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RESEARCH ARTICLE

Validation of the RBD Symptom Severity Scale in the North American Prodromal Synucleinopathy Consortium

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Abstract

Background and Objectives

REM sleep behavior disorder (RBD) is a parasomnia characterized by dream enactment. The International RBD Study Group developed the RBD Symptom Severity Scale (RBDSSS) to assess symptom severity for clinical or research use. We assessed the psychometric and clinimetric properties of the RBDSSS in participants enrolled in the North American Prodromal Synucleinopathy (NAPS) Consortium for RBD.

Methods

NAPS participants, who have polysomnogram-confirmed RBD, and their bedpartners completed the RBDSSS (participant and bedpartner versions). The RBDSSS contains 8 questions to assess the frequency and severity/impact of (1) dream content, (2) vocalizations, (3) movements, and (4) injuries associated with RBD. Total scores for participant (maximum score = 54) and bedpartner (maximum score = 38) questionnaires were derived by multiplying frequency and severity scores for each question. The Clinical Global Impression Scale of Severity (CGI-S) and RBD symptom frequency were assessed by a physician during a semi-structured clinical interview with participants and, if available, bedpartners. Descriptive analyses, correlations between overall scores, and subitems were assessed, and item response analysis was performed to determine the scale's validity.

Results

Among 261 study participants, the median (interquartile range) score for the RBDSSS-PT (participant) was 10 (4–18) and that for the RBDSSS-BP (bedpartner) was 8 (4–15). The median CGI-S was 3 (3–4), indicating moderate severity. RBDSSS-BP scores were significantly lower in women with RBD (6 vs 9, $p = 0.02$), while there were no sex differences in RBDSSS-PT scores (8 vs 10.5, $p = 0.615$). Positive correlations were found between RBDSSS-PT vs RBDSSS-BP (Spearman $r_s = 0.561$), RBDSSS-PT vs CGI-S ($r_s = 0.556$), and RBDSSS-BP vs CGI-S ($r_s = 0.491$, all $p < 0.0001$). Item response analysis showed a high discriminatory value (range 1.40–2.12) for the RBDSSS-PT and RBDSSS-BP (1.29–3.47).

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CGI-S = Clinician Global Impression Scale of Severity; ***DSM-V*** = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; **IRB** = institutional review board; **IRBDSG** = International RBD Study Group; **IRT** = item response theory; **NAPS** = North American Prodromal Synucleinopathy; **OSA** = obstructive sleep apnea; **PCL-5** = PTSD Checklist for DSM-5; **PHQ-9** = Patient Health Questionnaire-9; **PLMS** = periodic limb movements of sleep; **PTSD** = posttraumatic stress disorder; **RBD** = REM sleep behavior disorder; **RBDSSS** = RBD Symptom Severity Scale; **RBDSSS-BP** = RBDSSS-Bedpartner version; **RBDSSS-PT** = RBDSSS-Participant version; **RLS** = restless leg syndrome; **TBI** = traumatic brain injury; **vPSG** = video polysomnogram.

Discussion

We describe the RBDSSS with adequate psychometric and clinimetric properties to quantify RBD symptom severity and good concordance between participant and bedpartner questionnaires and between RBDSSS scores and clinician-assessed global severity.

Introduction

REM sleep behavior disorder (RBD) is a well-established prodromal marker of α-synucleinopathies.[1,2] Dream enactment behaviors in RBD vary in dream content, the types of behaviors,[3] and their impact on patients and bedpartners,[2] making RBD severity challenging to quantify. Whereas violent behaviors and injuries are well documented and often lead to patients seeking medical attention,[4] less injurious behaviors, disruption of sleep quality, and the need for separate sleeping arrangements can be just as distressing to patients and their partners. There is currently no simple and readily useable measure of RBD symptom severity for use in either clinical or research settings. The lack of effective outcome measures results in a lack of well-defined endpoints and challenges with the prescription and titration of symptomatic therapy in RBD in both clinical practice and interventional trials.

Quantification of RBD symptom severity has received limited attention. Previously, the International RBD Study Group (IRBDSG) recommended the standard Clinician Global Impression Scale of Severity (CGI-S) as an estimate of RBD severity for symptomatic clinical trials.[5] The CGI-S is a widely used 7-point scale that provides a clinician-determined summary measure for a given symptom (in this case, RBD severity), which ranges from normal (1) to extremely ill (7).[6] However, this scale can be highly subjective and challenging to standardize between clinicians, may weigh more heavily toward violent movements and potential for injury, and can be influenced by other patient factors (frailty, anticoagulation use, etc).[7] Scales for scoring RBD on video polysomnogram (vPSG) have been developed, including the RBD severity scale[8] and the RBD PSG score,[9] which record the frequency and severity of motor and vocal episodes during REM sleep captured on video. However, because vPSG-based scales require overnight in-laboratory vPSG recording and detailed, time-consuming analyses, these tools are challenging and costly to implement in routine clinical settings, especially when severity needs to be assessed repeatedly, such as during medication titration.

To fill this gap, the IRBDSG developed and revised an 8-item questionnaire, the RBD Symptom Severity Scale (RBDSSS), to assess RBD severity from both patient and bedpartner perspectives. An initial draft was created and presented to the IRBDSG in 2016 (by R.P.) and revised over the next 3 years in the clinical working group of the IRBDSG, followed by broad consultation and eventual approval by membership and executive board of the IRBDSG. There are 2 versions of the RBDSSS, one to be filled out by the patient (RBDSSS-PT) and a bedpartner version (RBDSSS-BP) was created to obtain information from a bedpartner independently. Because individuals with RBD are often unaware of events that occur while they are asleep,[10,11] they were encouraged to use the input of a bedpartner/another informant, whenever available. This scale is intended to be complementary to vPSG-based scales. French and Italian translations of the RBDSSS are also available with ongoing validation studies by M.L.F. (manuscript in preparation).

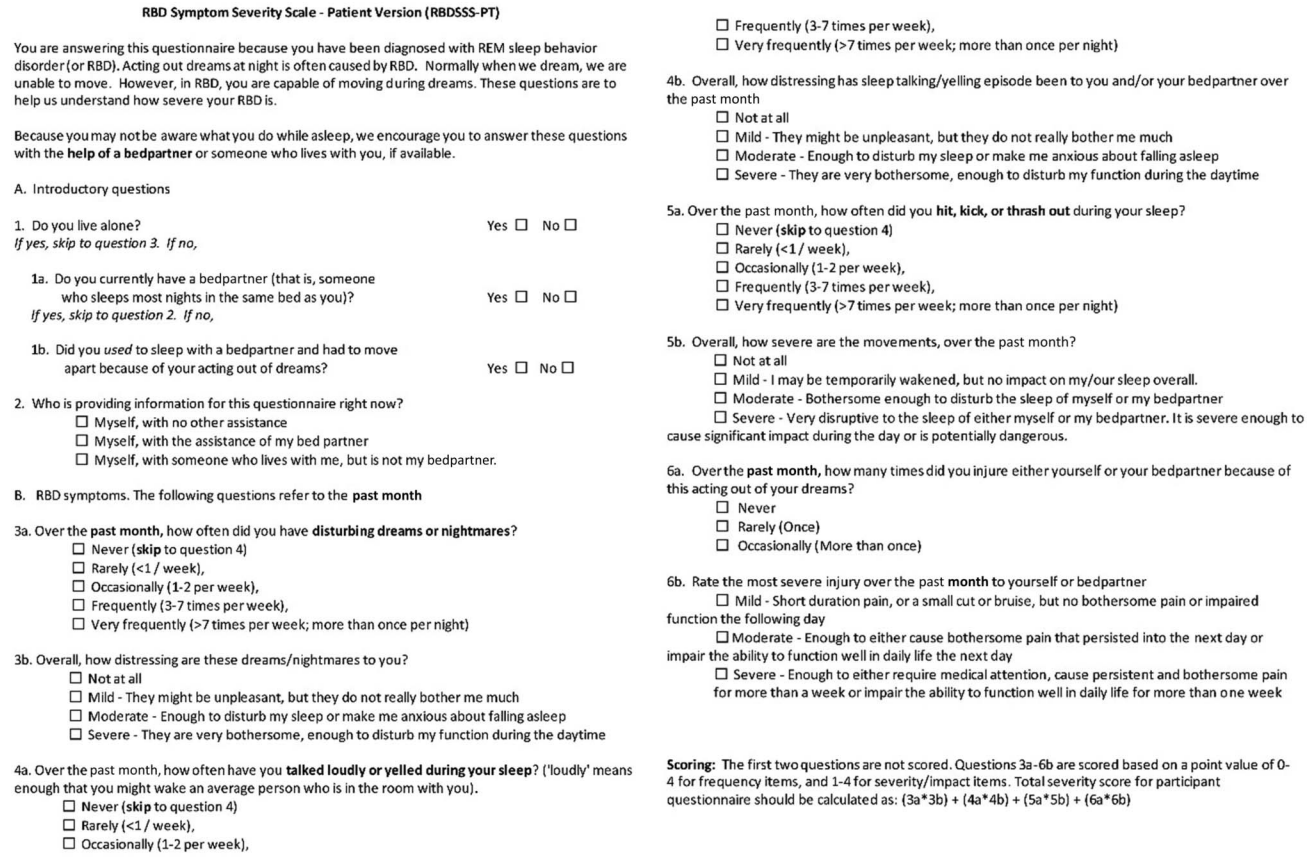
No prior validation studies of the RBDSSS in clinical or research settings have yet been described. The RBDSSS was filled out by participants in the North American Prodromal Synucleinopathy (NAPS) Consortium for RBD, a multisite cohort of patients with vPSG-confirmed diagnosis of idiopathic RBD.[12] In this article, we describe the features and scoring of the RBDSSS and its correlation to the CGI-S in participants enrolled in the NAPS cohort.

