Disability and Health Journal 7 (2014) 466–471

Disability and Health Journal

www.disabilityandhealthjnl.com

Research Paper

# Factors associated with poor sleep quality in patients with multiple sclerosis differ by disease duration

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## Abstract

**Background:** Sleep disturbance is a common symptom of multiple sclerosis (MS) and knowledge about factors that contribute to poor sleep quality is scarce.

**Objective:** The aim was to explore the differences in the prevalence and determinants of poor sleep quality in a sample of patients with MS with disease duration ⩽5 years and >5 years.

**Methods:** We collected data from 152 consecutive patients with MS; 66 patients (78% women, averaged 37.35 ± 10.1 years) were in the group with disease duration ⩽5 years and 86 patients (73.3% women, averaged 42.10 ± 9.4 years) in the group with disease duration >5 years. Patients filled out the Pittsburgh Sleep Quality Index, the Hospital Anxiety and Depression Scale, the Multidimensional Fatigue Inventory, one item of the Incapacity Status Scale regarding bladder problems and one item of the Short Form-36 regarding pain. Multiple linear regression was used to analyze the relationship between the study variables.

**Results:** The prevalence of poor sleep is significantly higher in patients with longer disease duration (34.8 vs. 51.2%). Anxiety, reduced motivation and mental fatigue (all $p < 0.05$) were associated with poor sleep quality in patients with disease duration ⩽5 years, whereas pain ($p < 0.01$), depression and mental fatigue (both $p < 0.05$) were in patients with disease duration >5 years.

**Conclusion:** Sleep problems are present in patients with MS with both short and long disease duration, but these problems are associated with different factors. These should be recognized and managed in addition to the treatment of sleep disorders. 

*Keywords:* Multiple sclerosis; Quality of sleep; Disease duration; Anxiety; Pain

Sleep disturbances are common symptoms of multiple sclerosis (MS), and their prevalence ranges from 47 to 62%.[1–6] Patients with MS report reduced quality of night sleep more frequently compared with the healthy population,[1,3,7] and this association with poorer health-related quality of life is also known.[3,5] Merlino et al, in their analysis with 120 patients, found that poor sleep was an independent predictor of a patient's mental and physical quality of life.[5] While more is known about the high prevalence and impact of sleep disturbances on quality of life in patients with MS,[1–5] less is known about the factors that contribute to poor sleep quality.

Previous research has shown that poor sleep is associated with fatigue, mood disorders, pain, nocturia, sexual dysfunction and the use of medication[4,5,8,9]; however, these analyses used only descriptive statistical methods[4,8,9] or correlations.[5] Few studies have found several independent variables to be associated with a reduced quality of sleep.[6,7,10] A case control study by Bøe Lunde et al explored sociodemographic and clinical associations with poor sleep in a sample

Authors have no conflict of interest to declare.

This is an original submission and all authors contributed to its production.

This work was supported by the Slovak Research and Development Agency under contract no. APVV-20-038305 (20%) and APVV-0220-10 (60%). Furthermore, this work was partially supported by the Agency of the Slovak Ministry of the Education, Science, Research and Sport of the Slovak Republic for the Structural Funds of the EU under project no. ITMS: 26220120058 (20%).

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1936-6574/$ - see front matter 
http://dx.doi.org/10.1016/j.dhjo.2014.05.004

of 90 patients with MS and 108 sex- and age-matched healthy controls. The results indicated that poor sleep is independently associated with female gender, use of immunotherapy and the high psychological burden of MS.[7] Neau et al reported associations of sleep disorders with disability, depression, anxiety, pain, spasticity and bladder dysfunction in a univariate analysis, although in a multivariate analysis only depression, disability and pain remained associated with poor sleep.[6] Bamer et al, in their study with 473 patients, found that depression, leg cramps, younger age, pain, female gender, fatigue and nocturia were associated with reduced quality of sleep. Depression accounted for the majority of the variance in sleep problems. Except the variables mentioned above, this study also showed that shorter disease duration was associated with more severe sleep complaints.[10]

On the basis of previous studies we can expect different factors to be related to poor sleep quality in patients with shorter and longer disease duration. Patients in the early stage of disease have a lower Expanded Disability Status Scale (EDSS) score, and the symptoms of MS are not so severe in comparison with those having longer disease duration.[11] Therefore, we can rather expect psychological factors and mood disorders to contribute to poor sleep quality in these patients. Both depression and anxiety occur in patients with MS.[12,13] The prevalence of anxiety seems to be higher when compared with depression in an early stage of disease.[14] Janssens et al showed an increase in the occurrence of reported anxiety symptoms soon after the announcement of the diagnosis to patients with MS.[15] Patients with longer disease duration are more disabled, have greater problems with ambulation,[11] have a higher prevalence of pain[16] and more severe sphincter dysfunction[17] than patients with shorter disease duration. Based on this, we can expect that factors related to the disease itself could be associated with poor sleep quality in patients with longer disease duration.

