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Obstructive Sleep Apnea and Fatigue in Patients with Multiple Sclerosis

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SCIENTIFIC INVESTIGATIONS

Study Objectives: The prevalence of obstructive sleep apnea (OSA) in persons with multiple sclerosis (MS) remains unknown, and little information exists regarding the relative contributions of OSA to symptoms of MS-related fatigue in the presence of other clinical and sleep-related confounders. The objectives of this study were to investigate the prevalence of diagnosed OSA and OSA risk among MS patients, and to assess relationships between fatigue severity, OSA, OSA risk, and sleep quality among persons with MS.

Methods: N = 195 MS patients completed a questionnaire comprised of items regarding OSA diagnosis, sleep quality and quantity, daytime symptoms, and 4 validated scales: the Epworth Sleepiness Scale, Fatigue Severity Scale, Insomnia Severity Index, and STOP-Bang questionnaire. Medical records were also accessed to examine clinical characteristics that may predict fatigue or OSA risk.

Results: N = 41 patients (21%) carried a formal diagnosis of OSA. N = 110 (56%) of all patients, and 38 (93%) of those with diagnosed OSA had STOP-Bang scores ≥ 3, indicating an elevated OSA risk. In regression models, the most significant predictors of higher FSS scores were higher STOP-Bang scores ($p = 0.01$), higher number of nocturnal symptoms ($p < 0.0001$), and higher disability level ($p < 0.0001$).

Conclusions: Sleep disturbances, and OSA in particular, may be highly prevalent yet underrecognized contributors to fatigue in persons with MS.

Keywords: obstructive sleep apnea, multiple sclerosis, fatigue, STOP-Bang, sleep disturbance

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Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that causes myelin destruction and axonal damage in the brain and spinal cord. Multiple sclerosis is the leading cause of non-traumatic neurological disability among young adults, and is associated with a variety of debilitating symptoms, including fatigue.

Fatigue affects up to 90% of multiple sclerosis patients at some point during their disease course.[1-4] This highly debilitating symptom imposes significant socioeconomic consequences[5] and is a leading cause of diminished quality of life among individuals with MS.[3] Although MS-related fatigue is often multifactorial, identification of treatable causes that may contribute to its severity is an essential element of management of this symptom.

Obstructive sleep apnea (OSA) may exacerbate fatigue severity in MS. This treatable disorder of sleep and breathing is a known cause of fatigue and related symptoms in general population studies,[6] and constitutes a significant risk factor for cardiovascular disease, metabolic syndrome, motor vehicle accidents, reduced productivity, cognitive dysfunction, and poor quality of life.[7-14] Yet, despite its impact in the general population, the extent to which OSA contributes to fatigue in persons with MS is poorly understood, and the prevalence of OSA in MS remains unclear. Whereas some contend that the prevalence of OSA is higher in MS patients than in the general population, heterogeneity in subjects studied, sample sizes, and outcome measures have led to highly variable estimates.[15-20]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Fatigue is one of the most common and debilitating symptoms experienced by persons with multiple sclerosis (MS), but little is known about the potential contributions of obstructive sleep apnea (OSA) or its frequency in patients with MS. The objectives of this study were to investigate the frequency of diagnosed OSA and elevated OSA risk among MS patients in a tertiary care center, and to assess relationships between fatigue severity, OSA, OSA risk, and sleep quality among MS patients.

Study Impact: Our findings suggest that OSA is highly prevalent in patients with MS, particularly among fatigued MS patients. Although a cross-sectional study cannot demonstrate that OSA or other sleep disturbances cause the fatigue that accompanies MS, the associations identified in this study indicate that if cause-and-effect relationships do exist, OSA and disturbed sleep could contribute substantially to fatigue that ranks among the leading complaints of patients with MS.

Furthermore, no standardized approach has been developed to identify clinical features that may signal OSA risk in individuals with MS. Research on distinguishing features of OSA versus other sleep related predictors of fatigue in MS could help clinicians identify patients most likely to benefit from sleep evaluations, and optimize fatigue management. The purpose of this study was to assess the frequency of diagnosed OSA and elevated OSA risk among MS patients in a tertiary MS center, and to assess relationships between fatigue severity, OSA, OSA risk, and sleep quality among persons with MS in the outpatient setting.