Methods

Study Participants

The NAPS study (a longitudinal observational study) enrolled patients who had clinical overnight vPSG to confirm the diagnosis of RBD (i.e., demonstrate REM sleep without

Figure 1 RBD Symptom Severity Scale—Patient Version



RBD Symptom Severity Scale - Patient Version (RBDSSS-PT)

You are answering this questionnaire because you have been diagnosed with REM sleep behavior disorder (or RBD). Acting out dreams at night is often caused by RBD. Normally when we dream, we are unable to move. However, in RBD, you are capable of moving during dreams. These questions are to help us understand how severe your RBD is.

Because you may not be aware what you do while asleep, we encourage you to answer these questions with the **help of a bedpartner** or someone who lives with you, if available.

A. Introductory questions

1. Do you live alone? Yes ☐ No ☐
If yes, skip to question 3. If no,

1a. Do you currently have a bedpartner (that is, someone who sleeps most nights in the same bed as you)? Yes ☐ No ☐
If yes, skip to question 2. If no,

1b. Did you *used* to sleep with a bedpartner and had to move apart because of your acting out of dreams? Yes ☐ No ☐

2. Who is providing information for this questionnaire right now?
☐ Myself, with no other assistance
☐ Myself, with the assistance of my bed partner
☐ Myself, with someone who lives with me, but is not my bedpartner.

B. RBD symptoms. The following questions refer to the **past month**

3a. Over the **past month,** how often did you have **disturbing dreams or nightmares**?
☐ Never (**skip** to question 4)
☐ Rarely (<1 / week),
☐ Occasionally (**1**-2 per week),
☐ Frequently (3-7 times per week),
☐ Very frequently (>7 times per week; more than once per night)

3b. Overall, how distressing are these dreams/nightmares to you?
☐ Not at all
☐ Mild - They might be unpleasant, but they do not really bother me much
☐ Moderate - Enough to disturb my sleep or make me anxious about falling asleep
☐ Severe - They are very bothersome, enough to disturb my function during the daytime

4a. Over the past month, how often have you **talked loudly or yelled during your sleep**? ('loudly' means enough that you might wake an average person who is in the room with you).
☐ Never (**skip** to question 4)
☐ Rarely (<1 / week),
☐ Occasionally (1-2 per week),
☐ Frequently (3-7 times per week),
☐ Very frequently (>7 times per week; more than once per night)

4b. Overall, how distressing has sleep talking/yelling episode been to you and/or your bedpartner over the past month
☐ Not at all
☐ Mild - They might be unpleasant, but they do not really bother me much
☐ Moderate - Enough to disturb my sleep or make me anxious about falling asleep
☐ Severe - They are very bothersome, enough to disturb my function during the daytime

5a. Over the past month, how often did you **hit, kick, or thrash out** during your sleep?
☐ Never (**skip** to question 4)
☐ Rarely (<1 / week),
☐ Occasionally (1-2 per week),
☐ Frequently (3-7 times per week),
☐ Very frequently (>7 times per week; more than once per night)

5b. Overall, how severe are the movements, over the past month?
☐ Not at all
☐ Mild - I may be temporarily wakened, but no impact on my/our sleep overall.
☐ Moderate - Bothersome enough to disturb the sleep of myself or my bedpartner
☐ Severe - Very disruptive to the sleep of either myself or my bedpartner. It is severe enough to cause significant impact during the day or is potentially dangerous.

6a. Over the **past month,** how many times did you injure either yourself or your bedpartner because of this acting out of your dreams?
☐ Never
☐ Rarely (Once)
☐ Occasionally (More than once)

6b. Rate the most severe injury over the past **month** to yourself or bedpartner
☐ Mild - Short duration pain, or a small cut or bruise, but no bothersome pain or impaired function the following day
☐ Moderate - Enough to either cause bothersome pain that persisted into the next day or impair the ability to function well in daily life the next day
☐ Severe - Enough to either require medical attention, cause persistent and bothersome pain for more than a week or impair the ability to function well in daily life for more than one week

Scoring: The first two questions are not scored. Questions 3a-6b are scored based on a point value of 0-4 for frequency items, and 1-4 for severity/impact items. Total severity score for participant questionnaire should be calculated as: (3a*3b) + (4a*4b) + (5a*5b) + (6a*6b)

The first 2 questions are not scored. Questions 3a–6b are scored based on a point value of 0–4 for frequency items and 1–4 for severity/impact items. Total severity score for participant questionnaire was calculated as follows: (3a × 3b) + (4a × 4b) + (5a × 5b) + (6a × 6b).

