Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Beyond fatigue: Assessing variables associated with sleep problems and use of sleep medications in multiple sclerosis

This article was published in the following Dove Press journal:
Clinical Epidemiology
12 May 2010
Number of times this article has been viewed

Alyssa M Bamer
Kurt L Johnson
Dagmar A Amtmann
George H Kraft

Department of Rehabilitation Medicine, University of Washington, Seattle, WA, USA

Background: Recent research indicates that sleep disturbances are common in persons with multiple sclerosis (MS), though research to date has primarily focused on the relationship between fatigue and sleep. In order to improve treatment of sleep disorders in MS, a better understanding of other factors that contribute to MS sleep disturbance and use of sleep medications in this population is needed.

Methods: Individuals with MS (N = 473) involved in an ongoing self-report survey study were asked to report on use of over-the-counter and prescription sleep medications. Participants completed the Medical Outcomes Study Sleep (MOSS) scale and other common self-report symptom measures. Multiple regression was used to evaluate factors associated with sleep problems and descriptive statistics were generated to examine use of sleep medications.

Results: The mean score on the MOSS scale was 35.9 (standard deviation, 20.2) and 46.8% of the sample had moderate or severe sleep problems. The majority of participants did not use over-the-counter (78%) or prescription (70%) sleep medications. In a regression model variables statistically significantly associated with sleep problems included depression, nighttime leg cramps, younger age, pain, female sex, fatigue, shorter duration of MS, and nocturia. The model explained 45% of the variance in sleep problems. Of the variance explained, depression accounted for the majority of variance in sleep problems (33%), with other variables explaining significantly less variance.

Conclusions: Regression results indicate that fatigue may play a minor role in sleep disturbance in MS and that clinicians should consider the interrelationship between depression and sleep problems when treating either symptom in this population. More research is needed to explore the possibility of under-treatment of sleep disorders in MS and examine the potential effectiveness of nonpharmaceutical treatment options.

Keywords: multiple sclerosis, sleep, depression, fatigue, nonpharmaceutical treatments, self-medication

Introduction

Multiple sclerosis (MS) is a demyelinating and degenerative disease of the central nervous system that affects approximately 2.5 million people worldwide.[1] Although the disease course may vary significantly among individuals, common symptoms of MS include changes in mobility, fatigue, spasticity, depression, pain, and cognitive decline.[2] Recent research has emerged that suggests sleep disturbances are also common in individuals with MS, with approximately 50% of individuals reporting sleep problems.[3,4] Treatment of sleep disorders in persons with MS is important because sleep dysfunction can potentially exacerbate other MS symptoms[5] (eg, mental health problems) and has recently been shown to be an independent predictor of quality of life.[6]

Correspondence: Alyssa M Bamer
University of Washington, Box 356590, Seattle, WA 98195, USA
Tel +1 303 953 8085
Fax +1 206 685 3244
Email adigiaco@u.washington.edu

In order to improve treatment of sleep disorders in MS, a better understanding of factors that contribute to MS sleep disturbance and use of sleep medications in this population is needed. Research to date has primarily focused on prevalence of sleep disorders[3,4] and the relationship between sleep and fatigue in MS.[7–12] While these studies have consistently shown that a relationship between sleep and fatigue exists in MS, sleep research from the general population and in other chronic conditions suggests that other factors, such as age, gender, and depression[5,13,14] may play a significant role in sleep disturbance in MS as well. There is some evidence in the MS literature, primarily from descriptive studies and qualitative research, that muscle spasms, periodic limb movements, nocturia, psychiatric illness, and pain may also contribute to sleep disturbances in MS.[11,15] However, to date studies in the MS literature have primarily examined the independent role of these factors in sleep, rather than in combination with fatigue or each other. In addition, no studies to date have examined the use of sleep medications in individuals with MS and associations between medication use and sleep outcomes.

Identifying factors that play a significant role in sleep disturbances in MS will contribute to improved MS care and treatment. Clinicians will be better able to target those factors most likely to contribute to disrupted sleep in their patient(s), and thus provide the treatment(s) most likely to improve sleep in their MS patients. In addition, as sleep has been shown to significantly impact overall health and quality of life,[6] we believe a vital component of MS care consists of improving sleep for patients with difficulties and will significantly contribute to improved quality of life. The objective of this study was therefore to examine the association between multiple demographic and disease characteristics with sleep problems using a multivariate regression approach. In addition, we sought to describe the use of sleep medications in this sample in order to better understand the prevalence of use in persons with MS.