Figure 1—Items comprising the STOP-Bang questionnaire (adapted from Chung et al.[24] and Chung et al.[25] with permission from Dr. Francis Chung).

STOP-Bang Questionnaire	
Snoring	Do you snore loudly (louder than talking or loud enough to be heard through dosed doors)?
Tired	Do you often feel tired, fatigued,or sleepy during the daytime?
Observed apnea	Has anyone observed you stop breathing during your sleep?
Blood **P**ressure	Do you have or are you being treated for high blood pressure?
BMI	BMI more than 35 kg/m^2?
Age	Age over 50 years old?
Neck Circumference	Are you a male with a neck circumference greater than 17 inches, or a female with a neck circumference greater than 16 inches?
Gender	Are you a male?

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

This survey study was approved by the University of Michigan (U-M) Institutional Review Board (IRBMED).

Subjects/Data Collection

All patients age 18 or older with a documented diagnosis of MS who did not have a concomitant neurological disorder that could increase OSA risk (such as stroke, Parkinson disease, or amyotrophic lateral sclerosis) were invited to participate.

Between July 2012 and March 2013, during routine clinic appointments, n = 203 consenting subjects who presented to the U-M Multiple Sclerosis Clinic for follow-up completed a self-administered survey comprised of questions regarding perceived sleep quality, sleep quantity, use of hypnotics and wake promoting agents, daytime symptoms, use of positive airway pressure devices (if applicable), and items adapted from the International Restless Legs Syndrome (RLS) Study Group essential diagnostic criteria.[21] Survey items were structured as yes/no questions and categorical responses, in which subjects were asked to circle their one best answer from list of options. Data on nocturnal symptoms that interfere with sleep were collected through multiple choice questions, wherein subjects were allowed to select one or more choices from a list of symptoms including pain, tingling, spasticity, feelings of restlessness, urinary urgency, anxiety, an inability to shut off the mind, muscle twitching, or "other" (which allowed subjects to write in their own response).

The survey also included 4 validated instruments: the Epworth Sleepiness Scale; the Fatigue Severity Scale; the STOP-Bang questionnaire; and, for subjects who endorsed difficulty sleeping on a separate survey item, the Insomnia Severity Index. The Epworth Sleepiness Scale (ESS) is an 8-item questionnaire that uses 4-point Likert scale items to quantify the likelihood of dozing in sedentary situations.[22] Scores ≥ 10 are consistent with excessive daytime sleepiness. The Fatigue Severity Scale (FSS) is a 9-item questionnaire that uses a 7-point Likert scale to assess the impact of fatigue in persons with MS and other chronic diseases. Average FSS scores ≥ 4 are suggestive of fatigue.[23] The STOP-Bang questionnaire is a screening tool consisting of 8 questions and measures that form the acronym STOP-Bang (**Figure 1**). Scores are based on yes/no answers for each item (score: 1/0). STOP-Bang scores ≥ 3 indicate elevated risk for OSA.[24,25] The Insomnia Severity Index (ISI) is a 7-item questionnaire with 5-point Likert scale responses designed to assess the nature, severity, and impact of insomnia in adults. Scores ≥ 15 reflect moderate clinical insomnia.[26]

Surveys were administered by qualified study staff (VK, KD, or JR—see Acknowledgments), blinded to subjects' clinical history. Patients completed their surveys in MS clinic examination rooms prior to seeing their MS specialists. Patients had opportunities to discuss questionnaire responses and symptoms with their physicians. In the event that research staff were not available, surveys were administered by the treating MS physician. Medical records were reviewed by the principal investigator (TB) to confirm eligibility and extract additional data on clinical variables that may influence sleep quality or fatigue level. Clinical variables recorded included age, gender, MS subtype (relapsing or progressive), MS disease duration at time of the survey (years), use of disease modifying or immunosuppressive therapy at the time of the survey (yes/no), documented diagnosis of clinical depression or active symptoms of depression as documented by the treating physician during the subject's clinical assessment on the day of the survey (yes/no), and a dichotomized estimate of disability [defined as

