Poor sleep quality and other symptoms affecting quality of life in patients with multiple sclerosis
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General discussion, implications and conclusions

This thesis is focused on the neuropsychiatric symptoms of multiple sclerosis (MS), especially on poor sleep quality in patients with MS. Emphasis is put on physical and psychological symptoms associated with MS, such as pain, depression, anxiety, fatigue or bladder dysfunction, and how they are related to poor sleep quality in MS. The thesis also focuses on the often overlooked bladder, bowel and sexual dysfunction and their relation to sleep quality and health-related quality of life in MS patients. In this chapter the main findings of the thesis are first summarized (8.1) and discussed (8.2). The subsequent section then refers to the strengths and limitations of the included studies (8.3). Finally, in the last part the implications for clinical practice and future research are presented (8.4).

8.1 Main findings

Research question 1 (Chapter 3)
Are bladder, bowel and sexual dysfunction associated with the physical and mental dimensions of HRQoL in patients stratified by duration of MS (≤5 years and >5 years)?
We found that more severe disability, as measured by the EDSS and bladder dysfunction, was associated with lower physical health status in both disease duration groups. More severe sexual dysfunction was associated with lower mental health status in the group of patients with disease duration of 5 years or less. Bladder, bowel or sexual dysfunction was not found to play a role in mental health status in the group of patients with longer disease duration.

Research question 2 (Chapter 4)
Are there differences in the prevalence and determinants of poor sleep quality in a sample of MS patients with disease duration ≤5 years and >5 years?
We found that the prevalence of poor sleep quality is significantly higher in patients with longer disease duration. Both disease duration groups differed in factors associated with poor sleep quality. The symptoms related to poor sleep quality in patients with disease duration of 5 years or less were anxiety, mental fatigue and reduced motivation, whereas pain,
depression and mental fatigue were associated with reduced sleep quality in patients with disease duration of more than 5 years.

**Research question 3 (Chapter 5)**

*Do gender differences exist in factors related to poor sleep quality in patients with MS?*

We found that factors associated with poor sleep quality in women concerned depression and anxiety, whereas pain was associated with poor sleep quality in men. Our results supported our expectations that different conditions may contribute to poor sleep quality in women and men with MS.

**Research question 4 (Chapter 6)**

*What are the interrelationships between pain, depression, fatigue and poor sleep quality?*

Our study showed that both pain and depression have a bidirectional relationship with sleep quality, with more severe pain or depression worsening sleep quality and vice versa. Moreover, almost half of the effect of pain on sleep quality was mediated by depression. Depression was also found to be the strongest predictor of mental fatigue and a significant mediator of the effect of pain on fatigue, with the role of poor sleep quality being much smaller.

**Research question 5 (Chapter 7)**

*Do depression, pain and physical fatigue mediate the association between sleep quality and functional disability in MS patients?*

We found that the relationship between poor sleep quality and disability in MS patients was indirect and fully mediated by depression, pain and physical fatigue. Our mediation model showed that poor sleep quality in MS patients may worsen depressive symptoms, pain and physical fatigue, which in turn may be associated with greater overall disability.

### 8.2 Discussion of the main findings

MS is a chronic disease that leads to progressive disability over time (1). Several MS-related impairments in body functions, together with limitations in activities and restrictions in participation, form the overall disability of people with MS, which is the main contributor to decreasing HRQoL in the MS population (2).

#### 8.2.1 Bladder, bowel and sexual dysfunction and their relationship with HRQoL

Bladder, bowel and sexual dysfunction are common MS-related disabilities (3-6). Despite their high prevalence, they are often overlooked.
Our study showed that all of the dysfunctions – bladder, bowel and sexual – can occur even in the early stage of disease. Bladder dysfunction, combined with neurological disability measured by the EDSS, was found to be a significant contributor to a lower perception of physical health in patients with shorter and longer disease duration groups (cut off point 5 years). Our findings are in line with the results of a study performed by Nortvedt et al., who observed an association of bladder dysfunction with HRQoL independently of other clinical data in a sample of 218 MS patients with disease duration from 9 to 19 years (3). The importance of bladder dysfunction in the early stage of MS controlled for other variables has not yet been analysed.