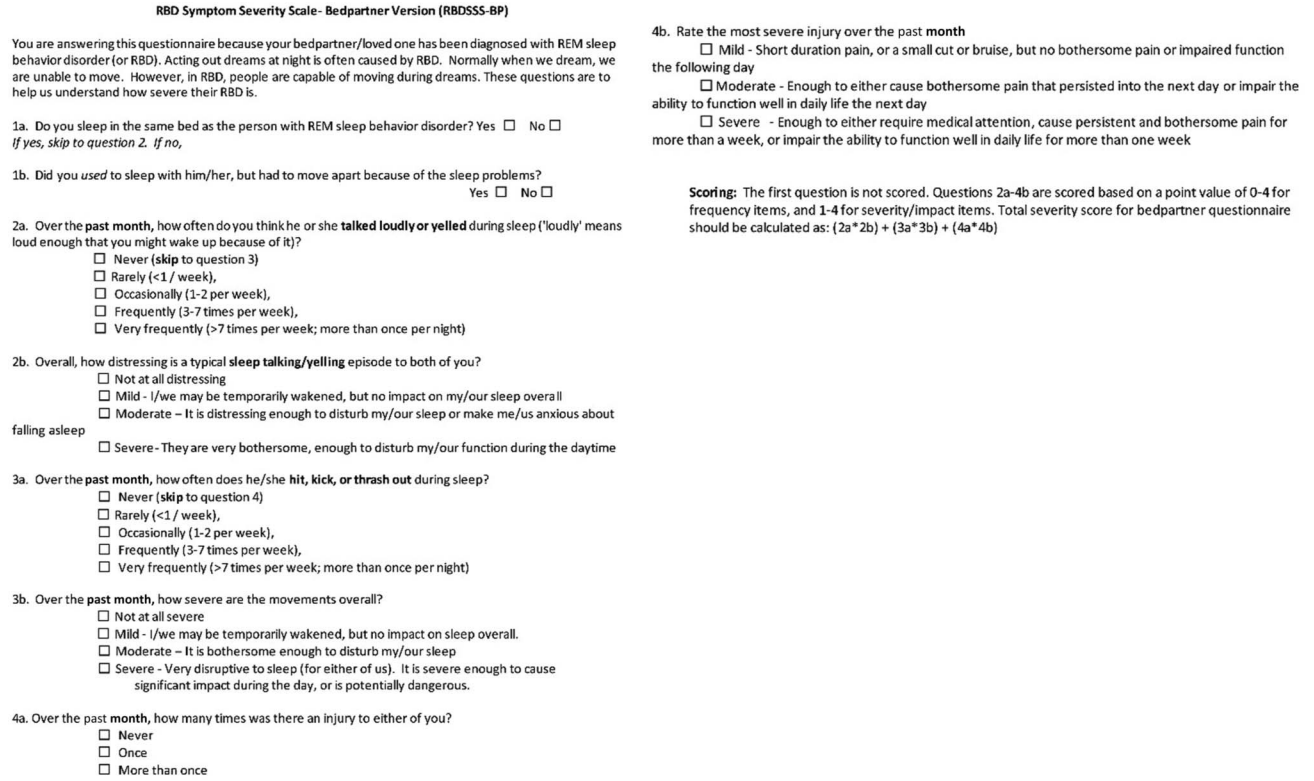
atonia) across 10 sites in North America. All vPSG data were reviewed by an NAPS investigator (E.S.L.) to ensure accurate diagnosis of RBD was made through sleep study and to rule out any mimics.[11] Patients with a diagnosis of an overt parkinsonian syndrome, dementia, multiple system atrophy, or other identifiable cause of RBD (e.g., narcolepsy, lesional RBD) were excluded. This analysis is based on data from the original NAPS cohort ("NAPS1") only. Data from completed RBDSSS-PT questionnaires were included in the analysis if they had corresponding CGI-S scores available. RBDSSS-BP scores were excluded for this analysis if they answered "I don't know" to questions about frequency of vocalizations, movements, and injuries. Participants completed multiple questionnaires and a comprehensive, semistructured clinical interview with questions related to RBD (including age at onset) by board-certified neurologists using standard protocols. Comorbidities such as history of concussion/traumatic brain injury (TBI), obstructive sleep apnea (OSA), restless leg syndrome (RLS), and posttraumatic stress disorder (PTSD) were reported by participants in their medical history and general health history. Participants also filled out several validated health history questionnaires such as Patient Health Questionnaire–9 (PHQ-9) and the PTSD checklist for DSM-V (PCL-5). If available, bedpartners or an informant (family member or friend with knowledge of the participant's day-to-day functioning) also completed questionnaires and a semistructured interview. Information regarding current and previous medications, specifically medications that may be associated with RBD symptoms and their temporal correlations to RBD, was also captured in the study. Treatment decisions for RBD symptoms were made by participants with their treating physicians independent of their NAPS participation. A detailed description of the NAPS Consortium (ClinicalTrials.gov NCT03623672) cohort can be found here.[13]

Participants and their bedpartners, if available, completed the RBDSSS-PT, and the RBDSSS-BP was independently completed by the bedpartner. A clinician completed the CGI-S on a 7-point scale ranging from normal/none (1) to most severely ill (7) based on an independent interview with the participant ± their bedpartners (i.e., the clinicians were blind to the responses on the RBDSSS).

Description of the RBDSSS

Both the participant and bedpartner versions of the scale consist of 3 core components, namely vocalizations, body movements, and injury (Figures 1 and 2). In the RBDSSS-PT,

Figure 2 RBD Symptom Severity Scale—Bedpartner Version



RBD Symptom Severity Scale- Bedpartner Version (RBDSSS-BP)

You are answering this questionnaire because your bedpartner/loved one has been diagnosed with REM sleep behavior disorder (or RBD). Acting out dreams at night is often caused by RBD. Normally when we dream, we are unable to move. However, in RBD, people are capable of moving during dreams. These questions are to help us understand how severe their RBD is.

1a. Do you sleep in the same bed as the person with REM sleep behavior disorder? Yes ☐ No ☐
If yes, skip to question 2. If no,

1b. Did you *used* to sleep with him/her, but had to move apart because of the sleep problems?
Yes ☐ No ☐

2a. Over the **past month,** how often do you think he or she **talked loudly or yelled** during sleep ('loudly' means loud enough that you might wake up because of it)?
☐ Never (**skip** to question 3)
☐ Rarely (<1 / week),
☐ Occasionally (1-2 per week),
☐ Frequently (3-7 times per week),
☐ Very frequently (>7 times per week; more than once per night)

2b. Overall, how distressing is a typical **sleep talking/yelling** episode to both of you?
☐ Not at all distressing
☐ Mild - I/we may be temporarily wakened, but no impact on my/our sleep overall
☐ Moderate – It is distressing enough to disturb my/our sleep or make me/us anxious about falling asleep
☐ Severe - They are very bothersome, enough to disturb my/our function during the daytime

3a. Over the **past month,** how often does he/she **hit, kick, or thrash out** during sleep?
☐ Never (**skip** to question 4)
☐ Rarely (<1 / week),
☐ Occasionally (1-2 per week),
☐ Frequently (3-7 times per week),
☐ Very frequently (>7 times per week; more than once per night)

3b. Over the **past month,** how severe are the movements overall?
☐ Not at all severe
☐ Mild - I/we may be temporarily wakened, but no impact on sleep overall.
☐ Moderate – It is bothersome enough to disturb my/our sleep
☐ Severe - Very disruptive to sleep (for either of us). It is severe enough to cause significant impact during the day, or is potentially dangerous.

4a. Over the past **month,** how many times was there an injury to either of you?
☐ Never
☐ Once
☐ More than once

4b. Rate the most severe injury over the past **month**
☐ Mild - Short duration pain, or a small cut or bruise, but no bothersome pain or impaired function the following day
☐ Moderate - Enough to either cause bothersome pain that persisted into the next day or impair the ability to function well in daily life the next day
☐ Severe - Enough to either require medical attention, cause persistent and bothersome pain for more than a week, or impair the ability to function well in daily life for more than one week

Scoring: The first question is not scored. Questions 2a-4b are scored based on a point value of 0-4 for frequency items, and 1-4 for severity/impact items. Total severity score for bedpartner questionnaire should be calculated as: (2a*2b) + (3a*3b) + (4a*4b)

The first question is not scored. Questions 2a–4b are scored based on a point value of 0–4 for frequency items and 1–4 for severity/impact items. Total severity score for participant questionnaire was calculated as follows: (2a × 2b) + (3a × 3b) + (4a × 4b).

a fourth component of dream content/nightmares (by nature less reliably reported by bedpartners) is also assessed. All components use the time scale of the previous 4-week period. Each component queries both the frequency of the behavior: never, rarely (<1 per week), occasionally (1–2 per week), frequently (3–7 per week), or very frequently (>7 per week, i.e., more than once per night), and the severity/impact of the behavior (none, mild, moderate, or severe). Additional questions (not scored) asked whether there is a regular bedpartner and if not, whether RBD symptoms required participants to sleep apart. The scale takes less than 5 minutes to complete. The English and French versions of the scale were used in the NAPS Consortium.

Scoring and Validation of Scale

Each question was assigned a point value of 0–4 based on frequency and 1–4 for severity/impact (none, mild, moderate, or severe), with higher values representing higher frequency or severity/impact. The exception to this scoring was for the injury questions where, to account for the low overall frequency of injury, the scoring range was between 0 and 2. Total RBDSSS scores for RBDSSS-PT (max score = 54) and RBDSSS-BP (max = 38) questionnaires were derived by multiplying assigned point values for frequency and severity (for each question) and summing them. Thus, the total severity score for the RBDSSS-PT was calculated as follows: (3a × 3b) + (4a × 4b) + (5a × 5b) + (6a × 6b) (Figure 1), and that for the RBDSSS-BP was calculated as follows: (2a × 2b) + (3a × 3b) + (4a × 4b) (Figure 2).