Table 1—Demographic and clinical findings

Variable	All MS patients (n = 195)	STOP-Bang		History of formal OSA diagnosis	
		≥ 3 (n = 110)	< 3 (n = 85)	Yes (n = 41)	No (n = 154)
Age (years, mean ± SD)	47.1 ± 12.1	50.3 ± 11.8*	43.0 ± 11.1	52.1 ± 10.4†	45.8 ± 12.2
Female, n (%)	128 (65.6)	58 (52.7)*	70 (82.3)	24 (58.5)	104 (67.5)
BMI (kg/m^2, mean ± SD)	29.6 ± 7.4	32.4 ± 7.8*	25.9 ± 4.7	32.9 ± 8.8†	28.7 ± 6.7
Disease duration (years, mean ± SD)	10.2 ± 8.2	11.3 ± 8.6*	8.8 ± 7.4	12.8 ± 9.6†	9.5 ± 7.7
MS Subtype					
Relapsing-Remitting, n (%)	145 (74.4)	76 (69.1)	69 (81.2)	26 (63.4)	119 (77.3)
Secondary Progressive, n (%)	41 (21)	25 (22.7)	16 (18.8)	11 (26.8)	30 (19.5)
Primary Progressive, n (%)	9 (4.6)	9 (8.2)*	0 (0)	4 (9.8)	5 (3.3)
Disease modifying therapy, n (%)	133 (68.2)	72 (65.5)	61 (71.8)	29 (70.7)	104 (67.5)
Beta-interferon	61 (31.3)	27 (24.6)*	34 (40.0)	12 (29.3)	49 (31.8)
Glatiramer Acetate	46 (23.6)	28 (25.5)	18 (21.2)	13 (31.7)	33 (21.4)
Natalizumab	17 (8.7)	10 (9.1)	7 (8.2)	1 (2.4)	16 (10.4)
Other	8 (4.1)	7 (6.4)	1 (1.2)	3 (7.3)	5 (3.3)
Expanded disability status scale score ≥ 6.0, n (%)‡	48 (24.6)	35 (31.8)*	13 (15.3)	11 (26.8)	37 (24.0)
Depression, n (%)	42 (21.5)	30 (27.3)*	12 (14.1)	8 (19.5)	34 (22.1)

Data shown as mean ± SD or n (%). Values followed by * indicate $p < 0.05$ for difference between STOP-Bang groups. Values followed by † indicate $p < 0.05$ for difference between history of formal OSA diagnosis groups. ‡Frequency of patients with Expanded Disability Scale (EDSS) scores ≥ 6.0, indicating need for an assistive device.

Expanded Disability Status Scale score < 6 (lower disability), or ≥ 6 (higher disability)]. Based on a standard neurological examination, the Expanded Disability Status Scale (EDSS) is a composite score that is commonly used to quantify disability level in patients with MS.[27] The composite is derived from ratings of 7 functional systems commonly affected in MS: visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder, and cerebral function. Scores < 6.0 indicate independent ambulation without the need for an assistive device such as a cane, walker, or wheelchair.

Statistical Methods

Statistical tests were performed using SAS version 9.2. Tests were two-sided with a level of statistical significance set at 0.05.

Bivariate relationships between Epworth scores, FSS scores, STOP-Bang scores, Insomnia Severity Index scores, perceived sleep latency and duration, nocturnal symptoms, and MS-specific characteristics were examined with Spearman correlation tests. Two-sample t-tests, Wilcoxon rank-sum tests, and χ^2 tests were used to examine differences in clinical variables and survey responses by OSA risk score (STOP-Bang score ≥ 3 vs. < 3) and OSA diagnosis. For OSA patients with information regarding treatment with continuous or bilevel positive airway pressure (PAP), 2-sample t-tests and Wilcoxon rank-sum tests were performed to compare Epworth and FSS scores, respectively, between compliant PAP users and non-compliant users/non-users.

Multiple linear regression models were constructed to assess sleep-related predictors of FSS scores, taking into account age, gender, BMI, disability status (dichotomized EDSS score), disease modifying therapy use, depression, and presence of restless legs syndrome as potential confounders. To reduce potential effects of multicollinearity between FSS scores and STOP-Bang scores (which includes an item for tiredness), additional regression analyses were conducted with STOP-Bang questionnaires scored with the tiredness item removed.