Regarding bowel dysfunction, we did not find a significant relation with perceived physical or mental health in MS patients with shorter or longer disease duration. We cannot compare these findings with previous ones, as no previous study has investigated the association of bowel dysfunction with HRQoL adjusted for other variables. An explanation for the lack of an association with HRQoL may be that bowel dysfunction comprises mostly concerned constipation. The majority of the patients in our sample (70%) marked this bowel dysfunction as being uncomfortable for them, but not changing their functioning. It might be that the more severe cases of bowel dysfunction, i.e. faecal incontinence, have a poorer HRQoL, but this group was rather small in our sample.

Furthermore, we explored whether sexual dysfunction in MS patients may explain their worse HRQoL. We found that sexual dysfunction was associated with low perceived mental health only in the group of the patients who were in the early stage of the disease. Our results might be explained in two ways. First by the age of patients: patients with shorter disease duration were significantly younger and may have had a higher frequency of sexual intercourse than those older and with longer disease duration. Kontula and Haavio-Mannila showed in their study that older age was significantly associated with less frequent sexual activity in a sample of 844 healthy people (7). A second explanation might be the adjustment to the disease in patients with a more advanced stage of disease (8). As increased age and a more advanced stage of the disease are not distinguishable, both explanations might be relevant.

8.2.2 Sleep quality and factors associated with poor sleep quality
Poor sleep quality is a common symptom associated with MS (9). In our study approximately 45% of the MS patients reported having poor sleep quality, with the prevalence being higher in women than in men. Women also rated their sleep on average as poorer than men, but these gender differences did not reach statistical significance. We also found that sleep problems can occur even during the first five years of the disease, although less frequently than in patients with longer disease duration. Up to now,
numerous MS-related symptoms have been found to be associated with poor sleep quality. Adequate recognition in patients of pain, depression, anxiety or bladder dysfunction as the most frequent determinants of poor sleep in the MS population may improve the treatment strategies for these patients.

**Determinants of poor sleep quality: the role of disease duration and gender**

We found that determinants of poor sleep quality vary by duration of MS. Anxiety was the most important symptom influencing sleep quality in patients with disease duration of 5 years or less, whereas pain and depression were the main contributors to poor sleep in patients with disease duration of more than 5 years. All symptoms of anxiety, depression, or pain have been previously found to be related to poor sleep (10), but the role of disease duration has not yet been considered. An explanation for these differences by disease duration in factors related to poor sleep may be that shortly after diagnosis patients suffer more from anxiety and fear connected with the uncertainty of the disease progression and that they realize that their life will change (11). In contrast, patients with longer disease duration have already adjusted to the presence of the disease (12), and the role of pain and depression is more relevant regarding the progressive neurological impairment and overall disability (13).

Furthermore, we found some differences regarding the factors influencing sleep in women and men. Anxiety and depression were the main symptoms contributing to poor sleep in women, whereas pain worsened sleep quality in men. No studies exist about the differences in determinants of poor sleep quality in women and men with MS. Previous studies conducted among the general population and among patients with other chronic conditions have shown that not only depression and/or anxiety (14, 15) but also pain was a specific contributor to poor sleep in women (16, 17). Our observation that pain worsens sleep in men and not in women with MS thus seems to be inconsistent with those previous studies. As the prevalence of anxiety, depression and pain was almost the same across the gender groups, our findings cannot be explained by the different prevalence of pain in women and men that was found in several studies in the general population (16, 17).

Thus, other factors may have played a role in the association of pain with poor sleep. For example, women with chronic postsurgical pain reported the highest pain intensity during the day, whereas men experienced higher intensities of pain in the evening (18). This observation could explain the more dominant role of pain in influencing sleep in men than in women. Furthermore, we used a self-reported pain scale, and research in this area indicates that males are less likely to self-report pain. When they do self-report, they often have difficulty explaining the extent
of their real pain experience (19). Thus, it can be deduced that women may have rated low intensity stimuli without the potential to influence sleep as already painful, whereas men have rated as painful only those which interfered with their sleep. The findings on different determinants of poor sleep by disease duration indicate that clinicians should apply a different approach when assessing poor sleep quality in patients with shorter and longer disease duration. Similarly, women and men with MS differ in factors disturbing their sleep. This observation should also be taken into account during the diagnostic process of poor sleep quality.

