Evaluation and management of the non-motor features of Parkinson's disease

Steven Wishart and Graeme J. A. Macphee

Abstract: Parkinson's disease (PD) is traditionally viewed as a motor disorder with a characteristic triad of tremor, rigidity and bradykinesia. There is now increasing awareness that PD is a complex systemic disorder with many nonmotor symptoms (NMS) which include autonomic dysfunction, sleep disorders, sensory and neuropsychiatric features. NMS become more common in severity and frequency with advancing disease when neuropsychiatric features such as cognitive impairment and psychosis dominate the clinical picture. NMS are strongly correlated with quality of life for patients and their families as well as institutional care placement. Despite their importance, NMS are poorly recognized by clinicians and often undeclared by patients. Use of a validated screening tool NMSQuest followed by specific symptom assessment instruments strengthens the recognition and holistic management of NMS in PD. Some NMS such as mood disturbance, anxiety, pain and insomnia may be improved by optimization of dopaminergic therapy. Conversely, psychosis, excess daytime somnolence or impulse control disorder (ICD) may be triggered by dopaminergic drugs. Other NMS such as dementia and severe depression may be unresponsive to dopaminergic treatment and may reflect perturbations in cholinergic, serotonergic or noradrenergic neurotransmitter function. These symptoms are more challenging to manage but may be ameliorated to some extent by agents such as acetylcholinesterase inhibitor or antidepressant drugs. This contribution reviews the evidence for the evaluation and management of key NMS in PD (apathy, anxiety, depression, psychosis, dementia, ICD, sleep disturbance, autonomic dysfunction, pain) and highlights the urgent need for both novel therapies and more controlled trials for current therapeutic strategies.

Keywords: dementia, depression, dopamine agonists, impulse control disorder, levodopa, nonmotor symptoms, Parkinson's disease, psychosis, sleep disorder

Introduction and background

Parkinson's disease (PD) is traditionally viewed as a progressive irreversible neurodegenerative motor disorder with core features of tremor, rigidity and bradykinesia, but there is now increasing recognition that PD is a systemic disorder with many nonmotor features [Chaudhuri and Schapira, 2009; Chaudhuri et al. 2006a]. The characteristic Lewy body pathology [Gibb and Lees, 1988] extends beyond the dopaminergic pathways in the nigrostriatal system into widespread brain areas and is also found in the peripheral autonomic nervous system including sympathetic ganglia, cardiac sympathetic efferents and the myenteric plexus [Forno, 1982]. Although dopaminergic depletion is the primary deficit in PD, multiple neurotransmitter systems including acetylcholine, noradrenaline and serotonin are also perturbed [Lang and Obeso, 2004]. It is unsurprising then that the clinical manifestations of PD are diverse and complex [Lim et al. 2009a].

Nonmotor symptoms (NMS) in PD include mental health problems, sleep disorders, autonomic dysfunction, pain and other miscellaneous symptoms (Table 1). In a prospective study of patients diagnosed with PD, NMS such as cognitive impairment, depression, falls and orthostatic hypotension dominated the

Correspondence to:
Graeme J. A. Macphee, FRCP
Medicine for the Elderly/
Movement Disorders
Clinic, Southern General
Hospital, Glasgow,
Scotland G51 4TF, UK
**graeme.macphee@
ggc.scot.nhs.uk**

Steven Wishart, MRCP
Medicine for the Elderly/
Movement Disorders
Clinic, Southern General
Hospital, Glasgow,
Scotland G51 4TF, UK

Table 1. Nonmotor symptoms in Parkinson's disease (adapted from Chaudhuri *et al.* [2006a]).

Neuropsychiatric symptoms
  Anxiety
  Apathy
  Cognitive impairment
  Compulsive and repetitive behaviour
  [usually drug induced]
  Confusion [may be drug induced]
  Delirium [may be drug induced]
  Dementia
  Depression
  Hallucinations, illusions, delusions
  Panic attacks

Sleep disorders
  Excessive daytime somnolence
  Insomnia
  Rapid eye movement [REM] sleep
  behaviour disorder
  Restless legs and periodic limb movements
  Sleep apnoea or disordered breathing
  Vivid dreaming

Autonomic symptoms
  Bladder dysfunction
  Coat-hanger pain
  Dry eyes [xerostomia]
  Erectile dysfunction
  Falls related to orthostatic hypotension
  Hypersexuality [usually drug induced]
  Nocturia
  Orthostatic hypotension
  Sexual dysfunction
  Sweating
  Urgency
  Urinary Frequency

Gastrointestinal symptoms [overlap with autonomic symptoms]
  Ageusia
  Constipation
  Dribbling of saliva
  Dysphagia and choking
  Faecal incontinence
  Incomplete voiding of bowel
  Nausea
  Reflux

Sensory symptoms
  Olfactory disturbance
  Pain
  Paraesthesia

Miscellaneous symptoms
  Fatigue
  Diplopia
  Blurred vision
  Seborrhoea
  Weight loss
  Weight gain [usually drug induced]

clinical picture at 15 years of disease [Hely *et al.* 2005] and have been linked to reduced quality of life (QoL) [Schrag *et al.* 2000]. Furthermore, certain NMS such as dementia and psychosis are associated with impaired function [Weintraub *et al.* 2004] and increased rates of institutionalization [Findley *et al.* 2003; Aarsland *et al.* 2000]. Despite this, motor symptoms often form the focus of attention during healthcare consultations leading to underrecognition and undertreatment of NMS [Shulman *et al.* 2002]. This is compounded by underreporting of NMS by patients who may not relate them to PD or are perhaps too embarrassed to mention them without prompting [Chaudhuri *et al.* 2010].

In a study of 545 patients the mean number of NMS per patient was 10.3 with urinary symptoms, depression and memory problems being the most commonly reported [Martinez-Martin *et al.* 2007]. The frequency of NMS increases with disease duration and severity [Barone *et al.* 2009] but may become apparent at any stage in the disease process. Indeed, some symptoms such as olfactory dysfunction [Stiasny-Kolster *et al.* 2005], constipation [Abbott *et al.* 2001], REM sleep behaviour disorder (RBD) [Schenck *et al.* 1996] and depression [Ishihara and Brayne, 2006] may predate the motor features [O'Sullivan *et al.* 2008]. The combination of such features may suggest a diagnosis of PD and screening for a 'premotor' stage of PD will become increasingly important as putative neuroprotective agents are investigated [Stern and Siderowf, 2010]. Although data are limited, NMS appear to occur at a similar or lower frequency in the rare but increasingly identified genetic forms of PD [Kasten *et al.* 2010].

The pathogenesis of these features has been linked to the Braak hypothesis of a six-stage pathological process in PD [Braak *et al.* 2003]. This posits that PD pathology starts not in the substantia nigra (SN) and midbrain but rather in the olfactory bulb and anterior olfactory nucleus (stage 1). It then ascends into the lower brain stem (stage 2) where degeneration of key nuclei such as the raphe nucleus, locus coeruleus and pedunculopontine nucleus may be responsible for prominent early sleep, autonomic and mood disturbances [Lim *et al.* 2009a]. The typical motor triad of PD is only apparent at stages 3 and 4 when the SN and mid and forebrain nuclei are affected. Stages 5 and 6 are associated with Lewy bodies in the limbic and mature neocortex and clinical

Table 2. Nonmotor features potentially caused or exacerbated by dopaminergic therapy.

Autonomic system
   Orthostatic hypotension*
   Serotonin syndrome [usually caused by combination of MAO-B inhibitor drugs and SSRI antidepressants]
Sleep
   Excess daytime somnolence [mainly dopamine agonist drugs]*
Gastrointestinal symptoms
   Nausea
   Constipation [anticholinergic agents such as tricyclic antidepressants and urinary anticholinergic drugs]*
   Diarrhoea [COMT inhibitor drugs such as entacapone and tolcapone]
Neurobehavioural
   Confusion*
   Hallucinations*
   Delusions*
   Dopamine dysregulation syndrome [levodopa]
   Impulse control disorder [including pathological gambling, hypersexuality, binge eating and compulsive shopping] — most commonly dopamine agonist therapies
   Punding — commonly levodopa or apomorphine - compulsive repetitive purposeless behaviours such as assembling and disassembling household appliances or collecting things.
Fibrotic complications [Cardiac valve fibrosis, pleuroperitoneal fibrosis, retroperitoneal fibrosis] associated with ergot dopamine agonist drugs [e.g. pergolide, cabergoline]
   Dyspnea*, oedema**
   Lower abdominal pain,
   Symptoms of renal impairment

*Also intrinsic to disease.
**Also caused by non-ergot dopamine agonists.
COMT, catechol—O—methyltransferase; MAO-B, monoamine oxidase-B inhibitor.

Table 3. Types of pain in Parkinson's disease and potential management approaches (adapted from Ford [2010]).

Type of pain	Management approaches
Musculoskeletal	Simple analgesia Physical and occupational therapy [PT/OT] to prevent contractures and optimize function Orthopaedic surgery if indicated for joint abnormalities
Neuropathic or radicular	Neuropathy screen Consider electromyography/nerve conduction studies PT/OT Decompressive surgery where indicated
Dystonia and dyskinesia	Optimise dopaminergic and antidyskinetic therapies Consider baclofen, apomorphine, anticholinergics, amantadine Botulinum toxin may be beneficial in selected patients Deep brain stimulation may have a role
Central	Neuropathic pain agents such as carbamazepine, gabapentin and tricyclic antidepressants may be helpful Opiates
Akathisia	Optimization of dopaminergic therapy Opiates Avoidance of neuroleptics

correlates include the development of hallucinations and dementia [Braak *et al.* 2005].

