Shedding light on depressive, anxiety and sleep disorders in Parkinson's disease

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English summary

Parkinson's disease (PD) is a neurodegenerative disorder affecting 1,350 out of 100,000 people in the Netherlands. The disease is known for its characteristic movement complaints or motor symptoms: trembling, rigidity, slowness, a disturbed balance and a decrease of spontaneous movement and mimicry. PD, however, is also accompanied by a range of non-motor symptoms, including dysfunctions of the autonomic nervous system (problems with the regulation of body temperature, blood pressure, bladder function, gastro-intestinal tract and sexual functions), sleep problems and psychiatric disorders.

Common psychiatric disorders in PD patients are psychosis, apathy, anxiety, depressive and impulse control disorders. These psychiatric disorders are caused by a combination of biological, social and psychological factors. Anxiety and depression, for example, are an understandable response to the diagnosis of PD: an incurable disease, that increasingly causes disability. Biological factors, however, also play an important causal role. Neuroimaging studies demonstrate that the neurobiological changes resulting from the neurodegenerative process are associated with psychiatric symptoms. Moreover, PD patients appear to be prone to disturbances of the circadian system. The circadian system synchronizes our personal biorhythm with the 24-hour societal rhythm. A disturbed circadian rhythm is associated with sleep and mood disorders, e.g. seasonal affective disorder.

Many PD patients suffer from sleep disturbances, ranging from excessive daytime sleepiness to insomnia. Specific sleep disorders, like the REM-sleep behaviour disorder, are also more common in PD patients than in the general population. About one in three PD patients develop an anxiety disorder during the course of the disease, and 17% a depressive disorder. In addition, a substantial amount of PD patients suffer from clinically relevant symptoms of anxiety or depression, without fulfilling diagnostic criteria for a psychiatric disorder. Anxiety and depression have a large negative impact on daily functioning and quality of life of both PD patients and their caretakers.

This thesis mainly focuses on anxiety, depressive and sleep disorders in PD. **Chapter 1** provides a general introduction on these subjects, and gives an outline of the aims of this thesis.

In PD patients, anxiety and depression often co-occur, and different studies found an association with sleep disorders. However, the diagnostic process of these disorders is hampered by an overlap and interaction with other PD-related symptoms. The aim of the first part of this thesis (**Chapter 2, 3 and 4**) is to gain more insight in anxiety, depressive and sleep disorders in patients with PD, their reciprocal relationships, and their association with other PD-related symptoms.

In **Chapter 2**, we studied the symptom dimensions of anxiety in a sample of 295 PD patients. Anxiety was measured with a questionnaire, the Beck Anxiety Inventory (BAI). The items of the BAI were subdivided in subscales, or symptom dimensions, using a principal component analysis. We found four 'somatic' subscales, measuring physical symptoms, and one 'affective' subscale, containing items on fearful cognitions and emotions. Looking at the relationships between these subscales and other PD-related symptoms, we found that all subscales had an association with the score on a questionnaire for depression. This confirms the strong relationship between anxiety and depression in PD found in previous studies. There was also a significant association between the somatic subscales and the scores on measuring instruments for autonomic dysfunctions and motor symptoms, while this association was

not statistically significant for the affective subscale. This suggests that the affective subscale of the BAI is a more 'pure' measure of anxiety, as it is not affected by 'noise' generated by physical symptoms of PD. However, a distinction between anxiety and physical symptoms would be artificial in clinical practice, as it is well-known that anxiety and physical symptoms are interwoven in PD patients. Anxiety and motor symptoms can mimic, but also cause and amplify one another.

As the diagnostics of anxiety disorders in PD patients is complex, PD patients with anxiety may be more easily detected in clinical practice if more was known about risk factors for anxiety. In **Chapter 3** we present the results of a longitudinal study on predictors of the course of anxiety in a group of 306 patients that were recently diagnosed with PD. We found four predictors: depressive symptoms, symptoms of impulse control disorders, cognitive impairment and the presence of a REM-sleep behaviour disorder. The course of symptoms of depression and impulse control disorders was similar to the course of anxiety: participants had more severe symptoms at baseline, and these symptoms decreased during the two years of follow-up. This could be explained by a psychological reaction to the diagnosis, followed by a psychological adjustment over time. The presence of cognitive dysfunctions at baseline was a risk factor for an increase in symptoms of anxiety during follow-up. This could be due to a decreased capacity to adjust to stressful situations due to cognitive disorders. Finally, the presence of a REM-sleep behaviour disorder was a predictor of an increase of anxiety. This may be the result of qualitatively poor sleep due to the sleep disorder. Research has demonstrated that poor night-time sleep negatively impacts the ability to regulate emotions, which might increase the risk of developing an anxiety disorder. A final possible explanation for the associations we found in this study, is a more diffuse underlying neurodegenerative process in PD patients with cognitive, sleep and psychiatric disorders, as neuropathological and neuroimaging studies suggest.

In **Chapter 2 and 3**, we found an association between depressive, anxiety and sleep disorders in PD. In **Chapter 4**, we studied the temporal relationship between these disorders more closely. In a cohort of 361 PD patients, we found that the relationship is bidirectional: participants with more severe symptoms of anxiety and depression were more likely to suffer from insomnia at follow-up, and vice versa, we found that insomnia was a predictor for more severe symptoms of anxiety after 6 months. We hypothesize that both anxiety / depression and insomnia can cause a downward spiral, in which one problem can cause and amplify the other.