Consequences of poor sleep quality
Poor sleep quality is a debilitating symptom with several consequences. We found that it can worsen fatigue, pain and depression and indirectly influence the overall disability of patients with MS. The results of our pathway analysis showed that depression and pain had a bidirectional relationship with sleep quality, with more severe depression or pain worsening sleep quality and vice versa. This finding implies that both symptoms are not just the determinants, but also the consequences of poor sleep. Furthermore, we extended the existing knowledge by showing that pain also contributed to poor sleep quality indirectly through its relationship with depression. Patients who reported increased levels of pain had more severe depressive symptoms, which in turn worsened their quality of sleep. This confirms the previous finding that the symptoms pain and depression tend to cluster (20). Care providers should pay more attention to search for pain in all patients with depression and vice versa.

More severe mental fatigue was found to be another consequence of poor sleep, which is consistent with previous research (21, 22). We found such a relationship in patients in both the early and advanced stage of disease. However, the association of poor sleep quality with fatigue was much weaker than previously reported (21, 23). In our pathway analysis the strongest predictor of mental fatigue was depression, which was also a significant mediator of the effect of pain on fatigue. These conflicting results may be explained by differences across the studies in the design of the regression models, with models containing different variables. It seems that models that have been adjusted for various potentially confounding variables like ours yield estimates of weaker associations of poor sleep and fatigue. This implies that previously reported findings may have been partially due to uncontrolled confounding. The finding of a negative influence of poor sleep quality on fatigue was also confirmed in a polysomnographic cross-sectional study by Veauthier et al (22). They suggested that in all MS patients suffering from fatigue, a careful history assessing sleep problems and, where appropriate, polysomnographic investigations should be done (22).
We showed that there was no direct relationship between poor sleep quality and disability measured by the EDSS, but that this relationship was fully mediated by depression, pain and fatigue. Our study is the first to evaluate this relationship from this perspective of mediation. More specifically, patients with MS who suffered from poor sleep were more depressed, had more severe pain and experienced more severe fatigue, which in turn might lead to greater functional disability. Previous research regarding this topic has presented conflicting results (24-26). Some studies confirmed that problematic sleep may be directly associated with greater disability (24, 25), whereas others did not confirm such a relationship (26). The latter group of studies explored the determinants of poor sleep in MS patients, but the model adjusted for several variables, including EDSS, did not show a significant association between poor sleep and disability. Our findings imply that the treatment of sleep problems may have beneficial effects beyond improving sleep. These conflicting results might be explained by the fact that authors adjusted their models for factors that we considered to be mediators. Further studies on this topic should be completed to confirm our results.

8.3 Strengths and limitations of the study

Among the strengths of this study are the relatively high response rate within our sample (72%) and the comprehensive method of collecting data on all MS patients at a clinic that covers a full catchment area. Furthermore, we used questionnaires that are internationally recognized, commonly used and carefully validated to obtain the data. All recorded answers were personally checked during the interview with the patient to avoid any confusion and to increase the validity of the answers. For Chapters 4-7 all patients were examined by the same neurologist, which prevented an interrater examination bias in determining functional disability measured by the EDSS. Employing SEM in the data analyses (Chapter 6,7) is another particular strength of our study.

Our study also has some limitations, however. All analyses on both samples concerned cross-sectional data, which did not allow us to explore the full causal relationships between the studied variables, though the use of SEM in Chapters 6 and 7 did somewhat support the validity of such inferences. Despite this, our findings should still be confirmed in longitudinal research. Second, most of the variables were measured by means of self-report questionnaires. Though we fully employed well-validated questionnaires, it would be interesting to include both self-reported sleep disturbances and those measured by e.g. polysomnograms to obtain a more comprehensive assessment of sleep problems. Third, in the sample reported on in Chapter 3, the participating MS patients were significantly younger than the non-respondents. This will have led to a
lower share in our sample of the oldest group with the longest disease duration and probably the most affected group of that age in particular. A consequence of this is that our results may be an underestimation of the impact of MS in the longer run.

Despite the relatively high prevalence of anxiety and depression among the study population, only 7% of patients have used antidepressants and/or anxiolytics, so the use of these drugs has not been taken into account. We also did not analyse the potential effects of other drugs (e.g. analgetic, antiepileptics or disease modifying treatment) on sleep quality or on symptoms contributing to poor sleep quality.

8.4 Implications for clinical practise and future research

Bladder and sexual dysfunction are associated with a significantly lower HRQoL score in MS patients even if they have had MS for a relatively short time, showing a need to pay more attention to these problems in routine care. Recognition, examination and proper treatment are needed to prevent the development of more severe dysfunction, and this also may lead to an improvement in HRQoL. All patients with MS who report bladder or sexual dysfunction should be sent for a urological or gynecological examination. The private nature of sexual dysfunction may inhibit a patient and the physician in communication about it during an interview. It might therefore be useful to use questionnaires as a screening method for the recognition of sexual problems.

