Rating Scales for Behavioral Symptoms in Huntington's Disease: Critique and Recommendations

Tiago A. Mestre MD MSc,[1*] Erik van Duijn MD PhD,[2] Aileen M. Davis PhD,[3] Anne-Catherine Bachoud-Lévi MD PhD, [4] Monica Busse,[5] Karen E. Anderson,[6] Joaquim J. Ferreira MD PhD,[7] Philipp Mahlknecht, MD, PhD ,[8] Vitor Tumas MD PhD,[9] Cristina Sampaio MD PhD, [10] Chris G. Goetz MD, [11] Esther Cubo MD,[12] Glenn T. Stebbins PhD, [11] Pablo Martinez-Martin PhD, [13] and the Members of the MDS Committee on Rating Scales Development

1 Parkinson's disease and Movement Disorders Center, Division of Neurology, Department of Medicine, The Ottawa Hospital Research Institute, University of Ottawa, Canada

2 Psychiatry Department, Leiden University Medical Centre, and Centre for Mental Health Care Delfland, Delft, Netherlands

3 Krembil Research Institute, University Health Network and Institute of Health Policy, Management and Evaluation and Rehabilitation Institute, University of Toronto, Canada

4 Assistance Publique-Hôpitaux De Paris, National Centre Of Reference For Huntington's Disease, Neurology Department; Université Paris Est, Créteil; INSERM U955 E01, Institut Mondor De Recherché Biomédicale, École Normale Supérieure, Créteil-Paris, France

5 School of Healthcare Sciences, Cardiff University, United Kingdom

6 Georgetown University, School of Medicine, Washington DC, USA

7 Neurology and Clinical Pharmacology, University of Lisbon, Institute of Molecular Medicine, Portugal

8 Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

9 Ribeirão Preto School of Medicine - University of São Paulo, Brazil

10 Cure for Huntington Disease Initiative Foundation, USA

11 Department of Neurological Sciences, Rush University Medical Center, Chicago, USA

12 Department of Neurology, Hospital Universitário Hermanos Yagüe, Burgos, Spain

13 National Center of Epidemiology and CIBERNED, Carlos III Institute of Health, Madrid, Spain

* Corresponding author:

Tiago A. Mestre

Parkinson's disease and Movement Disorders Center,

Division of Neurology, Department of Medicine,

University of Ottawa

1053 Carling Avenue, Ottawa ON K1Y 4E9

Canada

Telephone: +1 613 979 1513

E-mail: tmestre@toh.on.ca

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Abstract

Behavioral symptoms are an important feature of Huntington's disease and contribute to impairment in quality of life. The Movement Disorder Society commissioned the assessment of the clinimetric properties of rating scales in Huntington's disease in order to make recommendations regarding their use, following previously used standardized criteria. A systematic literature search was conducted to identify the scales used to assess behavioral symptoms in Huntington's disease. For the purpose of this review, seven behavioral domains were deemed significant in Huntington's disease: irritability, anxiety, depression, apathy, obsessive-compulsive behaviors, psychosis and suicidal ideation. We included a total of 27 behavioral rating scales, 19 of which were of a single behavioral domain, and the remaining 8 scales included multiple behavioral domains. Three rating scales were classified as "recommended" exclusively for *screening* purposes: the Irritability Scale for irritability, and the Beck Depression Inventory-II and the Hospital Anxiety and Depression Scale for depression. There were no "recommended" scales for other purposes such as diagnosis, severity or change in time or to treatment. The main challenges identified for assessment of behavioral symptoms in Huntington's disease are the co-occurrence of multiple behavioral symptoms, the particular features of a behavioral symptom in Huntington's disease, as well as the need to address stage- and disease-specific features, including cognitive impairment and lack of insight. The committee concluded that there is a need to further validate currently available behavioral rating scales in Huntington's disease to address gaps in scale validation for specific behavioral domains and purpose of use.

