

8 Non-Motor Symptoms in Parkinson's Disease

Dr V Metta and Professor KR Chaudhuri

University Hospital Lewisham, London, National Parkinson Foundation Centre of Excellence, Kings College, London, Institute of Psychiatry and Kings Health Partners

Introduction

Parkinson's disease results from degeneration of the substantia nigra pars compacta and the consequent dysfunction of the dopaminergic nigrostriatal pathway. Serotonergic and noradrenergic pathways are also affected. However, It has been recognized that non-dopaminergic and non-motor symptoms are sometimes present prior to diagnosis and these inevitably emerge with disease progression, impacting on morbidity, quality of life and mortality. The non-motor symptoms (NMS) of Parkinson's disease continue to be poorly recognized and inadequately treated in contrast with motor symptoms and a modern holistic approach to treatment of Parkinson's disease should therefore include recognition and assessment of non-motor symptoms.

Certain aspects of the non-motor symptoms (NMS) complex of Parkinson's disease can be improved with currently available treatments, but other features may be more refractory and require research into effective non-dopaminergic drug therapies for the future. After the description in 1817 of 'paralysis agitans' by James Parkinson [1], through the 20th century, the motor disorder of Parkinson's disease (PD) has been extensively researched, resulting in improved diagnostic accuracy and the development of robust assessment tools for the motor dysfunction of PD [1–4]. Many studies and clinical observations have suggested that non-motor symptoms such as sleep disorders, cognitive problems and bowel and bladder disorders are frequent in PD. However, it is only recently that research has focused on the effect of non-motor symptoms (NMS) on quality of life, institutionalization rates, health economics and mortality rates in PD [5–10]. The fact that NMS correlate with advancing age and disease severity suggests that these symptoms and their management will become increasingly important as the average life-expectancy of the population increases [10,11]. As an example, a recent prospective follow-up study (15–18 years) of 149 PD patients reported that the major disabling symptoms included cognitive decline, falls, hallucinations, depression, urinary incontinence, dementia and choking with a 40% institutionalizing rate [13]. An additional problem is that the NMS complex is frequently unrecognized by healthcare professionals, as reported by Shulman and colleagues [14]. This may be because physicians or nurses concentrate more on motor aspects, there may be unawareness that NMS are related to PD or the symptoms may not be declared to the healthcare professionals [12]. Recent work by the Parkinson's Disease Non Motor Group (PD-NMG) has led to the validation of the first comprehensive clinic-based self-completed NMS questionnaire and also a scale, the NMS scale that allows easy identification of NMS by the physician [15,16].

Without careful attention, NMS may remain undiagnosed and untreated. A recent international survey showed that up to 62% of NMS in PD might remain undeclared to health care professionals because patients are either embarrassed or unaware that the symptoms are linked to PD [15]. Using a screening tool can help identify the problem. For example, in a study using the NMS Questionnaire (NMSQ), PD patients reported 9-12 different NMS in their clinic visit, many of which had not been discussed with the doctor before being flagged by the NMSQ [137].

Pathogenesis

The pathological basis of the wide range of NMS that occur in PD is beyond the scope of this review. However, it is now clear that most NMS have a poor response to dopaminergic therapy and as such other pathways, including the serotonergic and noradrenergic pathways, are implicated [17]. Braak and colleagues have introduced the concept of a six-stage pathological process, beginning at 'induction sites' with degeneration of the olfactory bulb and the anterior olfactory nucleus (clinically manifest as olfactory dysfunction) at stage 1, while stage 2 reflects progression of the pathological

process to the lower brainstem [18,19]. The latter involves brainstem nuclei, which are thought to be key areas mediating NMS such as olfaction, sleep

homeostasis, constipation and central autonomic control. Several of these symptoms are now recognized as possible pre-motor features of PD. The typical clinical motor triad of PD emerges at Braak stages 3 and 4 with the involvement of the substantia nigra and other deep nuclei of the mid- and forebrain [15]. However, limitations of the Braak hypothesis include the fact that Braak based his classification on Lewy body pathology and not neuronal cell loss and as such the hypothesis needs further validation. The hypothesis does not also explain the occurrence of early hallucinations or dementia for instance in dementia with Lewy bodies.

