The Effect of Non-motor Symptoms on Quality of Life in Parkinson's Disease

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Abstract

Non-motor symptoms (NMS) are common in Parkinson's disease (PD), affecting up to 90% of patients during their illness, and include neuropsychiatric complications, autonomic disorders, sleep disturbances and sensory symptoms. Although NMS correlate strongly with advancing disease, they may precede the onset of motor symptoms by a number of years. It is increasingly recognised that NMS result in a significant burden for people with PD and affect quality of life (QoL) to a greater extent than motor features. However, NMS often remain undiagnosed and untreated. Herein we review the impact of common NMS on QoL for patients with PD.

Keywords

Non-motor symptoms, Parkinson's disease, quality of life, depression, anxiety, psychosis, cognitive impairment, sleep disorder, fatigue, autonomic dysfunction, sensory symptoms

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Parkinson's disease (PD) affects about 1–2% of the population over 65 years of age and up to 3–5% of people 85 years of age and older.[1] As the average age of the population increases, the prevalence of PD can be expected to rise. There is increasing awareness that the non-motor symptoms (NMS) of PD significantly contribute to the overall burden of the disease, which determines quality of life (QoL). With this in mind, it is essential to optimise the management of all aspects of PD. NMS (see *Table 1*) include neuropsychiatric complications, autonomic disorders, sleep disturbances and sensory symptoms. NMS affect the majority of patients during their illness and, although NMS correlate strongly with advancing disease, they may precede the onset of motor symptoms by a number of years.[2–5] It is increasingly recognised that NMS create a significant burden for people with PD and affect QoL to a greater extent than motor features.[6–14] Without careful attention, NMS may remain undiagnosed and untreated. A recent international survey showed that up to 62% of NMS in PD might remain undeclared to healthcare professionals because patients are either embarrassed or unaware that their symptoms are linked to PD.[15] Using a screening tool can help to identify the problem. For example, in a study using the NMS Questionnaire (NMSQ), PD patients reported nine to 12 different NMS in their clinic visit, many of which had not been discussed with the doctor before being flagged by the NMSQ.[16]

Scale and Impact of the Problem of Non-motor Symptoms in Parkinson's Disease

NMS occur in up to 90% of patients with PD during their disease course.[5] Shulman et al. studied 99 patients with PD without dementia and reported that over half had at least two NMS and 25% had more than three.[5] In a more recent study of 49 patients with PD, McKinlay et al. found that 77% reached the cut-off for one or more NMS, while 46% had three or more.[10] The PRIAMO study of 1,072 consecutive patients with PD found that 98.6% of patients reported at least one NMS.[6] The frequency of NMS increased with disease severity, and patients with cognitive impairment had more NMS than those without. In the latest validation study of the Non-Motor Symptoms Scale (NMSS) in PD, only two of 411 patients reported no NMS.[17] The same study suggested that there is a close and robust correlation between the overall burden of NMS, measured by the NMSS composite score, and QoL, measured by the Parkinson's Disease Questionnaire (PDQ-39). The correlation value (Spearman r=0.7) was stronger than the correlation between QoL and motor state. This study is one of the first to establish the close link between NMS and QoL in a statistical manner in an international study spanning PD patients across all disease stages.[17] Our review focuses on the impact of common NMS on QoL for patients with PD.

Neuropsychiatry

Neuropsychiatric symptoms are among the most common NMS in PD, constitute a major problem in management, cause reduced QoL for patients and increase care-giver distress.[18]

Depression and Anxiety

Depression can occur early and may precede motor symptoms. The rate of depression in community-based samples of patients with PD is approximately 30–40%.[19] Identification of mood disturbances is critical as it is well known that depression is the most significant predictor of QoL in patients with PD.[7,8,11,13,20,21] Anxiety is relatively under-investigated in PD, despite being present in up to 55.8% of patients.[6]

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

Neuropsychiatric
Depression
Anxiety
Panic attacks
Apathy
Hallucinations, delusions, illusions
Delirium (may be drug-induced)
Cognitive impairment
Sleep Disorders and Symptoms
Restless legs syndrome
Periodic leg movements
Rapid eye movement (REM) sleep behaviour disorder
Sleep-disordered breathing
Excessive daytime somnolence
Insomnia
Autonomic
Bladder urgency, frequency, nocturia
Sweating
Orthostatic hypotension
Sexual dysfunction
Gastrointestinal Symptoms
Dribbling of saliva
Dysphagia
Nausea
Vomiting
Reflux
Constipation
Faecal incontinence
Sensory Symptoms
Pain
Olfactory disturbance
Visual disturbance (blurred vision, diplopia)
Other Symptoms
Fatigue
Weight loss
Weight gain (may be drug-related)