Methods

Research participants

Study participants were involved in an ongoing longitudinal study of self-reported health outcomes in MS, which has been described elsewhere.[3,16,17] Participants were initially recruited through the Western Washington chapter of the National MS Society (NMSS) and initial letters of invitation were sent to 7,806 persons from the NMSS mailing list, which primarily included individuals who self-identified with the NMSS as having MS. Of the 1,629 (20.8%) to respond, 1,597 were eligible for and indicated interest in participation. Eligible individuals were required to report having a definitive diagnosis of MS and be aged at least 18 years. 1,271 individuals completed the initial survey between November 2006 and September 2007, either on paper or via the Internet, and paper survey responders with missing data were called up to four times to collect data via phone. A subset of 562 was randomly selected from the original subject pool of 1,271 to receive invitations to continue in the longitudinal survey study. The effectiveness of the randomization was explored and with the exception of ethnicity (noninvitees [98.5%] vs invitees [96.6%] were white; $P = 0.03$), no significant differences in demographics (age, gender, education, marital status, employment status) or disease characteristics (disease severity, duration, and relapsing type MS) were found between those invited to continue in the longitudinal study and not. Subsequent surveys were administered by mail every four months and participants received reminder letters and phone calls two and four weeks postadministration, respectively. Participants were called up to four times to collect missing data for each survey. A total of 513 (91.3%) individuals completed the second survey at four months, 488 (86.8%) completed the third survey at eight months, and 473 (84.2%) completed the fourth survey at 12 months. Due to late response, a total of nine and four individuals were not invited to continue at the eight- and twelve-month survey time points, respectively. Data reported in this paper are cross-sectional from the fourth survey time point (completed twelve months after the initial survey) because questions relevant to sleep had been included in this time point. All study procedures were approved by the Human Subjects Division at the University of Washington, and participants were paid $25 for completing each survey time point.

Measures

All measures were administered via self-report survey, and domains assessed primarily focused on the common symptoms of MS including pain, fatigue, depression, mobility changes, and sleep problems. Age, sex, and other demographic characteristics were also included for characterization of the study sample.

Primary outcome measures

Sleep problems were measured using the 12-item Medical Outcomes Study Sleep[18] (MOSS) scale, which is scored to yield six different sleep subscales and an overall sleep problems index (Sleep Problems Index II). Subscales are standardized to yield scores from zero to 100, with higher

scores on the Sleep Problems Index II and sleep disturbance subscales indicating more sleep problems or more sleep disturbance. The MOSS scale has been validated in large samples[18,19] and a comparison of this sample with normative scores was completed previously.[3]

In order to evaluate use of medications for sleep, participants were asked to separately report if they currently take prescription or over-the-counter medications to help with difficulties sleeping. If they reported yes, they were asked to indicate how often they take these medications, and response options included "less than once a week", "1–2 times a week", "3–4 times a week", and "every day".

Covariate measures

Depression was assessed using the nine-item Patient Health Questionnaire[20] (PHQ-9) depression module,[21] which is a brief self-report diagnostic and severity measure of depression. Items are scored on a scale from zero to three and summed to obtain overall depression severity scores, with higher scores indicating more depressive symptoms. The PHQ-9 has been extensively validated in multiple populations[21–25] and has been shown to have superior criterion validity for diagnosis of major depressive disorder compared with other depression screening questionnaires.[26] The PHQ-9 contains one item that refers to sleep difficulties, which was omitted from this analysis to reduce spurious associations between depression scores and sleep problems in the analyses. Thus, depression scores ranged from 0–24 in this study.