INTRODUCTION

Behavioral problems are important in Huntington's disease (HD), in addition to the motor and cognitive symptoms. The prevalence of behavioral problems in HD varies across studies with rates as high as 87%.[1] Apathy, depression, irritability and obsessive-compulsive behaviors are common in HD[2] and present across all stages of the disease. Behavioral symptoms, which have a negative impact on quality of life of patients and their caregivers, can precede the development of motor features that are most often used for a clinical diagnosis of HD in both clinical practice and research.[3,4] No treatment has been specifically developed for behavioral symptoms in HD.[5, 6] In order to develop effective interventions, rating scales need to provide psychometrically valid outcomes. Several rating scales, some of which were developed specifically for HD, are available and have been used to assess behavioral symptoms in HD. However, it is unclear which scales in HD are appropriate for screening, for assessing the severity of behavioral symptoms, the change in severity over time or after an intervention. In this review, we were mandated to assess all behavioral rating scales used in HD studies and to evaluate their validation in HD providing a recommendation on their use following criteria previously defined by the International Parkinson and Movement Disorder Society (MDS). For the purpose of this review, we considered seven behavioral domains that were deemed significant in HD: irritability, anxiety, depression, apathy, obsessive-compulsive behaviors, psychosis and suicidal ideation.[7]

METHODS

Organization and critique process

The Committee on Rating Scales Development of the MDS appointed a team of 10 members (sub-committee) to review rating scales used in HD to assess behavioral symptoms, these

members included neurologists, psychiatrists, a physiotherapist (all specialists in HD), and an expert in scale development and clinimetrics (A.M.D.). Two task force members evaluated each scale. If a task force member had been involved in the development of a scale, he/she was not involved in its review. Data were extracted into a *pro forma* provided by the MDS and adapted for the purpose of the current review. Scale assessment included the description of the scale, its availability, context of use, and reported clinimetric properties in patients with HD. All sub-committee members jointly assessed the completed reviews of the scales. Any unresolved issues and limitations of the critiqued scales were identified for discussion and reporting. The final recommendations were based on consensus among the sub-committee members and the liaison member of the Committee on Rating Scales Development of the MDS (EC).

Selection of scales

The methodology for this review was modeled on previously used methodology.[8] A literature search was performed using Medline on PubMed, Web of Science, EMBASE, and Psychinfo. The keywords used in the search included: "Huntington*" OR "Westphal variant" OR "juvenile Huntington*", and the terms "scale" OR "questionnaire" OR "index" OR "measure" as well as keywords related with the seven behavioral domains selected for the purpose of the review: depressi*, anxiety, obsessi*, compulsi*, apathy, irritability, delusion, psycho*, hallucination*, suicid*. For each identified scale, a search was conducted for the terms "Huntington's disease," or "Huntington disease" or "Huntington*" and the name of the scale. Manuscripts published before March 2015 were retrieved using the above search strategy and thoroughly screened by the chair of the sub-committee (T.A.M.) to ascertain which rating scale had been used in each study.

Inclusion/exclusion for review

Scales used at least once in HD populations (subjects at risk, presymptomatic gene carriers

and symptomatic HD patients) were included. Scales were excluded from review if: not available in English, only mentioned in reviews but not used in an original study, created for the sake of a specific study without any information about their structure or use, or full-paper not available (e.g., abstract format only).

Criteria for rating

We followed the Classification System For Scale Recommendation sued by MDS that uses three criteria: (1) Use in HD populations; (2) Use in HD by groups other than the original developers and data on its use were available; (3) The available clinimetric/psychometric data in HD supports the goals of screening, diagnosis) (e.g., evaluation of sensitivity/specificity, score cut-points, and reliability), measurement of measurement of severity or changes of severity in time (e.g., evaluation of reliability, construct validity, responsiveness and score discrimination across levels of symptom severity) (for further details, see table 1.)

RESULTS

Identified Scales and Their Utilization in Clinical Research

A total of 52 rating scales were identified that have been used in HD research studies. Fourteen of these rating scales were excluded after abstract review: twelve did not have a construct matching one of the domains selected for the review and two did not have a full-paper report available (Lille Apathy Rating Scale, UCSD Huntington's Disease-Behavioral Questionnaire). Of the remaining scales, 38 behavioral rating scales were included for further analyses. Eight scales that assess formal psychiatric diagnosis were identified and were included in our review. After detailed assessment, 11 behavioral rating scales and six diagnostic instruments were excluded (See *Supplementary material* part 1 for excluded scales/diagnostic instruments). The remaining 27 behavioral rating scales were grouped

according to the number of covered behavioral domains in single behavioral domain scales (n=19) and scales assessing multiple behavioral domains (n=8). Scales assessing a single behavioral domain were distributed as follows: depression (n=7), obsessive-compulsive behaviors (n=4), apathy (n=3), irritability (n=2), anxiety (n=2), and suicidal ideation (n=1). No single behavioral domain scale on psychosis was identified.

