

Other Non-Motor Guidance for CDE Use

Summary Statement

Parkinson's Disease CDE Subgroup: Other Non-Motor

This summary is the companion document to the NINDS Parkinson's Disease CDE Subgroup – Other Non-Motor Table (see **Table 1: NINDS CDE Subgroup – Other Non-Motor**).

I. Assessing “Other” Non-Motor Features in Parkinson's Disease

Non-motor features of Parkinson's disease (PD), including cognitive impairment, mood disorders, pain, autonomic dysfunction, and sleep disorders, are increasingly recognized, yet not as regularly assessed or adequately treated as the motor symptoms. Cognitive impairment and neuropsychiatric symptoms are highly prevalent in PD, with a significant impact on quality of life and independence; these two categories of non-motor symptoms have their own subgroup and separate CDE recommendations. The “Other” Non-Motor Features subgroup therefore focuses on the assessment of the remaining non-motor features of PD, separate from “Cognition” and “Psychiatry.” These non-motor symptoms have been less well studied and very few PD-specific assessment tools exist; it is often necessary to recommend scales that have not been designed or validated for PD. In some instances, appropriate scales are simply nonexistent. In other instances, scales are not appropriate, and procedures have been recommended instead.

The absence of appropriate screening measures has been glaringly evident, forcing the subgroup to frequently recommend single questions extracted from other scales as the most viable screening measure. We realize that the validity of an established scale does not transfer to individual questions if they are presented in a free-standing fashion and that these items should ideally be validated on their own before they are used.

The subgroup has not focused on non-specific non-motor questionnaires and has instead evaluated symptom specific scales. The sheer number of “other” non-motor features identified by the subgroup poses some problems for patient assessment in practical terms. Given the breadth of possible non-motor symptoms and the variability of individual experience for those living with PD, even a brief non-motor screening measure would require at least 19 individual questions to address each of the “other” non-motor features we have identified. Thus, it may not be feasible to address each of the “other” non-motor features in every clinical or research situation.

The scales and instruments identified by our subgroup are not designed to assess or even address the fluctuations – including non-motor features - that are so often a part of PD, particularly in individuals receiving dopaminergic therapy. This problem certainly is not unique to “other” non-motor features.

II. Categories of “Other” Non-Motor Features

a. Autonomic Dysfunction

1. Gastrointestinal

Virtually all levels of the GI tract may be affected in PD. Excess saliva, dysphagia, gastroparesis, reduced bowel movement frequency, and defecatory dysfunction all may occur. Some aspects of GI dysfunction are addressed within scales such as the MDS-UPDRS, MDS-NMS, and the SCOPA-AUT, and there are two validated scales dedicated to the assessment of all aspects of GI dysfunction in PD that can be used (the MDS Gastrointestinal Dysfunction Scale for Parkinson's Disease (MDS-GIDS-PD) and the Gastrointestinal Symptoms in Neurodegenerative Diseases Scale (GIND)). The MDS-GIDS-PD covers the 6 months prior to survey, while the GIND covers the 2 weeks prior to survey. Assessing three discreet aspects of GI dysfunction (excess saliva, dysphagia, and constipation) was also undertaken by the subgroup. For screening purposes, we have recommended extraction of single items from the MDS-UPDRS, realizing that this is not an ideal approach from a validation standpoint, or the use of the MDS-GIDS-PD or GIND. With regard to measurement instruments for these three aspects of GI dysfunction, no scales have been fully validated specifically for PD, but scales have been selected that have been validated in other settings. For studies specifically focused on these individual aspects of GI dysfunction, diagnostic instruments have been identified, such as the Videofluoroscopic Swallowing Study (Modified Barium Swallow Study), the Colon Transit Time Study, Defecography, and several methods of measuring

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saliva production. These studies typically require specialized equipment and collaboration with other specialists.