The modified version of the Fatigue Impact Scale[27,28] (MFIS) was included to evaluate severity of fatigue. The MFIS is a 21-item scale developed by the United States National Multiple Sclerosis Society for measuring fatigue in MS, and contains three subscores in addition to an overall fatigue score. Items are scored from zero to four with total scores ranging from zero to 84 and higher scores corresponding to more fatigue. The MFIS has been shown to more comprehensively assess fatigue in MS than other fatigue measures.[29]

A self-report version of the Expanded Disability Status Scale (EDSS),[30] a measure used to evaluate disease progression in MS, was also included in the survey. The self-report version has been shown to be highly correlated with the physician administered EDSS.[30] Individuals were scored from ≤4.0 to ≥8.0 based on responses to the mobility section of the EDSS. Individuals were categorized into minimal severity (≤4.0) representing no mobility aid use, intermediate severity (4.5–6.5) representing unilateral or bilateral mobility aid use, and advanced (≥7.0) severity representing primarily wheelchair use for mobility.

The domains of pain, restless legs, nocturia, nighttime leg cramps, and bed related immobility were assessed using single items. Pain was evaluated using an item adapted from the pain-intensity items of the Chronic Pain Grade scale.[31] Specifically, participants were asked "in the past week, how intense was your worst pain rated on a 0–10 scale where 0 is 'no pain' and 10 is 'pain as bad as can be.'" Numerical rating scales for pain intensity have demonstrated good psychometric properties and are widely used in pain research.[32] A single-item rapid screener for restless legs was included to assess likelihood of restless leg syndrome. This single-item screener has been shown to have excellent sensitivity and specificity in a neurological clinical practice population.[33] To assess nocturia, participants were asked a single yes or no question, "do you usually get up to go to the bathroom in the night," and if yes, how many times they got up on a typical night. For purposes of the regression individuals who got up at least twice to go to the bathroom in the night were considered as having problems with nocturia. Leg cramps and bed related immobility were assessed by asking participants how often they were bothered by the symptom on a typical week, and response options ranged from "never" to "almost always" on a five-point scale. The item stems to evaluate these two symptoms were specifically "leg cramps that interfere with your sleep" and "being unable to change your position easily on your own when lying in bed." The nocturia, leg cramps, and bed mobility items were all created by the study authors after consultation with MS clinicians.

Data analysis

Descriptive statistics were generated to describe the sample as well as use of over-the-counter and prescription sleep medications. Mean scores with standard deviation on the MOSS Problems Index II and sleep disturbance subscales were calculated for each category of medication use and for the population as a whole. In order to statistically compare sleep scores between groups of medication users, individuals were categorized into one of three groups for both prescription and over-the-counter medications: never users, sometime users (<1 week up to 3–4 times/week), and always users (every day). Wilcoxen rank-sum tests were conducted to compare scores on the sleep problems index and sleep disturbance subscales between these three groups for both prescription and over-the-counter medication use. Because of concerns about multiple testing, a Bonferroni correction to the alpha level of 0.05 was used, resulting in a required *P*-value cutoff of less than 0.004 for statistical significance.

Linear regression modeling was completed to identify factors associated with sleep problems in this sample. The dependant variable was sleep problems as measured by the MOSS Sleep Problems Index II. Independent variables examined in the analyses were identified a priori through a literature search and discussions with MS physicians. Backwards multiple linear regression modeling was utilized and the initial full model included the following independent variables: current age in years, duration of MS in years, EDSS level, gender, fatigue, depression, pain, nocturia, bed mobility, nighttime leg cramps, and restless legs. Based on earlier research indicating that fatigue in MS is affected by depression, a depression-fatigue interaction term was also tested in the final model. Variables were removed from the full model sequentially based on their *t*-statistic, and only variables significant at the alfa level of 0.05 were included in the final model. Adjusted R^2 contributions were also calculated for each variable independently to examine the variance explained in sleep problems by each variable independently beyond that explained by other variables already included in the model. This was done by ordering the variables according to their *t*-score, removing the variable with the smallest *t*-value, and calculating the difference in model adjusted R^2. This process was then repeated for each variable until only one variable remained in the model (depression was the final variable as it had the highest *t*-score). Unusual and influential data points as well as the regression assumptions of linearity, multicollinearity, normality of residuals, and homoscedasticity of residuals were thoroughly investigated. All assumptions were met and no unusual or influential data points were identified.

