Introduction
Value-based healthcare is a key aspect of modern approaches of delivery of medical care. Outcome measures are therefore a major aspect of addressing the importance of healthcare delivery and the objectives it aims to achieve. Besides motor symptoms, non-motor symptoms (NMS) in Parkinson’s disease (PD) drive quality of life across all stages of the disease, as well as societal costs. Objective measurement is possible using validated tools, both patient self-rated and healthcare professional-administered. Mixed motor and non-motor objective assessments are therefore recommended in order to achieve an adequate evaluation and management tailored to the patients’ specific needs [1]. Furthermore, the availability of assessment instruments for detecting and measuring NMS has allowed understanding of their importance, prevalence, presentation, progression, and impact on the patients’ daily life, and the evaluation of the effect of interventions in PD patients [2].

In this book chapter, we will summarize some of the key assessment tools for NMS, being the core symptoms during the early phase of PD [3]. First, we will review tools addressing NMS holistically and second, we will review tools addressing specific NMS (Table 2.1).

Holistic Assessment Tools for Non-Motor Symptoms in Parkinson’s Disease

Non-Motor Symptoms Questionnaire
The NMS Questionnaire (NMSQuest) is a screening instrument for the detection of NMS in patients with PD and was the first validated tool in 2006 that specifically assesses NMS in PD in a holistic manner. The NMSQuest is a self-administered questionnaire and is answered in a “yes” and “no” fashion that can be easily completed by the patient or carer within 5–7 minutes. It includes 30 items composed of nine different NMS domains: digestive (seven items); urinary (two items); apathy/attention/memory (three items);...
hallucinations/delusions (two items); depression/anxiety (two items); sexual function (two items); cardiovascular (two items); sleep disorders (five items); and miscellaneous (pain, weight change, swelling, sweating, diplopia) (five items) [4].

The total score (range: 0–30) is easily obtained from the sum of the “yes” responses, revealing the number of NMS experienced by the patient over the last month. Chaudhuri and colleagues proposed a grading classification of NMS burden based on the NMSQuest total score; 0 = no NMS; 1–5 NMS = mild burden; 6–9 NMS = moderate burden; 10–13 NMS = severe burden; and >13 NMS = very severe burden [5].

As a result of its design and content, the NMSQuest can be applied in other neurological disorders and has been already used in motor neuron disease (MND) and restless legs syndrome (RLS), for example [6, 7]. The NMSQuest has been translated into a number of different languages including Chinese (Mandarin), Dutch, French, German, Greek, Italian, Japanese, Malay, Spanish, Swedish, and is owned by the Movement Disorders Society (MDS) thus requires their permission for use.

The NMSQuest provides the clinician and specialist nurse, even at a primary care level, with a tool to easily screen for NMS in a simple manner which might help to refer patients to multidisciplinary care and can measure the effect of therapeutic interventions [8]. Grading of NMS using the NMSQuest is considered a quality standard for assessment of PD as also reflected in the NICE guidelines (2017) for PD [9].

**Non-Motor Symptoms Scale**

The Non-Motor Symptoms Scale (NMSS) for Parkinson’s disease (PD) was developed by the MDS Non-Motor-PD study group in order to comprehensively assess a wide spectrum of NMS in PD patients across all stages of the disease [10]. The 30-item scale includes nine different NMS domains: cardiovascular (two items), sleep/fatigue (four items), mood/cognition (six items), perceptual problems/hallucinations (three items), attention/memory (three items) gastrointestinal tract (three items), urinary (three items), sexual function (two items), and miscellaneous (four items). Each item is scored for severity (0 = not present to 3 = severe) and frequency (1 = rarely to 4 = daily) and then multiplied to obtain the item total score (0–12). By adding all corresponding item scores, the score for each domain is calculated. The NMSS total score is obtained from the sum of the nine domain scores and ranges between 0 and 360, with higher scores indicating a more severe NMS burden. Similar to the NMSQuest, based on the NMSS total score a NMS burden grading has been categorized as follows: 0 = no NMS; 1–20 = mild burden; 21–40 = moderate burden; 41–70 = severe burden, and ≥71 = very severe burden [11]. The NMSS is administered by a trained healthcare professional through direct questioning/interviewing of the patient and/or their carer and typically takes 10–15 minutes to complete. The NMSS has been internationally validated and is available in a number of different languages, including French, German, Italian, Norwegian, Spanish, Swedish, and Japanese [12–14]. More recently, the MDS has supported an update of the above described NMSS considering the strengths and weaknesses that have been noticed over the years. The primary clinimetric validation of the English version of the so-called Movement Disorder Society Non-Motor Rating Scale (MDS-NMS) has just been published [15]. Similar to the NMSS, the MDS-NMS is also health-professional completed, it includes 52 items grouped into 13 different non-motor domains: depression (five items), anxiety (four items), apathy (three items), psychosis (four items), impulse control and related disorders (four items), cognition (six items), orthostatic hypotension (two items), urinary (three items), sexual (two items), gastrointestinal (four items), sleep and wakefulness (six items), pain (four items), and other (five items; unintentional weight loss, decreased smell, physical fatigue, mental fatigue, and excessive sweating). Each item is scored by severity (0 = not present to 4 = severe) and frequency (0 = never to 4 = majority of time) and then multiplied to obtain the item total score (0–16). Total scale score range is 0 to 832 points.