Schrag et al. assessed determinants of QoL using the PDQ-39 in 97 patients with PD. They found that depression was the strongest predictor of QoL impairment and was more important than clinical features of the disease, postural instability or cognitive function.[13] These results were replicated in a larger community-based sample of 233 patients with PD, in which Karlsen et al. found that the variables most strongly predictive of worse QoL (a higher total score on the Nottingham Health Profile) were depression, self-reported insomnia and a low degree of independence.[20] Severity of parkinsonism contributed to a lesser extent. In a study of Indian patients with PD, Bahari et al. also found that depression (*Diagnostic and Statistical Manual of Mental Disorders III Revision* [DMS-III-R]) was the most significant factor impairing QoL (PD Quality of Life Questionnaire).[7]

In a cross-sectional study of 190 PD patients, Muslimovic et al. found that self-reported mood symptoms and axial impairment were the main determinants of worse QoL (PD Quality of Life Questionnaire) and that both depression and anxiety were related to QoL to a similar degree.[11] Rahman et al. looked at the relative contributions of PD symptoms to patient QoL (PDQ-39).[22] The psychiatric symptom cluster accounted for 41.8% of variance of PDQ-39, and depression, confusion and fatigue symptoms significantly predicted QoL. In addition, they found that depression (Beck Depression Inventory [BDI]) accounted for 40.8% of the variance in PDQ-39. Once the contribution of depression to QoL was taken into account, self-rated anxiety on the Beck Anxiety Inventory (BAI) accounted for a further 17.0% of the variance in QoL scores. In another study looking at both depression and anxiety, Carod-Artal et al. found that anxiety (Hospital Anxiety and Depression Scale—Anxiety [HADS-A]) and depression (Hospital Anxiety and Depression Scale—Depression [HADS-D]) both independently predicted QoL (PDQ-39), but the study did not assess which contributed the most.[23]

Having a history of depression may be sufficient to lead to worse QoL. Klepac et al. studied 152 non-demented patients with PD and found that a history of pre-morbid depression was independently associated with higher actual levels of depression (BDI) and anxiety (Hamilton Rating Scale for Anxiety [HAM-A]), poorer sleep (Pittsburg Sleep Quality Index [PSQI]) and worse QoL (PDQ-39).[24] Therefore, if a patient with PD has a history of depression, he or she may be a good candidate for early intervention.

Few studies have addressed whether improving mood translates into improved QoL. Menza et al. treated 52 PD patients with paroxetine, nortriptyline or placebo for eight weeks and then had a 16-week blind extension phase. Interestingly, no difference in QoL measures was found between the three groups. However, those with improvements in depression demonstrated significant gains in PDQ-8.[25] Thus, the conclusion was that QoL improves in those patients in whom depression is treated successfully.

Psychotic Symptoms/Hallucinations

Approximately one-third of chronically treated PD patients suffer from psychosis,[26] and while visual hallucinations are often benign, more sinister symptoms such as delusions, paranoid ideation and delirium become more frequent as the disease progresses. Early identification and management are crucial as psychotic symptoms are a significant risk factor for nursing home placement and are associated with higher mortality in advanced stages of PD.[27] Psychotic symptoms are closely linked to dopaminergic treatment, but drug therapy may not be the only cause. Aarsland et al. found that psychotic symptoms were associated with severe depressive symptoms and cognitive impairment, but that antiparkinsonian medication type, daily dose and treatment duration did not differ between the PD patients with and without psychosis.[28] Several risk factors for the development of psychotic symptoms have been identified: cognitive impairment, dementia, increased age, disease duration, disease severity, depression and sleep disorders.[26]

