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

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Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Both motor and non-motor symptoms contribute to disability and reduced quality of life. Fatigue is common in patients with PD, and one third of patients consider fatigue as their most disabling symptom. Despite a growing number of scientific publications about fatigue in PD, fundamental questions regarding the impact of fatigue on daily life and physical activity, as well as the assessment and treatment of fatigue remain unanswered.

Chapter 1 presents the rationale for this thesis. The overall objectives were threefold. First, we aimed to investigate the longitudinal association between on the one hand perceived fatigue and on the other hand disease-specific health-related quality of life (HRQOL) and actual performed physical activity in patients with PD. Subsequently, we developed a multivariable logistic regression model for predicting community walking in patients with PD. Second, we aimed to investigate the measurement properties of self-report fatigue questionnaires that are currently used in patients with PD. Third, we systematically reviewed the effect of pharmacological and non-pharmacological interventions on fatigue in patients with PD.

For the results presented in **Chapter 2**, **Chapter 3**, **Chapter 4** and **Chapter 6**, we analyzed data collected in the 'Rescue' trial (Rehabilitation in Parkinson's disease: strategies for cueing). This randomized clinical trial (RCT) was a collaboration between three European centers: Northumbria University, Newcastle upon Tyne (UK); Katholieke Universiteit Leuven, Leuven (Belgium); and the VU University Medical Center, Amsterdam (The Netherlands). This study used four repeated assessments over three months time to investigate the effects of cueing training on gait and gait-related activity in patients with PD. We used longitudinal regression analyses to investigate the relationship in time between on the one hand perceived fatigue and on the other hand HRQOL and actual performed physical activity.

Chapter 2 presents the longitudinal association between the impact of fatigue and HRQOL. We used baseline, 3-, 6- and 12-week assessments of the 'Rescue' trial. In this cohort of 153 patients, HRQOL was assessed with the Parkinson's disease Questionnaire-39 (PDQ-39) while the Multidimensional Fatigue Inventory (MFI) was used to assess fatigue. Time-independent and time-dependent factors were investigated for their bivariate association with HRQOL by applying random coefficient analysis.We showed that the impact of fatigue was significantly associated with poorer quality of life ($\beta = 0.24$, 95% confidence interval (CI) = 0.18 to 0.30). Adding depression

and anxiety to the regression model, significantly decreased the association between fatigue and HRQOL by 30.0% and 24.1% respectively. After controlling for all potential confounders (i.e. cueing training, age, gender, social support, disease duration, disease severity, motor impairment, cognition and medication intake), fatigue remained significantly associated with HRQOL (β = 0.12, 95% CI = 0.06 to 0.18, r^2 = 2.3%). These results show that patients who experience higher levels of fatigue report lower quality of life. However, the unique contribution of fatigue to overall HRQOL is rather small, and the longitudinal association between fatigue and HRQOL was distorted by depression and anxiety. This suggests that when evaluating fatigue in patients with PD, the influence of depression and anxiety should be considered.

In **Chapter 3** we investigated the longitudinal association between fatigue and physical activity in patients with PD. Subsequently, we determined whether this association was distorted by other factors. Data from baseline, 3-, 6-, and 12-week assessments were used (N = 153). The MFI was used to assess fatigue and ambulatory accelerometry to measure the amount of physical activity (defined as % dynamic activity during each monitoring session). We used random coefficient analysis to investigate time-independent and time-dependent factors for their bivariate association with dynamic activity. Our data showed that more fatigue was significantly associated with reduced physical activity (β = -0.099, standard error (SE) = 0.032, p = 0.002). This association was not significantly distorted by type of intervention, age, gender, social support, disease duration, disease severity, motor impairment, cognition, anxiety and medication intake. However, adding depression to the regression model caused a proportional increase of 22.2% in the regression coefficient of the MFI. After controlling for all candidate confounders, fatigue remained significantly associated with physical activity (β = -0.092, SE = 0.037, p = 0.013, r^2 = 2.0%). This finding suggests that patients who experience higher levels of fatigue are less physically active. However, the total explained variance of dynamic activity by fatigue alone is small, suggesting that fatigue is only a minor factor in the complex array of aspects that affect physical activity in patients with PD.

In **Chapter 4** we developed a multivariable logistic regression model to predict community walking in patients with PD. Gait speed, age, gender, marital status, disease duration, disease severity, motor impairment, balance, freezing of gait, fear of falling, previous falls, cognitive function, fatigue, anxiety and depression were investigated for their contribution to the model. We used data from baseline assessments of the 'Rescue' trial (N = 153). Community walking was evaluated using the mobility domain of the Nottingham Extended Activities of Daily Living Index (NEAI). Items are scored

on a 4-point scale ranging from 0 (not at all) to 3 (on your own). Patients who scored 3 points on item 1 ('Did you walk around outside?') and item 5 ('Did you cross roads?') were considered community walkers. Gait speed was measured with the 6-m or 10-m timed walking test. Seventy patients (46%) were classified as community walkers. We found that a gait speed of 0.88 m/s or higher correctly predicted 70% of patients as community walkers. The multivariable regression model, including gait speed and fear of falling, correctly predicted 78% of patients as community walkers. Our results show that timed walking tests are valid measurements to predict community walking and suggest that a rehabilitation program targeting gait speed and fear of falling may facilitate community walking in patients with PD.