To the best of our knowledge there is no study exploring the prevalence and factors associated with poor sleep quality separately by disease duration. Thus, the aim of our study was to explore the differences in prevalence and determinants of poor sleep quality in a sample of patients with MS with disease duration $\leqslant 5$ years and those with disease duration $> 5$ years.

## Methods

### *Sample and procedure*

The study comprised consecutive patients with MS from the eastern part of Slovakia. The patients were recruited between September, 2011 and May, 2013. Of the 241 patients with MS who were deemed eligible for the study, 182 patients initially agreed to participate (response rate of 76%). Patients with cognitive dysfunction determined by an MMSE score of $<24$ ($N = 1$) and those who initially agreed to participate but did not fill in the questionnaires ($N = 29$) were excluded. The final sample consisted of 152 patients.

The study was approved by the local Ethics Committee of the Faculty of Medicine, PJ Safarik University in Kosice, 2009. Each patient provided a signed informed consent form prior to the study.

The procedure started by sending an invitation letter, the questionnaires, a written informed consent form and a non-response sheet to the participants' home by postal mail. After two weeks, a trained interviewer called each patient in order to arrange a face-to-face interview, allowing clarification of the patient's responses and completion of missing answers in the questionnaires. A neurological examination was performed immediately after the interview; the same neurologist was used for all patients. Standardized neurological examination assessed seven functional systems: visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral.

### *Measures*

All questionnaires used in this study were translated from the original language. Next, a backwards translation was made to ensure that no meaning was lost in translation. Final changes in the translated version were made accordingly.[18]

#### *Sleep quality*

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval.[19] Nineteen individual items generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each component has a possible score of 0–3, where a higher score indicates a greater sleep problem.

The global PSQI score is the sum of all components scores (range 0–21); a score of $>5$ indicates poor sleep.[19] Cronbach's alpha was 0.87 in our sample.

#### *Anxiety and depression*

The Hospital Anxiety and Depression scale (HADS) is a self-administered 14-item scale with two subscales for detecting clinically significant depression (HADS-D) and anxiety (HADS-A).[20] Each item has response categories ranging from 0 (no problem) to 3 (extreme problem). The summary score for both subscales ranges from 0 to 21, with the higher score meaning worse condition. A score of 7 or lower indentifies non-cases, 8–10 possible cases, and $\geqslant 11$ definite cases.[20] In the present study Cronbach's alpha was 0.85 for the depression and 0.86 for the anxiety subscale.

#### *Fatigue*

Fatigue was assessed using the 20-item Multidimensional Fatigue Inventory (MFI-20), which measures five dimensions of fatigue: general fatigue, physical fatigue,

reduced activity, reduced motivation and mental fatigue.[21] There are 4 items in each dimension which are scored on a five-point Likert-scale. The total score in each dimension ranges from 1 (no fatigue) to 20 (highest possible fatigue).[21] In our sample Cronbach's alpha was 0.81 for general fatigue, 0.85 for physical fatigue, 0.83 for reduced activity, 0.71 for reduced motivation and 0.80 for mental fatigue.

*Bladder dysfunction*

Bladder dysfunction was assessed using the Incapacity Status Scale, which contains an item regarding bladder problems.[22] The patients were asked to circle one of the 5 responses: 0 – no difficulty; 1 – occasional hesitancy or urgency; 2 – frequent hesitancy or urgency or retention, and/or use of indwelling or external catheter applied or maintained by self, and/or intermittent catheterization by self; 3 – occasional incontinence and/or use of indwelling or external catheter applied or maintained by others, and/or intermittent catheterization by others; 4 – frequent incontinence. A higher score indicates more bladder problems.[22] The score was used as a continual variable.