Both the RBDSSS-PT and RBDSSS-BP are free for use for clinical purposes. They can also be freely used (without restriction or requirement for further permission) by not-for-profit academic research that has been approved by a research ethics board. Permission for use by for-profit organizations can be obtained from the IRBDSG (or contact the corresponding author).

Criterion Validity

Criterion validity refers to how well a test correlates with the gold standard. In this case, this was limited by the lack of a gold standard measure, so was indirectly assessed through correlation with the CGI-S. Correlation between total scores were assessed for the following dyads: RBDSSS-PT vs RBDSSS-BP, RBDSSS-PT vs CGI-S, and RBDSSS-BP vs CGI-S. Reliability between participant and bedpartner was assessed for each question separately except for question 3 (dream content), which was not applicable to the bedpartner questionnaire. Internal consistency was assessed by comparing intake questions about the frequency of "RBD-related behaviors" with the corresponding questions on the RBDSSS-PT about dream content, vocalizations, and movement (each

Table 1 Characteristics of Participants and RBD Severity Scores

	Total (n = 261)	Male individuals (n = 210)	Female individuals (n = 51)	*p* Value
Age, mean ± SD	65.3 ± 9.96	65.6 ± 10.1	64.3 ± 9.2	0.277
Age at symptom onset, mean ± SD	51.9 ± 15.7	52.3 ± 15.3	49.9 ± 17.0	0.410
Education, mean ± SD	16.2 ± 3.0	16.3 ± 3.0	16.0 ± 2.7	0.387
Medication use (lifetime), n (%)				
Any	207 (80.5)	172 (83.1)	35 (70.0)	0.046
Clonazepam	127 (49.0)	106 (51.0)	21 (41.2)	0.216
Melatonin	146 (55.9)	122 (58.1)	24 (47.1)	0.208
Other (dopamine agonists, etc.)	20 (7.7)	16 (7.6)	4 (7.8)	1.000
Current medication use, n (%)				
Any	184 (71.0)	156 (74.6)	28 (56.0)	0.014
Clonazepam	106 (40.6)	90 (42.9)	16 (31.4)	0.154
Melatonin	117 (44.8)	100 (47.6)	17 (33.3)	0.084
Other	14 (5.4)	12 (5.7)	2 (3.9)	1.000
Presence of comorbidities, n (%)				
OSA	124 (47.9)	109 (52.2)	15 (30.0)	0.007
RLS	51 (20.0)	38 (18.6)	13 (25.5)	0.327
PLMS	33 (13.5)	26 (13.1)	7 (15.2)	0.811
TBI	59 (22.7)	52 (24.9)	7 (13.7)	0.096
Validated mental health questionnaires, median (IQR)				
PHQ-9	3 (1–8)	3 (1–7)	4 (2–9)	0.303
PCL-5	6 (1–15)	6 (1–15)	7 (1–18)	0.544
RBDSSS data, median (IQR)				
RBDSSS-PT	10 (4–18)	10.5 (4–18)	8 (4–16)	0.615
RBDSSS-BP[a]	8 (4–15)	9 (4–15)	6 (3.5–10.5)	0.020
CGI-S	3 (3–4)	3 (3–4)	3 (2–4)	0.037

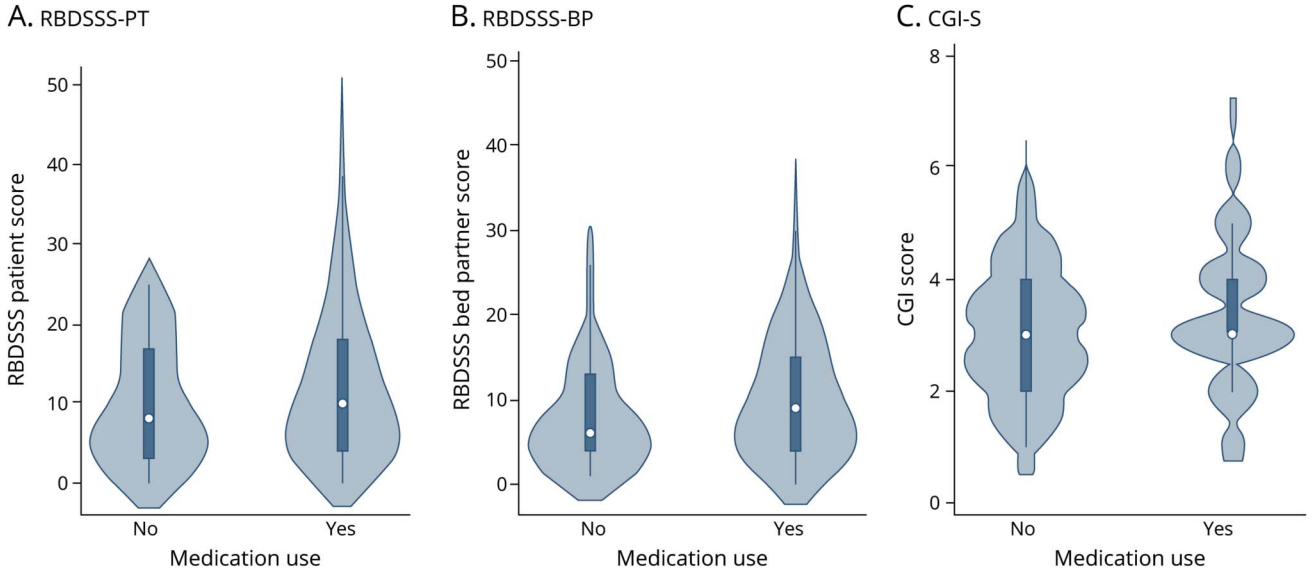
Abbreviations: CGI-S = Clinical Global Impression Scale of Severity; IQR = interquartile range; OSA = obstructive sleep apnea; PCL-5 = Posttraumatic Stress Disorder Checklist for DSM-5; PHQ-9 = Patient Health Questionnaire–9; PLMS = periodic limb movements of sleep; RBDSSS = RBD Symptom Severity Scale; RBDSSS-BP = RBDSSS-Bedpartner version; RBDSSS-PT = RBDSSS-Participant version; RLS = restless leg syndrome; TBI = traumatic brain injury.
[a] Available for 214 participants.

domain of RBDSSS). To determine which RBDSSS symptom best correlated with the CGI-S, each individual question was correlated with the CGI-S separately for the participant and bedpartner questionnaires.

Construct Validity Using Item Response Theory

Construct validity describes to what degree a test measures what it was intended to measure. We used the item response theory (IRT)[14,15] to further assess RBDSSS properties and responses to individual questions on the instrument. We used the Graded response model to reflect the Likert scale–type questions in our scale[14] to understand item properties and obtain adjusted weighted scores for each item/question. In brief, the IRT model allows evaluation of each item on a questionnaire, based on characteristics of the questions themselves and the person completing it (in our case, overall RBD severity as reported by participants or their bedpartners).[16] Category characteristic curves were generated for each question (separately for frequency and severity). For each item, the 50% probability of endorsing a particular choice for a question/item is denoted by the variable "theta, θ" (referred to here as RBD severity trait) or "difficulty parameter, b." Parameters defining sensitivity to change in overall RBD severity of an item are calculated as "discrimination parameter" or "a."

Figure 3 Violin Plots Showing RBD Severity Scores of (A) Patient (B) Bedpartner, and (C) CGI Scores by Medication Use (Lifetime)



Shape of violin plots show the probability density of RBD severity scores are concentrated around the median. The median RBD severity scores for both patient and bedpartner were numerically higher in patients treated with medication but statistically not different. CGI-S = Clinical Global Impression Scale of Severity; RBDSSS = RBD Symptom Severity Scale; RBDSSS-BP = RBD Symptom Severity Scale–Bedpartner version; RBDSSS-PT = RBD Symptom Severity Scale–Participant version.

