Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment

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Several studies, including work from the Parkinson's disease (PD) non-motor group and others, have established that the non-motor symptoms of PD are common, occur across all stages of PD, are under-reported, and are a key determinant of quality of life. Research suggests that the non-motor symptoms of the disease are frequently unrecognised by clinicians and remain untreated. Even when identified, there is a common perception that many of these symptoms are untreatable. The role of dopaminergic drugs in treating the various non-motor problems of PD, although clinically recognised, has received little attention. In this Review, we investigate the dopaminergic basis of the range of non-motor symptoms that occur in PD such as depression, apathy, sleep disorders (including rapid-eye movement sleep behaviour disorder), and erectile dysfunction. We discuss the evidence that these symptoms are treatable, at least in part, with various dopaminergic strategies and, where relevant, we also refer to the use of deep-brain stimulation of appropriate targets in the brain. This Review provides a comprehensive overview of the management of this challenging aspect of PD.

Introduction

Although the motor symptoms of Parkinson's disease (PD) are well defined, the non-motor features of this disorder are under-recognised and, consequently, under-treated. Non-motor symptoms and their management have been recognised by the UK National Institute for Clinical Excellence as an important unmet need in PD.[1–3] Results from a recent international survey show that up to 62% of non-motor symptoms of PD, such as apathy, pain, sexual difficulties, bowel incontinence, and sleep disorders, might remain undeclared to health-care professionals because patients are either embarrassed or unaware that the symptoms are linked to PD.[4] This under-reporting and under-recognition have important therapeutic and societal implications as many of these non-motor symptoms are treatable and, if left untreated, can have an adverse effect on quality of life. Additionally, non-motor symptoms are a frequent cause of hospitalisation and institutionalisation, which can increase the cost of care of patients with PD by four times.[1,5–8]

A large range of symptoms comprise the non-motor-symptom complex of PD (table 1) and several reviews have focused on these symptoms and the efforts made to quantify and manage them.[1,9,10] There are specific validated tools available for their assessment, including the non-motor questionnaire (NMS Quest), the non-motor scale (NMS Scale), the revised PD rating scale (UPDRS), and the scales for outcomes in PD (SCOPA).[9,11]

Non-motor symptoms of PD occur not only in advanced disease but also in early stages, and some symptoms such as olfactory deficit, constipation, rapid-eye movement (REM) sleep behaviour disorder (RBD), and depression might precede the expression of motor symptoms by more than a decade.[1,12] A UK brain bank clinicopathological study reported that, in a cohort of 433 patients with PD, 91 (21%) initially presented with non-motor symptoms, which led to frequent misdiagnosis, inappropriate referrals, and delayed treatment.[13] The occurrence of non-motor symptoms preceding the motor diagnosis of PD correlates closely with the progression of Lewy pathology in PD.[14,15] Although this association suggests that Lewy body deposition and neuronal dysfunction (but not death) begin in the olfactory bulb and lower medulla, the motor features of PD are not apparent until there is loss of dopaminergic neurons in the substantia nigra pars compacta. The axons from the substantia nigra pars compacta, ventral tegmental area, and hypothalamus—the key dopaminergic areas in the brain—project extensively to form four main pathways: the mesocortical, mesolimbic, nigrostriatal, and tuberoinfundibular pathways. These pathways mediate several non-motor symptoms such as cognition, sleep, and pain.

The importance of a dopaminergic contribution to non-motor symptoms in PD is highlighted by a recent PET study (figure 1), which reported in vivo evidence of dopamine dysfunction by ^{11}C-raclopride imaging in the hypothalamus of patients with PD.[16] This finding suggests at least a dopaminergic contribution to several non-motor symptoms of PD, such as sleep disorders, autonomic dysfunction, and neuro-endocrinal problems. A recent review has described the role of non-dopaminergic treatments in clinical trials aimed at management of some non-motor symptoms of PD such as depression, psychosis, cognition, excessive daytime sleepiness, and urge incontinence.[10] However, the fact that non-motor symptoms are not synonymous with a non-dopaminergic cause should be noted. In this Review, we investigate the potential of available dopaminergic treatments to improve certain aspects of non-motor symptoms (table 1). Where relevant, we have also referred to effects of deep-brain stimulation of the subthalamic nucleus and internal pallidum. Although deep-brain stimulation is not a specific dopaminergic therapy, it affects dopaminergic modulation within the nigrostriatal pathway.

Neuropsychiatric symptoms

Depression

The cognitive and neuropsychiatric non-motor symptoms of PD range from anxiety, apathy, and depression to frank dementia.[1,17] Depression is an important neuropsychiatric symptom in PD and can affect up to 45% of patients with the disease.[18] The clinical definition of depression in PD is complex and comprises features that might indicate early cognitive changes.[19] Dysfunction of a combination of dopaminergic, serotoninergic, and norepinephrinergic pathways in the limbic system has been implicated.[20] An in vivo imaging study that used ^{11}C-RTI-32 (a ligand that binds to dopamine-reuptake and norepinephrine-reuptake sites), detected decreased binding in the locus coeruleus and in the limbic system in patients with PD and depression compared with those who did not have depression.[20] The beneficial effect of dopaminergic therapy in mood disorders and apathy in PD might be partly explained by the fact that levodopa is taken up and decarboxylated in serotoninergic neurons, which can also convert levodopa to dopamine.