*Pain*

To assess pain, we asked participants the pain question from the SF-36[23]: 'in the past months, how intense was your pain?' The score ranges from 1 (no pain) to 6 (very severe pain), with a higher score indicating more severe pain.[23] The score was used as a continual variable.

*Sociodemographic and clinical data*

Sociodemographic data about the participants, including gender and age, were derived from the interview. Clinical data were obtained from medical records. Disability was assessed by the Expanded Disability Status Scale (EDSS). Disability is graded on a continuum from 0 (normal neurological examination) to 10 (death caused by MS). EDSS scores 1.0 to 4.5 refer to people with MS who are fully ambulatory. EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation.[24] Other clinical data consisted of clinical course (relapse-remitting form or secondary progressive form).[25] We dichotomized disease duration according to Kallmann et al[26] as $\leqslant 5$ and $>5$ years.

*Statistical analyses*

Statistical analyses were performed using SPSS 20.0 for Windows. Patients were divided into two groups according to disease duration; patients with disease duration $\leqslant 5$ years and those $>5$ years. Firstly, the study variables of the sample were described. *T*-tests, Mann–Whitney *U*-tests and Chi-square tests were conducted to determine the differences in scores between both disease duration subgroups. Next, the relationship between age, gender, anxiety, depression, pain, fatigue and bladder dysfunction were analyzed with multiple linear regression analysis (the enter method), using sleep quality by disease duration as the dependent variable. The statistical analyses were calculated separately for both groups.

## Results

The main clinical and demographic data for the whole sample and for the two subgroups are presented in Table 1. The MS sample consisted of 76% women; mean age was 40 ± 10 years. After dividing the sample, a total of 66 patients (78% women, averaged 37.35 ± 10.1 years old) remained in the group with shorter disease duration and 86 patients (73.3% women, averaged 42.10 ± 9.4 years old) in the group with longer disease duration. Patients with MS duration $\leqslant 5$ years were younger, had predominantly a relapse-remitting course of MS, lower EDSS and higher reduced activity than those with longer disease duration. More depressive patients and those with more severe bladder dysfunction were in the group of patients with disease duration $>5$ years. The prevalence of poor sleep in all patients was 44.1%; in the group with the duration of MS $>$ 5 years this was significantly higher (51.2% vs. 34.8%).

### *Poor sleep among patients with disease duration $\leqslant 5$ years*

The model consisting of age, gender, anxiety, depression, pain, bladder dysfunction and all dimensions of fatigue explained 43% of the variance in PSQI (Table 2). Variables significantly associated with poor sleep quality included anxiety ($\beta = 0.29$, $p \leqslant 0.02$) and two MFI domains – mental fatigue ($\beta = 0.31$, $p \leqslant 0.02$) and reduced motivation ($\beta = 0.44$, $p \leqslant 0.04$).

### *Poor sleep among patients with disease duration $>5$ years*

The variance in PSQI was explained by the same model that was used in the group of patients with shorter disease duration. The final model explained 43% of the variance in PSQI (Table 2). Pain was the strongest variable associated with poor sleep ($\beta = 0.27$, $p \leqslant 0.01$). Also, depression ($\beta = 0.26$, $p \leqslant 0.04$) and mental fatigue ($\beta = 0.24$, $p \leqslant 0.04$) showed a significant relationship with poor sleep.

## Discussion

We explored the differences in prevalence and determinants of poor sleep quality in a sample of patients with MS with disease duration $\leqslant 5$ years and $>5$ years. The prevalence of poor sleep is significantly higher in patients with longer disease duration. Both disease duration groups differed in factors associated with poor sleep quality. The determinants of poor sleep quality in patients with disease duration $\leqslant 5$ years were anxiety, reduced motivation and mental fatigue, whereas pain, depression and mental fatigue were associated with reduced sleep quality in patients with disease duration $>5$ years.