Based on the NMSS, the new MDS-NMS has been specifically improved with domains assessing cognition and other neuropsychiatric symptoms and a new domain to address impulse control and related disorders. Furthermore, a new subscale evaluating non-motor fluctuations has been added, an aspect that was not sufficiently captured with the NMSS. The estimated time to complete the MDS-NMS varies between 15 and
40 minutes according to the non-motor burden and health status of the respective patient.

In the research setting, the NMSS and now the new MDS-NMS serve as both primary and secondary outcome measures in clinical trials [1] which provide the scientific community with invaluable information on tracking disease progression, disease subgroups, and responses to existing and novel therapies [15].

The Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale

The great importance of the accurate detection and evaluation of NMS in PD was recognized by the MDS who in 2008 sponsored a revision of the original Unified Parkinson’s Disease Rating Scale (UPDRS) [16] initially designed [17]. The so-called MDS–UPDRS evaluates the severity of the main motor and non-motor manifestations in PD combining clinician-reported and patient-reported outcomes. The scale is composed of four sections: Part I, Non-Motor Aspects of Experiences of Daily Living (13 items); Part II, Motor Aspects of Experiences of Daily Living (13 items); Part III, Motor Examination (33 items); and Part IV, Motor Complications (six items). It takes approximately 30 minutes to complete the MDS-UPDRS.

Each item scores from 0 (normal) to 4 (severe), and the total score for each part is obtained from the sum of the item scores [16]. The total scale score range is 0 to 260, with higher scores indicating a more severe burden.

In more detail, the MDS-UPDRS Part I, the section of the MDS-UPDRS designed to evaluate NMS, includes 13 items, six rater-based, evaluated through interview, and seven through a self-completed patient questionnaire, each one evaluating the severity of a NMS relevant in PD. The MDS-UPDRS has been made available in numerous languages including Arabic, Chinese (traditional and simplified), Czech, Dutch, Estonian, French, German, Greek, Hebrew, Hindi, Hungarian, Italian, Japanese, Korean, Polish, Portuguese, Russian, Slovak, Spanish, Thai, and Turkish.

Gallagher and colleagues [18] analyzed the convergent validity of the MDS-UPDRS Part I and suggested that the MDS-UPDRS Part I, despite its brevity, appropriately reflects the burden of NMS in PD patients and is indicative of performance on an extensive battery of established scales, making the MDS-UPDRS Part I an easy and practical tool to assess the burden of NMS in PD.

The MDS-UPDRS is nowadays among the standardized clinical assessment tools most widely used in PD, having been cross-culturally adapted to many countries [19], and having proven good reliability and intra- and inter-observer validity [20–22]. As a limitation, one needs to acknowledge that completion time of the MDS-UPDRS is relatively long and, similar to the NMSS, needs specific training to be administered [2].

Specific Assessment Tools for Individual Non-Motor Symptoms in Parkinson’s Disease

For years, different rating scales have been developed to assess specific NMS in PD patients. In this section, we will review those PD-specific instruments that have been deemed as recommended by the MDS and that have been used in studies with newly diagnosed or early-stage PD patients.

