Clinical Predictors of disease progression in Parkinson's disease

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Chapter 8:

Summary, concluding remarks and future perspectives

In this thesis, longitudinal analyses have been performed on the PROPARK-Cohort, a hospital-based cohort of 421 patients followed for a period of five years. The main focus of this thesis was to determine which predictors and associated factors contributed to the development of certain non-motor symptoms in Parkinson's disease (PD). Strengths of our cohort study include the length of the follow-up period, broad clinical characterization, limited loss-to-follow-up and the large cohort size. The following non-motor symptoms have been addressed in this thesis: psychosis (hallucinations), dementia, excessive daytime sleepiness (EDS), insomnia, depression and anxiety.

Chapter 1 is the introduction of this thesis that describes the history of PD, its disease course and the challenges in current treatment methods for motor symptoms. In addition, a short introduction is presented regarding the different non-motor symptoms and their potential impact on the quality of life of patients with PD.
In the second part of this chapter, the aims are described and an outline of the non-motor symptoms addressed in this thesis is given. The importance of differentiating and identifying patients at risk to develop certain non-motor symptoms is illustrated, so that caregivers can better anticipate and recognize these symptoms. Furthermore, an overview of the different statistical methods applied in our analyses to identify risk factors of certain non-motor symptoms is provided. Chapter 1 ends with a chapter outline, in which the findings and shortcomings of past studies on this subject are presented.

Chapter 2 presents the main predictors for the development of hallucinations in PD. Twenty-one percent of the patients in our cohort had hallucinations at baseline, whereas 46% of the patients without hallucinations at baseline developed this feature during follow-up. We found that hallucinations in PD are caused by a combination of interacting risk factors that are associated with older age and more advanced disease.
In addition, longer disease duration, more severe depressive and autonomic symptoms, cognitive impairment, sleep disturbances and higher levodopa dose were associated with the development of hallucinations. This indicates that patients with these characteristics must be followed-up more carefully for the development of hallucinations. If these symptoms occur, adjustments of the medication regimen should be considered to prevent the development of psychosis. The identification of female sex as a risk factor for developing of hallucinations in PD was a new finding and should be verified in future studies.

In **chapter 3,** we report on the predictors for dementia in PD. Dementia is a frequent and devastating development in PD. Some longitudinal studies in PD have reported prevalence rates as high as 80-100% in cases that were followed up for 20 years.[1] In our cohort, thirty-

two percent of patients had dementia at baseline, while 26% of patients without dementia at baseline developed dementia within a follow-up period of five years. Similar to our findings regarding hallucinations in the previous chapter, we found that the onset of dementia in PD involves a combination of potentially interacting risk factors that are associated with higher age and more advanced disease. Motor symptoms such as postural instability and gait difficulty (PIGD), dyskinesias and non-dopaminergic symptoms such as autonomic dysfunction, EDS, hallucinations and depression are predictors of dementia in patients with PD.

The objective of **chapter 4** is to examine persistency, cross-sectional and longitudinal associations, and risk factors for EDS in patients with PD. Our cohort had a baseline prevalence rate of EDS of 43%, while 46% of the patients without EDS at baseline developed this symptom during follow-up. In addition, EDS was found to be a non-persistent symptom, although the persistency and the proportion of patients with EDS increased with longer follow-up. Male gender, insomnia, cognitive and autonomic dysfunction, hallucinations, less severe dyskinesias, dose of dopamine agonists and use of antihypertensives were associated with more severe EDS over time, while use of benzodiazepines was associated with less severe EDS symptoms. More EDS symptoms and a PIGD-dominant phenotype were risk factors for future EDS. These findings suggest that with longer disease duration, a large proportion of patients develop EDS. Some risk factors such as dose of dopamine agonists and the use of antihypertensives are modifiable, and patients with risk factors should be monitored to improve quality of life and reduce risk of harm.