The population attributable risk percent (PAR%) was calculated to estimate the potential impact of OSA on fatigue in MS. Calculation of a PAR% is based on 2 assumptions: first, that OSA diagnosis or high risk for OSA as reflected by the STOP-Bang (with underlying OSA in many cases) can cause fatigue in MS, and second, that the prevalences of these 2 risk factors in MS are similar to those observed in the current study. The PAR% then uses the excess frequency of the risk factor among fatigued vs. non-fatigued MS patients to estimate the proportion of fatigue (defined here as FSS score ≥ 4) among MS patients that would be eliminated by diagnosis and successful treatment of the underlying OSA or elevated OSA risk.[28] For this cross-sectional study, the formula used was:

$$PAR\ \% = Attributable\ Risk\ \% * Prevalence\ of\ Exposure$$

where Attributable Risk % was derived from odds ratio estimates rather than relative risk and the Prevalence of Exposure was the frequency of OSA diagnosis or high STOP-Bang score among the fatigued subjects.

RESULTS

One hundred percent of invited subjects (203/203) agreed to participate. However, 8 surveys were excluded from the analyses for the following reasons: missing or incomplete survey data (2), diagnosis other than MS (5), and concomitant neurological disease (1).

Baseline Data

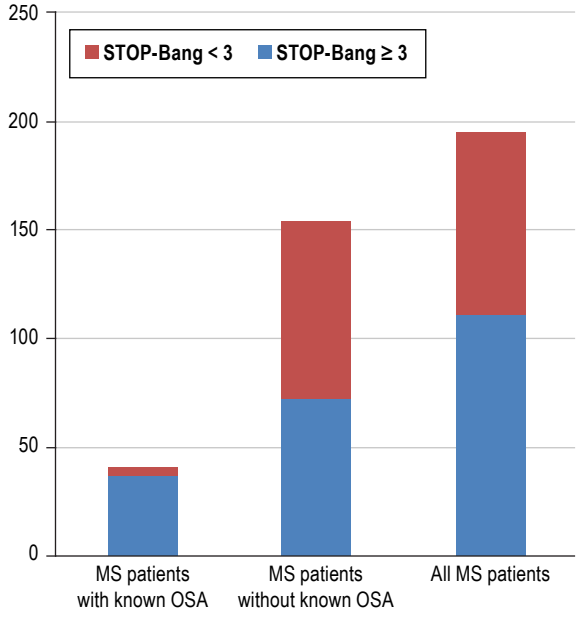
Demographic and sleep related characteristics for 195 MS patients are shown in **Tables 1** and **2**. Mean age was 47 years. Sixty-six percent of the participants were female, consistent

Table 2—Sleep characteristics, nocturnal behaviors, and daytime symptoms

Variable	All MS patients (n = 195)	STOP-Bang		History of formal OSA diagnosis	
		≥ 3 (n = 110)	< 3 (n = 85)	Yes (n = 41)	No (n = 154)
Sleep duration (mean ± SD)	6.6 ± 1.3	6.5 ± 1.3	6.7 ± 1.4	6.4 ± 1.5	6.6 ± 1.3
Number of nocturnal awakenings per night (mean ± SD)	2.1 ± 1.2	2.2 ± 1.2*	1.9 ± 1.2	2.4 ± 1.1†	2.0 ± 1.2
Sleep latency ≥ 1 hour, n (%)	86 (44.6)	53 (48.2)	33 (39.8)	21 (51.2)	65 (42.8)
Fatigue Severity Scale score (mean ± SD)	4.6 ± 1.8	5.1 ± 1.6*	4.0 ± 1.8	5.0 ± 1.6	4.5 ± 1.8
STOP-Bang score (mean ± SD)	3.2 ± 1.7	4.3 ± 1.3*	1.6 ± 0.6	4.8 ± 1.6†	2.8 ± 1.5
Epworth Sleepiness Scale score (mean ± SD)	8.1 ± 5.1	9.1 ± 5.0*	6.9 ± 5.1	9.0 ± 5.6	7.9 ± 5.0
Insomnia Severity Index score‡ (mean ± SD)	14.6 ± 5.6	14.8 ± 5.6	14.4 ± 5.7	17.0 ± 4.5†	14.0 ± 5.8
Use of hypnotics (occasionally, frequently, or always, n (%)	89 (46.8)	51 (47.2)	38 (46.3)	20 (50.0)	69 (46)
Use of wake-promoting agents, n (%)	45 (24.1)	35 (32.4)*	10 (12.7)	18 (43.9)†	27 (18.5)
Restless Legs Syndrome, n (%)	56 (29.8)	39 (36.8)*	17 (20.7)	17 (42.5)†	39 (26.4)