Overall, based on a detailed review, three behavioral rating scales were classified as "recommended": the Irritability Scale (IS) for irritability, and the Beck Depression Inventory (BDI) and the Hospital Anxiety and Depression Scale (HADS) for depression. Fourteen rating scales were classified exclusively as "suggested", (see Table 2). Ten rating scales were classified exclusively "listed" (see Table 3).

Critique of Behavioral Scales

We provide a summary description of the behavioral rating scales classified as recommended or suggested. See *Supplementary material* part 2. for a full description of all included behavioral rating scales.

I. SCALES WITH A SINGLE BEHAVIORAL DOMAIN ASSESSED

a. Irritability

<u>Irritability Scale (IS)</u>

The IS is designed to screen and rate the severity of irritability during the previous two to four weeks.[9, 10] The items are administered in a patient self-report and informant/caregiver-rated version of the IS. The IS has been used in studies with both presymptomatic and manifest HD populations,[9, 11, 12]. The IS has high internal consistency (Cronbach alpha of 0.90 and

higher).[12] A moderate inter-rater reliability for presence of irritability has been reported [11, 12] for the patient-completed and caregiver forms (overall ICC = 0.61, 95% CI = 0.50 – 0.72), being higher when spouses/partners are the informants (ICC = 0.75).[12] The IS inter-rater agreement is lower in the most cognitively impaired.[11] A degree of convergent validity (Spearman ρ=0.56) has been shown between the IS and the irritability item of the Unified HD Rating Scale (UHDRS).[12]

Recommendation: "recommended" for screening of irritability, "suggested" for assessing severity of irritability, as there are no data on reliability and other metrics to support the latter purpose.

b. Anxiety

Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is a 14-item questionnaire administered by clinical staff that evaluates the severity of anxiety.[13] The 14 items encompass a number of symptoms and are grouped into two domains: psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety).[13] The HAM-A has been used to evaluate anxiety in at-risk individuals and manifest HD,[14-16] and was used in one interventional trial for chorea.[15] The sparse clinimetric properties of the HAM-A available in HD show moderate divergent validity with the HAM-D (Pearson correlation: 0.49, p=0.001).[16]

Recommendation: "suggested" for assessing severity of anxiety, as reliability and other metrics remain to be characterized in HD.

State-Trait Anxiety Inventory (STAI)

The STAI is a self-reported scale composed of two subscales that evaluate current levels of

anxiety ("state anxiety" and "trait anxiety"). The STAI is widely used to assess for the presence and severity of anxiety in clinical settings.[17] Each item is scored on a four-point Likert-type scale from "not at all/almost never" to "very much so/always". Half the questions of each scale relate to the presence of anxiety while the other half relate to its absence. The STAI has been widely used in at-risk, presymptomatic and manifest HD for the assessment of severity of anxiety.[18-21] It is not suitable for use in advanced stages of HD, due to its self-report nature. There is evidence **of** good convergent validity (Spearman ρ (irritability, depression and anxiety scale/IDA –Anxiety subscale): 0.715 - 0.827) but weak divergent validity with overlap with depression and irritability as measured by the Irritability, depression and anxiety scale (IDA) scale (Spearman ρ: 0.646 - 0.806).[19]

Recommendation: "suggested" for assessing severity of anxiety, as reliability data are not available for HD.

c. Depression

Beck Depression Inventory (BDI)

The BDI is a widely used multiple-choice self-report inventory for evaluating the severity of depression. Each item relates to how the patient has been feeling during the past two weeks. The different versions of the BDI have been used in over 50 studies in people at risk, presymptomatic and manifest HD, including the REGISTRY study,[1] and the Neurobiological Predictors of Huntington's Disease study (PREDICT-HD).[3] The criterion validity of the BDI-II for the diagnosis of depression was studied in manifest HD against the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), providing an optimal cut-off score of 10/11 for the diagnosis of depression: sensitivity 1.00, specificity 0.66, and area under the curve of 0.856.[22] Inter-rater agreement between patients and caregivers for presence of depressive

mood using a single item of the BDI-I varied from moderate to good, with better agreement for intact cognition.[11]

Recommendation: "Recommended" for screening of depression, "suggested" for assessing severity of depression, as data are more complete and adequate for screening and sparse and incomplete in terms of reliability for assessment of severity of depression in HD. The BDI-II should be used as it is a revision of the BDI-I and reflects more recent DSM criteria.