Cognitive Impairment

Cognitive dysfunction affects 24% of patients with newly diagnosed PD,[29] while dementia affects up to 80% of PD patients with late-stage disease.[30] The correlation between cognitive impairment and QoL in patients with PD has been well-established.[9,13,21,31,32] Although having worse cognitive function predicts worse QoL, the relative impact is less than that of other NMS. Muslimovic et al. demonstrated that cognitive changes had little impact on functional outcome once the effect of motor and mood symptoms had been taken into account.[11] Co-morbid NMS seem to affect the strength of association between cognitive impairment and QoL. For example, Klepac et al. found an association between cognitive impairment and QoL but only in patients with lower depression scores; in patients with higher

depression scores, QoL was poor regardless of cognitive status. The authors also found that better visual attention/memory and better visuospatial and executive functioning in non-demented patients with PD is independently associated with better QoL.[33]

Sleep Disorders

Sleep disorders are among the most frequent NMS, occurring in up to 90% of people with PD,[34,35] and they usually start early in the disease course. They include restless legs syndrome (RLS), sleep-disordered breathing, rapid eye movement (REM) sleep behaviour disorder (RBD), excessive daytime somnolence (EDS) and insomnia. Although it is intuitive that sleep disorders would have a negative impact on patient QoL, this has not yet been adequately measured in PD. Interestingly, a small study of 11 patients with mild PD and seven patients with severe PD demonstrated that severity of disease did not differentially affect sleep disturbance.[36]

Restless Legs Syndrome

The frequency of RLS in PD is not well established. Study estimates range from 8 to 20%, but some authors have found no difference in prevalence between PD patients and controls.[37] In a cross-section analysis of 114 patients with PD, Gomez-Esteban et al. found that QoL as measured on the PDQ-39 did not differ between the PD patients with and without RLS.[37] Interestingly, in studies of patients with RLS but without PD, it has been demonstrated that RLS has a substantial negative impact on QoL – as much as other chronic neurological conditions such as stroke and PD.[38]

Rapid Eye Movement Sleep Behaviour Disorder

RBD is a frequently observed sleep disorder in people with PD, occurring in about one-third of patients, and may precede the development of cardinal motor features.[2] The problem is not benign, as self-injury and injury to the partner can occur during attacks. Little literature exists examining the effect of RBD on QoL. In a study comparing PD patients with and without RBD, Postuma et al. found that the groups did not differ in overall QoL (PDQ-39). However, the RBD group had lower 'general health' and 'emotional' subscores on the SF-36.[39]

Excessive Daytime Somnolence

EDS affects 15–50% of people with PD[40] and may be a pre-clinical marker of the disease.[3] Neuronal degeneration of the suprachiasmatic nucleus, which regulates the internal rhythm between sleep and wakefulness, may explain the early occurrence of EDS.[3] Additional contributing factors may include nocturnal sleep disruption and antiparkinsonian medications. Although it is intuitive that effectively identifying and managing EDS would improve patient QoL, there is currently little evidence.

Insomnia

The prevalence of insomnia in PD varies from 18 to 88% depending on the definitions used and the population assessed.[20,41,42] Many factors associated with PD may contribute to insomnia, including RLS, imbalance of REM and non-REM sleep, altered biological rhythms, altered breathing, effect of antiparkinsonian medications, motor fluctuations, autonomic impairments, stiffness, pain and difficulty turning in bed.[34] Insomnia and depressive symptoms have been found to be most strongly predictive of impaired overall QoL.[12,20] In a study of 102 PD patients living at home, Caap-Ahlgren and Dehlin found a strong correlation between insomnia and each of depression and pain. In addition, greater insomnia was associated with increased disease severity, and those patients with insomnia had worse QoL scores as measured by SF-36 than those without insomnia.[34] However, some authors have found only small correlations between sleep and QoL scores.[43]

Fatigue

Although fatigue is a prominent problem for many patients, occurring in up to 50%,[44,45] it is poorly understood and often overlooked.[46] It is the single most important reason cited by Americans for obtaining disability insurance payments for their PD.[47] Although often reported to be associated with depression, there is evidence that fatigue is a prominent feature of PD independently of depressive symptoms.[45,48] Herlofson and Larsen assessed 66 PD patients without depression or dementia using the Fatigue Severity Scale (FSS). Half of the sample had fatigue, and those with fatigue had more advanced disease and tended to have longer duration of disease.[45] Fatigue can also be a side effect of antiparkinsonian medications; however, in a study of non-demented, non-depressed, newly diagnosed PD patients with mild motor dysfunction, fatigue was found to be an early problem and not related only to medication.[49]