2. Urinary

Urinary symptoms in PD result from storage and/or voiding dysfunction. Bladder overactivity is the most frequent abnormality and the subgroup elected to focus on this aspect of PD urinary dysfunction, however bladder underactive or outflow obstruction may also occur. As with GI dysfunction, some aspects of urinary dysfunction are addressed within the MDS-UPDRS and the SCOPA-AUT but no scale specifically addressing bladder dysfunction in PD exists. For screening purposes, the subgroup once again elected to recommend a single item from the MDS-UPDRS. As measurement instruments we have selected questionnaires: International Prostate Symptom Scale (IPSS), the International Consultation on Incontinence Questionnaire-Overactive Bladder Module (ICIQ-OAB), and the Neurogenic Bladder Symptom Score (NBSS) as the scales of choice, and the ICIQ bladder diary. Though none of these have been validated specifically in the setting of PD, the IPSS has been used in studies evaluating urinary dysfunction in Parkinson's disease. It should be noted that the IPSS has been validated in males and in females. For studies specifically focused on urinary dysfunction, the generally accepted diagnostic instrument would be formal urodynamic testing, which would require special equipment and collaboration with a urologist.

3. Sexual

Sexual dysfunction has not been studied extensively in PD. No scales have been validated specifically for use in PD. Once again, the subgroup has chosen to extract single questions from other scales for a portion of the screening function. Since sexual dysfunction has been more extensively studied in men, screening items for both erectile dysfunction and for non-gender based sexual dysfunction have been listed. For men, both the International Index of Erectile Function (IIEF-5), also known as the Sexual Health Inventory for Men (SHIM) and individual items from the SCOPA-AUT have been selected, but for women (or for both sexes) items have been lifted from a larger scale (NMS-Quest); alternatively, a single item from the MDS-NMS may be used. For measurement instruments, one scale has been chosen for men (the International Index of Erectile Function) and one for women (the Female Sexual Function Index). They have been used in studies evaluating sexual dysfunction in men and women with Parkinson's disease, though validation specifically in the setting of PD is lacking.

4. Thermoregulatory

Thermoregulatory dysfunction has not been extensively studied in PD. Once again, individual items from more comprehensive scales have been chosen by the subgroup as screening instruments. For a measurement instrument, eight items addressing sudomotor function, drawn from the 73-item Composite Autonomic Symptom Scale (COMPASS), have been recommended since no scale specifically addressing thermoregulatory dysfunction in PD exists. For studies specifically addressing thermoregulatory dysfunction, diagnostic instruments such as the Quantitative Sudomotor Axon Reflex Test (QSART) and the Thermoregulatory Sweat Test (TST) may be utilized, although abnormalities in these tests are not specific for PD.

5. Cardiovascular

Orthostatic hypotension (OH) is the most widely recognized cardiovascular abnormality of PD. For screening purposes, three questions drawn from the SCOPA-AUT have been selected, with two items from the NMS-s or one item from the NMS-Q as alternates. The OHQ is designed to assess the severity of neurogenic orthostatic hypotension (nOH) and has been used in clinical trials in PD. Actual orthostatic blood pressure and pulse measurement, are appropriate as a measurement instrument and formal tilt table testing should be considered the diagnostic instrument. Although not directly assessing the issue of orthostatic hypotension, MIBG scanning as a measure of cardiac sympathetic denervation in PD is also considered as a diagnostic instrument.

6. Respiratory

Respiratory abnormalities have not been extensively studied in PD, although respiratory dysfunction is one of the most common causes for death in PD patients. No PD-specific scales have been developed.

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Some studies have noted a restrictive pattern of dysfunction (presumably due to chest wall rigidity) to be the predominant respiratory abnormality of PD, while others document an upper airway obstructive pattern. Spirometric studies, rather than subjective scales, appear to be the most appropriate method to assess respiratory function in PD. With this in mind, either the Maximum Voluntary Ventilation (MVV) or the Forced Expiratory Volume in the first second (FEV1) can be used as a screening instrument and also as a measurement instrument. For studies specifically addressing respiratory function in PD, full pulmonary function testing is the diagnostic measure of choice.

b. Sleep Dysfunction

1. Diagnosis of Sleep Disorders

The third edition of the book International Classification of Sleep Disorders, published in 2014 by the American Academy of Sleep Medicine, contains the diagnostic criteria of the sleep disorders that may be seen in patients with Parkinson disease including insomnia, obstructive sleep apnea, REM sleep behavior disorder, and restless legs syndrome.