There have been many attempts to use dopaminergic therapies, including levodopa and dopamine agonists, for the treatment of depression in PD. These studies were small open-label or non-randomised. Pramipexole, used to treat motor symptoms of PD, had shown antidepressant activity similar to fluoxetine and better than placebo in 174 patients with PD and depression[21] and was better than placebo as an add-on therapy to a mood stabiliser in treatment-resistant bipolar depression.[22] Rektorova and colleagues[23] did an 8-month, multicentre, prospective, randomised study comparing pramipexole to pergolide (an ergot-derived dopamine agonist) as add-on therapy to levodopa treatment in 25 men and 16 women with PD and mild or moderate depression who did not have dementia. The Montgomery-Asberg depression rating scale (MADRS) scores were decreased significantly in the pramipexole arm, whereas depression scores rated by the Zung self-rating depression scale were significantly decreased in both groups. The authors suggested that pramipexole has a specific antidepressant effect in PD on the basis of a possible effect of dopamine receptor agonism at limbic dopamine D3 receptors. However, the results indicated that the effect might also be seen with ergot agonists such as pergolide, which is also an agonist at dopamine D3 receptors, suggesting a

	Responsive to dopaminergic treatment
Neuropsychiatric symptoms	
Depression, apathy, anxiety	Yes
Anhedonia	Yes
Cognitive dysfunction	..
Attention deficit	..
Hallucinations, illusions, delusions	..
Dementia	..
Confusion	..
Panic attacks	Yes (when related to "off" period)
Sleep disorders	
Restless legs and periodic limb movements	Yes
REM behaviour disorder	Yes?
REM loss of atonia	..
Non-REM sleep-related movement disorders	..
Excessive daytime somnolence	..
Vivid dreaming	..
Insomnia	..
Sleep-disordered breathing	..
Autonomic symptoms	
Bladder disturbances	..
Urgency	Yes (detrusor overactivity)
Nocturia	Yes
Frequency	..
Sweating	..
Orthostatic hypotension	..
Erectile impotence	Yes
	(Continued in next column)
(Continued from previous column)	
Gastrointestinal symptoms	
Dribbling of saliva	Yes?
Ageusia	..
Dysphagia, choking	..
Reflux, vomiting	..
Nausea	..
Constipation	Yes
Unsatisfactory voiding of bowel	Yes
Faecal incontinence	
Sensory symptoms	
Pain	..
Primary pain related to Parkinsons's disease (central pain)	Yes
Secondary pain	..
Fluctuation-related pain (wearing off, dyskinesias)	Yes
Paraesthesia	..
Olfactory disturbance	..
Visual dysfunction (contrast sensitivity, colour vision)	..
Other symptoms	
Non-motor fluctuations	Yes
Autonomic symptoms	..
Cognitive or psychiatric symptoms	..
Sensory symptoms including pain	..
Fatigue	Yes

Yes?=some anecdotal reports of response to dopaminergic treatment. Some unmarked symptoms might also respond to treatment.

Table 1: **The non-motor symptom complex of Parkinson's disease**

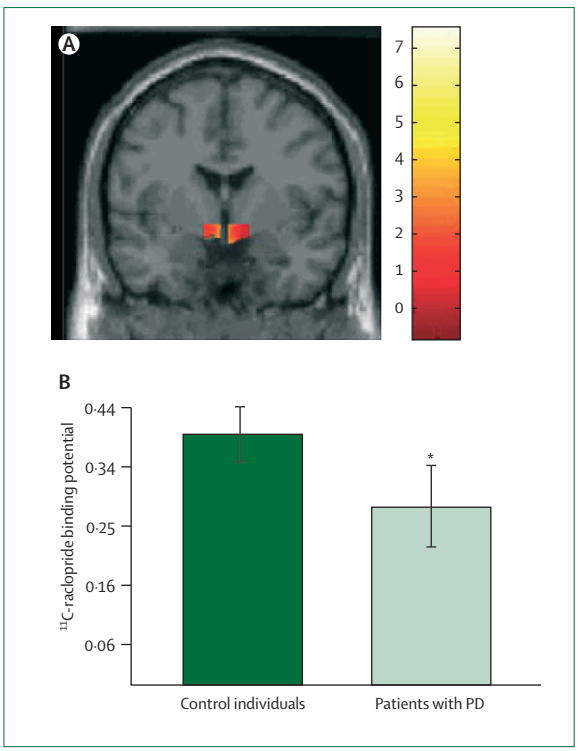

Figure 1: **Binding of ^{11}C-raclopride within the hypothalamus in individuals with and without PD**
(A) Coronal image from PET scan by use of statistical parametric mapping, with yellow-red areas indicating decreased binding of ^{11}C-raclopride within the hypothalamic region, in patients with PD compared with healthy control individuals (statistical parametric mapping results from the comparison between PD and controls). (B) Mean hypothalamic ^{11}C-raclopride binding potential values and standard deviation in control individuals versus patients with PD. *p=0·0005. Reprinted from Politis and co-workers,[16] with permission from Academic Press. PD=Parkinson's disease.