Pain

Several rating scales have been used in clinical research and practice for assessing pain in PD, such as the McGill Pain Questionnaire [23], the Brief Pain Inventory [24], and the Neuropathic Pain Symptoms Inventory [25]. However, there is only one PD-specific rating scale that has been classified as recommended for assessing pain by the MDS Task Force [26], the King’s PD Pain Scale (KPPS) [27]. There are also items on pain in the main comprehensive instruments for assessing NMS in PD, the NMSS (one item on pain), the MDS-NMS (one domain that includes different types of pain), and the MDS-UPDRS (one item on painful OFF-state dystonia). These scales have been presented earlier in this chapter.

The KPPS is composed of 14 items assessing musculoskeletal, chronic, fluctuation-related, nocturnal, orofacial, swelling, and radicular pain in the past month. Items are scored for severity (0 to 3) and frequency (0 to 4) and then multiplied to obtain the item total score. Total scale score range is 0 to 168 points, with higher scores indicating more pain. It is administered by a clinician through interview and it takes around 10 minutes to be completed. The KPPS has a complete validation study, with good acceptability, reliability, and

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validity. It has been used in clinical trials [28, 29], and has been demonstrated to be sensitive to changes due to treatment [30]. Among its weaknesses, the need for training of clinicians to recognize the nosological categories of pain included in the scale, the absence of information on the interpretability of scores, and the lack of versions adapted to and validated in languages other than English should be cited [26].

Sleep

Main PD-specific rating scales for assessing sleep disturbances include the SCales for Outcomes in PARkinson’s disease – Sleep (SCOPA-Sleep) and the Parkinson’s Disease Sleep Scale (PDSS) and its revised version (PDSS-2) [31–33]. Multidomain scales such as the NMSQuest, the NMSS, and the MDS-UPDRS include items that evaluate sleep disorders, and the MDS-NMS includes a six-item domain assessing sleep and wakefulness. These scales, together with other widely used generic instruments for evaluation of sleep disorders in PD, have been previously reviewed by the MDS and other authors [34, 35].

The SCOPA-Sleep was the first instrument specifically developed to assess sleep problems in PD. It is a self-completed scale, using the previous month as its time frame, composed of 12 items grouped in two domains: night-time sleep (five items) and daytime sleepiness (six items), scored from 0 (not at all) to 3 (very much). Higher scores in both domains reflect more severe sleep disorders. Cut-off points have been identified: 6/7 for nocturnal sleep to differentiate good sleepers from poor sleepers, and 4/5 for daytime sleepiness, to separate excessive daytime sleepiness from normal scores. The scale also contains a single question rating sleep quality on a seven-point scale (from slept very well to slept very badly) which is not included in the total scale score. The scale shows good reliability and validity in the validation studies, it is easy to complete (5–10 minutes), and seems to be sensitive to changes due to treatment [36, 37]. SCOPA-Sleep has been originally developed in Dutch, but it has been translated and validated in several languages, including English, Spanish, German, and Korean. Due to its properties, it is recommended and owned by the MDS [35]. Its limitations include the need for further studies on its responsiveness and interpretability and the lack of specific items addressing some sleep-related disturbances, such as RLS and REM behavior disorder (RBD).

The PDSS is a PD-specific, 15-item self-rated scale that mainly evaluates night-time sleep problems over the previous week, with only one item pertaining to daytime sleepiness. Each item is rated in a visual analog scale (VAS) from 0 (severe and always present) to 10 (not present). Item scores are summed, with a maximum total score of 150 indicative of absence of sleep problems. The PDSS has satisfactory psychometric properties and is easy to use; thus it is recommended for screening and measuring severity of sleep disturbances in PD [34, 35]. It has been proven to be responsive to changes due to treatment and it has been translated into several languages [38]. The scale has been used to characterize sleep problems and their physiological correlates in untreated PD patients [39–42]. However, patients could require explanation on how to score the VAS, and the scale does not include information from the caregiver. It does not screen for specific sleep disorders in PD, such as sleep apnea, RBD, or RLS and the only item on daytime somnolence is not enough to assess it.