Our findings of different symptoms associated with poor sleep quality in the early and later stages of the disease should be taken into account when considering an appropriate intervention. Depression or pain do contribute to poor sleep in patients with shorter disease duration, but it seems very likely that anxiety plays a more dominant role. Thus, physicians should pay more attention to the potential presence of anxiety in all patients who complain about poor sleep quality in the early stage of the disease. A short-term anxiolytic treatment combined with psychological interventions supporting coping strategies may lead to a decline in both symptoms and significantly improve quality of life in these patients. The same principle applies for patients with longer disease duration. Routine assessment of pain and depression and their specific treatment should be included into the management strategies of poor sleep quality.

A gender-differential approach should be applied when assessing poor sleep quality in women and men, as we found gender differences regarding the factors that contribute to poor sleep. The more dominant role of mood disorders in women than in men implies that anti-depressive treatment may be useful in women with poor sleep. Men with sleep problems can also suffer from mood disorders, but it seems that physical
symptoms such as pain have a more important role in disturbing their sleep. Thus, in men effective pain management in particular deserves attention. Adequate management strategies of sleep disturbances in both genders may also have beneficial effects beyond improving sleep. They may reduce depressive symptoms, levels of pain and physical fatigue, which in turn may lessen disability.

Next, an important implication of our findings regards the fact that pain, depression, anxiety, poor sleep quality and fatigue are closely linked with each other and could be defined as a symptom cluster to be handled as a cluster (27). If patients are complaining of at least one of the symptoms mentioned above, healthcare providers should pay more attention to the potential presence of the others. When treating patients with poor sleep quality, it is possible that treatment directed at all symptoms combined may be more effective than treating each separate symptom. For example, cognitive-behavioural therapy is promising for individuals with depression and comorbid insomnia in terms of alleviating both symptoms (28). Some antidepressants, such as tertiary amine tricyclic antidepressants, venlafaxine or duloxetine, also appear to be efficacious in the treatment of pain (29) and could therefore be used in people with depression and chronic pain. Reduction of both symptoms may in turn improve sleep and reduce fatigue. Our findings may support such handling of these highly prevalent and disturbing symptoms of MS.

Poor sleep quality is a common symptom with multiple determinants in MS patients and with major consequences on patients quality of life. Longitudinal research allowing the exploration of the full causal relationships is needed to confirm our findings. A few studies have demonstrated the effect of treating sleep on fatigue, and this shows a need for randomized controlled intervention studies to confirm such findings. As we found that pain, depression, poor sleep quality and fatigue are closely related to each other, future research should verify if treatment directed at all symptoms combined is indeed more effective than treating each separate symptom. Despite extensive research regarding the etiology of poor sleep quality in MS patients, the proportion of primary sleep disorders caused by demyelination or axonal damage in central nervous system and what treatment strategies should be used in such a case still remain unclear. Much work needs to be done to better understand the interrelationships between multiple neuropsychiatric MS-related symptoms and to develop the best therapeutic approach.

8.5 Conclusion
We found that bladder dysfunction has a negative impact on HRQoL in patients with MS irrespective of disease duration, whereas sexual dysfunction decreases the mental component of HRQoL in patients with
shorter disease duration. Moreover, we found that anxiety, depression, pain and fatigue are the most frequent symptoms related to poor sleep quality in MS patients, but that their influence on sleep quality differs by disease duration and by gender. Anxiety was the main contributor to poor sleep in patients with shorter disease duration, whereas pain and depression were associated with reduced sleep quality in patients with disease duration of more than 5 years. Regarding gender differences, we found that mood disorders (anxiety and depression) were the main symptoms contributing to poor sleep in women, whereas pain worsened sleep quality in men. Fatigue was found to be the frequent consequence of poor sleep, but we also found other possible consequences, such as worsening of depressive symptoms and pain severity. Finally, by means of these symptoms functional disability can worsen indirectly. Poor sleep quality is a frequent neuropsychiatric symptom of MS with multiple causes and consequences, which should be taken into account when treating patients with MS. Our findings provide major clues for improving the quality of life of MS patients.

References