2. Sleep Methods

Besides clinical history, scales, and questionnaires, there are some objective instruments that may evaluate sleep quality, sleep quantity, sleep architecture, sleep-wake patterns, and sleep disorders. They include 1) actigraphy that estimates the sleep-wake cycle over several weeks or months, 2) polysomnography that evaluates sleep architecture and the occurrence of sleep disturbances such as obstructive sleep apnea, REM sleep behavior disorder and periodic leg movements in sleep, and 3) the Multiple Sleep Latency Test (MSLT) that examines the presence of excessive daytime sleepiness.

3. Overall Sleep Quality

The Parkinson's Disease Sleep Scale 2nd Version (PDSS-2) is a questionnaire designed for Parkinson disease that addresses motor symptoms at night, sleep symptoms at night, and disturbed sleep. The Scale for Outcomes of Parkinson's Disease-Sleep (SCOPA-Sleep) is an instrument developed originally for research in Parkinson's disease that addresses nighttime sleep problems and excessive daytime sleepiness.

The Non-motor Symptoms Questionnaire (NMS-Quest) (PD-NMS) and The International Parkinson and Movement Disorder Society – Non-Motor Rating Scale (MDS-NMS) are questionnaires designed to identify the presence of non-motor symptoms including sleep disturbances in patients with Parkinson disease.

The Pittsburgh Sleep Quality Index (PSQI) is a widely used instrument that evaluates the subject quality of sleep, sleep habits, and sleep disturbances. It was not designed specifically for PD, in contrast to PDSS-2, SCOPA-Sleep, NMS-Quest and MDS-NMS.

4. Insomnia

PDSS-2, SCOPA-Sleep, NMS-Quest and MDS-NMS are instruments that contain items that evaluate the occurrence of insomnia. Additionally, the Insomnia Severity Index (ISI) evaluates the severity of sleep initiation, sleep maintenance, and early awakening. It is a widely used instrument that was not designed for Parkinson's disease. Diagnostic criteria for chronic insomnia have been formulated by the American Academy of Sleep Medicine. Polysomnography is not needed for the diagnosis and assessment of insomnia.

5. Excessive Daytime Sleepiness

PDSS-2, SCOPA-Sleep, NMS-Quest and MDS-NMS are instruments that contain items that evaluate the occurrence of excessive daytime sleepiness. The Epworth Sleepiness Scale (ESS) is recommended by the subgroup as a screening, measurement, and diagnostic instrument for excessive daytime sleepiness. The ESS is the most widely used subjective scale of daytime somnolence and has been used extensively in PD studies with good validation. The ESS incorporated three items designed to detect excessive daytime sleepiness in active situations for the diagnosis of sleep attacks in the setting of Parkinson disease patients. Other scales that can be used for the evaluation of excessive daytime sleepiness are

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the Stanford Sleepiness Scale (SSS) and the Karolinska Sleepiness Scale (KSS), that were designed for the general public. In studies requiring an objective measure of excessive daytime sleepiness, the Multiple Sleep Latency Test serves as the recommended diagnostic instrument.

6. Obstructive Sleep Apnea

Polysomnography is the accepted objective diagnostic instrument to detect obstructive sleep apnea. As screening, before the implementation of polysomnography, the presence of obstructive sleep apnea may be suggested by instruments such as STOP-BANG and the Berlin Questionnaire. No PD-specific scales exist to detect or suspect obstructive sleep apnea.

7. REM Sleep Behavior Disorder

The diagnosis of REM sleep behavior disorder requires video-polysomnography. There are several screening questionnaires and single questions for the screening of this parasomnia. However, the specificity of these instruments is low, making video-polysomnography the gold standard for the diagnosis of REM sleep behavior disorder. The Mayo questionnaire for REM sleep behavior disorder requires the presence of the bed partner because it was designed for subjects with cognitive impairment. The RBDQ-HK can be utilized for treatment monitoring.

8. Restless Legs Syndrome

The diagnosis of restless legs syndrome is made by clinical history and does not need the use of scales or polysomnography. Formal diagnostic criteria for restless legs syndrome have been developed by the International Restless Legs Syndrome Study Group (IRLSSG). This IRLSSG has also developed a rating scale as a measurement instrument for assessing severity of RLS symptoms. This scale can be used to monitor the effect of a medication for the symptomatology of restless legs syndrome.