Chapter 5 focuses on the course and factors associated with longitudinal changes in insomnia severity in patients with PD. Insomnia is a debilitating symptom in PD that has been scarcely investigated in a longitudinal design. Knowledge of factors associated with occurrence of insomnia may provide clues for an increased understanding of underlying pathophysiology and facilitate early detection. Linear mixed models (LMM) were used to identify factors associated with longitudinal changes in severity of insomnia symptoms and a generalized estimating equations (GEE) analysis was performed to determine which baseline variables were associated with the different aspects of insomnia (sleep initiation or maintenance difficulty). In our cohort, SCOPA-SLEEP-Nighttime Sleep (NS) scores were available for 412 patients at baseline, of whom 110 (27%) had insomnia (i.e. SCOPA-SLEEP-NS score ≥7). Of the remaining 302 patients, 99 (33%) developed insomnia at some point during follow-up. We found that more severe depressive symptoms, motor fluctuations, higher dopamine agonist doses and sleep medication use were independently associated

with more insomnia symptoms over time. The GEE analysis did not identify an unique set of determinants that affected specific aspects of insomnia.

The objective of **chapter 6** is to determine associated and predictive factors of depression in patients with PD. Depression is a common non-motor symptom in PD. Several studies identified depression as the main determinant of a poor quality of life in this population.[2,3] A major challenge for the diagnosis of depression in PD is the overlap of the symptoms associated with depression and the primary symptoms of PD (e.g. masked facies, slowness of movement, fatigue, weight change, loss of concentration, hyper- or insomnia).[4] Increased knowledge of associated and risk factors of depression in PD may facilitate its early detection, provide insight into the nature of this condition, and guide future intervention strategies. We found that the proportion of patients with depression was approximately 20% at baseline and that it remained stable during follow-up, with approximately half of the cases showing a persistent course. Female gender, more severe disability, more severe motor fluctuations, autonomic and cognitive dysfunction, insomnia and EDS were independently associated with more depressive symptoms over time. More baseline depressive symptoms, EDS and a higher levodopa dosage were risk factors for future depression. From these findings we can conclude that apart from motor fluctuations and levodopa dose, depressive symptoms in PD are mainly associated with factors of non-dopaminergic origin. This suggests that depression in PD is an inherent consequence of the progressive pathobiology of the disease, which may explain why treatment with currently available options is difficult.

The purpose of the study described in **chapter 7** is to evaluate which characteristics are associated with longitudinal changes in anxiety in PD. A recent systematic review found an average point prevalence of anxiety disorders in PD of 31%.[5] It is a common symptom in this population and has great influence on quality of life. However, little is known about risk factors for development of anxiety in PD. In this study, LMM was used to identify factors associated with longitudinal changes in Hospital Anxiety and Depression Scale – Anxiety (HADS-A) scores. In addition, survival analysis using data of non-anxious patients at baseline was performed to identify predictors for future anxiety (i.e. HADS-A≥11). Of the 409 patients with a HADS-A score available at baseline, 67 (16%) had anxiety, whereas 64 (19%) of the remaining 342 non-anxious patients developed anxiety after a mean follow-up of 2.6 years. Seventy percent of the patients with anxiety were also depressed. Female gender, cognitive impairment, depressive symptoms, autonomic dysfunction, insomnia and EDS at baseline were associated with more anxiety symptoms over time and, except for female gender and EDS, all these variables were also independent predictors of development of anxiety in non-anxious patients at baseline. Our findings suggest that the

future development of anxiety is associated with female gender, cognitive impairment, autonomic dysfunction, insomnia and EDS. In addition, anxiety and depression usually co-exist and share similar determinants, suggesting a common pathophysiological mechanism.

An overview of the most important longitudinal associations and risk factors described in this thesis is presented in Table 8.1.

Table 8.1: Overview of the results on longitudinal associations of non-motor symptoms in PD*