Pre-Motor Non-Motor Symptoms

A wide spectrum of NMS have been described in Parkinson's disease, as shown in Table 1. In addition, there are drug-induced non-motor symptoms. In line with the Braak staging, several NMS have been identified before the motor syndrome of PD emerges.

In the future, pre-motor identification or identification of 'at risk' individuals for PD may be based upon detection of some or a combination of NMS of PD. Examples include tests that combine olfactory abnormality detection with REM behaviour disorder (RBD) and functional imaging of the stratum (DAT Scan), or transcranial ultrasound imaging, which may show hyperechogenicity of the nigra in PD, although this is currently being investigated [20–22]. We review the four cardinal postulated NMS that may predict development of PD.

Olfaction

Impaired olfaction is one of the earliest and most common NMS of PD and has been shown to affect up to 90% of PD patients [21,25]. Olfactory deficits have been reported in asymptomatic relatives of patients with PD, some of whom subsequently became symptomatic [22]. Of 78 first degree asymptomatic relatives of patients with nonfamilial PD, 40 had hyposmia at baseline and 2 years later 4 had clinical PD [26]. Using the Brief Smell Identification Test (BSIT) in 2263 healthy Japanese–American subjects, Ross and colleagues reported a relative odds ratio for PD in the lowest BSIT centile of 4.3 ($p = 0.02$). A total of 163 patients had died and autopsy showed 17 with incidental lewy body disease [136]. In another study using DAT scan and transcranial sonography, Sommer and colleagues investigated 30 patients with idiopathic anosmia, of whom 11 had abnormal transcranial sonography (TCS) while 5/10 subjects had pathological DAT scan [27]. The pathophysiology is unclear but neuropathology and imaging studies have suggested structural and functional changes in the olfactory bulb [23]. Olfactory testing aims to identify deficits in:

- Odour detection
- Odour identification
- Odour discrimination

Odour detection and identification appear unrelated to disease stage or duration while odour discrimination is negatively correlated to severity of disease and may even be partially reversible after deep-brain stimulation [21].

REM Behaviour Disorder

RBD is a parasomnia, characterised by loss of the normal skeletal muscle atonia during REM sleep, thus enabling the patient to physically enact their dreams and, in some, vocalizations and abnormal movements are reported by bed partners [28,29]. The pathogenesis of RBD is unclear; however, there is evidence that it may arise as a result of degeneration of lower brainstem nuclei, including the pedunculopontine and subcoeruleal nucleus, areas related to Braak stage 2 [18,30].

Table 1 Non-motor symptoms of Parkinson's disease

Neuropsychiatric symptoms	Depression, apathy, anxiety
	Anhedonia
	Attention deficit
	Hallucinations, illusion, delusions
	Dementia
	Obsessional behaviour (usually drug induced), repetitive behaviour
	Confusion
	Delirium (could be drug induced)
	Panic attacks
Sleep disorders	Restless legs and periodic limb movements
	REM behaviour disorder and REM loss of atonia
	Non-REM sleep-related movement disorders
	Excessive daytime somnolence
	Vivid dreaming
	Insomnia
	Sleep disordered breathing
Autonomic symptoms	Bladder disturbances:
	Urgency
	Nocturia
	Frequency
	Sweating
	Orthostatic hypotension:
	Falls related to orthostatic hypotension
	'Coat hanger' pain
	Sexual dysfunction:
	Hypersexuality (likely to be drug induced)
	Erectile impotence
	Dry eyes (xerostomia)
Gastrointestinal symptoms (overlaps with autonomic)	Dribbling of saliva
	Ageusia
	Dysphagia/ choking
	Reflux, vomiting
	Nausea
	Constipation
	Unsatisfactory voiding of bowel
	Faecal incontinence
Sensory symptoms	Pain
	Paraesthesia
	Olfactory disturbance
Other symptoms	Fatigue
	Diplopia
	Blurred vision
	Seborrhoea
	Weight loss
	Weight gain (possibly drug induced)

