Non-motor Symptoms of Parkinson's Disease

Jyh-Gong Gabriel Hou*, Eugene C Lai

Parkinson's Disease Research, Education and Clinical Center, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, USA

SUMMARY

In addition to the typical motor symptoms (resting tremor, cogwheel rigidity, bradykinesia, postural instability) of Parkinson's disease (PD), non-motor symptoms are sources of considerable burden in people with PD, especially in elderly patients. The usual non-motor symptoms include cognitive declines, psychiatric disturbances (depression, psychosis, impulse control), autonomic failures (gastrointestinal, cardiovascular, urinary, sexual ability, thermoregulation), sleep difficulties, and pain syndrome. This review article discusses the characteristics, pathophysiology, epidemiology, and management of these symptoms. [International Journal of Gerontology 2007; 1(2): 53–64]

Key Words: dementia, depression, dysautonomia, non-motor symptoms, Parkinson's disease, psychosis, sleep

Introduction

Parkinson's disease (PD), first described by James Parkinson in 1817, is a chronic, progressive neurodegenerative disorder[1]. The pathologic hallmark is a deterioration of the substantia nigra of yet unknown causes, resulting in a deficiency of dopamine, an important neurotransmitter for the basal ganglia circuit. Its typical clinical symptoms are resting tremor, cogwheel rigidity, bradykinesia, and postural instability. Many affected patients are older than 55 years of age, and men seem to be slightly more predominantly affected than women[2].

While PD is mainly regarded as a movement disorder, patients suffer from not only motor symptoms, but also the non-motor symptoms which are also common and can significantly debilitate patients' activities as well as the quality of life. These complications include cognitive, psychiatric, autonomic, sleep and sensory disorders (Table). The non-motor symptoms may appear even before the motor symptoms are first noticed. But they are more troublesome in the more advanced stages of PD, when they can become major problems for the patients and often pose a challenge to the treating physicians[3,4]. With multiple medications often being used to treat PD, their side effects may further exacerbate the problems.

Epidemiology

Because of the varieties of symptoms, the prevalence of non-motor symptoms in PD patients is difficult to delineate precisely. It is estimated that about 16–70% of patients suffer from neuropsychiatric problems, including depression, anxiety, apathy or psychosis[5–7]. Cognitive deficits affect at least 20–40% of PD patients[8–10]. Sleep disturbances occur in more than a third of PD patients[11,12]. Dysautonomia, including constipation, orthostatic hypotension, urinary and sexual dysfunctions, is reported in more than half of the PD patients, according to a questionnaire-based study[13]. This European study and other studies also suggest that autonomic failures, including orthostatic dizziness, bladder dysfunctions, erectile dysfunctions and hyperhidrosis, are more prevalent in PD patients than control individuals

Correspondence to: Dr Jyh-Gong Gabriel Hou, Parkinson's Disease Research, Education and Clinical Center, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX 77030, USA.
E-mail: jhou@bcm.tmc.edu
Accepted: March 30, 2007

Table. *The non-motor symptom complex of Parkinson's disease*

Neuropsychiatric symptoms	Sleep disorders	Autonomic symptoms	Sensory and other symptoms
(A) Depression, apathy, anxiety (B) Compulsive-obsessive behavior (possibly drug induced), repetitive behavior (C) Attention deficit (D) Hallucinations, illusion, delusions (E) Delirium (F) Anxiety and panic attacks (G) Dementia	(A) REM sleep behavior disorder and REM loss of atonia (B) Non-REM-sleep related movement disorders (C) Insomnia (D) Excessive daytime somnolence (E) Restless legs and periodic limb movements (F) Nightmares or vivid dreams (G) Sleep disordered breathing (sleep apnea)	(A) Cardiovascular system: orthostatic hypotension; falls related to orthostatic hypotension; bradycardia or arrhythmia (B) Gastrointestinal system: sialorrhea; dysphagia and choking; reflux, vomiting, nausea; fecal constipation; fecal incontinence (C) Urinary system: bladder disturbances; urgency and frequency; nocturia; incontinence (D) Reproductive system: sexual dysfunction; erectile impotence; hypersexuality (possibly drug induced) (E) Thermoregulation: sweating; dry eyes (xerostomia); heat or cold intolerance	(A) Pain (B) Paraesthesia (C) Olfactory disturbance (D) Fatigue (E) Weight changes

Modified from Chaudhuri et al.[3]. REM = rapid eye movement.

without PD. These symptoms had a huge impact on their quality of life[13–15]. Using a comprehensive symptom survey, Siddiqui et al.[16] reported a significantly higher prevalence rate of increased salivation, dysphagia, decreased bowel movement, and orthostatic dizziness in PD patients compared with controls. Two studies showed that cardiac uptake of metaiodobenzylguanidine, an index of functional integrity and function of postganglionic neurons, was impaired in almost all patients with PD, independent of duration and severity of their parkinsonian symptoms[17,18].

Pathophysiology

Since non-motor symptoms comprise a variety of symptoms in different aspects, their involvement must be related to diffuse or multiple brain dysfunctions. Hallucination and psychosis can be related to the dopaminergic system in the prefrontal region. Depression is likely due to the decreased numbers of serotonin 5-hydroxyindolacetic acid (5-HT) neurons in the dorsal raphe nucleus and reduced dopamine neurons in the ventral tegmental area[19,20]. Cognitive function may be related to the depletion of dopamine in the head of the caudate nucleus, which participates in the basal ganglia-thalamocortical circuits involving different regions of the prefrontal cortex. Lewy body formation is abundant in these regions[21,22]. Urinary control may be from frontal cortex degeneration or autonomic nervous system dysfunction, and possibly in combination with prostate enlargement. Orthostatic hypotension is likely due to sympathetic denervation of the central control centers located at the dorsal vagal nucleus, nucleus ambiguus, and other medullary centers (caudal raphe nuclei, rostral ventrolateral medulla, and ventromedial medulla). These nuclei mainly control the sympathetic pre-ganglionic neurons via descending pathways[23,24]. Lewy bodies have been found in the myenteric plexus in PD patients. This explains the reason for constipation because of the loss of dopaminergic cells throughout the gastrointestinal tract[25].

