The impact of fatigue on daily activity in patients with Parkinson's disease

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Chapter 8

General discussion

In this chapter we will discuss the main findings of this thesis and their impact on clinical practice. From this perspective, recommendations are made for further research in patients with PD.

Main findings

The impact of fatigue on health-related quality of life and physical activity in Parkinson's disease

In **Chapter 2**, we showed for the first time that fatigue, measured by the Multidimensional Fatigue Inventory (MFI) [1], was longitudinally associated with poorer overall disease-specific health-related quality of life (HRQOL) and reduced physical activity (**Chapter 3**) in patients with PD. However, the impact of fatigue on HRQOL, measured by the Parkinson's Disease Questionnaire-39 (PDQ-39) [2] was confounded by anxiety and depression, whereas the longitudinal association between fatigue and actual performed physical activity, measured by ambulatory accelerometry, was significantly distorted by depression. Nevertheless, after controlling for potential confounders such as age, gender, social support, disease duration, disease severity, motor impairment, cognition, anxiety, depression and medication intake, fatigue remained significantly associated with overall HRQOL and physical activity. However, the unique longitudinal association between fatigue and on the other hand HRQOL and physical activity was negligibly small, explaining less than 3% of the variance in outcome. This finding suggests that fatigue is a relatively minor factor in the complex array of aspects that determine HRQOL and physical activity in patients with PD. Above findings are in line with previous cross-sectional studies that investigated the impact of fatigue on HRQOL [3] and physical activity [4] in patients with PD, and a recent study that used ambulatory accelerometry to investigate the relationship between fatigue and physical activity in patients with multiple sclerosis (MS) [5]. Another cross-sectional study found no association between fatigue and physical activity in patients with PD[6].

In **Chapter 2** we found that physical fatigue, measured with the MFI physical fatigue subscale, was most strongly associated with the PDQ-39 mobility domain and that mental fatigue, measured by the MFI mental fatigue subscale, was most strongly associated with cognitive aspects of HRQOL (i.e. PDQ-39 cognitions). These findings suggest that physical and mental fatigue are different symptoms [7] affecting different domains of HRQOL in patients with PD [8]. Therefore, assessment of fatigue should differentiate between physical and mental aspects of fatigue.

In **Chapter 4** we showed that gait speed and fear of falling correctly predicted 78% of patients with PD as community walkers. Although physical and mental aspects of fatigue showed statistically significant bivariate associations with community walking, none of these dimensions of fatigue contributed significantly to the multivariable logistic regression model. This suggests that a purported association between fatigue and community walking is spurious and that community walking is mainly determined by gait speed and fear of falling. This finding is in line with previous research that showed that fatigue did not significantly distort the association between gait speed and community walking in patients with stroke [9, 10].

Fatigue is one of the criterion symptoms for a major depressive disorder according to the DSM-5 [11] and depression has been related with poorer overall HRQOL [12] as well as altered physical activity [13]. Therefore, it is likely that depression is an important confounder in the relationship between on the one hand fatigue and on the other hand HRQOL and actual performed physical activity. A confounding factor must be associated with both the exposure and outcome under study and extraneous to the investigated relationship [14]. Our results show that depression was significantly associated with self-report HRQOL but not with actual performed physical activity. For this reason, depression may be considered an important effect modifier in the relationship between fatigue and actual performed physical activity in patients with PD, rather than a confounder. Above findings support our hypothesis postulated in **Chapter 7**, that depressed patients may respond differently to treatment for fatigue than non-depressed patients.

Although fatigue has been reported as a primary symptom in patients with PD [15], recent evidence [16-19] underlines that depression and other mood disorders are related to fatigue, suggesting that fatigue may be considered a secondary manifestation of disease [20]. Skorvanek and colleagues [18] investigated primary and secondary fatigue in 165 patients with PD; over 61% (N = 102) were classified as having secondary fatigue, thus experiencing underlying mood disorders or excessive daytime sleepiness that exacerbate feelings of fatigue [18]. These findings underline our results presented in **Chapter 2** and **Chapter 3** and imply that the management of fatigue should include the assessment of underlying mood and sleep disorders.

