

Redressing the Balance in Parkinson's Disease Management with a Greater Focus on Non-motor Symptoms and Care-giver Health

Susanna Lindvall,¹ Johan Lökk² and Michael Wainwright³

1. Vice President, European Parkinson's Disease Association (EPDA); 2. Senior Lecturer, Institute of Neurobiology, Care Sciences and Society, Karolinska Institute; 3. Medical Writer, Uppsala Science Park DOI:10.17925/ENR.2009.04.01.31

Abstract

A more widespread use of questionnaires and scales such as non-motor symptoms (NMS)-Quest and the non-motor symptoms scale (NMSS) has confirmed that NMS, such as sleeping difficulties and speech problems, are at least as troublesome for Parkinson's disease patients as the major motor symptoms. These NMS can have a profound negative effect on patient quality of life and on the health of the person providing care. This fact is now receiving more attention in clinical practice and measures are being taken to improve the recognition and treatment of NMS, and to provide better support for care-givers. As our knowledge base of NMS expands, we are increasingly finding that some of them, e.g. olfactory deficit and rapid eye movement (REM) sleep behaviour disorder, also occur early in Parkinson's disease, possibly pre-dating a diagnosis based on motor signs alone.

Keywords

Parkinson's disease, disease management, non-motor symptoms (NMS), quality of life, care-giver health, questionnaires/scales, NMSQuest, NMSS

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Correspondence: Susanna Lindvall, Swedish Parkinson's Disease Association, Skeppargatan 52, 11458 Stockholm, Sweden. E: susanna.lindvall@swipnet.se

Parkinson's disease (PD) is most commonly recognised as a movement disorder disease. Accordingly, motor symptoms (MS) have been the focus when making diagnoses, prescribing treatment and assessing its effect. Considerable progress has been made in all three areas and effective therapies are now available to improve the quality of life (QoL) of PD patients with early- and late-stage disease. Nevertheless, it is becoming increasingly recognised in clinical practice that non-MS (NMS), such as sleeping difficulties, depression and hallucinations, can be at least as troublesome for patients as the major MS. Furthermore, NMS often have a profound effect on care-giver QoL, an aspect of PD management that has also tended to be overlooked.

This article, intended for a readership with a broad interest in PD, reviews these 'neglected' sides of the disease and highlights the value of instruments (questionnaires/scales) for gathering information about NMS and their consequences for patients and carers.

Brief Clinical and Therapeutic Background

The progressive degeneration of the dopaminergic neurons located in the substantia nigra pars compacta depletes the production of the neurotransmitter substance dopamine (DA).¹ When this loss becomes substantial, the ability of the corpus striatum to guide motor behaviour diminishes and the classic symptoms of PD begin to manifest. Four primary MS² are recognised. The first is tremor, either in the hand or foot on one side of the body, usually appearing when the muscles are relaxed (hence the term 'resting tremor'). Tremor is the first symptom of PD in the majority of patients. Second is bradykinesia, when patients experience slow or incomplete movements such as walking with short, shuffling steps.

Third is rigidity, stiffness or inflexibility of the muscles that affects activities such as getting up from a sitting position. Rigidity may also cause pain and cramping. Fourth is postural instability, seen as impaired balance and co-ordination. Combined with the symptoms noted above, postural instability increases the risk of falling and leads to freezing, where patients feel stuck to the ground and find it difficult to start walking.

Although degeneration of the DA-releasing neurons is the generally recognised cause of PD, simply replacing DA is not a feasible therapy as the compound does not cross the blood-brain barrier. However, the precursor of DA (3,4-dihydroxy-L-phenylalanine or levodopa [L-dopa]) does, and administration of L-dopa (or DA agonists) subsequently forms the basis of the pharmacological treatment of PD today. DA agonists can be especially effective in combating motor complications during the early phase of the disease.

Effective Therapy Has Reduced the Major Visible Symptoms

Treatment with L-dopa and/or DA agonists has proved to be a highly effective way to reduce the major visible MS of PD. Their effects have been particularly impressive during advanced stages of the disease when severe on-off motor fluctuations and dyskinesias are especially troublesome for patients. Furthermore, continuous dopaminergic stimulation (CDS) with L-dopa (e.g. Duodopa®) or DA agonists (e.g. apomorphine) seems to be one of the most beneficial treatment options that we can offer today.³ The alternative strategy of small, multiple doses can, for example, result in pulsatile stimulation of the DA receptors, with dramatic response swings as a result. However, as patient evaluations continued to