Statistical Analyses

Descriptive statistics were used to describe the cohort characteristics. We reported continuous variables as medians and interquartile range values, while categorical variables were reported as numbers and percentages. The Fisher exact test or χ^2 test was used to compare categorical variables, and the nonparametric Wilcoxon rank sum test was applied for continuous variables. Nonparametric tests, including the Spearman correlation (r_s), were used to describe relationships between the RBDSSS and CGI-S. The effect of presence of other sleep comorbidities such as OSA, RLS, periodic limb movements of sleep (PLMS), TBI, and PTSD on the RBDSSS were determined. The relationship between the RBDSSS, CGI-S scores, and pharmacologic treatment with melatonin and/or clonazepam was also evaluated. Internal consistency between questions was measured by Cronbach α. The IRT was applied to both participant and bedpartner questionnaires. We used the Consensus-based Standards for the selection of health status Measurement Instruments reporting guidelines for studies on measurement properties as a guide for reporting results.[17] All statistical analyses were performed with the STATA version 17 (Statacorp., College Station, TX). A p value <0.05 was considered significant.

Standard Protocol Approvals, Registrations, and Patient Consents

All patients and/or their proxies provided written informed consent before their participation at each enrollment site, all of which received local institutional review board (IRB) approval. The University of Arizona IRB determined this analysis to be exempt from additional review.

Data Availability

Anonymized data not published within this article will be made available by the NAPS Consortium by request from qualified investigators.[12]

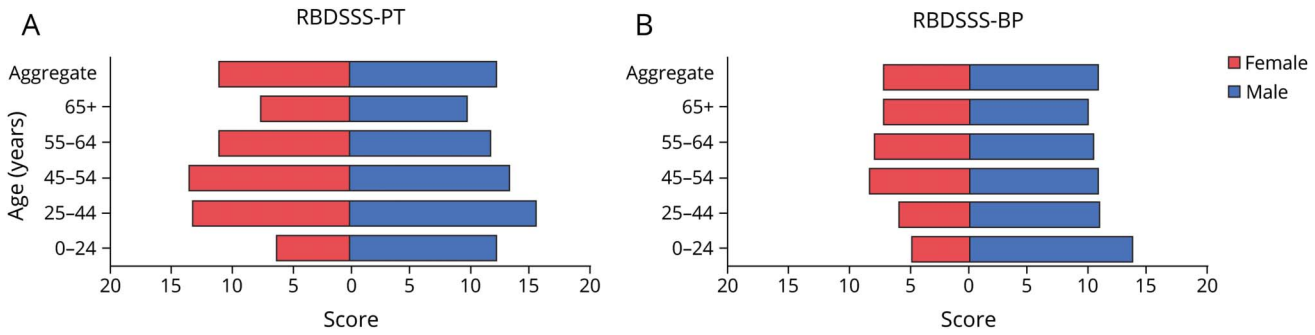
Results

The IRBDSG revised and developed the RBDSSS-PT and RBDSSS-BP. The participant and bedpartner versions are provided in Figures 1 and 2, respectively. Data from the first 261 NAPS consortium participants with completed RBDSSS-PT are included. Of them, 214 had corresponding RBDSSS-BP questionnaires completed, and 61 bedpartners had to move out to a different room due to RBD-related behavior. CGI-S scores were available for all 261 participants.

Characteristics of the RBDSSS

Our cohort was mostly male individuals (80.4%) and Caucasian (92.7%). Demographic characteristics for participants included in this analysis are summarized in Table 1. The median (interquartile range) score for the RBDSSS-PT was 10 (4–18) of possible 54 and that for the RBDSSS-BP was 8 (4–15) of possible 38. The median CGI-S was 3 (3–4), indicating moderate severity. Approximately 80.5% of participants had been treated with a medication for their RBD symptoms at some point, and 71% were receiving symptomatic treatment medications during evaluation (Table 1).

Figure 4 Distribution of RBDSSS-PT and RBDSSS-BP Scores by Sex and Age at RBD Symptom Onset



Sex differences in distribution of RBDSSS-PT (A) and RBDSSS-BP (B) for each decade of symptom onset. Red bars indicate women, and blue bars indicate men. RBDSSS = RBD Symptom Severity Scale; RBDSSS-BP = RBD Symptom Severity Scale–Bedpartner version; RBDSSS-PT = RBD Symptom Severity Scale–Participant version.

There was no difference in reported median RBDSSS-PT with the presence of other sleep comorbidities such as OSA (9 vs 11, $p = 0.21$), RLS (12 vs 9, $p = 0.14$), and PLMS (12 vs 9, $p = 0.29$). By contrast, the presence of PTSD was associated with higher RBDSSS-PT scores (13 vs 9, $p = 0.02$). Figure 3 shows that median RBDSSS-PT and RBDSSS-BP scores were similar between participants who were treated with medications (clonazepam or melatonin) over their lifetime compared with those who were not (RBDSSS-PT of 10 vs 8, $p = 0.22$ and RBDSSS-BP 9 vs 6, $p = 0.14$, respectively). Of 261 participants, 145 (56.9%) had been on an antidepressant at some point in their lifetime, 30 (11.5%) felt that their RBD symptoms began after they started antidepressants, and 41 (16.1%) felt that they had been on a medication that worsened their symptoms in the past. Only 7 (2.7%) were attributed to any medications by clinicians during their independent evaluation.

Sex Differences in RBD Severity Scores

The RBDSSS-PT median score for men in our cohort were similar to that for women (10.5 vs 8, $p = 0.615$). However, RBDSSS-BP median scores in women (i.e., reported scores by bedpartners of a female participant) were significantly lower compared with those in men (9 vs 6, $p = 0.02$). Similarly, the CGI-S for women was lower compared with that for men ($p = 0.04$). This pattern was true for all ages at onset of symptoms, as depicted in Figure 4, A and B. Among comorbidities, men had a higher frequency of OSA ($p = 0.007$). No sex differences were observed in other comorbidities, PHQ-9 scores, or PCL-5 scores (Table 1).

Correlation Analysis

A moderate correlation was observed between participant and bedpartner questionnaire ($r_s = 0.56$, $p < 0.0001$). The CGI-S correlated moderately with both the RBDSSS-PT and RBDSSS-BP ($r_s = 0.56$ vs $r_s = 0.49$, both $p < 0.001$), with a slightly stronger correlation for the participant version ($p < 0.001$). Figure 5, A–C depicts the correlation between each dyad. RBDSSS-PT and RBDSSS-BP individual items demonstrated a moderate correlation for frequency of vocalization, movements, and injury ($r_s = 0.64$, 0.50, and 0.42 respectively, $p < 0.0001$). Similarly, for severity/impact of vocalization, movements, and injuries, correlation between the RBDSSS-PT and RBDSSS-BP demonstrated Spearman ρ values of 0.24 ($p = 0.002$), 0.10 ($p = 0.203$), and 0.42 ($p < 0.0001$), respectively. The RBDSSS-PT version demonstrated good internal consistency with a Cronbach α of 0.83, while the RBDSSS-BP had an acceptable internal consistency with a corresponding Cronbach α of 0.75.