Studies have shown that PD patients have more fatigue and poorer QoL than healthy individuals or people with other chronic conditions, such as diabetes.[50] In addition, PD patients with fatigue have significantly worse QoL than PD patients without fatigue.[45] Using different measures of fatigue, Havlikova et al., Rahman et al. and Qin et al. each found that presence of fatigue predicted worse QoL (PDQ-39).[12,22,44]

The disability suffered by patients due to fatigue is significant: over half of patients with PD list fatigue as one of their three most disabling symptoms, and one-third list fatigue as the single most disabling symptom.[51] In a study from The Netherlands, 43% of 90 non-depressed patients with PD suffered from fatigue and 15% rated fatigue as their worst symptom.[52]

Sensory Symptoms

PD was previously thought to be a primary motor disorder. It has now become widely accepted that sensory symptoms, including pain, hyposmia and visual dysfunction, are prevalent in patients with PD and have a negative impact on QoL.

Pain

Pain affects up to 74% of PD patients[53] and, due to its heterogenous aetiology, presents a complex diagnostic and management issue. Pain can be secondary to PD (dystonic pain or akathitic discomfort), due to co-morbid conditions (diabetic neuropathy) or a result of PD symptoms aggravating underlying non-PD pain (abnormal gait worsening osteoarthritic hip pain).

Regardless of aetiology, pain negatively affects QoL in patients with PD.[22,53,54] Roh et al. studied 82 Korean patients with PD using the SF-36, breaking it down into the mental and physical component scores (MCS and PCS, respectively).[53] Pain, measured on a visual analogue scale (VAS), showed moderate correlation with decreased QoL, worse Unified Parkinson Disease Rating Scale (UPDRS) III, more severe depression and more somatic complaints. VAS and depression had the most detrimental impact on PCS and MCS, respectively. Pain was significantly influenced by depression and motor symptoms, as also shown by Karlsen et al.[20]

In a study assessing chronic pain in PD, Negre-Pages et al. found the prevalence to be 62%.[55] The same study found that patients with PD-related pain had worse QoL (PDQ-39) than PD patients with non-PD-related pain and PD patients with no pain.[55] Patients with PD have less frequent analgesic consumption than non-PD patients, which may reflect under-reporting or under-treatment.[55]

Olfactory Disturbance

Olfactory dysfunction may affect up to 90% of PD patients and has been shown to be a pre-clinical marker for the disease.[3,56,57] There is a paucity of research on the impact of olfactory dysfunction suffered by patients with PD.

Autonomic Dysfunction

Autonomic dysfunction is an important NMS of PD and includes a range of problems such as urinary, cardiovascular, sexual and gastrointestinal symptoms. These problems can occur early in the disease course and are not necessarily related to disease duration or severity.[58,59] Autonomic symptoms occur significantly more often in patients with PD than in age-matched controls and have a major impact on the daily life of those with PD. In a study of 141 hospitalised patients with PD, 50% rated the effect of autonomic symptoms as 'a lot' or 'very much'.[59]

Bladder Dysfunction

Bladder dysfunction, including urgency, nocturia, frequency and incontinence, is reported more commonly and has a greater impact on the daily life of patients with PD than in age-matched controls.[59] The impact can be severe: urogenital infections are a frequent cause of death in parkinsonism.[60]

Using a representative sample of a community-living Canadian population, Pohar and Allyson Jones found that having urinary incontinence results in an additional burden for the PD patient.[61] In a questionnaire-based assessment of pelvic dysfunction in patients with PD, Sakakibara et al. found that patients with PD had a significantly higher frequency of urinary urgency, daytime and night-time frequency, incontinence, hesitancy, poor stream and straining than the control group.[62] Patients with PD reported more dissatisfaction with bladder dysfunction than controls. Rahman et al. found that urinary incontinence had an effect on QoL (PDQ-39) in patients with PD, but the result was not statistically significant; however, urinary incontinence did emerge as a predictor of QoL.[22]

Sexual Dysfunction

Sexual dysfunction is common in PD but no studies have examined its effect on QoL using validated measures. A decrease in libido, sexual intercourse and orgasm, and problems with erection and ejaculation, occur significantly more frequently in patients with PD than in controls.[62] Although one might expect sexual dysfunction to negatively affect patients, Sakakibara et al.[62] found that the rate of dissatisfaction with sexual dysfunction was not significantly higher for patients with PD compared with controls.[62]

