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An examination of four models predicting fatigue in multiple sclerosis

Lauren B. Strober, Peter A. Arnett *

Psychology Department, Penn State University, 522 Bruce V. Moore Bldg., College of the Liberal Arts, University Park, PA 16802-3105, USA

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Abstract

Fatigue is a common symptom of multiple sclerosis (MS) that is purported to cause significant distress and have detrimental effects on daily functioning, social and occupational obligations, and overall well-being. The prevalence of fatigue in MS is high, with 53–87% of patients reporting significant problems with fatigue across different studies reported in the literature. The cause of fatigue in MS is still poorly understood. Some researchers have suggested that fatigue is a direct consequence of the MS disease process, but several studies have failed to find a relationship between disease severity and MS fatigue. A number of investigations have reported that depression and sleep are significantly related to fatigue in MS, as well as to one another. The purpose of the present investigation was to examine the relationships among disease severity, depression, and sleep disturbance in MS, and their possible role in predicting fatigue. Four models were proposed to explore these relationships. The best fitting model showed that all three were significant independent contributors to fatigue in MS, accounting for 43% of the variance, with sleep disturbance reigning as the largest contributor. Furthermore, although disease severity predicted fatigue in our sample, both depression and sleep disturbance emerged as stronger predictors. These findings suggest that, beyond core physical/neurological MS symptomatology, there are other factors that contribute to fatigue in MS, namely, depression and sleep disturbance.

Keywords: Multiple sclerosis; Depression; Sleep disturbance; Disability; Fatigue

* Corresponding author. Tel.: +1 814 863 1733; fax: +1 814 863 7002.
E-mail address: paa6@psu.edu (P.A. Arnett).

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1. Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system with a varying course and uncertain prognosis. Beyond primary symptoms—neurological effects thought to be a direct effect of changes in the central nervous system from the disease—individuals with MS suffer from many secondary consequences of the disease, such as fatigue, depression, and sleep disturbance. Secondary symptoms are thought to ensue as a consequence of primary symptoms. For example, a patient may become depressed because she/he can no longer engage in a hobby, such as crocheting, because the direct (i.e., primary) neurological effects of the disease have caused severe fine motor problems. Given the high prevalence of these purported secondary factors in MS and their uncertain etiology, there remains debate as to whether or not they may be a direct consequence of the disease (i.e., primary), as well. For instance, some patients may develop depression because of a direct result of demyelinating plaques disrupting those networks in the brain responsible for emotional regulation.

Many individuals with MS report fatigue as one of their most disabling symptoms. Additionally, depression is common in MS (Minden & Schiffer, 1990), with some studies suggesting that there is a 50% lifetime risk of major depression (Sadovnik et al., 1996). Lastly, sleep disturbance, though it has received relatively little attention in the literature, has been speculated to cause significant problems in functioning for those suffering from MS (e.g., Clark et al., 1992). The goal of the present investigation was to examine the inter-relatedness of sleep, depression, and fatigue in MS, in addition to level of disability. Specifically we evaluated four models involving these factors, all focusing on predicting fatigue. What follows is a brief overview of fatigue, depression, and sleep disturbance in MS, followed by an examination of studies that have evaluated some interaction of these variables and level of disability.

1.1. Fatigue

Fatigue is a common and disabling symptom of MS. Some MS investigators have defined MS fatigue as a feeling of physical tiredness and lack of energy, distinct from sadness or weakness (Krupp, Alvarez, LaRocca, & Scheinberg, 1988). Others have described it as extreme tiredness and the need to rest (Freal, Craft, & Coryell, 1984). Subjectively, patients may complain of feeling “washed out,” “exhausted,” or “lacking in energy” (Smith, Samkoff, & Scheinberg, 1993). There are several other features of fatigue that are characteristic of MS patients. MS patients typically report that their fatigue prevents sustained physical functioning, comes on easily, interferes with their physical functioning and meeting responsibilities, causes frequent problems, and is worsened by heat (Krupp et al., 1988). Fatigue has also been shown to be a central cause of MS patients being unable to maintain full-time employment (Jongbloed, 1998). Besides these overt limitations, fatigue in MS has been shown to be associated with lowered positive affect, psychological distress, and a sense of loss of control (Krupp, 2003). Further, when taking a more qualitative, phenomenological approach to examining fatigue in MS, Flenser, Ek, and Soderhamn (2003) provided a thorough and eloquent description of patients’ experience of fatigue which included a lowered sense of self-worth, feelings of shame, sorrow, and anger related to their perceptions of their fatigue. Despite its signature in MS and its pervasive nature, the cause of fatigue in MS is still poorly understood. Although some investigators have asserted that fatigue is a direct consequence of the disease process itself (e.g., Colosimo et al., 1995; Iriarte, Carreno, & de Castro, 1996; Kroencke, Lynch, & Denney, 2000), some view fatigue in MS as a result of other secondary complaints, in particular, depression and sleep disturbance (e.g., Bakshi, Czarnecki, et al., 2000; Bakshi, Shaikh, et al., 2000; Schwartz, Coulthard-Morris, & Zeng, 1996; Tachibana et al., 1994).

