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## Fatigue, mood disorders and sleep problems in patients with Parkinson's disease

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# Discussion, clinical implications

General technological and scientific progress over the past decades have also affected health care and the values held there. Merely surviving is no longer the primary outcome of medical interventions, and the health care strategies have started to be oriented on the quality of life of the patients, especially for patients suffering from chronic diseases. Quality of life, together with morbidity and mortality, have thus become among the important measures of health care.

Parkinson's disease (PD) is a chronic neurological disorder. The current concept of PD has moved from just a 'movement' disorder to a movement disorder associated with a wide variety of nonmotor symptoms. The aim of this thesis was to explore the association of certain nonmotor presentations (fatigue, sleep disorders, mood disorders) and the quality of life of PD patients and to explore the character of the interrelations between these nonmotor symptoms based on the conceptual model of ICF (1). In this final chapter the main findings of this study will be summarized (7.1), discussed (7.2) and completed with practice implications and proposals and recommendations for future research (7.3).

## 7.1 Main findings

### 7.1.1. Research question 1a

*Is there a relationship between daytime and nighttime sleep disturbances and quality of life?*

Sleep problems are well-known and well-described non-motor symptoms in PD. They play an important role in the lives of PD patients, negatively influencing their quality of life. They may result from uncontrolled motor complications, medication side-effects, or as a result of degeneration of the neuro-anatomical substrate responsible for the sleep-wake cycle (2).

When bivariate correlation analyses were performed, sleep disorders were significantly correlated with depression and anxiety, with the observed associations stronger for anxiety than for depression. Looking more closely at quality of life (QoL), this was significantly correlated with poor quality of nighttime sleep as well as with excessive daytime sleepiness. In addition, linear regression analyses were performed to evaluate the effect of the nighttime sleep disturbances measured with PSQI or daytime sleepiness measured with ESS as well as disease severity and mood

disorders. Different results were obtained when analyzing separately for the model with PSQI and for the model with ESS. PSQI appeared to be a significant predictor of QoL, but ESS was not.

Disease severity was another factor that significantly influenced QoL in both models. However, our results show only anxiety as being a significant factor associated with QoL in both the model with PSQI and the model with ESS. Depression was not significant in either model. Our results thus showed an important contribution of nighttime sleep disturbances and anxiety to poor QoL.

### **7.1.2. Research question 1b**

*How are different fatigue domains related to different QoL domains and is there a difference between the physical and mental dimensions of QoL?*

Recent developments in fatigue in PD showed that fatigue is a multidimensional construct and that its dimensions are independent from each other (3). The presence of fatigue in PD patients predicts the worsening of all QoL domains. The most affected were the domains Bodily Discomfort, Mobility and Emotional well-being. Focusing on the different components of fatigue, mental domains (especially mental fatigue) were predictors of psychological QoL domains (Emotional well-being, Stigma, Social support, Cognition, Communication). Physical dimensions of fatigue (reduced activity) were predictors of the domains Mobility, ADL and Stigma. Fatigue in general appeared to be a predictor of the domains Emotional well-being and Bodily Discomfort.

In addition to fatigue, worse disease severity is another important factor associated with worse QoL in all QoL domains except Cognition and Social support. Age, gender or disease severity did not show significant relationships with QoL in general. Looking closely at different QoL domains, longer disease duration was associated with Emotional well-being, higher age with Cognition and female gender with Bodily discomfort. The present study was not controlled for depression and sleep disorders, as there is an overlap in symptomatology – sleep problems and fatigue are among the diagnostic criteria for depression, and vice versa.

### **7.1.3. Research question 2**

*Is there a relationship between nighttime or daytime sleep problems and fatigue, or are they independent from each other?*

Our results showed that neither sleepiness during the day, nor nocturnal sleep problems (quality of sleep) contributed to fatigue in any of the five fatigue domains: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. Depression, however, did contribute significantly to all five fatigue domains, and functional status

to four domains. These results thus mean that fatigue and sleepiness, or nighttime sleep disturbances, are distinct, but interrelated symptoms, though these terms are often used interchangeably, or under the general rubric of being 'tired'. Our results thus confirm that they are the distinct problems requiring different diagnostic or therapeutic strategies in response to patient complaints.

### **7.1.3. Research question 3a**

*Do mood disorders or comorbidities contribute to the development of fatigue?*

Until now, fatigue has been considered a consequence of muscle rigidity or the higher age of PD patients. Despite increased knowledge about fatigue, its etiology is not fully understood, and biological as well as psychosocial factors may play a role. Although new questionnaires were developed to actively search for this problem, clinicians lack strategies for managing fatigue. Recognition of factors leading to fatigue and their proper management could improve QoL due to this nonmotor problem of PD patients.

