Non-motor symptoms: the core of multi-morbid Parkinson's disease

Non-motor symptoms of Parkinson's disease are the leading cause of poor quality of life both for people with Parkinson's disease and their caregivers. Non-motor symptoms are almost universal in Parkinson's disease yet are under-recognized and under-treated. This article considers the causes and aspects of treatment.

Parkinson's disease is the second commonest neurodegenerative disorder. In the UK, about 127 000 people have Parkinson's disease; this is predicted to rise to approximately 160 000 by 2020 (Parkinson's UK, 2012). The annual incidence of Parkinson's disease is 12–20 per 100 000 (De Lau and Breteler, 2006) with a prevalence rate varying from 65.6–169 (Marttila and Rinne, 1981).

The common perception is that Parkinson's disease is a motor disorder largely mediated by dopamine loss in the nigro-striatal pathway in the brain, expressing the classical symptom complex of rest tremor, bradykinesia and rigidity. However, Parkinson's disease is now known to be as much a non-motor disorder as a motor disorder (*Table 1*) and the range of non-motor symptoms present one of the biggest challenges to clinicians and health-care professionals treating patients with Parkinson's disease (Chaudhuri et al, 2006a; Stern et al, 2012). Despite this, non-motor symptoms remain widely under-researched and under-treated, impacting on clinical care and the quality of life of patients and carers (Martinez-Martin et al, 2011).

Table 1. Some key issues supporting the notion that Parkinson's disease is not just a motor disorder

James Parkinson outlines several non-motor issues such as sleepiness, cognitive problems, autonomic dysfunction in his original essay describing Parkinson's disease
Some non-motor symptoms can predate motor symptoms by up to 10–15 years
Late onset hyposmia and rapid eye movement sleep behaviour disorder have emerged as possible 'pre-motor' markers of motor Parkinson's disease
Pathology of Parkinson's disease includes degeneration of non-dopaminergic nuclei and pathways, including serotonergic, cholinergic and noradrenergic, from the onset of illness
Patients consistently rate non-motor symptoms as most bothersome
The burden of non-motor symptoms appears to be the key determinant of quality of life of people with Parkinson's disease
In the long term patients are troubled by non-motor symptoms more than motor issues such as stiffness and dyskinesias (Hely et al, 2008)
Some have considered Parkinson's disease to be a neuropsychiatric disorder

Dr Anna Sauerbier *is NIHR Biomedical Research Centre Research Fellow and* **Professor K Ray Chaudhuri** *is Consultant Neurologist and Professor of Neurology and Movement Disorders in the National Parkinson Foundation International Centre of Excellence, King's College London, London, and National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre and Dementia Unit at South London and Maudsley NHS Foundation Trust and King's College London, London SE5 9RS*

Correspondence to: Professor KR Chaudhuri (ray.chaudhuri@nhs.net)

A typical Parkinson's disease patient, irrespective of the clinical severity of the motor stage, may exhibit 10–12 non-motor symptoms (Chaudhuri et al, 2006b), and non-motor symptoms are common even in untreated Parkinson's disease at presentation. Furthermore non-motor symptoms are recognized as an important unmet need in Parkinson's disease in the UK by the National Institute for Health and Clinical Excellence (2006) and are a frequent cause of hospitalization with serious social and economic consequences (Schrag et al, 2000; Hagell et al, 2002). In patient-based studies, patients with Parkinson's disease listed problems such as pain, sleep disorders and anxiety as being 'most bothersome' ahead of motor problems (Gulati et al, 2004; Politis et al, 2010). A more recent study in over 8000 patients, using the validated non-motor symptoms questionnaire (NMSQuest), reported the widespread impact of non-motor symptoms on patients (Breen and Drutyte, 2013).

What are the non-motor symptoms of Parkinson's disease?

In his classic 'Essay on the Shaking Palsy' James Parkinson referred to sleep disturbance, constipation, dysarthria, dysphonia, dysphagia, sialorrhoea, urinary incontinence and 'at the last, constant sleepiness with slight delirium'; all outlining the burden of non-motor symptoms (Alves et al, 2008). Non-motor symptoms encompass a wide range of symptoms from gastrointestinal to sleep disorders, from cognitive to apathy and depression, reflecting the wide range of neuropeptide involvement within the central and peripheral nervous system (*Table 2*). In addition, many non-motor symptoms in Parkinson's disease may arise as a consequence of drug therapy or disease-related complications (*Tables 2* and *3*).

While some non-motor symptoms dominate in the early and untreated phase of Parkinson's disease, some dominate in the 'pre-motor' stage (impaired olfaction and autonomic dysfunction, depression) while others appear to complicate the clinical picture throughout (pain, fatigue) and especially Parkinson's disease at its later (dementia, apathy, dysautonomia) advanced stages (Hawkes et al, 2010).

Pathophysiology

The modern concept of Parkinson's disease underpins the fact that the clinical phenotype of Parkinson's disease is not the consequence of the loss of a single monoamine neurotransmitter, dopamine, but instead a pathological process that represents the effects of widespread brain and peripheral (such as autonomic pathways, enteric nervous system, heart) Lewy body disease. This results in a final pathway of deficits in multiple neurotransmitter pathways including the cholinergic, noradrenergic and serotonergic systems (Kingsbury et al, 2010; Halliday et al, 2011; Jellinger, 2012). Dysfunctions within these systems underpin the emergence of many non-motor symptoms of Parkinson's disease such as depression, anxiety, sleep disorders, autonomic dysfunction and cognitive dysfunction.