Depression Intensity Scale Circles (DISCs)

The DISCs is a simple and intuitive six-point scale developed to assess current depressed mood in those who may have difficulty completing conventional assessments, such as patients with cognitive and/or communicative deficits. It does not assess cognitive depressive thoughts or somatic equivalents of depression. The scale has been used in HD patients to screen for depression with acceptable sensitivity (0.92) and specificity (0.82) reported in a single validation study in HD using the SCAN as the gold standard.[22] No other clinimetric data are available in HD patients.

Recommendation: "Suggested" for screening of depression, as data available are scarce and require further assessment.

Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a scale that requires the clinician to have some experience with depression. A self-report version is also available. The scale covers mood (four items), anxiety, appetite, sleep, functional status, ability to think, and general psychiatric distress, but do not include somatic or psychomotor symptoms of depression. The MADRS has been used in six studies in patients with HD.[19, 23-27] One of these studies showed that patient-reported MADRS scores

were significantly correlated with the depression (Spearman ρ: 0.90, $p \leq 0.001$) and anxiety (Spearman ρ: 0.77, $p \leq 0.001$) subscales of the IDA scale, as well as with its irritability subscales (Spearman ρ: 0.62-0.67, $p \leq 0.001$), but not with the caregiver-rated patient irritability measured by the Irritability-Apathy Scale (IAS).[19]

Recommendation: "Suggested" for assessing severity of depression, as limited clinimetric data exist in HD.

Hamilton Depression Rating Scale (HAM-D)

The HAM-D is a widely used and accepted interviewer-rated scale for evaluating the severity of depression over the previous week. It was originally developed for hospital inpatients suffering from affective disorder, which explains the emphasis on melancholic and physical symptoms of depression. The HAM-D has been used in many studies in HD to assess depressive symptoms,[16, 28, 29] including clinical trials.[30-34] It has been shown to correlate with the "depressed mood" item of the UHDRS (r=0.917).[35] The use of the HAM-D in clinical trials has been associated with variable results in terms of a change over time (see further details in Discussion). [30-33]

Recommendation: "Suggested" for assessing severity of depression, as there is a lack of data on reliability for a higher level of recommendation of its use in HD.

d. Apathy

Apathy Scale (AS)

The AS assesses the presence and severity of apathy, and considers cognitive, emotional, and behavioral symptoms, with the patient being questioned by the clinician. The AS is a modified and abridged version of the Apathy Evaluation Scale which was originally

developed for patients with PD. It has been used in several studies to assess apathy in presymptomatic and manifest HD patients.[11, 37-40] Caregiver information can be used to complete the scale if there are concerns about HD patients having a lack of insight.[11, 37, 38] Inter-rater agreement for the presence of apathy in HD varies according to cognitive impairment, being poor for those with lower MMSE scores (k=0.11 vs. k=0.57 for those with more intact cognition).[11] There is a strong association between the AS and a DSM-IV diagnosis of depression in HD (OR: 23.84, 95% CI: 2.40 - 237, p=0.007).[40] AS scores have not been found to correlate with hypokinesia in HD.[37]

Recommendation: "Suggested" for screening of apathy. Association with depression requires further characterization.

