

Validation of the Mayo Sleep Questionnaire to Screen for REM Sleep Behavior Disorder in a Community-Based Sample

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SCIENTIFIC INVESTIGATIONS

Objective: To validate a questionnaire focused on REM sleep behavior disorder (RBD) in a community-based sample.

Background: RBD is a parasomnia manifested by recurrent dream enactment behavior during REM sleep. While confirmation of RBD requires the presence of REM sleep without atonia on polysomnography (PSG), a screening measure for RBD validated in older adults would be desirable for clinical and research purposes.

Methods: We had previously developed the Mayo Sleep Questionnaire (MSQ) to screen for the presence of RBD and other sleep disorders. We assessed the validity of the MSQ by comparing the responses of subjects' bed partners with the findings on PSG. All subjects recruited from 10/04 to 12/08 in the Mayo Clinic Study of Aging—a population-based study of aging in Olmsted County, Minnesota—who had also undergone a previous PSG were the focus of this analysis.

Results: The study sample included 128 subjects (104 male; median age 77 years [range 67-90]), with the following clinical diag-

noses at baseline assessment: normal (n = 95), mild cognitive impairment (n = 30), and mild Alzheimer disease (n = 3). Nine (5%) subjects had RBD based on history and PSG evidence of REM sleep without atonia. The core question on recurrent dream enactment behavior yielded sensitivity (SN) of 100% and specificity (SP) of 95% for the diagnosis of RBD. The profile of responses on four additional subquestions on RBD improved specificity.

Conclusions: These data suggest that the MSQ has adequate SN and SP for the diagnosis of RBD among elderly subjects in a community-based sample.

Keywords: Sleep disorders, parasomnias, dementia, Alzheimer disease, dementia with Lewy bodies, parkinsonism

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Sleep disorders such as rapid eye movement (REM) sleep behavior disorder (RBD), periodic limb movements during sleep (PLMS), restless legs syndrome (RLS), sleepwalking (SW), obstructive sleep apnea (OSA), sleep related leg cramps (SRLC), and insomnia can result in adverse effects on mood, cognitive functioning, and quality of life, especially in those with a neurological disorder. Treatment of these disorders often results in improved quality of life. The presence of RBD also has diagnostic relevance in those with a neurodegenerative disease, as RBD is far more common in the synucleinopathies such as Parkinson disease, dementia with Lewy bodies, multiple system atrophy, or primary autonomic failure.¹ Polysomnography (PSG) is necessary to establish the diagnoses of RBD, PLMS, and OSA, but may not be practical in some settings due to expense, limited availability, scheduling difficulties, incomplete coverage by third-party payers, or other factors.

A validated screening measure for key sleep disorders could assist in identifying patients who would benefit from a formal sleep medicine evaluation and PSG. Such a screening measure could also be useful for research purposes, particularly in epidemiologic studies of sleep disorders.

BRIEF SUMMARY

Current Knowledge/Study Rationale: While confirmation of REM sleep behavior disorder (RBD) requires the presence of REM sleep without atonia on polysomnography (PSG), a screening measure for RBD validated in older adults would be desirable for clinical and research purposes. We assessed the validity of the Mayo Sleep Questionnaire (MSQ) by comparing the responses of subjects' bed partners with the findings on PSG in a community-based sample (n = 128).

Study Impact: The core question on recurrent dream enactment behavior yielded sensitivity (SN) of 100% and specificity (SP) of 95% for the diagnosis of RBD. These data suggest that the MSQ has adequate SN and SP for the diagnosis of RBD among elderly subjects in a community-based sample.

The Mayo Sleep Questionnaire (MSQ) is a screening measure that poses questions about RBD, PLMS, RLS, SW, OSA, and SRLC. It was designed to be used for clinical and research purposes in a variety of settings, and RBD is the focus of interest with this measure. As a screening measure, high sensitivity is desired. The history of the development of the MSQ has been previously described.²

We recently reported validation data on the MSQ compared to PSG focused on RBD in a large cohort of aged subjects, most

of whom had cognitive impairment and/or parkinsonism due to an underlying neurodegenerative disorder, in which the SN was 98% and SP was 74%.² While these findings are encouraging for the MSQ to be considered a valid screening tool for RBD, the generalizability of the findings to a population of elderly subjects was a limitation. The data reported herein is focused on an entirely separate sample of community-dwelling elderly individuals living in Olmsted County, Minnesota.

DESIGN/METHODS

Mayo Sleep Questionnaire

The MSQ is a 16 question scale that screens for the presence of RBD, PLMS, RLS, SW, OSA, and SRLC based on responses from bed partners, who are asked if a behavior has been exhibited *at least three times in the past*. Some questions are ignored depending if certain questions are answered affirmatively. The MSQ was copyrighted in 2009 by the Mayo Foundation for Medical Education and Research, and permission is granted for non-commercial patient care and research purposes. It is available free to the public and can be downloaded from this website: <http://www.mayoclinic.org/pdfs/MSQ-copyrightfinal.pdf>. The data presented refer to the primary question on RBD (Question 1). If the bed partner provides a “yes” response to this question, subquestions 1b-1e are completed, as shown below:

1. Have you ever seen the patient appear to “act out his/her dreams” while sleeping? (punched or flailed arms in the air, shouted or screamed).

If yes,

- a. How many months or years has this been going on? (data on this subquestion were not analyzed in this analysis)
- b. Has the patient ever been injured from these behaviors (bruises, cuts, broken bones)?
- c. Has a bed partner ever been injured from these behaviors (bruises, blows, pulled hair)?
- d. Has the patient told you about dreams of being chased, attacked, or that involve defending himself/herself?
- e. If the patient woke up and told you about a dream, did the details of the dream match the movements made while sleeping?