Table 2. The range of non-motor symptoms in Parkinson's disease, classified according to whether directly related to Parkinson's disease pathophysiology, drug therapy or a combined aetiology (see also *Table 3*)

Symptom		Related to Parkinson's disease pathophysiology	Related to drug therapy	Contribution from both
Cognitive and neuropsychiatric symptoms	Cognitive impairment (ranging from mild cognitive impairment to frank dementia)	++	-	-
	Anxiety	+/-	++	+
	Major depression	++	+/-	+/-
	Apathy	++	-	-
	Delirium	+/-	++	+/-
	Hallucinations, delusions, illusions	+	++	+
	Panic attacks (could be 'off' period related)	+	++	+
Sleep disorders and dysfunctions	Excessive daytime somnolence, sudden onset of sleep (narcolepsy without cataplexy)	++	++	++
	Insomnia (onset and maintenance)	++	+	+
	Non-rapid eye movement parasomnias (confusional wandering, sleep talking)	++	-	-
	Rapid eye movement sleep behaviour disorder	++	-	-
	Restless legs syndrome	+	+	+
	Periodic leg movements	+	+	+
	Sleep-disordered breathing	++	-	-
Autonomic dysfunction	Bladder urgency, frequency, nocturia	++	+/-	+/-
	Orthostatic hypotension	++	+	++
	Post-prandial hypotension	++	+/-	+/-
	Sexual dysfunction	++ (↓)	++ (↑)	++
	Erectile dysfunction	+	-	-
	Thermoregulatory abnormalities (hyperhidrosis)	++	+	+
Gastrointestinal symptoms	Dribbling of saliva	++	+/-	+/-
	Dysphagia	++	+/-	+/-
	Ageusia (change in taste sensation)	++	+/-	+/-
	Constipation	++	+/-	+/-
	Faecal incontinence	++	+/-	+/-
	Nausea	+/-	++	+/-
	Reflux	+/-	++	+/-
	Vomiting	+/-	++	+/-
Other non-motor symptoms	Central fatigue	++	+/-	+/-
	Functional anosmia or hyposmia	++	-	-
	Visual disturbances (blurred vision, transient diplopia, impaired contrast-sensitivity, colour vision)	++	+/-	+/-
	Weight gain (could be related to impulse control disorders)	++	+	+
	Weight loss	++	+/-	+/-

Friederick Lewy described Lewy bodies in the dorsal vagal nucleus in 1913 and then Braak described a bottom-up process, suggesting that the beginning of Parkinson's disease may also involve the olfactory nucleus. Braak suggested a six-stage pathological process based on Lewy body formation and deposition beginning at induction sites with degeneration of the olfactory bulb and the anterior olfactory nucleus and the lower medulla at stage 1, while stage 2 reflects progression of the pathological process to the lower brainstem with involvement of serotonin (median raphe) and noradrenaline (locus coeruleus) nuclei in the brainstem and pons (Braak et al, 2003, 2004). Clinically, this correlates with late onset hyposmia (olfactory bulb and nucleus) as well as rapid eye movement behaviour disorder (lower brainstem), recognized as pre-motor markers of Parkinson's disease (*Table 4*). Lower brainstem nuclei mediate some key non-motor symptoms such as olfaction, sleep homeostasis, depression and cognition, pain, constipation and central autonomic vagal control.

Table 3. Dopaminergic drug-induced non-motor symptoms seen in patients with Parkinson's disease

Behavioural non-motor symptoms	Dopamine dysregulation syndrome (usually linked to levodopa intake associated with obsessional 'pill popping')
	Impulse control disorders (e.g. compulsive gambling, hypersexuality, binge eating)
	Hallucinations, delusions, psychosis
Non-motor fluctuations occurring as a complication	Cognitive or psychiatric (depression, anxiety, anxious-depressed)
	Dysautonomic
	Sensory or pain
	Visual blurring
'Other' non-motor symptoms	Ankle swelling
	Dopamine agonist withdrawal syndrome
	Non-motor symptoms linked to acute parkinsonian emergencies such as Parkinson hyperpyrexia syndrome

Table 4. Possible pre-motor features of Parkinson's disease

	Non-motor symptoms	Relevant findings reported
Commonly associated	Late onset hyposmia	Evidence that hyposmia and abnormal dopamine active transporter scan may suggest 43% develop motor Parkinson's disease in 4 years (Jennings et al, 2013)
	Rapid eye movement sleep behaviour disorder	17.7% at 5 years, 40.6% at 10 years, 52.4% at 12 years, risk higher if coupled with abnormal dopamine active transporter scan (Postuma et al, 2009)
	Constipation	2.7–4.5 times excess in the risk of Parkinson's disease in men with <1 bowel movement/day (Abbott et al, 2001)
	Depression	Increased risk of developing Parkinson's disease (Leentjens et al, 2003)
Association described	Excessive daytime sleepiness	Three times excess in the risk of Parkinson's disease in men with excessive daytime sleepiness *vs* men without excessive daytime sleepiness (Abbott et al, 2005)
	Erectile dysfunction	3.8 times more likely to develop Parkinson's disease (Gao et al, 2007)
	Pain	Increased risk of developing Parkinson's disease (Lin et al, 2013)
	Fatigue	Increased risk of developing Parkinson's disease (Kang et al, 2013)
	Visual impairment (contrast sensitivity, colour vision)	Case studies (Diederich et al, 2010)
	Pre-morbid personality traits	Retrospective studies (Todes and Lees, 1985)