Apathy subscale of the Frontal Systems Behavior Scale (FrsBE)

The FrsBE, formerly named Frontal Lobe Personality Scale was designed to measure frontal lobe behavior syndromes theoretically associated with three distinct frontal subcortical circuits: apathy, disinhibition, and executive dysfunction. [41] A total score as well as three subscale scores are calculated. Clinician, family- and self-rated parallel forms are available. While it is an easy to use scale for assessing frequency of symptoms, and can be used in patients with dementia, problems with reverse coding and factor analysis warrant refinement of item composition.[41, 42] A modified 18-item version of the FRsBE has been used.[42] The Apathy subscale of the FrsBE has been used in large observational and imaging studies (PREDICT-HD, IMAGE-HD) in presymptomatic and early HD.[3, 41-43] No clinimetric validation study has been performed specifically in HD, and most of the data were generated in a mixed population that included manifest HD, PD, dementias of different etiologies, head injury and stroke.[41]

Recommendation: "suggested" for assessing severity of apathy. The FrsBE lacks clinimetric assessment in a "pure" HD population.

Apathy Evaluation Scale (AES)

The AES was developed to quantify abnormalities in goal-directed behavior, goal-related thought content and emotional indifference related with apathy. Three versions are available: clinician (AES-C), self-rated (AES-S) and informant (AES-I) versions. The AES-C and AES-S are the most widely used. The AES-C requires minimal training. In HD, there is evidence of convergent validity of the AES-C behavioral dimension with the apathy factor of the Problem Behaviors Assessment for Huntington's Disease (PBA-HD; Pearson correlation, $r = 0.50$, $p<0.01$), and of divergent validity for depression measured by the PBA-HD (Pearson correlation, $r = 0.16$, p=n.s.). [44] There is one HD study using the AES-S to assess drug effects,[45] and another study which does not clearly specify which of the AES scales it uses (presumably the AES-C).[44]

Recommendation: "Suggested" for assessing severity of apathy. In virtue of the risk of lack of insight by HD patients, the AES-C is favored.

e. Obsessive Compulsive Behaviors

Schedule of Compulsions, Obsessions and Pathological Impulses (SCOPI)

The SCOPI is a validated, multidimensional self-report scale developed to screen and measure the severity of obsessive-compulsive behaviors. [46] It comprises five subscales: checking, cleanliness, compulsive rituals, hoarding, and pathologic impulses. [46] The SCOPI has been used in PREDICT-HD and IMAGE-HD studies.[43, 47, 48] The PREDICT study results

showed an inverted-U pattern of increasing obsessive-compulsive behaviors with probability of motor phenoconversion.[49]

Recommendation: "Suggested" for assessing severity of obsessive-compulsive behaviors. Core clinimetric properties (i.e., reliability, validity) of the SCOPI require assessment in HD.

II. SCALES WITH MULTIPLE BEHAVIORAL DOMAINS ASSESSED

Irritability, depression and anxiety scale (IDA)

Behavioral domains assessed in review: Irritability, depression and anxiety

The IDA is a self-reported scale initially developed to assess primarily irritability with a component of outward (behavioral expression of irritability) and inward (thoughts of self-arm) irritability.[50] Measures of depression and anxiety were also included,[50] but the different domains of the IDA frequently are reported separately. Each item of the IDA is rated on a four-point scale. The full version of the IDA has rarely been used in HD.[19] The Snaith's Irritability Self-Assessment Scale (SIS) corresponds to the set of items related to irritability found in the IDA. The SIS has been used in various studies in HD in both presymptomatic and manifest HD populations, [19, 51-54] at times in conjunction with the HADS as a composite psychiatric morbidity score coined HADS-SIS.[53, 55] In HD, good convergence validity has been demonstrated with the IAS for inward irritability (Spearman $\rho = 0.80$) and poor divergent validity (as the correlations are in the moderate to high range) has been reported with the MADRS (Spearman $\rho = 0.62$ and 0.67) and the STAI (Spearman $\rho = 0.66$ and 0.8) for both outward and inward irritability subscales.[19]

Recommendation: "Suggested" for assessing severity of irritability, with a need to assess

reliability in HD.

Irritability-Apathy Scale

Behavioral domains considered for review: Irritability and apathy

The IAS was developed to measure apathy and irritability in patients with dementia, including Alzheimer's disease (AD) and HD. [56] Each item of the apathy subscale is scored by the caregiver from 1-5, while on the irritability subscale one item is scored from 1-5, and the four remaining items are scored from 1-3. It is weighted towards behavioral aspects.[56] The IAS has been used to assess irritability[14, 19, 56] and apathy[14] in HD patients. There is a good internal consistency (Cronbach alpha ranging from 0.66 – 0.81), inter-rater reliability (kappa= 0.98) and test-retest (kappa= 0.88) reliability for both the apathy and the irritability subscales.[56] There is some evidence of validity of the irritability subscale,[56] but the validity of the apathy subscale is unknown.[56]

Recommendation: "Suggested" for assessing the severity of irritability, with a scarce clinimetric assessment in HD.