Outcome	Variables from survival analysis[a]	Variables from LMM[b]
Hallucinations[c]	Female gender ↑ Age-at-onset Dyskinesias EDS Autonomic dysfunction	Female gender ↑ Age-at-onset Dyskinesias EDS Autonomic dysfunction
Dementia[d]	↑ Age ↓ Education EDS ↑ Levodopa dose	↑ Age ↓ Education EDS PIGD ↑ Levodopa dose
EDS	Baseline EDS PIGD dominant phenotype Autonomic dysfunction (UR) Antihypertensive medication	Male gender ↓ Dyskinesias Cognitive impairment Hallucinations Insomnia Autonomic dysfunction (UR, GI) ↑Dopamine agonists dose Antihypertensive medication Not using benzodiazepines
Insomnia[e]	Depressive symptoms	Motor fluctuations Depressive symptoms ↑Dopamine agonists dose Use of sleep medication
Depression	Baseline depressive symptoms EDS ↑ Levodopa dose	Female gender ADL impairment Motor fluctuations Cognitive impairment Insomnia EDS Autonomic dysfunction (CV,UR) Antidepressant use
Anxiety	Cognitive impairment Insomnia Autonomic dysfunction (CV)	Female gender Cognitive impairment Insomnia EDS Autonomic dysfunction (GI, CV) Antidepressant use Benzodiazepine use

Abbreviations: LMM, linear mixed models; EDS, excessive daytime sleepiness; PIGD, postural instability gait difficulty; UR, urinary tract; GI, gastrointestinal; CV, cardiovascular; ADL, activities of daily living

**All variables are listed in descending order of the strength of association with a certain non-motor symptom*

[a]*Which factors are associated with an increased risk to develop a certain symptom in patients who are free of this symptom at baseline?*
[b]*Which factors are associated with longitudinal changes in the severity of a certain symptom?*
[c]*Original manuscript (Chapter 2) did not include a LMM analysis; LMM analysis yielded the same results as the survival analysis.*
[d]*Original analysis described in chapter 3 did not include a LMM analysis; LMM analysis yielded the same results as the survival analysis, except for PIGD as an additional finding.*
[e]*Survival analysis not described in the original publication. After performing the survival analysis, only depressive symptoms was significantly associated with insomnia.*

Concluding remarks

This thesis is based on analyses of data from a large longitudinal cohort of 421 PD patients, followed-up over a period of five years. Survival analysis and linear mixed models (LMM) were applied to identify baseline predictors for the development of a certain non-motor symptom over time. In essence, we tried to find answers to two questions, namely: "Which factors are associated with longitudinal changes in the severity of a certain symptom?" (LMM); and "Which factors are associated with an increased risk to develop a certain symptom in patients who are free of this symptom at baseline?" (Survival analysis). The first method (LMM) gives us a more complete view of factors associated with the variation of a certain symptom over time. The main advantages of this method is that we could use the data from all of our patients in the cohort and that it can deal missing outcomes in data. The second method (survival) is especially interesting from a clinical perspective, because it identifies which factors are responsible for the development of a certain symptom in patients who do not have that symptom at baseline. A potential disadvantage of this method is that a cut-off score has to be used to classify patients. Using a cut-off score to classify patients renders the risk of potential misclassification (over- or underestimation of potential predictors) since individual patient's scores may fluctuate around the cut-off.

At the start of this project, the focus of our studies was on survival analysis. Subsequently it became clear that both methods are complementary. When applied in combination, both methods provide a more comprehensive view of the longitudinal course of particular symptoms. Consequently, LMM was not applied in the original journal publications of chapter 2 (hallucinations) and chapter 3 (dementia). However, after applying the LMM analyses, similar results were found by both methods for these two symptoms, supporting the robustness of our initial findings. The application of a cut-off score also resulted in lower prevalence rates for anxiety and depression in our study. This difference can also be explained by the fact that other studies used different assessment methods to evaluate both symptoms in PD. For anxiety, some studies applied the Diagnostic Mental Manual criteria (DSM) to classify patients.[6] Though this could give a more accurate diagnosis of anxiety and allows identifying the specific subcategory of anxiety disorder (e.g. social phobia, panic disorder), it does not provide information regarding the severity of the symptoms. Another explanation for the lower prevalence rate for anxiety in our study could be the fact that we applied a more conservative cut-off of 10/11 ('probable anxiety') instead of 7/8 ('possible anxiety'), which could have led to an underestimation of anxiety rates in our study.