Non-motor symptoms, idiopathic Lewy body disease and Parkinson's disease

For the purposes of clinical practice, studies and trials, Parkinson's disease is still diagnosed using the UK Parkinson's disease Brain Bank criteria which are based entirely on motor symptoms, do not include key non-motor symptoms such as hyposmia in the criteria, and list autonomic dysfunction as an exclusion criteria (Hughes et al, 1992; National Institute for Health and Clinical Excellence, 2006). This has prompted a call to redefine Parkinson's disease and its diagnostic criteria. Some authors have suggested that Parkinson's disease could be subdivided into three stages, a preclinical, pre-motor and motor stage, with non-motor symptoms being the sole determinant of the pre-motor stage (Stern et al, 2012).

Studies have suggested that a number of non-motor symptoms are pre-motor markers of Parkinson's disease, with some such as late onset hyposmia and rapid eye movement behaviour disorder being the most robust (Boeve et al, 2001; Berendse and Ponsen, 2006). It is now estimated that approximately 40% of patients demonstrating 'idiopathic' rapid eye movement behaviour disorder will go on to develop typical motor Parkinson's disease in 10 years time, the figures rising with further passage of time. Similarly, a study from the USA reported a high rate of conversion to motor Parkinson's disease of patients suffering from 'idiopathic' hyposmia who also show reduced dopamine transporter activity (Jennings et al, 2013). The range of non-motor symptoms described as possible pre-motor features of Parkinson's disease are listed in *Table 4*.

Self reporting of non-motor symptoms by patients and relationship to quality of life

Non-motor symptoms are reported as 'most bothersome' by patients both with early (within 6 years) and advanced Parkinson's disease (Politis et al, 2010). In a recent study by Breen and Drutyte (2013) on behalf of Parkinson's UK, the impact of non-motor symptoms was surveyed in over 10 000 people with Parkinson's using NMSQuest. People who had younger onset Parkinson's disease reported a greater impact of non-motor symptoms, particularly in relation to memory, depression and sleep, and scores on NMSQuest were inversely correlated with quality of life. European studies selectively addressed the impact of the burden of non-motor symptoms on health-related quality

of life in Parkinson's disease and reported that non-motor symptom burden has the closest correlation with health-related quality of life and those with the highest non-motor symptom scores had the worst health-related quality of life (Findley, 2007; Martinez-Martin et al, 2011).

Clinical assessment of non-motor symptoms as a whole

Until 2006, non-motor symptoms could only be assessed piecemeal in clinical practice. For instance, one could selectively assess sleep dysfunction or cognitive dysfunction using validated Parkinson's disease-specific scales but such assessments would not provide a holistic picture of the multi-morbid patient. Since this time, however, several initiatives such as the SCOPA scales (Scales for Outcomes in Parkinson's disease), NMSQuest and the non-motor symptoms scale (NMSS), as well as the new version of the Movement Disorder Society-Unified Parkinson's Disease Rating scales, have tried to address the measurement and self reporting of non-motor symptoms in clinical practice (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003; Goetz et al, 2007). Of these, NMSQuest remains the only validated self-reporting tool for non-motor symptoms in a 'holistic' manner validated for Parkinson's disease. It is recommended by learned societies such as the Movement Disorders Society, American Academy of Neurology, National Institute of Neurological Disorders and Stroke Parkinson's Disease Common Data Elements Working Group as well as patient groups such as Parkinson's UK, the European Parkinson's Disease Association and Parkinson Society Canada.

NMSQuest can be easily completed by patients (with help from carers) in the consulting room. It lists the non-motor symptoms relevant to clinical practice with 30 items completed in a 'yes' and 'no' fashion. The importance of using NMSQuest is evident in an European study, where the use of NMSQuest identified that non-motor symptoms were not discussed or considered in clinical consultations in over 50% of cases (Chaudhuri et al, 2010) and led to suboptimal treatment in many. This was only redressed when the clinician became aware of the non-motor symptoms after using NMSQuest. Based on this a suggested scheme of examination of patients in the clinic using NMSQuest (the King's-ISCII classification) is shown in *Figure 1*. In the current Best Practice Tariff recommendations for the NHS in the UK, one of the parameters is to ensure that non-motor symptoms have been considered using the NMSQuest (Department of Health, 2013).