The Hospital Anxiety and Depression Scale (HADS)

Behavioral domains considered for review: Anxiety and depression

The HADS is a widely used patient-completed scale developed to screen for current anxiety and depression in general (non-psychiatric) medical outpatients. It consists of two subscales which assess anxiety and depression levels. The HADS is weighted toward the emotional aspects of depression and does not include physical and cognitive symptoms, or suicidal ideation. The anxiety subscale covers panic and generalized anxiety. The HADS has been

used to assess depressive and (more rarely) anxiety symptoms in several studies in at-risk, presymptomatic, and manifest HD populations.[22, 43, 47, 48, 51, 53, 54, 57-59] The HADS has been used together with the SIS (HADS-SIS).[53, 55] Excellent sensitivity (1.00) and good specificity (0.79) have been reported in HD for the HADS-depression subscale, using the SCAN diagnosis of depression.[22] A factor analysis conducted in HD populations supports an eight-item version of the HADS to be used as a measure of general distress equally distributed by anxiety and depression items.[60]

Recommendation: "Recommended" for screening depression, and "suggested" for assessing the severity of depression, as there are no reliability data in HD for a higher level of recommendation of use for severity.

Problem Behaviors Assessment for Huntington's Disease - Short Form (PBA-s)

Behavioral domains considered for review: Depression/affective, apathy and irritability

The PBA-s is a semi-structured interview designed specifically for rating the severity and frequency of behavioral abnormalities in HD over the previous four weeks.[61] The short form is derived from the original PBA-HD[61] and includes apathy, irritability and affective subscales, with the latter including items of "depressed mood", "anxiety" and "suicidal ideation". The PBA-s has one item for "paranoid thinking" and another for "hallucinations".[62] The PBA-s can be completed in by a clinician trained in its use, and relies on patient and caregiver recall, as well as clinician judgment.[63] The PBA-s has been used in a few studies in HD in presymptomatic and early manifest HD, many of them with samples from TRACK-HD,[64] reporting the total scores of the PBS-s or its subscores. The apathy subscore has been used in isolation.[65, 66] Factor analysis reveals that a three-factor solution

explains 57.4% of total variance.[62] The PBA-s is being used in ongoing clinical trials. For inter-rater reliability, weighted kappa was 0.74 for severity and 0.76 for frequency. After accepting a ±1 point variation for presence of 'agreement',[62] the 'clinically significant' weighted kappa was 0.94 for severity and 0.92 for frequency. There is no assessment of reliability for each one of the behavioral factors alone. [62] There is more data available for the PBA-HD but these cannot be assumed to apply to the PBA-s.[38, 67]

Recommendation: "Suggested" for screening of behavioral symptoms, including depression/affective, apathy and irritability domains in HD, and the overall severity of behavioral symptoms in HD. The PBA-s warrants a more comprehensive clinimetric assessment.

Neuropsychiatric Inventory (NPI)

Behavioral domains assessed in review: Depression, apathy, irritability, psychosis, and anxiety.

The NPI was developed to distinguish frequency and severity of behavioral changes that occur in AD and other dementias, and to facilitate rapid behavioral assessment through the use of screening questions. There are various versions of the NPI. The 10-item version assesses 10 neuropsychiatric disturbances: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, and aberrant motor behaviors (for other versions, Supplementary material part 2.). A total NPI score and scores for the individual symptom domains are calculated. The NPI symptom domain scores have been used in HD to assess neuropsychiatric manifestations in various studies.[68-71] In clinical trials, only the total score of the NPI has been used to characterize the study population and never as a primary outcome.[30, 72] The limited clinimetric data available

in HD reveal overlap of the different domains, namely irritability with anxiety (r=0.88), and depression (r=0.48).[69] There are no data on reliability of the NPI in HD.