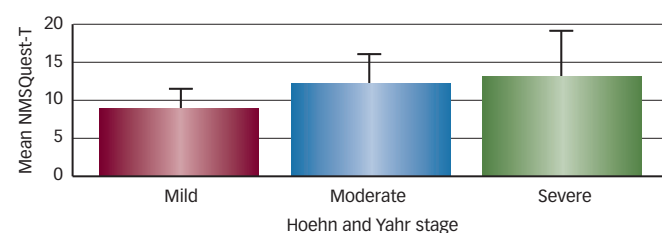
Table 1: Non-motor Symptoms in Parkinson's Disease Patients

Pain	Depression
Dementia or confusion	Fear or anxiety
Speech difficulties	Sleep disorders
Hallucinations	Constipation
Urological problems	Dribbling saliva
Swallowing problems	Olfactory deficit
Memory difficulties	Slowness in thinking
Cardiovascular problems	Loss of energy
Skin problems	Double vision
Sexual dysfunction	Compulsive behaviour, e.g. gambling

Table 2: Frequency and Distribution of Positive Answers Regarding Non-motor Symptoms

Domain	Number of Items	% of the Maximum	Positive Answers		
			Median	Mean±SD	Range
Digestive	7	29	2	2.0±1.6	0–7
Urinary	2	59	1	1.2±0.8	0–2
Memory	3	42	1	1.2±1.1	0–3
Hallucinations/ delusions	2	17	0	0.4±0.6	0–2
Depression/ anxiety	2	48	1	0.9±0.8	0–2
Sexual function	2	33	1	0.7±0.8	0–2
Cardiovascular	2	32	0	0.6±0.7	0–2
Sleep disorder	5	37	2	1.9±1.4	0–5
Miscellany	5	25	1	1.3±1.2	0–5

Classified by NMSQuest categories in a study of 545 Parkinson's disease patients. Used with permission from Martinez-Martin et al., 2007.⁸ SD = standard deviation.

Figure 1: NMSQuest-T Values Increase with Disease Severity Measured by Hoehn and Yahr Staging

Used with permission from Martinez-Martin et al., 2007.⁸

confirm the positive effects of L-dopa/DA agonist therapy on MS (e.g. a large majority of the patient's day spent in 'on' plus almost complete elimination of dyskinesias), the unresolved problem of NMS began to emerge.

Emerging Information of Non-visible Symptoms

In surveys where PD patients were asked to rate the matters they regarded as most important for their QoL, they frequently selected non-motor aspects as being more important than motor problems.⁴ For example, they rated pain, sleep problems, cardiovascular problems and urological problems as areas of special concern, and generally felt NMS to be more debilitating than MS. Furthermore, their NMS were not picked up as easily by physicians or neurologists and therefore tended to go untreated. This all points to a need for increased attention to be given to recognising and treating NMS as a

means of improving the QoL of people living with PD, as well as for those caring for them.

Common Non-motor Symptoms

The list of NMS now regarded as being capable of impairing the QoL of PD patients is long. *Table 1* summarises a number of commonly recognised symptoms today. Many of the listed symptoms can be further broken down into sub-categories. For example, sleep disorders include rapid eye movement (REM) behaviour, restless legs syndrome and periodic limb movements and excessive daytime somnolence.

Investigating the Extent and Impact of Non-motor Symptoms

Thanks to movement laboratories, special cameras, computer equipment/software and, latterly, simple video recordings, it has been relatively easy to assess the degree of a patient's motor symptoms and evaluate the effect of different therapies. Assessing the wide range of NMS associated with PD and quantifying their effect on patient QoL is not equally straightforward; nevertheless, it is clear that NMS complicate the lives of PD patients. Many NMS do not respond well to L-dopa therapy and contribute significantly to morbidity. For PD patients being looked after by a care-giver, their NMS are likely to have a profound effect on the latter's day-to-day life as well.

For example, dysarthria, a neurological speech impairment, is one of the most frequent and disabling NMS of PD. The main audible symptoms include monotony of pitch and loudness, imprecise consonants and a harsh voice. Dysarthria occurs in about 90% of people with autopsy-confirmed PD, yet despite its negative effect on communication between patients and those close to them, only 2 or 3% receive specialist treatment.⁵ Another example is visual hallucinations, which may be more distressing to carers than to patients, who often tend not to seek treatment for this problem.