Chapter 5 presents a systematic review in which we critically appraised, compared and summarized the measurement properties of self-report fatigue questionnaires. We searched, up to November 2010, MEDLINE, EMBASE, PsycINFO, CINAHL and SPORTdiscus for studies that validated self-report fatigue questionnaires in patients with multiple sclerosis (MS), PD or stroke. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist was used to assess the methodological quality of studies and to perform a qualitative data synthesis to rate measurement properties for each questionnaire. Thirty-eight studies out of 5,336 records met our inclusion criteria, evaluating 31 questionnaires. Moderate evidence was found for adequate internal consistency and structural validity of the multidimensional Fatigue Scale for Motor and Cognitive functions (FSMC) and adequate reliability and structural validity of the Unidimensional Fatigue Impact Scale (U-FIS) in patients with MS. The Functional Assessment of Chronic Illness Therapy Fatigue subscale (FACIT-F) and Fatigue Severity Scale (FSS) showed promise for the unidimensional assessment of fatigue in patients with PD, and the Profile Of Mood States Fatigue subscale (POMS-F) for stroke. None of the multidimensional fatigue questionnaires were adequately validated in patients with PD or stroke. These results however, should be considered with caution, as the level of evidence supporting the overall quality of most measurement properties was limited. In addition, studies investigating measurement error, responsiveness and interpretability were lacking.

In **Chapter 6** we used the COSMIN taxonomy to investigate internal consistency, test-retest reliability, measurement error, structural validity, and floor and ceiling effects of the MFI in patients with PD. One hundred and fifty-three patients who participated in the 'Rescue' trial completed the MFI at baseline and week 3. Cronbach's α for internal consistency of the MFI-total and all subscales ranged from 0.74 (reduced motivation subscale) to 0.92 (MFI-total). The intraclass correlation coefficient ranged from 0.65

for the mental fatigue subscale to 0.81 for the physical fatigue subscale. The smallest detectable change ranged from 6 points for the physical fatigue and reduced motivation subscales, to 24 points for the MFI-total. Bland and Altman analyses showed no systematic differences between assessments. A floor effect was found for mental fatigue and ceiling effects for the physical fatigue and reduced activity subscales. Principal component analysis yielded a four-factor model. The first factor was interpreted as a combination of the general fatigue and physical fatigue dimensions and the other three factors as the mental fatigue, reduced motivation and reduced activity dimensions. Our results show that the MFI is a reliable and valid questionnaire to assess fatigue in patients with PD. However, it remains unclear if measurement error is acceptable in the assessment of change, and whether the originally proposed five dimensions of the MFI validly measure the different aspects of fatigue in patients with PD. The found four-factor model shows that the general fatigue subscale, which has been proposed as a short assessment of fatigue, mainly reflects physical aspects of fatigue. This suggests that this subscale may not be valid to represent all dimensions of fatigue measured with the MFI. The construct of underlying dimensions of fatigue has to be confirmed in future studies. Furthermore, methodologically sound studies on anchor-based responsiveness and the minimal important change scores of fatigue measures are needed in patients with PD.

Chapter 7 presents a Cochrane Review in which we investigated the effect of pharmacological and non-pharmacological interventions on fatigue in patients with PD. We searched, up to December 2013, CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO, PEDro and the WHO International Clinical Trials Registry Platform Search Portal for randomized controlled trials (RCTs). Eleven studies out of 1,136 records met our inclusion criteria, evaluating a total of 1817 patients. Nine studies investigated the effects of medication (i.e. levodopa-carbidopa, memantine, rasagiline, caffeine, methylphenidate, modafinil or doxepin) and two studies investigated the effect of exercise on fatigue. We found low quality evidence that doxepin reduced the impact of fatigue on ADL or fatigue severity (one study, N = 12, standardized mean difference (SMD) = -1.50, 95% CI = -2.84 to -0.15), and high quality evidence that rasagiline reduced or slowed down the progression of physical aspects of fatigue (one study, N = 1,176, SMD = -0.27, 95% CI = -0.39 to -0.16, I^2 = 0%). We found no evidence that exercise significantly reduced the impact of fatigue on ADL or fatigue severity (two studies, N = 57, SMD = -0.45, 95% CI = -1.21 to 0.32, I^2 = 44%) in patients with PD. Based on the current evidence, no clear recommendations for the treatment of subjective fatigue in PD can be made. Doxepin may reduce the impact of fatigue on ADL and fatigue severity and rasagiline may be effective in reducing levels of physical fatigue in PD. However,

these findings have to be confirmed in future RCTs. As depressive disorders may modify the effect of interventions on subjective fatigue in patients with PD, treatment of fatigue should always be accompanied by assessment of underlying depression.

In **Chapter 8** we discuss the main results of this thesis and present implications for clinical practice and research. Although patients with PD often complain that fatigue has an impact on HRQOL and limits their physical activities, we found that perceived fatigue is relatively a minor factor in the complex of aspects that determine HRQOL and physical activity. The found longitudinal associations between on the one hand fatigue and on the other hand HRQOL and physical activity were distorted by mood disorders. This suggests that the evaluation of fatigue in patients with PD should include screening for underlying depression and anxiety. The distortion of the longitudinal association between fatigue and physical activity by depression may suggest the involvement of neurobiological stress system dysfunction in the adaptation to, and recovery from physical activity in patients with fatigue. Therefore, underlying mood disorders and sleep disorders should be treated before patients participate in an exercise program that aims to improve effort capacity.

Results in **Chapter 5** and the principal component analysis in **Chapter 6** show inadequate structural validity of the self-report fatigue questionnaires used in patients with PD. This limitation 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 and may improve precise measurement of fatigue.

No clear recommendations can be made for the treatment of subjective fatigue. Combined pharmacological and exercise interventions 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. Patient characteristics, such as underlying depression, anxiety and other factors that contribute to HRQOL and physical activity, should be assessed and managed first before treating fatigue in patients with PD.