Results

The mean age of participants (N = 473) was 52.3 years and mean disease duration was 14.5 years. The large majority of participants were female (82.7%) and most were married or living with a significant other (68.3%). The mean score on the MOSS Sleep Problems Index II for the sample was 35.9 (standard deviation [SD], 20.2) and on the sleep disturbance subscale it was 32.6 (SD, 25.9). Of variables included in the regression model, restless leg-like symptoms were endorsed most often (50.7%), followed by nocturia (36.0%), leg cramps (35.4% report sometimes or greater), and bed mobility problems (27.1% report sometimes or greater). Additional sample characteristics can be found in Table 1.

The majority of participants did not use over-the-counter (78%) or prescription (70%) sleep medications (Table 2). Individuals who used prescription medications tended to use them every day with 19.5% of the sample reporting everyday use and only 10.6% reporting intermittent use. In contrast, only 7.8% of the sample used over-the-counter medications every day while 14.2% of the sample reported intermittent use. In statistical comparisons of scores between never, sometime, and always users of prescription medications we found that "never users" had significantly lower sleep problems and sleep disturbance scores than either "sometime" or "always users" on both subscales ($P \leq 0.0001$ for all comparisons). For over-the-counter medication users, "never users" had significantly lower sleep problems scores ($P = 0.002$) than "always users" and lower sleep disturbance scores than both "sometime" ($P = 0.002$) or "always" ($P < 0.0001$) users. No tests between "sometime" and "always users" were statistically significant after Bonferroni adjustment. Additional information on sleep problems and sleep disturbances scores can be found in Table 2.

Variables statistically significantly associated with sleep problems included depression, nighttime leg cramps, younger age, pain, female sex, fatigue, shorter duration of MS, and nocturia (Table 3). EDSS level, bed mobility, and restless legs were not significantly associated and were dropped from the model. The fatigue-depression interaction term was also

Table 1 Study participant characteristics (N = 473)

	Mean ± SD n (%)
Sleep problems (MOSS Sleep Problems Index II)	35.9 ± 20.2
Sleep disturbance (MOSS Sleep Disturbance Subscale)	32.6 ± 25.9
Age (years)	52.3 ± 10.9
Female	391 (82.7)
Duration of MS (years)	14.5 ± 9.9
EDSS category	
Mild (≤4.0)	145 (30.7)
Moderate (4.5–6.5)	240 (50.9)
Severe (≥7.0)	87 (18.4)
Education level	
≤High school/GED	68 (14.4)
Technical/some college	180 (38.1)
Bachelors degree	140 (29.6)
Graduate degree	85 (18.0)
Married	323 (68.3)
Depression (PHQ-9)	6.5 ± 5.25
Fatigue (MFIS)	38.8 ± 17.9
Pain	4.7 ± 3.3
Nocturia	170 (36.0)
Restless leg-like symptoms	240 (50.7)
Leg cramps	165 (35.4)
Bed mobility problems	127 (27.1)

Abbreviations: EDSS, Expanded Disability Status Scale; GED, General Education Development test; MFIS, Modified Fatigue Impact Scale; MOSS, Medical Outcomes Study Sleep; MS, multiple sclerosis; PHQ-9, Patient Health Questionnaire; SD, standard deviation.

Table 2 Sleep aid medication use

	n (%)	Sleep problems	Sleep disturbance
Prescription medications			
Never use	331 (70.0)	32.4 ± 19.3[a]	27.9 ± 24.4[a]
<1/week	17 (3.6)	40.8 ± 18.4	39.3 ± 23.1
1–2 times/week	16 (3.4)	52.7 ± 16.3	56.5 ± 24.4
3–4 times/week	17 (3.6)	54.0 ± 20.2	56.0 ± 28.5
Every day	92 (19.5)	41.3 ± 19.7	39.9 ± 25.4
Over-the-counter medications			
Never use	369 (78.0)	34.0 ± 19.7[b]	29.3 ± 24.7[c]
<1/week	28 (5.9)	31.9 ± 19.2	29.6 ± 21.6
1–2 times/week	17 (3.6)	52.1 ± 20.8	55.2 ± 27.4
3–4 times/week	22 (4.7)	43.1 ± 16.2	46.5 ± 23.7
Every day	37 (7.8)	45.5 ± 21.4	48.6 ± 28.4