Using general linear model analysis, we found that mood disorders and worse disease severity are the most important factors associated with fatigue. Worse disease severity was related to all fatigue domains, as is depression. Anxiety was connected with Reduced motivation and General fatigue domains.

We also expected comorbidities to influence fatigue, as fatigue was said to be frequent in patients after stroke or with cardiovascular diseases or diseases of the joints. Our results, however, did not show significant associations of comorbidities with fatigue, and neither did age, gender, disease duration or education level.

### **7.1.4. Research question 3b**

*Is there a causal relation between disease severity and depression and fatigue; and between depression and fatigue themselves?*

When looking at causal relations between depression and disease severity and fatigue using LISREL analysis, we found that worse disease severity and worse depression both lead to worse General fatigue, Reduced activity and Mental fatigue. Worse disease severity separately causes worse Physical fatigue. Only depression (but not worse disease severity) causes more fatigue in the Reduced motivation domain.

## **7.2 Discussion of the main findings**

Our results showed that fatigue and nighttime sleep disturbances are important contributors to worse Quality of Life. Sleep disorders are among the most frequent complaints of PD patients; Martinez-Martin et al.

reported insomnia in 45.7% of patients and excessive daytime sleepiness in 31.1% using the newly developed Nonmotor Symptoms Questionnaire in an observational, multicenter, international cross-sectional study (4). In a longitudinal study by Gjerstad et al. sleepiness was observed to increase its prevalence to 54% over an 8-year period (5).

Our results showed both poor quality of sleep and sleepiness to have significant associations with mood disorders, with associations stronger for anxiety than for depression. While the relationship between sleep problems and depression has been well described in the literature (6), the observed connection between sleep problems and anxiety is relatively new. The first association between depression and sleep disorders in PD patients was described by Tandberg et al. in 1998 in a community-based study, when depression, together with longer L-dopa therapy, correlated with the occurrence of sleep problems (7). Currently Buysse et al. reported in a longitudinal study a strong relationship between depression and insomnia and considered these two problems to be comorbid with each other, rather than sleep problems being secondary to depression (8). Anxiety and its associations with sleep disturbances were only recently studied by Borek et al. in a sample of 185 PD patients in 2006. They reported anxiety to have significant correlations with excessive daytime sleepiness together with male gender and longer disease duration, but not with nighttime sleep problems (9).

When analyzing the influence of sleep problems on QoL, only Scaravilli et al., in a short report, published significant correlations between poor nighttime sleep and poorer quality of life (10). The influence of daytime sleepiness has not been studied. We found significant correlations between both excessive daytime sleepiness and poor nighttime sleep with overall QoL. Looking at regression analysis, different results were found, however. Nocturnal sleep disturbances were a significant predictor of poor QoL, but excessive daytime sleepiness was not. In addition, mood disorders are important contributors to poorer QoL. Our results showed anxiety to be a significant predictor of poorer QoL in both the model with nocturnal sleep problems and the model with excessive daytime sleepiness, but depression did not show significant relationships, thus showing that anxiety is a much more important factor related to QoL compared with depression.

Fatigue is another important nonmotor feature of PD and is considered to be one of most disabling nonmotor features of the disease. Its etiology is not known, though biological changes in brain neurotransmitter mechanisms (11) or clinical and psychosocial variables may play a role (3,12).

Research in populations with a chronic neurological disease such as multiple sclerosis or amyotrophic lateral sclerosis has shown fatigue to be associated with lower levels of QoL. In PD patients the relationship

between fatigue and QoL was first described in 2000 by Larsen et al., who reported more fatigue and poorer QoL in patients with PD compared to patients with diabetes mellitus or healthy individuals; they measured QoL using a generic instrument (13).

When disease-specific QoL questionnaire was used, the presence of fatigue in PD patients showed to predict a worsening of all QoL domains (14). The most affected were the domains Bodily Discomfort, Mobility and Emotional Well-being. Focusing on the different components of fatigue, mental domains (especially Mental fatigue) were predictors of the psychological QoL domains (Emotional well-being, Stigma, Social support, Cognition, Communication), while the physical dimensions of fatigue (Reduced activity) were predictors of Mobility, ADL and Stigma domains. Fatigue in general appeared to be a predictor of the Emotional Well-being and Bodily Discomfort domains.

In addition, worse functional status is another factor significantly associated with worse QoL for all QoL domains except Cognition and Social Support. The relationship between worse functional status and worse QoL was shown by Karlsen et al. in a community-based sample of 111 patients; they did not find that motor complications significantly influenced QoL scores measured with the Nottingham Health Profile (15). In contrast, Chapuis et al. using a disease-specific questionnaire on a sample of 143 PD patients, found worse motor scores were connected with worse scores for Mobility and ADL (16). The influence of sociodemographic variables on QoL have been described in the literature with conflicting results. Furthermore, we found longer disease duration to be associated with worse Emotional well-being, and female gender to be associated with worse Bodily Discomfort domain, a finding similar to those of Behari and Chapuis (16,17).

