158(1):214-20.
PUBMED | CROSSREF

50. Tamer C, Melek IM, Duman T, Oksüz H. Tear film tests in Parkinson's disease patients. *Ophthalmology* 2005;112(10):1795.
PUBMED | CROSSREF

51. Ekker MS, Janssen S, Seppi K, Poewe W, de Vries NM, Theelen T, et al. Ocular and visual disorders in Parkinson's disease: common but frequently overlooked. *Parkinsonism Relat Disord* 2017;40:1-10.
PUBMED | CROSSREF

52. Shibasaki H, Tsuji S, Kuroiwa Y. Oculomotor abnormalities in Parkinson's disease. *Arch Neurol* 1979;36(6):360-4.
PUBMED | CROSSREF

53. Shaikh AG, Xu-Wilson M, Grill S, Zee DS. 'Staircase' square-wave jerks in early Parkinson's disease. *Br J Ophthalmol* 2011;95(5):705-9.
PUBMED | CROSSREF

54. Gitchel GT, Wetzel PA, Baron MS. Pervasive ocular tremor in patients with Parkinson disease. *Arch Neurol* 2012;69(8):1011-7.
PUBMED | CROSSREF

55. Rana AQ, Kabir A, Dogu O, Patel A, Khondker S. Prevalence of blepharospasm and apraxia of eyelid opening in patients with parkinsonism, cervical dystonia and essential tremor. *Eur Neurol* 2012;68(5):318-21.
PUBMED | CROSSREF

56. Yoon WT, Chung EJ, Lee SH, Kim BJ, Lee WY. Clinical analysis of blepharospasm and apraxia of eyelid opening in patients with parkinsonism. *J Clin Neurol* 2005;1(2):159-65.
PUBMED | CROSSREF

57. Pieri V, Diederich NJ, Raman R, Goetz CG. Decreased color discrimination and contrast sensitivity in Parkinson's disease. *J Neurol Sci* 2000;172(1):7-11.
PUBMED | CROSSREF

58. Weil RS, Schrag AE, Warren JD, Crutch SJ, Lees AJ, Morris HR. Visual dysfunction in Parkinson's disease. *Brain* 2016;139(11):2827-43.
PUBMED | CROSSREF

59. Archibald NK, Clarke MP, Mosimann UP, Burn DJ. The retina in Parkinson's disease. *Brain* 2009;132(Pt 5):1128-45.
PUBMED | CROSSREF

60. Koh SB, Suh SI, Kim SH, Kim JH. Stereopsis and extrastriate cortical atrophy in Parkinson's disease: a voxel-based morphometric study. *Neuroreport* 2013;24(5):229-32.
PUBMED | CROSSREF

61. Sun L, Zhang H, Gu Z, Cao M, Li D, Chan P. Stereopsis impairment is associated with decreased color perception and worse motor performance in Parkinson's disease. *Eur J Med Res* 2014;19(1):29.
PUBMED | CROSSREF

62. Gibson G, Mottram PG, Burn DJ, Hindle JV, Landau S, Samuel M, et al. Frequency, prevalence, incidence and risk factors associated with visual hallucinations in a sample of patients with Parkinson's disease: a longitudinal 4-year study. *Int J Geriatr Psychiatry* 2013;28(6):626-31.
PUBMED | CROSSREF

63. Goetz CG, Stebbins GT, Ouyang B. Visual plus nonvisual hallucinations in Parkinson's disease: development and evolution over 10 years. *Mov Disord* 2011;26(12):2196-200.
PUBMED | CROSSREF

64. Fénelon G, Mahieux F, Huon R, Ziégler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain* 2000;123(Pt 4):733-45.
PUBMED | CROSSREF

65. Barnes J, David AS. Visual hallucinations in Parkinson's disease: a review and phenomenological survey. *J Neurol Neurosurg Psychiatry* 2001;70(6):727-33.
PUBMED | CROSSREF

66. Bares M, Brázdil M, Kanovský P, Jurák P, Daniel P, Kukleta M, et al. The effect of apomorphine administration on smooth pursuit ocular movements in early Parkinsonian patients. *Parkinsonism Relat Disord* 2003;9(3):139-44.
PUBMED | CROSSREF