1.2. Depression

The observation that depression is often seen in MS can be traced back as far as Charcot's (1887) descriptions of the disease. Individuals with MS have often been initially misdiagnosed as having primary affective or other psychiatric disorders, despite obvious neurological symptomatology (Shnek, Foley, LaRocca, Smith, & Halper, 1995). Possible biological causes of depression in MS have been investigated. Depression in MS has been shown to be associated with temporal lobe lesions (Berg et al., 2000; Honer, Hurwitz, Li, Palmer, & Paty; Ron & Logsdail, 1989; Zorcon et al., 2002), as well as those in the periventricular region and the frontal lobes (Reischies, Baum, Brau, Hedde, & Schwindt, 1988). Bakshi, Czarnecki, et al. (2000) and Bakshi, Shaikh, et al. (2000) have also implicated the frontal and parietal lobes as relevant to the presentation of depression in MS. Furthermore, depression has been found to be more severe in those with lesions of cerebral involvement versus spinal cord involvement (Rabins et al., 1986; Schiffer & Babigian, 1984). Contrary to these findings, other investigators have asserted that depression in MS is more closely related to psychosocial factors (Feinstein, 1995; Huber, Rammohan, Bornstein, & Christy, 1993; Shnek et al., 1995). Other factors that have been shown to be relevant and possible predictors of depression in MS include coping styles (Boyle, Clark, Klonoff, Paty, & Oger, 1991), the interaction between cognitive dysfunction and coping styles (Arnett, Higginson, Voss, & Randolph, 2002), and perceived level of social stress and support (Feinstein, Kartsounis, Miller, Youl, & Ron, 1992; Ron & Logsdail, 1989). With such diverse contributors identified by different studies, it has been suggested that depression in MS may be best thought of as due to an interaction of biological, psychological and social factors (Minden & Schiffer, 1990, 1991).

1.3. Sleep disturbance

Though sleep difficulties have been relatively less studied in the MS literature, their possible effects on those with MS have been suggested and theorized to be an important area for future research (Devins et al., 1993; Ferini-Strambi et al., 1994; Leo, Rao, & Bernardin, 1991; Saunders, Whitman, & Schaumann, 1991; Taphoorn et al., 1993). The limited research available suggests that MS patients are three times more likely to experience sleep difficulties than healthy controls (Clark et al., 1992). Recent estimations have also shown that MS patients are twice as likely to have reduced sleep quality (Lobentanz et al., 2004). A few investigations have explored the neurological causes of sleep disturbance in MS (Clark et al., 1992; Ferini-Strambi et al., 1994). For instance, Ferini-Strambi et al. (1994) found that sleep disturbance in MS was related to periodic leg movement (PLM). Furthermore, those who complained of

PLM also had a significantly higher lesion load in the cerebellum. MS patients have also been shown to have significantly reduced sleep efficiency and experience more awakenings during sleep compared to healthy controls. Clark et al. (1992) reported that lesions in the right and left frontal supraventricular white matter, and the deep white matter of the right insula were related to the presence of sleep complaints. Though evidence suggests that sleep disturbance may have some direct neurological basis in MS, other researchers have suggested that it may be the secondary effect of other symptoms such as bladder incontinence, muscle stiffness and spasms, and possibly an underlying depression (Saunders et al., 1991). A review of the literature shows that MS patients display more nocturnal awakenings due to such causes as opposed to direct neurological factors such as nocturnal respiratory involvement or circadian rhythm abnormalities (Leo et al., 1991; Saunders et al., 1991; Tachibana et al., 1994; Taphoorn et al., 1993). Our research has also shown that MS patients who complain of sleep disturbance tend to attribute it to such physical factors. In a recent study, we found that 62% of our sample complained of some sort of difficulty with sleep, with more than half of these patients endorsing physical symptoms such as bladder incontinence, muscle stiffness and leg spasms as the primary reason for sleep difficulties (Strober, Arnett, Polen, & Bruce, 2002). Finally, more recent research found that MS patients with fatigue were more likely to experience disrupted sleep than non-fatigued MS patients and healthy controls (Attarian, Brown, Duntley, Carter, & Cross, 2004).