Our next question was to evaluate how the presence of sleep disturbances, either during the daytime (excessive daytime sleepiness) or during the nighttime (poor quality of sleep), contribute to fatigue. All the variables are difficult to distinguish from each other, as patients frequently describe all of them as simply "being tired". However sleepiness, fatigue and apathy are separate nonmotor complaints requiring different therapeutic strategies and management.

We performed two separate series of multiple linear regression analyses using all the fatigue domains as dependent variables and excessive daytime sleepiness as an independent variable in the first series of analyses and poor quality of sleep as an independent variable in the second series of analysis. Both were controlled for age, gender, disease duration, functional status and depression. We decided against controlling for depression to avoid a bias, as depression contributes to the presence of fatigue even in our own results.

Our results showed that fatigue is independent from both excessive

daytime sleepiness and poor quality of sleep during nighttime. Fatigue is far more influenced by depression and worse functional status. This knowledge is relatively new, as previous research was performed by Alves et al. (18), who compared PD patients with and without excessive daytime sleepiness and found that both groups had high levels of fatigue, indicating the possibility that fatigue may result from sleepiness, but not necessarily so. The relative independence of fatigue and sleepiness was also reported for multiple sclerosis patients in a study by Kaynak et al. (19), although these two populations are difficult to compare as MS and PD affect different age groups.

The identification of possible treatable factors leading to fatigue is important, as their proper management may thus decrease fatigue. For this reason we evaluated depression and anxiety; comorbidities such as cardiovascular diseases, diseases of bones and joints, renal, and hepatal diseases; functional status; disease duration; and the sociodemographic variables age, gender, and level of education. A general linear model analysis was used to evaluate 5 different fatigue domains as dependent variables. Our study showed that neither age, gender, disease duration nor level of education were related to any fatigue dimension. Worse functional status was significantly associated with all the fatigue domains, the strongest for the physical fatigue and weakest for the reduced motivation domain. Depression was significantly related to all the fatigue domains, mental as well as physical, while anxiety showed relations with General Fatigue and Reduced Motivation.

Associations of functional status with fatigue are in contrast with previous studies. A study by Karlsen et al. (20) found no relationship between disease severity measured by UPDRS and fatigue in a sample of 233 PD patients. The findings are similar to those of a study by Lou et al. (3), who in a sample of 39 PD patients did not find correlations between disease severity and any of the dimensions of the MFI. Concerning depression, our findings of the association of depression with all the fatigue domains are partly similar to the findings of Lou et al. (3); in their sample of 39 PD patients depression was related to the mental dimensions of fatigue (mental fatigue), but not with physical fatigue.

Comorbidities did not show significant associations with fatigue, although many patients with cardiovascular disease, stroke or rheumatoid arthritis report higher incidence of fatigue (21-23). These results thus support findings that fatigue is an independent nonmotor feature of Parkinson`s disease.

The next step for the evaluation of factors associated with fatigue was the analysis of possible causal relationships between depression, functional status and fatigue. For this reason we performed LISREL analysis to examine how disease severity explains the different fatigue domains, how disease severity explains depression, and how disease

severity explains via depression the different fatigue domains. To our knowledge such research has not previously been performed. Our results showed that worse disease severity and worse depression both lead to worse General fatigue, Reduced activity and Mental fatigue. Worse disease severity separately causes worse Physical fatigue. Only depression (but not worse disease severity) causes more fatigue in the Reduced motivation domain.

There were limitations to the present research. Our sample consisted mostly of patients who were able to come for the examination and interview – either alone or with a family member as a companion – so we suppose that non-responders were patients with worse functional status, mostly bedridden. Despite the rather low response rate, in this selected population fatigue, sleep disorders and quality of life of PD patients is already a serious problem, so we expect this to be even worse in the total PD patients group.

### **7.3 Recommendations for research**

The results of this thesis show only some of the interesting associations between nonmotor symptoms of Parkinson's disease and quality of life of PD patients, as well as the interrelationships between nonmotor features themselves.

It would be interesting to explore these relationships in various stages of the disease. Patients in an early stage report different problems and require a different approach than patients with advanced Parkinson's disease. This later stage is characterized by the presence of motor complications that could enter into the previously developed relationships, e.g. between depression and fatigue or sleep disorders and QoL, and influence the behavior of certain variables (e.g. motor complications, if they occur during nighttime, may be associated with worsening of sleep problems and thus contribute to worsening of QoL). Patients with advanced PD thus may represent a sample with a different kind of relationships between variables. So a future study could concentrate on two separate analyses in these two different PD patient populations using comparative statistics.