wider dopamine-mediated class effect in the treatment of depression in PD. Barone and co-workers[24] reported the results of a multicentre, open-label, randomised, assessor-blinded, 12-week trial that compared pramipexole with sertraline, a conventional antidepressant in patients with PD and depression.[25] Either open-label pramipexole (1·5–4·5 mg/day) or sertraline (50 mg/day) were given to 67 patients with PD and major depression but no motor complications. In both groups, the Hamilton depression rating scale score decreased throughout treatment but a greater proportion of patients recovered (defined by a final Hamilton depression rating scale score of 8 or less) in the pramipexole group than in the sertraline group (61% *vs* 27%, p=0·006). Therefore, pramipexole was shown to have greater antidepressant effects compared with sertraline, although small doses of sertraline were used. Additionally, there was a greater motor benefit with pramipexole than sertraline, which could have contributed to the improvement seen in depression scores.

Results from observational studies have suggested that anhedonia, regarded as a core symptom of depression also improves with treatment with pramipexole.[26] On the basis of these observations, a multicentre, double-blind, placebo-controlled trial of adjunct pramipexole versus placebo in stable levodopa-treated patients with PD and depression was initiated.[27] The recent Ropinirole 24-Hour Efficacy and Safety Evaluation in PD (EASE-PD) adjunct study, a phase III, multicentre, double-blind, randomised, placebo-controlled study in advanced cases of PD, assessed the antiparkinsonian efficacy of prolonged-release ropinirole, another D2/D3 dopamine agonist. As a secondary outcome measure, mood was assessed by use of the Beck depression inventory, which showed a significant effect with prolonged-release ropinirole compared with placebo (p<0·02). This finding suggests that an antidepressant action might also be evident with ropinirole, although, improved motor scores could also have confounded interpretation.[26] Other antidepressant drugs might also work via dopaminergic pathways. Buproprion is an antidepressant drug used in PD and is thought to act, at least in part, by inhibition of dopamine reuptake, as suggested from PET studies of the human dopamine transporter.[28] Sertraline, an established antidepressant, is a selective serotonin-reuptake inhibitor with an additional stimulant action due to dopamine-reuptake inhibition.[29]

Anxiety

Anxiety usually coexists with depression and motor fluctuations and can respond to dopaminergic therapy.[30] Anxiety disorders usually comprise generalised anxiety, panic attacks, and social phobia and might be the result of specific neurobiological or neuropeptide abnormalities associated with PD.[31] Clinically, anxiety can occur as a dopamine-dependent event as part of "wearing off" (often manifested as panic attacks) and would therefore respond to dopaminergic strategies aimed to prevent wearing off. Similarly, depression-related anxiety might also respond to dopaminergic treatment, although, in some patients, anxiety can remain a constant underlying problem that is independent of dopaminergic state and that might not respond to dopaminergic therapy.[31]

In a double-blind, randomised, crossover study, the effects of immediate-release or controlled-release levodopa on anxiety were compared in 14 patients with PD after overnight withdrawal of PD medications.[32] The State Trait Anxiety Inventory and a visual analogue scale for anxiety were used and assessments were made before and after (0·5, 1·0, 2·0, 2·5, 3·5, 5·0, and 6·0 h) levodopa treatment. Visual analogue scale scores showed a non-significant effect and a tendency towards decreased anxiety (p=0·06), with no difference between immediate-release or controlled-release levodopa. Patients with wearing off had a significant reduction in their visual analogue scale anxiety scores 3·5 h after taking the immediate-release formulation compared with patients who did not have wearing off (3·6 ± 1·5 *vs* 5·2 ± 0·8, p=0·02). However, a randomised but unblinded study showed a significant improvement in anxiety after deep-

brain stimulation of the subthalamic nucleus compared with conventional and best medical treatment at 6 months of follow-up.[33] In an observational study by Wijtas and co-workers,[34] fluctuation-related anxiety was reported to be significantly lowered after deep-brain stimulation of subthalamic nucleus in advanced PD. This finding could suggest that aspects of anxiety in PD might also be improved by the motor benefits seen after deep-brain stimulation of the subthalamic nucleus or by a possible limbic effect of subthalamic nucleus stimulation.

Apathy

Apathy is a specific symptom of PD that can occur with or without depression. Therefore, apathy might also coexist with anxiety disorder and mask itself as depression. A dopaminergic basis is possible, although, as seen in anxiety disorders, apathy can be unresponsive to dopaminergic therapy.

In a recent study, Czernecki and co-workers[35] reported that eight patients with PD who had not received dopaminergic treatment, and who developed apathy after subthalamic nucleus stimulation, showed a notable improvement 6 weeks after treatment with ropinirole. Improvement in apathy as rated by the apathy scale and apathy inventory, and mood as rated by the MADRS scale improved substantially. The authors suggested that dopamine deficiency, possibly involving the limbic areas, can cause apathy and be reversed by dopaminergic treatment. There are anecdotal reports of dopamine agonists improving apathy in some patients with PD,[36] whereas an observational study indicated that levodopa treatment reversed apathy in the "on" state compared with the "off" state.[37]