1.4. Associations among fatigue, disease severity, depression, and sleep disturbance

As mentioned earlier, the purpose of this investigation is to examine a model that will capture the interactions of fatigue, depression, and sleep disturbance in MS, and in particular, will help delineate possible pathways to fatigue in MS. Previous studies have found associations between these variables, however, few have included all three in their design to better understand their roles and interactions in MS. Additionally, no study examining all three factors has considered that measures of depression applied to MS are confounded with both sleep and fatigue items. To date, investigations that have examined fatigue and depression or sleep and depression in MS have been limited due to the item overlap of sleep and fatigue items included in depression measures (cf. Voss et al., 2002). Hence, another contribution of the present study is not only to understand these relationships better, but to employ better measures of the three domains and eliminate the confound of item overlap between the measures assessing them.

Disability or disease activity has been found to be associated with fatigue in some studies (Colosimo et al., 1995; Iriarte et al., 1996; Kroencke et al., 2000), but not others (Bakshi et al., 1999; Bakshi, Czarnecki, et al., 2000; Bakshi, Shaikh, et al., 2000; Codella et al., 2002; Filippi et al., 2002; Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Fisk, Ritvo, et al., 1994; Freal et al., 1984; Krupp et al., 1988; Van der Werf et al., 1998; Vercoulen et al., 1996). Some investigators have sought to explore other factors that might more consistently predict fatigue, such as depression. However, the results of these studies have been mixed as well, with some finding a significant association between fatigue and depression (Bakshi, Czarnecki, et al., 2000; Bakshi, Shaikh, et al., 2000; Fisk, Pontefract, et al., 1994; Fisk, Ritvo, et al., 1994; Ford et al., 1998; Schwartz et al., 1996), and others failing to report such an association (Iriarte et al., 1996; Krupp et al., 1988; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989; Vercoulen et al., 1996).

Depression has also been found to be related to disability by some studies (e.g., McIvor, Riklan, & Reznikoff, 1984), while others have failed to show such a relationship (Huber et al., 1993; Joffe, Lippert, Gray, Sawa, & Horwath, 1987; Minden, Orav, & Reich, 1987; Minden & Schiffer, 1990; Rabins et al., 1986). The association of sleep disturbance with fatigue, depression, and disease severity has received less attention, but sleep disturbance has been found to be significantly related to depression (Clark et al., 1992; Devins et al., 1993; Leo et al., 1991; Saunders et al., 1991) as well as fatigue (Attarian et al., 2004; Krupp, Jandorf, Coyle, & Mendelson, 1993). Finally, Tachibana et al. (1994) found no correlation between sleep disturbance and disease severity.

Though there is some evidence that fatigue, depression, and sleep dysfunction may be related in MS, the existing literature lacks any research that examines these three factors and their possible joint or interactive effects. In the present study, we examined four models designed to predict fatigue that included all of these variables. Although many other causal pathways involving these variables are possible, we focused on fatigue as the outcome variable because patients describe fatigue as their most debilitating symptom more often than any other symptom. Providing a model that can accurately predict such a symptom is valuable because it may suggest avenues for treatment.

Prior research in other disorders similar to MS (i.e., systemic lupus erythematosus, chronic fatigue syndrome (CFS) and rheumatoid arthritis) has explored such models predicting fatigue (Huyser et al., 1998; McKinley, Ouellette, & Winkel, 1995; Morriss, Wearden, & Battersby, 1997). For instance, in Lupus, patients' disease activity has little value in predicting fatigue, but with sleep disturbance and depression as mediators, disease activity predicts a substantial amount of fatigue (McKinley et al.). Specifically, McKinley et al. found that disease activity, depression, and sleep difficulties predicted 48% of the variance in fatigue in lupus, with depression and sleep shown to have a mediating and reciprocal interaction. Similarly, Huyser et al. (1998) showed that, in rheumatiod arthritis, the best predictors of fatigue included psychosocial variables whereas disease activity was not one of the strongest predictors. Lastly, Morriss et al. (1997) found that 87% of CFS patients and 100% of depressed controls in their sample met criteria for a sleep disorder, but the prevalence of daytime tiredness and naps was significantly higher in the CFS patients. Additionally, sleep complaints preceded fatigue in only 20% of the CFS patients. However, sleep complaints worsened as the underlying condition, depression in the depressed sample, and chronic fatigue in the CFS sample, worsened. These studies provide further evidence that sleep disturbance and depression are both related to fatigue and that they would be fruitful to consider in other disorders (like MS) where depression, fatigue, and sleep problems are common.