Longitudinal data suggest that RBD may predate motor symptoms in up to 40% of patients [31–33]. A retrospective study of 44 patients with RBD by Iranzo and colleagues in 2006 revealed that 45% of patients developed a neurological disorder such as PD, multiple system atrophy (MSA) or dementia with Lewy body after a mean of 11.5 years [34]. Therefore, this study supports the suggestion that RBD is linked to preclinical PD. Stiasny-Kolster and colleagues have suggested that the combination of olfactory deficit and isolated RBD could be screened by DAT scan as a possible pre-motor testing

for individuals at risk of developing PD [35]. A total of 30 RBD patients had increased olfactory threshold and PD occurred in 5, while DAT scans were abnormal in 3/11 [35]. Postuma and colleagues investigated the role of RBD as a potential marker of PD using colour vision, olfaction, motor speed testing, autonomic function and depression rating in 25 patients with RBD and compared with controls [36]. In 50% of RBD patients who scored poorly in one test, performance was poor in other tests, suggesting that olfactory dysfunction and depression may occur concurrently in RBD [36]. More recently, Postuma et al have suggested that there is a 40% risk of developing a parkinsonian syndrome at 10 years in those who develop idiopathic RBD.

Depression

Depression is the most common psychiatric complication of PD and can affect 10–70% of PD patients [37–40]. Depression may arise as a result of damage to serotonergic as well as limbic noradrenergic and dopaminergic neurotransmission, as shown in a positron emission tomography (PET) study that showed that depressed PD patients have reduced decreased cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5HT1A) levels and reduced cortical 5HT1A receptor binding compared with non depressed patients [41]. A cross-sectional study has recently reported an association between elevated plasma homocysteine levels, depression and cognitive impairment in PD [42]. Other studies have suggested that depression, like RBD and hyposmia, may precede the development of PD [43–46]. Nilsson and colleagues reported that depressed patients are more likely to develop PD than osteoarthritis or diabetes, while a retrospective cohort study by Schurmann and colleagues reported that at the time of diagnosis of idiopathic PD, 9.2% had a lifetime diagnosis of depression compared with 4.2% of controls [44,45]. However, it is important to be aware that retrospective studies may not be reliable due to recall bias. A PD test battery developed by Montgomery and colleagues, including tests for depression (Beck Depression Inventory), olfactory testing (The University of Pennsylvania Smell Identification Test [UPSIT]) and a simple motor task of wrist flexion and extension, showed significant impairment in first-degree relatives of PD from controls [46].

Constipation

Constipation is one of the most common NMS and may precede the development of PD [47,48]. The dorsal–vagal nucleus may be implicated, suggesting a link with Braak stage 2 [47,49]. In a prospective study, Abbott and colleagues followed the bowel habits of 6790 men for 24 years and reported that those with constipation had a threefold risk (odds ratio [OR]: 2.7; $p = 0.007$) of developing PD after a mean interval of 12 years from initial constipation and 96 developed PD [50]. Edwards and colleagues investigated the involvement of the gastrointestinal tract in PD in 98 patients and reported that symptoms such as constipation, abnormal salivation, dysphagia and nausea were more common in PD patients than in controls [51]. Constipation in PD does not respond well to dopaminergic a treatment, suggesting a non-dopaminergic mechanism in the pathogenesis [47].

Non-Motor Symptoms and Screening for PD

NMS that result from non-dopaminergic pathology, such as olfaction, depression, autonomic dysfunction and RBD, are a target for the development of PD screening tests [15]. The onset of dopaminergic cell loss occurs years before the motor symptoms appear and at diagnosis there is a reduction of 60–70% of the dopaminergic neurons and a reduction of dopamine by 80% [52,77]. Screening of individuals at increased risk will be important if measures to slow the neurodegenerative process, if available, can be introduced at an earlier stage. TCS of the substantia nigra has been suggested as a possible screening tool for PD [20]. Studies have shown that more than 90% of PD patients have increased echogenicity of the substantia nigra that can be detected early in the disease [20]. However, the findings need to be replicated at other centres before the widespread use of this technique.