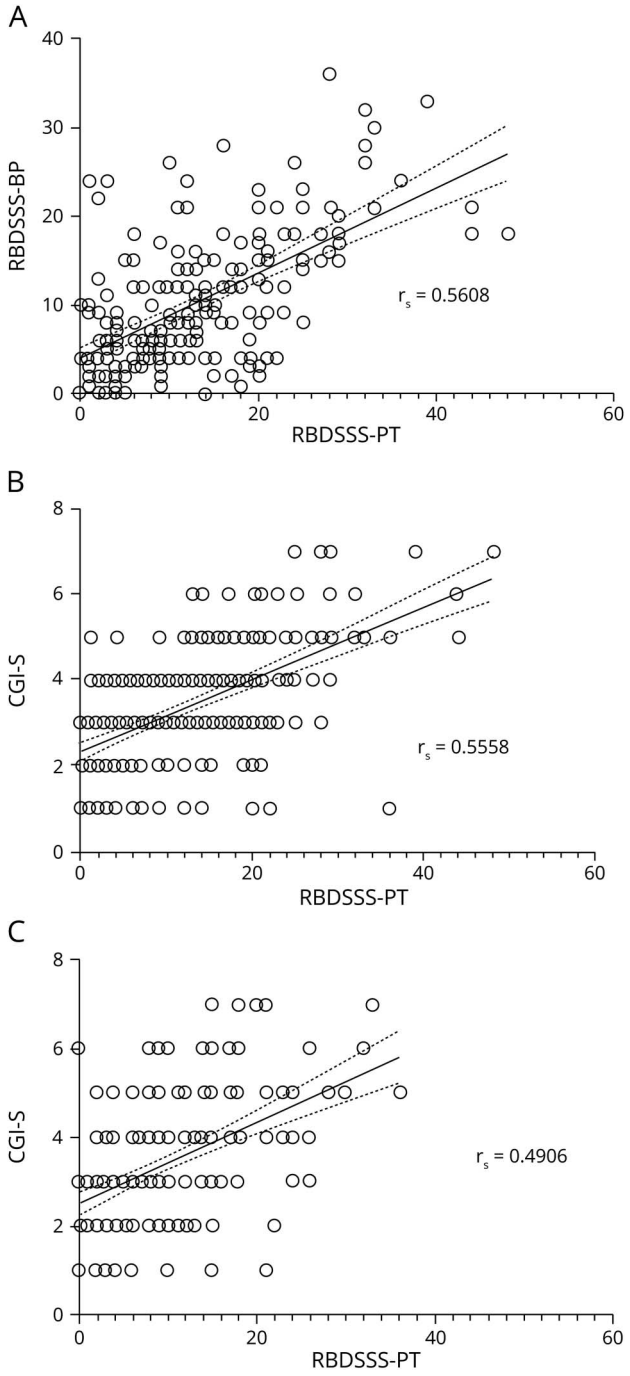
Questions about frequency of dream content, vocalization, and movement correlated moderately with RBD-related behavior frequency on the intake interview with a Spearman ρ coefficient of 0.47, 0.51, and 0.46, respectively (all $p < 0.0001$). Frequency of injury was directly correlated to intake items about injury with Spearman ρ correlation of 0.41 ($p < 0.0001$).

In the RBDSSS-PT questionnaire, the item on movements (question 5) correlated best with the CGI-S ($r_s = 0.54$, $p < 0.0001$), followed by dream content ($r_s = 0.45$, $p < 0.0001$) and vocalizations ($r_s = 0.44$, $p < 0.0001$). The component on injuries (question 6) RBDSSS-PT seemed to correlate least with the CGI-S ($r_s = 0.28$, $p < 0.0001$). In the RBDSSS-BP, the questions on vocalization (question 2) and movement (question 3) had similar correlations to CGI-S ($r_s = 0.45$ and 0.44, $p < 0.0001$, respectively). The RBDSSS-BP component on injuries (question 4) also correlated less strongly with the CGI-S (0.21, $p < 0.002$).

Analysis of Validity Using the IRT

The category characteristic curve for the frequency and severity of each component/question is depicted in eFigure 1 (RBDSSS-PT, links.lww.com/WNL/D316) and eFigure 2 (RBDSSS-BP, links.lww.com/WNL/D317). The frequency and severity within each category (question/component on the questionnaire) do not share the same pattern in parameter distribution. The IRT analysis determined that increase in component scores correctly described increasing levels of RBD severity trait (θ), but the rate of increment is

Figure 5 Correlations Between the RBDSSS-PT, RBDSSS-BP, and CGI-S



(A) Correlation between the RBDSSS-PT and RBDSSS-BP, $r = 0.5608$, n = 214. (B) Correlation between the RBDSSS-PT and CGI-S, $r = 0.5558$, n = 261. (C) Correlation between the RBDSSS-BP and CGI-S, $r = 0.4906$, n = 214. All correlations are significant with $p < 0.0001$. Solid line represents linear regression with dashed lines representing 95% CIs. CGI-S = Clinical Global Impression Scale of Severity; RBDSSS = RBD Symptom Severity Scale; RBDSSS-BP = RBD Symptom Severity Scale–Bedpartner version; RBDSSS-PT = RBD Symptom Severity Scale–Participant version

inconsistent across the different components. That is to say, as the overall RBD severity trait increases (θ on x-axis), there is increasing probability of endorsing a higher frequency or higher impact/severity score on individual components on the scale. However, the increase in RBD severity is not linearly related to increase in frequency or impact. For example, at higher levels of overall RBD severity, only a slight increase in severity correlated with a greater impact due to movements or vocalizations, whereas in the milder ranges, a relatively larger increase in severity was required for participants to feel more impact (Table 2, denoted by difficulty parameter (b)). The difficulty parameters were not evenly distributed around zero and demonstrated a considerable level of fluctuation between different thresholds across components. If behaviors were less frequent (on the multiple choice), for example, the following components: dreams < vocalizations < movements < injury (from least severe to most severe) were reflective of increasing RBD severity trait in that order. This trend did not hold true for the highest frequency choice. There were no consistency in the severity/impact item categories such that for each category chosen, either movement or dream content may depict higher RBD severity. This meant that, for a given overall RBD severity trait, impact/severity of individual behaviors (vocalizations or movements) may be variable and may not necessarily be higher in movements than vocalizations or dream content. If, however, the highest category of impact was selected for injury questions, this was indicative of very high overall RBD severity showing that all participants consistently associated injuries with high severity trait. The detailed properties of the RBDSSS-PT questionnaire, difficulty (b) and discrimination (a), are described in Table 2.

For discrimination (sensitivity to changes in overall severity), question 5b (movement severity) demonstrated the highest value (2.12) while 4a (vocalizations frequency) demonstrated the lowest (1.40). This means that questions about severity/impact of movements performed best at discriminating between participants with different RBD severity. The descending sequence of the questions' discrimination power ("a") was 5b (movement severity), 4b (vocalization severity), 5a (movement frequency), 3a (dream frequency), 6a (injury frequency), 3b (dream content severity), 6b (injury severity), and 4a (vocalization frequency). The discrimination parameters for all the questions, however, fell within high (1.35–1.69) to very high (>1.70), indicating a modest variation in item discrimination.

The properties of the RBDSSS-BP questionnaire, difficulty (b) and discrimination (a), are described in eTable 1 (links.lww.com/WNL/D318). For difficulty parameters, within the same frequency category, injuries > movements > vocalizations were related to higher RBD severity trait (in that order). For discrimination, item 3b (movements distress) demonstrated the highest value (3.60) like the RBDSSS-PT questionnaire, while 4b (distress with Injuries) demonstrated the lowest (1.29). In the bedpartner questionnaires, the discrimination power of the movement severity question was higher than the corresponding component of participant questionnaire. Of interest, the severity/impact of injuries had poorer discriminatory power between participants with varying RBD severity trait, perhaps because of a ceiling effect.

Table 2 Item Response Theory Parameters of Each RBDSSS-Patient Questionnaire Item and Its Rank of Information Amount

ID	Items	Discrimination (a)	Difficulty (b)			
			≥1	≥2	≥3	4
Dream content						
3a	Over the past month, how often did you have disturbing dreams or nightmares?	1.94	−1.69	−0.16	1.03	2.3
3b	Overall, how distressing are these dreams/nightmares to you?	1.76		−1.35	0.71	2.39
Vocalizations						
4a	Over the past month, how often have you talked loudly or yelled during sleep?	1.40	−1.33	0.07	1.23	2.59
4b	Overall, how distressing are talking/yelling episodes been to you over the past month?	2.07		−0.77	0.91	2.27
Movements						
5a	Over the past month, how often did you hit, kick, or thrash out during your sleep?	2.00	−1.18	0.17	1.28	2.50
5b	Overall, how severe are the movements over the past month?	2.12		−1.21	0.61	2.19
Injuries						
6a	Over the past month, how many times did you injure either yourself or your bedpartner because of movements during sleep?	1.78		0.87		2.00
6b	Rate the most severe injury over the past month to yourself or bedpartner related to movements during your sleep	1.63	0.83	2.29	3.51	

The difficulty parameter ("b") represents the 50% probability that an individual with a certain RBD severity endorses a category choice or higher in a question/item. The numbers 1, 2, 3, and 4 are the choices in each question (none—very frequent for frequency items and mild-severe for severity/impact items). Discrimination parameter ("a") represents overall sensitivity of an item in detecting overall RBD severity.