PD is characterized by a dopaminergic degenerative process affecting neurons in the substantia nigra. This results in the disruption in the basal ganglia circuitry. How the degenerative processes damage both the nigrostriatal system and other brain regions is not completely clear. Braak et al.[26] hypothesized that the degenerative process starts from the base of the brain. The olfactory bulbs may be the first to be involved, followed by the lower brain stem that affects autonomic functions as well as sleep. Subsequently, substantia nigra

and other nuclei in the midbrain are affected, thus manifesting the typical motor symptoms of PD. Eventually, the limbic system and frontal neocortex are involved, resulting in cognitive and psychiatric symptoms in the advanced PD stages. Although yet to be confirmed, Braak et al.'s hypothesis nicely illustrates the evolving symptoms in PD, including both motor and non-motor manifestations[26–28].

Depression

Depression is a very common feature in patients with PD. The reported prevalence from various studies is between 16% and 70%[5–7]. Such variations are due to the different diagnostic criteria used in different studies. Major depressive disorder defined by DSM-IV may not be very common in PD patients, but depressive symptoms certainly have a high prevalence rate in PD. It is thought that complex interactions between norepinephrine, serotonin and dopamine systems are interrupted in brains of PD patients. The mechanisms are not clear yet. Some studies revealed decreased concentrations of 5-HT, a serotonin metabolite, in the cerebrospinal fluid and reduced cortical 5-HT1A receptor binding in PD[29]. Another study suggested the role of an allelic variation in the serotonin transporter gene[30].

The diagnosis of depression in PD can be challenging, since flat affect, psychomotor slowing, fatigue, and decreased libido may be frequently mistaken for PD motor symptoms. The characteristics of depression in PD are decreased energy and motivation, losing interest, feelings of sadness, helplessness and hopelessness, changes in weight, sleep and appetite, irritability, and thoughts of suicide. Approximately 7–32% of PD patients are diagnosed with major depression, according to DSM-IV diagnostic criteria[31]. However, the depression is reported to be qualitatively different in that many depressed PD patients have greater rates of anxiety, pessimism, irrationality, and less guilt and self-reproach, compared with those of non-PD patients with major depression[32,33]. There can be fluctuations between a normal affect and a depressive state in their emotions. The episodes of depression may be more frequent during the "off" medication stage and may improve when the motor symptoms are better treated[34]. Interestingly, depression has been found to be more prevalent in patients with the akinetic-rigid type of PD, compared with those with the tremor-predominant type, and in patients with right-sided motor symptoms[35,36]. Furthermore, greater depression is probably associated with greater motor symptom severity in PD[37].

Reactive depression is another form of depression experienced by newly diagnosed PD patients and others with more advanced disease who are losing independence and control because of changes in motor functioning and feelings of helplessness[6,25]. Other social factors, including job loss with subsequent changes in income or loss of identity, may also contribute to depression. Concurrent memory difficulty, communication problems, and sleep interruptions, all add to the severity of depression and anxiety. They contribute substantially to increased morbidity and caregiver burdens.

Treating PD patients with depression has not been different from treating patients with other forms of depressive disorders. Selective serotonin reuptake inhibitors (SSRIs) are most frequently used. This is generally safe, although a small number of patients were reported to develop serotonin syndrome from combined use of SSRI and selegiline, a monoamine oxidase B inhibitor[38]. The effectiveness of SSRI in the treatment of PD depression is still not determined. There have not been large-scale, of double-blind, placebo-controlled studies conducted. A meta-analysis found disappointing benefits of SSRI treatment in older PD patients with depression[39]. Other treatments of choice include tricyclic antidepressants. While this class of medications has the additional benefit in reducing tremor by their anticholinergic action, the side effects, including confusion, orthostatic hypotension, dry mouth or constipation, often limit their use. Rarely, electroconvulsive therapy is used in patients with medication-refractory depression. It may improve motor function in PD patients[40,41].

Anxiety

There can be periodic anxiety and panic attacks. Anxiety disorders are more prevalent in PD patients than age-matched controls, although it is often underdiagnosed[42]. The prevalence rate is at least 40%[43]. Panic attacks easily occur in patients who develop erratic motor fluctuations during "off" periods. It usually improves after the patient achieves the "on" state[44]. "On" state dyskinesia may also induce anxiety. Thus, anxiety attacks seem more related with the motor fluctuations in PD patients. Benzodiazepine, buspirone, and SSRI may help reduce such anxiety[45]. However, better control

of PD motor symptoms may be more helpful in reducing anxiety and fearfulness.

Cognitive Decline and Dementia

Dementia in PD may not be evident until the later stages. Although the cognitive decline reported in PD is subtle and does not often interfere with daily functioning, PD patients have been shown to demonstrate cognitive slowing and executive dysfunctioning problems at earlier stages[46]. Longitudinal research has described PD-related cognitive deficits in language, visuospatial functioning, long-term memory, and executive functioning that are greater than those expected from normal aging. The percentage of patients with cognitive deficits is estimated to be approximately 20%[8,10]. However, the prevalence varies widely according to different studies. For example, a Norwegian study of PD patients indicated that the 8-year prevalence in developing dementia was 78.2%[47].

The cognitive dysfunction in PD may be a consequence of disruption not only in the primary motor circuit but also in a number of interconnected pathways from the basal ganglia to the cortex. Dopamine depletion in the lateral orbitofrontal and dorsolateral prefrontal circuits has been suggested as a possible mechanism of cognitive impairment in PD[48]. Cholinergic cell loss in the nucleus basalis of Meynert is prominent in PD. The disturbances of dopamine–acetylcholine dependent alterations in synaptic plasticity may also be responsible for dementia in PD[49].