The pathophysiology of NMS is underpinned by dysfunction of both dopaminergic and nondopaminergic pathways [Chaudhuri and Schapira, 2009; Lang and Obeso, 2004]. It is clear that some NMS such as pain, anxiety and restless legs may be related to motor fluctuations or 'wearing off' and these symptoms may be amenable to modification of treatment [Witjas *et al.* 2002]. However, many NMS do not

respond to, or may worsen with dopaminergic therapy, e.g. cognitive dysfunction and dysautonomia. Table 2 summarizes NMS which may be caused or exacerbated by anti-Parkinson's drug therapy. Therapeutic 'conflicts' may arise in treating a range of NMS in an individual patient. For example, using antimuscarinic drugs to treat bladder dysfunction may worsen intrinsic cognitive impairment. Clinicians managing NMS must be aware of other common age-related conditions in people with PD since some 'declared' NMS may be due to unrelated comorbidities, e.g. constipation and weight loss caused by colonic carcinoma [Macphee and MacMahon, 2009].

The importance of NMS has been recognised at a national level in the UK by the National Institute for Clinical Excellence and guidance on the treatment of some NMS has been incorporated in the clinical guideline on PD [National Institute for Health and Clinical Excellence, 2006]. In 2010, further evidence-based guidance on the treatment of selected NMS has been published by the Scottish Intercollegiate Guidelines Network (SIGN) in 'Diagnosis and pharmacological management of PD' [Grosset *et al.* 2010; Scottish Intercollegiate Guidelines Network, 2010] along with a 'Practice Parameter, Treatment of nonmotor symptoms of Parkinson disease' by the American Academy of Neurology (AAN) [Zesciewicz *et al.* 2010]. This paper follows an earlier AAN publication on treatment of depression, dementia and psychosis [Miyasaki *et al.* 2006]. Both reports highlight the lack of robust evidence for treatment of many NMS. Because many NMS are not reported in the clinic, the present review emphasizes the importance of identification and assessment of NMS with appropriate screening and assessment instruments. Multidisciplinary inputs from physiotherapy, occupational and speech and language therapy, dietetics and specialist nurse are crucial in the holistic management of NMS but a full discussion of these is beyond the scope of this review.

Identification and evaluation of NMS
The Unified Parkinson's Disease Rating Scale (UPDRS) was originally developed in the 1980s and is the most widely used clinical rating scale for the disorder. NMS were not included in the original UPDRS. Following review by the Movement Disorder Society an updated version has recently been validated and includes 11 NMS (MDS-UPDRS) [Goetz *et al.* 2008].

A multidisciplinary group of international experts in PD formulated and validated the NMS screening Questionnaire (NMS Quest) comprising 30 individual items to provide a more comprehensive assessment of NMS [Martinez-Martin *et al.* 2007; Chaudhuri *et al.* 2006b]. The questionnaire is a self-completed tool used to identify NMS which require further evaluation during the consultation. The questionnaire is only used for screening and does not rate or grade the symptoms and therefore cannot be used to assess treatment effects.

The NMS Scale conversely measures the frequency and severity of NMS [Chaudhuri *et al.* 2007] and is being incorporated in therapeutic trials [Honig *et al.* 2009]. Other tools include the scales for outcomes in Parkinson's disease (SCOPA) [Propark Study, 2010]. Improved recognition of 'wearing off' NMS may be achieved by use of a validated questionnaire [Stacy *et al.* 2005]. The utility and limitations of assessment instruments for individual NMS are discussed briefly under the relevant symptoms.

Neuropsychiatric symptoms

Apathy
Apathy can occur as a feature of other illness (e.g. hypothyroidism, hypogonadism) or as a specific symptom of PD which may be attributable to disturbances in basal ganglia and fronto-cortical connections [Pluck and Brown, 2002]. Cognitive impairment and mood disturbance as well as fatigue are frequently associated with apathy and there is considerable overlap in these NMS [Aarsland *et al.* 2009a]. Apathy may occur in up to 30% of patients in the absence of depression [Aarsland *et al.* 2009a; Levy *et al.* 1998] and is challenging to manage. Patients typically show lack of motivation with indifference to their behaviour although considerable distress occurs in carers because of perceived 'laziness' [Campbell and Duffy, 1997]. There is limited evidence as to the benefit of pharmacological therapies. Dopamine agonists, amantadine and modafinil have been suggested [Aarsland *et al.* 2009a]. Methylphenidate, an amphetamine-like derivative, may improve fatigue and apathy [Mendonca *et al.* 2007] but has the potential for abuse.

Anxiety

Anxiety affects up to 50% of patients with PD [Pontone *et al.* 2009; Leentjens *et al.* 2008] and is associated with earlier age of onset, higher rates of motor fluctuation and early morning dystonia. Subtypes of anxiety include panic disorder, generalized anxiety and phobias [Pontone *et al.* 2009]. Generalized anxiety and panic attacks may be associated with 'off' periods and in such cases usually respond to optimizing dopaminergic therapy. Conversely, anxiety and mania may be due to excess ingestion of levodopa therapy as part of the dopamine dysregulation syndrome [Evans and Lees, 2004] which is discussed later.

Current evidence regarding the assessment and treatment of anxiety in PD is very limited [Leentjens *et al.* 2008]. Selective serotonin reuptake inhibitor (SSRI) drugs are often used in clinical practice partly because of the association of anxiety with depression. Although there is no significant trial data to support the use of standard anti-anxiety therapies, e.g. benzodiazepines, clinical experience suggests a benefit for these agents in selected patients. Caution is required because of the potential adverse effects on balance, cognition and alertness.

Depression

Mood disorders including depression are common in PD but prevalence rates vary widely in the literature. A systematic review suggested that the prevalence of major depressive disorder was 17% in patients with PD, that of minor depression 22% and dysthymia 13%. Clinically significant depressive symptoms were present in 35% of patients [Reijnders *et al.* 2008].

Depression in PD is associated with increased functional impairment and disability [Weintraub *et al.* 2004]. In a retrospective cohort study, a strong association was found between depression and subsequent development of PD [Schurman *et al.* 2002]. This evidence, together with an inconsistent relationship between depression and severity of motor symptoms [Schrag *et al.* 2001; Brown and Jahanshahi, 1995], suggests that depression is not simply a reaction to disability but at least partly related to intrinsic disease. Although the relationship between the pathophysiology of PD and depression remains unclear dysfunction of a combination of dopaminergic, serotoninergic and norepinephrinergic pathways in the limbic system is likely [Remy *et al.* 2005].

Recognition of depression may be difficult because of the overlap between depressive and somatic symptoms of PD such as flat affect, reduced motivation and withdrawal from social activities. People with PD and depressive symptoms often manifest less self-blame and guilt than patients with primary depression. Conversely, features of anxiety and panic and anhedonia are common. Assessment should include the relationship between mood and 'on–off' motor fluctuations [Witjas *et al.* 2002] since such fluctuant dysphoria may respond to a review of dopaminergic therapy.

A wide range of assessment tools have been used in evaluating depression in PD but none were specifically developed for PD. Self-rating scales which may be used include the Beck Depression Inventory [Visser *et al.* 2006], the Hospital Anxiety and Depression Scale [Mondolo *et al.* 2006], and the Geriatric Depression Scale [Weintraub *et al.* 2007; McDonald *et al.* 2006]. The Hamilton Depression Rating Scale (HAM-D) [Dissanyaka *et al.* 2007] and the Montgomery–Asberg Depression Rating Scale (MADRS) are clinician-rated scales which may be used for screening and assessment of severity [Marsh *et al.* 2006], but a structured interview involving relatives and carers is the gold standard for diagnosis [Scottish Intercollegiate Guidelines Network, 2010]. Provisional diagnostic criteria based on the DSM IV criteria are available [Marsh *et al.* 2006], but the construct of depression in PD is the subject of an ongoing study of mood states in PD [PD PROMS study, 2010].

There is a lack of robust evidence for the treatment of depression in PD and firm recommendations on drug therapy cannot be made. Treatment effects may be less than in elderly depressed patients without PD [Weintraub *et al.* 2005]. In clinical practice many clinicians use SSRI drugs because of their good tolerability although tremor, akathisia and Parkinsonism may be worsened. Citalopram has shown some efficacy, albeit less than desipramine in a short-term controlled trial [Devos *et al.* 2008], but more recently nortriptyline demonstrated efficacy in PD depression while controlled-release paroxetine did not [Menza *et al.* 2009]. In patients receiving a monoamine oxidase (MAO)-B inhibitor (such as selegiline) caution is needed with SSRI drugs because of a potential, but rare interaction that can precipitate serotonin syndrome

[Richard *et al.* 1997]. This is characterized by the sudden onset of cognitive and behavioural changes, autonomic instability, and neuromuscular changes such as myoclonus, hyperreflexia, rigidity and trismus [Kipps *et al.* 2005].

Although the best evidence for treatment of depression in PD is for tricyclic antidepressants [Devos *et al.* 2008; Miyasaki *et al.* 2006], this is in the context of short-term trials and relatively common adverse effects which may worsen or precipitate NMS such as constipation and confusion. Mirtazapine is a presynaptic alpha-2-adrenoceptor antagonist which is increasingly used in clinical practice to treat depression in PD. Other agents which may be employed include tricyclic-related drugs (trazodone), the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine and the selective norardrenaline reuptake inhibitor, reboxetine [Aarsland *et al.* 2009a].