To help redress the poor recognition of NMS in clinical practice, and to provide better tools for managing them, the international PD Non-Motor Group (PDNMG) was set up by K Ray Chaudhuri, P Martinez-Martin, AHV Schapira and a group of dedicated neuroscientists at the Movement Disorders Unit at King's College Hospital in London. This group recognised that PD patients frequently experience a broad range of symptoms and therefore brought together a multidisciplinary team of neurologists, geriatricians, psychologists, sleep experts, nurse specialists and cognitive experts. Significantly, the group also included patient representatives. A major 2006 review of NMS by the group⁶ largely reinforced this view of NMS, confirming that they tend to dominate the clinical picture at advanced disease stages and that they are very problematic for patients, resulting in reduced QoL and lower survival. In contrast to MS, it was also observed that NMS are often poorly recognised and insufficiently treated.

The authors highlighted the need for improved methods to grade the symptoms and named several as being suitable: Parkinson's disease questionnaire (PDQ)-39, PDQ-8 and EuroQoL (EQ)-5D for health-related QoL, the Mini-Mental Parkinson Test, the Hospital Anxiety and Depression scale, the Hamilton Depression rating scale and the Beck Depression Inventory for cognitive symptoms, SCOPA-Aut for autonomic matters and the PD Sleep Scale and Epworth Sleepiness Scale for sleep disorders.

Non-motor Symptoms Questionnaire Results Closely Correlate with Patient Quality of Life

The PDNMG devised and used two main types of questionnaire in an attempt to better evaluate NMS and thereby facilitate their diagnosis and management: a self-reported screening questionnaire for patients/carers (NMSQuest), and a quantitative scaling questionnaire for health professionals encompassing the whole range of NMS experienced by people with PD: the non-motor symptoms scale (NMSS). The NMSQuest self-completed screening tool was set up as a simple yet comprehensive means to draw attention to the presence of NMS and initiate further investigation. Thirty questions were included, only yes or no answers were required and it was estimated that patients would need between just five and seven minutes to complete the questionnaire before visiting a doctor or PD nurse.

When the NMSQuest was tested in a 2008 international pilot study of 96 healthy controls and 123 patients with various stages of treated and untreated PD,⁷ it was noted that the majority of patients (and carers) felt that the questionnaire was clear and straightforward to fill in. Significantly, 90% said that the symptoms listed reflected concerns closely correlated with their day-to-day QoL. PD patients reported at least 10 different NMS on average per patient and the number of symptoms correlated significantly with advancing disease and duration of disease. In addition, problems such as diplopia (double vision), dribbling, apathy and taste and smell problems were never previously disclosed to the health professionals. Of those with PD, 78% felt that the questionnaire helped doctors treat their condition better. It thus helped to remedy the widely held belief that many NMS are not picked up by specialists during consultation.

The following year, the definitive version of NMSQuest was used to assess 545 PD patients.⁸ This study, performed in outpatient clinics at a wide range of centres in several countries in a large population of patients with early- and late-stage disease, confirmed the prevalence of a wide range of NMS. On average, patients reported nine to 12 symptoms and only eight patients (1.6%) declared no NMS at all. Of the nine domains in the NMSQuest, the urinary category scored highest, while depression/anxiety and apathy/attention/memory were the second and third most prevalent categories, respectively. A more detailed analysis showed that the urinary symptoms of nocturnal and urgency were present in 61.9 and 55.8%, respectively, of patients with NMS. Table 2 summarises the frequency and distribution of positive responses classified by NMSQuest domains.

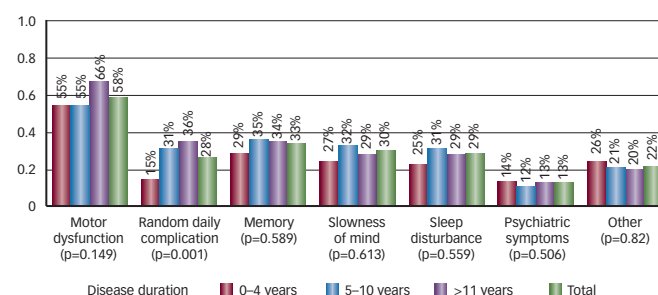
The study also revealed a strong correlation with disease severity. Hoehn and Yahr (H&Y) staging showed increasing total non-motor symptoms (NMS) scores (NMSQuest-T) with advancing disease (see Figure 1). NMSQuest-T values were 8.8 ± 4.9 , 12 ± 5.2 and 13 ± 5.5 at H&Y stages 1 to 2.5 (mild), stage 3 (moderate) and stages 4 and 5 (severe), respectively. It is suggested that non-dopaminergic NMS dominate the clinical picture of PD after a duration of 15 years.