The four competing models to be examined are outlined in Fig. 1. These four models have been formulated based upon on the presence of certain relationships among these constructs in MS samples and from findings in other studies that attempt to predict fatigue in similar disorders.

In the first model, based mostly on the work of McKinley et al. (1995) and Huyser et al. (1998), disease severity is thought to have an effect on fatigue, but through the mediational influence of depression and sleep disturbance. In Model 2, consistent with the liter-

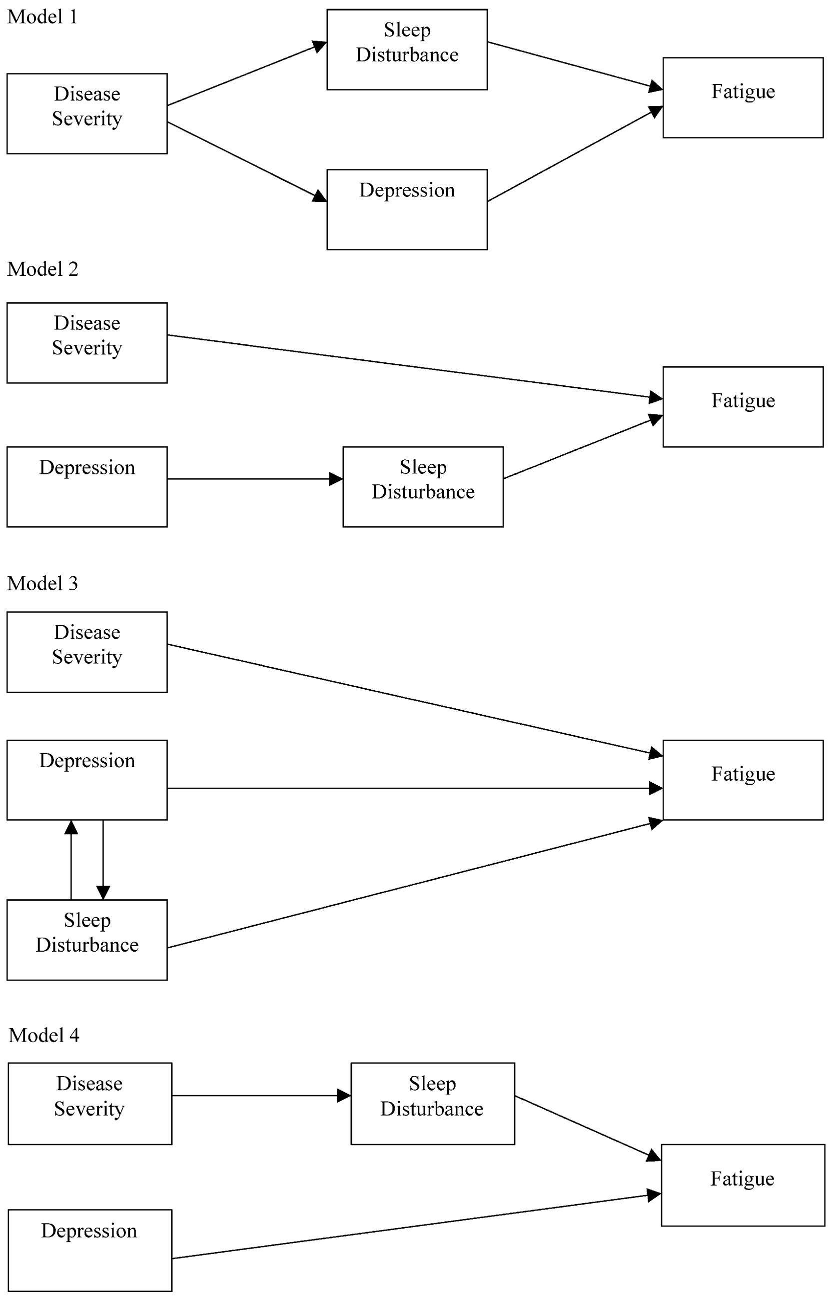

Fig. 1. Four models predicting fatigue with depression, sleep disturbance, and disease severity as predictors.