c. Sensory Dysfunction

1. Vision Impairment

The aspect of vision impairment in PD that has received the most attention is impairment of contrast sensitivity, which reflects retinal involvement. Other aspects of vision, including oculomotor (convergence insufficiency) and cortical visual (color vision), may also be affected in the setting of PD. PD-specific vision questionnaire, the Visual Impairment in Parkinson's Disease Questionnaire (VIPD-Q), has been developed but not yet externally validated. The VIPD-Q evaluates four domains: 1) ocular surface; 2) intraocular; 3) oculomotor; and 4) optic nerve; as well as one item for visual hallucinations. The Pelli-Robson chart is recommended as both a screening and a measurement instrument for impairment of contrast sensitivity. It is the oldest and most widely known of the charts that have been developed for office testing of visual contrast sensitivity. It has not been validated specifically for use in PD but has been used extensively in ophthalmologic practices and research. More sophisticated measures for assessing visual contrast sensitivity are used in some research settings but would not be feasible for widespread use. Optical Coherence Tomography (OCT) has recently been shown to demonstrate direct morphologic evidence of retinal involvement in PD and thus may be useful as a diagnostic instrument in studies specifically focusing on vision impairment in PD.

2. Olfaction Impairment

Impairment of olfaction has been extensively studied in PD and the most frequently employed testing instrument has been the 40-item University of Pennsylvania Smell Identification Test (UPSIT). Shorter modifications of this study that are more suitable as a screening instrument have been developed. In this regard, the 12-item Brief Smell Identification Test – Version B (also known as the Cross-Cultural Smell Identification Test) is particularly appealing because the odors it contains are well-known in most cultures and many of the odors it contains have been shown to be impaired in PD patients. It has been validated and found to have high sensitivity, specificity, and predictive value in patients with PD. The full 40-item UPSIT, however, is more appropriate for use as a measurement instrument and a diagnostic instrument. A short screening questionnaire, the Hyposmia Rating Scale, has also been developed and may help identify those requiring more thorough olfactory assessment.

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3. Pain

Pain is increasingly recognized as a non-motor feature of PD and may even be a presenting feature (e.g., “frozen shoulder”). Pain in PD is often multifactorial, which can complicate its assessment. The King’s Parkinson’s Disease Pain Scale was recently developed specifically for the assessment of pain in PD and has been validated in multiple languages. A self-report screening questionnaire, the King’s Parkinson’s Disease Pain Questionnaire, has also been created. The Brief Pain Inventory (BPI)-Short Form is a generic instrument that measures pain intensity and has been validated in PD. It has been used extensively in the study of pain and has demonstrated validity and reliability across cultures. Although a Visual Analogue Scale has most frequently been used in PD studies as an instrument for measuring pain severity and change over time, the Numerical Rating Scale – Box 21 Scale is recommended by the subgroup because it appears to be less error prone in an elderly population. There is no objective diagnostic instrument for diagnosing or measuring pain.

d. Other Non-Motor Dysfunction

1. Fatigue

Fatigue is very common in PD and can have disabling effects on daily life and function. Additional complexity in the distinction between physical and cognitive fatigue also exists in PD. For screening purposes, we have again recommended a single question from the MDS-UPDRS. The Parkinson Fatigue Scale (PFS-16) was designed to evaluate the physical aspects of fatigue in PD and its effects on daily function; it deliberately excludes the emotional and cognitive features of fatigue. The PFS-16 has been used in multiple studies and validated in several languages (Spanish, Swedish, Chinese, Italian, Greek, and Turkish). As an additional rating instrument, the 9-item FSS is recommended. No objective diagnostic instrument for fatigue exists.

2. Nutritional Status

Nutritional status is not actually a non-motor feature of PD in and of itself. However, it does tie in with gastrointestinal dysfunction and weight loss. Therefore, the subgroup has designated the MNA as a screening instrument for nutritional status. It is a validated measure that has been used in PD. No single measurement instrument has been by the subgroup. Formal dietary assessment serves as the diagnostic instrument.

3. Weight Loss/Weight Change

For this item, formal scales are not necessary (or perhaps one should say that a scale of a different type is necessary). Weight or Body Mass Index (BMI) can be utilized as the assessment tool.