The MSQ takes less than two minutes for the bed partner to complete. Further information about the administration of the questionnaire has been published previously.² The definitions for sleep-related phenomena, polysomnographic procedures and their interpretation, validations procedures, and data analyses used in this study are also identical to those published previously.²⁻⁴

Subjects

All subjects enrolled in the Mayo Clinic Study of Aging (MCSA) from October 1, 2004, (the incident date for the population-based recruitment protocol), to December 31, 2008, whose bed partner/informant completed the MSQ, and the participant had undergone a PSG over the period January 1, 2003, through December 31, 2008, were included in the study. The details of the study population, recruitment strategy, assessment protocol, etc., are presented elsewhere.⁵ Briefly, all subjects are community-dwelling residents of Olmsted County, Minneso-

ta, aged 70-89 at baseline, who were recruited in a randomly-selected fashion. The participation rate was 62%, which is similar to many other community-based studies on aging (this point is explained in Roberts et al.⁵). Subjects were classified as having normal cognition (NC), mild cognitive impairment (MCI),⁶ clinically probable Alzheimer disease (AD),⁷ or another syndrome based on published criteria. Almost all (126/128) subjects had undergone PSG for clinical purposes (110 for suspected OSA, 6 for suspected periodic limb movements causing insomnia or hypersomnia, and 10 for suspected RBD), while 2 (1 for suspected OSA and 1 for suspected RBD) had undergone PSG as part of a research study (NIA AG15866, Alzheimer’s Association IIRG-05-14560). Ten of the 11 suspected RBD subjects were male. Most had undergone PSG prior to enrollment in the MCSA.

Statistical Analyses

The sensitivity (SN) and specificity (SP) and associated 95% confidence intervals (95% CI) were calculated for Question 1. Secondary analyses were performed to test for potential differences in SN and SP based on the timing of MSQ in relation to the PSG (MSQ before PSG versus PSG before MSQ). Additional comparisons using χ^2 or t-test analyses were also carried out to determine the optimum combination of responses that could differentiate true positives from false positives, and true negatives from false negatives, provided that adequate numbers in each cell warranted use of these statistical measures. The data and interpretation relating to RBD are presented below; the methodology, findings and discussion relating to the other sleep disorders assessed by the MSQ are presented in the supplemental material.

Ethics

All procedures and analyses have been approved by the Mayo Foundation Institutional Review Board.

RESULTS

Demographic Features and Clinical Diagnoses

The study sample was composed of 128 subjects, with the core demographic features and clinical diagnoses shown in **Table 1**. Most subjects were male, and most were in the 70- to 90-year-old age range. All subjects had bed partners who completed the MSQ (by definition), of whom 99% were spouses and the other two were unwed companions of the opposite sex. Ninety-five (74%) were normal controls, 30 (23%) had MCI, and 3 (3%) had mild AD.

As described in the supplemental material, most subjects were referred for PSG to verify clinical suspicion for OSA (117 of 128). This was reflected in the very high frequency of OSA in the sample: the mean (range) of AHI values was 23 (0-58); 126 subjects (98%) had OSA based on an AHI ≥ 10 , and 125 (98%) had an AHI ≥ 15 .

Validation of the RBD Questions

Since 20 subjects failed to attain REM sleep on their PSG, and hence REM sleep could not be scrutinized for assessing EMG tone, a total of 108 subjects had data that could be ana-

lyzed. Eleven of these 108 subjects had EMG tone considered equivocally increased (rated as a 2); hence 97 formed the basis for most analyses. Nine (9%) subjects had recurrent dream enactment behavior by history associated with unequivocally increased EMG tone during REM sleep, thereby confirming the diagnosis of RBD; there were no subjects diagnosed with RBD based on PSG criteria only (i.e., there were no subjects who had increased EMG tone during REM sleep plus apparent dream enactment behavior during REM sleep, but no prior history of dream enactment behavior). Four of the subjects had normal EMG atonia during REM sleep associated with a “yes” response to Question 1 by their bed partner—these represent false positive cases. Thirteen other cases with a “no” response to Question 1 had REM sleep without atonia but no history of dream enactment behavior. These were considered to be true negatives. There were no false negative cases.

The core question on recurrent dream enactment behavior yielded a SN of 100% and SP of 95% (Table 2). These values changed minimally when the 11 cases with equivocal EMG tone findings were considered together with the group with abnormal EMG atonia (rating of 1; SN 100%, SP 96%). These values also changed minimally when the 11 cases with equivocal EMG tone findings were considered together with the group with normal EMG atonia (rating of 0; SN 100%, SP 94%). There were 55 subjects who completed the MSQ prior to PSG, and 42 who completed the PSG prior to the MSQ; the SN and SP values were also similar regardless of whether the MSQ was completed before (SN 100%, SP 98%) or after (SN 100%, SP 92%) the PSG.

As shown in Table 3, there were 13 (13%) subjects whose response to question 1 was affirmative, of whom 9 (69%) subjects were considered true positive and 4 subjects (31%) whose response were considered false positive. The frequencies of affirmative responses to subquestions 1b, 1c, 1d, and 1e were different between the true positive and false positive groups, but the frequencies for the groups were often less than 5, which limited the ability to use χ^2 or t-test analyses. The true positive group tended to have affirmative responses to each subquestion, at least 3 of the subquestions, as well as all 4 of these 4 subquestions. The one false positive case who responded affirmatively to 3 of these 4 questions had an AHI value of 37. There was no apparent difference between the false positive and false negative groups with regard to affirmative responses to questions 5 and 6 concerning obstructive sleep apnea, nor in PSG indices of OSA.

One might predict that subjects with Parkinson disease or dementia with Lewy bodies would be more likely to have RBD, and hence more likely to have affirmative responses to MSQ Question 1. Three of the subjects in this analysis had PD, and two did indeed had affirmative responses on MSQ Question 1, but neither case attained REM sleep on their PSG, and thus RBD could not be confirmed. The other PD case had a negative response and normal EMG atonia during REM sleep. Another case was classified as multiple domain MCI at baseline, and had an affirmative response to MSQ Question 1, but also did not attain REM sleep on his PSG; he subsequently developed dementia, visual hallucinations, and parkinsonism and was diagnosed with DLB. Upon review of the clinical records of the 2 PD cases and the 1 MCI case who subsequently developed DLB, all carried the diagnosis of probable RBD prior to and after their PSGs, as the diagnosis of RBD was strongly suspected despite the lack of confirmation on PSG due to the absence of REM sleep.

