Chapter 2

The burden of non-motor symptoms

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Although most of the symptoms of Parkinson's disease (PD) seem to be motor-based, the non-motor symptoms (NMSs) of PD, often overshadowed, also constitute a major clinical challenge. The NMSs of PD, including neuropsychiatric, cognitive, gastrointestinal and sensory, not only are observed in later stages but also predominate in the early stages of PD. Research suggests that NMSs are present at onset, while some can precede the motor symptoms, often by many years [1–3]. The identification of premotor stages is based on the early detection of the combination of NMSs with PD detection: for example, olfactory changes are the most common NMS presenting in the early stages of PD and occur in 90% of the patients [4,5]. Surveys reveal that 90% have at least one NMS, whereas 10% of PD patients exhibit five NMSs [6]. NMSs seem to be present before the diagnosis of PD and also inevitably emerge with progression of the disease, thus having an impact on patients' health-related quality of life (HRQoL) and placing an increased burden on caregivers.

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The burden of non-motor symptoms on patients' health-related quality of life

Two important shifts

Interest in patients' HRQoL, and patient-reported outcomes including QoL measures, started when therapeutic interventions changed their focus from postponing death to improving HRQoL. As PD is a chronic debilitating condition, so far without cure, specialists became interested in measuring the impact of the disease and treatments in terms of HRQoL [7,8].

Recently, a second shift occurred, and there has been growing interest in measuring not only motor symptoms, but also NMSs. First, measures about specific NMSs, developed for the general population, were included in PD studies. Later on, there was an effort to develop domain-specific questionnaires for PD, such as the SCales for Outcomes in PArkinson's disease (SCOPA). Finally, specific scales, comprising a large number of NMSs in a single measure, such as the NMS Questionnaire (NMSQuest) and the NMS Scale (NMSS), were developed [9].

Studies using non-motor symptom measures

There is a high consistency of findings in studies using PD-specific NMS measures (Figure 2.1). Patients report, on average, 9–11 symptoms on the NMSQuest, the most frequent symptoms being nocturia, urgency, constipation and 'the blues'. The number of symptoms increases with Hoehn and Yahr (H&Y) stage [22] and disease duration. The mean severity score on the NMSS ranges from 31 to 91.

The most common NMSS domains are mood and sleep, and the NMSS scores are significantly associated with H&Y stage and motor symptoms. The relationship between NMSS and HRQoL is high, consistent and robust (Spearman $r = 0.70$ with PDQ-39 or -8) [15,18].

Motor versus non-motor symptoms: effect on patients' health-related quality of life

NMSs seem to have a greater impact on patients' HRQoL than motor symptoms [23–25]. The most frequent HRQoL determinants found in

a HRQoL review of PD were depression and H&Y stage, followed by disability, disease duration and gait disorders [7].

A study specifically analyzing the impact of motor symptoms and NMSs on patients' HRQoL found that, although motor variables contributed to 19% of the variance, inclusion of non-motor factors significantly improved the model (62%) [26]. The most important predictors of HRQoL were depression, sleep disorders and fatigue and, to a lesser extent, UPDRS motor score and H&Y stage.

Further research

NMSs have a great impact on patients' HRQoL. This relationship, when using the NMSS, is robust and of high magnitude. More research is needed to ascertain which domains of the NMSS mostly impact on which HRQoL aspects, and whether NMSs predict HRQoL in the medium or long term. Longitudinal studies are very important, because there is strong evidence that some NMSs may be preclinical characteristics of PD [27]. Finally, there are insufficient studies comparing the contribution of motor and non-motor symptoms on HRQoL, using specific NMS measures.

The burden of patient's non-motor symptoms on the caregiver

NMSs cause a significant burden to not only the patient's life, but also the caregiver's life. Figure 2.2 summarizes the main studies about the patient factors influencing the caregiver's QoL and burden.

The impact of the disease on the caregiver's wellbeing can be measured in terms of QoL or specific measures of burden. Questionnaires of the caregiver's QoL include the SF-36 [52], EQ-5D [53], WHOQOL-BREF [54] and the Scale of Quality of Life of Caregivers [55]. Older patients with lower HRQoL, higher disability and more severe motor and neuropsychological affectation are taken care of by caregivers with lower HRQoL [37,39,45,49].