When interpreting the results of our analyses it is important to consider the composition of our study population. Our study is hospital-based and not population-based, and we applied

a pre-stratification strategy based on age-at-onset and disease duration. This may have affected the prevalence, the severity of certain symptoms and therefore the generalizability of our findings. However, the objective of our study was not to calculate the incidence proportion of a certain non-motor symptom, but to identify predictors for the development of this symptom. We cannot rule out that the increase in variation in age-at-onset and disease duration caused by our sampling strategy may have affected the strengths of the identified relations to some extent if compared to what would have been found in a population-based sample. Still, most associations found in our study, were quite strong. Hence it is unlikely that a selection bias may have contributed to the identification of predictors that are not generalizable to other populations. For instance, the predictors we described for EDS in chapter 3 were largely similar to those found by the Norwegian population-based study.[7]

The interaction of PD with age

Age was found to be an independent predictor of dementia in our study. This finding has been reported by several longitudinal studies and altogether this suggests an intrinsic relation between age and advancing disease which underlies the development of many late complications of PD.[8-11] Other symptoms that are mainly seen in older patients with advanced PD include autonomic dysfunction, PIGD, hallucinations and freezing.[12] Past studies showed that age also seems to interact with the severity of motor symptoms. In a prospective cohort study of non-demented PD cases, the combined effect of increasing age (>72 years) and severity of motor signs (median total Unified Parkinson's Disease Rating Scale motor score>24) was associated with a 10-fold risk of dementia, whereas the risk of dementia for PD patients with an age equal to or less than 72 years and motor signs (median total Unified Parkinson's Disease Rating Scale motor score>24) was not significantly elevated.[13]

In addition, we found that age also predicted a more persistent course of certain non-motor symptoms. For instance, in **chapter 6** we found that patients with persistent depression were often older at baseline (Table S6.1).

In fact, several studies suggested that age is an important modulating factor in the disease progression of PD. In an 8-year longitudinal study, patients who were older at onset had a more rapid decline in motor function, with an average annual decline of 2.6 points for those 50 years of age and 3.8 points for those who were 70.[14] Furthermore, a review on disease progression patterns of PD done by van Rooden et al. also showed that the disease profile of an older age-at-onset is associated with a more rapid disease progression.[15] Our study supports this finding and we found that a higher age-at-onset of PD indeed puts a patients more at risk to develop hallucinations (**chapter 2**).

The role of gender in non-motor symptoms

While PD in general seems to occur more frequently in men and at an earlier age in men,[16,17] we found that several non-motor symptoms of PD (hallucinations, depressive- and anxiety symptoms) occur more frequently in women. Earlier studies have already reported the association between female gender and depression/anxiety in PD, and it is a well-known phenomenon that females in the general population have a higher lifetime risk to develop depression or anxiety.[18,19] However, the higher risk for females to develop hallucinations has not been reported earlier and is a new finding. A potential explanation for this finding could be that female patients are more susceptible to develop side-effects of dopaminergic medication, which is supported by an earlier finding that female patients more often suffer from levodopa-induced dyskinesias.[20] This higher susceptibility for dopaminergic medication-induced side-effect in females is possibly due to the mediating effect of estrogen on the bioavailability of levodopa in the body.[21] This phenomenon could also explain why females have slower disease progression and milder motor deterioration in PD. According to an earlier single photon emission computed tomography (SPECT) study, this difference is probably due to a higher physiological striatal dopamine level in female PD patients.[22] There is also some evidence that other non-motor symptoms occur more frequently in males such as dementia and EDS.[8,10,23] In our study, we only confirmed this association for EDS, the higher risk for males to develop dementia was not found and some past longitudinal studies also did not find an association between male gender and dementia.[24,25] Altogether, our findings suggest that there is a clear role for gender in the development of some specific non-motor symptoms (EDS, depression and anxiety), while for other symptoms this relationship still needs to be confirmed by future studies (dementia and hallucinations).