The discrimination parameters for all the questions, however, fell within moderate (0.65–1.34) to very high (>1.70).

Discussion

In this study, we describe the development and psychometric and clinimetric properties[18] of a participant-reported and informant-observed measure of RBD symptom severity for use in clinical and research settings. Our findings show that the RBDSSS demonstrates good internal consistency, adequate validity, and sensitivity/discriminatory value to measure RBD severity in participants with PSG-confirmed idiopathic RBD. Among individual items, questions about movement impact/severity were most sensitive at discriminating overall RBD severity between participants. Items inquiring about frequency and impact of injury were most indicative of the highest overall RBD severity, as shown by our IRT analysis. Because the RBDSSS takes less than 5 minutes for participants/patients and/or bedpartners to complete, it can be efficiently used to provide estimates of RBD symptom severity in both clinical and research settings.

The RBDSSS-PT and RBDSSS-BP are participant/patient–reported and observer-reported, overlapping measures of impact of disease,[19] which could be helpful toward improving shared decision-making.[18] Symptom reporting is also increasingly used in clinical trials.[19] We demonstrate moderate correlations between participants' and bedpartners' perception of RBD severity. Of note, these scales were filled out during enrollment into the study and not during diagnosis or at onset of symptoms; correlations between the RBDSSS-PT and RBDSSS-BP may differ when measured at different time points in the disease. The RBDSSS-PT demonstrated slightly greater internal consistency than the bedpartner version, suggesting that addition of the dream content item improves the questionnaire. In our cohort, participant scores showed modest correlations with the CGI-S, whereas the correlation with bedpartner scores was relatively weaker. This maybe reflective of the NAPS protocol, where the clinician primarily used the participant intake interview to determine the CGI-S. The CGI-S, although subjective, is considered the current "gold standard" for clinical trials and was previously recommended by the IRBDSG for use in trial settings.[5] However, negative clinical trials for symptomatic treatments[1] has fueled discussion regarding the need for more standardized endpoints for RBD severity. The CGI-S is also limited by 7-point distribution range. Participants with similar CGI-S scores demonstrate a wider distribution of RBDSSS scores as noted in Figure 5, which may permit detection of more nuanced changes in severity. This needs to be evaluated further in the future with longitudinal assessments using this scale. Furthermore, patient-reported outcomes and clinician perception of severity can differ substantially,[20] and participant/patient and bedpartner perception maybe more useful in determining need for intervention.

The RBDSSS can be considered as a nonoverlapping instrument to PSG measures of severity, including RBD severity scores and quantification of REM sleep muscle activity (i.e., REM sleep without atonia).[9,21-26] Whereas PSG-based scales would have an important advantage in minimizing recall bias, analyses of dream enactment on video demonstrate considerable intraindividual variability in quality and quantity of RBD-related behaviors between each night.[27] If multiple nights are required, PSG-based severity scales will have cost and tolerability limitations when applied to clinical settings or in clinical trials requiring repeated assessments. The RBDSSS addresses the severity and frequency of RBD episodes over a month, providing a broader time frame than PSG-based scores, and may be conveniently repeated during multiple visits during follow-ups or throughout the course of a clinical trial to track the progression and effect of treatment. Another key feature of the RBDSSS is that it weighs both frequency and impact to assess severity, whereas other overlapping questionnaire-based scales may only assess one of these aspects.[28]

The IRT has been used successfully in several neurologic conditions to develop and validate patient-reported scales.[29,30] The IRT can assess relationships between item scores and latent trait (θ, overall RBD severity in this study) in a sample-invariant manner making the outcome more reliable and valid.[14,31] Analysis using graded response theory (specific subtype of IRT used in this study) showed that the RBDSSS assesses RBD severity effectively across a range of overall RBD severity (−4 to +4). Specifically, a higher frequency of RBD behavior was associated with higher RBD severity. Furthermore, all items presented high to very high (a >1.70) discriminatory properties to RBD severity with appropriate scaling to overall RBD severity, where a >1 is usually desirable.[16] Although the RBDSSS is multidimensional and items reflect multiple behaviors noted in dream state, questions about movements during sleep seem to correlate best with the CGI. There was relatively low correlation between the RBDSSS-PT and RBDSSS-BP in the movement impact item, which may be related to the fact that most movements do not waken patient, although frequently disturb their bedpartner. In the graded response model, questions about movement impact also had the highest discriminatory value for both bedpartner and participant questionnaires. This component is most sensitive to slight changes in overall RBD severity and therefore maybe helpful in longitudinal monitoring. The injury-specific component, while not sensitive to slight changes, does seem to correlate with highest RBD severity and is therefore more specific for higher overall RBD severity. This is likely because injuries are a significant factor in decreased quality of life for patients and bedpartners, leading to the need to sleep apart with reduced intimacy between partners.[2] The individual items of frequency and severity/impact assess RBD severity trait adequately. This means symptomatic treatments may use individual item response as an outcome measure for treatment efficacy in future clinical trials.

Idiopathic RBD is more commonly diagnosed in men than women[32] as has been consistently demonstrated across multiple studies.[33] This is also reflected in our cohort because more men were enrolled than women. We noted sex differences in overall RBD severity reported by bedpartners and clinicians, although the participant-reported RBD severity scores were no different between sexes. Accordingly, there was a trend for women to be less likely to be treated with medications compared with men in their lifetime (bedpartner impact is the most common driver of treatment decisions in clinical practice). Whether this difference has a biological underpinning is not known. A study in Japan has directly assessed RBD severity between sexes using the RBD questionnaire—Japanese version, and found no differences in severity[34] based on sex. One study reported that women with RBD may have greater REM sleep phasic muscle activity.[32,34] Studies of clinical RBD severity and injury have found inconsistent differences between sexes; while some studies have found that men seem to have more vigorous dreams with injuries and potential for injury[32,35]; another study focused primarily on injury in patients with RBD found similar reported injury between sexes.[4] Injuries and violent dream enactment behaviors could lead to greater perceived severity of RBD by bedpartners. On the contrary, women tend to live longer and may therefore be less likely to have a bedpartner, leading to difficulty in ascertaining the true severity of RBD in women.

The strength of this study is that it evaluated a large cohort of well-defined, vPSG-confirmed RBD. However, the use of the RBDSSS is currently limited to population with idiopathic RBD. The RBDSSS requires validation in larger clinical practice cohorts with idiopathic RBD and symptomatic RBD occurring in association with established neurodegenerative synucleinopathies and other neurologic diseases where RBD is very common. While the scale demonstrates good properties, longitudinal assessments to determine minimal clinically meaningful change and association with fluid biomarkers will be beneficial. Future investigations should also correlate scale scores with RBD symptoms objectively detected through portable home-monitoring devices. The RBDSSS also does not address the measurement of REM sleep without atonia in the absence of overt clinical manifestations and the unknown risk of progression to full RBD that may be associated with it. Finally, it is of note that the NAPS cohort is predominantly Caucasian, male, and based in North America, thereby limiting generalizability.

In conclusion, we describe the validity of the RBDSSS, an easy-to-administer participant-reported and bedpartner-reported RBDSSS in idiopathic RBD. Of note, the RBDSSS is free for use in clinical practice and can be used without restriction for not-for-profit academic research. The RBDSSS demonstrates reliable clinimetric properties for measuring RBD severity and good concordance with the CGI-S. While further studies are required, the RBDSSS has potential for use in clinical and research setting for monitoring both natural progression and response to treatment and thus assist in understanding this important sleep condition.