In **Chapter 2** and **Chapter 3** we showed that motor impairment is significantly associated with fatigue, HRQOL and actual performed physical activity. However, in contrast to depression, motor impairment did not significantly distort the longitudinal association between on the one hand fatigue, and on the other hand HRQOL and actual performed physical activity. These results support the hypothesis that decreased

physical activity in patients with chronic fatigue should primarily be understood in terms of reduced effort tolerance (i.e. impaired neurobiological stress system functioning) rather than reduced effort capacity [21]. Therefore, underlying mood disorders and sleep disorders should be treated before patients participate in an exercise program that aims to improve effort capacity.

There are some study limitations that should be acknowledged that restrict the external validity of the regression models presented in **Chapter 2**, **Chapter 3** and **Chapter 4**.

First, we used data collected in the 'Rescue trial' (Rehabilitation in Parkinson's disease: strategies for cueing), a randomized clinical trial (RCT) that investigated the effect of cueing training on gait and gait-related activity in patients with PD [22]. In this cohort of 153 patients with PD, subjects were excluded if they had comorbid conditions that interfered with participation in cueing training. This made it impossible to investigate the impact of comorbid neurological, cardiopulmonary and orthopedic conditions on the relationship between fatigue, and on the other hand HRQOL and physical activity. Second, subjects with severe cognitive impairments were excluded and medical management of the patients in the trial was aimed at optimizing dopamine levels to maintain smooth motor output. In addition, all measurements were performed in the on phase. Therefore, the external validity of the multivariate models has to be confirmed in the general population of patients with PD. Finally, we were not able to control for sleep disorders and apathy, while it is conceivable that these may distort the association between fatigue and on the other hand HRQOL and physical activity.

In the present thesis, we focused on the impact of perceived fatigue on HRQOL and physical activity. We did not specifically measure aspects of fatigability. Although perceived fatigue and fatigability have been reported as distinct symptoms [23, 24], one may argue that both symptoms may influence each other [20]. To improve our understanding how these symptoms interact and contribute to HRQOL and physical activity in patients with PD, we suggest that future research incorporates self-report assessment of fatigue and objective quantification of fatigability.

Measurement properties of self-report fatigue questionnaires in Parkinson's disease

The large number of unidimensional and multidimensional questionnaires that we identified in **Chapter 5** underlines the lack of consensus about self-report fatigue assessment in patients with neurological disorders. We critically appraised 31 self-report fatigue questionnaires. Taking the methodological quality of the investigated

measurement properties into account, we recommended the Unidimensional Fatigue Impact Scale (U-FIS) [25] and the multidimensional Fatigue Scale for Motor and Cognitive functions (FSMC) [26] for the assessment of fatigue in patients with MS. The Functional Assessment of Chronic Illness Therapy Fatigue subscale (FACIT-F) [27] and Fatigue Severity Scale (FSS) [27] showed promise for the unidimensional assessment of fatigue in patients with PD, and the Profile Of Mood States Fatigue subscale (POMS-F) [28] for patients with stroke. No multidimensional questionnaires were adequately validated in patients with PD.

Although we concluded that the FACIT-F and the FSS show promise for the unidimensional assessment of fatigue in patients with PD, some concerns can be raised regarding the use of these questionnaires for outcome assessment. First, measurement error remains to be investigated in patients with PD. This makes it difficult to judge if these questionnaires are suitable (i.e. responsive) for detecting clinically meaningful changes in fatigue. Second, based on studies that used item response theory (IRT) methods [27, 29, 30], we concluded that there was evidence for inadequate structural validity of the FACIT-F and FSS in patients with PD. These findings suggest that items within the FACIT-F and the FSS measure different aspects of fatigue and that IRT-adapted versions of these questionnaires may more specifically measure the impact of fatigue on activities in daily life (ADL) when compared to the original versions. Therefore, we recommend the use of the IRT-adapted versions of the FACIT-F and FSS instead of the original versions to assess the impact of fatigue on ADL in patients with PD.