Data shown as mean ± SD or n (%). Values followed by * indicate $p < 0.05$ for difference between STOP-Bang groups. Values followed by † indicate $p < 0.05$ for difference between history of formal OSA diagnosis groups. ‡Insomnia Severity Index scores for n = 109 (56.8%) subjects who endorsed difficulty sleeping.

Figure 2—Frequency of high STOP-Bang scores among all MS patients, and those with and without a formal diagnosis of OSA.



with the gender distributions seen in MS in the United States. Mean disease duration was 10.2 years. Sixty-eight percent were on disease modifying therapy. Per medical records, 74% carried a diagnosis of relapsing-remitting MS, while 26% had progressive disease (primary progressive or secondary progressive MS). Forty-one patients (21%) endorsed a formal diagnosis of OSA (63% diagnosed at our center). Thirty-two patients with OSA were prescribed PAP. Of these, 17 reported compliant use (defined here as PAP use ≥ 4 h per night, most nights per week). Fifty-six (30% of 188 responders) answered "yes" to all 4 International Restless Legs Syndrome (RLS) Study Group essential screening questions, meeting clinical diagnostic criteria for RLS.

Eighty-five percent of patients endorsed at least one nocturnal symptom (pain, tingling, spasticity, feelings of restlessness, urinary urgency, anxiety, an inability to shut off the mind, muscle twitching, or other) to interfere with their ability to get a good night's sleep, with 54% of patients endorsing ≥ 3 of these symptoms (not shown in table). Nocturnal symptoms most frequently reported to interfere with sleep included pain, spasms, nocturia, and an inability to shut off one's mind (endorsed by 41%, 40%, 40%, and 50% of subjects, respectively).

Validated Instruments

One hundred ten (56%) of all patients, and 38 (93%) of those with diagnosed OSA had STOP-Bang scores ≥ 3 (**Figure 2**). For all patients, the mean Fatigue Severity Scale score (FSS) and Epworth score were 4.6 (SD 1.8) and 8.1 (SD 5.1), respectively.

For 109 patients who endorsed difficulty sleeping, the mean Insomnia Severity Index score was 14.6; 50 (46%) of these subjects had Insomnia Severity Index scores ≥ 15, reflecting moderate clinical insomnia. Mean FSS and Epworth scores among these subjects were 5.0 and 8.7, respectively.

Bivariate Analyses (Tables 1 and 2)

Mean FSS scores were significantly higher in patients with STOP-Bang scores ≥ 3 (5.1 vs. 4.0, $p < 0.0001$). There was also a trend toward higher FSS scores in patients with documented OSA compared to the remainder of the sample (5.0 vs. 4.5, $p = 0.1049$).

Moderately strong correlations emerged between the FSS score and the STOP-Bang score, Epworth score, and Insomnia Severity Index score (**Table 3**). FSS scores also correlated with mean number of perceived nocturnal awakenings and number of nocturnal symptoms. Individual nocturnal symptoms that correlated best with FSS score included pain (rho = 0.39, $p < 0.0001$), spasms (rho = 0.45, $p < 0.0001$), and twitching (rho = 0.37, $p < 0.0001$) (not shown in table).

STOP-Bang scores correlated more strongly with FSS scores (rho = 0.33, $p < 0.0001$), than with Epworth scores (rho = 0.22, $p = 0.0035$). STOP-Bang scores also correlated with mean number of nocturnal awakenings and number of nocturnal symptoms.

Among patients who carried a diagnosis of OSA, compliant PAP users in comparison to the remaining patients showed no significant differences in FSS scores ($p = 0.2819$) or Epworth scores ($p = 0.2691$).