PD patients at a higher risk of developing demenia include: (1) age older than 70 years; (2) Unified Parkinson's Disease Rating Scale motor score of more than 25 (moderate to advanced impairment); (3) coexisting depression; (4) development of mania, agitation, disorientation or psychosis when treated with levodopa; (5) facial masking at presentation; (6) exposure to psychologic stress; (7) presence of cardiovascular abnormalities; (8) low socioeconomic status and educational level; and (9) predominant bradykinesia, and postural and gait disturbance. Tremor or other parkinsonian signs are less associated with dementia[10,50,51].

Cognitive impairment in PD is usually distinguished from that of Alzheimer's type, which reveals more amnestic quality of memory loss. In contrast, PD patients encompass the clinical symptoms of cognitive slowing, impaired memory recall and retrieval, and executive deficits. These symptoms are summarized as "dysexecutive syndrome", in which acquisition and delayed recall are defective, while recognition memory remains intact[52]. However, the distinctions usually may not be very clear. About 15–30% of demented patients with PD may also have coexisting Alzheimer's disease and exhibit symptoms of impaired language, memory, and visuospatial functioning earlier in the course of the disease, including the presence of aphasia, agnosia, and apraxia[53,54]. Another important differential diagnosis is dementia with Lewy bodies (DLBs), which also manifests dementia, autonomic failure, and parkinsonian symptoms. As a general rule, DLB patients show fluctuations in mental symptoms, visual hallucinations, and more prominent lower body parkinsonism. The motor symptoms of parkinsonism usually occur together with cognitive decline[55]. Again, the clinical features are frequently not reliable in making a clear differentiation. A confirmed diagnosis usually depends on the results of autopsy. A typical pathologic picture of DLBs shows widespread Lewy bodies located in the neocortex and basal ganglia[56].

Rivastigmine, an acetylcholinesterase inhibitor that has been used in the symptomatic treatment of patients with mild to moderate Alzheimer's disease, was also shown to be effective in the treatment of dementia in PD[57,58]. Other cholinesterase inhibitors may also be beneficial, although large-scale randomized controlled studies have yet to be conducted[59]. Memantine, which is an *N*-methyl-D-aspartate receptor antagonist beneficial in Alzheimer's dementia, has not been shown to be effective in PD dementia[60]. One study even suggested that it worsened both the motor and cognitive functions in PD[61].

Psychosis and Hallucination

Hallucination occurs in PD, more frequently in the advanced stages. Psychosis and visual hallucination are common, dose-dependent adverse effects of anti-PD medications, in combination with disease progression and medical illnesses[62]. Risk factors include advancing age, presence of dementia, and polypharmacy. Patients who experience hallucination generally have a certain degree of cognitive decline. They also have a worse prognosis, with higher mortality rates[63]. In addition, delusions, paranoid ideation, and delirium may also become more frequent as the disease progresses.

Hallucination is usually visual in nature, in contrast to auditory hallucination in schizophrenia[64]. Patients may report seeing small animals, insects, children, or their deceased relatives or friends. In the early stages, patients retain insight that the hallucinations are not real. Symptoms are commonly more severe toward the evening, known as "sun-downing"[65]. Patients may experience frightening dreams or night terrors that can lead to acting or lashing out during the dream state. Another common delusion is that of spousal infidelity, for either male or female patients[64,66]. These symptoms can be aggravated by dopaminergic and other psychoactive medications. Any medical illness, even as mild as an upper respiratory tract infection or diarrhea, may trigger or worsen the demented or psychotic symptoms. They are best managed by either simplifying the patient's psychoactive medications or reducing the dopaminergic drugs.

Typical neuroleptics significantly increase extrapyramidal symptoms in PD and should not be used. Atypical neuroleptics, such as quetiapine or clozapine, may be used in the evening to relieve such symptoms[67–69]. However, not all atypical neuroleptics are safe or free from extrapyramidal side effects. Olanzapine and risperidone were both shown to worsen the motor symptoms in PD and should not be used[70,71].

Sleep Disturbance

Sleep disturbances are common problems in PD patients. Because of depression and/or hallucination, patients may become restless at night and have difficulty falling asleep. Those at higher risk for pathologic sleep are male patients with advanced disease, cognitive impairment, drug-induced psychosis, and orthostatic hypotension[72]. After falling asleep, patients may still wake up frequently because of stiffness of their bodies or urinary urgency at night. As a result, they have difficulty achieving restful sleep.

Rapid eye movement (REM) behavior sleep disorder (RBD) is very likely to occur. It is characterized by loss of atonia during REM sleep, resulting in excess motor activity during dreaming. It is highly related to neurodegenerative disorders, including PD[73,74]. Recent studies suggested RBD may occur well before the emergence of PD symptoms. Approximately half of the patients with RBD will eventually develop PD, and so RBD may be an indicator of presymptomatic PD[75]. Interestingly, the movements during REM sleep show little signs of parkinsonism. This could be attributed to the motor signals from the cortex during REM sleep bypassing the extrapyramidal system[76]. Management of this disorder requires adjusting dopaminergic medications to smaller dosages, especially toward the night. Long-acting dopamine agonists may also be considered[77,78]. Clonazepam has been widely used in this condition, but side effects such as excessive sedation have to be monitored[72].

Excessive daytime sleepiness (EDS) is common. In addition to fatigue that many PD patients experience, the lack of sleep during the night also sets up a vicious cycle for poor sleep hygiene. This sleepiness can be disabling, often approaching levels observed in disorders of sudden-onset sleep, namely narcolepsy/cataplexy. Polysomnographic studies have shown transition from wakefulness to stage II sleep within seconds[79]. In addition, dopaminergic drugs, especially dopamine agonists, can further cause sedation and sudden onset of sleep[80–82]. Management is usually by adjusting the timing of medications, or breaking the vicious cycle by improving patients' night-time sleep. Modafinil may help relieve EDS. However, while this medicine does not deteriorate PD symptoms, several randomized controlled trials revealed that it either had no significant benefit or produced only modest improvement[83–85].