Recently, a double-blind controlled trial has suggested that the dopamine agonist pramipexole may improve depressive symptoms in PD, largely independently of improvements in motor disability, perhaps through adjunctive effects on noradrenergic and serotonergic function [Barone *et al.* 2010]. Electroconvulsive therapy has been employed in refractory depression in PD often with concurrent motor improvements [Moellentine *et al.* 1998].

Psychosis

Psychosis is one of the key neuropsychiatric features of PD [Hely *et al.* 2005] and florid persistent expression in later disease is strongly correlated with the need for nursing home placement [Goetz and Stebbins, 1993] as well as increased mortality in such patients [Goetz and Stebbins, 1995]. Symptoms can range from relatively mild visual hallucinations, illusions or 'sense of presence' (where the patient retains insight and often finds them less troublesome than carers and relatives) to frank paranoia and delusions which are often persecutory or accusatory in nature. Auditory and tactile hallucinations are less common [Aarsland *et al.* 2009a]. Psychotic symptoms are probably primarily related to underlying progressive neurodegeneration and neuronal dysfunction [Kulisevsky *et al.* 2008; Williams and Lees, 2005] but can be precipitated by dopaminergic therapy. Psychosis affects up to 60% of patients and is more common in older onset PD with cognitive impairment, and REM sleep behaviour disorder [Forsaa *et al.* 2010]. Psychosis is more likely to be associated with dopamine agonist therapy than levodopa and is associated with dementia and a more aggressive course of PD [Forsaa *et al.* 2010].

Assessment should include a general medical and medication review to determine any reversible organic causes of psychosis. If psychosis persists once secondary causes are excluded dopaminergic therapy should be reduced by withdrawing nonessential dopaminergic treatments such as anticholinergics and amantadine. Gradual withdrawal is essential due to the risk of precipitating a neuroleptic malignant-like syndrome with hyperpyrexia, autonomic dysfunction, alteration in mental status, rhabdomyolysis and renal failure. This is now more correctly called Parkinsonism hyperpyrexia syndrome [Kipps *et al.* 2005].

If symptoms of psychosis fail to resolve with the above measures, MAO-B inhibitors, dopamine agonists and catechol-O-methyltransferase (COMT) inhibitor drugs should generally be withdrawn next but it is important to consider the temporal relationship of a recently introduced drug or dose titration to the emergence of psychosis. While such therapy changes may reduce psychotic symptoms, this may be at the expense of worsening Parkinsonism and a balance between good motor control and a clear sensorium may be difficult to attain.

Mild psychotic symptoms do not necessarily require treatment if they do not cause the patient any distress. Where treatment is indicated typical antipsychotics such as haloperidol should not be used. The best evidence for treating psychosis in PD is for low-dose clozapine [Freiling *et al.* 2007; Merims *et al.* 2006]. This has been shown to be effective in reducing psychotic symptoms without exacerbating PD but intensive monitoring is required to detect the potential side effect of agranulocytosis [Iqbal *et al.* 2003]. Where weekly monitoring of blood count is not possible quetiapine is often used in low dosage in clinical practice but strong evidence for efficacy is lacking [Scottish Intercollegiate Guidelines Network, 2010; Ondo *et al.* 2005]. Olanzapine is not helpful and worsens motor symptoms [Goetz *et al.* 2000].

Cognitive impairment and dementia

Cognitive impairment is common in PD even from the early stages. Specific deficits include set switching difficulty, impaired executive function and reduced verbal fluency and visuospatial abilities [Aarsland *et al.* 2009a]. Many patients with mild cognitive deficit will develop dementia as the disease progresses and the point prevalence overall in PD is around 30% with the incidence rate increased four to six times as compared with controls [Aarsland and Kurtz, 2010]. In the Sydney cohort follow-up study, 83% of the survivors were diagnosed with dementia at 20 years [Hely *et al.* 2008]. Established risk factors for early dementia are old age, severity of motor symptoms (in particular, postural and gait disturbances), mild cognitive impairment and visual hallucinations [Aarsland and Kurz, 2010]. Genetic factors may also be pertinent. The CamPaIGN longitudinal study of cognitive impairment and dementia [Williams-Gray *et al.* 2009] recently reported that age >72 years, reduced semantic fluency and inability to copy an intersecting pentagons figure, were significant predictors of dementia at 5 years. The microtubule-associated protein tau (MAPT) H1/H1 genotype was associated with increased risk of dementia at 5 years with functional effects on tau transcription. In contrast, COMT genotype had no effect on dementia but was associated with effects on frontostriatal function which may have a more dopaminergic basis and better prognosis.

If dementia develops more than 1 year after the onset of the motor features of PD it is usually referred to as PD with dementia (PDD). Those who develop dementia within 1 year of the onset of Parkinsonian features are classified as dementia with Lewy bodies (DLB). This is an arbitrary division and in clinical practice, the distinction between the two is often difficult and they are usually now considered as part of a spectrum of Lewy body disorders [Aarsland *et al.* 2009a].

Organic causes of delirium must be excluded prior to diagnosing dementia. It is particularly important to look for co-existing depression which may cause a 'pseudo dementia'. A variety of cognitive assessments may be utilised in the assessment of dementia. The MDS task force has published two papers on diagnosis of dementia [Dubois *et al.* 2007; Emre *et al.* 2007], the second of which recommends two levels of assessment. The first level incorporates the Mini Mental State Examination (MMSE) test and does not require knowledge of detailed neuropsychological testing. However, the MMSE test is insensitive to many aspects of cognitive impairment in PD. Recently the Montreal Cognitive Assessment (MOCA) has been shown to be more sensitive [Zadikoff *et al.* 2008] and deploys a battery of tests to assess executive function, higher-level language abilities, memory, and complex visuospatial processing in PD.

All patients should have a thorough medication review and consideration given to gradual and slow withdrawal of dopamine agonists, anticholinergics, amantadine and selegiline where appropriate as these drugs may exacerbate cognitive problems.

There is evidence to suggest that there is a cholinergic deficit in PD which may be greater than that in Alzheimer's disease [Bohnen *et al.* 2003]. Accordingly cholinesterase inhibitor drugs may be an appropriate therapy in treating cognitive decline. The current evidence suggests cholinesterase inhibitors may be effective in treating mild to moderate dementia in PD particularly in those with visual hallucinations, behavioural disorders and psychosis [Burn *et al.* 2006; Aarsland *et al.* 2004]. Not all patients benefit and a significant number of patients experience side effects such as tremor or vomiting necessitating dose reduction or withdrawal. The best evidence is for rivastigmine [Emre *et al.* 2004] which is the only licensed therapy in the UK, although donepezil has also been partially effective in small randomized controlled studies [Ravina *et al.* 2005; Leroi *et al.* 2004].

Glutamatergic overactivity may also play a part in cognitive decline in PD. Memantine is a low affinity N-methyl D-aspartate (NMDA) antagonist drug which has shown promise in the treatment of PD dementia in a short-term study [Aarsland *et al.* 2009b].

Impulse control disorder and dopamine dysregulation syndrome

A wide range of impulsive and compulsive behaviours such as pathological gambling, hypersexuality, compulsive shopping and binge eating likened to behavioural addictions have been reported in PD patients in the last decade [Stamey and Jankovic, 2008; Weintraub and Potenza, 2006] and are usually triggered by

dopaminergic therapy particularly dopamine agonists [MacMahon and Macphee, 2008; Grosset *et al.* 2006]. Repetitive purposeless behaviours known as 'punding' or excess hobby-ism are also recognized. These behaviours may affect up to 14% of patients [Weintraub *et al.* 2010] and are often covert and undeclared to family members and health professionals [Grosset *et al.* 2006]. The recent SIGN guideline [Grosset *et al.* 2010] highlights the need to warn patients and families of these iatrogenic NMS prior to initiation of therapy. Practitioners need to remain vigilant throughout the treatment course as these features may emerge some time after the introduction of treatment. Optimal management remains uncertain but reduction or withdrawal of dopamine agonists with a shift to levodopa-based therapy is associated with improvement in the majority, but not all cases [Macphee *et al.* 2009; Mamikonyan *et al.* 2008].

Dopamine dysregulation syndrome (DDS) is a related disorder akin to a substance addiction when patients escalate their treatment with levodopa beyond that needed for motor control [Evans and Lees, 2004]. Appetitive behaviours such as pathological gambling and hypersexuality may emerge in DDS with significant psychoso-cial, legal and financial consequences. Management is taxing since attempts to reduce therapy may lead to dysphoria, pain and anxiety in the absence of 'off' period motor disability. Atypical antipsychotic drugs and psychological input may be necessary to control distressing behaviour [Galpern and Stacy, 2007].

Sleep disorders
Sleep disorders are common in PD affecting 60% of patients compared with 33% of controls and 45% of people with diabetes mellitus [Tandberg *et al.* 1998]. Several tools have been validated as bedside tools including the 'scales for outcomes in PD — sleep' (SCOPA-sleep) and the Parkinson's disease Sleep scale (PDSS) [Martinez- Martin *et al.* 2008]. The Epworth sleep scale (ESS) is a generic instrument which scores the propensity to fall asleep in everyday situations [Johns, 1991]. In any sleep disorder in PD, a thorough sleep history should be mandatory and advice on good sleep hygiene given [Reading, 2007]. Polysomnography and multiple sleep latency tests are gold standard diagnostic evaluations [Dhawan *et al.* 2006] although in the majority of sleep disorders may

not add significant diagnostic information [Reading, 2007].