In **Chapter 5**, we focused on the assessment of perceived fatigue by self-report questionnaires. Therefore, we excluded studies that validated instruments measuring fatigability by quantifying decline in performance [20]. Given the methodological limitations of available self-report questionnaires, one may argue that objective measurement of performance may be a more precise assessment of fatigue. However, perceived fatigue and fatigability have been reported as distinct symptoms in patients with PD [23, 24], suggesting that self-report questionnaires and performance tests do measure different aspects of fatigue in patients with PD.

In **Chapter 6** we showed that the MFI [1] is a reliable and valid instrument to assess the multidimensional aspects of fatigue in patients with PD. However, it remains unclear if measurement error is acceptable and whether the originally proposed five dimensions validly measure the different aspects of fatigue in patients with PD. In line with studies in patients with cancer [31, 32], the original dimensions of the MFI were not replicated in our principal component analysis (PCA). Furthermore, we found moderate correlations between most extracted factors. These findings illustrate the

complex interrelatedness and the difficulty to distinguish between different aspects of fatigue in patients with PD.

The MFI general fatigue subscale has been proposed as a short assessment for fatigue and considered as a global score for fatigue [1]. However, based on our four-factor model and previous published results in patients with cancer [31, 32], this subscale reflects mainly physical aspects of fatigue and does not validly measure all dimensions of fatigue. Therefore, we recommended the summed score of all 20 items (MFI-total) to obtain a global indication of fatigue as measured by the MFI. The general fatigue and physical fatigue subscales may be interpreted as one subscale measuring physical aspects of fatigue [31, 32].

Previous research suggested that physical fatigue and mental fatigue are different symptoms in patients with PD [7]. This hypothesis is supported by the results presented in **Chapter 6**. First, the PCA clearly distinguished aspects of mental fatigue from the physical dimensions of fatigue measured by the MFI. Second, the ceiling effects for the physical fatigue and reduced activity subscales as well as the floor effect for the mental fatigue subscale, suggest that mental fatigue and physical fatigue are distinctly different symptoms, at least in the sample included in our study. Above findings suggest that the physical fatigue and mental fatigue subscales can be used to differentiate between both aspects of fatigue in patients with PD. However, others have questioned the validity of the mental fatigue subscale as items such as 'I can concentrate well' and 'My thoughts easily wander' may reflect cognitive dysfunction rather than fatigue per se [33]. Schiehser and colleagues [33] validated and recommended the Modified Fatigue Impact Scale (MFIS), a commonly used instrument in patients with MS, for the assessment of physical and mental aspects of fatigue in patients with PD.

Our findings, presented in **Chapter 5** and **Chapter 6**, illustrate that the currently available self-report questionnaires that assess fatigue have limitations. These limitations may be overcome by the development of IRT-adapted versions of existing self-report fatigue questionnaires. Furthermore, the development of IRT-calibrated item banks allows unidimensional assessment of fatigue by computer adapted testing. The recently developed Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue item bank may be helpful in this regard. However, the use of this item bank in patients with neurological disorders remains to be evaluated [34]. In addition, studies on anchor-based responsiveness and the minimal important change score of self-report fatigue questionnaires are needed to establish whether an instrument can detect meaningful changes in patients with MS, PD and stroke.

Pharmacological and non-pharmacological interventions for fatigue in Parkinson's disease

Neurotransmitter imbalance in the basal ganglia may cause fatigue in patients with neurological disorders [35, 36]. Therefore, pharmacological interventions that target neurotransmitter balance in the basal ganglia may reduce fatigue. The results presented in **Chapter 7** suggest that doxepin may reduce fatigue and that rasagiline may reduce, or slow down the progression of physical aspects of fatigue in patients with PD. No evidence was found for the effectiveness of levodopa-carbidopa, memantine, caffeine, methylphenidate or modafinil on fatigue. Based on the current evidence however, no clear recommendations can be provided for the use of pharmacological interventions to treat fatigue in patients with PD.