Our research was based on cross-sectional data. However longitudinal data could provide us with more satisfactory information and allow us to explain the causal relationships between the variables. One way to find the answers to these questions is to observe patients through a prospective study in which individuals are examined several times. Our data showed that relationships between variables are very complex, and that multidirectional longitudinal data could explore the



causal pathways. We expect, based on our response rate in this study, a selective loss to follow up in a longitudinal study. Besides, as PD patients become older, they will have newly developed comorbidities that might influence some of the variables of interest, like fatigue.

As the exact etiology of certain nonmotor symptoms is not clear, psychological factors may possibly play a role. It might also be of interest to investigate how some personal characteristics interact with nonmotor symptoms like fatigue or some sleep problems. The Type D personality profile or the Eysenck personality test could be used for such research in a cross-sectional as well as a longitudinal study.

Very interesting information on quality of life could be provided by a multicenter study – the observations of Slovak patients in the area of East Slovakia and Dutch patients in Groningen, for example. As the patients in both countries have similar access to healthcare and medication, the observed differences in the different dimensions of quality of life could be explained by cross-cultural differences in non-medical factors between the cohorts.

## **7.4 Implications for practice**

### **Sleep disorders**

An interview with a PD patient should include sleep habits, presence of nocturnal sleep disruption (snoring, respiratory pauses, movements in sleep) and a complete drug history. The Epworth Sleepiness Scale (ESS) provides a useful tool that is practical in an office setting for evaluating the presence and severity of EDS. Additional evaluation for nocturnal sleep disturbances, including sleep apnea or PLMD, may identify those patients who are sleepy secondary to nighttime sleep deprivation. An evaluation by PSQI and lab tests like polysomnography and a multiple sleep latency test can diagnose these primary sleep disorders (24,25). PD patients who are sleepy are at increased risk of traffic accidents and should be cautioned not to drive (25).

Evaluation of sleep habits and their improvement is an important part of therapy. Treatment of daytime sleepiness in PD includes the assessment of a patient for possible nocturnal sleep disturbances. Sleep apnea, periodic limb movements and other disorders that disrupt nocturnal sleep should be considered, as should the side-effects of medications. If the onset of EDS follows initiation or increased dosage of dopaminergic therapy, either a reduction in dose or a switch to another drug may be necessary (26). If sleepiness is persistent and not responsive to medication adjustments, the use of stimulants may be warranted. Modafinil, a stimulant drug useful in

narcolepsy, may be of modest benefit, as has been shown in two controlled studies in a small number of PD patients with excessive daytime sleepiness (27,28).

### **Anxiety**

Some patients with anxiety disorders related to PD may benefit from behavior modification techniques. However, pharmacologic therapy is often needed. Certain antidepressants are approved for the treatment of a range of anxiety disorders; these agents include paroxetine, escitalopram and venlafaxine. Benzodiazepines should be considered for more severe anxiety, although patients should be counseled in regard to potential adverse effects, such as sedation, further cognitive deterioration and balance problems, which may increase the risk of falls. Similar to the general population, SSRIs may be helpful in the treatment of panic disorder, social phobia and generalized anxiety disorder in PD.

### **Depression**

In some patients, especially those with early PD, treatment with antiparkinsonian medications may improve depression. Unfortunately, well-designed clinical trials have not been performed. Otherwise, the treatment of depression in PD is similar to the treatment used in non-PD cases of depression.

As with all central nervous system-active medications used to treat the associated features of PD, it is important to monitor motor functioning if an antidepressant is initiated. Tricyclic antidepressants are effective in treating depression in PD and may even reduce motor symptoms (29). Treatment with TCAs is restricted by adverse effects, such as the worsening of cognitive functions. PD patients also have increased susceptibility to anticholinergic side effects, including delirium and hypotension. Most PD specialists use SSRI agents as a first-line treatment, including fluoxetine, sertraline, paroxetine, and fluvoxamine, because of the lack of anticholinergic and sedative side effects. In the most severe cases of depression in PD, electroconvulsive therapy, as was proposed by Lemke, may be of benefit (29).

Caring for patients is a task that becomes increasingly complex and demanding as the severity of disease progresses. Patient-centered treatment should include: early referral to a specialist, with regular reviews; multidisciplinary assessment, with access to a range of therapies; management with appropriate medication; and management of non-motor symptoms, including depression, anxiety, sleep disturbances and other. Patients should receive education and information about the disease. Building a support network of general practitioners, specialists

in movement disorders field, nursing homes and family are extremely essential for improving quality of life of PD patients.

### **General considerations**

In PD patients it is not only the objective motor deficits but rather the mechanisms to cope with the impaired functions and subjective experience of deficits that determine mainly the quality of life and subjective well-being. Interpersonal psychotherapy, cognitive therapy, training of social functions and relaxation therapy appear to positively affect quality of life and the course of PD.

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