Excessive daytime somnolence
The aetiology of excessive daytime somnolence (EDS) is usually multifactorial and may be secondary to the disease process, dopaminergic medications or any of the other sleep disorders [Gjerstad, 2006]. EDS is often an intrinsic feature of the disease with genetic propensity [Arnulf, 2005] and is associated with cognitive impairment in the later stages of PD.

Treatment should focus on improving nocturnal sleep quality and finding any reversible causes such as depression, poor sleep hygiene or sedative medication. Obstructive sleep apnoea may also be relatively common as a cause of EDS in PD [Arnulf, 2005]. Sudden onset of sleep 'attacks' have been reported as a 'narcolepsy like' pheno-type [Arnulf *et al.* 2002] in patients receiving dopamine agonist drugs and specific warnings on driving and operating machinery should be given to patients at initiation and during dose titration [Grosset *et al.* 2010].

Modafinil is used in the treatment of narcolepsy and has been shown to be effective in improving patients' perception of wakefulness in PD [Ondo *et al.* 2005; Adler *et al.* 2003], but lacks evidence of objective improvements [Zesiewicz *et al.* 2010]. The European Medicines Agency recently completed a review of the safety and effectiveness of modafinil in July 2010 [European Medicines Agency, 2010] and concluded that because of adverse effects this agent should only be used in the treatment of narcolepsy. Owing to the lack of robust evidence of objective improvements in wakefulness, modafanil and melatonin (as described later) are not currently recom-mended in the latest UK guideline [Scottish Intercollegiate Guidelines Network, 2010].

Insomnia
Insomnia may be secondary to difficulty in falling asleep or in maintaining sleep. The latter is often affected by nocturnal akinesia (inability to turn over), 'wearing-off' overnight resulting in re-emergence of motor symptoms, pain and stiffness and nocturia [Dhawan *et al.* 2006]. Levodopa is effective in reducing sleep-associated motor symptoms although data on improvements in objective sleep parameters is lacking [Zesiewicz *et al.* 2010]. There is insufficient evidence on the use of controlled-release

levodopa preparations or the addition of COMT inhibitors to treat nocturnal akinesia, but they may be of benefit [Dhawan *et al.* 2006]. Melatonin has been suggested due to its effects on modulating the sleep–wake cycle but evidence is limited [Medeiros *et al.* 2007; Dowling *et al.* 2005]. Other approaches include long-acting oral dopamine agonist drugs such as modified release once-daily ropinirole [Pahwa *et al.* 2007] or prolonged-release pramipexole or use of rotigotine delivered via a transdermal patch [Le Witt *et al.* 2007; Poewe *et al.* 2007] or continuous infusion of the parenteral dopamine agonist, apomorphine [Gancher *et al.* 1995]. Cabergoline is also an effective long-acting dopamine agonist drug [Hogl *et al.* 2003] but is now a second-line agent because of concerns regarding pulmonary and valvular fibrosis [Committee on Safety of Medicines and Medicines Control Agency, 2002].

Restless legs syndrome and periodic limb movements of sleep

Restless legs syndrome (RLS) may affect 20% of patients with PD [Ondo *et al.* 2002]. The dopamine agonist drugs pramipexole and ropinirole are used in the management of RLS in the general population but there is a paucity of controlled trial evidence of efficacy in the context of PD. Levodopa has been shown to decrease spontaneous movements in bed and may be of benefit in patients with periodic limb movements of sleep (PLMS) [Leeman *et al.* 1987].

RBD

RBD is characterized by the absence of atony during REM sleep allowing patients to act out their dreams which are often vivid and frightening in nature. The disorder can be a precursor for the development of PD and may antedate the motor symptoms for many years [Schenck *et al.* 1996]. It is important to differentiate RBD from vivid dreams and hallucinations caused by dopaminergic therapy. The most effective treatment for RBD is clonazepam [Schenck and Mahowald, 2002] which has been described as the 'steroid' of sleep disorder [Reading, 2007]. Caution is necessary with this drug if sleep apnoea is suspected. Other treatments such as melatonin and pramipexole have limited study evidence [Schmidt *et al.* 2006; Boeve *et al.* 2003].

Autonomic dysfunction

Orthostatic hypotension

Orthostatic hypotension (OH) occurs in around 50% of people with PD associated with central and peripheral autonomic disturbance [Allcock, 2010; Allcock *et al.* 2003] as well as a side effect of dopaminergic therapy. It may be a cause of falls and fatigue but is frequently asymptomatic, perhaps because of the association with cognitive decline [Allcock *et al.* 2006]. If OH is a prominent feature early in the disease a diagnosis of multisystem atrophy should be considered [Chaudhuri, 2001].

Efforts should be made to reduce or eliminate antihypertensive medications and patients should be advised to keep well hydrated. Raising the head of the bed to 30–40°, and using elastic stockings may be helpful. Domperidone is a D2 receptor agonist often used along with dopaminergic therapies in patients with OH and is thought to work by modulating noradrenaline release peripherally [Schoffer *et al.* 2007]. Salt-retaining steroids such as fludrocortisone [Schoffer *et al.* 2007] the sympathomimetic midodrine (currently unlicensed in the UK) [Low *et al.* 1997] and indomethacin [Abate *et al.* 1979] have also been used with some success in small clinical trials. There is currently insufficient evidence to recommend these medications [Scottish Intercollegiate Guidelines Network, 2010; Zesiewicz *et al.* 2010] but they are commonly used in practice. Pyridostigmine and octreotide are other potential therapeutic agents [Allcock, 2010]. L-threo-DOPS (Droxidopa) is a synthetic precursor of norepinephrine approved by the FDA in the USA to treat OH [Zesiewicz *et al.* 2010].

Gastrointestinal dysfunction

Dysphagia is common in the later stages of PD and is associated with silent aspiration and recurrent lower respiratory tract infections [Pfeiffer, 2003]. All patients with suspected swallowing difficulties should be referred to a speech and language therapist (SLT) for further assessment.

Constipation and problems with complete evacuation affects at least 50% of patients with PD [Martinez-Martin *et al.* 2007] and is due to loss of central and colonic dopaminergic neurons prolonging bowel transit time [Pfeiffer, 2003]. Ensuring optimal fluid intake, fibre supplements

and increasing exercise may be of benefit. Stool softeners such as docusate and osmotic laxatives (lactulose) may be employed but polyethylene glycol solution available in the UK as Movicol® is usually the most effective agent [Zangaglia *et al.* 2007]. An important clinical observation is that treatment of constipation often ameliorates PD symptoms perhaps by improving drug delivery in the upper gastrointestinal tract through a gastrocolic reflex [Stocchi, 2009]

The subcutaneous dopamine agonist apomorphine may improve anorectal dysfunction and bladder dysfunction [Christmas *et al.* 1988]. Botulinum toxin has been used to improve outlet obstruction in PD but with inconclusive results [Albanese *et al.* 2003]. Intrajejunal levodopa/carbidopa gel infusion (Duodopa) is a relatively new but expensive delivery system which aims to provides continuous dopaminergic stimulation. This method has been reported to improve constipation and other NMS including sleep, fatigue, attention, memory, urinary and pain problems in an open study [Honig *et al.* 2009]. The relative benefits of apomorphine, duodopa and deep brain stimulation (DBS) in advanced PD have recently been reviewed and the absence of direct comparative trials highlighted [Clarke *et al.* 2009].

Sialorrhoea
Drooling of saliva is a distressing and embarrassing symptom for patients and family. All patients should have optimization of dopaminergic therapy, SLT assessment and review of swallowing ability with advice on regular swallowing and auditory cueing devices if required. If these measures fail to control symptoms, further options include anticholinergic drugs but these are limited by their potential to cause adverse effects particularly confusion. Glycopyrrolate has been suggested as a preferable option because of its inability to cross the blood–brain barrier [Chou *et al.* 2006] and scopolamine transdermal patches are used successfully in clinical practice. Sublingual 1% atropine solution twice daily is suggested in the NICE guideline [National Institute for Health and Clinical Excellence, 2006]. Injection of salivary glands with botulinum toxin A may be considered [Sullivan *et al.* 2000] although this is a more invasive and unlicensed indication. Further studies on clinimetric evaluation of scales and management of drooling of saliva in PD are required. See the full review by Chou and colleagues for more details [Chou *et al.* 2006].

Urinary dysfunction
Bladder dysfunction is common in PD [Winge and Fowler, 2006]. Nocturia is the commonest early symptom, although daytime urgency and frequency with incontinence may emerge. Most commonly the pathophysiology is related to detrusor hyperreflexia due to disinhibition of the pontomesencephalic micturition centre. Antimuscarinics such as oxybutinin, propiverine, solifenacin and tolterodine [Andersson, 2004] are used in the general population for overactive bladder syndrome (OAB) and although evidence is lacking in PD their mode of action and widespread use supports a benefit. Caution is necessary because of the potential of these drugs to cause confusion. Drugs with less propensity to cross the blood–brain barrier such as trospium chloride and tolterodine may be preferable [Winge and Fowler, 2006, Andersson, 2004], although robust evidence is lacking. Desmopressin has been reported to ameliorate nocturia [Suchowersky *et al.* 1995].