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References

1. Videnovic A, Ju YES, Arnulf I, et al. Clinical trials in REM sleep behavioural disorder: challenges and opportunities. *J Neurol Neurosurg Psychiatry*. 2020;91(7):740-749. doi: 10.1136/jnnp-2020-322875
2. Dauvilliers Y, Schenck CH, Postuma RB, et al. REM sleep behaviour disorder. *Nat Rev Dis Primers*. 2018:4(1):19. doi:10.1038/s41572-018-0016-5
3. Cygan F, Oudiette D, Leclair-Visonneau L, Leu-Semenescu S, Arnulf I. Night-to-night variability of muscle tone, movements, and vocalizations in patients with REM sleep behavior disorder. *J Clin Sleep Med*. 2010;6(6):551-555. doi:10.5664/jcsm.27988
4. McCarter SJ, St Louis EK, Boswell CL, et al. Factors associated with injury in REM sleep behavior disorder. *Sleep Med*. 2014;15(11):1332-1338. doi:10.1016/j.sleep.2014.06.002
5. Schenck CH, Montplaisir JY, Frauscher B, et al. Rapid eye movement sleep behavior disorder: devising controlled active treatment studies for symptomatic and

neuroprotective therapy-a consensus statement from the International Rapid Eye Movement Sleep Behavior Disorder Study Group. *Sleep Med*. 2013;14(8):795-806. doi:10.1016/j.sleep.2013.02.016
6. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)*. 2007;4(7):28-37.
7. Jun JS, Kim R, Byun JI, et al. Prolonged-release melatonin in patients with idiopathic REM sleep behavior disorder. *Ann Clin Transl Neurol*. 2019;6(4):716-722. doi:10.1002/acn3.753
8. McCarter SJ, Boswell CL, St Louis EK, et al. Treatment outcomes in REM sleep behavior disorder. *Sleep Med*. 2013;14(3):237-242. doi:10.1016/j.sleep.2012.09.018
9. Consens FB, Chervin RD, Koeppe RA, et al. Validation of a polysomnographic score for REM sleep behavior disorder. *Sleep*. 2005;28(8):993-997. doi:10.1093/sleep/28.8.993
10. Schenck CH. Expanded insights into idiopathic REM sleep behavior disorder. *Sleep*. 2016;39(1):7-9. doi:10.5665/sleep.5300
11. Fernández-Arcos A, Iranzo A, Serradell M, Gaig C, Santamaria J. The clinical phenotype of idiopathic rapid eye movement sleep behavior disorder at presentation: a study in 203 consecutive patients. *Sleep*. 2016;39(1):121-132. doi:10.5665/sleep.5332
12. NAPS Consortium for REM Sleep Behavior Disorder [online]. Accessed August 3, 2023. naps-rbd.org.
13. Elliott JE, Lim MM, Keil AT, et al. Baseline characteristics of the North American Prodromal Synucleinopathy cohort. *Ann Clin Transl Neurol*. 2023;10(4):520-535. doi:10.1002/acn3.51738
14. Nguyen TH, Han HR, Kim MT, Chan KS. An introduction to item response theory for patient-reported outcome measurement. *Patient*. 2014;7(1):23-35. doi:10.1007/s40271-013-0041-0
15. Edelen MO, Reeve BB. Applying item response theory (IRT) modeling to questionnaire development, evaluation, and refinement. *Qual Life Res*. 2007;16(suppl 1):5-18. doi:10.1007/s11136-007-9198-0
16. Bichi AA, Talib R. Item response theory: an introduction to latent trait models to test and item development. *Int J Eval Res Educ*. 2018;7(2):142. doi:10.11591/ijere.v7i2.12900
17. Gagnier JJ, Lai J, Mokkink LB, Terwee CB. COSMIN reporting guideline for studies on measurement properties of patient-reported outcome measures. *Qual Life Res*. 2021;30(8):2197-2218. doi:10.1007/s11136-021-02822-4
18. Carrozzino D, Patierno C, Guidi J, et al. Clinimetric criteria for patient-reported outcome measures. *Psychother Psychosom*. 2021;90(4):222-232. doi:10.1159/000516599
19. Deshpande P, Sudeepthi BL, Rajan S, Abdul Nazir C. Patient-reported outcomes: a new era in clinical research. *Perspect Clin Res*. 2011;2(4):137-144. doi:10.4103/2229-3485.86879
20. Forkmann T, Scherer A, Boecker M, Pawelzik M, Jostes R, Gauggel S. The clinical global impression scale and the influence of patient or staff perspective on outcome. *BMC Psychiatry*. 2011;11:83. doi:10.1186/1471-244X-11-83
21. Sixel-Döring F, Trautmann E, Mollenhauer B, Trenkwalder C. Rapid eye movement sleep behavioral events: a new marker for neurodegeneration in early Parkinson disease? *Sleep*. 2014;37(3):431-438. doi:10.5665/sleep.3468
22. Figorilli M, Lanza G, Congiu P, et al. Neurophysiological aspects of REM sleep behavior disorder (RBD): a Narrative review. *Brain Sci*. 2021;11(12):1588. doi:10.3390/brainsci11121588
23. Frauscher B, Iranzo A, Högl B, et al. Quantification of electromyographic activity during REM sleep in multiple muscles in REM sleep behavior disorder. *Sleep*. 2008;31(5):724-731. doi:10.1093/sleep/31.5.724
24. Montplaisir J, Gagnon JF, Fantini ML, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. *Mov Disord*. 2010;25(13):2044-2051. doi:10.1002/mds.23257
25. Ferri R, Rundo F, Manconi M, et al. Improved computation of the atonia index in normal controls and patients with REM sleep behavior disorder. *Sleep Med*. 2010;11(9):947-949. doi:10.1016/j.sleep.2010.06.003
26. McCarter SJ, St Louis EK, Sandness DJ, et al. Diagnostic REM sleep muscle activity thresholds in patients with idiopathic REM sleep behavior disorder with and without obstructive sleep apnea. *Sleep Med*. 2017;33:23-29. doi:10.1016/j.sleep.2016.03.013
27. Sixel-Döring F, Schweitzer M, Mollenhauer B, Trenkwalder C. Intraindividual variability of REM sleep behavior disorder in Parkinson's disease: a comparative assessment using a new REM Sleep Behavior Disorder Severity Scale (RBDSS) for clinical routine. *J Clin Sleep Med*. 2011;7(1):75-80. doi:10.5664/jcsm.28044
28. Li SX, Wing YK, Lam SP, et al. Validation of a new REM sleep behavior disorder questionnaire (RBDQ-HK). *Sleep Med*. 2010;11(1):43-48. doi:10.1016/j.sleep.2009.06.008
29. Luo Y, Yang J, Zhang Y. Development and validation of a patient-reported outcome measure for stroke patients. *Health Qual Life Outcomes*. 2015;13:53. doi:10.1186/s12955-015-0246-0
30. Buatois S, Retout S, Frey N, Ueckert S. Item response theory as an efficient tool to describe a heterogeneous clinical rating scale in de Novo idiopathic Parkinson's disease patients. *Pharm Res*. 2017;34(10):2109-2118. doi:10.1007/s11095-017-2216-1
31. de Siqueira Tosin MH, Goetz CG, Luo S, Choi D, Stebbins GT. Item response theory analysis of the MDS-UPDRS motor examination: tremor vs. nontremor items. *Mov Disord*. 2020;35(9):1587-1595. doi:10.1002/mds.28110
32. Castelnuovo A, Marelli S, Mombelli S, Salsone M, Ferini-Strambi L. Idiopathic RBD: the role of gender. *J Neurol*. 2020;267(7):2157-2158. doi:10.1007/s00415-020-09968-0
33. Teman PT, Tippmann-Peikert M, Silber MH, Slocumb NL, Auger RR. Idiopathic rapid-eye-movement sleep disorder: associations with antidepressants, psychiatric diagnoses, and other factors, in relation to age of onset. *Sleep Med*. 2009;10(1):60-65. doi:10.1016/j.sleep.2007.11.019
34. Takeuchi N, Sasai-Sakuma T, Inoue Y. Gender differences in clinical findings and α-synucleiopathy-related markers in patients with idiopathic REM sleep behavior disorder. *Sleep Med*. 2020;66:216-219. doi:10.1016/j.sleep.2019.11.1261
35. Zhou J, Zhang J, Li Y, et al. Gender differences in REM sleep behavior disorder: a clinical and polysomnographic study in China. *Sleep Med*. 2015;16(3):414-418. doi:10.1016/j.sleep.2014.10.020