Sweating

There is a paucity of work examining the impact of sweating on QoL in PD, despite studies showing that it affects almost half of patients.[59] Swinn et al. assessed 77 consecutive patients with PD using a novel questionnaire and found that almost two-thirds reported a problem with sweating – a significantly higher proportion than in the controls. Although sweating disturbances were related to other symptoms of autonomic dysfunction, there was no association with overall QoL (PDQ-39 and EuroQ-5D). The responses to the questionnaire highlighted the impact of sweating on daily life: patients with sweating frequently felt cold/uncomfortable (33%), had disturbed sleep (29%), had to change nightwear (8%), were limited in social activities (4%), felt embarrassed (8%) and felt down (20%).[63]

Orthostatic Hypotension

Half of patients with PD complain of non-specific symptoms such as giddiness, transitory defective vision, nausea, cerebral hypoxaemia and dizziness.[60] Loss of consciousness is rare but can lead to serious injury.[60] Orthostatic hypotension is the most frequent cardiovascular symptom, reported by almost half of hospital inpatients with PD.[59,60] Blood pressure not only drops significantly upon rising, but also fails to normalise again over many minutes. In a study by Magerkurth et al. of consecutive hospitalised PD patients, orthostatic dizziness had more impact on the daily lives of patients with PD than on age-matched controls.[59]

Dribbling of Saliva

Dribbling of saliva is a frequent complaint in patients with PD, occurring in 30–74%, and results not only from excess production of saliva but also from infrequent or impaired swallowing.[40,64] Like other NMS, drooling can pre-date the diagnosis of PD and is often under-treated.[64] In an analysis of 63 PD patients with drooling, 73% had mild to moderate drooling and 27% had severe or profuse drooling. Dribbling of saliva had both emotional and social consequences in up to 77% of patients – and to a significantly greater in patients with more severe drooling.[64]

Dysphagia

Nine out of 10 patients with PD develop dysphagia during the course of their disease.[65] The consequences are severe as aspiration pneumonia is the leading cause of death in this group.[66]

There are few studies investigating the impact of dysphagia on QoL in patients with PD. Plowman-Prine et al. compared PD patients with dysphagia versus those without, using swallow-specific QoL (SWAL-QOL), general QoL (PDQ-39) and depression (BDI) as outcome measures. Both the dysphagic and non-dysphagic groups had a mild to moderate reduction in SWAL-QOL, although the dysphagic group had worse total SWAL-QOL scores. The worse the SWAL-QOL score, the worse the general QoL, which is perhaps not surprising given the overlap of questions in the two measures. The dysphagic group had significantly worse social function and mental health than the non-dysphagic group. Depression increased with worse SWAL-QOL. Interestingly, patient-reported SWAL-QOL was not related to disease duration or severity, suggesting that dysphagia is an important issue not only in advanced disease but throughout all stages of disease.[67]

Using a semi-structured interview and qualitative analysis in a sample of 37 patients with PD, Miller et al. found that dysphagia affects not only the lives of people with PD but also their carers, and swallowing impairment need not be severe before having a significant impact.[68] The consequence of dysphagia is not limited to difficulty chewing and swallowing, but also applies to activities surrounding mealtimes such as shopping, preparation and socialisation.[68]

Constipation

Constipation is a common NMS of PD and may precede the development of motor symptoms.[69] Magerkurth et al. did not find a significant difference in prevalence of constipation in hospitalised PD patients compared with age-matched healthy controls, but PD patients more frequently rated the problem as having 'a lot' or 'very much' impact on daily life.[59] In an outpatient sample of PD patients, Rahman et al. found that constipation had an effect on QoL scores only when using less stringent p-values than were set *a priori.* However, constipation was found to be a predictor of QoL.[22] Conversely, Sakakibara et al. found that PD patients had a significantly higher frequency of constipation and difficulty in expulsion and had more dissatisfaction with bowel dysfunction than the control group.[62]

Conclusion

In summary, NMS are common in patients with PD, although they are often overlooked. NMS result in a significant burden for people with PD and negatively affect QoL. Further studies are needed to assess the effect of treating NMS on improving QoL. ■

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