NMS appear to correlate strongly with health-related QoL, and failure to identify and treat these symptoms is likely to worsen the situation significantly, even in the face of an apparently stable motor state. The NMSQuest questionnaire is thus considered to

Table 3: Effect on Health Reported by Parkinson's Disease Carers in the UK Parkinson's Disease Society 2007 Survey of More Than 13,000 Members⁹

Effect	Reported (%)
Stress or anxiety	87
Fatigue	69
Problems with sleep	61
Mild depression	49
Backache	43
High blood pressure	32
Difficulty concentrating	27

Figure 2: Parkinson's Disease Patient Symptoms Considered the Most Troublesome for Carers in Terms of Care-giving Duration



Used with permission from Lökk, 2008.¹⁰

have an important role in routine clinical practice when drawing up care plans for managing PD patients.

NMSQuest proved to be an excellent screening instrument for patients and care-givers, and the same can be said for the unified NMSS, this time for healthcare professionals. NMSS, which is also divided into nine domains containing 30 questions, addresses the need for simple identification and comprehensive assessment of NMS in patients with PD. To quantify disabling NMS in the 2008 study,⁷ 242 PD patients free from dementia were analysed in a pilot study on the clinimetric validation of NMSS. As with the NMSQuest data, the NMSS findings revealed a significant NMS burden that correlated well with the progression of PD.

Therefore, these studies highlight the value of focused questionnaires in bringing NMS to light: NMSQuest accurately registers the perception of PD patients of NMS, and NMSS confirms the close correlation between NMS and their QoL.

The Care-giver Situation – A Major UK Survey

With good justification, the care-giver's situation could easily be labelled the care-giver's plight. In 2007, the UK Parkinson's Disease Society conducted the largest ever survey in the UK of people with Parkinson's and carers of people living with the condition.⁹ More than 13,000 members responded and the results clearly showed that most PD carers and their families are not receiving the support or information they need.

Most informal care-givers (91%) were looking after a spouse or partner and 93% lived in the same household. Care-givers under 55 years of age were more likely to be looking after a parent (35%). A high proportion of care-givers of working age either gave up or reduced work in order to care, with the result that more than half (55%) were

financially worse off. Furthermore, just over half of the care-givers felt that their own health had suffered since living with or caring for someone with PD; for example, nearly nine out of 10 reported stress or anxiety. Table 3 summarises the health effects on care-givers who reported deterioration in their physical or mental health. This care-giver burden was compounded by the fact that only 29% of carers in the UK were aware of their right to a local services assessment that could result in additional help being provided.

Health Impact of Caring for Parkinson's Disease Patients

Several scientific studies have investigated and confirmed care-giver burden (defined as the extent to which informal care-givers perceive that their health and social life are being adversely affected because of their care-giving) in neurodegenerative dementia populations as well as in studies on traumatic brain injuries. Even care-givers of patients with less severe cognitive impairment have been observed to be more prone than normal to depression and associated symptoms. In PD, we are now beginning to see more studies examining the impact of the disease on informal care-givers. The recent study by Lökk, for example, evaluated care-giver strain in terms of different psychosocial domains and disease duration.¹⁰

The study comprised a cross-sectional telephone interview survey using a structured questionnaire of 451 care-givers randomly selected from the registry of the Swedish Parkinson's Disease Association. Four hundred and four care-givers with a mean age of 68.5 years responded. Ninety-eight per cent were spouses (62% women, 38% men). Although the mean general health condition of the care-givers was regarded as satisfactory, disease-related stress was reported by 61% and insufficient sleep by 36% of the responding care-givers, with the latter symptom showing a significant increase with disease duration. Daily physical health problems included tiredness and sleep disturbance (more than 30%), hypertension (27%), muscle strain, headache and fatigue (17%) and gastrointestinal problems (14%).

The greatest worry expressed by the carers was not being able to take care of the PD patient (46%). This was followed by patient neuropsychiatric problems (25%) such as impaired cognition and hallucinations. The most troublesome patient symptoms were motor dysfunction (58%), but NMS such as impaired memory (33%), slowness of mind (30%), sleep disturbance (29%) and psychiatric symptoms (13%) were all regarded as causing carer strain. Furthermore, many of these symptoms were experienced regularly. Impaired memory was also a cause of carer worry: 37% of care-givers had to remind patients to take their daily anti-PD medication, for example. Figure 2 summarises the PD patient symptoms that gave carers most cause for concern.

The study concluded that PD imposes a vast strain on care-givers, and it was noted that more than half of those who responded experienced little or no understanding of their situation.