Cognitive dysfunction

Cognitive impairment is a common feature of advanced PD, with dementia affecting up to 80% of patients with late-stage disease.[19] However, cognitive dysfunction can occur in the early stages of PD and can present as a frontal dysexecutive syndrome, which might manifest as difficulty in maintaining an adaptive response against competing alternatives.[38] Patients with PD can also have visuospatial or visuoperceptual deficits.[39] A study of patients with early PD found that 72 of 126 (57%) had mild cognitive impairment at baseline with a cutoff of more than 1·0 SD below the normal levels for age.[40] However, the notion of mild cognitive impairment in PD is contentious. The early cognitive changes of PD might involve the caudate and corticostriatal pathways.[41] Abnormalities of dopamine uptake and brain metabolism in cortical targets of striatal dopaminergic fibres have been reported.[42,43]

There is evidence that at least a component of the cognitive dysfunction associated with PD can be improved with dopaminergic therapy.[44,45] Early reports suggest that safinamide (a drug with multiple mechanisms of action, including inhibition of monoamine oxidase B and antiglutamatergic activity) can improve cognitive and motor function in PD.[46] The method of delivery of dopamine could be important, with a gradual rise in

Panel 1: **Non-motor symptoms potentially exacerbated by dopaminergic treatment in Parkinsons's disease**

Antiparkinson drug related

Autonomic
- Parkinson hyperpyrexia syndrome or neuroleptic malignant syndrome*
- Serotonin syndrome†
- Malignant parkinsonism*
- Orthostatic hypotension

Fibrotic complications
- Cardiac
- Retroperitoneal
- Pleuropulmonary

Behavioural and neuropsychiatric
- Hallucinations
- Delusions
- Dopamine dysregulation syndrome
- Punding (activity characterised by compulsive fascination with, and performance of, repetitive, mechanical tasks, such as assembling and disassembling objects or collecting household objects)
- Impulse control disorders

Sleep related
- Excessive daytime sleepiness

Gatrointestinal
- Nausea
- Diarrhoea (related to intake of catechol-O-methyl transferase inhibitors)

Non-parkinsonian drug related
- Ankle swelling
- Blurred vision
- Weight gain
- Diarrhoea

*On dopaminergic drug withdrawal. †Interaction of or reaction to monoamine oxidase B inhibitors, tricyclic antidepressants, and selective serotonin-reuptake inhibitors commonly implicated.

	Slow-wave sleep	REM sleep	Wakefulness
Low-dose effect (possibly activating D2 autoreceptors)	Increased	Increased	Reduced: excessive daytime sleepiness
High-dose effect (via D1 receptors)	Decreased	Decreased	Increased: insomnia

REM=rapid-eye movement.

Table 2: **The variable effects of dopaminergic drugs and dopamine agonists on wakefulness and somnolence**

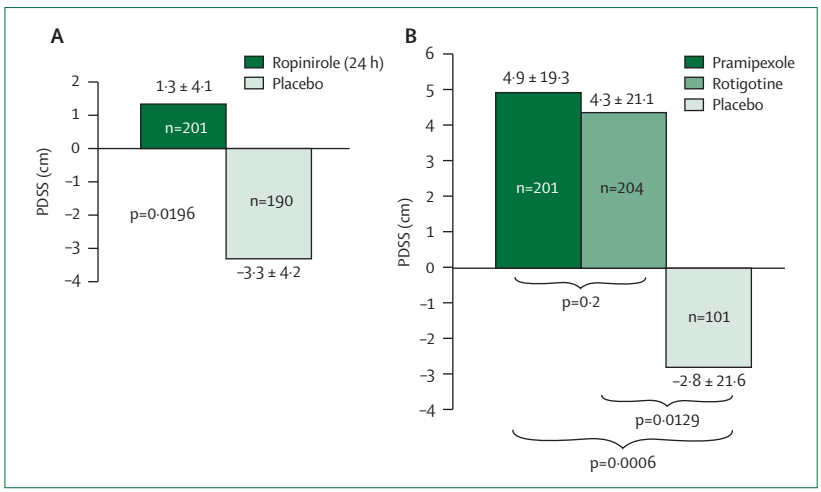

Figure 2: **Effect of dopamine agonists on the PDSS total score**
(A) Extended-release ropinirole versus placebo (EASE-PD study). (B) Pramipexole versus rotigotine transdermal patch, and placebo (CLEOPATRA study). All active strategies, but not placebo, led to an improvement in overall PDSS score (higher scores denote improvement).[26,56] CLEOPATRA=Clinical Efficacy of Pramipexole and Transdermal Rotigotine in Advanced Parkinson's Disease. EASE-PD=Ropinirole 24-Hour Efficacy and Safety Evaluation in PD. PDSS=Parkinson's disease sleep scale.

concentrations having the greatest effect on working memory.[45–47] Dopaminergic treatment, however, does have the potential to worsen cognitive function, particularly in patients with advanced disease (panel 1).