Four of the subjects had PSG evidence of unequivocally increased EMG tone during REM sleep but no apparent dream enactment behavior on the PSG. In each case, the clinician did not record a history of recurrent dream enactment behavior at

Table 1—Demographic and clinical data

	Frequency
Age at PSG (years)	
60-69	7
70-79	68
80-89	52
90+	1
Total	128
Median	77 years
Sex, Male	104 (89%)
Bed partner, Spouse	126 (99%)
Neurologic diagnosis	
Cognitively normal	95 (3 with single stroke, 2 with PD)
MCI	30
SD-amnesic	16 (1 with PD)
MD-amnesic	9 (2 with single stroke, 1 with PD)
SD-non-amnesic	4 (1 with single stroke)
MD-non-amnesic	1
AD	3

AD, Alzheimer disease; MCI, mild cognitive impairment; SD, single domain; MD, multiple domain; PD, Parkinson disease; PSG, polysomnogram.

Table 2—Sensitivity and specificity of Question 1 on the Mayo Sleep Questionnaire for PSG-proven RBD*

	DEB and RSWA	No DEB	
MSQ Q1 - Yes	9	4	SN 100% (95%CI: 0.63-1.0)
MSQ Q1 - No	0	84	SP 95% (95%CI: 0.88-0.98)
Total	9	88	

95%CI, 95% confidence interval; DEB, dream enactment behavior by history and/or PSG is present; MSQ, Mayo Sleep Questionnaire; PSG, polysomnogram; Q1, question one; RBD, rapid eye movement sleep behavior disorder; +RSWA, rapid eye movement sleep without atonia is present; SN, sensitivity; SP, specificity. *Caveats: 20 patients did not attain REM sleep on their PSG, and thus their data were not included; 9 (7% of cohort) met established criteria for the diagnosis of RBD; 11 patients had equivocal EMG findings in REM sleep and their data are excluded from the analysis shown above (2 with DEB and 9 without DEB), with their data included (n = 108), the SN remains 100% and SN is 96%; 13 patients had RSWA without a clinical history of DEB or any DEB present on PSG.

Table 3—Comparison between true positive and false positive responders in relation to MSQ and PSG variables

MSQ Item	Number with affirmative response	DEB and RSWA (true positives)	No DEB (false positives)
1. Act out dreams	13	9 (69%)	4 (31%)
1b. Patient injury	2	2 (100%)	0 (0%)
1c. Bed partner injury	5	4 (80%)	1 (20%)
1d. Dream content	12	9 (75%)	3 (25%)
1e. Actions mimic dream	11	9 (82%)	2 (18%)
≥ 3 of subquestions 1b-1e	5	4 (80%)	1 (20%)
All 4 of subquestions 1b-1e	2	2 (100%)	0 (0%)
5. Snort/choke awake	6	3 (50%)	3 (50%)
6. Stopped breathing	8	5 (63%)	3 (36%)
PSG Index	Number with PSG finding		
Mean AHI	13	19.1 ± 8	26.7 ± 7
AHI ≤ 5	0	0	0
AHI ≥ 10	13	9	4
AHI ≥ 20	7	3	4

AHI, apnea/hypopnea index; DEB, dream enactment behavior by history and/or PSG; MSQ, Mayo Sleep Questionnaire; PSG, polysomnogram; RBD, rapid eye movement sleep behavior disorder; RSWA, rapid eye movement sleep without atonia.

the time that the PSG was performed, indicating that such patients had evidence of RSWA. The clinical diagnoses at the time of PSG were NC in 3 and MCI in 1. Recurrent dream enactment behavior evolved *after* the PSG in the MCI case, and he has since developed PD and is currently on carbidopa/levodopa therapy.

Another 7 cases had equivocally increased EMG tone during REM sleep but no apparent dream enactment behavior on PSG and could be considered as having “equivocal RSWA.” All were diagnosed at baseline as NC.

DISCUSSION

The MSQ satisfies all criteria that are typically considered as important for a screening tool to be useful, including high sensitivity and adequate specificity, good safety, low cost, easy administration, minimal inconvenience or discomfort upon administration, and acceptability of patients and clinicians.

An affirmative response to question 1 was 100% sensitive for RBD in this population of community-dwelling elderly individuals residing in Olmsted County, MN, and the specificity was adequate at 95%. We suggest that those subjects in whom question 1 of the MSQ is answered affirmatively by someone knowledgeable about the subject’s sleep behavior be classified as having “probable RBD” (pRBD).⁸⁻¹⁰

Similar to our previous results,² false positives occurred in those with OSA, which is consistent with the known phenomenon of apparent dream enactment behavior in those with untreated OSA.¹¹ Based on these data, a history of one or more of the core features of RBD as reflected on subquestions 1b-1e, adequately differentiates those with true RBD from those without. If a goal is to use this tool to screen for RBD, then Question 1 alone is a highly sensitive means to do this. If a goal is to use this tool to differentiate RBD from OSA, the specificity of 95% is high, and the profile of responses on subquestions 1b-1e perform well to increase specificity further. PSG remains as the optimal method to make this determination, but depending on the goal of use for the MSQ, PSG may or may not be critical

for some analyses or circumstances. These findings suggest that among older individuals residing in a community setting with normal cognition or mild cognitive impairment, the MSQ is an excellent screening tool for the presence or absence of RBD.

The three cases (2 PD and 1 MCI who evolved to DLB) who screened positive for RBD based on the affirmative response to Question 1 but did not attain REM sleep on PSG are also noteworthy. The clinicians caring for these cases diagnosed each of them with probable RBD and were treating them as such (all with melatonin to decrease RBD frequency/severity). Judging from these observations and strong association of PD and DLB with RBD, it is reasonable to presume that such cases also likely would have been true positive cases had they attained REM sleep on their PSGs.