The role of dopamine agonists

As mentioned earlier, non-motor symptoms have a significant impact on the quality of life in patients with PD. Antiparkinsonian agents are mainly targeted towards dopaminergic (motor) symptoms and often provide no benefit for non-motor symptoms, which are mainly of non-dopaminergic origin.[26] There is some evidence that dopamine agonists could improve depressive symptoms in PD, but this relationship was not consistently found.[27,28] Nevertheless, dopamine agonists could cause or even worsen other non-dopaminergic symptoms such as EDS,[29] hallucinations,[30] orthostatic hypotension[31] and impulse control disorders such as compulsive shopping or excessive gambling.[32,33] In our study, we found that higher doses of dopamine agonists is an independent predictor of EDS and insomnia. Dopamine agonists could have an impact on sleep in PD in different ways. Firstly, treatment with dopamine agonists increases the patients risk to develop visual hallucinations without insight, which in turn could cause nocturnal sleep disturbances such as sleep fragmentation,

vivid dreams/nightmares and acting out dreams.[34] Further, dopamine agonists have biphasic effects on sleep-wakefulness and this effect has been attributed to D2 receptor stimulation; at low doses they reduce wakefulness and enhance sleep, whereas at high doses they induce opposite effects.[35] The importance of dopamine agonist dose on the occurrence of a non-motor symptom is also illustrated by the study by Evans et al.,[36] who found that impulse control disorders are associated with an increased dopaminergic activation of the ventral striatum.[36]

In conclusion, while certain non-motor symptoms are inherent components of PD that increase in severity as the disease progresses, others are inarguably caused by antiparkinsonian medication. This also raises the question of whether the occurrence of certain non-motor symptoms such as EDS, hallucinations, insomnia and impulse-control disorders could be prevented, since these symptoms are mainly caused by antiparkinsonian medication. The answer is two-fold, on the one hand, identifying the patients at risk could prevent the development of certain medication-induced symptoms. In fact, the precaution of prescribing dopamine agonists for elderly patients with PD due to their increased risk to develop hallucinations is already applied in daily practice. On the other hand, there is some evidence that certain non-motor symptoms can occur in drug-naïve patients. For example, the Norwegian EDS study that was performed on 153 de novo PD patients found that 18 patients were already diagnosed with EDS at baseline (without any treatment), which highlights the multifactorial origin of EDS in PD.[7]

Predominant nondopaminergic complex

For several non-motor symptoms in our study (EDS, depression and anxiety), we found strong associations with a cluster of similar predictors. Interestingly, the same cluster of predictors were identified as part of a coherent predominantly non-dopaminergic (PND) symptom complex.[37] This symptom complex is present early in the disease course and worsens with disease progression, which likely is the consequence of progressive α-synuclein aggregate-related synaptopathy and axon degeneration of the nervous system.[38-40] The PND symptom complex consists of six nondopaminergic symptoms: cognitive impairment, depressive symptoms, EDS, psychotic symptoms, autonomic dysfunction, and PIGD. In the original publication on the PND complex, anxiety was not included in the analysis. Interestingly, however, our findings on predictors of anxiety in **chapter 7** suggest that this symptoms is yet another component of this complex. The symptoms of this complex largely do not improve on dopaminergic medication and might therefore be a better indicator of progressive underlying pathobiology of PD. In addition, other studies also suggest that specific nondopaminergic PD signs such as PIGD are more strongly associated with the development of dementia than traditional dopa-responsive signs such as rigidity.[41]

Collectively, the important role of predominantly non-dopaminergic symptoms along the course of the disease, highlight the need for efficacious medication which targets the fundamental pathobiology of PD.

Future perspectives

Non-motor symptoms in PD are common and have been increasingly recognized as an integral part of PD. New clinical diagnostic criteria have recently been published by the concerned Movement Disorders Task Force, which defines that at least one non-motor symptom should be present after a disease duration of five years.[42] The importance of non-motor symptoms in PD is also reflected in the recognition of a new stage of PD (prodromal PD), which is present before the onset of motor symptoms.[43] Prodromal PD is characterized by a predominant presence of non-motor symptoms which are related to the involvement of nondopaminergic structures of the brain and peripheral nervous system. Examples include EDS, constipation, impaired olfaction, depression and REM-sleep behavioural disorder (RBD).[43] Research into this prodromal stage of PD is rapidly expanding and could aid in the earlier identification of patients at risk to develop PD and help to select patients for potential neuroprotective therapy.