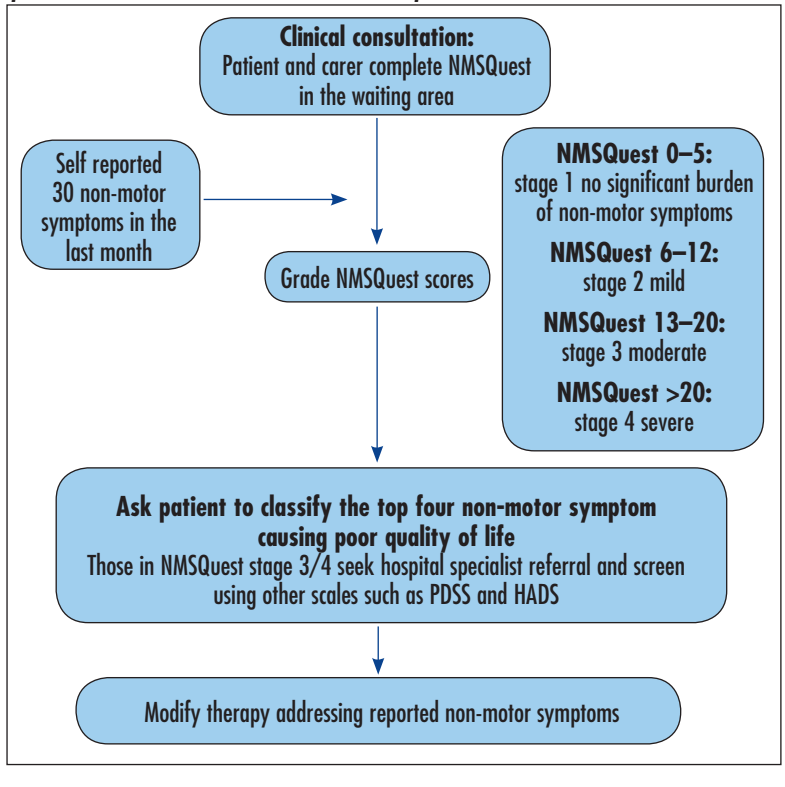
Case illustrations

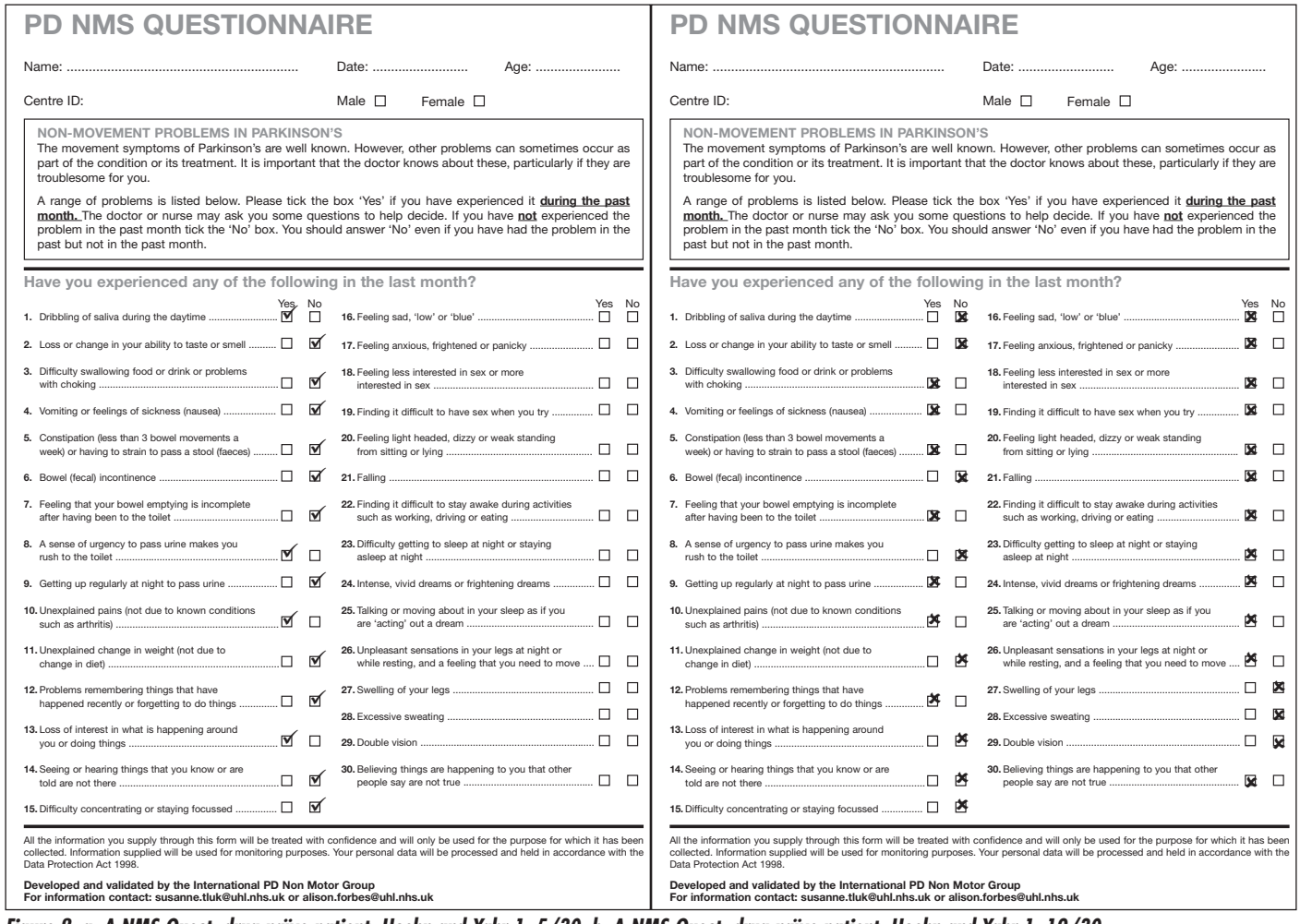
Figures 2a and *b* illustrate two patients who have completed the NMSQuest. Both are untreated and while one has five positive non-motor symptoms out of 30 questions, the other, another newly diagnosed patient with similar motor disability, has 19 non-motor symptoms. While the first patient reports mainly problems with dribbling of saliva during the daytime, urgency to pass urine, unexplained pain and feeling light headed, dizzy or weak from sitting or lying, the second patient presents with a wider range of non-motor symptoms. On closer observation, the second patient mainly presents with problems concerning the sleep and autonomic system, so would need a different management plan to the first patient. This would include management of sleep disorders, dribbling of saliva and bladder problems in addition to motor management of Parkinson's disease. This also outlines the importance of addressing non-motor symptoms using NMSQuest in the clinic, both in the primary and secondary care setting, so that symptoms are not missed thus compromising the quality of care. Gender-related differences are minimal (Martinez-Martin et al, 2012).