The 11 cases with RSWA (four with definite RSWA, seven rated as equivocal RSWA) are also of interest. While some consider cases with this PSG findings to represent “subclinical RBD,” we do not believe a sufficient number of cases with RSWA have been followed prospectively to know whether most or all develop definite RBD. Thus, the PSG finding of RSWA is more appropriate to classify such cases until prospective analyses adequately address this issue.

Utility as a Clinical or Research Tool

The utility of a screening measure such as the MSQ for RBD among patients undergoing evaluation for a slowly progressive disorder affecting cognition and/or parkinsonism on a neurodegenerative basis has been reviewed previously.² The high sensitivity and adequate specificity of the MSQ for RBD in both an aging and dementia cohort, and now in a separate community-based elderly cohort, suggest that its use would be appropriate in a variety of clinical settings involving elderly patients—primary care practices, memory disorder/behavioral neurology clinics, movement disorder clinics, geriatric medicine clinics, sleep disorder centers, etc.

The potential of the MSQ as a research tool is also promising, and only a few examples will be presented and re-empha-

sized here.² Due to the ease of use as a screening tool and high SN and SP as demonstrated by these analyses, the MSQ could be incorporated into the standard assessment of participants in any aging research program, with a positive screen for RBD increasing the clinician's suspicion for an evolving synucleinopathy. Since performing PSGs on a large number of subjects may not be practical, the MSQ may also be useful in determining the incidence or prevalence of RBD in epidemiologic studies, especially since the only prevalence data (0.05%) on RBD is based on a telephone questionnaire.¹² Screening for RBD in population-based studies could also identify those with probable RBD for a variety of research questions. Many analyses have been conducted with the MSQ thus far in Olmsted County, Minnesota,^{10,13-15} and the utility of such screening appears promising. The MSQ has already shown utility in estimating the risk of developing mild cognitive impairment/dementia or parkinsonism among those who screen positive for RBD in a community-based cohort of older subjects,¹⁰ in identifying and assessing the frequency of probable RBD among subjects with mild dementia,⁸ in studying the frequency and timing of probable RBD in those with Parkinson disease with or without dementia,¹⁶ in assessing the frequency of probable RBD in those with restless legs syndrome compared to essential tremor,⁹ and in assessing differential neurotransmitter denervation changes among Parkinson disease patients with and without probable RBD.¹⁷

The MSQ can also be used prospectively to determine if those with probable RBD in middle or old age ranges who do not have cognitive or motor problems are at a higher risk of developing a PD, MCI, or DLB.^{10,18-21} This will be particularly important when synuclein-active agents are available to test for disease-modifying properties.^{1,19,22-26}

The high SN (96-100%) for the MSQ and other various screening measures on RBD²⁷⁻³⁰ may appear to be “too good to be true,” as few screening measures in clinical medicine have SN so high. Yet the high SN likely reflects the rather unique features of the disorder—if any patient has RBD, the features are so consistent across individuals that any questions involving recurrent dream enactment behavior will likely be answered affirmatively and result in a positive screen. These other screening measures also involved study populations where males represented the clear majority of cases.²⁷⁻³⁰

REM Sleep Without Atonia

The finding of RSWA in 11 of the subjects is also of interest. One might argue that subjects with RSWA could be viewed as “false negative” cases in our analyses since they had “no” responses to Question 1 on the MSQ, but since there was no history of dream enactment behavior at the time the PSG was performed and no dream enactment behavior present during REM sleep on the PSG, such cases were appropriately viewed as true negatives. The one case with RSWA plus MCI who subsequently began exhibiting recurrent dream enactment behavior as well as other features characteristic of PD underscores the potential clinical relevance of following patients longitudinally when RSWA is identified on PSG.

Qualifications and Limitations

The same qualifications and limitations to the MSQ and the analyses, as noted previously,² are applicable to the current anal-

ysis. The MSQ was developed to screen for RBD and other key sleep disorders, and it should not be used as the sole mechanism for making a diagnosis of any of the sleep disorders queried by the measure. The validation also was performed retrospectively by using responses on the MSQ and comparing the responses to the gold standards of clinical assessment and PSG, which may be inaccurate. A prospective approach would be reasonable for future analyses. The analyses in this paper primarily involved older male individuals, yet this is similar to the other validation studies on RBD screening measures.²⁷⁻³⁰ The MSQ also does not distinguish between RBD due to a neurodegenerative cause or due to secondary causes such as medications. As a result, the SN and SP may vary depending on the setting and population of patients in a validation analysis. Optimally, future prospective validations of the MSQ should be used with standardized clinical assessments and PSGs in a variety of settings, including individuals with no sleep complaints and in samples with equal numbers of men and women. Nevertheless, our findings among elderly subjects in two separate cohorts with SN 98% to 100% and SP 74% to 95% suggest that the MSQ has adequate SN and SP for the diagnosis of RBD, and those who screen positive can be considered to represent “probable RBD” cases.

ABBREVIATIONS

AD, clinically probable Alzheimer disease
AHI, apnea/hypopnea index
DLB, dementia with Lewy bodies (as defined by the clinical syndrome)
EMG, electromyography
ESS, Epworth Sleepiness Scale
FN, false negative
FP, false positive
LBD, Lewy body disease (as defined by pathology)
MCI, mild cognitive impairment
MSQ, Mayo Sleep Questionnaire
OSA, obstructive sleep apnea
PD, Parkinson disease
PLMS, periodic limb movements during sleep
PSG, polysomnography
RBD, REM sleep behavior disorder
REM, rapid eye movement
RLS, restless legs syndrome
RSWA, REM sleep without atonia
SN, sensitivity
SP, specificity
SRLC, sleep related leg cramps
SW, sleepwalking
TN, true negative
TP, true positive

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Supplemental Material

DESIGN/METHODS

The definitions for sleep-related phenomena, polysomnographic procedures and their interpretation, validations procedures, and data analyses used in this study are also identical to those published previously.¹⁻³

RESULTS

Validation of the PLMS Question

The MSQ and PSG data from all 128 subjects were analyzed for this question on repeated jerking of the legs. As shown in **Table S1**, the SN and SP values using cut-off values of 5, 10, 15, and 30 for PLMI ranged from 27% to 29% for SN and 85% to 86% for SP; these were minimally different regardless of the cut-off. Values were similar regardless of the timing of MSQ completion relative to the PSG and site of evaluation (data not shown).