Table 3—Correlations (Spearman rho [p-value]) between fatigue and sleep-related measures

	FSS	STOP-Bang	ESS	ISI	# of nocturnal awakenings	# of nocturnal symptoms
FSS	–	0.33 (< 0.0001)	0.44 (< 0.0001)	0.48 (< 0.0001)	0.30 (< 0.0001)	0.58 (< 0.0001)
STOP-Bang	–	–	0.22 (0.0035)	0.08 (0.4157)	0.21 (0.0048)	0.26 (0.0003)
ESS	–	–	–	0.32 (0.0013)	0.24 (0.0017)	0.37 (< 0.0001)
ISI	–	–	–	–	0.44 (< 0.0001)	0.38 (< 0.0001)
# of nocturnal awakenings	–	–	–	–	–	0.53 (< 0.0001)

Table 4—Summary of published studies that used prospective polysomnography (PSG) in persons with MS

Author	Year of publication	Study site	Mean age (years)	EDSS score (reported mean or median)	Subjects with sleep-related breathing disorders, as proportion of all subjects (%)
Ferini-Strambi	1994	Italy	39.9	3.8	3/25 (12%)
Kaminska	2012	Canada	47.3	3.6	36/62 (58%)
Kaynak	2006	Turkey	37	2.4 and 1.8 (for fatigued and non-fatigued subjects, respectively)	0/27 (0%)
Neau	2012	France	40 (for n = 25 subjects selected for PSG)	4.1 and 2.2 (for fatigued subjects with or without excessive daytime sleepiness, respectively)	0/25 (0%, from n = 205 patients selected to undergo PSG)
Veauthier	2011	Germany	43.2	2.0	8/66 (12%)

Regression Analyses

Number of nocturnal symptoms (regression parameter = 0.44, SE = 0.07, $p < 0.0001$), higher EDSS scores (regression parameter = 1.1, SE = 0.27, $p < 0.0001$), and STOP-Bang scores (regression parameter = 0.25, SE = 0.10, $p = 0.01$) were the strongest predictors of FSS scores, after adjustment for age, gender, BMI, sleep duration, number of nocturnal awakenings, depression, disease modifying therapy use, and presence of RLS. In separate models adjusted for the same predictor variables, the number of nocturnal symptoms also predicted ESS scores (regression parameter = 0.63, SE = 0.25, $p = 0.012$), but there was no significant association between the STOP-Bang and ESS scores. Diagnosis of OSA (regression parameter = 3.6, SE = 1.24, $p = 0.0049$) and number of nocturnal symptoms (regression parameter = 1.37, SE = 0.30, $p < 0.0001$) most strongly predicted the ISI after controlling for age, gender, BMI, depression, disability status, and presence of RLS.

Modified STOP-Bang Analyses (tiredness item removed)

The proportion of fatigued subjects, as compared to non-fatigued subjects, with elevated STOP-Bang scores remained significantly higher when the tiredness item was removed from the STOP-Bang questionnaire (43% vs. 28%, χ^2 $p = 0.0389$). Twenty-nine patients (74.4%) with a confirmed OSA diagnosis had modified STOP-Bang scores ≥ 3. Correlations between FSS score and modified STOP-Bang score remained significant in Spearman correlation tests (rho = 0.22, $p = 0.0028$), and in regression models adjusted for depression, EDSS score, sleep duration, disease modifying therapy use, and presence of RLS (regression parameter = 0.15, SE = 0.07, $p = 0.0459$); but statistical significance diminished in models adjusted further for age, gender, BMI, mean number of nocturnal awakenings, and number of nocturnal symptoms (regression parameter = 0.14, SE = 0.11, $p = 0.1805$).

Population Attributable Risk Percent (PAR %)

The PAR% for documented OSA as a risk factor for fatigue in MS patients was 11%. The PAR% for elevated OSA risk as defined by the STOP-Bang was 40%.

DISCUSSION

In this study, one-fifth of MS patients surveyed in a large tertiary MS practice carried a formal diagnosis of OSA, and a substantially higher proportion of patients (more than half) were found to be at elevated risk for OSA based on the STOP-Bang questionnaire. Obstructive sleep apnea risk emerged as a significant predictor of fatigue, after adjustment for other important clinical and sleep related predictors of fatigue, including number of nocturnal symptoms and disability status. Although this study was cross-sectional and cannot prove cause and effect, the findings suggest that OSA is highly prevalent in patients with multiple sclerosis, particularly among fatigued MS patients, and that OSA and other causes of disturbed sleep could contribute substantially to fatigue severity.