The PDSS-2 was designed to overcome two of the shortcomings of the PDSS: the scoring system has been replaced by a Likert-type one (from 0, never, to 4, very frequent), and all the 15 items are focused on nocturnal sleep [33]. Maximum total score is 60, reflecting higher sleep problems severity. Cut-off values have been determined: ≥15 points have been determined to distinguish between good and bad sleepers, and ≥18 to define clinically relevant PD-specific sleep disturbances [43, 44]. Its time frame is the last week, and is easily self-responded, taking around 10 minutes to be completed. The PDSS-2 has satisfactory reliability and validity, it seems to be responsive to changes, and it has versions in several languages. A roommate-based version in Spanish has been also tested [45, 46]. In drug-naïve PD patients, the RBD as assessed with the PDSS-2 was associated with cognitive dysfunction, anxiety, and other sleep disturbances [47]. However, there is a need for further studies on its responsiveness.

Autonomic Dysfunction

The rating scales for assessing dysautonomia have been reviewed by two MDS Task Forces [48, 49].
There are several instruments for assessing autonomic symptoms, such as the Drooling Rating Scale (DRS), Sialorrhea Clinical Scale for PD (SCS-PD), and the Composite Autonomic Symptom Scale (COMPASS). The main global, PD-specific measure for autonomic dysfunction is the SCOPA-Autonomic (SCOPA-AUT), although the NMSQuest, the NMSS, the MDS-UPDRS, and the MDS-NMS contain items or domains focused on autonomic symptoms [50].

The SCOPA-AUT is a self-completed instrument composed of 25 items assessing the following domains: gastrointestinal (seven items), urinary (six items), thermoregulatory (four items), pupillomotor (one item), and sexual (two items for men and two items for women). The response options for each item range from 0 (never) to 3 (often), with higher total scores reflecting worse autonomic functioning. It is easy to apply (around 10 minutes), and has good psychometric properties using both Classical Test Theory and Item Response Theory, although its association with objective physiological autonomic measures is not clear [51]. Using the SCOPA-AUT, researchers have found there are autonomic symptoms in early stages of PD, although mild, and they can be an early marker of cognitive impairment in de novo PD patients [52, 53]. The SCOPA-AUT has been translated and validated in several languages. It is a recommended scale by the MDS, but several limitations must be accounted for: its sensitivity for screening orthostatic symptoms is low and its responsiveness has not been determined.

**Fatigue**

Fatigue is a prominent NMS in PD patients, even in early stages, and thus, it has been addressed in a high number of studies using a wide variety of rating scales. The MDS Task Force on fatigue recommended the use of the instruments Fatigue Severity Scale (FSS) for both screening and severity rating; the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT), and the Parkinson Fatigue Scale-16 item (PFS-16) for screening; and the Multidimensional Fatigue Inventory (MFI) for severity [54]. Between the multidimensional instruments, the MDS-UPDRS and the NMSS contain one item on fatigue, and the MDS-NMS includes one item on physical fatigue and one item on mental fatigue.

The PFS-16 is the only PD-specific instrument available for assessing fatigue. It is focused on physical, but not on cognitive or emotional, aspects of fatigue, and includes items on the impact of fatigue in activities of daily living [55]. The item response options range from 1 (strongly disagree) to 5 (strongly agree), and the final score can be calculated as the mean of item responses, using a binary approach (options agree and strongly agree score as 1 and the rest as 0), or summing the 16 items’ scores. The time frame is the last 2 weeks, and it takes around 15 minutes to be administered. It has versions validated in several languages, with satisfactory psychometric properties, although the binary scoring showed lower measurement precision [56]. The PFS-16 is useful to detect fatigue and assess changes due to treatment in early PD patients [57]. The main criticism is this scale may not adequately reflect clinically significant non-physical aspects of fatigue [54].

**Neuropsychiatric Symptoms**

Several MDS Task Force committees have reviewed the available rating scales for the main neuropsychiatric symptoms in PD, that can be present even in early stages: anxiety, depression, apathy, fatigue, psychosis, and impulsive and compulsive behaviors [54, 58–61].

For anxiety, none of the revised scales, all generic, reached the category of recommended. For this reason, a new PD-specific scale, the Parkinson Anxiety Scale (PAS) was developed [62]. The PAS includes 12 items, grouped into subscales for persistent and episodic anxiety and avoidance behaviors. Items are scored from 0 (not or never) to 4 (severe or almost always), with a maximum total score of 48 points, suggestive of severe anxiety. A cut-off ≥14 points for anxiety has been suggested. It is a brief and easy-to-apply scale, with clinician- and patient-rated versions and good psychometric properties. In an Italian study, 58.4% of early PD patients showed anxiety symptoms using the PAS [60, 63]. The disadvantages of the PAS include the lack of information on its responsiveness and its adequateness for patients with dementia.