Validation of the RLS Questions

Table S2 shows data and analyses on Question 3 regarding the typical symptoms described by patients with RLS; MSQ data from all 128 subjects were compared to clinical diagnoses and details in their medical record. The SN was 84% and the SP was 96%. Responses were similar regardless of the timing of MSQ completion relative to the PSG and site of evaluation (data not shown).

Four (3%) subjects had an affirmative response to this question but failed to have sufficient evidence in the medical record to warrant an RLS diagnosis (false positive). The true positive group tended to have the “after 6 pm” response to subquestion 3b, and have both an affirmative response to subquestion 3a regarding symptom improvement with leg movement plus the “after 6 pm” response to subquestion 3b. Two of the three false negative cases were using carbidopa/levodopa for mild RLS for many years, and were asymptomatic for at least 2 years according to the review of the clinical records. The other false negative case had endorsed all RLS features, but viewed the symptoms so mild that he did not wish to undergo treatment.

Validation of the Sleepwalking Question

The MSQ and PSG data and clinical records from all 128 subjects were analyzed for this question on sleepwalking. Three (2%) subjects clearly had a history of repeated bouts of somnambulism, of whom two had an affirmative response to Question 4 (true positive). Only one exhibited sleepwalking behavior emerging from stage 3 sleep. As shown in **Table S3**, the SN was 67% and SP was 100%.

Validation of the OSA Questions

The MSQ and PSG data and clinical records from all 128 subjects were analyzed for Question 5 on snorting/choking oneself awake and Question 6 on observed apnea. The primary reason for most of these subjects undergoing clinical PSGs in the first place was the suspicion of OSA (117 out of 128), and this was reflected in the very high frequency of OSA as shown on PSG. The mean (and range) of AHI values was 23 (0-58).

Table S1—Validation of the periodic limb movement question

	PLMI ≥ 5	PLMI < 5	
MSQ Q2 - Yes	27	4	SN 27/99 = 27%
MSQ Q2 - No	72	25	SP 25/29 = 86%
Total	99	29	
	PLMI ≥ 10	PLMI < 10	
MSQ Q2 - Yes	26	5	SN 26/94 = 28%
MSQ Q2 - No	68	29	SP 29/34 = 85%
Total	94	34	
	PLMI ≥ 15	PLMI < 15	
MSQ Q2 - Yes	25	6	SN 25/87 = 29%
MSQ Q2 - No	62	35	SP 35/41 = 85%
Total	87	41	
	PLMI ≥ 30	PLMI < 30	
MSQ Q2 - Yes	22	8	SN 22/76 = 29%
MSQ Q2 - No	54	44	SP 44/52 = 85%
Total	76	52	

Dx, diagnosis; MSQ, Mayo Sleep Questionnaire; PLMI, periodic limb movement index; Q, question number; SN, sensitivity; SP, specificity.

Table S2—Validation of the restless legs syndrome questions

	RLS Dx - Yes	RLS Dx - No	
MSQ Q3 - Yes	16	4	SN 16/19 = 84%
MSQ Q3 - No	3	101	SP 101/105 = 96%
Total	19	105	

Dx, diagnosis; MSQ, Mayo Sleep Questionnaire; RLS, restless legs syndrome; Q, question number; SN, sensitivity; SP, specificity.

Table S3—Validation of the sleepwalking question

	SW Dx - Yes	SW Dx - No	
MSQ Q4 - Yes	2	0	SN 2/3 = 67%
MSQ Q4 - No	1	125	SP 125/125 = 100%
Total	3	123	

Dx, diagnosis; MSQ, Mayo Sleep Questionnaire; Q, question number; SN, sensitivity; SP, specificity; SW, sleepwalking.

One hundred twenty-six (98%) subjects had OSA based on an AHI ≥ 5, 126 (98%) had OSA based on an AHI ≥ 10, and 125 (98%) had OSA based on an AHI ≥ 15. Nineteen (15%) had moderately severe OSA based on an AHI ≥ 30.

As shown in **Table S4**, the highest SN (62%) resulted if an affirmative response was given to either Question 5 or Question 6, and the SP was the same (100%) if either or both responses on these questions were negative. SN was similar regardless of the AHI cut-off used from 5 to 15. Values were similar regardless of the timing of MSQ completion relative to the PSG and site of evaluation (data not shown).

As most patients with clinically significant OSA are hypersomnolent, SN and SP were also calculated purely based on the total score on the ESS based on the informant's assessment, regardless of the responses to Questions 5 and 6. Using an AHI ≥ 5 representing OSA, and a total ESS score ≥ 10 representing excessive daytime somnolence, the SN and SP for ESS scores

Table S4—Validation of the obstructive sleep apnea questions

	AHI ≥ 5	AHI < 5		
MSQ Q5 - Yes	49	0	SN	49/126 = 39%
MSQ Q5 - No	77	2	SP	2/2 = 100%
Total	126	2		

Using the cut-off of AHI ≥ 10, the values did not change (SN = 39%, SP = 100%). Using the cut-off of AHI ≥ 15, only SP changed (SN = 38%, SP = 67%).

	AHI ≥ 5	AHI < 5		
MSQ Q6 - Yes	72	0	SN	72/126 = 57%
MSQ Q6 - No	54	2	SP	2/2 = 100%
Total	126	2		

Using the cut-off of AHI ≥ 10, the values did not change (SN = 57%, SP = 100%). Using the cut-off of AHI ≥ 15, only SP changed (SN = 57%, SP = 67%).