A significant portion of patients may suffer restless leg syndrome (RLS) that results in sleep disturbance[86–88]. It is characterized by an uncomfortable feeling of the lower extremities that urges the patients to move. It occurs mostly when patients are at rest or during the night. Moving or walking will help patients feel better subjectively. It often occurs in combination with the symptoms of periodic limb movement during sleep, a repetitive, myoclonic jerky limb movement present mainly when patients are asleep. Both conditions severely affect the sleep quality of patients. Prevalence of RLS in PD patients was reported to be higher than that in other non-PD patients[3,89,90]. The pathophysiology is still unclear, although various central dopaminergic systems are believed to be involved in both PD and RLS[91]. Dopamine agonists, such as ropinirole and pramipexole, are effective in controlling RLS[92–95]. Levodopa is also effective in controlling the symptoms, although augmentation is a concern. This limits the usefulness of levodopa as a first-line choice for treatment of RLS. Other medications, including gabapentin, clonazepam and opiates, have been shown to relieve RLS symptoms[96–98].

One study even reported that deep brain stimulation of the subthalamic nucleus also improved RLS[99].

Autonomic Dysfunctions

Autonomic dysfunctions in PD patients are manifested in several different systemic symptoms. These generally include cardiovascular (orthostatic hypotension, cardiac arrhythmia), gastrointestinal (gastric dysmotility, indigestion, constipation, and regurgitation), urinary (frequency, urgency or incontinence), sexual (impotence or hypersexual drive), and thermoregulatory (excessive sweating or intolerance of heat or cold) dysfunctions[4,25]. The pathophysiology of dysautonomia in PD is thought to be from degeneration and dysfunction of the nuclei that mediate autonomic functions, such as the dorsal vagal nucleus, nucleus ambiguus, and other medullary centers (rostral ventrolateral medulla, ventromedial medulla, caudal raphe nuclei), which exert differential control on the sympathetic preganglionic neurons via descending pathways[100].

Cardiovascular System

Orthostatic hypotension is a particular concern. The symptoms include position-related dizziness, fatigue or even fainting. Position-related dizziness often leads to falls in PD patients. It may be a subtle sign in the early stage of PD and may not manifest as a major problem until later stages[101]. Dopaminergic medications usually do not significantly help. They may even worsen the symptoms, especially with dopamine agonists[102,103]. Treatment of orthostatic hypotension is mostly symptomatic. For those patients who also take regular antihypertensive medications, the balance between these and Parkinson medications should be sought. Patients are encouraged to drink appropriate amounts of water and consume more salt. They should be taught to get up slowly from a sitting position and wait for a while before initiating their gait to prevent the sudden decrease of blood pressure on positional changes. Compression stockings may also improve the condition. In more severe cases, antihypotensive medications may be necessary to improve orthostatic hypotension symptoms. The commonly used drugs are fludrocortisone (a salt-retaining mineralocorticoid) or midodrine (a selective, peripherally acting alpha-adrenergic agonist). In an epidemiologic study, 9.1% of PD patients required such medications to treat orthostatic hypotension[104].

Gastrointestinal System

Gastrointestinal symptoms are a common problem in PD. Dysphagia, heartburn, medication-related nausea, and constipation are the predominant symptoms[105]. Constipation is the most frequently encountered problem. It can be one of the early signs even before the appearance of the motor symptoms of PD[13,106]. Slower bowel movement and decreased mobility exacerbate the severity of constipation. This can especially be a serious problem for older patients, as they do not exercise enough and may not take adequate amounts of fluid. At least 59% of PD patients suffer from constipation as compared with 21% in age-matched non-PD patients[107]. Byrne et al.[108] reported that constipation in PD is commonly a consequence of anorectal sphincter and pelvic floor dysfunctions[108]. Fewer than three bowel passages in a week will raise the clinicians' concern for constipation. Patients are advised to take plenty of high-fiber food (dietary bulk) and fluid. Reducing anticholinergic medications will also help. Regular exercise can improve bowel motility. Stool softeners, laxatives, and enemas may also be used to relieve persistent symptoms[109,110].

Dysphagia may become more problematic as PD progresses and can lead to choking and aspiration pneumonia. Softening of foods may help, whereas others may need to thicken their liquids. Evaluation by a speech pathologist or otolaryngologist can be helpful. Patients are instructed not to rush, and to eat and chew thoroughly before swallowing[111]. However, for some patients with advanced disease, a feeding gastrostomy may be necessary to improve nutrition and quality of life and avoid aspiration[112].

Nausea troubles many PD patients, especially when they suffer the side effects of levodopa, dopamine agonists or other parkinsonian medications. This can be explained by the stimulation of dopaminergic receptors in the brain stem nausea center and the peripheral tissues, including receptors on the gastrointestinal tract, resulting in irregular peristalsis. To correct this condition, sometimes simply changing the medication schedule may help. Other options include extra carbidopa to block the conversion of levodopa to dopamine in the peripheral tissues more effectively. Certain antiemetic (or appetite-increasing) medications, like chlorpromazine, cisapride or metoclopramide, block dopaminergic receptors both peripherally and centrally and should be avoided as they will cause worsening of PD symptoms[113].

Urinary and Sexual Systems

Urinary urgency or incontinence due to a spastic bladder occurs in approximately 27–39% of PD patients[114]. A questionnaire-based study regarding autonomic functions of PD patients versus a control group of elderly non-PD subjects found the PD patients with twofold greater occurrence of bladder problems and fourfold risk of other autonomic problems, when compared with the controls[115]. The patients complained of urinary frequency and urgency, but with little urinary output each time. Prostate enlargement is common among older patients. It usually becomes an obstacle for emptying urine completely. Nocturnal urinary urgency is also common. Many patients have the urge to urinate frequently at night as their sleep becomes fragmented. Urinary incontinence will occur if patients walk slowly and cannot reach the bathroom in time. It seems that the severity of bladder dysfunction is correlated with the progression of PD[116]. Appropriate dosage of anticholinergics or alpha-blockers helps relieve the frequency problems. The use of dopaminergic medications to improve bladder function has been reported but is generally not reliable[117,118].