Notes: Sleep problems were measured using the MOSS Sleep Problems Index II subscale and sleep disturbance using the MOSS sleep disturbance subscale. Sometimes users were defined as those in the middle three categories (<1/week to 3–4 times/week). Wilcoxon rank sum tests were used for statistical comparisons and *P*-values <0.004 were considered significant due to Bonferroni adjustment for multiple tests. [a]Score is statistically significantly different compared to both sometimes users and every day users (all $P < 0.0001$). [b]Score is statistically significantly different compared to every day users ($P = 0.002$). [c]Score is statistically significantly different compared to sometimes ($P = 0.002$) and every day users ($P < 0.0001$).

dropped from the final model due to statistical insignificance. Individual R^2 contributions indicate that depression explains the majority of variance in sleep problems (33%), with other variables explaining significantly less variance. Pain, age, and leg cramps explain approximately 3% additional variance each with the remaining variables, including fatigue, explaining less than 1%. The final model was highly significant with a final model adjusted R^2 of 0.45.

Discussion

Until recently, little attention has been given to the question of sleep adequacy in MS, and the majority of sleep research in MS has focused on the relationship between fatigue and sleep.[7–12] Sleep has been identified as a significant problem for this population with approximately 50% of persons reporting problems[3,4] and research is needed to examine factors that can mitigate the impact of poor sleep on quality of life of people living with MS. This paper is a first step in this process. We have sought to identify the extent to which patients with MS manage their sleep through medications, and to identify potentially modifiable symptoms or factors which are associated with sleep difficulties.

In general, little is known about medication use for sleep in either the general population or within specific disease groups. However, two studies on sleep aid use in the general US population found that 5.3% of people aged 18–45 years[34] and 8% of people aged 18–65 years[35] used prescription medications at least once for sleep over the past year and 10% of individuals in both studies used over the counter medications.[34,35] In another study of adults aged over 45 years with osteoarthritis and sleep difficulties, 17% used prescription and 12% over the counter medications for sleep.[36] In this study 36% of individuals reported using prescription or over the counter sleep medications at least 1–2 times a week. This suggests

Table 3 Multiple linear regression results examining statistically significant factors associated with sleep problems in MS (N = 465)

Model predictor	Coefficient	Final model adjusted R^2				0.45
		Standard error	Standardized beta coefficient	*t*-score	*P*-value	R^2 contribution
Depression	1.47	0.23	0.33	6.51	<0.001	0.329
Leg cramps	3.44	0.80	0.18	4.30	<0.001	0.039
Age	–0.28	0.07	–0.15	–3.80	<0.001	0.030
Pain	0.96	0.27	0.16	3.63	<0.001	0.029
Female sex	4.44	1.69	0.08	2.63	0.009	0.005
Fatigue	0.15	0.06	0.13	2.41	0.016	0.008
Duration of MS	–0.19	0.09	–0.1	–2.29	0.023	0.005
Nocturia	3.61	1.61	0.09	2.24	0.025	0.004

Notes: The sleep problems outcome was defined using the Sleep Problems Index II subscale of the MOSS Scale.
Abbreviations: MOSS, Medical Outcomes Study Sleep; MS, multiple sclerosis.

that a considerably larger percentage of individuals reporting sleep difficulties with MS are using pharmaceutical sleep aids than the level reported in the general population, though this level is similar to use in the osteoarthritis population with sleep problems. The results indicate that patients with MS, and possibly their health care providers, may be more aware of the need for therapeutic sleep, or, alternatively, that patients with MS have greater problems with sleep. More research is needed to better understand why people with MS who experience sleep problems use or do not use medications and to understand what nonpharmacological strategies people may be employing.