Prevalence of Non-Motor Symptoms of PD

A recent international study validating a self-completed non-motor questionnaire (NMSQuest) by Chaudhuri and colleagues revealed that non-motor symptoms are highly prevalent in PD patients (with the exception of insomnia, nausea and vomiting, bowel incontinence, insomnia and nocturia)

across all stages and disease duration compared with age- matched controls, and some patients reported more than ten symptoms each [16]. This study also showed that NMS can occur in all disease stages and the number of symptoms correlates with disease duration and severity [16].

The NMS complex of PD is frequently unrecognized by healthcare professionals. In a prospective study of 101 patients, Shulman and colleagues demonstrated that neurologists failed to identify the major NMS such as depression, sleep disturbances, anxiety and fatigue in more than 50% of the patients [14]. NMS symptoms can easily be missed as there is a tendency to concentrate on the motor aspects of PD. Frequently, physicians are unaware that NMS are related to PD [15]. In some cases the symptoms are not declared to the healthcare professional [16]. The problem is compounded by the fact that there is a lack of clinically validated instruments for assessing NMS in a comprehensive and unified fashion so as to enhance early identification and evaluate the effect of treatment [14]. Recently the first comprehensive clinic-based NMS questionnaire (NMSQuest), which allows easy identification of NMS by the physician, has been validated [15]. The NMS scale, which rates the symptoms in terms of frequency and severity, has also been validated in two major international studies in over 600 patients [138,139].

Non-Motor Symptoms

Cognition

The cognitive/neuropsychiatric NMS of PD range from anxiety state, apathy and depression to frank dementia [53–56]. Psychosis is the key factor requiring nursing-home placement and depression causes a significant negative impact on the quality of life in PD [7–9].

Anxiety and Apathy

Anxiety disorders are common in PD and may also be a preclinical risk factor [55,56]. Several types of panic disorders have been described in PD but the most common forms are panic disorders, social phobia and generalized anxiety disorder [58]. The disorder may also be related to drug-induced non-motor symptoms of PD [59]. Apathy has now been established as a distinctive symptom of PD and is more common in PD patients than equally disabled osteoarthritic patients, indicating a neurodegenerative contribution [60–62]. Apathy may respond to dopaminergic medication such as levodopa, but involvement of other neurotransmitter pathways is likely [63].

Psychosis and Visual Hallucinations

Up to 40% of patients experience visual hallucinations, usually benign, while more sinister symptoms, such as delusions (accusatory), paranoid ideation and delirium, become more frequent as the disease progresses and interfere significantly with daily activities [64]. While visual hallucinations are commonly viewed as a side effect of anti-PD treatments such as amantadine, anticholinergics, selegiline, dopamine agonists and less commonly, levodopa, neuronal degeneration itself may be causative [65]. Delirium may occur in advanced dementia or may be induced by concurrent infection or in association with Parkinsonism–hyperpyrexia or neuroleptic malignant syndrome [66]. Onofri and colleagues have cited RBD as a possible risk factor for hallucinations in a follow-up study of PD patients with RBD and other risk factors include cognitive impairment, age and duration of PD [67]. Dopaminergic drugs can induce psychiatric symptoms by disrupting sleep, leading to vivid dreams, hallucinations and finally delirium [68]. Genetic predisposition, for example, a polymorphism in the cholecystokinin gene has also been postulated as a causal factor [69]. A proposed mechanism for dopamine dysregulation syndrome is abnormal dopamine regulation within the nucleus accumbens and decreased activation of the mesolimbic reward system [70, 71].

Cognitive Dysfunction

Dementia complicates up to 40% of PD cases, a rate approximately six-times higher than normal healthy subjects [72]. Hely and colleagues reported cognitive decline with rates as high as 84% in their long-term (15–18 years) follow up study of PD patients [13]. Dementia in PD is similar to that caused by lesions of the prefrontal cortex, characterized by a dysexecutive syndrome with impairment of visuo–spatial abilities and memory on a background of loss of response to dopaminergic drugs [73,74]. Nigral cellular degeneration, loss of cholinergic cells in the nucleus basalis of Meynert, and

the presence of cortical and subcortical Lewy bodies, have been implicated [75,76]. Like Alzheimer's disease, hippocampal volume is diminished in PD with dementia [77].