Conclusions

Although the last 30 years have witnessed major advances in the management of the MS of PD, a wide range of NMS such as depression, sleep disorders and hallucinations continue to trouble PD patients and have a negative impact on their QoL. In advanced PD in particular, NMS tend to dominate the clinical situation. Fortunately, NMS are now receiving greater attention.¹¹ The PDNMG continues to play a prominent role in this work and its NMSS/NMSQuest questionnaires have proved to be valuable instruments for building up the information bank on NMS. They have even indicated that, contrary to common belief, many NMS occur early in PD. Furthermore, some problems, e.g. olfactory deficit, REM sleep behaviour disorder and male erectile dysfunction, may even pre-date a diagnosis of PD based on motor signs.¹²

While it is not the intention of this article to discuss therapeutic strategies, we can note that continued progress with continuous dopaminergic stimulation should help decrease or eliminate severe motor complications and thus alleviate one of the biggest concerns for care-givers (see Figure 2). In addition, many NMS, e.g. depression, constipation, nausea, restless legs and urological problems, can be treated by traditional means; however, harder-to-treat symptoms may require new, non-dopaminergic pharmaceutical preparations not yet introduced. This may well go hand-in-hand with the search for treatments that slow neurodegeneration.

Finally, the PD patient and care-giver situations are inevitably intertwined. Recognising care-givers as a group at risk of poor health and thereby providing them with better support will ultimately benefit the QoL of their patients as well. ■

Susanna Lindvall is Vice President of the European Parkinson's Disease Association (EPDA), President of the Swedish Parkinson Foundation, a member of the steering committee of the Swedish Parkinson Academy and a member of the Human Stem Cell Research Committee of the Karolinska Institute in Stockholm. She is the co-author of several books and articles about Parkinson's disease.

Johan Lökk is a Senior Lecturer at the Institute of Neurobiology, Care Sciences and Society at the Karolinska Institute in Stockholm. He is also a Senior Consultant and Chief Physician in the Geriatric Department of Karolinska University Hospital in Stockholm. He is the author of many scientific papers and books on Parkinson's and Alzheimer's diseases. Professor Lökk completed his specialist training in geriatrics in 1983 and internal medicine in 1987, received his PhD in 1991 and was appointed Associate Professor in 1998.

Michael Wainwright is a medical writer with a special interest in Parkinson's disease. He has a BSc in microbiology from the University College of Wales.

- Lotharius J, Brundin P, Impaired dopamine storage resulting from alpha-synuclein mutations may contribute to the pathogenesis of Parkinson's disease, *Hum Mol Genet*, 2002;11:2395–2407.
- Tolosa E, Gaig C, et al., Diagnosis and the premotor phase of Parkinson disease, *Neurology*, 2009;72(Suppl. 7):S12–20.
- Antonini A, Continuous dopaminergic stimulation from theory to clinical practice, *Parkinsonism Relat Disord*, 2007; S24–8.
- Chaudhuri KR, Martinez-Martin P, Schapira AH, et al., International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study, *Mov Disord*, 2006;21(7):916–23.
- Hartelius L, Speech and Parkinson's disease, 9th Scandinavian Meeting: From Diagnosis to Management of Parkinson's Disease' Scandmodis (Scandinavian Movement Disorders Society), Copenhagen, 27–28 March 2009.
- Chaudhuri R, Healy DG, Schapira AHV, Non-motor symptoms of Parkinson's disease: diagnosis and management, *Lancet Neurology*, 2006;5:235–45.
- Chaudhuri KR, Martinez-Martin P, Quantitation of non-motor symptoms in Parkinson's disease, *Eur J Neurol*, 2008;15(Suppl. 2):2–7.
- Martinez-Martin P, Schapira AH, Stocchi F, et al., Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients, *Mov Disord*, 2007;22(11):1623–9.
- Life with Parkinson's today – room for improvement. © Parkinson's Disease Society of the United Kingdom, 2008.
- Lökk J, Caregiver strain in Parkinson's disease and the impact of disease duration, *Eur J Phys Rehabil Med*, 2008;44: 39–45.
- Truong DD, Bhidayasiri R, Wolters E, Management of non-motor symptoms in advanced Parkinson disease, *J Neurol Sci*, 2008;266:216–28.
- Chaudhuri KR, Naidu Y, Early Parkinson's disease and non-motor issues, *J Neurol*, 2008;255(Suppl. 5):33–8.

tel / fax: +44 (0) 1732 457 683

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