Many patients, particularly men, may have concurrent obstructive symptoms and a postresidual micturition volume measure and exclusion of infection should be undertaken before commencing these agents. In complex cases particularly where there is consideration of multiple system atrophy as the pathological correlate, urodynamic studies are warranted [Winge and Fowler, 2006].

Sexual dysfunction
Sexual dysfunction in PD may arise through complex and interacting physical, psychological and social factors [Brown *et al.* 1990]. Erectile dysfunction affects 60–70% of men with PD [Papatsoris *et al.* 2006] and may be treated with phosphodiesterase inhibitors such as sildenafil (after screening for other medical causes and excluding any contraindications) [Hussain *et al.* 2001; Zesiewicz *et al.* 2000]. If this proves unsuccessful a referral to urology should be considered. In women difficulties are often encountered with arousal, low sexual desire and anorgasmia. Dopamine agonists may improve libido and function [Pohanka *et al.* 2005] but may also trigger hypersexuality and other impulse control problems [Weintraub *et al.* 2010; Evans and Lees, 2004].

Pain

Pain is common in PD and affects up to 40% of patients [Ford, 1998]. At least five distinct types of pain have been described with pain secondary to dystonia and dyskinesia being the most common [Ford, 2010]. Oral (burning mouth) and genital pain may also occur as a primary sensory disturbance in PD [Ford *et al*. 1996]. Patients with orthostatic hypotension may complain of pain in a 'coat-hanger' distribution over the shoulders and neck.

Although primary central causes of pain are less common studies have shown a reduction in pain threshold [Djaljetti *et al*. 2004] and altered spinal nociception in patients with PD [Mylius *et al*. 2009]. The substantia nigra has been found to modulate impending pain within the dorsal horn of the spinal cord, which is probably mediated by dopaminergic descending inhibitory pathways originating in the midbrain. Disruption of these inhibitory pathways may be responsible for the increased spinal nociception and hence decreased pain thresholds in PD [Mylius *et al*. 2009].

The assessment of pain in PD should include its relation to motor fluctuations as well as a screen for other musculoskeletal pathologies such as osteoporosis, arthritic changes and contractures. Pain associated with 'off' motor fluctuations often responds to modification of dopaminergic therapy. In addition to simple analgesia multidisciplinary input from physiotherapy and occupational therapy is often beneficial for musculoskeletal pain. Table 2 summarizes the types of pain found in PD together with potential management approaches although robust outcome evidence is lacking.

Effects of surgery on NMS

DBS of the subthalamic nucleus (STN) is an effective treatment for motor symptoms not controlled by medical therapy in advanced PD [Krack *et al*. 2003]. STN-DBS has been associated with improvements in sleep architecture [Monaca *et al*. 2004; Iranzo *et al*. 2002], urodynamics [Seif *et al*. 2004], constipation [Zibetti *et al*. 2007] and also nonmotor fluctuations particularly sensory, dysautonomic and cognitive fluctuations [Witjas *et al*. 2007]. There has been concern regarding the effect of DBS on global cognition but any deterioration appears modest in very carefully selected patients [Witt *et al*. 2008]. The most common complications are decreased verbal fluency and mild impairments in executive function and memory [Witt *et al*. 2008; Parsons *et al*. 2006]. The effect of STN-DBS on neurobehavioural symptoms is more contentious with both improvements and deleterious effects reported on depression, anxiety, apathy, impulse control disorder and dopamine dysregulation syndrome [Voon *et al*. 2006; Burn and Troster 2004; Houeto *et al*. 2002]. Suicide and suicidal ideation have been reported postoperatively in case reports. Factors influencing the outcome of surgery include presurgical comorbidities, e.g. cognitive impairment, psychiatric or personality disorder, surgical issues such as target selection (Globus pallidus *versus* subthalamic nucleus) and postoperative management, as well as psychosocial adjustment to a major life event and natural disease progression. A full discussion of the effects of DBS on NMS is outside the scope of this contribution: Lim and colleagues provide a full review [Lim *et al*. 2009b].

Conclusions

NMS are common, complex and challenging symptoms to treat in PD. They are often poorly recognized by professionals and are often undeclared by patients. Recognition of NMS using validated screening tools such as the NMS QUEST followed by more detailed assessment and management of individual problems utilising a multidisciplinary approach will improve the quality of life for people living with PD and reduce misdiagnosis and delays in treatment. There is an urgent need to develop better treatments for many NMS particularly those that may have a nondopaminergic basis.

Conflict of interest statement

Graeme J.A. Macphee was an Academic Advisor to the international PD Non Motor group which developed the NMS QUEST and NMS Scale. He has participated in advisory boards for GSK, Boehringer Ingelheim, Teva/Lundbeck, Merck Serono, Solvay and UCB and has received honoraria from Genus and Orion.

References

Aarsland, D. and Kurtz, M.W. (2010) The epidemiology of dementia associated with Parkinson's disease. *J Neurol Sci* 289: 18–22.

Aarsland, D., Ballard, C., Walker, Z., Bostrom, F., Alves, G., Kossakowski, K. *et al.* (2009b) Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double blind, multicenter trial. *Lancet Neurol* 8: 613–618.

Aarsland, D., Larsen, J., Tandberg, E. and Laake, K. (2000) Predictors of nursing home placement in Parkinson's disease: a population based, prospective study. *J Am Geriatr Soc* 48: 938–942.

Aarsland, D., Marsh, L. and Schrag, A. (2009a) Neuropsychiatric symptoms in Parkinson's disease. *Mov Disord* 24: 2175–2186.

Aarsland, D., Mosimann, U.P. and McKeith, I.G. (2004) Role of cholinesterase inhibitors in Parkinson's disease and dementia with Lewy bodies. *J Geriatr Psychiatry Neurol* 17: 164–171.

Abate, G., Polimeni, R.M., Cuccurullo, F., Puddu, P. and Lenzi, S. (1979) Effects of indomethacin on postural hypotension in Parkinsonism. *BMJ* 2: 1466–1468.

Abbott, R.D., Petrovitch, H., White, L.R., Masaki, K.H., Tanner, C.M., Curb, J.D. *et al.* (2001) Frequency of bowel movements and the future risk of Parkinson's disease. *Neurology* 57: 456–462.

Adler, C.H., Caviness, J.N., Hentz, J.G., Lind, M. and Tiede, J. (2003) Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Mov Disord* 18: 287–293.

Albanese, A., Brisinda, G., Bentivoglio, A.R. and Maria, G. (2003) Treatment of outlet obstruction constipation in Parkinson's disease with botulinum neurotoxin A. *Am J Gastroenterol* 98: 1439–1440.

Allcock, L. (2010) Orthostatic hypotension in Parkinsons disease. *ACNR* 10: 51–52.

Allcock, L.M., Kenny, R.A., Mosimann, U.P., Tordoff, S., Wesnes, K.A., Hildreth, A.J. *et al.* (2006) Orthostatic hypotension in Parkinson's disease: association with cognitive decline? *Int J Geriatric Psychiatry* 21: 778–783.

Allcock, L.M., Ullyart, K., Kenny, R. and Burn, D.J. (2003) Frequency of orthostatic hypotension in a community acquired cohort of patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 75: 1470–1471.

Andersson, K.E. (2004) Antimuscarinics for treatment of overactive bladder. *Lancet Neurol* 3: 46–53.

Arnulf, I. (2005) Excessive daytime sleepiness in Parkinsonism. *Sleep Med Rev* 9: 185–200.

Arnulf, I., Konofal, E., Merino-Andreu, M., Houeto, J., Mesnage, V., Welter, M. *et al.* (2002) Parkinson's disease and sleepiness: an integral part of PD. *Neurology* 58: 1019–1024.

Barone, P., Antonini, A., Colosimo, C., Marconi, R., Morgante, L., Avarello, T.P. *et al.* (2009) The Priamo Study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord* 24: 1641–1649.

Barone, P., Poewe, W., Albrecht, S., Debieuvre, C., Massey, D., Rascol, O. *et al.* (2010) Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo controlled trial. *Lancet Neurol* 9: 573–580.

Boeve, B.F., Silber, M.H. and Ferman, T.J. (2003) Melatonin for treatment of REM sleep behaviour in neurological disorders: results in 14 patients. *Sleep Med* 4: 281–284.

Bohnen, N.I., Kaufer, D.I., Ivanco, L.S., Lopresti, B., Koeppe, R.A., Davis, J.G. *et al.* (2003) Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. *Arch Neurol* 60: 1745–1748.

Braak, H., Del Tredici, K., Rub, U., de Vos, R.A., Jansen Steur, E.N. and Braak, E. (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 24: 197–211.

Braak, H., Rüb, U., Jansen Steur, E.N.H., Del Tredici, K. and de Vos, R.A. (2005) Cognitive status correlates with neuropathologic stage in Parkinson disease. *Neurology* 64: 1404–1410.

Brown, R. and Jahanshahi, M. (1995) Depression in Parkinson's disease: a psychosocial viewpoint, In: Weiner, W.J. and Lang, A.E. (eds). Behavioral neurology of movement disorders, Vol. 65, Raven Press: New York, pp. 61–84.

Brown, R.G., Jahanshahi, M., Quinn, N. and Marsden, C.D. (1990) Sexual function in patients with Parkinson's disease and their partners. *J Neurol Neurosurg Psychiatry* 53: 480–486.

Burn, D., Emre, M., McKeith, I., De Deyn, P.P., Aarsland, D., Hsu, C. *et al.* (2006) Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease. *Mov Disord* 21: 1899–1907.