Acting as a serotonin reuptake inhibitor, the effect of doxepin on fatigue may be explained by recent findings by Pavese and colleagues [37]. They found that fatigue in patients with PD was associated with reduced serotonergic function in the basal ganglia and limbic structures [37]. Although the lack of evidence for the effect of dopaminergic medication on fatigue in patients with PD may be surprising, recent studies [37, 38] showed that patients with and without fatigue had similar striatal dopamine transporter binding. This suggests that dopaminergic nigrostriatal degeneration is not a factor contributing to fatigue in patients with PD. However, reduced Flurorine-18-dopa (18F-dopa) uptake in the insular cortex in patients with fatigue suggests a possible link between fatigue and loss of extrastriatal dopaminergic function [37]. Above findings suggest the involvement of the serotonergic system in fatigue, and it is likely that changes in the serotonin-dopamine balance within the basal ganglia contribute to fatigue in patients with PD [37]. These findings however, have to be confirmed in future studies aimed to increase brain level of serotonin and serotonergic transmission [37].

Although there has been increasing support for non-pharmacological interventions as an adjuvant to pharmacological treatment in patients with PD [39], our meta-analysis in **Chapter 7** shows that exercise did not significantly affect the impact of fatigue on ADL and fatigue severity in patients with PD. This is disappointing, as accumulating evidence suggests that exercise improves depression in the general population [40]. In addition, intensive goal-based exercise therapy combined with aerobic training may to some degree restore neuroplasticity within the basal ganglia in patients with PD [41, 42]. With that, exercise and aerobic training, may alleviate fatigue in patients with PD.

Despite our broad search strategy, we found no studies that investigated the effect of cognitive-behavioral therapy on fatigue in patients with PD. Programs that target be-

havioral or cognitive aspects of maladaptive behavior or coping related to fatigue, may have positive effects in patients with PD. Furthermore, these programs accommodate recent developments in conceptualizing health as a patient's ability to cope and to self manage disease without focusing on complete wellbeing [43].

The lack of effect in the studies included in our Cochrane Review may be explained by a number of methodological issues. First, despite the development of more robust IRT-adapted versions, the original FSS was commonly used as outcome measure. Eight out of eleven studies used the FSS to investigate the effect of interventions on fatigue in patients with PD. As the FSS may measure aspects of both impact of fatigue on ADL and fatigue severity, the summed total score may obscure underlying improvement in one of these specific constructs. The use of IRT-adapted versions of the FSS [27, 29, 30] may improve precision of outcome measurement. Therefore, we suggest that future studies should include different item-versions of the FSS; this allows sensitivity analyses that facilitate the selection of the most responsive version of the FSS. Second, most studies did not select patients on the basis of fatigue severity or underlying depressive disorders. One may argue that interventions may be more beneficial in patients explicitly reporting subjective fatigue and, as mentioned previously, it is likely that patients with depressive disorders respond different to treatment for fatigue than non-depressed patients. Third, Lou and colleagues [7] suggested that physical and mental fatigue are different symptoms in patients with PD and need to be managed separately. Unfortunately, none of the studies identified in **Chapter 7** investigated interventions that targeted physical or mental aspects of fatigue specifically. Finally, no studies investigated the effect of multimodal programs on fatigue. This is surprising, as fatigue is believed to result from several interacting factors [36], and recent evidence shows that a majority of patients experience comorbid depression, anxiety, or sleep disorders that may exacerbate feelings of fatigue [16, 18, 19].

The results presented in **Chapter 7** illustrate the lack evidence for the treatment of fatigue in patients with PD. As fatigue may be secondary to motor symptoms, mood and sleep disorders, effort should be made to manage these symptoms, since some patients might benefit [17]. Dopaminergic medication, if necessary in combination with antidepressants, may improve effort capacity and effort tolerance. A combination of pharmacological interventions and exercise therapy that target factors contributing to fatigue and physical activity may provide synergistic benefits and may alleviate symptoms of subjective fatigue in patients with PD. However, the effects of these multimodal programs have to be investigated in future RCTs.

Implications for practice

It is believed that fatigue has a negative impact on HRQOL and patients often complain that fatigue limits their physical activity. However, the impact of fatigue on HRQOL and physical activity in patients with PD is small and likely distorted by depression and anxiety. Therefore, the evaluation of fatigue should always encompass a comprehensive assessment of mood disorders.

Although the FACIT-F and the FSS show promise for the unidimensional assessment of fatigue, the structural validity of these self-report questionnaires seems to be inadequate. Robust IRT-adapted versions of these instruments allow a more valid and accurate measurement of fatigue in patients with PD. The MFI can be used to distinguish physical and mental aspects of fatigue in patients with PD but structural validity of the MFI remains to be confirmed in future studies.