	AHI ≥ 5	AHI < 5		
MSQ Q5 or Q6 - Yes	78	0	SN	78/126 = 62%
MSQ not Yes for Q5 or Q6	48	2	SP	2/2 = 100%
Total	126	2		

Using the cut-off of AHI ≥ 10 or AHI ≥ 15, the values did not change (SN = 62%, SP = 100%).

	AHI ≥ 5	AHI < 5		
MSQ Q5 and Q6 - Yes	43	0	SN	43/126 = 34%
MSQ not Yes for Q5 and Q6	83	2	SP	2/2 = 100%
Total	126	2		

Using the cut-off of AHI ≥ 10, the values did not change (SN = 34%, SP = 100%). Using the cut-off of AHI ≥ 15, only SP changed (SN = 34%, SP = 67%).

AHI, apnea/hypopnea index; MSQ, Mayo Sleep Questionnaire; Q, question number; SN, sensitivity; SP, specificity.

≥ 10 representing OSA were 42% and 52%, respectively. As expected, SP increased but SN decreased with increasing AHI using only the total ESS score. Considering the responses on Questions 5 and 6 along with the total ESS score, the SN and SP for an affirmative response to either Question 5 or Question 6 plus a total ESS score ≥ 10 representing OSA (AHI ≥ 5) were 71% and 42%, respectively. If one considers Question 8 on the level of alertness on the MSQ, with any value < 10 on this question along with an affirmative response to either Question 5 or Question 6 representing OSA (AHI ≥ 5), the SN was 69% and SP was 53%. Therefore, SN increases when factoring a measure of subjective daytime sleepiness (ESS score ≥ 10) or a measure of suboptimal alertness (MSQ Question 8 < 10) with questions regarding snorting/choking awake or observed apneic pauses, with SN around 70% for either sleepiness/alertness measure with the more typical OSA historical features.

Validation of the SRLC Question

The MSQ and clinical records from 128 subjects were analyzed for Question 7 on sleep related leg cramps. Twelve

Table S5—Validation of the sleep related leg cramp question

	SRLC Dx - Yes	SRLC Dx - No		
MSQ Q7 - Yes	11	38	SN	11/12 = 92%
MSQ Q7 - No	1	78	SP	78/106 = 74%
Total	12	106		

Dx, diagnosis; MSQ, Mayo Sleep Questionnaire; Q, question number; SN, sensitivity; SP, specificity; SRLC, sleep related leg cramps.

Table S6—Summarized data on maximizing sensitivity when screening for key sleep disorders using the MSQ +/- ESS

Sleep disorder	MSQ question(s) answered affirmatively	Sensitivity
RBD	Q1	100%
SRLC	Q7	92%
RLS	Q3	84%
OSA	Q5 or Q6, plus ESS total score ≥ 10	71%
SW	Q4	67%
PLMS	Q2	27%

ESS, Epworth Sleepiness Scale; MSQ, Mayo Sleep Questionnaire; OSA, obstructive sleep apnea; PLMS, periodic limb movement disorder; Q, question number; RBD, REM sleep behavior disorder; RLS, restless legs syndrome; SRLC, sleep related leg cramps; SW, sleepwalking.

(9%) subjects clearly had SRLC and were using either quinine or tonic water (which has dilute quinine in it) before bedtime for treatment. Thirty-eight (30%) had affirmative responses to this question, and since these subjects did not carry a diagnosis of SRLC, were not being treated as such, and did not have comments in the medical records to suggest their presence, these were considered false-positive responses. As shown in **Table S5**, the SN was 92% and SP was 74%. Values were similar regardless of the timing of MSQ completion relative to the PSG and site of evaluation (data not shown).

Validation of the Alertness Question

One would predict that the subjective assessment of level of alertness as rated on Question 8 would be inversely correlated with the subjective assessment of the chance of dozing as rated on the ESS (i.e., the higher the value for Question 8, the lower the value for ESS). The scores on the level of alertness question are correlated with the scores on the ESS (R² = 0.1176, p < 0.05). One can therefore conclude that the level of alertness as assessed on this question is inversely correlated to the chance of dozing as rated on the ESS.

DISCUSSION

Summary

The primary goal of the MSQ is to screen for the presence of several key sleep disorders, and particularly RBD. A summary of data on maximizing the sensitivity when screening for the sleep disorders using the MSQ ± ESS is shown in **Table S6**. Screening measures which are simple, inexpensive, and easily tolerated, and also achieve SN rates of at least 70%, are gener-

ally considered useful measures in clinical medicine. The data presented herein suggests that the MSQ achieves the intended goal of reasonable SN for most of the sleep disorders assessed on the scale in a sample of aged individuals who largely have either normal cognition or mild cognitive impairment.

There are several questionnaires used in sleep medicine. The Pittsburgh Sleep Quality Index⁴ has been used for many years, and the reliability and validity has been established for primary insomnia.⁵ While PSG is not viewed as necessary in the routine assessment of patients with insomnia, PSG is important if features of OSA, PLMS, or narcolepsy are present.⁶ The numerous other questionnaires pertinent to the key sleep disorders assessed by the MSQ are discussed below.

Periodic Limb Movements during Sleep

For Question 2 the SN was 27% to 29% and SP was 85% to 86% regardless of the cut-off for the diagnosis of PLMS. These findings suggest that this question regarding repeated jerking of the legs is not adequately predictive of the presence of PLMS in this patient population. The poor sensitivity of this question is also consistent to what is often seen in routine clinical practice, in which the presence of nocturnal leg jerks as acknowledged by the patient or bed partner does not correlate well with the findings on PSG. However, the absence of PLMS is better predicted. Therefore, if a clinician is seeking to investigate whether PLMS are contributing to insomnia or hypersomnia, then a negative response on this question may be clinically useful.

Comparison with Other Measures

Despite having a question on the MSQ very similar to the one posed two other screening measures, the SN and SP values for the MSQ are low compared to other measures.^{7,8} This is likely due in part to the validation for these two measures being based on clinical interview and not PSG—PLM presence and frequency can only be determined by PSG. Furthermore, PLMs can be symptomatic or asymptomatic for patients as well as bed partners. The high frequency of false negative responses, and hence subpar SN, may reflect the high frequency of PLMs in patients yet lack of appreciation of PLMs by bed partners in this patient population.