Sexual dysfunctions, including erectile difficulty, loss of libido, and anorgasmia, are common in male PD patients[119]. Erectile dysfunction was nearly twice as frequent in PD patients, compared with controls from a questionnaire-based study[115]. Patients rarely give information despite its significance on quality of life. Sildenafil has been reported to be effective for erectile dysfunction in patients without obvious cardiovascular risk factors[120–122]. Other patients may suffer a completely opposite problem, which is sexual impulse control. Patients, particularly those taking dopaminergic medications, may become obsessive and compulsive in gambling, shopping, spending or even sex. Pergolide mesylate, when added to L-DOPA, was reported to significantly improve all sexual functions in younger male PD patients who were still interested in sexual activities[123]. However, some argued that dopamine agonists may induce impulse control disorders in PD, resulting in hypersexuality in these patients[124,125]. Dopamine agonists did not actually improve erectile dysfunction in these patients. The effects of impulse control difficulties on PD patients will need further investigation.

Thermoregulation

PD patients may experience cold or heat intolerance. A more common problem is excessive sweating (hyperhidrosis). A study found that complaints of sweating disturbances were not correlated with disease severity but did correlate with other symptoms of autonomic dysfunction. Sweating problems occurred predominantly in "off" periods and in "on" periods with dyskinesias. It was almost three times more common than in controls who did not have PD[126]. Excessive sweating occurred mainly on the face, head, and trunk. It may be explained by decreased activation of sweat glands in the palms of the hands, suggesting that axial hyperhidrosis can be a compensatory phenomenon for reduced sympathetic function in the extremities[127]. This phenomenon results in reduced quality of life of the patients, in the areas of daily activities as well as social interactions[126]. Botulinum toxin injections may relieve local areas of hyperhidrosis, though it has no effect on the body function or thermoregulation.

Conclusion

Non-motor symptoms in PD are usually more complicated and difficult to manage than typical PD motor symptoms. However, they are usually overlooked and not properly treated. Physicians should be aware of the need to evaluate the neuropsychiatric, cognitive, autonomic, and sleep complications of PD. Early recognition of non-motor symptoms is essential, as effective treatment can reduce morbidity and improve the quality of life of PD patients.

Acknowledgments

We thank Ellen Matthiesen for her editorial assistance.

References

1. Parkinson J. An essay on the shaking palsy. J Neuropsychiatry Clin Neurosci 2002; 14: 223–36; Discussion, 222.
2. Tanner CM, Aston DA. Epidemiology of Parkinson's disease and akinetic syndromes. Curr Opin Neurol 2000; 13: 427–30.
3. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006; 5: 235–45.
4. Adler CH. Nonmotor complications in Parkinson's disease. Mov Disord 2005; 20 (Suppl 11): S23–9.

5. Habermann-Little B. An analysis of the prevalence and etiology of depression in Parkinson's disease. J Neurosci Nurs 1991; 23: 165–9.
6. Kostic VS, Filipovic SR, Lecic D, Momcilovic D, Sokic D, Sternic N. Effect of age at onset on frequency of depression in Parkinson's disease. J Neurol Neurosurg Psychiatry 1994; 57: 1265–7.
7. Hantz P, Caradoc-Davies G, Caradoc-Davies T, Weatherall M, Dixon G. Depression in Parkinson's disease. Am J Psychiatry 1994; 151: 1010–4.
8. Pollock M, Hornabrook RW. The prevalence, natural history and dementia of Parkinson's disease. Brain 1966; 89: 429–48.
9. Emre M. Dementia associated with Parkinson's disease. Lancet Neurol 2003; 2: 229–37.
10. Rippon GA, Marder KS. Dementia in Parkinson's disease. Adv Neurol 2005; 96: 95–113.
11. 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: 388–93.
12. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain 2000; 123: 331–9.
13. Magerkurth C, Schnitzer R, Braune S. Symptoms of autonomic failure in Parkinson's disease: prevalence and impact on daily life. Clin Auton Res 2005; 15: 76–82.
14. 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: 67–71.
15. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov Disord 2004; 19: 1306–12.
16. Siddiqui MF, Rast S, Lynn MJ, Auchus AP, Pfeiffer RF. Autonomic dysfunction in Parkinson's disease: a comprehensive symptom survey. Parkinsonism Relat Disord 2002; 8: 277–84.
17. Braune S, Reinhardt M, Schnitzer R, Riedel A, Lucking CH. Cardiac uptake of [^{123}I] MIBG separates Parkinson's disease from multiple system atrophy. Neurology 1999; 53: 1020–5.
18. Taki J, Nakajima K, Hwang E-H, Matsunari I, Komai K, Yoshita M, et al. Peripheral sympathetic dysfunction in patients with Parkinson's disease without autonomic failure is heart selective and disease specific. Eur J Nucl Med 2000; 27: 566–73.
19. Paulus W, Jellinger K. The neuropathologic basis of different clinical subgroups of Parkinson's disease. J Neuropathol Exp Neurol 1991; 50: 743–55.
20. Brown AS, Gershon S. Dopamine and depression. J Neural Transm Gen Sect 1993; 91: 75–109.
21. Middleton FA, Strick PL. Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. Brain Cogn 2000; 42: 183–200.
22. Clower DM, Dum RP, Strick PL. Basal ganglia and cerebellar inputs to 'AIP'. Cereb Cortex 2005; 15: 913–20.
23. Benarroch EE. Central neurotransmitters and neuromodulators in cardiovascular regulation. In: Mathias CJ, Bannister R, eds. Autonomic Failure, 4th edition. Oxford: Oxford University Press, 1999; 37–44.
24. Goldstein DS, Holmes CS, Dendi R, Bruce SR, Li ST. Orthostatic hypotension from sympathetic denervation in Parkinson's disease. Neurology 2002; 58: 1247–55.
25. Dewey RB Jr. Autonomic dysfunction in Parkinson's disease. Neurol Clin 2004; 22 (3 Suppl): S127–39.
26. Braak H, Del Tredici K, Bratzke H, Hamm-Clement J, Sandmann-Keil D, Rub U. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). J Neurol 2002; 249 (Suppl 3): III/1–5.
27. Braak H, Del Tredici K, Rub U, de Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003; 24: 197–210.
28. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 2004; 318: 121–34.
29. Doder M, Rabiner EA, Turjanski N, Lees AJ, Brooks DJ. Brain serotonin 5HT1A receptors in Parkinson's disease with and without depression measured by positron emission tomography with 11C-WAY 10635. Mov Disord 2000; 15: 213.
30. Mossner R, Henneberg A, Schmitt A, Syagailo YV, Grassle M, Hennig T, et al. Allelic variation of serotonin transporter expression is associated with depression in Parkinson's disease. Mol Psychiatry 2001; 6: 350–2.
31. Veazey C, Aki SO, Cook KF, Lai EC, Kunik ME. Prevalence and treatment of depression in Parkinson's disease. J Neuropsychiatry Clin Neurosci 2005; 17: 310–23.
32. Henderson R, Kurlan R, Kersun JM, Como P. Preliminary examination of the comorbidity of anxiety and depression in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992; 4: 257–64.
33. Slaughter JR, Slaughter KA, Nichols D, Holmes SE, Martens MP. Prevalence, clinical manifestations, etiology, and treatment of depression in Parkinson's disease. J Neuropsychiatry Clin Neurosci 2001; 13: 187–96.
34. Cummings JL. Depression and Parkinson's disease: a review. Am J Psychiatry 1992; 149: 443–54.
35. Cole SA, Woodard JL, Juncos JL, Kogos JL, Youngstrom EA, Watts RL. Depression and disability in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1996; 8: 20–5.
36. Starkstein SE, Petracca G, Chemerinski E, Teson A, Sabe L, Merelllo M, et al. Depression in classic versus