There are several measures of caregivers' burden, the three most commonly used measures being: the Zarit Caregiver Burden Inventory [56]; the Caregiver Burden Inventory [57]; and the Subjective and Objective

Studies using specific non-motor symptom scales for Parkinson's disease

Reference	Sample	Symptoms, domains or score: M ± SD (range)	Most common symptoms or domains	Associated factors
NMSQuest	***n* = 100–545**	**Mean number of symptoms: 9 to 11**	**Nocturia, urgency, constipation, depression**	**H&Y stage, disease duration**
Chaudhuri, et al (2006) [10]	123 PD patients (multinational)	Symptoms: 9.6	Symptoms: nocturia (67%), urgency (61%), remembering (51%)	H&Y stage ($r = 0.31$), disease duration ($r = 0.22$)
Martinez-Martin, et al (2007) [11]	545 PD patients (multinational)	Symptoms: 10.3 ± 5.4 (0–28)	Symptoms: nocturia (62%), urgency (56%), constipation (52%) Domains: digestive, sleep	Age of onset (before/after 50 years), disease duration, H&Y stage
Chaudhuri, et al (2010) [12]	242 PD patients (multinational)	Symptoms: 10.9 ± 5.6	Symptoms: nocturia (65%), urgency (60%), concentrating (50%) Domains: gastrointestinal, sleep	NMSs present more in akinesia PD type
Wang, et al (2010) [13]	117 PD patients (China)	Not reported	Symptoms: constipation (56%), sad/blues (43%), remembering (41%)	Malnutrition
Cervantes-Arriaga, et al (2010) [14]	100 PD patients (Mexico)	Symptoms: 10.6 ± 5.5 (1–26)	Not reported	H&Y ($r < 0.25$, $p < 0.05$)
NMSS	***n* = 22–242**	**Mean of NMSS scores: 31–90**	**Domains: mood and sleep**	**H&Y stage, quality of life, motor symptoms**
Chaudhuri, et al (2007) [15]	242 PD patients (multinational)	NMSS score: 56.5 ± 40.7 (0–243)	Not reported	PDQ-8 ($r = 0.70$); H&Y ($r = 0.33$); UPDRS section 4 ($r = 0.49$); UPDRS section 3 ($r = 0.35$)
Honig, et al (2009) [16]	22 patients with advanced PD receiving intrajejunal levodopa infusion (multinational)	NMSS score at baseline: 89.9 ± 56.5; at follow-up: 39.4 ± 33.9	Not reported	Change in NMSS score associated with: PDQ-8 ($r = 0.61$). UPDRS complications ($r = 0.55$); dyskinesia score ($r = 0.41$) and proportion of day in off ($r = 0.54$)

Kim, et al (2009) [17]	23 new PD patients (Korea)	Number of symptoms: 8.3 ± 4.0 (3–17). NMSS score: 37.0 ± 28.9	Symptoms: nocturia (65%), forget things (61%), restless legs (52%)	H&Y stage ($r = 0.43$, with number of symptoms)
Martinez-Martin, et al (2009) [18]	411 PD patients (multinational)	NMSS score: 57.1 ± 44.0 (0–233)	Domains with higher mean scores: mood/apathy (11.2), sleep/fatigue (9.6), urinary (9.0)	Group differences: disease duration, H&Y stage and CISI-PD severity level ($p < 0.001$). Correlations: PDQ-39 ($r = 0.70$). SCOPA-AUT ($r = 0.64$). EQ-5D index ($r = 0.57$). Other correlations ($r = 0.38$–0.51): H&Y; SCOPA-M, -PC and -COG; CISI-PD; PDSS
Wang, et al (2009) [19]	126 PD patients (China)	NMSS score: 31.06 ± 30.88 (0–177)	Domains with higher mean scores: mood (8.26), sleep/fatigue (6.33), miscellany (3.84)	Correlations with: sleep (PSQI, $r = 0.63$); anxiety (HAMA, $r = 0.52$); depression (GDS, $r = 0.45$)
Cervantes-Arriaga, et al (2010) [14]	100 PD patients (Mexico)	NMSS score: 69.7 ± 56.9 (0–237)	Not reported	H&Y ($r < 0.25$, p 0.05)
Checklist of 48 NMSs grouped into 12 domains	***n* = 1072–1130**	**Mean number of symptoms: 8**	**Domains: gastrointestinal**	**H&Y stage, quality of life**
Barone, et al (2009) [20]	1072 PD patients (Italy)	Symptoms: 7.8 ± 4.9 (0–32) Domains: 5.5 ± 2.5 (0–12)	Symptoms: fatigue (58%), anxiety (56%), leg pain (38%) Domains: psychiatric (67%), sleep (64%), gastrointestinal (61%)	H&Y stage (all domains except cardiovascular); cognitive impairment (6 domains); PDQ-39 (all domains)
Colosimo, et al (2010) [21]	1130 PD patients (Italy)	Symptoms: 8 Domains: 5.5	Domains: gastrointestinal (62%), pain (61%), urinary (58%)	None analyzed