67. Büttner T, Kuhn W, Patzold T, Przuntek H. L-Dopa improves colour vision in Parkinson's disease. *J Neural Transm Park Dis Dement Sect* 1994;7(1):13-9.
PUBMED | CROSSREF

68. Doty RL. Olfactory dysfunction in Parkinson disease. *Nat Rev Neurol* 2012;8(6):329-39.
PUBMED | CROSSREF

69. Rodríguez-Violante M, Lees AJ, Cervantes-Arriaga A, Corona T, Silveira-Moriyama L. Use of smell test identification in Parkinson's disease in Mexico: a matched case-control study. *Mov Disord* 2011;26(1):173-6.
PUBMED | CROSSREF

70. Jellinger KA. The pathomechanisms underlying Parkinson's disease. *Expert Rev Neurother* 2014;14(2):199-215.
PUBMED | CROSSREF

71. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* 2008;79(4):368-76.
PUBMED | CROSSREF

72. Tarakad A, Jankovic J. Chapter seventeen - anosmia and ageusia in Parkinson's disease. In: Chaudhuri KR, Titova N, editors. *International Review of Neurobiology*. Boston, MA: Academic Press; 2017, 541-56.

73. Kashihara K, Hanaoka A, Imamura T. Frequency and characteristics of taste impairment in patients with Parkinson's disease: results of a clinical interview. *Intern Med* 2011;50(20):2311-5.
PUBMED | CROSSREF

74. Garcia-Esparcia P, Schlüter A, Carmona M, Moreno J, Ansoleaga B, Torrejón-Escribano B, et al. Functional genomics reveals dysregulation of cortical olfactory receptors in Parkinson disease: novel putative chemoreceptors in the human brain. *J Neuropathol Exp Neurol* 2013;72(6):524-39.
PUBMED | CROSSREF

75. Rana AQ, Yousuf MS, Awan N, Fattah A. Impact of progression of Parkinson's disease on drooling in various ethnic groups. *Eur Neurol* 2012;67(5):312-4.
PUBMED | CROSSREF

76. Zlotnik Y, Balash Y, Korczyn AD, Giladi N, Gurevich T. Disorders of the oral cavity in Parkinson's disease and parkinsonian syndromes. *Parkinsons Dis* 2015;2015:379482.
PUBMED | CROSSREF

77. Hanaoka A, Kashihara K. Increased frequencies of caries, periodontal disease and tooth loss in patients with Parkinson's disease. *J Clin Neurosci* 2009;16(10):1279-82.
PUBMED | CROSSREF

78. Cersosimo MG, Raina GB, Calandra CR, Pellene A, Gutiérrez C, Micheli FE, et al. Dry mouth: an overlooked autonomic symptom of Parkinson's disease. *J Parkinsons Dis* 2011;1(2):169-73.
PUBMED | CROSSREF

79. Del Tredici K, Hawkes CH, Ghebremedhin E, Braak H. Lewy pathology in the submandibular gland of individuals with incidental Lewy body disease and sporadic Parkinson's disease. *Acta Neuropathol* 2010;119(6):703-13.
PUBMED | CROSSREF

80. Cersósimo MG, Perandones C, Micheli FE, Raina GB, Beron AM, Nasswetter G, et al. Alpha-synuclein immunoreactivity in minor salivary gland biopsies of Parkinson's disease patients. *Mov Disord* 2011;26(1):188-90.
PUBMED | CROSSREF

81. Coates C, Bakheit AM. Dysphagia in Parkinson's disease. *Eur Neurol* 1997;38(1):49-52.
PUBMED | CROSSREF

82. Leopold NA, Kagel MC. Prepharyngeal dysphagia in Parkinson's disease. *Dysphagia* 1996;11(1):14-22.
PUBMED | CROSSREF

83. Haehner A, Tosch C, Wolz M, Klingelhoefer L, Fauser M, Storch A, et al. Olfactory training in patients with Parkinson's disease. *PLoS One* 2013;8(4):e61680.
PUBMED | CROSSREF

84. Yagi T, Asakawa A, Ueda H, Ikeda S, Miyawaki S, Inui A. The role of zinc in the treatment of taste disorders. *Recent Pat Food Nutr Agric* 2013;5(1):44-51.
PUBMED | CROSSREF