Nocturnal NMS

Nearly all PD patients have sleep disturbances which usually starts early in the disease [78–80]. The pathogenesis of sleep disruption is multifactorial but degeneration of central sleep regulation centres in the brainstem and thalamocortical pathways is likely to be important. The pedunculopontine nucleus, locus coeruleus and the retro rubral nucleus influence normal REM atonia and phasic generator circuitry and have been implicated in the pathogenesis of RBD [81–83]. The range of sleep conditions that occur in PD are shown in Table 2. Other factors that may contribute to sleep disruption include motor symptoms, anxiety and depression, and dopaminergic treatment. Some NMS cause abnormalities in the primary sleep architecture and have a secondary effect on the quality of sleep, such as nocturia causing bedwetting if the patient is too rigid to get out of bed or restless legs syndrome causing frequent arousal. Obstructive sleep apnoea, not necessarily associated with obesity, and a narcoleptic pattern of rapid onset of sleep are also important causes of sleep-related morbidity in PD [78,85].

Table 2 Sleep-related non-motor features of Parkinson's disease

Insomnia	Fragmentation of sleep
	Sleep-maintenance insomnia
	Sleep-onset insomnia
Motor function-related	Akinesia (difficulty turning)
	Restless legs
	Periodic limb movements of sleep
Urinary difficulties	Nocturia
	Nocturia with secondary postural hypotension
Neuropsychiatric/parasomnias	Depression
	Vivid dreams
	Altered dream content
	Nightmares
	Night terrors
	Sleep talking
	Nocturnal vocalisations
	Somnambulism
	Hallucinations
	Panic attacks
	REM behaviour disorder
	Non-REM-related sleep disorders
Treatment-related motor	Nocturnal off-period-related tremor
	Dystonia
	Dyskinesias
	Off-period-related pain/paraesthesia/muscle cramps
Urinary	Off-period-related incontinence of urine
Treatment-related motor	Nocturnal off-period-related tremor
	Dystonia
	Dyskinesias
	Off-period-related pain/paraesthesia/muscle cramps

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) and involuntary dozing affects up to 50% of PD patients and may be preclinical marker [84,85]. EDS is important to recognize as it may considerably impact quality of life in PD [87]. EDS is associated with poor concentration and memory, which may result in road accidents and accidents at work [88] Saper and colleagues proposed the concept of a flip-flop switch, which is responsible for the sleep–wake cycle in primates [88]. Dopaminergic dysfunction and

neuronal degeneration can destabilize the switch and its regulators, promoting rapid transitions to sleep. Hypocretin, neuronal activity-related pentraxin (NARP) and dynorphin releasing neurones have also been implicated but not confirmed as having a regulatory role [89].