Table 1
Sample characteristics by disease duration

| | All | Disease duration ⩽5 years | Disease duration >5 years | |
|---|---|---|---|---|
| | *N* (%) or Mean ± SD (range) | *N* (%) or Mean ± SD (range) | *N* (%) or Mean ± SD (range) | *p* value |
| No. of patients, *n* | 152 | 66 | 86 | |
| Gender | | | | |
| Female | 115 (75.7) | 52 (78.8) | 63 (73.3) | ns |
| Male | 37 (24.3) | 14 (21.2) | 23 (26.7) | ns |
| Disease duration | 7.54 ± 5.4 (1–28) | 2.9 ± 1.5 (1–5) | 11.1 ± 4.6 (6–28) | **<0.001** |
| Age (years) | 40.0 ± 10.0 (18–61) | 37.3 ± 10.2 (18–61) | 42.10 ± 9.4 (21–61) | **0.003** |
| Clinical course | | | | |
| RR | 122 (80.3) | 66 (100) | 56 (65.1) | **<0.001** |
| SP | 30 (19.7) | 0 | 30 (34.9) | **<0.001** |
| EDSS | 3.2 ± 1.4 (1.0–8.0) | 2.5 ± 1.0 (1.0–6.0) | 3.6 ± 1.4 (1.5–8.0) | **<0.001** |
| PSQI | 5.8 ± 3.6 (0–16) | 5.3 ± 3.4 (0–13) | 6.2 ± 3.6 (0–16) | ns |
| Poor sleep (PSQI > 5) | 67 (44.1) | 23 (34.8) | 44 (51.2) | **0.045** |
| HADS-anxiety | 6.8 ± 4.3 (0–17) | 6.2 ± 4.3 (0–17) | 7.2 ± 4.3 (0–17) | ns |
| ⩾8 | 67 (44.1) | 26 (40.0) | 41 (47.7) | ns |
| HADS-depression | 5.7 ± 4.2 (0–19) | 4.8 ± 4.2 (0–17) | 6.3 ± 4.1 (0–19) | **0.015** |
| ⩾8 | 49 (32.2) | 18 (27.3) | 31 (36.0) | ns |
| Pain (SF-36) | 2.78 ± 1.3 (1–5) | 2.56 ± 1.2 (1–5) | 2.95 ± 1.4 (1–5) | ns |
| Bladder problems (ISS ⩾ 1) | 87 (57.2) | 28 (42.4) | 59 (68.6) | **<0.001** |
| Fatigue | | | | |
| General fatigue | 14.0 ± 4.4 (4–20) | 13.2 ± 4.7 (4–20) | 14.5 ± 4.2 (6–20) | ns |
| Physical fatigue | 1.4 ± 4.9 (4–20) | 12.5 ± 5.0 (4–20) | 14.1 ± 4.7 (4–20) | ns |
| Reduced activity | 11.0 ± 4.8 (4–20) | 10.0 ± 4.8 (4–20) | 11.7 ± 4.7 (4–20) | **0.026** |
| Reduced motivation | 8.5 ± 3.7 (4–20) | 8.0 ± 3.6 (4–16) | 8.9 ± 3.7 (4–20) | ns |
| Mental fatigue | 10.3 ± 4.5 (4–20) | 9.6 ± 4.5 (4–20) | 10.9 ± 4.4 (4–20) | ns |

RR, relapse-remitting course; SP, secondary-progressive course; EDSS, Expanded Disability Status scale; PSQI, Pittsburgh Sleep Quality Index; HADS, Hospital Anxiety and Depression Scale; SF-36, Short Form Health Survey; ISS, Incapacity Status Scale, T-test, Mann–Whitney U-test and chi-square tests were used to determine the differences between the subgroups. Bold values indicate the significance $p < 0.05$.

Our study showed that the prevalence of poor sleep is significantly higher in patients with longer disease duration. We found the prevalence of poor sleep in the whole sample to be lower than described in previous papers.[1–4,6] This result might be explained by the shorter mean disease duration in our sample compared with those in samples from previous studies: the result in the group with longer disease duration is consistent with previous findings.[1–4,6]

Table 2
Linear regression model: determinants associated with poor sleep in the group of patients with disease duration ⩽5 years and >5 years

| | PSQI | |
|---|---|---|
| Disease duration | ⩽5 years | >5 years |
| Age | −0.13 (0.25) | −0.05 (0.58) |
| Gender | −0.12 (0.29) | −0.04 (0.66) |
| Depression (HADS-D) | 0.22 (0.09) | **0.26 (0.04)** |
| Anxiety (HADS-A) | **0.29 (0.02)** | −0.07 (0.54) |
| Bladder dysfunction (ISS) | −0.04 (0.67) | 0.12 (0.22) |
| Pain (SF-36) | 0.22 (0.06) | **0.27 (0.01)** |
| General fatigue | 0.27 (0.18) | 0.01 (0.96) |
| Physical fatigue | −0.26 (0.27) | 0.14 (0.41) |
| Reduced activity | −0.02 (0.91) | −0.28 (0.06) |
| Reduced motivation | **0.44 (0.02)** | 0.23 (0.08) |
| Mental fatigue | **0.31 (0.04)** | **0.24 (0.04)** |
| $R^2$/adjusted $R^2$ | 0.53/0.43 | 0.50/0.43 |