Figure 2.1 Studies using specific non-motor symptom scales for Parkinson's disease . CISI-PD, Clinical Impression of Severity Index for Parkinson's Disease; GDS, Geriatric Depression Scale; HAMA, Hamilton Rating Scale for Anxiety; H&Y, Hoehn and Yahr scale; NMS, non-motor symptom; NMSQuest, Non-Motor Symptoms Questionnaire; NMSS, Non-Motor Symptoms Scale; PD, Parkinson's disease; PDQ-39, Parkinson's disease Questionnaire – 39 items; PDQ-8, Parkinson's disease Questionnaire – 8 items; SCOPA-AUT, SCales for Outcomes in PArkinson's disease – Autonomic; SCOPA-COG, SCales for Outcomes in PArkinson's disease – Cognition; SCOPA-M, SCales for Outcomes in PArkinson's disease – Motor; SCOPA-PC, SCales for Outcomes in PArkinson's Disease – Psychiatric Complications; UPDRS, Unified Parkinson's disease Rating Scale.

Studies about patient's factors influencing the caregiver's quality of life

Reference	Study type: sample, country, design	Patient factors: disease related, NMS, motor symptoms, others	Outcome measure: caregiver's burden; caregiver's QoL
Miller et al (1998) [28]	54 dyads (patient–caregiver), UK, multiple regression	**NMS:** depression	**Caregiver's burden:** GHQ-30, Depression (GDS, BDI); Machine Strain Scale
Carter et al (2004) [29]	380 caregivers, USA, group differences	**Disease related:** disease severity	**Caregiver's burden:** Family Care(giving) Inventory
Meara et al (1999) [30]	79 caregivers, UK, correlations	**NMS:** depression, cognition **Disease related:** disease severity	**Caregiver's burden:** depression (GDS-15)
Habermann (2000) [31]	8 caregivers, USA, qualitative study	**NMS:** Feelings of struggle and frustration	**Caregiver's burden:** interview about challenges that CG experience
Fernandez et al (2001) [32]	45 dyads, USA, multiple regression	**Disease related:** disease duration	**Caregiver's burden:** depression (HAMD, BDI)
Caap-Ahlgren and Dehlin (2002) [33]	65 dyads, Sweden, multiple regression	**NMS:** depression **Others:** disability	**Caregiver's burden:** scale, depression (GDS)
Edwards and Scheetz (2002) [34]	41 caregivers, USA, multiple regression	**Others:** activities of daily living	**Caregiver's burden:** Zarit Caregiver Burden Inventory
Happe and Berger (2002) [35]	106 caregivers, Germany, multiple regression	**Disease related:** disease severity (with caregiver's sleep) **NMS:** depression (with caregiver's depression), sleep (with caregiver's sleep)	**Caregiver's burden:** Caregiver Burden Inventory, depression (CES-D); sleep
Thommessen et al (2002) [36]	58 couples, Norway, structural equation modelling	**NMS:** cognition, depression	**Caregiver's burden:** Relative Stress Scale