Dysautonomia

Autonomic dysfunction is associated with various movement disorders, most commonly Parkinson's disease and MSA, and it can be an important feature in the differential diagnosis of Parkinsonian disorders [90]. The symptoms of dysautonomia in PD may include orthostatic hypotension, bladder dysfunction, gastrointestinal dysfunction (particularly constipation), sexual dysfunction and hyperhidrosis. The pathophysiology is complicated and is thought to include dysfunction or degeneration of the nucleus ambiguus, the dorsal–vagal nucleus and various medullary centres that modulate the activity of the sympathetic pre-ganglionic neurons (these include the rostral ventrolateral medulla, ventromedial medulla and the caudal raphe nuclei) [91]. Modulation of the central autonomic network is thought to be disrupted through degeneration of cholinergic, monoaminergic and serotonergic nuclei [91]. Magerkurth and colleagues reported a statistically significant increase of orthostatic dizziness, bladder dysfunction (mainly urge incontinence and frequency), hyperhidrosis and erectile dysfunction in PD patients compared with the controls [92]. Reports of bowel dysfunction, including constipation and feeling full, were also increased in PD patients, but this was not statistically significant [92]. Approximately 50% of PD patients rated the impact of the autonomic symptoms on their daily lives as 'a lot' or 'very much' [92]. The NMSQuest study also confirmed that dysautonomic symptoms were significantly more prevalent in PD patients than in controls, and the total number of non-motor symptoms correlated with the stage of the disease [16]. Goldstein and colleagues used beat-to-beat blood pressure measurements during performance of the Valsalva manoeuvre to detect sympathetic neurocirculatory failure in PD patients, and 6-[18F] fluorodopamine to estimate sympathetic cardiac innervation. They found that all 9 of the PD patients who had sympathetic neurocirculatory failure, and 11 of the 15 PD patients who did not have neurocirculatory failure, demonstrated sympathetic cardiac denervation, relative to controls. This contrasted dramatically with the results from MSA patients, who did not show evidence of sympathetic cardiac denervation. The results suggest that cardiac denervation is not related to severe or late-stage disease and catecholamine function in PD may be defective not only in the brain but also in the heart [93]. Meta-[123I] iodobenzylguanidine (MIBG) is a noradrenaline analogue, taken up by postganglionic sympathetic neurons, and has been used to analyze the sympathetic cardiac activity in PD patients with orthostatic hypotension. It has been found to be reduced in patients with PD, both with and without orthostatic hypotension [94]. This often differs from MSA, in which cardiac MIBG uptake is usually normal. Nocturia, frequency and urgency are common complaints in PD patients and functional imaging studies show that dopaminergic mechanisms may be involved in bladder control [95].

Fatigue

Fatigue is a common complaint in Parkinson's disease and is reported to have a negative impact on the quality of life [96]. Fatigue may be related to other non-motor features of PD such as depression, sleep disturbances and dementia [97]. However, studies have shown that fatigue is a non-motor, which may occur independently of other non-motor symptoms [98].

Sexual dysfunction

Both reduced and increased sex drive has been reported in PD [99], and it is thought that this may represent another dysautonomic symptom of the disease. Testosterone deficiency has been implicated in this process and testosterone replacement therapy improved a range of motor and non-motor symptoms in a trial of ten PD patients with signs of testosterone deficiency [100]. In PD patients with bilateral subthalamic stimulation, rates of sexual dysfunction of 76.5% have been reported [101]. Hypersexuality and other forms of aberrant sexual behaviours and drive are part of the dopamine dysregulation syndrome, which occurs with dopaminergic drug treatment [71].

Pain

Pain is one of the major clinical symptoms in PD but its pathophysiology is unclear. Medial and lateral pain syndromes are recognized and medial pain pathways are composed of parabrachial nucleus and locus coeruleus projecting to the secondary somatosensory cortex and the anterior cingulate, thus suggesting that there may be a link between early PD and pain [102,103]. Various pain syndromes described may be related to motor fluctuations, early morning dystonia or secondary causes such as musculo-skeletal pain [104,105]. In some cases retroperitoneal fibrosis related to use of some ergot dopamine agonist may present as deep visceral pain. Oral (burning mouth syndrome) and genital pain may rarely occur and needs to be recognized [106].

Drug-Induced NMS and ‘Wearing Off’ Phenomenon

PD patients on long-term levodopa treatment may experience the ‘wearing-off’ phenomenon, which may be associated with NMS such as anxiety, pain, tingling, coldness of limbs, restless legs and ‘unclear thinking’ [15]. Hillen and colleagues reported that 17% of patients experienced non-motor symptoms associated with the wearing-off phenomenon, which included sensory dyspnoea, nausea, facial flushing, hunger and pain [107]. Stacy and colleagues have developed and validated a specific wearing-off patient questionnaire to aid clarification and better definition of the wearing-off-related motor and NMS in PD [108].

Management of Non-Motor Symptoms

Robust controlled studies are virtually nonexistent for the treatment of NMS in PD. However, there is some evidence from a handful of controlled trials for the treatment of certain NMS in PD, in particular depression, cognitive decline, psychosis and EDS. Moreover, the effect of these treatments on quality of life in PD is lacking, and many trials include only small numbers of patients.