85. Hobson P, Islam W, Roberts S, Adhiyman V, Meara J. The risk of bladder and autonomic dysfunction in a community cohort of Parkinson's disease patients and normal controls. *Parkinsonism Relat Disord* 2003;10(2):67-71.
PUBMED | CROSSREF

86. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Parkinsonism Relat Disord* 2011;17(1):10-5.
PUBMED | CROSSREF

87. Kim JS, Lee SH, Oh YS, Park JW, An JY, Park SK, et al. Cardiovascular autonomic dysfunction in mild and advanced Parkinson's disease. *J Mov Disord* 2016;9(2):97-103.
PUBMED | CROSSREF

88. Oh YS, Kim JS, Kim YI, Yang DW, Koo J, Jung HO, et al. Circadian blood pressure and heart rate variations in de novo Parkinson's disease. *Biol Rhythm Res* 2014;45(3):335-43.
CROSSREF

89. Senard JM, Raï S, Lapeyre-Mestre M, Brefel C, Rascol O, Rascol A, et al. Prevalence of orthostatic hypotension in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997;63(5):584-9.
PUBMED | CROSSREF

90. Goldstein DS, Holmes CS, Dendi R, Bruce SR, Li ST. Orthostatic hypotension from sympathetic denervation in Parkinson's disease. *Neurology* 2002;58(8):1247-55.
PUBMED | CROSSREF

91. Jain S, Goldstein DS. Cardiovascular dysautonomia in Parkinson disease: from pathophysiology to pathogenesis. *Neurobiol Dis* 2012;46(3):572-80.
PUBMED | CROSSREF

92. Allcock LM, Kenny RA, Burn DJ. Clinical phenotype of subjects with Parkinson's disease and orthostatic hypotension: autonomic symptom and demographic comparison. *Mov Disord* 2006;21(11):1851-5.
PUBMED | CROSSREF

93. Sharabi Y, Goldstein DS. Mechanisms of orthostatic hypotension and supine hypertension in Parkinson disease. *J Neurol Sci* 2011;310(1-2):123-8.
PUBMED | CROSSREF

94. Swinn L, Schrag A, Viswanathan R, Bloem BR, Lees A, Quinn N. Sweating dysfunction in Parkinson's disease. *Mov Disord* 2003;18(12):1459-63.
PUBMED | CROSSREF

95. Leta V, van Wamelen DJ, Rukavina K, Jaakkola E, Sportelli C, Wan YM, et al. Sweating and other thermoregulatory abnormalities in Parkinson's disease: a review. *Ann Mov Disord* 2019;2(2):39-47.
CROSSREF

96. Coon EA, Low PA. Thermoregulation in Parkinson disease. *Handb Clin Neurol* 2018;157:715-25.
PUBMED | CROSSREF

97. Pursiainen V, Haapaniemi TH, Korpelainen JT, Sotaniemi KA, Myllylä VV. Sweating in Parkinsonian patients with wearing-off. *Mov Disord* 2007;22(6):828-32.
PUBMED | CROSSREF

98. Wang N, Gibbons CH, Lafo J, Freeman R. α-Synuclein in cutaneous autonomic nerves. *Neurology* 2013;81(18):1604-10.
PUBMED | CROSSREF

99. Donadio V, Incensi A, Leta V, Giannoccaro MP, Scaglione C, Martinelli P, et al. Skin nerve α-synuclein deposits: a biomarker for idiopathic Parkinson disease. *Neurology* 2014;82(15):1362-9.
PUBMED | CROSSREF

100. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol* 2003;2(2):107-16.
PUBMED | CROSSREF

101. Cersosimo MG, Benarroch EE. Pathological correlates of gastrointestinal dysfunction in Parkinson's disease. *Neurobiol Dis* 2012;46(3):559-64.
PUBMED | CROSSREF

102. Asai H, Udaka F, Hirano M, Minami T, Oda M, Kubori T, et al. Increased gastric motility during 5-HT_4 agonist therapy reduces response fluctuations in Parkinson's disease. *Parkinsonism Relat Disord* 2005;11(8):499-502.
PUBMED | CROSSREF

103. Shin CM, Lee YJ, Kim JM, Lee JY, Kim KJ, Choi YJ, et al. DA-9701 on gastric motility in patients with Parkinson's disease: a randomized controlled trial. *Parkinsonism Relat Disord* 2018;54:84-9.
PUBMED | CROSSREF