Restless Legs Syndrome

The SN was 84% and SP was 96% for Question 3 regarding the symptoms typically described by patients with RLS, suggesting that this question is reasonably accurate at predicting the presence, and more accurate at predicting the absence, of RLS in this patient population. The true positive cases also had a greater tendency to answer as one would expect to the subquestions about symptoms being relieved by leg movement or walking around (subquestion 3a) and being maximal after 6 pm (subquestion 3b). The gold standard for the diagnosis of RLS was based on the data available in the medical record, and while the 4 false positive cases had many features of RLS, they did not meet our *a priori* criteria for diagnosis. The 3 false negative cases were either well-treated on RLS therapy, or had RLS so mild that treatment was deferred. It is possible that the patients did not complain about RLS symptoms to their bed partners thereby leading to a negative response by the bed partners. A prospective study using a screening measure like the MSQ combined with a standardized clinical

assessment by sleep clinicians would more optimally determine the SN and SP of any screening measure for RLS.

Utility as a Clinical Tool

Screening for RLS could be useful in a variety of settings—primary care practice, neurologic clinic, sleep disorders center, executive health clinic, fibromyalgia clinic, etc. Those who screen positive would warrant a clinical assessment to determine if such patients meet IRLS criteria for the diagnosis. Since the SN of the MSQ in this population was poor, the utility of this scale for RLS screening in other patient populations may not be much better. However, RLS certainly compromises the ability to fall and stay asleep, mood, quality of life in neurologically normal individuals,⁹ and RLS likely has similar effects in those with cognitive impairment ± parkinsonism. Accurately predicting the absence of RLS could at least exclude RLS as a likely cause of insomnia if the inability to fall and stay asleep is the focus of clinical questions.

Utility as a Research Tool

RLS has been studied as a potential risk factor for the development of Parkinson disease, with no convincing data to support this contention being found.¹⁰ RLS has not been studied as a potential risk factor for or an early manifestation of DLB or AD. The frequency of RLS in disorders other than Parkinson disease has also not been rigorously studied, and therefore a questionnaire on RLS could be used for these purposes.

Comparison with Other Measures

The diagnosis of RLS is purely based on the history/interview and not on PSG findings, and the few validation studies for RLS questionnaires have used a structured diagnostic interview or an in-person evaluation by a knowledgeable clinician as the gold standard. The more recently developed RLS questionnaires^{11,12} have included questions which focus on the four core International RLS criteria,¹³ and it stands to reason that those patients with RLS will respond affirmatively to all four core criteria questions when completing a questionnaire and respond similarly to questions in an in-person interview. Measures such as the Global Sleep Assessment Questionnaire (GSAQ) system and the MSQ which were developed prior to the publication of the International RLS criteria focused on these same core criteria. Validation of the Cambridge-Hopkins questionnaire (CH-RLSq) revealed a SN of 87% and SP of 94% for the diagnosis of RLS,¹¹ while the SN was 93% and SP was 99% using the Restless Legs Syndrome-Diagnostic Instrument (RLS-DI) scale.¹² The higher SN and SP values for the CH-RLSq and RLS-DI compared to the MSQ is due in part to the relatively retrospective nature of our analysis, which again may reflect the lack of sufficient documentation in the medical record, yet also mild and well-treated status of some apparent false negatives. Another consideration is that other disorders can “mimic” RLS—some patients responded affirmatively to the four core RLS features but expert clinicians diagnosed them with sleep-related leg cramps, positional discomfort, or local leg pathology.¹⁴

Sleepwalking

The SN was 67% and SP was 100% for Question 4 regarding the sleepwalking/somnambulism, suggesting that this question

is not very accurate at predicting the presence of somnambulism in this patient population. Yet only three subjects clearly met criteria for the diagnosis of somnambulism, and the relatively low SN reflects the single false negative case out of three who truly have SW. These data suggest that SW may not be an important issue in older subjects.

Comparison with Other Measures

The SN and SP values for the MSQ for sleepwalking were similar to the Munich Parasomnia Screening (MUPS) tool. Yet only nine true positive cases have been identified among 214 subjects who have been screened by the MSQ or MUPS, suggesting far greater numbers of subjects should be assessed.

Obstructive Sleep Apnea

Using an AHI cut-off of 5 for the diagnosis of OSA, the responses on Questions 5 and 6 yielded maximal values for SN of 62% and SP of 100%, suggesting that these questions are relatively poor at predicting the presence OSA, but accurate at predicting the absence of OSA in this patient population. Yet the data are likely skewed, as only 2 subjects did not have OSA, and thus the specificity of these questions for OSA may be artificially inflated in this cohort. Including data from either the ESS or Question 8 from the MSQ increases the SN somewhat to around 70%, and thus interpreting data on Questions 5 and 6, plus either the ESS or Question 8, offer the best SN from these measures.

Utility as a Clinical Tool

A screening measure for OSA would be useful for clinical purposes; those who would screen positive should be considered for PSG and a nasal CPAP trial if not already being treated. Considering (a) the known cardiovascular and cerebrovascular morbidity associated with untreated OSA,¹⁵ (b) the effects of untreated OSA on cognition, mood, and quality of life for patients and their bed partners,^{16,17} (c) the improvement in cognition, mood, and quality of life that CPAP provides to patients and their bed partners who have no coexisting neurologic disorders,¹⁸ (d) the recent evidence showing improvement in cognition with CPAP therapy in patients with Alzheimer disease and OSA,¹⁹ (e) the recent evidence and our own clinical experience that many patients with dementia and/or parkinsonism certainly can tolerate nightly CPAP therapy and benefit from its use,^{20,21} and f) the benefit in parkinsonism that sleep provides in those with Parkinson disease (“sleep benefit”),²² there are ample reasons to screen for OSA in patients with cognitive impairment ± parkinsonism and proceed with PSG and CPAP therapy in those who are deemed appropriate. The challenge is that the MSQ, like several other measures, is not reliably accurate at predicting the presence of even mild OSA.