Drug-related non-motor symptoms

When analysing symptoms reported by patients it is important to take into consideration that non-motor symptoms can be caused by drugs. In order to differentiate between drug-induced symptoms and early non-motor symptoms of Parkinson's disease a study has shown that urinary symptoms, excessive daytime sleepiness, restless leg syndrome, attention deficit and hyposmia are useful, all being suggestive of Parkinson's disease-related non-motor symptoms rather than drug-related symptoms (Kim et al, 2013). Impulse control disorders are a key challenge to the treatment of Parkinson's disease and often present in the form of compulsive shopping, eating, gambling, hypersexuality and various types of 'hobbyisms'. While the prevalence of

Figure 1. Suggested scheme of examination of patients in the clinic using NMSQuest. HADS= hospital anxiety and depression scale; NMSQuest = non-motor symptoms questionnaire; PDSS = Parkinson's disease sleep scale. From Chaudhuri et al (2009).





PD NMS QUESTIONNAIRE

Name: ..... Date: ..... Age: .....

Centre ID: Male ☐ Female ☐

NON-MOVEMENT PROBLEMS IN PARKINSON'S

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it **during the past month.** The doctor or nurse may ask you some questions to help decide. If you have **not** experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

Have you experienced any of the following in the last month?

	Yes	No
1. Dribbling of saliva during the daytime	☑	☐
2. Loss or change in your ability to taste or smell	☐	☑
3. Difficulty swallowing food or drink or problems with choking	☐	☑
4. Vomiting or feelings of sickness (nausea)	☐	☑
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	☐	☑
6. Bowel (fecal) incontinence	☐	☑
7. Feeling that your bowel emptying is incomplete after having been to the toilet	☐	☑
8. A sense of urgency to pass urine makes you rush to the toilet	☑	☐
9. Getting up regularly at night to pass urine	☐	☑
10. Unexplained pains (not due to known conditions such as arthritis)	☑	☐
11. Unexplained change in weight (not due to change in diet)	☐	☑
12. Problems remembering things that have happened recently or forgetting to do things	☐	☑
13. Loss of interest in what is happening around you or doing things	☑	☐
14. Seeing or hearing things that you know or are told are not there	☐	☑
15. Difficulty concentrating or staying focussed	☐	☑
16. Feeling sad, 'low' or 'blue'	☐	☐
17. Feeling anxious, frightened or panicky	☐	☐
18. Feeling less interested in sex or more interested in sex	☐	☐
19. Finding it difficult to have sex when you try	☐	☐
20. Feeling light headed, dizzy or weak standing from sitting or lying	☐	☐
21. Falling	☐	☐
22. Finding it difficult to stay awake during activities such as working, driving or eating	☐	☐
23. Difficulty getting to sleep at night or staying asleep at night	☐	☐
24. Intense, vivid dreams or frightening dreams	☐	☐
25. Talking or moving about in your sleep as if you are 'acting' out a dream	☐	☐
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	☐	☐
27. Swelling of your legs	☐	☐
28. Excessive sweating	☐	☐
29. Double vision	☐	☐
30. Believing things are happening to you that other people say are not true	☐	☐

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1998.

Developed and validated by the International PD Non Motor Group
For information contact: susanne.tluk@uhl.nhs.uk or alison.forbes@uhl.nhs.uk

PD NMS QUESTIONNAIRE

Name: ..... Date: ..... Age: .....

Centre ID: Male ☐ Female ☐

NON-MOVEMENT PROBLEMS IN PARKINSON'S

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it **during the past month.** The doctor or nurse may ask you some questions to help decide. If you have **not** experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

Have you experienced any of the following in the last month?