In the second part of this thesis, we shift the focus from diagnostics to treatment. The pharmacological treatment of sleep disorders, anxiety and depression is associated with side effects, like an increased risk of falls. Many PD patients prefer non-pharmacological treatment options, because they already have to use a lot of medications to ameliorate the symptoms of PD. Therefore, there is an increasing interest in non-pharmacological treatments. In the second part of this thesis (**Chapter 5 to 9**) we focus on non-pharmacological treatment options for PD patients.

In **Chapter 5**, I present the results of a meta-analysis on the effects of two psychological interventions, cognitive behavioural therapy and mindfulness-based therapies, on psychological distress on patients with three different neurodegenerative disorders: PD, multiple sclerosis and Huntington's disease. We did not find any randomized, controlled clinical trials studying patients with Huntington's disease. Overall, studies in PD and multiple sclerosis patients had insufficient methodological quality, but showed a small to moderate therapeutic effect, suggesting that psychological interventions could have a positive effect on psychological wellbeing in these patients.

In **Chapter 6**, we introduce light therapy as a non-pharmacological treatment option for insomnia and depressive disorders in PD. In this review, we describe how the circadian system can be negatively impacted by various factors, resulting in a desynchronization of the circadian rhythm with the societal 24-hour rhythm. Multiple studies in PD patients found a phase shift and decreased amplitude of the circadian rhythm. We hypothesize that this circadian disturbances are a causal factor in the frequent occurrence of sleep and depressive disorders in PD. Light therapy can restore circadian rhythmicity, and is therefore a potential non-pharmacological treatment option for sleep and depressive disorders in PD patients. Previous studies on this subject confirm the positive effects of light therapy on sleep, mood and motor symptoms in PD patients. However, no randomized, controlled studies were performed yet; we target this issue in the final chapters of this thesis.

In **Chapter 7** we describe the results of an industry-initiated, multicentre, double-blind, randomized clinical trial on the efficacy and safety of Spectramax light therapy as an adjuvant treatment for PD. We randomized 92 PD patients to treatment with Spectramax light therapy or control light therapy. The Spectramax light therapy device emits 950 Lux blue/green light with a specific bandwidth, which is thought to be specifically effective in PD patients. We expected no effects of the control light therapy on the circadian system. Participants were treated at home for one hour daily for a total period of six months. At the end of treatment, we found no difference between both treatment groups on the primary outcome, the sum score of Part I, II and III of the Movement Disorders Society – Unified Parkinson's Disease Rating Scale, which is a measure for motor and non-motor symptoms of PD. We did find, however, a larger decrease in non-motor symptoms, including psychiatric symptoms, in the group treated with Spectramax light therapy, as well as a larger improvement of quality of life and a trend-effect on excessive daytime sleepiness. Treatment with Spectramax light therapy was not associated with any clinically relevant adverse effects, and was generally well-tolerated. These results suggest that Spectramax light therapy may have a positive effect on non-motor symptoms, warranting further research.

In **Chapter 8** we describe the study protocol of a double-blind randomized clinical trial initiated by our own research team, in which we compare the effects of bright light therapy on depression in PD with control light therapy. Participants in this study were diagnosed with PD and a depressive disorder. They were treated for 30 minutes in the morning and evening for a period of three months with either bright light therapy (white light, 10,000 Lux) or a control light (dimmed white light, 200 Lux) of which we expected no effect on the circadian system. In both groups, we imposed sleep-wake structure due to fixed timing of light therapy: all participants had to get up at a fixed time for morning light therapy and were advised to go to bed approximately one hour after evening therapy. The primary outcome measure was depression severity, as assessed with the Hamilton Depression Rating Scale. Secondary outcomes were – amongst others – sleep and the salivary concentrations of melatonin and cortisol, which are markers of the circadian rhythm.

In **Chapter 9**, we present the results of this study. Both treatment groups showed an improvement of sleep and mood. However, a combination of sleep-wake structuring and bright light therapy did not result in a statistically significant larger decrease in depressive symptoms, than sleep-wake structuring and control light therapy. Based on these findings, we cannot recommend bright light therapy as a treatment for depressive disorders in PD patients. Nevertheless, in 44% of participants in the control group and 56% of participants in the light therapy group, the depressive disorder was in remission at the end of treatment. We hypothesize that the reduction in depressive symptoms in both groups is partially

due to a placebo-effect, and partially to an improvement of the sleep-wake rhythm. We did find a significant difference between-group difference in subjective sleep quality at the end of treatment: there was a larger improvement in the group treated with bright light therapy, as compared to the control group. Moreover, participants treated with bright light therapy showed a significant decrease in cortisol concentrations after treatment. We therefore hypothesize that the improvement of subjective sleep quality is due to a decreased cortisol secretion in response to bright light therapy.

In **Chapter 10**, I summarize and comment on the findings of this thesis. I describe how there is a reciprocal interaction and overlap between anxiety, depressive and sleep disorders and other PD-related symptoms, which complicates both the diagnostic process and treatment of PD patients. In this chapter, I make a plead for a more integrated psycho-somatic concept of PD, and a multidisciplinary treatment of PD patients. Moreover, I discuss the importance of research on the different phenotypes of PD, qualitative research and n = 1 studies, that can provide a starting point for a more personalized treatment of PD patients. I argue that the etiology of anxiety, depressive and sleep disorders in PD patients is multifactorial, and that psychological as well as biological factors, including circadian disturbances, play an important role. As light therapy has a positive effect on various non-motor symptoms in PD, this non-pharmacological treatment option is an interesting subject for future research.