If one is attempting to rule out OSA for clinical purposes, the absence of affirmative responses on Questions 5 and 6 may assist the clinician in reducing the suspicion of OSA in such patients.

Utility as a Research Tool

OSA is common, particularly among the elderly, but is grossly underdiagnosed.²³ While dementia or delirium solely due to OSA is likely very rare,²⁴ it is a treatable contributor to cognitive impairment. In those with dementia plus OSA, with the recent data substantiating the positive effects of CPAP therapy

on improving patient cognitive functioning, functional status, mood, and quality of life, and also caregiver mood and quality of life,^{19,20} one could argue that screening for OSA in those with MCI and dementia is warranted so that these important clinical issues could be assessed on a research basis. Yet the SN data suggests that the MSQ is not adequate in predicting the presence of OSA, and other measures (perhaps overnight oximetry) would be more useful in identifying potential research subjects.

The high SP of the MSQ for excluding the presence of OSA could be more useful than its value in predicting the presence of OSA. As reviewed in the primary paper on RBD, affirmative responses to Question 1—particularly the primary question on recurrent dream enactment behavior—is most likely to be specific for RBD in the absence of OSA. Therefore, negative responses on the MSQ for OSA increase the likelihood of RBD when Question 1 is answered affirmatively.

Comparison with Other Screening Measures

There are numerous other screening measures for OSA, and the SN and SP for these measures vary widely, with most achieving SN in the 66% to 93% range and SP in the 50% to 95% range.²⁵⁻³⁰ Hence, the SN (62%) and SP (100%) considering responses on both Questions 5 and 6 of the MSQ for OSA using an AHI threshold of 5 compares similarly to most other measures, and including either the ESS or Question 8 data increases SN to around 70%, although SP decreases. The main drawback for all of these measures is the relatively high frequency of both false positives and false negatives; the false positive responses reflect the relative insensitivity of loud snoring, choking, observed apnea, and daytime hypersomnolence for OSA, and the false negative responses reflect the presence of OSA in the absence of these otherwise typical OSA features.

Sleep Related Leg Cramps

The SN was 92% and SP was 74% for Question 7 regarding the symptoms typically described by patients with SRLC, suggesting that this question is accurate at predicting the presence of SRLC in this patient population, but specificity was moderate. As in RLS, the gold standard for the diagnosis of SRLC was based on the data available in the medical record, and hence either the patient already carried the diagnosis of SRLC and was possibly being treated as such, or the patient was unable to provide an adequate history to the clinician such that the clinician documented this in the medical record. The bed partners who completed the MSQ provided responses based on the patients' prior descriptions of SRLC symptoms or previously observing the obvious discomfort that arises during a cramp. Since some individuals and their bed partners may not have voiced concerns about SRLC to their clinicians, or the clinicians neglected to note their concerns in the medical record, it is possible that some proportion of the “false positives” were in fact true positives. A prospective study using a screening measure like the MSQ combined with a standardized clinical assessment by sleep clinicians would more optimally determine the SN and SP of any screening measure for SRLC.

Utility as a Clinical Tool

Sleep-related leg cramps are painful and can disrupt sleep onset, sleep continuity, and quality of life. Management has be-

come more challenging since the US Food and Drug Administration ordered the discontinuation of marketing of unapproved quinine-containing products (<http://www.fda.gov/medwatch/safety/2006/safety06.htm#Quinine>), with some patients having few other options for therapy other than massage and consuming tonic water and potassium-containing fruits and vegetables. A screening tool could permit identification of those with this disorder so that counseling and management with non-toxic treatments could lead to clinical improvement.

Utility as a Research Tool

While SRLC are viewed to be relatively common, the frequency in the population and possible association with other medical and neurologic disorders has not been rigorously studied. Among the cognitively impaired with insomnia and sleep fragmentation, SRLC could be contributing to patient and bed partner sleep disruption, and effective treatment could improve sleep and quality of life; this issue has not been studied. The high sensitivity (92%) of the MSQ for SRLC makes this an attractive screening tool for studying SRLC.

Comparison with Other Measures

The only other screening measure that assessed SLRC—the Munich Parasomnia Screening tool (MUPS)—had an SN of 100% and SP of 93%.⁸ The MSQ and MUPS are therefore excellent for screening for SRLC.

Alertness

The level of alertness as assessed in Question 8 correlated inversely with the total score on the ESS reasonably well. This suggests that the degree of alertness is inversely correlated with the chance of dozing.

Utility as a Clinical Tool

While an inverse correlation between alertness and sleepiness makes intuitive sense, assessing one's level of alertness (such as is done on the maintenance of wakefulness test) may or may not reflect similar constructs or brain mechanisms as assessing one's chance of dozing (such as is done on the multiple sleep latency test). In other words, the clinical implications of struggling to maintain alertness are likely different than the implications of the tendency to fall asleep easily. Future work using the MSQ, ESS, MWT, and MSLT may offer insights into these differences and the value of using this question on the MSQ for clinical purposes. As noted above, this question on level of alertness may add to the SN of the other questions relating to OSA on the MSQ.

Utility as a Research Tool

One example where Question 8 on the MSQ could be studied is in DLB patients to determine if any correlation exists between the level of alertness and the core feature of fluctuations. The underlying substrate for fluctuations in cognition and arousal in DLB remains enigmatic, and if fluctuations represent one or more primary sleep disorders impacting alertness, this could also have research implications in those who have normal cognition or MCI. For example, impaired alertness may contribute to fluctuations, or represent a hypersomnolence syndrome, and these factors could be studied as early features of

evolving Lewy body disease similar to how RBD is now being studied in very early PD and DLB.

Comparison with Other Measures

Other than the ESS, no other validation data exist using simple screening measures compared to PSG, MSLT, or MWT.

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