ature that fatigue may be a primary symptom of MS (Colosimo et al., 1995; Iriarte, Subira, & de Castro, 2000; Kroencke et al., 2000), disease severity is hypothesized to have a direct and independent effect on fatigue. Additionally, using standard conceptualizations of depression suggesting that sleep disturbance stems from depression (American Psychiatric

Association, 1994), this model examines whether depression results in fatigue via its effect on sleep disturbance. Model 3 is based upon the same premise as Model 2, but does not assign temporal precedence between depression and sleep. This model allows for independent effects from all three variables, keeping depression and sleep problems as correlated constructs. Lastly, Model 4 makes a cleaner distinction between MS symptomatology and depression in its design. This model states that if sleep is disturbed by MS symptomatology (e.g., bladder incontinence, muscle spasm, etc.) and subsequently leads to fatigue, then depression may be associated with fatigue, but remain independent of any MS symptomatology when predicting fatigue.

2. Method

2.1. Participants

Participants included 16 men and 61 women with MS (see Table 1 for other demographics). Participants were recruited from neurologists and a local chapter of the MS Society located in the Northwestern United States. Inclusion criteria included a diagnosis of definite or probable MS based on Poser et al. (1983). Of the 77 patients, 73 were diagnosed with clinically definite and four with clinically probable MS. Exclusion criteria include history of alcohol/drug abuse; history or current diagnosis of a neurological disorder besides MS; severe visual or motor impairment that may impede cognitive testing; evidence of a premorbid learning disability; and severe physical or neurological impairment that would make evaluation difficult. Participants also received a brief written neuropsychological report at the completion of testing in return for participation.

2.2. Procedures

Participants underwent an extensive neuropsychological evaluation as part of an ongoing study of cognitive and emotional changes in MS. A psychosocial interview was conducted on the same day and prior to testing. The battery consisted of cognitive tests interspersed with self-report measures of depression, anxiety, fatigue, and other psychosocial factors. Participants also completed self-report questionnaires the week prior to testing.

Table 1

Participant demographics	*M* (S.D.)	Range
Age	46.6 (8.2)	27–65
Years since diagnosis	7.3 (6.1)	0–34
EDSS	4.7 (1.5)	0–8
FIS Total	67.4 (37.6)	0–138
BDI Total	11.0 (8.0)	0–40

Note. EDSS: Expanded Disability Status Scale; FIS: Fatigue Impact Scale; BDI: Beck Depression Inventory.

2.3. Measures

2.3.1. Fatigue Impact Scale (FIS)

The FIS is a scale used to rate the extent to which fatigue has been a problem for the patient within the past month, including the day of testing (Fisk, Pontefract, et al., 1994; Fisk, Ritvo, et al., 1994). The rating system used is a Likert scale ranging from 0 to 4, with 0 being "No problem" and 4 being "Extreme problem." The scale consists of 40 items assessing such domains as interest in social situations to the amount of rest needed throughout the day. The FIS yields both a total score and three component scales (cognitive fatigue, physical fatigue, and social fatigue). Eleven items are conceptually similar to depressive symptoms, so these items were eliminated from the scale. The resulting total and component scores were used throughout the analyses. The internal and external reliability of this modified scale was assessed. A Cronbach's alpha of .97 was obtained for the 29 items, as compared to a .98 for the entire FIS scale. Additionally, both the full and modified FIS scales were correlated with another fatigue measure (Fatigue Severity Scale) which yielded a correlation of .68 ($P < .001$) and .71 ($P < .001$), respectively. Lastly, there was a strong correlation between the full FIS and modified FIS ($r = .99$, $P < .001$). These data suggest that the basic integrity of the FIS was not compromised due to the deletion of the eleven items.