In order to identify factors in addition to fatigue that may play a role in sleep disorders in the MS population, we completed a multiple linear regression to explore the role of multiple factors, identified through both the MS and general sleep literature, on sleep problems in this population. Our results suggest that there are a number of factors (depression, pain, leg cramps, fatigue, and nocturia) that may contribute to sleep problems in MS that are potentially modifiable, and when treated could improve sleep in MS patients. In addition, our results indicate that of these, depression is most highly associated with sleep difficulties. This suggests that, as is the case in the general population, treatment of sleep problems should be considered in concert with treatment for depression, and that individuals with MS and depression should be assessed for sleep disorders by their treating physician. This finding is also significant in that the substantial majority of the research on sleep in MS has focused on the relationship between fatigue and sleep. However, our results suggest that fatigue may play less of a role in sleep than previously thought, and that other factors, such as depression, leg cramps, and pain management, should be addressed by physicians and patients in discussions related to sleep difficulties. Surprisingly, restless leg symptoms were not associated with sleep problems, even though about 50% of persons reported restless leg symptoms. However, leg cramps may explain much of the same variance in sleep problems as restless legs because a univariate regression of restless legs was statistically significant. Thus, both leg cramps and restless legs should be discussed by patients and physicians when addressing factors that may significantly impact the patient's sleep.

Identifying factors associated with sleep in MS is of key importance as sleep disorders are known to have an impact on mental health, overall physical health, quality of life, and have been related to lower work productivity and higher utilization of health care services.[5,6] Additionally, sleep may be even more important for people with MS as recent research suggests that sleep is needed for the optimization of brain function following plasticity. Some sleep research suggests that slow wave sleep is necessary to downscale the synaptic strength of new brain circuits resulting from the plastic process to a baseline level that is energetically sustainable, and is also beneficial for learning and memory.[37] This plasticity is necessary for MS patients to maintain both physical and mental function as their disease progresses and occurs as a compensatory mechanism as neural loss progresses in the central nervous system in persons with MS.[38] Thus, this research suggests that sleep may play a significant role in maintaining function in MS and may have impacts beyond those seen in other chronically ill or disability populations because of the critical role plasticity plays for maintaining function. However, more research is needed to explore this hypothesis.

Because this study was completed using cross-sectional data, the directional effects of the significant predictors on sleep cannot be determined. For example, we cannot say that depression causes sleep problems, only that they are significantly associated and that they occur together in this study population. Future research (eg, clinical trials, longitudinal studies) is needed to explore the causal nature of the relationships identified here and to examine what treatments targeted to the specific factors associated with sleep difficulties would have the highest impact on reducing sleep problems in persons with MS. In addition, this study used self-reported data as the only source of information and did not include physician assessments or medical records. Therefore, we are only able to examine the relationships between self-reported symptoms rather than actual diagnostic outcomes such as insomnia disorder, sleep apnea, or narcolepsy with objective assessment by tools such as polysomnography. Thus, our conclusions can only generally inform decisions about treatment of these specific disorders and future research is needed to determine which factors are significantly associated with each type of sleep disorder. The sleep problems index outcome used in this study is generally though to most closely measure the construct of insomnia, though includes other items related to sleep disordered breathing and narcolepsy. Because fatigue and depression have been found to commonly co-exist in individuals in this population and may be causally related, we also investigated the potential for a fatigue–depression interaction effect in our model. Though this interaction was not statistically significant in our final model, this may be due to the fact that power to detect interaction effects is lower than power to detect main effects. Future studies related to sleep in MS should continue to consider the potential interaction of fatigue and

depression. Lastly, because this study was completed using data collected at one time during a longitudinal study, the representativeness of the study population has some bias. For example, though dropout was minimal over the course of the four surveys, there was some attrition and individuals who dropped out of the study tended to have more depression and pain than those who remained in the study. Thus, this sample is likely to be less depressed and have less pain than the general population of persons with MS.

To the best of our knowledge, this is the first paper to look at the problem of inadequate sleep in the MS population and medication use related to sleep. In our study we have identified a number of factors associated with poor sleep, and challenged the popular conception that fatigue is the most important factor related to poor sleep in this population. Considering that persons with MS have a progressive neurological condition affecting their central nervous system, and that neural loss and brain atrophy appear to be, to some extent, independent of conventional and available disease modifying treatments, it is vital in the management of this disease that all therapeutic measures possible be addressed to optimize brain function and plasticity. In addition, there is little evidence in the literature with respect to the efficacy of over the counter or prescription sleep aids for people with MS and there may be consequences in terms of suppression of slow-wave sleep for various pharmacological sleep aids.[39] Given that tricyclic antidepressants can be used to improve sleep and treat depression, and the significant finding here with respect to the relationship between sleep problems and depression, further research on the use of TCAs and other depression treatments in MS may be warranted. In addition to pharmacological approaches, there is also emerging evidence of the efficacy of self management[40] and cognitive behavioral therapy[41,42] to enhance sleep, and research into the application of these techniques to people with MS seems desirable due to the potential lack of efficacy and side effects[43] of sleep pharmaceutics and their potential interruption of slow wave sleep cycles.