The main multidimensional scales for NMS in PD also include questions for assessing anxiety; the NMSQuest, the NMSS, and the MDS-UPDRS each have one item, while the MDS-NMS has a four-item domain, focused on general anxiety,
panic attacks, and worries about being in public and in social situations [15].

For depression, three generic rating scales reached the classification recommended by the MDS Task Force: the Hamilton Depression Scale (Ham-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Beck Depression Inventory-II (BDI-II). No PD-specific rating scale for depression exists, but the MDS Task Force does not recommend developing new scales [59]. Multidimensional PD rating scales also contain items for assessing depression: one in NMSQuest, NMSS, and MDS-UPDRS and a domain in the MDS-NMS [59]. In this instrument, the five items that compose the domain are addressed to assess the emotional component of depression: sadness, difficulty experiencing pleasure, hopelessness, negative thoughts, and feelings that life is not worth living.

Apathy is also a component of the main multidimensional rating scales for PD: the NMSQuest, the NMSS, and the MDS-UPDRS, with one item on apathy in each one; and the MDS-NMS with a domain composed of three items. The MDS Task Force on apathy categorized one PD-specific rating scale as recommended, the Apathy Scale (AS) [64, 65]. This scale consists of 14 items, scored from 0 (a lot) to 3 (not at all) for items 1–8, and from 0 (not at all) to 3 (a lot) for items 9–14. Maximum total score, indicative of severe apathy, is 42 points. The cut-off value for the presence of apathy is ≥14 points. The AS is rapid, simple, and suitable for screening and has demonstrated good reliability, validity, and sensitivity to change. It has been specifically validated in early-stage PD patients, and some studies have shown that apathy is present in up to 26% of these patients [66, 67]. However, there are concerns about its adequateness for PD patients with dementia.

For psychosis, the MDS Task Force recommended the following generic rating scales: the Neuropsychiatric Inventory (NPI), the Schedule for Assessment of Positive Symptoms (SAPS), the Positive and Negative Syndrome Scale (PANSS), and the Brief Psychiatric Rating Scale (BPRS) [58]. Before this review, some PD-specific scales for assessing psychosis have been developed and validated: the Parkinson Psychosis Questionnaire (PPQ), the Ardouin Scale of Behavior in Parkinson’s Disease (ASBPD), and the Scales for Outcomes in Parkinson’s Disease-Psychiatric Complications (SCOPA-PC) [69–71]. Parkinson’s disease-related psychosis is captured in other validated multidomain scales such as the MDS-UPDRS, the NMSS, and the MDS-NMS, with a domain composed of four items. The Scale for Evaluation of Neuropsychiatric Disorders in Parkinson’s Disease (SEND-PD) is another PD-specific instrument that evaluates the presence and severity of psychotic symptoms, mood/apathy, and impulse control disorders (ICD) [72].

The MDS Task Force reviewed the instruments for assessing impulsive and compulsive behaviors, recommending the Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP) for screening, the QUIP-Rating Scale (QUIP-RS) for screening and severity rating, the Self-Assessment Scale For Dopamine Dependent Behaviors in Parkinson’s Disease (Ardouin short screen), recommended for severity assessment, and the Scale for Outcomes in Parkinson’s Disease–Psychiatric Complications (SCOPA-PC), recommended only for the assessment of hypersexuality and gambling/shopping [61].

**Conclusion**

The assessment of NMS in a holistic manner using a burden-based strategy or a more detailed individual NMS-based assessment is feasible in a clinical setting with the available validated tools as addressed in this chapter [1]. Some symptoms may remain unnoticed by the patient (sleep disorders, for example) or undeclared (as sexual problems), and rating scales and questionnaires can be essential for adequately assessing the patient and for monitoring and adjusting treatment to the patient’s specific needs [73]. It is indeed important that objective measurements are incorporated into clinical practice as well as clinical studies and form part of evidence-based management guidelines as well as audit process. To achieve this, selection of the most appropriate instrument for each specific application is required and should be guided by information on its psychometric properties and its main characteristics, such as length or measured construct. The MDS section on rating scales and reviews can help researchers and clinicians to select the most appropriate instrument. The construction of new instruments, the study of the psychometric
attributes of some of them, and the exploration of new forms of administration (item banks, wearables) are future developments in this field.

References