Recommendation: "Suggested" for assessing severity of behavioral symptoms, including depression, apathy, irritability, psychosis, and anxiety as individual items of the NPI.

The Unified Huntington's Disease Rating Scale, behavioral section (UHDRS-b)

Behavioral domains considered for review: Irritability/aggression, apathy, depression, obsessive-compulsive behaviors, and psychosis.

The UHDRS-b was developed to assess behavioral abnormalities in HD. The emphasis of the UHDRS is on clinical features that are likely to show rapid progression and that can be assessed briefly.[73] The UHDRS-b covers depression, apathy, anxiety, irritability/aggression, obsessive-compulsive behaviors, and psychosis. Each item is rated for severity and frequency on a five-point scale referring to the previous month. The total score for each item is obtained by multiplying frequency by severity. The UHDRS has been used in numerous studies of HD and randomized controlled trials, either using the total score or specific item domains.[2, 74-81] A cut-off score of ≥ 6 for presence of depressed mood was reported using the corresponding item of the UHDRS-b.[35] While the internal consistency with a Cronbach alpha of UHDRS-b was 0.83,[73] factor analyses have shown heterogeneous factor solution for depression and irritability.[2, 75, 82] Convergent validity has been reported between the depression items of the UHRDS-b and the item 'Feel sad' of the BDI (correlation coefficient: 0.834, $p<0.01$).[35] There are no data available for reliability.

Recommendation: "Suggested" for assessing severity and screening of behavioral symptoms, including irritability, apathy, depression, obsessive-compulsive behaviors and psychosis, considering the individual items of the UHDRS-b. Further clinimetric testing

is required to support its use with a higher level of recommendation.

Schedules for Clinical Assessment in Neuropsychiatry

Behavioral domains considered for review: Depression, apathy, irritability, psychosis, anxiety, obsessive-compulsive behaviors and suicidal ideation.

The SCAN consists of an inventory containing most neuropsychological domains allowing for a computer-based diagnosis according to DSM-IV and/or ICD-10.[83] It was developed for epidemiological purposes in general psychiatric populations. At its core is the Present State Examination (PSE 10). The PSE 10 has 23 sections to be used according to the patient's symptoms. The PSE (versions 9 and 10) have been used to screen for depression, but not the other domains, in multiple studies in HD.[22, 84-86] The PSE-10 was used as the gold standard for criterion validity of self-reported depression rating scales in HD.[22] There are no other data related to clinimetrics for the PSE-10. The latest version of the SCAN has not been yet updated for the DSM-V.

Recommendation: "Suggested" for screening of depression. Further clinimetric testing is required to support its use at a higher level of recommendation.

DISCUSSION

In the current review, we conclude that for some behavioral domains in HD there are scales that we can recommend **only** for screening, based on the methodology followed by the MDS for the assessment of scale development. For irritability, the IS is recommended for screening purposes. For depression, the BDI-II and the HADS are recommended for screening purposes only. For other behavioral domains, a number of scales are suggested. No recommended or suggested scales for psychosis or suicidal behavior were identified. These recommendations differ slightly from those provided on the NINDS-Common Data Elements which is explained by the current review being based on explicit rules for inclusion and exclusion of scales as well as for the recommendation levels provided, and not a consensus-based report as was the case for NINDS-Common Data Elements.

These findings of our review highlight a gap in scale development in HD for apathy, anxiety, obsessive-compulsive behaviors, psychosis, and suicidal behavior with the need to validate scales for the assessment of severity of behavioral symptoms in HD. For both rating scales developed and validated specifically in HD for a global assessment of behavioral symptoms, the assessment of reliability performance is warranted. The knowledge about these measurement properties will allow a more meaningful use of these scales in HD studies, namely in the context of clinical trials.

The current review identified various challenges in the development and application of behavioral rating scales in HD:

- Behavioral symptoms observed in HD may not fit formal diagnoses suggested by international classification systems such as the DSM[7] that are frequently used as the

gold standard for psychiatric diagnoses. In addition, there is no widely accepted definition of behavioral symptoms in HD, including irritability, apathy, or depression. This is a limitation in the assessment of scale validity in HD.