Obstructive sleep apnea (OSA) is well recognized as a major public health challenge in the United States.[29] Despite its importance, its prevalence in persons with MS remains unknown, with estimates ranging from 0% to 58% in published studies (see **Table 4** for a summary of these studies).[15,17-19] There are several potential reasons for the high variability among these findings and our estimates of OSA frequency.

Primary outcome measures differed across studies, most of which were not designed to assess OSA prevalence. Selection bias is also a concern, particularly among studies that utilize laboratory-based research PSG, as these studies have the potential to disproportionately select the most highly motivated or severely affected individuals, thus leading to an overestimation of OSA prevalence. Conversely, subject selection methods, and in particular, enrollment restrictions based on disability status and age in the Ferini-Strambi and Kaynak studies (**Table 4**) may have led to an underestimation of OSA prevalence among the wider population of all MS patients. Previous studies from our center and others suggest that progressive MS subtypes and increased level of disability are risk factors for OSA in MS.[16] Similarly, another risk factor is age, which correlates positively with progressive MS subtypes and disability and is an independent risk factor for OSA.[30-32]

Finally, differences in PSG acquisition and scoring methods may in part explain variability in study results. Though home sleep apnea studies offer a simpler method to diagnose sleep related breathing disorders, these devices have not been validated in patients with MS, and may be insensitive to more subtle or complex sleep related breathing disorders such as upper airway resistance syndrome or central sleep apnea.

Though our estimates of OSA frequency fall within the range of previous estimates, the striking difference between the proportion of patients with an established diagnosis of OSA (21%) and those at risk for OSA based on STOP-Bang scores (56%) is also noteworthy and may reflect suboptimal OSA diagnosis patterns seen in the general population. While symptomatic OSA (defined as OSA in the setting of functional impairment due to hypersomnolence) affects at least 3% adults in the U.S., the prevalence of occult apnea when excessive daytime sleepiness is not required to establish the diagnosis may be as high as 9% for women and 24% for men.[29]

Under-recognition of other symptoms that may signal OSA—such as fatigue—may also explain the discrepancy we found, particularly in patients who suffer disproportionately from fatigue because of a comorbid condition (MS). Whereas MS-related fatigue is most often described as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activity,"[33] many patients use this term interchangeably with sleepiness, which is classically defined as an increased propensity to fall asleep. Though diurnal sleepiness is a physiological process driven by internal and external circadian influences, excessive sleep drive may result in many of the same consequences as fatigue, including reduced cognitive and psychomotor performance, psychological distress, and reduced quality of life.[34] In addition, a shared collection of popular descriptors for both terms—including tiredness, exhaustion, loss of energy, and lassitude—make separation of fatigue and sleepiness particularly challenging. Furthermore, both symptoms may be exacerbated by a number of acute and chronic medical conditions, as well as several sleep disorders.[35] Despite traditional emphasis on sleepiness as a primary consequence of sleep apnea, many non-MS subjects who have OSA report that problems with fatigue, tiredness, or lack of energy supersede their problems with sleepiness.[6] Moreover, recent data from our group and others suggest that MS patients with sleep problems are more likely than controls without MS to emphasize fatigue, as opposed to sleepiness.[36] Our current data support these findings, and provide further evidence that OSA is a consequential yet under-recognized comorbidity in persons with MS, that may more commonly present with fatigue, rather than sleepiness.