Acknowledgments

The contents of this manuscript were developed under grants from the Department of Education, NIDRR grant numbers H133B031129 and H133B080025, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Health (Grant 5U01AR052171). However, these contents do not necessarily represent the policy of the Department of Education, and you should not assume endorsement by the Federal Government. The authors would also like to thank Laura Gibbons, PhD, for her assistance with data analysis, and Rana Salem, MA, for her role in data management and cleaning. The authors report no conflicts of interest in this work.

References

1. National Multiple Sclerosis Society. Who gets MS? 2010. Available from: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/who-gets-ms/index.aspx. Accessed March 9, 2010.
2. Crayton HJ, Rossman HS. Managing the symptoms of multiple sclerosis: a multimodal approach. *Clin Ther*. 2006;28(4):445–460.
3. Bamer AM, Johnson KL, Amtmann D, Kraft GH. Prevalence of sleep problems in individuals with multiple sclerosis. *Mult Scler*. 2008;14(8):1127–1130.
4. Tachibana N, Howard RS, Hirsch NP, Miller DH, Moseley IF, Fish D. Sleep problems in multiple sclerosis. *Eur Neurol*. 1994;34(6):320–323.
5. Manocchia M, Keller S, Ware JE. Sleep problems, health-related quality of life, work functioning and health care utilization among the chronically ill. *Qual Life Res*. 2001;10(4):331–345.
6. Merlino G, Fratticci L, Lenchig C, et al. Prevalence of 'poor sleep' among patients with multiple sclerosis: an independent predictor of mental and physical status. *Sleep Med*. 2009;10(1):26–34.
7. Attarian HP, Brown KM, Duntley SP, Carter JD, Cross AH. The relationship of sleep disturbances and fatigue in multiple sclerosis. *Arch Neurol*. 2004;61(4):525–528.
8. Hossain JL, Ahmad P, Reinish LW, Kayumov L, Hossain NK, Shapiro CM. Subjective fatigue and subjective sleepiness: two independent consequences of sleep disorders? *J Sleep Res*. 2005;14(3):245–253.
9. Kaynak H, Altintas A, Kaynak D, et al. Fatigue and sleep disturbance in multiple sclerosis. *Eur J Neurol*. 2006;13(12):1333–1339.
10. Merkelbach S, Schulz H. What have fatigue and sleepiness in common? *J Sleep Res*. 2006;15(1):105–106.
11. Stanton BR, Barnes F, Silber E. Sleep and fatigue in multiple sclerosis. *Mult Scler*. 2006;12(4):481–486.
12. Strober LB, Arnett PA. An examination of four models predicting fatigue in multiple sclerosis. *Arch Clin Neuropsychol*. 2005;20(5):631–646.
13. Benca RM, Peterson MJ. Insomnia and depression. *Sleep Med*. 2008;9 Suppl 1:S3–S9.
14. Pallesen S, Nordhus IH, Omvik S, Sivertsen B, Tell GS, Bjorvatn B. Prevalence and risk factors of subjective sleepiness in the general adult population. *Sleep*. 2007;30(5):619–624.
15. Fleming WE, Pollak CP. Sleep disorders in multiple sclerosis. *Semin Neurol*. 2005;25(1):64–68.
16. Johnson KL, Bamer AM, Fraser RF. Disease and demographic characteristics associated with unemployment among working age adults with multiple sclerosis. *International Journal of MS Care*. 2009;11(3):137–143.
17. Johnson KL, Bamer AM, Yorkston KM, Amtmann D. Use of cognitive aids and other assistive technology by individuals with multiple sclerosis. *Disabil Rehabil Assist Technol*. 2009;4(1):1–8.
18. Hays R, Stewart A. Sleep measures. In: Stewart A, Ware J, editor. *Measuring Functioning and Well-being: The Medical Outcomes Study Approach*. Durham, NC: Duke University Press; 1992.
19. Spritzer KL, Hays RD. *MOS Sleep Scale: A Manual for Use and Scoring*, Version 1.0. Los Angeles, CA; RAND; 2003.
20. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA*. 1999;282(18):1737–1744.
21. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–613.
22. Cannon DS, Tiffany ST, Coon H, Scholand MB, McMahon WM, Leppert MF. The PHQ-9 as a brief assessment of lifetime major depression. *Psychol Assess*. 2007;19(2):247–251.
23. Lamers F, Jonkers CC, Bosma H, Penninx BW, Knottnerus JA, van Eijk JT. Summed score of the Patient Health Questionnaire-9 was a reliable and valid method for depression screening in chronically ill elderly patients. *J Clin Epidemiol*. 2008;61(7):679–687.