akinetic-rigid Parkinson's disease. Mov Disord 1998; 13: 29–33.
37. Schrag A, Jahanshahi M, Quinn NP. What contributes to depression in Parkinson's disease? Psychol Med 2001; 31: 65–73.
38. Richard IH, Kurlan R, Tanner C, Factor S, Hubble J, Suchowersky O, et al. Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Parkinson Study Group. Neurology 1997; 48: 1070–7.
39. Weintraub D, Morales KH, Moberg PJ, Bilker WB, Balderston C, Duda JE, et al. Antidepressant studies in Parkinson's disease: a review and meta-analysis. Mov Disord 2005; 20: 1161–9.
40. Aarsland D, Larsen JP, Waage O, Langeveld JH. Maintenance of electroconvulsive therapy for Parkinson's disease. Convuls Ther 1997; 13: 274–7.
41. Moellentine C, Rummans T, Ahlskog JE, Harmsen WS, Suman VJ, O'Connor MK, et al. Effectiveness of ECT in patients with parkinsonism. J Neuropsychiatry Clin Neurosci 1998; 10: 187–93.
42. Menza MA, Robertson-Hoffman DE, Bonapace AS. Parkinson's disease and anxiety: comorbidity with depression. Biol Psychiatry 1993; 34: 465–70.
43. Walsh K, Bennett G. Parkinson's disease and anxiety. Postgrad Med J 2001; 77: 89–93.
44. Menza MA, Sage J, Marshall E, Cody R, Duvoisin R. Mood changes and "on-off" phenomena in Parkinson's disease. Mov Disord 1990; 5: 148–51.
45. Menza M, Marin H, Kaufman K, Mark M, Lauritano M. Citalopram treatment of depression in Parkinson's disease: the impact on anxiety, disability, and cognition. J Neuropsychiatry Clin Neurosci 2004; 16: 315–9.
46. Weintraub D, Stern MB. Psychiatric complications in Parkinson disease. Am J Geriatr Psychiatry 2005; 13: 844–51.
47. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 2003; 60: 387–92.
48. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986; 9: 357–81.
49. Calabresi P, Picconi B, Parnetti L, Di Filippo M. A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine-acetylcholine synaptic balance. Lancet Neurol 2006; 5: 974–83.
50. Cooper B, Holmes C. Previous psychiatric history as a risk factor for late-life dementia: a population-based case-control study. Age Ageing 1998; 27: 181–8.
51. Haugarvoll K, Aarsland D, Wentzel-Larsen T, Larsen JP. The influence of cerebrovascular risk factors on incident dementia in patients with Parkinson's disease. Acta Neurol Scand 2005; 112: 386–90.
52. Pillon B, Boller F, Levy R, Dubois B. Cognitive deficits and dementia in Parkinson's disease. In: Boller F, Cappa S, eds. Aging and Dementia. Amsterdam: Elsevier, 2001; 311–72.
53. Bertrand E, Lechowicz W, Szpak GM, Lewandowska E, Dymecki J, Wierzba-Bobrowicz T. Limbic neuropathology in idiopathic Parkinson's disease with concomitant dementia. Folia Neuropathol 2004; 42: 141–50.
54. Iseki E. Dementia with Lewy bodies: reclassification of pathological subtypes and boundary with Parkinson's disease or Alzheimer's disease. Neuropathology 2004; 24: 72–8.
55. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005; 65: 1863–72.
56. McKeith IG, Ballard CG, Perry RH, Ince PG, O'Brien JT, Neill D, et al. Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology 2000; 54: 1050–8.
57. Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 2004; 351: 2509–18.
58. Siddiqui MA, Wagstaff AJ. Rivastigmine: in Parkinson's disease dementia. CNS Drugs 2006; 20: 739–47.
59. Boeve BF. Evidence for cholinesterase-inhibitor therapy for dementia associated with Parkinson's disease. Lancet Neurol 2005; 4: 137–8.
60. Inzelberg R, Bonuccelli U, Schechtman E, Miniowich A, Strugatsky R, Ceravolo R, et al. Association between amantadine and the onset of dementia in Parkinson's disease. Mov Disord 2006; 21: 1375–9.
61. Menendez-Gonzalez M, Calatayud MT, Blazquez-Menes B. Exacerbation of Lewy bodies dementia due to memantine. J Alzheimers Dis 2005; 8: 289–91.
62. Diederich NJ, Goetz CG, Stebbins GT. Repeated visual hallucinations in Parkinson's disease as disturbed external/internal perceptions: focused review and a new integrative model. Mov Disord 2005; 20: 130–40.
63. Goetz CG, Stebbins GT. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. Neurology 1995; 45: 669–71.
64. Chou KL, Messing S, Oakes D, Feldman PD, Breier A, Friedman JH. Drug-induced psychosis in Parkinson disease: phenomenology and correlations among psychosis rating instruments. Clin Neuropharmacol 2005; 28: 215–9.
65. Fenelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 2000; 123: 733–45.

66. Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. Int J Geriatr Psychiatry 1999; 14: 866–74.
67. Miyasaki JM, Shannon K, Voon V, Ravina B, Kleiner-Fisman G, Anderson K, et al. Practice Parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006; 66: 996–1002.
68. Merims D, Balas M, Peretz C, Shabtai H, Giladi N. Rater-blinded, prospective comparison: quetiapine versus clozapine for Parkinson's disease psychosis. Clin Neuropharmacol 2006; 29: 331–7.
69. Tariot PN, Schneider L, Katz IR, Mintzer JE, Street J, Copenhaver M, et al. Quetiapine treatment of psychosis associated with dementia: a double-blind, randomized, placebo-controlled clinical trial. Am J Geriatr Psychiatry 2006; 14: 767–76.
70. Yang SY, Kao Yang YH, Chong MY, Yang YH, Chang WH, Lai CS. risk of extrapyramidal syndrome in schizophrenic patients treated with antipsychotics: a population-based study. Clin Pharmacol Ther 2007; 81: 586–94.
71. Frieling H, Hillemacher T, Ziegenbein M, Neundorfer B, Bleich S. Treating dopamimetic psychosis in Parkinson's disease: structured review and meta-analysis. Eur Neuropsychopharmacol 2007; 17: 165–71.
72. Stacy M. Sleep disorders in Parkinson's disease: epidemiology and management. Drugs Aging 2002; 19: 733–9.
73. Onofrj M, Thomas A, D'Andreamatteo G, Iacono D, Luciano AL, Di Rollo A, et al. Incidence of RBD and hallucination in patients affected by Parkinson's disease: 8-year follow-up. Neurol Sci 2002; 23 (Suppl 2): S91–4.
74. Lauterbach EC. The neuropsychiatry of Parkinson's disease and related disorders. Psychiatr Clin North Am 2004; 27: 801–25.
75. Postuma RB, Lang AE, Massicotte-Marquez J, Montplaisir J. Potential early markers of Parkinson disease in idiopathic REM sleep behavior disorder. Neurology 2006; 66: 845–51.
76. De Cock VC, Vidailhet M, Leu S, Texeira A, Apartis E, Elbaz A, et al. Restoration of normal motor control in Parkinson's disease during REM sleep. Brain 2007; 130: 450–6.
77. Barone P, Amboni M, Vitale C, Bonavita V. Treatment of nocturnal disturbances and excessive daytime sleepiness in Parkinson's disease. Neurology 2004; 63 (8 Suppl 3): S35–8.
78. Poryazova RG, Zachariev ZI. REM sleep behavior disorder in patients with Parkinson's disease. Folia Med (Plovdiv) 2005; 47: 5–10.
79. Rye DB. Excessive daytime sleepiness and unintended sleep in Parkinson's disease. Curr Neurol Neurosci Rep 2006; 6: 169–76.
80. Andreu N, Chale JJ, Senard JM, Thalamas C, Montastruc JL, Rascol O. L-dopa-induced sedation: a double-blind cross-over controlled study versus triazolam and placebo in healthy volunteers. Clin Neuropharmacol 1999; 22: 15–23.
81. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999; 52: 1908–10.
82. 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: 853–8.
83. Hogl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K, et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. Sleep 2002; 25: 905–9.
84. Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. Mov Disord 2003; 18: 287–93.
85. Ondo WG, Fayle R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. J Neurol Neurosurg Psychiatry 2005; 76: 1636–9.
86. 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.
87. Rye DB. Parkinson's disease and RLS: the dopaminergic bridge. Sleep Med 2004; 5: 317–28.
88. Poewe W, Hogl B. Akathisia, restless legs and periodic limb movements in sleep in Parkinson's disease. Neurology 2004; 63 (8 Suppl 3): S12–6.
89. Krishnan PR, Bhatia M, Behari M. Restless legs syndrome in Parkinson's disease: a case-controlled study. Mov Disord 2003; 18: 181–5.
90. Poewe W, Hogl B. Akathisia, restless legs and periodic limb movements in sleep in Parkinson's disease. Neurology 2004; 63 (8 Suppl 3): S12–6.
91. Nomura T, Inoue Y, Nakashima K. Clinical characteristics of Restless legs syndrome in patients with Parkinson's disease. J Neurol Sci 2006; 250: 39–44.
92. Ondo W, Romanyshyn J, Vuong KD, Lai D. Long-term treatment of restless legs syndrome with dopamine agonists. Arch Neurol 2004; 61: 1393–7.
93. Montplaisir J, Karrasch J, Haan J, Volc D. Ropinirole is effective in the long-term management of restless legs syndrome: a randomized controlled trial. Mov Disord 2006; 21: 1627–35.
94. Bogan RK, Fry JM, Schmidt MH, Carson SW, Ritchie SY; TREAT RLS US Study Group. Ropinirole in the treatment of patients with restless legs syndrome: a US-based

