## Defining Core Instruments

This summary is the companion document to the NINDS Parkinson’s disease CDE Working Group – Psychiatry Table (see Table 1: NINDS CDE Workgroup – Psychiatry Table). The “Strongly Recommended” instruments on the Workgroup Table are included as suggestions for studies with a primary focus on a particular disorder (i.e., it is strongly recommended that the Hamilton Depression Rating Scale be at least one of the depression rating scales in a PD study with a focus on depression, in order to allow comparisons across studies). The Psychiatry Subgroup acknowledges that these instruments could not be recommended as “Core” or “Required” in every PD study. However, if the MDS- UPDRS will be used as a “Core” instrument for all PD studies, then at the very least, minimal data will be collected in all studies for depression, psychosis, anxiety, apathy, and dopamine dysregulation syndrome. For additional details about the use of assessment instruments for common psychiatric disorders in PD, readers are referred to the recommendations of recent task forces1-4. It is important to note that many instruments were validated against a DSM-IV-TR diagnosis, and instruments may need to be re-validated when DSM-V is published.

## . Factors to Consider When Assessing Psychiatric Symptoms in Parkinson's Disease

### Psychiatric disorders in Parkinson's disease

Numerous psychiatric symptoms or disorders can occur in the context of Parkinson’s disease (PD), including depression, anxiety, apathy, psychosis, impulse control disorders, and disorders of sleep and wakefulness. The etiology of psychiatric disorders is likely complex, including to varying degrees psychological factors, disease-related pathophysiological changes, and PD treatment-induced effects. There is increasing awareness of the importance of psychiatric complications in PD, including their deleterious effects on function, quality of life, long-term outcomes, and caregiver burden.

### Heterogeneity

There is significant inter-individual heterogeneity in the presentation and course of psychiatric disorders in PD, making it difficult to characterize the phenomenology and epidemiology of psychiatric disorders in this population at a group level. For instance, depression in PD may range from mild to severe, symptoms may cycle or be persistent over time, and symptom profiles can vary significantly between patients.

### Variability

There can be significant intra-individual variability in the presentation of psychiatric symptoms in PD, making it difficult at times to average symptoms over an extended period and highlighting the importance of establishing as much consistency as possible when repeated assessments are performed. For instance, patients with motor fluctuations may experience significant dysphoria or anxiety during "off" periods, but may be euthymic during "on" periods.

### Co-morbidity

Psychiatric disorders in PD are highly co-morbid in general (e.g., depressive and anxiety disorders), and many psychiatric disorders are also associated with cognitive impairment. Therefore, if a particular psychiatric disorder is assessed, one might also consider assessment of common co-morbid conditions. In addition, some instruments purported to assess signs and symptoms of a particular disorder may assess symptoms of a common co-morbid disorder (e.g., some depression rating instruments contain anxiety items as well). The influence of co-morbid psychiatric disorders on scale performance has not been well studied.

### Symptom overlap

Psychiatric symptoms occurring in the context of PD may be due either to an underlying co-morbid psychiatric disorder or to the effects of the disease itself. For instance, certain symptoms of major depressive episode (e.g., insomnia or hypersomnia, fatigue, and psychomotor retardation) are common in PD patients without depression. Ratings of such symptoms can be based on an inclusive, exclusive, or etiologic approach, and the general recommendation is to use an inclusive approach.

### Effect of PD medications

The effects of standard PD pharmacotherapies (e.g., levodopa, dopamine agonists, and MAO-B inhibitors) on psychiatric and cognitive symptoms in PD remains unclear. Important patient-level variables in this regard likely include stage of disease, specific medication dosage, total medication exposure, and baseline level of cognitive impairment.

### Functional neurosurgery

The effects of functional neurosurgery, specifically deep brain stimulation (DBS), on psychiatric and cognitive symptoms also remains unclear. Both improvement and worsening in particular symptoms have been reported, suggesting significant inter-individual variability. Important patient-level variables in this regard include pre-operative psychiatric and cognitive status and post-operative changes in PD pharmacotherapy.

### At-risk populations for PD

Certain non-motor disorders may occur as part of a pre-motor syndrome in PD. These include depression, anxiety, and rapid eye movement behavior disorder (RBD). When studying an enriched at-risk population for PD, consideration should be given to assessing these disorders.

### De novo or early PD

Although many psychiatric symptoms and disorders become increasing common with advancing disease severity, a full range of psychiatric and cognitive complications can be present early in the course of the disease. Thus, at disease onset depression, anxiety, and cognitive deficits may be present, and in early PD psychosis can occur in the context of exposure to PD pharmacotherapy.

### Fluctuations

There is increasing recognition that patients with motor fluctuations typically experience non-motor fluctuations (NMFs) as well, including dysphoria, anxiety and changes in cognition. Assessment of psychiatric symptoms occurring as part of NMFs requires use of different assessment instruments, as most existing psychiatric assessment instruments are not designed to assess sporadic symptoms.