2.3.2. Chicago Multiscale Depression Inventory

The Chicago Multiscale Depression Inventory was specifically designed to assess depression in MS and other medical groups (Nyenhuis et al., 1998). It consists of three subscales: Evaluative, Mood, and Vegetative. Each subscale contains 14 items and patients are asked to rate on a scale of 1–5 the extent to which each word/phrase describes them during the past week, including today with "1" being "Not at All" and "5" being "Extremely." For the purpose of this study, ratings on the Vegetative scale were removed due to confounds of sleep and fatigue included in the items on this scale. For our sample, depression was measured by a total score of only the combined Evaluative and Mood scales.

2.3.3. Sickness Impact Profile (SIP) Sleep & Rest Scale

The Sickness Impact Profile (SIP) consists of 14 subscales that are related to medical illness and the amount or lack of activities performed by those that are ill (Gilson et al., 1975). Patients are given statements and asked only to endorse those that describe them that day. In this study, the Sleep & Rest subscale was used to assess sleep disturbance. The statements that are included in this subscale range from sleep patterns to sleepiness throughout the day. Three items conceptually similar to fatigue were removed and the remaining items were used as a purer measure of sleep independent of fatigue.

2.3.4. Sleep composite

Though many measures include a sleep disturbance item, few measures have been designed to exclusively measure sleep disturbance by self-report. For the present study, a sleep composite was designed to include sleep items that were included on the Beck Depression Inventory (BDI; Beck & Steer, 1987), Chicago Multiscale Depression Inventory (MDI) and SIP Sleep & Rest Scale. *Z*-scores were calculated for each item based on the scores from the total sample, yielding a composite that included eight individual items relating to sleep disturbance. The Cronbach's alpha for this new scale was .76. This composite was the major index of sleep disturbance used in the analyses (see Appendix A).

2.3.5. Expanded Disability Status Scale (EDSS)

The EDSS is a scale that measures physical and neurological disability in MS (Kurtzke, 1983). The scale measures functional systems, including pyramidal, cerebellar, brain stem, and sensory. Ratings are made on a 0–10 scale, ranging from no physical disability/disturbance in functional systems (0) to extreme functional system disturbance (i.e., 9.5). Higher EDSS scores indicate greater disability. Ratings of the EDSS were used as the primary measure of disease severity in the present study.

3. Results

All statistical analyses were conducted using SPSS 10.1 computer software in conjunction with SPSS AMOS 4.0. Examination of the relationship between each of the independent variables and fatigue was established using Pearson correlation coefficients. Disease severity was related to fatigue, but not to depression or sleep disturbance. However, depression and sleep disturbance were related and fatigue was significantly correlated with all three constructs of the model—disease severity, depression, and sleep disturbance (see Table 2).

Multiple regression analyses were next conducted to examine the collective role that these variables play in predicting fatigue. A hierarchical regression entering the variables in the order of the magnitude of their zero-order correlations with fatigue showed that each predictor accounted for significant independent variance in fatigue (see Table 3). Sleep disturbance was the greatest predictor of fatigue, followed by depression, and lastly, disease severity. Taken together, these variables accounted for 43% of the variance in fatigue.

Finally, path analysis was employed to test the models depicted in Fig. 1 (see Table 4). To examine each model, fit indices were chosen that took the relatively small sample size into consideration. In particular, the chi-square to degrees of freedom ratio (CMIN/df) was chosen over the chi-square. A ratio less than 2 suggests that the model is considered to be acceptable (Ullman, 1996). Additionally, the Comparative Fit Index (CFI), a revised Normed Fit Index

Table 2
Pearson correlation coefficients of disease severity, depression, sleep disturbance, and fatigue

	EDSS	MDIME	Sleep	mFIS
EDSS	–	.09	.06	.34**
MDIME	–	–	.37**	.47**
Sleep	–	–	–	.49**

Note. EDSS: Expanded Disability Status Scale; MDMIE: Chicago Multiscale Depression Inventory Mood and Evaluative scales; sleep: sleep composite; mFIS: Modified Fatigue Impact Scale.

** $P < .01$.

Table 3
Hierarchical regression analyses of sleep disturbance, depression, and disease severity predicting fatigue

Variable entered	*B*	S.E. (*B*)	*β*
Step 1			
Sleep disturbance	2.80	0.57	.49***
Step 2			
Sleep disturbance	2.10	0.57	.37***
Depression	0.60	0.18	.34**
Step 3			
Sleep disturbance	2.06	0.54	.36***
Depression	0.56	0.17	.31**
Disease severity	5.63	1.69	.30**

Note. R^2 = .24 for Step 1; ΔR^2 = .10 for Step 2; ΔR^2 = .09 for Step 3 (*Ps* < .01).
** $P < .01$.
*** $P < .001$.