Burn, D.J. and Troster, A.I. (2004) Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *J Geriatr Psychiatry Neurol* 17: 172–180.

Campbell, J.J. and Duffy, J.D. (1997) Treatment strategies in amotivated patients. *Psychiatr Ann* 27: 44–49.

Chaudhuri, K.R. (2001) Autonomic dysfunction in movement disorders. *Curr Opin Neurol* 14: 505–511.

Chaudhuri, K.R., Healy, D.G. and Schapira, A. (2006a) Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol* 5: 235–245.

Chaudhuri, K.R., Martinez-Martin, P., Brown, R.G., Sethi, K., Stocchi, F., Odin, P. *et al.* (2007) The metric

properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. *Mov Disord* 22: 1901–1911.

Chaudhuri, K.R., Martinez-Martin, P., Schapira, A., Stocchi, F., Sethi, K., Odin, P. *et al.* (2006b) An international multicentre pilot study of the first comprehensive self-completed non-motor symptoms questionnaire for Parkinson's disease: the NMSQuest study. *Mov Disord* 21: 916–923.

Chaudhuri, K.R., Prieto-Jurcynska, C., Naidu, Y., Mitra, T., Frades-Payo, B., Tluk, S. *et al.* (2010) The nondeclaration of nonmotor symptoms of Parkinson's Disease to health care professionals: an international study using the nonmotor symptoms questionnaire. *Mov Disord* 25: 704–709.

Chaudhuri, K.R. and Schapira, A.V.H. (2009) Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* 8: 464–474.

Chou, K.L., Evatt, M., Hinson, V. and Kompoliti, K. (2006) Sialorrhea in Parkinson's disease: A review. *Mov Disord* 22: 2306–2313.

Christmas, T.J., Kempster, P.A., Chapple, C.R., Frankel, J.P., Lees, A.J., Stern, G.M. *et al.* (1988) Role of subcutaneous apomorphine in Parkinsonian voiding dysfunction. *Lancet* 2: 1451–1453.

Clarke, C., Worth, P., Grosset, D. and Stewart, D. (2009) Systematic review of apomorphine infusion, levodopa infusion and deep brain stimulation in advanced Parkinson disease. *Parkinsonism Related Disord* 15: 728–741.

Committee on Safety of Medicines and Medicines Control Agency (2002) Fibrotic reactions with pergolide and other ergot-derived dopamine receptor agonists. *Curr Prob Pharmacovigil* 28: 1–6.

Devos, D., Dujardin, K., Poirot, I., Moreau, C., Cottenan, O., Thomas, P. *et al.* (2008) Comparison of desipramine and citalopram treatments for depression in Parkinson's Disease: a double blind, randomised, placebo controlled study. *Mov Disord* 23: 850–857.

Dhawan, V., Healy, D.G., Pal, S. and Chaudhuri, K.R. (2006) Sleep-related problems of Parkinson's disease. *Age Ageing* 35: 220–228.

Dissanayaka, N.N., Sellbach, A., Matheson, S., Marsh, R., Silburn, P.A., O'Sullivan, J.D. *et al.* (2007) Validity of Hamilton Depression Inventory in Parkinson's disease. *Mov Disord* 22: 399–403.

Djaldetti, R., Shifrin, A., Rogowski, Z., Sprecher, E., Melamed, E. and Yarnitsky, D. (2004) Quantitative measurement of pain sensation in patients with Parkinson disease. *Neurology* 62: 2171–2175.

Dowling, G.A., Mastick, J., Colling, E., Carter, J.H., Singer, C.M. and Aminoff, M.J. (2005) Melatonin for sleep disturbances in Parkinson's disease. *Sleep Med* 6: 459–466.

Dubois, B., Burn, D., Goetz, C., Aarsland, D., Brown, R., Broe, G.A. *et al.* (2007) Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. *Mov Disord* 22: 2314–2324.

Emre, M., Aarsland, D., Albanese, A., Byrne, E.J., Deuschl, G., De Deyn, P.P. *et al.* (2004) Rivastigmine for dementia associated with Parkinson's Disease. *N Engl J Med* 351: 2509–2518.

Emre, M., Aarsland, D., Brown, R., Burn, D.J., Duyckaerts, C., Mizuno, Y. *et al.* (2007) Clinical and diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord* 22: 1689–1707.

Evans, A. and Lees, A.J. (2004) Dopamine dysregulation syndrome in Parkinson's Disease. *Curr Opin Neurol* 17: 393–398.

European Medicines Agency (2010) http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Modafinil/human_referral_000236.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580024e9a (accessed 27 August 2010).

Findley, L., Aujla, M.A., Bain, P.G., Baker, M., Beech, C., Bowman, C. *et al.* (2003) Direct economic impact of Parkinson's disease: a research survey in the United Kingdom. *Mov Disord* 18: 1139–1455.

Ford, B. (1998) Pain in Parkinson's Disease. *Clin Neurosci* 5: 63–72.

Ford, B. (2010) Pain in Parkinson's disease. *Mov Disord* 25: 98–103.

Ford, B., Louise, P., Greene, P. and Fahn, S. (1996) Oral and genital pain syndromes in Parkinson's disease. *Mov Disord* 11: 421–426.

Forno, L.S. (1982) Pathology of Parkinson's disease, In: Marsden, C.D. and Fahn, S. (eds). Movement Disorders, Butterworth Scientific: London, pp. 25–40.

Forsaa, E., Larsen, J.P., Wentzel- Larsen, T., Goetz, C.G., Stebbins, G.T., Aarsland, D. *et al.* (2010) A 12 year based prospective study of psychosis in Parkinsons disease. *Arch Neurol* 67: 996–1001.

Frieling, H., Hillemacher, T., Ziegenbein, M., Neundorfer, B. and Bleich, S. (2007) Treating dopamimetic psychosis in Parkinson's disease: Structured review and meta-analysis. *Eur Neuropsychopharmacol* 17: 165–171.

Galpern, W.R. and Stacy, M. (2007) Management of impulse control disorders in Parkinson's disease. *Curr Treat Options Neurol* 9: 189–197.

Gancher, S.T., Nutt, J.G. and Woodward, W.R. (1995) Apomorphine infusional therapy in Parkinson's disease: clinical utility and lack of tolerance. *Mov Disord* 10: 37–43.

Gibb, W.R.G. and Lees, A.J. (1988) The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 51: 745–752.

Gjerstad, M. (2006) Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? *Neurology* 67: 853–858.

Goetz, C.G., Blasucci, L.M., Leyrgans, S. and Pappert, E.J. (2000) Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. *Neurology* 55: 789–794.

Goetz, C.G. and Stebbins, G.T. (1993) Risk factors for nursing home placement in advanced Parkinson's disease. *Neurology* 43: 2227–2229.

Goetz, C.G. and Stebbins, G.T. (1995) Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. *Neurology* 45: 669–671.

Goetz, C.G., Tilley, B.C., Shaftman, S.R., Stebbins, G.T., Fahn, S., Martinez-Martin, P. *et al.* (2008) Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Scale presentation and clinimetric testing results. *Mov Disord* 23: 2129–2170.

Grosset, D.G., Macphee, G.J.A. and Nairn, M. (2010) Diagnosis and pharmacological management of Parkinson's disease: summary of SIGN guidelines. *BMJ* 340: b5614.

Grosset, K.A., Macphee, G., Pal, G., Stewart, D., Watt, A., Davie, J. *et al.* (2006) Problematic gambling on dopamine agonists: Not such a rarity. *Mov Disord* 21: 2206–2208.

Hely, M.A., Morris, J.G.L., Reid, W.G.J. and Trafficante, R. (2005) Sydney Multicenter study of Parkinson's disease: Non-L-Dopa-responsive problems dominate at 15 years. *Mov Disord* 20: 190–199.

Hely, M.A., Reid, W.G., Adena, M.A., Halliday, G.M. and Morris, J.G. (2008) The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord* 23: 837–844.

Hogl, B., Rothdach, A., Wetter, T.C. and Trenkwalder, C. (2003) The effect of cabergoline on sleep, periodic leg movements in sleep, and early morning motor function in patients with Parkinson's disease. *Neuropsychopharmacology* 28: 1866–1870.

Honig, H., Antonini, A., Martinez-Martin, P., Forgacs, I., Faye, G.C., Fox, T. *et al.* (2009) Intrajejunal levodopa infusion in Parkinson's disease: A pilot multicenter study of effects on nonmotor symptoms and quality of life. *Mov Disord* 24: 1468–1474.

Houeto, J.L., Mesnage, V., Mallet, L., Pillon, B., Gargiulo, M., du Moncelet. *et al.* (2002) Behavioural disorders, Parkinson's disease and subthalamic stimulation. *J Neurol Neurosurg Psychiatry* 72: 701–707.

Hussain, I.F., Brady, C.M., Swinn, M.J., Mathias, C.J. and Fowler, C.J. (2001) 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* 71: 371–374.

Iranzo, A., Valldeoriola, F., Santamaría, J., Tolosa, E. and Rumia, J. (2002) Sleep symptoms and polysomnographic architecture in advanced Parkinson's disease after chronic bilateral subthalamic stimulation. *J Neurol Neurosurg Psychiatry* 72: 661–664.

Iqbal, M.M., Rahman, A., Husain, Z., Mahmid, S.Z., Ryan, W.G. and Feldman, J.M. (2003) Clozapine: a clinical review of adverse effects and management. *Ann Clin Psychiatry* 15: 33–48.