### Cognitive impairment

Some degree of cognitive impairment occurs in most PD patients, and deficits may occur initially early in the disease course. Depending on the severity of cognitive impairment and possible co-morbid apathy, consideration needs to be given to the validity of the self-reported responses to queries about psychiatric symptoms, and whether an informed other should be included in the assessment process. The influence of cognitive status on psychiatric scale performance has not been well studied, although the Cornell Scale for Depression in Dementia (CSDD) has been found to be a valid tool for identifying depressive disorders in patients with PD across a spectrum of cognitive impairment.

### Other possible confounders

When conducting clinical research in the psychiatric and cognitive complications of PD, consideration should be given to the fact that any test that is timed or involves motor abilities may be affected by core PD symptoms, and variably affected if administered during "on" vs. "off" periods for patients with fluctuations, regardless of any non-motor impairments. Core PD symptoms (e.g., fatigue or fluctuations in alertness), psychiatric symptoms (e.g., distractibility due to active hallucinations or anxiety), and PD pharmacotherapy side effects (e.g., sedation) may also affect performance.

## . Individual Disorders

### Depression

Depression is common in PD and it is associated with a variety of negative outcomes. There remain, however, many unresolved issues surrounding the identification and measurement of depression in the context of PD. Diagnostic criteria are confounded by the symptoms of PD itself, fluctuations in movement disorders, apathy, and cognitive impairment. There have been attempts to construct alternative diagnostic criteria, but at present, the DSM-IV criteria remain the gold standard. All applications of these criteria, as well as rating scales, must be done in the context of a clinical interview by a clinician experienced in PD.

In addition, it should be noted that DSM-IV lists, in addition to formal criteria for major depressive disorder, many other mood disorders which have not been studied extensively in patients with PD. The appendices also list proposed criteria for minor depression, brief recurrent depression and a number of other mood disorders that could be relevant to PD.

The diagnosis and measurement of depression in PD is therefore an evolving area. We have attempted to guide researchers in their choice of screening, diagnostic and measurement tools, but recognize that many areas of uncertainty exist. One area of increasing importance in psychiatry is assessment of suicide risk; it is increasingly recognized that death or suicide ideation are not uncommon, and the FDA recently issued a Guidance for Industry titled “Suicidality: Prospective Assessment of Occurrence in Clinical Trials ([U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) Guidance for Industry Suicidal Ideation and Behavior](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf) ).

### Anxiety

Increasing attention is being directed towards the assessment and measurement of anxiety symptoms and disorders in patients with PD. A need for valid and reliable approaches to the diagnosis and evaluation of anxiety disorders in PD is justified by the common occurrence of anxiety disturbances in PD, including before its formal diagnosis.

Several challenges affect the assessment of anxiety disorders and anxiety phenomena in PD. First is that a substantial number of patients have clinically significant anxiety disturbances that are specific to PD or fail to have all the symptoms needed to meet criteria for a typical DSM-IV anxiety diagnosis (i.e., generalized anxiety disorder, panic disorder, agoraphobia, specific phobias, social phobia, post-traumatic stress disorder, and obsessive-compulsive disorder). Examples of such ‘atypical’ anxiety disorders include recurrent panic attack-like episodes, often associated with fluctuating motor effects to antiparkinsonian therapy, or extreme situational anxiety associated with akinesia or freezing of gait. Specific diagnostic criteria for PD-specific anxiety disturbances would facilitate their recognition and investigations of treatments, and there is also a need to include the atypical PD-specific anxiety disturbances in analyses of scale performance.

Even when features of a typical anxiety disorder are evident in a patient with PD, the DSM diagnostic criteria pose an additional quandary with respect to symptom attribution. A specific example is provided in the DSM for social phobia, in that the fear of being observed does not meet criteria as a symptom if it is ‘solely’ accounted for by trembling in patients with PD. In general, an inclusive approach to symptom attribution has been recommended in such cases.

### Apathy

Research on apathy scales in Parkinson’s disease (PD) is limited. Apathy is a common syndrome in PD occurring in up to 70% of PD patients and causing significant disability. A major obstacle to further research has been a common definition for apathy. The generally accepted definition is a lack of motivation, but operationally apathy needs to be differentiated from other syndromes such as depression. Specifically apathy needs to be differentiated from anhedonia (i.e., the loss of interest and pleasure), which is a key symptom of major depressive episode in DSM-IV. The most commonly accepted definition of apathy is the proposed diagnostic criteria first described by Starkstein and Leentjens, and adapted from Marin. Although this definition is generally accepted, the criteria are nevertheless “proposed” and research in this area would be strengthened by developing definitive diagnostic criteria.

### Psychosis

Psychosis in PD has a well-characterized temporal and clinical profile of hallucinations and delusions which is different than the pattern seen in other psychotic disorders (e.g., substance-induced psychosis or schizophrenia). Psychosis in PD generally occurs later in the course of PD, but may occur at any stage. It is associated with a poor prognosis, including nursing home placement and death, and once established psychosis is usually chronic. The etiology of psychosis in PD is complex and associated with exposure to PD medications, Lewy body pathology, imbalances of monoaminergic neurotransmitters, and visuospatial processing deficits.