Martinez-Martin et al (2004) [37]	86 dyads, Spain, correlations	**Disease related:** disease duration and severity **NMS:** Neuropsychological disorders Questionnaire (verbal communication, mental state, depression, sleep, bladder incontinence, perception alterations) **Motor symptoms:** UPDRS (I–IV) **Others:** disability	**Caregiver's QoL:** Scale of Quality of Life of Caregivers
Pal et al (2004) [38]	40 PD patients and 23 caregivers, Canada, correlations	**NMS:** depression, anxiety and sleep	**Caregiver's burden:** caregiver's depression, anxiety and sleep
Martinez-Martin et al (2005) [39]	57 dyads, Spain, multiple regression	**Motor symptoms:** UPDRS (I–III) **Others:** disability (ISAPD-ADL); QoL (PDQ-8)	**Caregiver's QoL:** Scale of Quality of Life of Caregivers
Cifu et al (2006) [40]	49 dyads, USA, correlations	**Disease related:** disease severity **NMS:** cognition **Motor symptoms:** motor examination **Others:** disability	**Caregiver's burden:** Zarit Caregiver Burden Inventory; Caregiver Distress Scale
Schrag et al (2006) [41]	123 caregivers, UK, correlations	**Disease related:** disease duration and severity **NMS:** depression, hallucinations, confusion, falls **Others:** disability, QoL	**Caregiver's burden:** Caregiver Burden Inventory, depression (BDI) **Caregiver's QoL:** Scale of Quality of life of Caregivers
Schestatsky et al (2006) [42]	21 dyads, Brazil, correlations	**Others:** patient's age	**Caregiver's QoL:** WHOQOL-BREF

Figure 2.2 Studies about patient's factors influencing the caregiver's quality of life (continues overleaf).

Studies about patient's factors influencing the caregiver's quality of life (continued)

Reference	Study type: sample, country, design	Patient factors: disease related, NMS, motor symptoms, others	Outcome measure: caregiver's burden; caregiver's QoL
Aarsland et al (2007) [43]	94 caregivers, Norway, multiple regression	**NMS:** depression, cognition (Relative Stress Scale), depression, neuropsychiatric symptoms, cognition (caregiver's depression and distress)	**Caregiver's burden:** Relative Stress Scale; depression (BDI); distress (GHQ-12)
Aarsland et al (2007) [43]	537, multinational, descriptive	**NMS:** agitation, psychosis, mood	**Caregiver's burden:** caregiver's distress (Neuropsychiatric Inventory)
Kim et al (2007) [44]	76 caregivers, Korea, group differences	**Disease related:** disease duration (with subjective burden) and severity (with objective burden) **Others:** disability (UPDRS II with objective and subjective burden)	**Caregiver's burden:** subjective and objective Burden Scale
Martinez-Martin et al (2007) [45]	80 dyads, Spain, multiple regression	**Disease related:** disease severity **NMS:** mood (depression, anxiety) **Others:** QoL (EQ-5D), disability	**Caregiver's burden:** Zarit Caregiver Burden Inventory, HADS **Caregiver's QoL:** SF-36, EQ-5D
Carter et al (2008) [46]	219 caregivers, USA, multiple regression	**Disease related:** cognition (delayed recall), depression **Others:** disability (UPDRS-ADL)	**Caregiver's burden:** Family Care (giving) Inventory; depression (CES-D)
Lokk (2008) [47]	404 caregivers, Sweden, structured interview	**Disease related:** disease duration **NMS:** cognition, hallucinations, memory, bradyphrenia, sleep **Motor symptoms:** motor dysfunction, motor complications	**Caregiver's burden:** questions about perceived worry, stress, mood and sleep **Caregiver's QoL:** EQ-5D visual analogue scale (0–10)

Martinez-Martin et al (2008) [48]	286 dyads, Spain, multiple regression	**Disease related:** disease severity (with caregiver's burden and depression) **NMS:** sleep, cognition, NMS (with caregiver's burden), NMS (with caregiver's QoL) **Motor symptoms:** motor complications (with caregiver's burden) **Others:** disability, QoL, age (with caregiver's burden), patient's QoL (with caregiver's QoL)	**Caregiver's burden:** Zarit Caregiver Burden Inventory, caregiver's anxiety and depression (HADS) **Caregiver's QoL:** EQ-5D
D'Amelio et al (2009) [49]	Caregivers, Italy, path analysis	**NMS:** behavioral problems (with burden); cognitive impairment (with QoL) **Others:** patient–caregiver relationship (with burden); perceived social support (with burden); frequency of breaks (with QoL)	**Caregiver's burden:** Caregiver Burden Inventory **Caregiver's QoL:** Scale of Quality of Life of Caregivers
Stella et al (2009) [50]	50 dyads, Brazil, correlations	**Disease related:** disease severity and age of onset (dementia group) **NMS:** neuropsychiatric symptoms **Others:** UPDRS functional (dementia and depression patient groups)	**Caregiver's burden:** distress score of Neuropsychiatric Inventory
Roland et al (2010) [51]	5 spouses, Canada, semi-qualitative	**Others:** motor fluctuations, safety	**Caregiver's burden:** repertory grid