104. Shin HW, Chung SJ. Drug-induced parkinsonism. *J Clin Neurol* 2012;8(1):15-21.
PUBMED | CROSSREF

105. Salat-Foix D, Suchowersky O. The management of gastrointestinal symptoms in Parkinson's disease. *Expert Rev Neurother* 2012;12(2):239-48.
PUBMED | CROSSREF

106. Araki I, Kuno S. Assessment of voiding dysfunction in Parkinson's disease by the international prostate symptom score. *J Neurol Neurosurg Psychiatry* 2000;68(4):429-33.
PUBMED | CROSSREF

107. Lemack GE, Dewey RB Jr, Roehrborn CG, O'Suilleabhain PE, Zimmern PE. Questionnaire-based assessment of bladder dysfunction in patients with mild to moderate Parkinson's disease. *Urology* 2000;56(2):250-4.
PUBMED | CROSSREF

108. Campos-Sousa RN, Quagliato E, da Silva BB, de Carvalho RM Jr, Ribeiro SC, de Carvalho DF. Urinary symptoms in Parkinson's disease: prevalence and associated factors. *Arq Neuropsiquiatr* 2003;61(2B):359-63.
PUBMED | CROSSREF

109. Seki S, Igawa Y, Kaidoh K, Ishizuka O, Nishizawa O, Andersson KE. Role of dopamine D1 and D2 receptors in the micturition reflex in conscious rats. *Neurourol Urodyn* 2001;20(1):105-13.
PUBMED | CROSSREF

110. Yoshimura N, Kuno S, Chancellor MB, De Groat WC, Seki S. Dopaminergic mechanisms underlying bladder hyperactivity in rats with a unilateral 6-hydroxydopamine (6-OHDA) lesion of the nigrostriatal pathway. *Br J Pharmacol* 2003;139(8):1425-32.
PUBMED | CROSSREF

111. Sakakibara R, Uchiyama T, Yamanishi T, Kishi M. Genitourinary dysfunction in Parkinson's disease. *Mov Disord* 2010;25(1):2-12.
PUBMED | CROSSREF

112. Kim KJ, Jeong SJ, Kim JM. Neurogenic bladder in progressive supranuclear palsy: a comparison with Parkinson's disease and multiple system atrophy. *Neurourol Urodyn* 2018;37(5):1724-30.
PUBMED | CROSSREF

113. Brown RG, Jahanshahi M, Quinn N, Marsden CD. Sexual function in patients with Parkinson's disease and their partners. *J Neurol Neurosurg Psychiatry* 1990;53(6):480-6.
PUBMED | CROSSREF

114. Basson R. Sexuality and Parkinson's disease. *Parkinsonism Relat Disord* 1996;2(4):177-85.
PUBMED | CROSSREF

115. Jacobs H, Vieregge A, Vieregge P. Sexuality in young patients with Parkinson's disease: a population based comparison with healthy controls. *J Neurol Neurosurg Psychiatry* 2000;69(4):550-2.
PUBMED | CROSSREF

116. Papatsoris AG, Deliveliotis C, Singer C, Papapetropoulos S. Erectile dysfunction in Parkinson's disease. *Urology* 2006;67(3):447-51.
PUBMED | CROSSREF

117. Langston JW, Forno LS. The hypothalamus in Parkinson disease. *Ann Neurol* 1978;3(2):129-33.
PUBMED | CROSSREF

118. Nakum S, Cavanna AE. The prevalence and clinical characteristics of hypersexuality in patients with Parkinson's disease following dopaminergic therapy: a systematic literature review. *Parkinsonism Relat Disord* 2016;25:10-6.
PUBMED | CROSSREF

119. Gomes CM, Sammour ZM, de Bessa Junior J, Barbosa ER, Lopes RI, Sallem FS, et al. Neurological status predicts response to alpha-blockers in men with voiding dysfunction and Parkinson's disease. *Clinics (Sao Paulo)* 2014;69(12):817-22.
PUBMED | CROSSREF

120. Ashour R, Jankovic J. Joint and skeletal deformities in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Mov Disord* 2006;21(11):1856-63.
PUBMED | CROSSREF