randomized, double-blind, placebo-controlled clinical trial. Mayo Clin Proc 2006; 81: 17–27.
95. Oertel WH, Stiasny-Kolster K, Bergtholdt B, Hallstrom Y, Albo J, Leissner L, et al. Pramipexole RLS Study Group. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). Mov Disord 2007; 22: 213–9.
96. Lesage S, Hening WA. The restless legs syndrome and periodic limb movement disorder: a review of management. Semin Neurol 2004; 24: 249–59.
97. Kurlan R, Richard IH, Deeley C. Medication tolerance and augmentation in restless legs syndrome: the need for drug class rotation. J Gen Intern Med 2006; 21: C1–4.
98. Montagna P. The treatment of restless legs syndrome. Neurol Sci 2007; 28 (Suppl 1): S61–6.
99. Driver-Dunckley E, Evidente VG, Adler CH, Hillman R, Hernandez J, Fletcher G, et al. Restless legs syndrome in Parkinson's disease patients may improve with subthalamic stimulation. Mov Disord 2006; 21: 1287–9.
100. Benarroch EE. Central neurotransmitters and neuromodulators in cardiovascular regulation. In: Mathias CJ, Bannister R, eds. Autonomic Failure, 4th edition. Oxford: Oxford University Press, 1999; 37–44.
101. Goldstein DS. Orthostatic hypotension as an early finding in Parkinson's disease. Clin Auton Res 2006; 16: 46–54.
102. Kujawa K, Leurgans S, Raman R, Blasucci L, Goetz CG. Acute orthostatic hypotension when starting dopamine agonists in Parkinson's disease. Arch Neurol 2000; 57: 1461–3.
103. Etminan M, Gill S, Samii A. Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. Drug Saf 2003; 26: 439–44.
104. Desboeuf K, Grau M, Riche F, Fradin M, Bez J, Montastruc JL, et al. Prevalence and costs of parkinsonian syndromes associated with orthostatic hypotension. Therapie 2006; 61: 93–9.
105. Khan NL, Graham E, Critchley P, Schrag AE, Wood NW, Lees AJ, et al. Parkin disease: a phenotypic study of a large case series. Brain 2003; 126: 1279–92.
106. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol 2003; 2: 107–16.
107. Kaye J, Gage H, Kimber A, Storey L, Trend P. Excess burden of constipation in Parkinson's disease: a pilot study. Mov Disord 2006; 21: 1270–3.
108. Byrne KG, Pfeiffer R, Quigley EM. Gastrointestinal dysfunction in Parkinson's disease: a report of clinical experience at a single center. J Clin Gastroenterol 1994; 19: 11–6.
109. Ueki A, Otsuka M. Life style risks of Parkinson's disease: association between decreased water intake and constipation. J Neurol 2004; 251 (Suppl 7): vii18–23.
110. Jost WH, Eckardt VF. Constipation in idiopathic Parkinson's disease. Scand J Gastroenterol 2003; 38: 681–6.
111. Miller N, Noble E, Jones D, Burn D. Hard to swallow: dysphagia in Parkinson's disease. Age Ageing 2006; 35: 614–8.
112. Diamond A, Jankovic J. Treatment of advanced Parkinson's disease. Expert Rev Neurother 2006; 6: 1181–97.
113. Sempere AP, Duarte J, Cabezas C, Claveria LE, Coria F. Aggravation of parkinsonian tremor by cisapride. Clin Neuropharmacol 1995; 18: 76–8.
114. Winge K, Skau AM, Stimpel H, Nielsen KK, Werdelin L. Prevalence of bladder dysfunction in Parkinson's disease. Neurourol Urodyn 2006; 25: 116–22.
115. 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: 67–71.
116. Winge K, Friberg L, Werdelin L, Nielsen KK , Stimpel H. Relationship between nigrostriatal dopaminergic degeneration, urinary symptoms, and bladder control in Parkinson's disease. Eur J Neurol 2005; 12: 842–50.
117. Winge K, Werdelin LM, Nielsen KK, Stimpel H. Effects of dopaminergic treatment on bladder function in Parkinson's disease. Neurourol Urodyn 2004; 23: 689–96.
118. Uchiyama T, Sakakibara R, Hattori T, Yamanishi T. Short-term effect of a single levodopa dose on micturition disturbance in Parkinson's disease patients with the wearing-off phenomenon. Mov Disord 2003; 18: 573–8.
119. Papatsoris AG, Deliveliotis C, Singer C, Papapetropoulos S. Erectile dysfunction in Parkinson's disease. Urology 2006; 67: 447–51.
120. Zesiewicz TA, Helal M, Hauser RA. Sildenafil citrate (Viagra) for the treatment of erectile dysfunction in men with Parkinson's disease. Mov Disord 2000; 15: 305–8.
121. Hussain IF, Brady CM, Swinn MJ, Mathias CJ, Fowler CJ. Treatment of erectile dysfunction with sildenafil citrate (Viagra) in parkinsonism due to Parkinson's disease or multiple system atrophy with observations on orthostatic hypotension. J Neurol Neurosurg Psychiatry 2001; 71: 371–4.
122. Raffaele R, Vecchio I, Giammusso B, Morgia G, Brunetto MB, Rampello L. Efficacy and safety of fixed-dose oral sildenafil in the treatment of sexual dysfunction in depressed patients with idiopathic Parkinson's disease. Eur Urol 2002; 41: 382–6.
123. Pohanka M, Kanovsky P, Bares M, Pulkrabek J, Rektor I. The long-lasting improvement of sexual dysfunction in patients with advanced, fluctuating Parkinson's disease

induced by pergolide: evidence from the results of an open, prospective, one-year trial. Parkinsonism Relat Disord 2005; 11: 509–12.

124. Cannas A, Solla P, Floris G, Tacconi P, Loi D, Marcia E, et al. Hypersexual behaviour, frotteurism and delusional jealousy in a young parkinsonian patient during dopaminergic therapy with pergolide: a rare case of iatrogenic paraphilia. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30: 1539–41.
125. Weintraub D, Potenza MN. Impulse control disorders in Parkinson's disease. Curr Neurol Neurosci Rep 2006; 6: 302–6.
126. Swinn L, Schrag A, Viswanathan R, Bloem BR, Lees A, Quinn N. Sweating dysfunction in Parkinson's disease. Mov Disord 2003; 18: 1459–63.
127. Schestatsky P, Valls-Sole J, Ehlers JA, Rieder CR, Gomes I. Hyperhidrosis in Parkinson's disease. Mov Disord 2006; 21: 1744–8.