(NFI) that adjusts for sample size, and the Incremental Fit Index (IFI), which addresses the issues of parsimony and sample size while taking the degrees of freedom into account, were used. Both of these indices range from 0 to 1.0, with a value greater than .90 representing good fit (Byrne, 2001).

Model 1 posited that disease severity played a role in both depression and sleep disturbance in MS, and that depression and sleep disturbance mediated the relationship between disease severity and fatigue. This model was a poor fit to the data. Model 2 held that disease severity was independent from depression and sleep disturbance but that depression was an a priori cause of sleep disturbance that, in turn, led to fatigue. This model was also a poor fit with the data. Model 3 was the best fitting of the competing models. This model depicted independent effects from all three variables, and kept depression and sleep problems as correlated constructs without assigning temporal precedence to either and also kept disease severity unrelated to both depression and sleep disturbance. Lastly, Model 4 was tested. This model attempted to make a cleaner distinction between MS symptomatology and depression by implying that sleep disturbance is caused exclusively by MS symptomatology and that depression may be independently associated with fatigue. Model fit estimates showed that this model was also a poor fit to the data.

Table 4
Fit indices of four competing models

Model	CMIN/d.f.	CFI	IFI	Model fit
Model 1	8.85	0.64	0.70	Poor fit
Model 2	3.05	0.72	0.75	Poor fit
Model 3	0.33	1.00	1.00	Best fit
Model 4	5.99	0.31	0.39	Poor fit

Note. CMIN/d.f.: chi-square to degrees of freedom ratio; CFI: Comparative Fit Index; IFI: Incremental Fit Index.

4. Discussion

The purpose of this investigation was to examine the inter-relationships among depression, disease severity, sleep disturbance, and fatigue in MS. In particular, four different models designed to explain fatigue in MS were evaluated. The central theme of all four models was that disease severity, depression, and sleep disturbance all contributed to fatigue in MS. Each model was derived based on evidence in the literature that may explain the inter-relationships among these constructs. The best fitting model was Model 3. Model 3 indicated that disease severity, depression, and sleep disturbance all independently predicted fatigue in MS. Furthermore, this model showed that disease severity was independent of depression and sleep disturbance, but that the latter two were correlated. Along these lines, Model 2 also allowed for disease severity to have its own unique contribution to fatigue in MS, and allowed for an association between depression and sleep disturbance that was separate from disease severity. However, it proposed that depression in MS leads to sleep disturbance, which in turn, leads to fatigue, above and beyond the fatigue already experienced due to simply having MS. Based upon this models' poor fit to the data, it supports the idea that a temporal association between depression and sleep disturbance does not appear warranted. Model 4 was based on research indicating that many people who complain of sleep disturbance attribute it to physical MS symptoms, as opposed to depressive symptomatology. This model is consistent with some of our findings that suggest that sleep complaints in MS are more often attributed to physical complaints as opposed to factors thought to be associated with depression, i.e., rumination. However, in our present study, this model was the poorest fit.

Lastly, Model 1, which was adopted based on research in other disorders similar to MS, indicated that increased disease activity or disability led one to experience both depression and sleep disturbance, and that these two in turn lead to increased fatigue. This model suggested that, in a large part, disease severity alone does not lead to fatigue, but will lead to mediating factors that cause fatigue. This model demonstrated a poor fit as well. It is presumed that one reason for this is that disease severity was found to be unrelated to both depression and sleep disturbance, despite their high association with fatigue. This suggested, as was confirmed in a competing model, that depression and sleep disturbance contribute to fatigue in MS independently of disease severity. This is an important finding because many have speculated that the fatigue experienced in MS is, in a large part, due to disease severity. The good fit of Model 3 suggests that depression and sleep disturbance lead to fatigue independent of MS disease severity, at least as measured by the EDSS. Overall, these model tests provide evidence that disease severity makes a unique contribution to fatigue in MS. Additionally, these data show that depression and sleep disturbance, together, independent of disease severity, contribute to fatigue as well.