24. Martin A, Rief W, Klaiberg A, Braehler E. Validity of the Brief Patient Health Questionnaire Mood Scale (PHQ-9) in the general population. *Gen Hosp Psychiatry*. 2006;28(1):71–77.
25. Fann JR, Bombardier CH, Dikmen S, et al. Validity of the Patient Health Questionnaire-9 in assessing depression following traumatic brain injury. *J Head Trauma Rehabil*. 2005;20(6):501–511.
26. Lowe B, Spitzer RL, Grafe K, et al. Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses. *J Affect Disord*. 2004;78(2):131–140.
27. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci*. 1994; 21(1):9–14.
28. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis*. 1994;18 Suppl 1:S79–S83.
29. Tellez N, Rio J, Tintore M, Nos C, Galan I, Montalban X. Does the Modified Fatigue Impact Scale offer a more comprehensive assessment of fatigue in MS? *Mult Scler*. 2005;11(2):198–202.
30. Bowen J, Gibbons L, Gianas A, Kraft GH. Self-administered expanded disability status Scale with functional system scores correlates well with a physician-administered test. *Mult Scler*. 2001;7(3):201–206.
31. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain*. 1992;50(2):133–149.
32. Jensen M, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R, editors. *Handbook of Pain Assessment (2nd ed)*. New York, NY: Guilford; 2000:135–151.
33. Ferri R, Lanuzza B, Cosentino FI, et al. A single question for the rapid screening of restless legs syndrome in the neurological clinical practice. *Eur J Neurol*. 2007;14(9):1016–1021.
34. Johnson EO, Roehrs T, Roth T, Breslau N. Epidemiology of alcohol and medication as aids to sleep in early adulthood. *Sleep*. 1998;21(2): 178–186.
35. Roehrs T, Hollebeek E, Drake C, Roth T. Substance use for insomnia in metropolitan Detroit. *J Psychosom Res*. 2002;53(1):571–576.
36. Allen KD, Renner JB, DeVellis B, Helmick CG, Jordan JM. Racial differences in sleep medication use: a cross-sectional study of the Johnston County Osteoarthritis Project. *Ann Pharmacother*. 2008; 42(9):1239–1246.
37. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev*. 2006;10(1):49–62.
38. Burke M, Mahurin R, Bowen JD. Differential brain compensation for cognitive versus motor processes in early relapsing-remitting multiple sclerosis subjects without clinical impairment. *Mult Scler*. 2006;12: S43–S44.
39. Doerr JP, Hirscher V, Riemann D, Voderholzer U. [Disturbances of slow-wave sleep and psychiatric disorders.]. *Nervenarzt*. 2010;81(3): 347–354.
40. Stepanski EJ, Wyatt JK. Use of sleep hygiene in the treatment of insomnia. *Sleep Med Rev*. 2003;7(3):215–225.
41. Dolan DC, Taylor DJ, Bramoweth AD, Rosenthal LD. Cognitive-behavioral therapy of insomnia: A clinical case series study of patients with co-morbid disorders and using hypnotic medications. *Behav Res Ther*. 2010;48(4):321–327.
42. Becker PM, Sattar M. Treatment of sleep dysfunction and psychiatric disorders. *Curr Treat Options Neurol*. 2009;11(5):349–357.
43. Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ*. 2000;162(2): 225–233.