121. Kim YE, Jeon BS. Musculoskeletal problems in Parkinson's disease. *J Neural Transm (Vienna)* 2013;120(4):537-42.
PUBMED | CROSSREF

122. Pandey S, Kumar H. Assessment of striatal & postural deformities in patients with Parkinson's disease. *Indian J Med Res* 2016;144(5):682-8.
PUBMED | CROSSREF

123. Kim YE, Kim HJ, Yun JY, Lee WW, Yang HJ, Kim JM, et al. Musculoskeletal problems affect the quality of life of patients with Parkinson's disease. *J Mov Disord* 2018;11(3):133-8.
PUBMED | CROSSREF

124. Srivanitchapoom P, Hallett M. Camptocormia in Parkinson's disease: definition, epidemiology, pathogenesis and treatment modalities. *J Neurol Neurosurg Psychiatry* 2016;87(1):75-85.
PUBMED

125. Barone P, Santangelo G, Amboni M, Pellecchia MT, Vitale C. Pisa syndrome in Parkinson's disease and parkinsonism: clinical features, pathophysiology, and treatment. *Lancet Neurol* 2016;15(10):1063-74.
PUBMED | CROSSREF

126. Finsterer J, Strobl W. Presentation, etiology, diagnosis, and management of camptocormia. *Eur Neurol* 2010;64(1):1-8.
PUBMED | CROSSREF

127. Gerton BK, Theeler B, Samii A. Backpack treatment for camptocormia. *Mov Disord* 2010;25(2):247-8.
PUBMED | CROSSREF

128. Schroeteler FE, Fietzek UM, Ziegler K, Ceballos-Baumann AO. Upright posture in parkinsonian camptocormia using a high-frame walker with forearm support. *Mov Disord* 2011;26(8):1560-1.
PUBMED | CROSSREF

129. de Sèze MP, Creuzé A, de Sèze M, Mazaux JM. An orthosis and physiotherapy programme for camptocormia: a prospective case study. *J Rehabil Med* 2008;40(9):761-5.
PUBMED | CROSSREF

130. Bartolo M, Serrao M, Tassorelli C, Don R, Ranavolo A, Draicchio F, et al. Four-week trunk-specific rehabilitation treatment improves lateral trunk flexion in Parkinson's disease. *Mov Disord* 2010;25(3):325-31.
PUBMED | CROSSREF

131. Capecci M, Serpicelli C, Fiorentini L, Censi G, Ferretti M, Orni C, et al. Postural rehabilitation and Kinesio taping for axial postural disorders in Parkinson's disease. *Arch Phys Med Rehabil* 2014;95(6):1067-75.
PUBMED | CROSSREF

132. Bonanni L, Thomas A, Varanese S, Scorrano V, Onofrj M. Botulinum toxin treatment of lateral axial dystonia in Parkinsonism. *Mov Disord* 2007;22(14):2097-103.
PUBMED | CROSSREF

133. Tassorelli C, De Icco R, Alfonsi E, Bartolo M, Serrao M, Avenali M, et al. Botulinum toxin type A potentiates the effect of neuromotor rehabilitation of Pisa syndrome in Parkinson disease: a placebo controlled study. *Parkinsonism Relat Disord* 2014;20(11):1140-4.
PUBMED | CROSSREF

134. Dupeyron A, Viollet E, Coroian F, Gagnard C, Renard D, Castelnovo G. Botulinum toxin-A for treatment of Pisa syndrome: a new target muscle. *Parkinsonism Relat Disord* 2015;21(6):669-70.
PUBMED | CROSSREF

135. von Coelln R, Raible A, Gasser T, Asmus F. Ultrasound-guided injection of the iliopsoas muscle with botulinum toxin in camptocormia. *Mov Disord* 2008;23(6):889-92.
PUBMED | CROSSREF

136. Colosimo C, Salvatori FM. Injection of the iliopsoas muscle with botulinum toxin in camptocormia. *Mov Disord* 2009;24(2):316-7.
PUBMED | CROSSREF

137. Fietzek UM, Schroeteler FE, Ceballos-Baumann AO. Goal attainment after treatment of parkinsonian camptocormia with botulinum toxin. *Mov Disord* 2009;24(13):2027-8.
PUBMED | CROSSREF