Sleep dysfunction

Dopamine has a complex role in the sleep-wake cycle, and, in PD, sleep-related problems might be dopamine sensitive.[47] Dopamine shares structural similarity with several wake-promoting drugs, and dopaminergic cell groups in the rat ventral periaqueductal grey matter seem to be selectively active during wakefulness, with Fos expression, which mediates a precise sleep-wake cycle.[48] Lesions of this area led to 20% increased sleep in rats.[48] An analogous scenario is seen in dopamine neurons of the midbrain (the ventral tegmental area), which mediate arousal and wakefulness. The ventral tegmental area receives projections from hypocretin neurons (key hypothalamic peptides that mediate wakefulness and are typically almost absent in narcolepsy), the pedunculopontine nucleus (implicated in the pathogenesis of RBD), and the extended amygdala. Projections from the ventral tegmental area link thalamocortical arousal via the thalamus and the limbic system.[47,48] The hypothalamus is a key sleep and autonomic regulatory centre and is central to the proposed "sleep switch".[49] Dopaminergic drugs, however, have variable effects on sleep (table 2). At low doses, these drugs promote slow-wave and REM sleep and induce somnolence (possibly via the D2 autoreceptors), whereas, at high doses, they reduce slow-wave and REM sleep and induce wakefulness.[47,48] Clinical experience suggests that somnolence reported during the titration phase of some dopamine agonists seems to be diminished after the highest maintenance dose is reached. Another role of dopaminergic drugs is reversal of nocturnal "off" state-related symptoms, which contribute to sleep-maintenance insomnia by causing frequent awakenings at night.[50]

Insomnia

Sleep-onset insomnia (ie, difficulty in falling asleep) and sleep-maintenance insomnia (ie, difficulty in maintaining sleep for periods of time) are common in PD. Although sleep-onset insomnia is associated with PD itself and its effect on sleep, sleep-maintenance insomnia could be due to a range of problems such as nocturnal akinesia and "off" state-related motor and non-motor symptoms (eg, nocturia, restless legs syndrome and periodic limb movements, and reversal of sleep patterns).[50,51] In a double-blind, placebo-controlled trial in elderly patients with PD, levodopa and carbidopa combination tablets given at bedtime were reported to improve sleep quality (as measured subjectively and by measurement of spontaneous movements in bed) from 67% to 93% and improve early-morning walking.[52] Stocchi and co-workers[53] reported that treatment with slow-release levodopa and carbidopa combination tablets led to a significant improvement in mean nocturnal akinesia scores compared with controls, although the number of hours slept, number of awakenings, sleep latency, or general sleep satisfaction were not improved. Another study reported that sustained-release levodopa and benserazide combination tablets substantially improved nocturnal akinesia (ability to turn in bed) and total time awake (which was significantly decreased from 2·13 to 0·67 h in a 12-month, open-label trial of 15 patients with PD and disruptive nocturnal symptoms.[54] The use of a targeted nocturnal dopamine agonist for nocturnal akinesia was first investigated in an open-label, comparative, observational study in patients with PD with severe sleep disruption caused by nocturnal motor symptoms.[55] In this study, cabergoline, a long-acting ergot dopamine agonist, was compared with controlled-release levodopa. Morning ratings of motor UPDRS and the King's College Hospital PD rating scale scores were significantly improved ($p<0·05$) after cabergoline treatment, but not levodopa treatment, in 40 patients with PD, suggesting that the long duration of action of cabergoline was more beneficial than shorter-acting drugs. The role of sustained dopaminergic stimulation throughout the night was further investigated in a recent double-blind, double-dummy, randomised controlled trial that compared the efficacy of pramipexole and transdermal rotigotine in advanced-stage PD.[56] Sleep parameters were measured by use of the validated PD sleep scale, and both pramipexole and rotigotine patch resulted in small but significant improvements in the overall PD sleep scale scores compared with placebo (figure 2). Improvements were also noted in sleep akinesia. Similar results were reported with extended-release ropinirole in the EASE-PD adjunct study (figure 2).[26]

Periodic limb movements, restless legs syndrome, and akathisia

Both periodic limb movements and restless legs syndrome are closely linked and are sensitive to dopamine, with dopamine agonists being the drugs of choice for initial treatment of these disorders.[57,58] Several studies have reported a two-fold increase in the prevalence of restless legs syndrome in PD, and periodic limb movements is another frequent cause of sleep disruption.[59,60] Akathisia is common in advanced-stage PD with akinetic rigid phenotype and can overlap with symptoms of restless legs syndrome. Changes in mesocortical dopamine pathways have been implicated.[61] There are no controlled trials of the use of dopamine agonists in patients with PD and restless legs syndrome apart from a small placebo-controlled study. This study reported that continuous apomorphine infusion, a non-ergot dopamine agonist, given subcutaneously overnight resulted in significantly reduced nocturnal discomfort, decreased leg movements, and improved pain and spasm scores in six patients.[62] An open-label study of 15 patients with PD and periodic limb movements who received cabergoline reported reduced periodic limb movements in sleep, although there were increased numbers of awakenings and stage shifts.[63] In this study, levodopa also decreased the frequency of periodic limb movements from 43 per night to 28–33 per night.[52] Akathisia can respond to dopaminergic treatment when it presents as part of wearing off, but might need specific therapy with drugs such as clozapine.[61]