	Yes	No
1. Dribbling of saliva during the daytime	☐	☒
2. Loss or change in your ability to taste or smell	☐	☒
3. Difficulty swallowing food or drink or problems with choking	☒	☐
4. Vomiting or feelings of sickness (nausea)	☒	☐
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	☒	☐
6. Bowel (fecal) incontinence	☐	☒
7. Feeling that your bowel emptying is incomplete after having been to the toilet	☒	☐
8. A sense of urgency to pass urine makes you rush to the toilet	☐	☒
9. Getting up regularly at night to pass urine	☒	☐
10. Unexplained pains (not due to known conditions such as arthritis)	☒	☐
11. Unexplained change in weight (not due to change in diet)	☐	☒
12. Problems remembering things that have happened recently or forgetting to do things	☒	☐
13. Loss of interest in what is happening around you or doing things	☐	☒
14. Seeing or hearing things that you know or are told are not there	☐	☒
15. Difficulty concentrating or staying focussed	☐	☒
16. Feeling sad, 'low' or 'blue'	☒	☐
17. Feeling anxious, frightened or panicky	☒	☐
18. Feeling less interested in sex or more interested in sex	☒	☐
19. Finding it difficult to have sex when you try	☒	☐
20. Feeling light headed, dizzy or weak standing from sitting or lying	☒	☐
21. Falling	☒	☐
22. Finding it difficult to stay awake during activities such as working, driving or eating	☒	☐
23. Difficulty getting to sleep at night or staying asleep at night	☒	☐
24. Intense, vivid dreams or frightening dreams	☒	☐
25. Talking or moving about in your sleep as if you are 'acting' out a dream	☒	☐
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	☒	☐
27. Swelling of your legs	☐	☒
28. Excessive sweating	☐	☒
29. Double vision	☐	☒
30. Believing things are happening to you that other people say are not true	☒	☐

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1998.

Developed and validated by the International PD Non Motor Group
For information contact: susanne.tluk@uhl.nhs.uk or alison.forbes@uhl.nhs.uk

Figure 2. a. A NMS Quest, drug naïve patient, Hoehn and Yahr 1, 5/30. b. A NMS Quest, drug naïve patient, Hoehn and Yahr 1, 19/30.

impulse control disorder with levodopa remains around 0.7–7%, it rises up to 14–17% in patients treated with dopamine agonists (Weintraub et al, 2010). Suddenly stopping dopamine agonists can lead to the dopamine agonist withdrawal syndrome (Rabinak and Nirenberg, 2010). Dopamine agonist withdrawal syndrome is characterized by psychiatric as well as physical symptoms that occur after having stopped a dopamine agonist and do not respond to levodopa, antidepressants and anxiolytics but improve with dopamine agonists (Rabinak and Nirenberg, 2010).

Non-motor fluctuations

Fluctuations of motor symptoms during on and off periods are well known and typically occur after the initiation of levodopa therapy. What is less well appreciated is that fluctuations can also occur in relation to the non-motor symptoms, and motor 'off' periods may be associated with either worsening of several non-motor symptoms or unmasking of non-motor symptoms which are only present during off stages (*Table 1*) (Storch et al, 2013). This has important implications for diagnosis and treatment as, for example, the treatment of 'off' related depression would be long-acting dopaminergic drugs to reduce off periods rather than the use of an antidepressant.

Treatment of non-motor symptoms

There are a range of non-motor symptoms that are symptomatic in Parkinson's disease and non-motor symptoms such as fatigue, pain, sexual dysfunction, apathy in Parkinson's disease for which there is little or no robust evidence for treatment. The guidelines of the American Academy of Neurology (2010) and more recently the Movement Disorder Society reviewed the therapeutic issues in relation to these non-motor symptoms (Zesiewicz et al, 2010; Seppi et al, 2011). *Table 5* gives a broad overview of the treatment of some of the more common non-motor symptoms in patients with Parkinson's disease.

Conclusions

Non-motor symptoms of Parkinson's disease are present from the very early stages of Parkinson's disease, well before the 'classic' motor symptoms start, to the end stage and present the biggest treatment challenge for clinicians and health-care professionals. Non-motor symptoms are regarded by patients as the most bothersome and current treatment strategies as well as research remains suboptimal in relation to non-motor symptoms of Parkinson's disease. Awareness is the key to management of non-motor symptoms and simple validated tools such as

NMSQuest will help empower patients to declare non-motor symptoms and obtain treatment. Medical and allied health professionals need to be more aware of non-motor symptoms in Parkinson's disease right from the point at which Parkinson's disease is diagnosed. BJHM

This review presents independent research funded by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre and Dementia Unit at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The authors would like to thank Professor Pablo Martinez-Martin and his team for supporting and performing all data analysis related to non-motor symptoms studies reported in this review.

Conflict of interest: Professor K Ray Chaudhuri is the Chairman of the International Parkinson's and Movement Disorders Society Non Motor Parkinson's Study group and he led the development of NMSQuest; Dr A Sauerbier: none.