Ishihara, L. and Brayne, C. (2006) A systematic review of depression and mental illness preceding Parkinson's disease. *Acta Neurol Scand* 113: 211–220.

Johns, M.W. (1991) A new method for measuring daytime sleepiness: The Epworth Sleepiness scale. *Sleep* 14: 540–545.

Kasten, M., Kertelge, L., Brüggemann, N., van der Vegt, J., Schmid, A., Tadi, V. *et al.* (2010) Nonmotor symptoms in genetic Parkinson disease. *Arch Neurol* 67: 670–676.

Kipps, C.M., Fung, V., Grattan-Smith, P., de Moore, G.M. and Morris, J. (2005) Movement disorder emergencies. *Mov Disord* 20: 322–334.

Krack, P., Batir, A., Van Blercom, N., Chabardes, S., Fraix, V., Ardouin, C. *et al.* (2003) Five year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 349: 1925–1934.

Kulisevsky, J., Pagonabarraga, J., Pascual-Sedano, B., Garcia-Sanchez, C. and Gironelli, A. for the Trapecio study group. (2008) Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. *Mov Disord* 23: 1889–1896.

Lang, A.E. and Obeso, J.A. (2004) Challenges in Parkinson's disease: restoration of the nigrostriatal dopamine system is not enough. *Lancet Neurol* 3: 309–316.

Leeman, A.L., O'Neill, C.J., Nicholson, P.W., Deshmukh, A.A., Denham, M.J., Royston, J.P. *et al.* (1987) Parkinson's disease in the elderly: response to and optimal spacing of night time dosing with levodopa. *Br J Clin Pharmacol* 24: 637–643.

Leentjens, A.F., Dujardin, K., Marsh, L., Martinez-Martin, P., Richard, I.H., Starkstein, S.E. *et al.* (2008) Anxiety rating scales in Parkinson's disease: critique and recommendations. *Mov Disord* 23: 2015–2025.

Leroi, I., Brandt, J., Reich, S.C., Lykestos, C.C., Grill, S., Thompson, R. *et al.* (2004) Randomised placebo-controlled trial of Donepezil in cognitive impairment in Parkinson's Disease. *Int J Geriatric Psychiatry* 19: 1–8.

Levy, M.L., Cummings, J.L., Fairbanks, L.A., Masterman, D., Miller, B.L., Craig, A.H. *et al.* (1998) Apathy is not depression. *J Neuropsychiatry Clin Neurosci* 10: 314–319.

Le Witt, P.A., Lyons, K.E. and Pahwa, R. (2007) Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. *Neurology* 68: 1262–1267.

Lim, S.Y., Fox, S.H. and Lang, A.E. (2009a) Overview of the extranigral aspects of Parkinson Disease. *Arch Neurol* 66: 167–172.

Lim, S.Y., Moro, E. and Lang, A.E. (2009b) Non-motor symptoms of Parkinson's disease and the effects of deep brain stimulation, In: Chaudhuri, K.R., Schapira, A., Tolosa, E. and Poewe, W. (eds). Non Motor Symptoms of Parkinson's Disease, Oxford University Press: Oxford.

Low, P.A., Gilden, F.L., Freeman, R., Sheng, K.N. and McElligott, M.A. (1997) Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized double blind multicenter study. Midodrine study group. *J Am Med Assoc* 277: 1046–1051.

MacMahon, D.G. and Macphee, G.J. (2008) Dopamine agonists and impulse control disorders in Parkinson's disease. *Prog Neurol Psychiatry* 12: 5–9.

Macphee, G.J., Copeland, C., Stewart, D., Grosset, K. and Grosset, D.G. (2009) Clinical follow up of pathological gambling in Parkinson's disease in the West Scotland study. *Mov Disord* 24: 2430–2431.

Macphee, G.J.A. and MacMahon, D.G. (2009) Non motor symptoms and comorbidity in Parkinson's disease, In: Chaudhuri, K.R., Schapira, A., Tolosa, E. and Poewe, W. (eds). Non Motor Symptoms of Parkinson's Disease, Oxford University Press: Oxford.

Mamikonyan, E., Siderowf, A.D., Duda, J.E., Potenza, M.N., Horn, S., Stern, M.B. *et al.* (2008) Long-term follow-up of impulse control disorders in Parkinson's disease. *Mov Disord* 23: 75–80.

Marsh, L., McDonald, W.M., Cummings, J. and Ravina, P. (2006) Provisional diagnosis criteria for depression in Parkinson's Disease: report of an NINDS/NIMH Work Group. *Mov Disord* 21: 148–158.

Martinez-Martin, P., Schapira, A., Stocchi, F., Sethi, K., Odin, P., MacPhee, G. *et al.* (2007) Prevalence of Nonmotor symptoms in Parkinson's Disease in an international setting; Study using Nonmotor Symptoms Questionnaire in 545 patients. *Mov Disord* 22: 1623–1629.

Martinez-Martin, P., Visser, M., Rodriguez-Blazquez, C., Marinus, J., Chaudhuri, R., van Hilten, J.J. and on behalf of the SCOPA-Propark and ELEP groups. (2008) SCOPA-sleep and PDSS: Two scales for assessment of sleep disorder in Parkinson's disease. *Mov Disord* 23: 1681–1688.

McDonald, W.M., Holtzheimer, P.E., Haber, M., Vitek, K.L., McWhorter, K. and DeLong, M. (2006) Validity of the 30-item geriatric depression scale in patients with Parkinson's Disease. *Mov Disord* 21: 1618–1622.

Mendonca, D.A., Menezes, K. and Jog, M.S. (2007) Methylphenidate improves fatigue scores in Parkinson disease: a randomized controlled trial. *Mov Disord* 22: 2070–2076.

Medeiros, C.A., Carvalhedo de Bruin, P.F., Lopes, L.A., Magalhaes, M.C., de Lourdes Seabra, M. and de Bruin, V.M. (2007) Effect of exogenous melatonin on sleep and motor dysfunction in Parkinson's disease: a randomized, double blind, placebo controlled study. *J Neurol* 254: 459–464.

Menza, M., Dobkin, R.D., Martin, H., Mark, M.H., Gara, M., Buyske, S. *et al.* (2009) A controlled trial of antidepressants in patients with Parkinson's disease and depression. *Neurology* 72: 886–892.

Merims, D., Balas, M., Peretz, C., Shabtai, H. and Giladi, N. (2006) Rater-blinded, prospective comparison: Quetiapine *versus* Clozapine for Parkinson's Disease psychosis. *Clin Neuropharmacol* 29: 331–337.

Miyasaki, J.M., Shannon, K., Voon, V., Ravina, B., Kleiner-Fisman, G. and Anderson, K. (2006) Practice Parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson's disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 66: 996–1002.

Moellentine, C., Rummans, T., Ahlskog, J.E., Harmsen, W.S., Suman, V.J., O'Connor, M.K. *et al.* (1998) Effectiveness of ECT in patients with parkinsonism. *J Neuropsychiatry Clin Neurosci* 10: 187–193.

Monaca, C., Ozsancak, C., Jacquesson, J.M., Poirot, I., Blond, S., Destee, A. *et al.* (2004) Effects of bilateral subthalamic stimulation on sleep in Parkinson's disease. *J Neurol* 251: 214–218.

Mondolo, F., Jahanshani, M., Grana, A., Biasutti, E., Cacciatori, E. and di Benedeto, P. (2006) The validity of the hospital anxiety and depression scale and the geriatric depression scale in Parkinson's disease. *Behav Neurol* 17: 109–115.

Mylius, V., Engau, I., Teepker, M., Stiasny-Kolster, K., Schepelmann, K., Oertel, W.H. *et al.* (2009) Pain sensitivity and descending inhibition of pain in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 80: 24–28.

National Institute for Health and Clinical Excellence (2006) Parkinson's Disease. NICE guideline 35, June 2006.

Ondo, W.G., Fayle, R., Atassi, F. and Jankovic, J. (2005a) Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. *J Neurol Neurosurg Psychiatry* 76: 1636–1639.

Ondo, W.G., Tintner, R., Vuong Dat, K., Lai, D. and Ringholz, G. (2005b) Double blind placebo controlled

unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Mov Disord* 20: 958–963.

Ondo, W.G., Vuong, K.D. and Jankovic, J. (2002) Exploring the relationship between Parkinson disease and restless legs syndrome. *Arch Neurol* 59: 421–424.

O'Sullivan, S.S., Williams, D.R., Gallagher, D.A., Massey, L.A., Silveira-Moriyama, L. and Lees, A.J. (2008) Non-motor symptoms as presenting complaints in Parkinson's Disease: a clinicopathological study. *Mov Disord* 23: 101–106.

Pahwa, R., Stacy, M.A., Factor, S.A., Lyons, K.E., Stocchi, F., Hersh, B.P. *et al.* (2007) Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. *Neurology* 68: 1108–1115.

Papatsoris, A.G., Deliveliotis, C., Singer, C. and Papapetropoulos, S. (2006) Erectile dysfunction in Parkinson's disease. *Urology* 67: 447–451.

Parsons, T.D., Rogers, S.A., Braaten, A.J., Woods, S.P. and Tröster, A.I. (2006) Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *Lancet Neurol* 5: 578–588.

PD PROMS study (2010) Available at: http://public. ukcrn.org.uk/search/StudyDetail.aspx?StudyID=2519 (accessed 12 August 2010).

Pfeiffer, R.F. (2003) Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol* 2: 107–116.