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Parkinson's Disease CDE Subgroup – Other Non-Motor Table 1

Type of Instrument	CATEGORIES							
	GI - Salivation	GI - Dysphagia	GI - Constipation	Urinary	Sexual	Thermoregulatory	Cardiovascular	Respiratory
Screening Instrument ¹	MDS-UPDRS 2.2 SCOPA-AUT #2 or NMSS #19	MDS-UPDRS 2.3 or SCOPA-AUT #1, 3 or NMS-Q #3 or NMSS #20 or GIDS-PD #9	MDS-UPDRS 1.11 or SCOPA-AUT #5, 6 or NMS-Q #5, 7 or NMSS #21 or COMPASS-31 #20, 21, 22, 23 or GIDS- PD #1-4	MDS-UPDRS 1.10 or SCOPA- AUT #8, 9, 10, 11, 12, 13 or NMS-Q #8, 9 or NMSS #22, 23, 24 or COMPASS-31 #24, 25, 26	Males: SCOPA- AUT #21, 22 or SHIM Both - NMS-Q #18, 19 or NMSS #25, 26	SCOPA-AUT #17, 18, 20, 21 or NMS-Q #18, or NMSS #30 or COMPASS-31 #8	SCOPA-AUT #14, 15, 16 or NMS-Q #20 or NMSS #1-2 COMPASS-31 #1, 2, 3, 4	Maximum Voluntary Ventilation Test or FEV ₁
Rating Scale ²	Drooling Rating Scale (alternate DSFS)	Swallowing Disturbance Questionnaire	Rome III/IV Constipation Module	ICIQ-OAB or IPSS	Males: IIEF Females: BISF-W	COMPASS - 8 items	OHQ, or OGS Orthostatic Blood Pressure Measurement	Maximum Voluntary Ventilation Test or FEV ₁
Diagnostic Criteria ³	Standard Criteria	Standard Criteria	Fewer than three bowel movements per week	Standard Criteria	International Consensus Panels	Standard Criteria	Systolic Drop >20mmHg, Diastolic Drop >10mmHg	Standard Criteria
Diagnostic Instrument ³	Saliva Measurement Tests	Video Fluoroscopic Swallowing Study (aka MBS)	Colon Transit Study Defecography Anorectal Manometry	Urodynamic testing	None	QSART and TST	Formal Tilt Table Testing	Formal Pulmonary Function Testing
Required Instrument ⁴				MDS-UPDRS				

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Type of Instrument	CATEGORIES										
	Sleep					Sensory Dysfunction			Other		
	Insomnia	Excessive Daytime sleepiness	Sleep apnea	REM Sleep behavior disorder	Restless Leg Syndrome	Vision Impairment	Olfaction Impairment	Pain	Fatigue	Nutritional Status	Weight loss
Screening Instrument ¹	If sleep is primary outcome: SCOPA-Sleep nighttime subscale. If not: UPDRS #1.7	If sleep is primary outcome: Epworth Sleepiness Scale. If not: UPDRS #1.8	Berlin Questionnaire	RBD Screening Questionnaire (Stiasny-Kolster)	Cambridge-Hopkins RLS-Questionnaire	Pelli-Robinson Chart	Brief Smell Identification Test Version B (12-item)	BPI (9-item short version)	MDS-UPDRS	MNA - validated, used in PD, avail in mult languages	Weight or BMI
Rating Scale ²	SCOPA-sleep Nighttime Subscale	Epworth sleepiness scale	None	None	IRLSSG Rating Scale (IRLS)	Pelli-Robinson Chart	UPSIT (40 item)	Numerical rating scale, 21-point box scale	FSS	None	Weight or BMI
Diagnostic Criteria ³	American Academy of Sleep Medicine Criteria	Epworth Score > 10 or Standard Criteria on MSLT	American Academy of Sleep Medicine Criteria	American Academy of Sleep Medicine Criteria	IRLSSG diagnostic criteria	Standard Criteria	Standard Criteria	International Association for the Study of Pain criteria	None	None	None
Diagnostic Instrument ³		Multiple Sleep Latency Test	polysomnogram	polysomnogram	None	Optical Coherence Tomography	UPSIT (40 item)	None	None	Formal Dietary Assessment	Weight or BMI
Required Instrument ⁴								BPI	MDS-UPDRS	n/a	wt. (kg)

¹ Screening Instrument – For initial identification of possible disorder

² Rating Scale – For measurement of disorder severity and change over time

³ Diagnostic Criteria and Instrument – Categorization of patients into those with and without a disorder

⁴ Required Instrument – for study that has primary focus on this other non-motor disorder