Another important lesson from this thesis is that certain non-motor symptoms are still poorly studied in a longitudinal design. While dementia in PD has been extensively evaluated in longitudinal studies, this is not the case for other non-motor symptoms such as EDS, insomnia, depression and anxiety. This may be explained by the more recent growing interest in role of other predominantly non-dopaminergic symptoms in PD. Therefore, most available research on predictors for non-motor symptoms in PD has been conducted in a cross-sectional design. In addition, past studies on this topic usually were underpowered. To identify risk factors with some degree of certainty, a considerable amount of patients must have developed an outcome of interest to obtain a solid notion of the robustness of the identified risk factors. Therefore, adequate cohort size (to prevent lack of power/type II error) and sufficient length of follow-up are important criteria in the design of longitudinal studies. Our study contributes to the existing knowledge regarding prognostic factors for disease progression patterns in PD, and important strengths of our study are related to the large cohort size, the long follow-up duration and the limited dropout. However, several important non-dopaminergic symptoms including impulse-control disorders, apathy, pain and freezing while “on” on dopaminergic medication, have not or scarcely been evaluated in longitudinal studies (our’s included), and require further attention.

While several associations that were found by earlier studies have now been confirmed longitudinally by analyses presented in this thesis, there are still several potentially

interesting baseline variables that have not been studied. Examples include RBD as a potential risk factor for developing psychosis or dementia, sleep-disordered breathing for EDS and pain for depression and so forth. However, the assessment of some of these symptoms, for example RBD is complicated. The minimal diagnostic criteria for RBD as defined by the revised International Classification of Sleep Disorders (ICSD) require electromyographic (EMG) evidence of maintained muscle tone in submental muscles or excessive activity in limb muscles during REM sleep, with one of the following: sleep-related injury or disruptive behaviour by history or abnormal sleep behaviours during REM sleep during polysomnography.[44] The complexity of criteria of RBD render its evaluation in a large prospective cohort difficult.

Progression patterns and individualizing treatment in PD

Growing evidence suggests that rate of progression is an important characteristic of subtypes in PD. Our study shows that a combination of demographic and disease-related factors are determinants for developing symptoms related to the PND complex, which likely is a solid clinical proxy of disease severity and progression. Additionally, patients may also differ with respect to how they respond the medication and their susceptibility to develop side-effects. Some patients experience adequate symptomatic control after many years on levodopa or dopamine agonists, while others experience a limited benefit of the treatment and develop more side-effects such as hallucinations and EDS. This individual variability in drug response could be caused by a genetic diversity in genes that code for enzymes involved in drug processing and drug receptor interaction.[45,46] Pharmacogenomics is a promising field that investigates which genetic markers are associated with differences in individual drug response. One possibility to address this is by examining which single nucleotide polymorphisms (SNPs) are associated with interindividual differences in metabolism, absorption, efficacy or side effects. A SNP is a DNA sequence variation occurring when a single nucleotide (A, T, C or G) in the genome differs between paired chromosomes in an individual. A genetic variation can be considered a 'SNP', when it occurs at a frequency of 1% or higher in a population.[47] Current research on 'pharmacogenetic' markers in PD has mainly focused on genes coding for processes involved in the metabolism of neurotransmitters that play a role in the pathogenesis of PD, such as dopamine receptors, dopamine transporters, monoamine oxidase A and B (MAO-A/B) and catechol-O-methyltransferase (COMT).[46] Differences between patients concerning their pharmacogenetics profile may explain the large variability between patient encountered in clinical practice on the level of effectiveness and toxicity of drugs. For example, there is some evidence that patients with the COMT Met/Met polymorphism are more at risk to develop dyskinesias, EDS and hallucinations.[49-51]

Our study shows that certain features of the clinical profile of PD are associated with an increased risk to develop a particular non-motor symptoms, e.g. EDS. Pharmacogenetic profiling may therefore be important in those patients who harbour these risk factors, since they are more prone to develop medication-induced symptoms. Knowledge from longitudinal studies does not only contribute to more insight in the underlying pathobiology of PD, but it could also help the caregiver to monitor patients with particular risk factors more closely and adjust treatment if necessary. In addition, more insight in these predictors could also contribute to a better identification of patients who benefit from potential disease-modifying or neuroprotective therapies. For the future, we hope to see more longitudinal data on the disease progression in PD from large cohorts, combined with a 'pharmacogenetic' profile of every patient. In this way, evidence-based medicine can make its transformation into 'personalized' medicine.