RBD

RBD was first reported by Schenck and co-workers[64] and is a well known parasomnia typically characterised by vivid and usually frightening dreams or nightmares. These nightmares are associated with a paradoxical simple or complex movement during REM sleep when muscles usually are atonic.[65,66] Symptoms of RBD can predate the diagnosis of PD and a latent period of 12·7±7·3 years after the onset of RBD has been reported.[65,67,68] In a recent study, Postuma and colleagues[69] estimated the 5-year risk of neurodegenerative disease to be 17·7% and the 10-year risk to be 40·6% after RBD was diagnosed in patients without signs of parkinsonism. Although the pathological basis of RBD are unclear, the disorder seems to be associated with degeneration of lower brainstem nuclei, such as the pedunculopontine and peri-ceruleal nucleus, which have connections with the dopaminergic ventral tegmental area in the midbrain. Studies in cats suggest that brainstem areas such as the laterodorsal tegmental nucleus, peri-locus caeruleus region, nucleus reticularis magnocellularis, and the ventrolateral reticulospinal tracts and the pedunculopontine nucleus are involved.[66] In human beings, degeneration of the sublaterodorsal nucleus with its direct and indirect projections to the spinal interneurons has been associated with the pathophysiology of RBD.[66] Structures such as the substantia nigra are also linked to REM and non-REM sleep circuits. The beneficial effect of pramipexole in the treatment of RBD has been reported,[70] although this finding has not been investigated in a controlled study. Levodopa has also been effective in open-label studies.[67,71,72] Clonazepam is probably the most effective treatment for RBD in patients with PD, although gabapentin and melatonin have also been used effectively in some cases.[65,66]

Autonomic symptoms

Urinary bladder

Dopaminergic pathways affect urinary bladder-related symptoms in PD, and data from animal studies indicate that the dopamine receptors have different effects on the pontine micturition centre; the striatal D1 receptors inhibit the micturition reflex, whereas the D2 receptors activate it.[73,74] Detrusor overactivity is common in PD and is clinically translated to the complaint of urinary urgency, which can be caused by a combination of under-active D1 activity with possible exacerbation by D2 stimulation. Additionally, patients with PD have difficulty with voiding, which can be the result of a disorder of bladder contractility or an abnormal sphincter action caused by bradykinesia, which seems to be reversible by apomorphine injection.[75,76]

An "on" state is usually associated with reduced voiding difficulty, although the results of dopaminergic treatment are conflicting. Levodopa can worsen or improve urgency and detrusor overactivity. Uchiyama and co-workers[75] examined 18 patients with PD during "off" and "on" phases with urodynamic studies before treatment and about 1 h after receiving levodopa 100 mg. Symptoms improved in all patients who had voiding difficulty, although urinary urgency and urge incontinence was unchanged or aggravated. D1 and D2 receptors seem to have different effects on bladder control: pergolide, a dopamine agonist with possible D1 agonist activity, had beneficial effects in animals,[77] whereas a study noted improvement in nocturia in three patients who were switched from bromocriptine to pergolide.[78] However, pergolide is no longer recommended for use in PD as there is a considerable risk of development of cardiac valvular fibrosis. Deep-brain stimulation of the subthalamic nucleus has a beneficial effect on bladder function in PD by improving bladder capacity and reflex volume; this effect is possibly secondary to improved sensory motor integration and improvement of higher-order processing of afferent activity.[79,80]

Nocturia

In the NMS Quest study, up to 62% of patients complained of nocturia, which might have occurred because of a combination of increased urine output at night, decreased bladder capacity, and possible impairment of sleep due to nocturnal akinesia.[81]

In an open-label, international, multicentre study of 54 patients, a significant beneficial effect of rotigotine

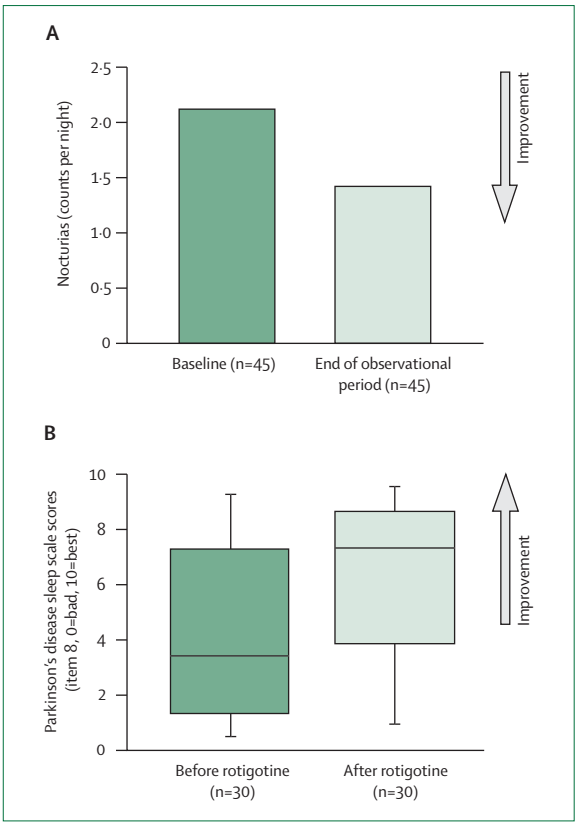

Figure 3: **Data from two open-label studies showing improvement in nocturia after treatment with rotigotine transdermal patch**
(A) Improvement in nocturia counts (p=0·0001). (B) Improvement in item 8 of the Parkinson's disease sleep scale, which specifically refers to nocturia. The plot in B shows nocturia mean scores and confidence intervals at baseline and after 5· 6 months of rotigotine transdermal patch (Wilcoxon signed rank test p=0·0001). Rotigotine was used as adjunctive treatment with other stable antiparkinsonian treatment. Lines within box plots indicates mean value. Data compiled from references 82 and 83.

transdermal patch for nocturia in patients with PD was reported, which was supported by a single-centre study of 30 patients (figure 3).[82,83] There are no controlled trials that have investigated nocturia and dopaminergic therapy as yet.