138. Galbusera F, Bassani T, Stucovitz E, Martini C, Ismael Aguirre MF, Berjano PL, et al. Surgical treatment of spinal disorders in Parkinson's disease. *Eur Spine J* 2018;27(Suppl 1):101-8.
PUBMED | CROSSREF

139. Poewe WH, Lees AJ. The pharmacology of foot dystonia in parkinsonism. *Clin Neuropharmacol* 1987;10(1):47-56.
PUBMED | CROSSREF

140. Umemura A, Oka Y, Ohkita K, Yamawaki T, Yamada K. Effect of subthalamic deep brain stimulation on postural abnormality in Parkinson disease. *J Neurosurg* 2010;112(6):1283-8.
PUBMED | CROSSREF

141. Ha AD, Jankovic J. Pain in Parkinson's disease. *Mov Disord* 2012;27(4):485-91.
PUBMED | CROSSREF

142. Rana AQ, Kabir A, Jesudasan M, Siddiqui I, Khondker S. Pain in Parkinson's disease: analysis and literature review. *Clin Neurol Neurosurg* 2013;115(11):2313-7.
PUBMED | CROSSREF

143. Ford B. Pain in Parkinson's disease. *Mov Disord* 2010;25 Suppl 1:S98-103.
PUBMED | CROSSREF

144. Beiske AG, Loge JH, Rønningen A, Svensson E. Pain in Parkinson's disease: prevalence and characteristics. *Pain* 2009;141(1-2):173-7.
PUBMED | CROSSREF

145. Wallace VC, Chaudhuri KR. Unexplained lower limb pain in Parkinson's disease: a phenotypic variant of "painful Parkinson's disease". *Parkinsonism Relat Disord* 2014;20(1):122-4.
PUBMED | CROSSREF

146. Brefel-Courbon C, Payoux P, Thalamas C, Ory F, Quelven I, Chollet F, et al. Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Mov Disord* 2005;20(12):1557-63.
PUBMED | CROSSREF

147. Friedman J, Friedman H. Fatigue in Parkinson's disease. *Neurology* 1993;43(10):2016-8.
PUBMED | CROSSREF

148. Abe K, Takanashi M, Yanagihara T. Fatigue in patients with Parkinson's disease. *Behav Neurol* 2000;12(3):103-6.
PUBMED | CROSSREF

149. Herlofson K, Larsen JP. Measuring fatigue in patients with Parkinson's disease - the Fatigue Severity Scale. *Eur J Neurol* 2002;9(6):595-600.
PUBMED | CROSSREF

150. Kang SY, Ma HI, Lim YM, Hwang SH, Kim YJ. Fatigue in drug-naïve Parkinson's disease. *Eur Neurol* 2013;70(1-2):59-64.
PUBMED | CROSSREF

151. Chaudhuri A, Behan PO. Fatigue and basal ganglia. *J Neurol Sci* 2000;179(S 1-2):34-42.
PUBMED | CROSSREF

152. Chaudhuri A, Condon BR, Gow JW, Brennan D, Hadley DM. Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome. *Neuroreport* 2003;14(2):225-8.
PUBMED | CROSSREF

153. Yamamoto S, Ouchi Y, Onoe H, Yoshikawa E, Tsukada H, Takahashi H, et al. Reduction of serotonin transporters of patients with chronic fatigue syndrome. *Neuroreport* 2004;15(17):2571-4.
PUBMED | CROSSREF

154. Pavese N, Metta V, Bose SK, Chaudhuri KR, Brooks DJ. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. *Brain* 2010;133(11):3434-43.
PUBMED | CROSSREF

155. Lou JS, Kearns G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. *Mov Disord* 2001;16(2):190-6.
PUBMED | CROSSREF

156. Hagell P, Brundin L. Towards an understanding of fatigue in Parkinson disease. *J Neurol Neurosurg Psychiatry* 2009;80(5):489-92.
PUBMED | CROSSREF

157. Mendonça DA, Menezes K, Jog MS. Methylphenidate improves fatigue scores in Parkinson disease: a randomized controlled trial. *Mov Disord* 2007;22(14):2070-6.
PUBMED | CROSSREF

158. Schrag A, Jahanshahi M, Quinn N. How does Parkinson's disease affect quality of life? A comparison with quality of life in the general population. *Mov Disord* 2000;15(6):1112-8.
PUBMED | CROSSREF