- The traditional classification systems have several shortcomings: an overlap between the physical manifestations of psychiatric syndromes and the physical manifestations of HD (e.g. weight loss may be present regardless of the mood status and may not be directly associated with depression). Other behavioral symptoms that may be part of a behavioral spectrum in HD and lack a proper definition include hostility, agitation, disinhibition and impulsivity. Like apathy, no gold standard exists for the assessment of these neuropsychiatric features.
- There is a co-occurrence of behavioral symptoms in HD when assessed by behavioral rating scales, namely the case of depressed mood and anxiety clustered in a single factor (PBA-s), apathy and depression (Apathy Scale), and irritability and anxiety (Irritability self-assessment scale of the IDA). This overlap may be secondary to the limitations of currently used rating scales in terms of their construct when applied to HD, but may suggest that there are behavioral constructs specific to HD that should be considered when developing behavioral rating scales for use in this patient population.
- The validation process of behavioral rating scales in HD should consider the existence of identifiable disease stages. The current discussion of new formal diagnostic criteria for HD may provide a framework for defining disease stages in which behavioral symptoms and scale use can be rigorously assessed in prodromal or symptomatic HD populations.[87] For example, rating scales may be specifically developed to capture subtler changes at a prodromal stage and require different clinimetric properties than when validated to be used in a symptomatic stage. Another aspect to consider when

validating a clinical rating scale is the effect on behavioral symptoms of medications used in HD.

- The presence of cognitive impairment and lack of insight of patients should be considered in scale development in HD, in particular, considerations about the validity of self-rating and caregiver-rated scales in HD should be taken into account. The use of self-report scales is not generally recommended, particularly in advanced stages, but lack of insight may already be present at the prodromal stage. The use of collateral information should be considered when developing scales to assess behavioral symptoms in HD. This consideration requires that specific clinimetric properties have to be considered during the development of the corresponding rating scale: caregiver reliability as well as the necessity of ensuring the same caregiver is used in longitudinal assessments.
- No single domain scale for psychosis or suicidal behavior met the "suggested" or "recommended" criteria. While there are items of the UHDRS-b and PBA-s for psychotic symptoms, these have not been specifically validated for this cluster of behaviors. The Columbia Suicidal Severity Rating Scale, which is widely used in HD clinical trials for assessing suicidal ideation, requires clinimetric testing in HD to be considered appropriate in the setting of HD trials.

In conclusion, there are ''recommended'' rating scales for screening of depression and irritability in HD. There are no scales recommended for assessing severity or change of severity over time, an important need when considering interventional studies for behavioral symptoms in HD. Currently, the committee recommends further development of available behavioral rating scales in order to fill the gaps identified. Both HD-specific scales and those

originally developed in non-HD populations can be used or modified in future development efforts, rather than developing a completely new scale(s).

Author Roles.

Tiago A. Mestre:

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: A. Writing of the first draft; B. Review and Critique;

Erik van Duijn:

1. Research project: A. Conception, C. Execution;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: B. Review and Critique;

Aileen M. Davis:

1. Research project: B. Organization, C. Execution;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: B. Review and Critique;

Anne-Catherine Bachoud-Lévi

1. Research project: C. Execution;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: B. Review and Critique;

Monica Busse

1. Research project: C. Execution;
2. Statistical Analysis: not applicable;

3. Manuscript Preparation: B. Review and Critique;

Karen E. Anderson

1. Research project: not applicable;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: B. Review and Critique;

Joaquim J. Ferreira

1. Research project: C. Execution;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: B. Review and Critique;

Philipp Mahlknecht

1. Research project: C. Execution;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: B. Review and Critique;

Vitor Tumas

1. Research project: C. Execution;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: B. Review and Critique;

Cristina Sampaio

1. Research project: A. Conception, C. Execution;
2. Statistical Analysis: not applicable;

3. Manuscript Preparation: B. Review and Critique;

Chris G. Goetz

1. Research project: none;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: B. Review and Critique;

Esther Cubo

1. Research project: none;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: B. Review and Critique;

Glenn T. Stebbins

1. Research project: none;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: B. Review and Critique;

Pablo Martinez-Martin

1. Research project: none;
2. Statistical Analysis: not applicable;
3. Manuscript Preparation: B. Review and Critique;

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