Sexual dysfunction

Sexual dysfunction is common in patients with PD, and presentations include erectile dysfunction, loss of libido, or hypersexuality.[1,84] These symptoms might in part be related to neuronal degeneration affecting central sympathetic neurons and postganglionic fibres.[85] Studies by Robinson and Mishkin[86] in monkeys showed that stimulation of the dorsal putamen and anterior region of internal capsule induced erections. Others have reported penile erection after deep-brain stimulation of the thalamus.[87]

There are no clinical trials investigating the specific effects of dopaminergic drugs for the treatment of erectile dysfunction or loss of libido in PD, even though sexual arousal and increased libido are recognised side-effects of such drugs.[88] In a recent study, 14 of 15 men taking adjunctive dopamine agonists developed hypersexuality within 8 months of receiving the dopamine agonist.[89] Hypersexuality has also been reported after various other dopaminergic therapies, including levodopa. Apomorphine injections have been used for erectile dysfunction in individuals without PD; in PD, apomorphine has been reported to cause penile erections.[90,91] Therefore, apomorphine could be investigated for erectile dysfunction in PD.

Gastrointestinal symptoms

Constipation is a common non-motor feature of PD and studies suggest a severe loss of both central and colonic dopaminergic neurons.[92] Edwards and co-workers[93] studied eight patients with PD by use of defaecography and anorectal manometrics. After apomorphine treatment, defaecographic abnormalities were normalised in one of three patients and all five individuals who underwent repeated anorectal manometry showed substantial improvements in manometric parameters. The authors concluded that apomorphine can correct anorectal dysfunction in PD and suggested that abnormalities of defaecation and anorectal function occur as a consequence, at least in part, of dopamine deficiency secondary to the pathological changes of PD. Data from a multi-centre, open-label observational study that used intrajejunal infusion of duodopa in patients with advanced-stage PD suggest an improvement in constipation and other bowel symptoms in addition to other non-motor symptoms.[94]

Sensory symptoms

Pain

Dopamine can modulate pain at several levels within the nervous system, including the spinal cord, thalamus, periaqueductal grey, basal ganglia, and cingulate cortex.[95,96] Unexplained pains are a major component of the non-motor symptom complex of PD; the NMS Quest study reported pain in 29% (158 of 545) of patients.[81] A recent study, the DOPAMIP (Douleur et maladie de Parkinson en Midi-Pyrénées) survey in southwest France, examined the occurrence of chronic pain in 450 patients with PD compared with age-matched and sex-matched patients who had other chronic disorders. 62% of patients with PD had at least one form of chronic pain.[97] The pain had an average intensity of 60 mm of 100 mm on a visual analogue scale and was twice that reported in the control patients after adjusting for co-morbidity. Similar figures were reported in a recent Italian case-control survey, which noted that, overall, 70% of the population studied had pain.[98]

There have been various classifications for categorising pain in PD, and a substantial proportion of pain in this disorder is caused by motor fluctuations and dyskinesias secondary to dopaminergic treatment.[99] Additionally, pain in PD might present as central pain, oro-facial pain, limb

pain, or musculo-skeletal pain. Motor fluctuation and dyskinesia-related pain, along with central pain, are probably associated with PD so can be described as PD pain, whereas other forms of pain are secondary and not directly related to PD so can be described as non-PD pain (panel 2). There might be some overlap between categories; for instance, orofacial pain, a secondary pain, might respond to dopaminergic treatment. Central pain in PD might be dopamine mediated; Brefel-Courbon and colleagues[100] reported that the pain threshold to cold is substantially lower in patients with PD who were withdrawn from treatment compared with controls, and that the threshold normalised after levodopa therapy. Another study investigated the pathophysiology of primary central pain (no obvious cause) in nine patients with PD and primary central pain, nine patients with PD without pain, and nine controls. Individuals who had PD and primary central pain showed hyperalgesia and absence of habituation of sympathetic sudomotor response to repetitive pain. These abnormalities were improved by treatment with levodopa 100 mg.[101] The authors suggested that the origin of primary central pain in PD is based on dysfunction of dopaminergic-dependent autonomic centres, which regulate autonomic function and inhibitory control of pain. Djaldetti and co-workers[102] reported that the threshold of heat pain was lower in patients with PD and pain, and more so on the affected side where PD is most apparent, compared with individuals without pain. This finding suggests that endogenous pain in PD is associated with increased sensitivity to some specific painful stimuli. Nocturnal pain and orofacial pain might also be alleviated by dopaminergic therapy.