Pluck, G.C. and Brown, R.G. (2002) Apathy in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 73: 636–642.

Poewe, W.H., Rascol, O., Quinn, N., Tolosa, E., Oertel, W.H., Martignoni, E. *et al.* (2007) Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. *Lancet Neurol* 6: 513–520.

Pohanka, M., Kanovsky, P., Bares, M., Pulkrabek, J. and Rektor, I. (2005) 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* 11: 509–512.

Pontone, G.M., Williams, J.R., Anderson, K.E., Chase, G., Goldstein, S.A., Grill, S. *et al.* (2009) Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. *Mov Disord* 24: 1333–1338.

Propark Study (2010) SCOPA, http://www.scopa-propark.eu (accessed 11 August 2010).

Ravina, B., Putt, M., Siderowf, A., Farrar, J.T., Gillespie, M., Crawley, A. *et al.* (2005) Donepezil for dementia in Parkinson's Disease: a randomised double blind, placebo controlled, crossover study. *J Neurol Neurosurg Psychiatry* 76: 934–939.

Reading, P. (2007) Parasomnias: the spectrum of things that go bump in the night. *Pract Neurol* 7: 6–15.

Reijnders, J.S., Ehrt, U., Weber, W.E., Aarsland, D. and Leentjens, A.F. (2008) A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord* 23: 183–189.

Remy, P., Doder, M., Lees, A., Turjanski, N. and Brooks, D. (2005) Depression in Parkinson's Disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain* 128: 1314–1322.

Richard, I.H., Kurlan, R., Tanner, C., Factor, S., Hubble, J., Suchowersky, O. *et al.* (1997) Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Parkinson Study Group. *Neurology* 48: 1070–1077.

Schenck, C.H., Bundlie, S.R. and Mahowald, M.W. (1996) Delayed emergence of a Parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. *Neurology* 46: 388–393.

Schenck, C.H. and Mahowald, M.W. (2002) REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. *Sleep* 25: 20–38.

Schmidt, M.H., Koshal, V.B. and Schmidt, H.S. (2006) Use of Pramipexole in REM sleep behaviour disorder: results from a case series. *Sleep Med* 7: 418–423.

Schoffer, K.L., Henderson, R.D., O'Maley, K. and O'Sullivan, J.D. (2007) Nonpharmacological treatment, fludrocortisone, and domperidone for orthostatic hypotension in Parkinson's disease. *Mov Disord* 22: 1543–1549.

Schrag, A., Jahanshahi, M. and Quinn, N. (2000) What contributes to quality of life in patients with Parkinson's Disease? *J Neurol Neurosurg Psychiatry* 69: 308–312.

Schrag, A., Jahanshahi, M. and Quinn, N. (2001) What contributes to depression in Parkinson's disease. *Psychol Med* 31: 65–73.

Schurman, A.G., van den Akker, M., Ensinck, K., Metsemakers, J., Knottnerus, J.A., Leentjens, A. *et al.* (2002) Increased risk of Parkinson's Disease after depression: a retrospective cohort study. *Neurology* 58: 1501–1504.

Scottish Intercollegiate Guidelines Network (2010) Diagnosis and Pharmacological Management of Parkinson's Disease. SIGN guideline 113, January 2010.

Seif, C., Herzog, J., van der Horst, C., Schrader, B., Volkmann, J. and Deuschl, G. (2004) Effect of subthalamic deep brain stimulation on the function of the urinary bladder. *Ann Neurol* 55: 118–120.

Shulman, L.M., Taback, R.L., Rabinstein, A.A. and Weiner, W.J. (2002) Non-recognition of depression and other non-motor symptoms in Parkinson's Disease. *Parkinsonism Relat Disord* 8: 193–197.

Stacy, M., Bowron, A., Guttman, M., Hauser, R., Hughes, K., Larsen, J.P. *et al.* (2005) Identification of motor and nonmotor wearing-off in Parkinson's disease: comparison of a patient questionnaire *versus* a clinician assessment. *Mov Disord* 20: 726–733.

Stamey, W. and Jankovic, J. (2008) Impulse control disorders and pathological gambling in patients with Parkinson disease. *Neurologist* 14: 89–99.

Stern, M.B. and Siderowf, A. (2010) Parkinson's at risk Syndrome: Can Parkinson's disease be predicted? *Mov Disord* 25: 89–93.

Stiasny-Kolster, K., Doerr, Y., Möller, J.C., Hoffken, H., Behr, T.M., Oertel, W.H. *et al.* (2005) Combination of 'idiopathic' REM sleep behaviour disorder and olfactory dysfunction as possible indicator for synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT. *Brain* 128: 126–137.

Stocchi, F. (2009) Gastrointestinal dysfunctions in Parkinson's disease, In: Chaudhuri, K.R., Schapira, A., Tolosa, E. and Poewe, W. (eds). Non Motor Symptoms of Parkinson's Disease, Oxford University Press: Oxford.

Suchowersky, O., Furtado, S. and Rohs, G. (1995) Beneficial effect of intranasal desmopressin for nocturnal polyuria in Parkinson's disease. *Mov Disord* 10: 337–340.

Sullivan, J.D., Bhatia, K.P. and Lees, A.J. (2000) Botulinum toxin A as a treatment for drooling saliva in PD. *Neurology* 55: 606–607.

Tandberg, E., Larsen, J.P. and Karlsen, K. (1998) A community-based study of sleep disorders in patients with Parkinson's disease. *Mov Disord* 13: 895–899.

Visser, M., Leentjens, A.F., Marinus, J., Stiggelbout, A.M. and van Hillen, J.J. (2006) Reliability and validity of the Beck depression inventory in patients with Parkinson's disease. *Mov Disord* 21: 668–672.

Voon, V., Kubu, C., Krack, P., Houeto, J.-L. and Tröster, A.I. (2006) Deep brain stimulation: Neuropsychological and neuropsychiatric issues. *Mov Disord* 21: S305–S327.

Weintraub, D., Koester, J., Potenza, M.N., Siderowf, A.D., Stacy, M. and Voon, V. (2010) Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* 67: 589–595.

Weintraub, D., Moberg, P., Duda, J., Katz, I.R. and Stern, M.B. (2004) Effect of Psychiatric disease and other nonmotor symptoms on disability in Parkinson's disease. *JAGS* 52: 784–788.

Weintraub, D., Morales, K.H., Moberg, P.J., Bilker, W.B., Balderston, C., Duda, J.E. *et al.* (2005) Antidepressant studies in Parkinson's Disease: a review and meta-analysis. *Mov Disord* 20: 1161–1169.

Weintraub, D., Saboe, K. and Stern, M.B. (2007) Effect of age on geriatric depression scale performance in Parkinson's Disease. *Mov Disord* 22: 1311–1315.

Weintraub, D. and Potenza, M.N. (2006) Impulse control disorders in Parkinson's disease. *Curr Neurol Neurosci Rep* 6: 302–306.

Williams, D. and Lees, A.J. (2005) Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study. *Lancet Neurol* 4: 605–610.

Williams-Gray, C.H., Evans, J.R., Goris, A., Foltynie, T., Ban, M. and Robbins, T.W. (2009) The distinct cognitive syndromes of Parkinson's disease: a 5 year follow-up of the CamPaIGN cohort. *Brain* 132: 2958–2969.

Winge, K. and Fowler, C.J. (2006) Bladder dysfunction in Parkinsonism: mechanisms, prevalence, symptoms, and management. *Mov Disord* 21: 737–745.

Witjas, T., Kaphan, E., Azulay, J.P., Blin, O., Ceccaldi, M., Pouget, J. *et al.* (2002) Nonmotor fluctuations in Parkinson's Disease: frequent and disabling. *Neurology* 59: 408–413.

Witjas, T., Kaphan, E., Régis, J., Jouve, E., Chérif, A.A., Péragut, J.-C. and Azulay, J.P. (2007) Effects of chronic subthalamic stimulation on nonmotor fluctuations in Parkinson's disease. *Mov Disord* 22: 1729–1734.

Witt, K., Daniels, C., Reiff, J., Krack, P., Volkmann, J., Pinsker, M.O. *et al.* (2008) Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicenter study. *Lancet Neurol* 7: 605–614.

Zadikoff, C., Fox, S.M., Tang Wai, D.F., Thomsen, T., de Bie, R.M.A., Wadia, P. *et al.* (2008) A comparison of the mini mental state exam to the Montreal Cognitive Assessment in identifying cognitive deficits in Parkinson's disease. *Mov Disord* 23: 297–299.

Zangaglia, R., Martignoni, E., Glorioso, M., Ossola, M., Riboldazzi, G., Calandrella, D. *et al.* (2007) Macrogol for the treatment of constipation in Parkinson's disease: a randomized placebo-controlled study. *Mov Disord* 22: 1239–1244.

Zeseiwicz, T.A., Sullivan, I., Arnulf, K.R., Chaudhuri, J.C., Morgan, G.S., Gronseth, J. *et al.* (2010) Practice Parameter: Treatment of nonmotor symptoms of Parkinson disease: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 74: 924–931.

Zesiewicz, T.A., Helal, M. and Hauser, R.A. (2000) Sildenafil citrate (Viagra) for the treatment of erectile dysfunction in men with Parkinson's disease. *Mov Disord* 15: 305–308.

Zibetti, M., Torre, E., Cinquepalmi, A., Rosso, M., Ducati, A. and Bergamasco, B. (2007) Motor and nonmotor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. *Eur Neurol* 58: 218–223.