In the past several years diagnostic criteria for psychosis in PD have been proposed, and a thorough review of psychosis rating scales in PD conducted. In addition, a Movement Disorders Society sponsored effort to develop and validate a new rating scale specifically for psychosis in PD is ongoing.

### Impulse control disorders

Compared with other psychiatric disorders in PD, impulse control disorders (ICDs) have only recently gained recognition in PD, soon after the introduction and common use of newer dopamine agonist medications. The presentation and severity of ICD symptoms in PD varies widely, and overlaps with normal, pleasurable human behaviors. In addition, ICDs seem related to, but also distinct in some ways, from other syndromes reported to occur in PD, including dopamine dysregulation syndrome (DDS), punding, and hobbyism. Research to develop and validate assessment instruments specific to the ICDs and related behaviors that occur in PD is in its infancy, so most commonly the ICD screening instruments, rating scales, and diagnostic criteria used in PD are those that were developed and have been used for similar disorders in the general population.

## References

1. Leentjens AF, Dujardin K, Marsh L, et al. Apathy and anhedonia rating scales in Parkinson's disease: critique and recommendations. Mov Disord. 2008; 23:2015-2025.
2. Leentjens AFG, Dujardin K, Marsh L, et al. Anxiety rating scales in Parkinson's disease: critique and recommendations. Mov Disord. 2008; 23:2004-2014.
3. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. Mov Disord. 2007; 22:1077-1092. PMCID: PMC17394234.
4. Fernandez HH, Aarsland D, Fénelon G, et al. Scales to assess psychosis in Parkinson's disease: critique and recommendations. Mov Disord. 2008; 23:484-500.

Table 1 NINDS CDE Workgroup – Psychiatry Recommended CDE’s

| Type of Instrument | Depression | Anxiety | Psychosis | Apathy | ICDs | Global |
| --- | --- | --- | --- | --- | --- | --- |
| Screening Instrument[[1]](#footnote-1) | Beck Depression Inventory (BDI)[[2]](#endnote-1)  15-item Geriatric Depression Scale (GDS-15)i | Hospital Anxiety and Depression Scale (HADS)i | MDS-UPDRS Part I | Apathy Scale i | Questionnaire for Impulsive-Compulsive Behaviors in Parkinson’s Disease (QUIP)i  South Oaks Gambling Screen (SOGS)i | MDS-UPDRS Part I  Neuropsychiatric Inventory (NPI)[[3]](#endnote-2) |
| Rating Scale[[4]](#footnote-2) | Hamilton Depression Rating Scale-17 item (HDRS-17)ii  Montgomery-Asberg Rating Scale (MADRS)ii | Hamilton Anxiety Rating Scale (HARS)ii | 1. Brief Psychiatric Rating Scale (BPRS)  2. Schedule for the Assessment of Positive Symptoms (SAPS) | Apathy Scale i | Gambling - Gambling Symptom Assessment Scalei  Buying - Buying Questionnairei  Sexual behavior -Sexual Compulsivity Scalei  Eating - Compulsive Eating Scalei | Neuropsychiatric Inventory (NPI) |
| Diagnostic Criteria[[5]](#footnote-3) | DSM-IV-TR | DSM-IV-TR | Proposed diagnostic criteria for psychosis in Parkinson’s disease | Proposed diagnostic criteria for the syndrome of apathy | Gambling - DSM-IV criteria for pathological gambling  Buying - McElroy criteria for buying  Sexual behavior - Voon criteria for sexual behavior  Eating - Modified proposed DSM-IV binge eating disorder criteria | None recommended. |
| Diagnostic Instrument1 | Structured Clinical Interview for DSM-IV (SCID)ii | Structured Clinical Interview for DSM-IV (SCID)ii | None recommended. | None recommended. | Gambling - Structured Clinical Interview for Pathological Gambling | None recommended. |
| Strongly Recommended Instrument[[6]](#footnote-4) | Hamilton Depression Rating Scale-17 (HDRS-17)ii | Hamilton Anxiety Rating Scale (HARS)ii | 1. Brief Psychiatric Rating Scale (BPRS)  2. Schedule for the Assessment of Positive Symptoms (SAPS) | Apathy Scale i | None. | Neuropsychiatric Inventory (NPI)ii |

1. Screening Instrument - For initial identification of possible disorder; [↑](#footnote-ref-1)
2. SA = self-administered [↑](#endnote-ref-1)
3. RA = rater-administered [↑](#endnote-ref-2)
4. Rating Scale - For measurement of disorder severity and change over time; [↑](#footnote-ref-2)
5. Diagnostic Criteria and Instrument – Categorization of patients into those with and without a disorder; [↑](#footnote-ref-3)
6. Strongly Recommended Instrument – strongly recommended for a study with a focus on this psychiatric disorder to allow comparison with previous studies; [↑](#footnote-ref-4)