There are no specific studies of pain and dopaminergic therapy in PD, although a study of six patients with nocturnal pain and restless legs syndrome showed marked improvement of pain after overnight apomorphine infusion.[62] "Off" period-associated pain improved after deep-brain stimulation of the subthalamic nucleus and after treatment with therapies that aimed to stop "off" state-related non-motor pain effectively by use of the continuous dopaminergic stimulation idea, such as apomorphine or duodopa overnight infusion.[34] Loher and colleagues[103] reported a notable reduction in "off" state-related pain after bilateral pallidal stimulation in advanced-stage PD.

Visual function

Visual impairment affecting colour and contrast discrimination has been suggested as a possible pre-motor marker for PD.[104,105] There is evidence that dopaminergic deficiency of PD could lead to a primary visual dysfunction. Innervation around the fovea is largely dopaminergic and, in patients with untreated PD, autopsy studies show that retinal dopamine concentration is decreased compared with in patients with treated PD, in whom dopamine concentrations return to normal.[104,106] These changes can account for retinal dysfunction in PD and have been confirmed by electroretinography.[107,108] At a higher level, reduced metabolism and hypoperfusion in the occipital cortex can lead to defective visual processing, whereas patients with RBD can have defective colour discrimination.[105] Willis has suggested that the retino-diencephalic/mesencephalic-pineal axis is primarily involved in PD and leads to dopamine-melatonin imbalance, implicating the visual system in the genesis of PD.[109] There are few specific studies focusing on visual deficit and the effect of dopaminergic treatment. PD patients describe blurred vision, typically at lower luminosity during "off" periods and this is likely to be related to foveal retinal dopaminergic neuronal dysfunction.[110] Dopaminergic strategies aimed to overcome wearing off would help these visual symptoms.

***Panel 2:* A proposed classification of pain in Parkinson's disease**

- Musculoskeletal pain
- Parkinsons's disease-related chronic pain (might respond to dopaminergic therapy)
  - Central pain
  - Visceral pain
- Fluctuation-related pain (dopaminergic therapy responsive)
  - Dyskinetic pain
  - "Off" period dystonia-related pain
  - "Off" period generalised pain
- Nocturnal pain (usually dopaminergic therapy responsive)
  - Pain related to restless legs syndrome or periodic limb movement
  - Nocturnal akinesia-linked pain
- Coat-hanger pain (pain around the shoulder area; rare in Parkinsons's disease and linked to postural hypotension)
- Oro-facial pain
  - Temporo-mandibular joint pain
  - Bruxism-related pain
  - Burning mouth syndrome (might be levodopa responsive)
- Peripheral limb or abdominal pain
  - Drug induced
    - Peripheral oedema-linked pain
    - Lower bowel pain associated with retroperitoneal fibrosis

Non-motor fluctuations, pulsatile, and continuous dopaminergic stimulation

Non-motor fluctuations can commonly occur in PD and, in some cases, might cause greater discomfort than motor fluctuations. Witjas and co-workers[111] have classified non-motor fluctuations into three subtypes: dysautonomic, cognitive and psychiatric, and sensory or pain. These subtypes are thought to occur secondary to pulsatile dopaminergic therapy, with similar pathogenesis to motor fluctuations. In another study, the same authors[112] reported

Search strategy and selection criteria

References for this Review were identified through searches of PubMed and Google Scholar with the search terms "non motor", "Parkinson's disease", and "dopaminergic treatment" as the main keywords between January, 1960, and November, 2008. Information was also obtained from international congress proceedings published in journals specialising in movement disorders, parkinsonism and related disorders, and neurology. Papers were cited on the basis of importance in relation to non-motor features of PD, evidence of dopaminergic dysfunction, and treatment with dopaminergic drugs. Additionally, some references were obtained from presentations from international meetings. Papers not published in English and abstracts from local or national meetings were excluded.

that anxiety (66%), drenching sweats (64%), slowness of thinking (58%), fatigue (56%), and akathisia (54%) were the most common non-motor fluctuations and these correlated with motor disability and pulsatile levodopa treatment. Stacy and co-workers[113] have also classified and defined motor and non-motor wearing off symptoms in PD by use of a new wearing off questionnaire, which aids clinical management of such symptoms.

On the basis of the observations outlined here, therapies that use continuous dopaminergic stimulation might have a beneficial effect in abolishing or reducing the non-motor fluctuations in PD. Such treatments would include levodopa-based therapies, particularly duodopa intrajejunal infusion, 24-h apomorphine infusion, rotigotine transdermal patch, and oral long-acting (once-daily) dopamine agonists. In this context, deep-brain stimulation of the subthalamic nucleus is also useful because this strategy might have some dopaminergic modulatory action within the nigrostriatal pathway.

Conclusions

A range of non-motor symptoms of PD seem to have a dopaminergic contribution. Therefore, some of these symptoms, which are typically regarded as non-responsive to dopaminergic drugs, might respond to targeted dopaminergic therapy. However, this possibility has to be balanced against the fact that some non-motor symptoms might be exacerbated by dopaminergic drugs. Robust clinical trials focusing on the use of specific dopaminergic drugs to treat some key non-motor symptoms, such as RBD, pain, restless legs syndrome, and depression, are scarce, but several small or non-randomised studies suggest efficacy of some of these therapies. In the near future, a substantial number of clinical trials investigating this important unmet need in PD is anticipated.

Contributors
Both authors contributed equally to the preparation of this Review.

Conflicts of interest
We have no conflicts of interest.

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