Figure 2.2 Studies about patient's factors influencing the caregiver's quality of life (continued). BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; GDS, Geriatric Depression Scale; GHQ2, General Health Questionnaire-2; HADS, Hospital Anxiety and Depression Scale; HAMD, Hamilton Rating Scale for Depression; H&Y, Hoehn and Yahr staging; ISAPD, Intermediate Scale for Assessment of Parkinson's Disease; NMS, non-motor symptoms; PD, Parkinson's disease; PDQ-8, Parkinson's disease Questionnaire – 8 items; QoL, quality of life; SF-36, Short Form Health Survey – 36 items; UPDRS, Unifies Parkinson's Disease Rating Scale; WHOQOL-BREF, World Health Organization Quality of Life – Brief.

Burden Scale [58]. Measures of specific symptoms or general distress have also been used to measure caregivers' burden.

The disease-related factors that most affect caregivers' burden are severity and duration. Almost half of the revised studies identified the patient's disability as an important determinant of the caregiver's burden. However, few studies found a significant association between motor dysfunction and the caregiver's burden [37,40,47,48]. Relative to NMSs, the caregiver's burden seems to be mostly affected by the patient's depression and impaired cognitive function, followed by sleep disturbances and hallucinations. A study specifically comparing the effect of motor and non-motor symptoms in the caregiver found that a patient's depression and cognitive impairment had a greater impact on a caregiver's depression and strain than a patient's disability [46]. Research about the impact of NMSs, using specific NMS measures, on caregivers' burdens and QoL is needed.

Economic costs

PD is the second most common neurodegenerative disorder; it increases with age and affects about 1 million people in the USA and about 5 million people worldwide [59]. Given the progressive nature of PD, such an increase will have a significant impact on the burden of the health-care system and caregivers, with considerable caregiving required in the later stages of PD [59].

NMSs range from autonomic and neuropsychiatric symptoms to sleep disturbances and sensory problems. Although cognitive impairment has a lesser impact compared with other NMSs, it continues to be one of the major reasons for admission to institutional care [60,61]. Autonomic dysfunction can occur early in the disease and may not necessarily be related to disease severity. One study reported that half the sample of hospitalized PD patients rated autonomic symptoms as 'a lot' or 'very much' [62].

In the UK, the annual direct costs for patients living in full-time institutional care was estimated at about £19 338, five times higher than in the home setting [63]. Costs for NMS drug therapy increase with clinical progression of symptoms, thus contributing to higher economic costs, especially for patients with a fixed income from pensions and govern-

ment benefits [61,64]. Economic costs are doubled by each H&Y stage, especially after stage 2.0 [65].

NMSs also account for the burden of hidden costs such as sick leave, early retirement and informal care not only for patients but also for caregivers in certain instances. The cost burden of NMSs is significantly high, especially in patients with advanced PD and increasingly severe symptoms, for whom there is a poorer QoL, reduced productivity and a greater need for health-care services, which in turn have an impact on direct and indirect costs.

Thus, identifying disease-modifying treatments early in the disease, before any functional or motor disability appears, is critical in reducing costs and preserving QoL. Evidence suggests that initial therapy with non-levodopa agents is cost-effective, prolongs time to levodopa initiation and delays the onset of dyskinesias [66,67]. Results of the ADAGIO trial hint that rasagiline can reduce the progression of NMSs, as assessed using Movement Disorder Society (MDS)-UPDRS [68–70].

Conclusions

There is a significant interrelationship of severity of disease, QoL, patient's and caregiver's burden, and cost of illness. NMSs contribute to the overall PD burden, which is a major determinant of QoL. An increasing awareness of 'at-risk' individuals, based on detection of some or a combination of NMSs, is essential for an early identification of PD patients. Identification of prodromal patients plays a key factor in preventing the burden of economic costs and improving QoL of patients and caregivers. Keeping this in mind, it becomes important to optimize the management of all aspects of NMSs in PD.

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