Based on the current evidence, it is difficult to provide recommendations for the treatment of fatigue in patients with PD. Doxepin may reduce the impact of fatigue on ADL and fatigue severity; however, this finding has to be confirmed in future RCTs. Rasagiline may reduce levels of physical fatigue in patients with PD, whereas no evidence was found for the effectiveness of levodopa-carbidopa, memantine, caffeine, methylphenidate, modafinil and exercise. Patient characteristics, such as characteristics of perceived fatigue and underlying mood disorders, should be considered when treating fatigue in patients with PD. Effective pharmacological treatment of underlying depression, anxiety and sleep disorders may improve effort tolerance and should precede participation in an exercise program that aims to improve effort capacity. A combination of dopaminergic treatment, antidepressants and exercise therapy may provide synergistic benefits not seen with either intervention alone.

Implications for research

The findings presented in this thesis suggest that fatigue and physical activity in patients with PD should be understood in terms of reduced effort tolerance and is linked to abnormalities of the neurobiological stress system and changes in the serotonin-dopamine balance within the basal ganglia. However, the exact underlying neurobiological pathways that contribute to perceived fatigue, HRQOL and physical activity remain unclear. Future translational research programs should focus on the assumed underlying neurohormonal mechanisms, neurotransmitter balance and clinical aspects reflecting effort capacity, effort tolerance and physical activity in patients with PD. For this purpose, studies with a longitudinal research design

are needed using repeated measurements in time. The clinical assessments should cover the different levels of International Classification of Functioning, Disability and Health (ICF) [44], with both self-report and objective measurement of physical activity using ambulatory accelerometers. In addition to self-report assessment of fatigue, quantifying fatigability may improve our understanding of peripheral control systems that contribute to perceived fatigue in patients with PD. These intensive repeated measurements in time allow us to investigate the short term and long term quasi-causal association between, on the one hand, fatigue and on the other hand HRQOL, actual performed physical activity and underlying neurobiological and peripheral mechanisms in patients with PD. Furthermore, these measurements may provide insight in diurnal physical activity in patients with PD, and how patients learn to cope with their fatigue.

Structural validity of self-report fatigue questionnaires should be confirmed in studies that use robust IRT methods. Moreover, the development of IRT-calibrated item banks allows the unidimensional assessment of fatigue by computer adapted testing. Studies on anchor-based responsiveness and the minimal important change score of fatigue questionnaires in patients with MS, PD and stroke are needed to establish whether an instrument can detect meaningful changes. Reaching international consensus about a core set of self-report fatigue questionnaires that should be included in RCTs will facilitate combining study results in meta-analyses.

Well-designed and adequately powered RCTs are needed to investigate the effect of intensive goal-based exercise in combination with aerobic training on exercise capacity, exercise tolerance, fatigue and HRQOL in patients with PD. Future studies should focus on programs that target the behavioral or cognitive aspects of maladaptive behavior or coping related to fatigue in patients with PD. Finally, the role of patient characteristics, such as characteristics of perceived fatigue and underlying mood disorders should be considered when studying the impact of pharmacological and non-pharmacological interventions for fatigue.

Concluding remarks

Although patients with PD often complain that fatigue has an impact on HRQOL and limits their physical activities, our data suggest that fatigue is a relatively minor factor in the complex array of aspects that determine HRQOL and physical activity. Underlying depressive symptoms distort the longitudinal association between, on the one hand, fatigue and on the other hand HRQOL and physical activity in patients with

PD. This suggests the involvement of neurobiological stress system dysfunction in the adaptation and recovery from physical activity. Self-report fatigue questionnaires validated in patients with PD currently show inadequate structural validity; therefore, the development of IRT-adapted versions and IRT-calibrated item banks is needed. At present, no clear recommendations can be made for the treatment of subjective fatigue. Patient characteristics, such as characteristics of perceived fatigue, underlying depression, anxiety and other factors that contribute to HRQOL and physical activity should be managed first when treating fatigue in patients with PD.

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