Our data also highlight the importance of a step-wise approach in the clinical assessment of fatigued MS patients, and suggest that more effort is needed to determine the most appropriate screening tools to identify MS patients who would most benefit from formal sleep evaluations. The STOP-Bang is a sensitive, reliable screening tool for OSA, frequently used in outpatient sleep clinics and in the evaluation of surgical patients undergoing preoperative workups. Recent studies in the general population suggest that STOP-Bang scores ≥ 3 have a positive predictive value of 75% to 85% to detect OSA.[24,37] Dias and authors were the first to study the utility of this instrument in the outpatient MS setting. In an anonymous survey study of MS patients, the authors reported that STOP-Bang scores positively correlated with FSS scores, particularly in males.[38] They also noted that 42% of subjects were at high-risk for OSA based on STOP-Bang scores. As their survey was conducted anonymously, no data regarding disease course, disability status, other sleep disturbances, or medical history (to confirm a diagnosis of OSA) were available for the analyses. Our study now confirms some of these findings, even after accounting for other important MS-specific and sleep related variables that can influence fatigue. Although formal validation studies are still necessary to evaluate the specificity and positive predictive value of the STOP-Bang in patients with MS, our study is the first to examine the association between OSA diagnosis and high STOP-Bang scores in patients with MS, and our results provide some of the first data to suggest that the STOP-Bang as a screen for OSA retains validity in the setting of MS. If we assume that the positive predictive value of the STOP-Bang among patients without MS can be extrapolated to those with MS, this would suggest that at least 75% of our 110 subjects with elevated STOP-Bang scores (42% of our entire sample) would have OSA if formally tested with PSG—considerably more than the 41 patients (21%) who carried formal diagnoses of OSA already.

Another covariate that emerged as a strong predictor of FSS score was the number of nocturnal symptoms reported to interfere with sleep. More than half of our patients endorsed multiple nocturnal symptoms. While numerous studies have identified pain as a predictor of poor sleep quality, fatigue, and overall diminished functioning in MS patients,[39,40] our findings underscore the point that nocturnal discomfort experienced by MS patients may be described in terms other than pain. More importantly, our data highlight the importance of addressing treatable symptoms that may cause fatigue in patients with MS through reduced sleep efficiency or other mechanisms.

Our study has some limitations. Despite compelling associations between sleep disturbances and fatigue, conclusions about cause-and-effect relationships cannot be drawn from these cross-sectional data. It is also possible that the high prevalence of diagnosed OSA may, in part, reflect referral characteristics of our center. Furthermore, though most (63%) of the 41 respondents who endorsed a diagnosis of OSA had been evaluated at our sleep center (allowing for PI confirmation), the remaining

subjects were diagnosed at outside institutions. Some of the latter subjects may not have been formally diagnosed with OSA by clinical overnight PSG. We believe the likelihood of this is low, however, given that most of these subjects also had a diagnosis of OSA listed in their medical chart.

We also chose to focus on subjects who carried a diagnosis of OSA at the time of the survey. While this strategy did not allow assessment of survey responses prior to initiation of OSA treatment such as PAP (which could reduce fatigue or sleepiness), our approach permitted us to minimize selection bias that could obscure OSA prevalence estimates in our clinic population, and allowed a substantially larger sample size. Though no significant associations were noted between PAP use and FSS or Epworth scores, this finding should be interpreted with caution given the limited number of PAP-treated and compliant subjects. This lack of association also may reflect contributions to fatigue from other MS-related features that do not respond to treatment with PAP.

Finally, to reduce respondent burden, we relied on medical records to adjust for depression as a dichotomized variable, as opposed to use of a quantitative depression scale in our analyses. While this method may have provided a less sensitive assessment of the association between depression and fatigue, we believe that it maximized the likelihood of obtaining high quality survey responses most germane to our primary clinical questions within the limited time frame during which surveys could be administered. Also to reduce respondent burden, only subjects who endorsed difficulty sleeping on a single, initial survey question were asked to complete the Insomnia Severity Index. This approach may have limited our ability to detect and characterize all cases of insomnia.

In conclusion, our data provide new evidence that sleep disturbances, and OSA in particular, may be highly prevalent yet under-recognized contributors to fatigue in persons with MS. Clinicians caring for these patients should maintain a low threshold to screen MS patients for OSA, and endeavor to identify underlying nocturnal symptoms that could affect sleep quality and contribute to daytime fatigue. The present study did not involve an epidemiologic cohort sample, and the calculated PAR % must therefore be interpreted as an estimate using available data and assuming that OSA can play a causal role in development of fatigue. However, the PAR % estimates calculated in this study raise the possibility that a substantial portion of MS-related fatigue—between 11% and 40%—could be eliminated by diagnosis and successful treatment of OSA in patients with MS.

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