Abbott RD, Petrovitch H, White LR et al (2001) Frequency of bowel movements and the future risk of Parkinson's disease. *Neurology* **57**: 456–62

Abbott RD, Ross GW, White LR et al (2005) Excessive daytime sleepiness and subsequent development of Parkinson disease. *Neurology* **65**: 1442–6

Alves G, Forsaa EB, Pedersen KF, Dreetz Gjerstad M, Larsen JP

Table 5. Range of treatment options for non-motor symptoms in Parkinson's disease

Non-motor symptoms	Commonly used strategies	Investigational or reported treatment options (usually with weak evidence base based on open label or observational reports)	
Dribbling of saliva	Oral atropine drops	Parotid and submandibular botulinum toxin injections (only recommended under specialist supervision in centres with experience in technique. Potential for major side effects)	
	Swallow timer and upright positioning of head		
Erectile dysfunction	Sildenafil (Viagra)	Tadalafil (Cialis)	
	Psychological assessment		
Excessive daytime sleepiness	Sleep hygiene	Caffeine intake	
	Modafinil (recommended)	A2a receptor antagonists (currently in clinical trial)	
Depression/ anxiety	Antidepressants: tricyclics as part of non-motor fluctuations	Longer acting dopamine agonist or levodopa with entacapone (non motor off)	
	Selective serotonin-reuptake inhibitors	Infusional therapies (non motor off)	
	Selective noradrenaline-reuptake inhibitors		
	Anxiety: anxiolytics		
Psychosis (hallucination and delusion)	Quetiapine	Clozapine (atypical antipsychotic that need regular blood tests for agranulocytosis)	
	Acetylcholinesterase inhibitor		
Dementia	Rivastigmine	Memantine	
	Donepezil	Other acetylcholinesterase inhibitor	
Constipation	Fibre-rich diet	Pre-defecation dopaminergic stimulation	Soluble L-dopa
	Macrogol		Apomorphine injection (subcutaneous)
	Lactulose	Psyllium husks	
Bladder dysfunction (nocturia)	Avoid night-time diuretics	Possible use of D1 receptor active long-acting dopamine agonists (rotigotine patch, apomorphine infusion)	
	Desmopressin or analogue spray		
Bladder dysfunction (urgency/frequency)	Oxybutinin, tamsulosin and related agents		
Orthostatic hypotension	Volume replenishment, drinks of water, rehydration	Pharmacotherapy	
	Avoid prolonged bed rest	Indomethacin	
	Exercise as much as can be tolerated	Ephedrine	
	Avoid alcohol, diuretics, antihypertensives	Midodrine (with specialist supervision)	
	Waist-high support stockings		
	Sodium chloride supplementation of meal		
	Pharmacotherapy		
	Fludrocortisone		