Adjusted $R^2$: explained variance; gender: male gender was set as the reference category; HADS-D, Hospital Anxiety and Depression Scale – depression subscale; HADS-A, Hospital Anxiety and Depression Scale – anxiety subscale; ISS, Incapacity Status Scale; SF-36, Short-Form Health Survey. Bold values indicate the significance $p < 0.05$.

In this study, we confirmed our expectations that anxiety was significantly associated with poor sleep in the group of patients with shorter disease duration, but it did not play a significant role in the patients with longer disease duration. This finding is similar to that of Bøe Lunde et al showing that a high psychological burden of MS was independently associated with poor sleep quality,[7] although they did not consider the role of the disease duration. Our results underline the role of anxiety in the early course of disease. Furthermore, we found that depression is significantly associated with poor sleep in patients with disease duration longer than 5 years. In patients with shorter disease duration depression did not show any significant association with sleep problems. Our findings are in line with the results of earlier studies in that they showed depression to be associated with poor sleep.[6,10,27,28] Bamer et al, in a sample of 473 patients with mean disease duration of 14.5 years, described depression as a major determinant of poor sleep.[10] Another study by Neau et al showed anxiety and depression to be associated with sleep disorders; however, after controlling for other clinical variables only the association with depression remained significant. The mean disease duration of those patients was 11.6 years.[6] From our findings on anxiety and depression it must be concluded that both play a different role regarding quality

of sleep, depending on disease duration: in the early group anxiety is more important, and in the late group depression. The possible explanation for this difference may be that soon after the diagnosis patients suffer more from anxiety and fear connected with the uncertainty of the disease progression.[14] On the other hand, patients with longer disease duration have already adjusted to the presence of disease,[29] and the role of depression is more significant regarding the progressive disability and impairment in ambulatory status.[30]

Next, we found that pain was the strongest variable associated with poor sleep quality in our sample of patients with disease duration of more than 5 years. This is consistent with the findings of previous studies showing a negative association between pain and the quality of night sleep.[6,10] Pain is a very frequent distressing symptom associated with MS and is reported by more than half of patients with MS[31]; its prevalence increases with greater disability and longer disease duration.[16]

In our study only the mental aspects of fatigue were found to be associated with poor sleep quality in both groups; reduced motivation and mental fatigue in the group with shorter disease duration and mental fatigue in the group with longer disease duration. The majority of the research on sleep in MS has been focused on the relationship between fatigue and sleep disturbances.[4,9,32] Most studies have shown an association between these two conditions.[4,9,33,34] An increased risk of fatigue in patients with MS suffering from a sleep disorder was also confirmed in a polysomnographic cross-sectional study by Veauthier et al.[35] These results are in line with our findings. This relationship might be explained by the way that poorer sleep quality can lead to greater fatigue, but the design of our study did not allow us to clarify such a pathway. Further research with case control studies and longitudinal data is needed to clarify these causal pathways.

To the best of our knowledge, this is the first study showing differences in the prevalence and determinants of poor sleep quality in a sample of patients with disease duration $\leqslant 5$ years and those with disease duration $> 5$ years. Some limitations of this study should be mentioned. Most of the variables were evaluated by means of self-reported questionnaires, although these have been used in different cultural settings and properly translated. In our sample the women-to-men ratio was a bit higher (75.7% women), so the results may better explain the sleep quality of women than men. A third limitation is that the study has a cross-sectional design, which does not provide us information about changes over time and thus does not allow us to explore the causal pathways between the studied variables.

## Conclusion

We found that sleep problems are present in patients with MS in the early and late disease course, but they are associated with different factors. Our results highlight the need to recognize these factors and consequently to apply a suitable approach to the treatment of sleep disorders. In patients with shorter disease duration the management of anxiety and the mental component of fatigue may lead to improvement in the quality of sleep, whereas in patients with longer disease duration efforts should be taken to treat pain and depression. It would be interesting to follow the sample over time. Longitudinal data could provide us with more information regarding causal relationships between sociodemographic and clinical factors and poor sleep quality.

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