Dopaminergic treatment has some effect on depressive symptoms. Only pramipexole has been investigated for its potential beneficial effect in depression and Corrigan and colleagues reported antidepressant activity similar to fluoxetine [109]. Other dopaminergic agonists including ropinirole (not pergolide) may have the same effect [110,111]. However, some studies have reported precipitation of mania with pramipexole and ropinirole [112]. Tricyclic antidepressants (TCA) and selective serotonin uptake inhibitors (SSRIs) have remained the major classes of drugs used for treatment of depression in PD [110]. However, SSRIs such as fluoxetine or fluvoxamine should be avoided in patients receiving selegiline as it can induce the potentially fatal serotonin syndrome [110].

Treatment of psychosis in PD remains complicated as withdrawing dopaminergic treatment or introducing antipsychotics may worsen the parkinsonian state. However, there is good evidence that newer atypical antipsychotics, e.g., clozapine, may be beneficial [113]. The evidence of efficacy of quetiapine is controversial as a recent trial has shown no beneficial effect of quetiapine for PD psychosis [114]. The newer antipsychotics bind loosely and dissociate rapidly from D2 receptors, allowing an almost normal dopaminergic transmission [115]. Several studies have shown that clozapine improves the psychosis rating scales [113,116].

Dopaminergic treatment has a limited effect on cognitive impairment in PD. Loss of cholinergic cells forms the basis of treatment for dementia in PD. The EXelon in Parkinson’s disease dementia Study (EXPRESS) for efficacy of rivastigmine in dementia associated with PD represents advances in treatment of aspects of NMS in PD using non-dopaminergic treatment [117]. The cholinesterase inhibitor rivastigmine was shown to have a significant effect on dementia in PD as rated by dementia scores [117]. In another double blind, placebo controlled trial donepezil was also shown to improve dementia [118].

There is evidence from two small trials to support the use of modafinil for EDS in PD [119,120]. Although the sample size was small, Adler and colleagues demonstrated that modafinil was effective for the treatment of EDS [119]. However, a recent larger double-blind, placebo-controlled trial in 40 patients did not show efficacy of modafinil for EDS in PD [121]. There are no controlled trials for treatment of RBD but there are claims that night-time dosing with levodopa and use of clonazepam or pramipexole may reduce involuntary nocturnal movements during sleep [32]. Most clinical

experience is based on use of clonazepam but it is necessary to exercise caution as sleep-disordered breathing may coexist with RBD and can be worsened by clonazepam.

Controlled trial evidence regarding the treatment of autonomic dysfunction in PD is only available for drooling and erectile dysfunction. Both botulinum toxin A and B injected into the parotid and/or submandibular glands can be an effective treatment for drooling in PD [122]. Erectile dysfunction can be treated effectively in PD with the use of sildenafil without the occurrence of side effects, in particular postural blood pressure [123]. There is little research available for treatment of constipation, which is a very common presenting symptom in PD; however, in one study, macrogol was shown to be effective [124].

Although deep-brain stimulation of the subthalamic nucleus is an effective treatment for motor symptoms of PD, its effect on non-motor symptoms is unclear [125]. Kalteis and colleagues reported an improvement in psychiatric symptoms such as depression, anxiety and psychological symptoms in a study of 33 patients after subthalamic nucleus deep brain stimulation [126]. There have been reports of decreased verbal and executive functioning after subthalamic nucleus deep brain stimulation [127].

Dopaminergic therapy appears to be unhelpful for most of the NMS of PD unless these are linked to motor fluctuations. Many NMS of PD may have a non dopaminergic basis and symptoms usually do not respond to dopaminergic treatment [36]. Indeed, dopaminergic therapy may precipitate some non-motor problems in PD such as the dopamine dysregulation syndrome and orthostatic hypotension [70].

Conclusions

Delayed detection of NMS may lead to disability and poor quality of life, increasing the cost of care of PD in the society. NMS such as visual hallucinations, dementia and falls are a major source of hospitalization and institutionalization. Recognition of non-motor symptoms is therefore essential for the holistic management of PD and the importance of a multidisciplinary approach, including support for carers, cannot be overemphasized [5].

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