(2008) Epidemiology of Parkinson's. *J Neurol* **255**: 18–32
Berendse HW, Ponsen MM (2006) Detection of preclinical Parkinson's disease along the olfactory trac(t). *J Neural Transm Suppl* **70**: 321–5
Boeve BF, Silber MH, Ferman TJ, Lucas JA, Parisi JE (2001) Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. *Mov Disord* **16**: 622–30
Braak H, Del Tredici K, Rueb U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobio Aging* **24**: 197–210
Braak H, Ghebremedhin E, Rüb U, Bratzke H, Del Tredici K (2004) Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res* **318**: 121–34
Breen K, Drutyte G (2013) Non motor symptoms of PD disease: the patients perspective. *J Neural Transm* **120**: 531–5
Chaudhuri KR, Healy D, Schapira AHV (2006a) The non motor symptoms of PD disease. Diagnosis and management. *Lancet Neurol* **5**: 235–45
Chaudhuri KR, Martinez Martin P, Schapira AHV et al (2006b) An international multicenter pilot study of the first comprehensive self-completed non-motor symptoms questionnaire for Parkinson's disease: The NMSQuest study. *Mov Disord* **21**: 916–23
Chaudhuri KR, Martinez-Martin P, Sherman R et al (2009) The non motor staging of Parkinson's disease: results from an international pilot study. *Neurology* **72**: A 322
Chaudhuri KR, Prieto-Jurcynska C, Naidu Y 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**: 704–9
De Lau LML, Breteler MMB (2006) Epidemiology of Parkinson's disease. *Lancet Neurol* **5**: 525–35
Department of Health (2013) Payment by Results Guidance for 2013-14. www.gov.uk/government/uploads/system/uploads/attachment_data/file/214902/PbR-Guidance-2013-14.pdf (accessed 27 November 2013)
Diederich NJ, Pieri V, Hipp G, Rufra O, Blyth S, Vaillant M (2010) Discriminative power of different nonmotor signs in early Parkinson's disease. A case-control study. *Mov Disord* **25**: 882–7
Findley L (2007) The economic impact of Parkinson's disease. *Parkinsonism Relat Disord* **13**: S8–S12
Gao X, Chen H, Schwarzschild MA et al (2007) Erectile function and risk of Parkinson's disease. *Am J Epidemiol* **166**: 1446–50
Goetz CG, Fahn S, Martinez-Martin P et al (2007) Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Sacle (MDS-UPDRS): process, format and clinimetric testing plan. *Mov Disord* **22**: 41–7
Gulati A, Forbes A, Stegie F et al (2004) A clinical observational study of the pattern and occurrence of non-motor symptoms in PD disease ranging from early to advanced disease. *Mov Disord* **19**: S406
Hagell P, Nordling S, Reimer J, Grabowski M, Persson U (2002) Resource use and costs in a Swedish cohort of patients with PD disease. *Mov Disord* **17**: 1213–20
Halliday G, Lees A, Stern M (2011) Milestones in Parkinson's disease-clinical and pathological features. *Mov Disord* **26**: 1015–21
Hawkes CH, Del Tredici K, Braak H (2010) A timeline for Parkinson's disease. *Parkinsonism Relat Disord* **16**: 79–84
Hely MA, Reid WG, Adena MA et al (2008) The Sydney multicentre study of Parkinson's disease: inevitability of dementia at 20 years. *Mov Disord* **23**: 837–44
Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* **55**: 181–4
Jellinger KA (2012) Neuropathology of sporadic PD disease: evaluation and change of concepts. *Mov Disord* **27**: 8–30
Jennings D, Siderowf A, Stern M et al (2013) Evaluating phenoconversion to PD in the PARS prodromal cohort. *Mov Disord* **28**(Suppl.1): S59–60
Kang SY, Ma HI, Lim YM, et al (2013) Fatigue in drug-naïve Parkinson's disease. *Eur Neurol* **70**: 59–64
Kim JS, Youn J, Shin H, Cho JW (2013) Nonmotor symptoms in drug-induced parkinsonism and drug-naïve Parkinson disease. *Can J Neurol Sci* **40**: 36–41
Kingsbury AE, Bandopadhay R, Silveira-Moriyama L et al (2010) Brain stem pathology in PD disease: an evaluation of the Braak staging model. *Mov Disord* **25**: 2508–15
Leentjens AF, Van den AM, Metsemakers JF et al (2003) Higher incidence of depression preceding the onset of Parkinson's disease: a register study. *Mov Disord* **18**: 414–18
Lin CH, Wu RM, Chang HY et al (2013) Preceding pain symptoms and Parkinson's disease: a nationwide population-based cohort study. *Eur J Neurol* **20**: 1398–404
Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR, on behalf of the NMSS Validation Group (2011) The Impact of Non Motor Symptoms on Health-Related Quality of Life of patients with Parkinson's disease. *Mov Disord* **26**: 399–406
Martinez-Martin P, Falup Pecurariu C, Odin P et al (2012) Gender related differences in burden of non-motor symptoms in Parkinson's disease. *J Neurol* **259**: 1639–47
Marttila RJ, Rinne UK (1981) Epidemiology of Parkinson's disease-and overview. *J Neural Transm* **51**: 135–48
Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease (2003) The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. *Mov Disord* **18**: 738–50
Nègre-Pagès L, Regragui W, Bouhassira D, Grandjean H, Rascol O (2008) Chronic pain in Parkinson's disease: the cross-sectional French DoPaMiP survey. *Mov Disord* **23**: 1361–9
National Institute for Health and Clinical Excellence (2006) Parkinson's Disease. National clinical guideline for diagnosis and management in primary and secondary care. http://guidance.nice.org.uk/CG35 (accessed 29 November 2013)
Nilsson FM, Kessing LV, Bolwig TG (2001) Increased risk of developing Parkinson's disease for patients with major affective disorder: a register study. *Acta Psychiatr Scand* **104**: 380–6
Parkinson's UK (2012) Parkinson's prevalence in the United Kingdom-2009. www.parkinsons.org.uk/sites/default/files/parkinsonsprevalenceuk.pdf (accessed 21 November 2013)
Politis M, Wu K, Molloys S, G Bain P, Chaudhuri KR, Piccini P (2010) Parkinson's disease symptoms: the patient's perspectives. *Mov Disord* **25**: 1646–51
Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J (2009) Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behaviour disorder. *Neurology* **72**: 1296–300
Rabinak CA, Nirenberg MJ (2010) Dopamine agonist withdrawal syndrome in Parkinson disease. *Arch Neurol* **67**: 58–63
Schrag A, Jahanshahi M, Quinn N (2000) What contributes to quality of life in patients with PD disease? *J Neurol Neurosurg Psychiatry* **69**: 308–12
Seppi K, Weintraub D, Coelho M et al (2011) The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. *Mov Disord* **26**: S42–80
Stern MB, Lang A, Poewe W (2012) Toward a redefinition of Parkinson's disease. *Mov Disord* **27**: 54–60
Storch A, Schneider CB, Wolz M et al (2013) Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. *Neurology* **80**: 800–9
Todes CJ, Lees AJ (1985) The pre-morbid personality of patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* **48**(2): 97–100
van Hilten JJ, Weggeman M, van der Velde EA, Kerkhof GA, van Dijk JG, Roos RA (1993) Sleep, excessive daytime sleepiness and fatigue in Parkinson's disease. *J Neural Transm Park Dis Dement Sect* **5**: 235–44
Weintraub D, Koester J, Potenza MN et al (2010) Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* **67**: 589–95
Zesiewicz TA, Sullivan KL, Arnulf I 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**: 924–31

KEY POINTS

- Non-motor symptoms of Parkinson's disease are the leading cause of poor quality of life for both people with Parkinson's disease and their caregivers.
- Aspects of non-motor symptoms are now recognized as possible biomarkers for 'pre-motor' stage and 'early' stage of Parkinson's disease.
- Use of NMSQuest should be adopted in the clinic to provide 'holistic' care.
- Non-motor symptoms of Parkinson's disease can be treated, once identified, by a range of dopaminergic, non-dopaminergic and non-pharmacological strategies.