Although no prior studies have examined all of the constructs assessed in the current study simultaneously, many have explored the relationships among these constructs, yielding diverse results. As a basis for comparison with previous findings, brief overviews of the subsets of these relationships are explored. As stated earlier, some investigators have construed fatigue as being a primary, or direct consequence of MS. Consistent with this conceptualization, greater disability or disease severity significantly predicted fatigue in the present study. Depression was also shown to be related to fatigue in this sample, supporting the notion that other factors may play host to enduring fatigue in MS, above and beyond core disease symptomatology. Lastly, although sleep disturbance has received little attention in the MS literature, the current findings suggest that more consideration of it may be warranted in attempts to understand fatigue in MS. It is important to highlight that sleep disturbance was the best predictor of fatigue in the present study and was significantly related to depression, as previous studies suggest.

Another purpose of this study was to address the utility of using modified and unconfounded measures of depression and fatigue. Following the suggestions of some investigators (e.g., Mohr et al., 1997), this study was conducted using modified measures that eliminated the overlap items of depression, sleep, and fatigue in hopes that any relationships found would be more clearly interpretable because the measures were not confounded by item overlap. Despite eliminating overlapping items, a significant relationship between fatigue and both depression and sleep disturbance was still found in the present study. Our findings provide stronger support than prior work for the notion that both depression and sleep disturbance are truly related to fatigue in MS and that these relationships are not simply due to item overlap between the measures used.

There were limitations to the present research. Although the current investigation is one of few that has attempted to integrate sleep disturbance into the understanding of fatigue in MS, the measure of sleep disturbance used has limitations. In particular, the composite measure of sleep disturbance was derived from varying measures as opposed to one comprehensive measure. That said, our composite measure was shown to have acceptable levels of internal consistency reliability. A related limitation is that only self-report was used to assess sleep disturbance. The inclusion of others' reports, observational reports, in addition to physiological measures of sleep would provide a more comprehensive evaluation of sleep and related problems. Similarly, self-reports of fatigue were obtained in this investigation. Given the uncertain etiology and subjective nature of fatigue in MS (i.e., Schwid, Covington, Segal, & Goodman, 2002) and findings that self-report does not always correlate with objective measures of fatigue (Paul, Beatty, Schneider, Blanco, & Hames, 1998), there are limitations to using only self-report of fatigue in MS. Reliance on self-report measures of fatigue is not only a limitation to the current investigation, but a critical concern for research on fatigue in MS, in general.

A second limitation of the present study is that these data are not longitudinal, which means that no clear temporal inferences can be made concerning the role of these factors in predicting fatigue over time, an important consideration if these data are to be considered clinically. Again, given the diverse findings in the literature and the pervasive impact that fatigue has in MS, the importance of longitudinal studies investigating the factors that cause fatigue in MS cannot be underestimated. Finally, despite the EDSS being widely used to assess disease severity in prior research, more sensitive and broad-based measures of disability (i.e., Multiple Sclerosis Functional Composite) have been suggested more recently (Rudick et al., 1997) and should be considered for future studies.

Despite these limitations, the present study has important implications. For one, the use of measures that were modified to make "purer" distinctions among sleep disturbance, depression, and fatigue provide evidence that these factors are related and not just inflated due to item overlap. The present findings also imply that treatment of depression and sleep disturbance, as well as MS disability, may lessen the experience of fatigue in MS and improve the quality of life for those suffering. Again, the importance of longitudinal studies of MS samples is emphasized by the current findings, because showing a relationship is not enough to draw inferences on what temporally precedes fatigue in MS. Lastly, the most important implication of the present investigation is the finding that sleep disturbance was the most significant predictor of fatigue when compared to disease severity and depression, the more popular culprits for explaining fatigue in MS. This suggests that future research on fatigue in MS should consider exploring sleep disturbance in more detail, with the hope that this potentially treatable cause of fatigue may relieve this most debilitating symptom in these patients.

Appendix A. Sleep composite items and source

Item	Item content	Source
1	I am sleeping or dozing most of the time—day and night	SIP Sleep & Rest
2	I sit around half-asleep	SIP Sleep & Rest
	I sleep less at night, for example, wake up too early, don’t fall asleep for a long time, awaken frequently	SIP Sleep & Rest
4	I sleep or nap more during the day	SIP Sleep & Rest
5	Easily awakened	MDI item 4
6	Fitful sleep	MDI item 25
7	Trouble falling asleep	MDI item 31
8	Difficulty Sleeping	BDI item 16

Note. SIP: Sickness Impact Profile; MDI: Chicago Multiscale Depression Inventory; BDI: Beck Depression Inventory.

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