REFERENCES

1. Hely M, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord* 2008;23:837-844.
2. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? *J Neurol Neurosurg Psychiatry* 2000;69:308-312.
3. van Uem JM, Marinus J, Canning C, et al. Health-Related Quality of Life in patients with Parkinson's disease--A systematic review based on the ICF model. *Neurosci Biobehav Rev* 2016;61:26-34.
4. Hoogendijk WJ, Sommer IE, Tissingh G, Deeg DJ, Wolters EC. Depression in Parkinson's disease. The impact of symptom overlap on prevalence. *Psychosomatics* 1998;39:416-421.
5. Broen MP, Narayen NE, Kuijf ML, Dissanayaka NN, Leentjens AF. Prevalence of anxiety in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord* 2016;31:1125-1133.
6. Dissanayaka NN, Sellbach A, Matheson S, et al. Anxiety disorders in Parkinson's disease: prevalence and risk factors. *Mov Disord* 2010; 25: 838-845.
7. Tholfsen LK, Larsen JP, Schulz J, Tysnes OB, Gjerstad MD. Development of excessive daytime sleepiness in early Parkinson disease. *Neurology* 2015;85:162-168.
8. Biglan KM, Holloway RG, McDermott MP, Richard IH. Risk factors for somnolence, edema, and hallucinations in early Parkinson disease. *Neurology* 2009;69:187–195.
9. Anang JB, Gagnon JF, Bertrand JA, et al. Predictors of dementia in Parkinson disease: a prospective cohort study. *Neurology* 2014;83:1253-1260.
10. Hughes TA, Ross HF, Musa S, et al. A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. *Neurology* 2000;54:1596-1602.
11. Williams-Gray CH, Mason SL, Evans JR, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *J Neurol Neurosurg Psychiatry* 2013;84:1258-1264.
12. Varanese S, Birnbaum Z, Rossi R, Di Rocco A. Treatment of advanced Parkinson's disease. *Parkinsons Dis* 2011;2010:480260.
13. Levy G, Schupf N, Tang MX, et al. Combined effect of age and severity on the risk of dementia in Parkinson's disease. *Ann Neurol* 2002; 51:722–729.
14. Alves G, Wentzel-Larsen T, Aarsland D, et al. Progression of motor impairment and disability in Parkinson disease: A population-based study. *Neurology* 2005; 65:1436–1441.
15. van Rooden SM, Heiser WJ, Kok JN, Verbaan D, van Hilten JJ, Marinus J. The identification of Parkinson's disease subtypes using cluster analysis: a systematic review. *Mov Disord* 2010;25:969-978.
16. de Lau LM, Giesbergen PC, de Rijk MC, et al. Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study. *Neurology* 2004;63:1240–1244.
17. Wooten GF, Currie LJ, Bovbjerg VE, et al. Are men at greater risk for Parkinson's disease than women? *J Neurol Neurosurg Psychiatry* 2004;75:637–639.

18. Beekman AT, Bremmer MA, Deeg DJ, et al. Anxiety disorders in later life: a report from the Longitudinal Aging Study Amsterdam. *Int J Geriatr Psychiatry* 1998;13: 717-726.
19. Sagna A, Gallo JJ, Pontone GM. Systematic review of factors associated with depression and anxiety disorders among older adults with Parkinson's disease. *Parkinsonism Relat Disord* 2014;20:708-715.
20. Hassin-Baer S, Molchadski I, Cohen OS, et al. Gender effect on time to levodopa-induced dyskinesias. *J Neurol* 2011;258:2048–2053.
21. Arabia G, Zappia M, Bosco D, et al. Body weight, levodopa pharmacokinetics and dyskinesia in Parkinson's disease. *Neurol Sci* 2002;23:S53–S54.
22. Haaxma CA, Bloem BR, Borm GF, et al. Gender differences in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007;78:819-824.
23. Iranzo A, Santamaría J, Rye DB, et al. Characteristics of idiopathic REM sleep behaviour disorder and that associated with MSA and PD. *Neurology* 2005;65:247–252.
24. Hobson P, Meara J. Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. *Mov Disord* 2004;19:1043-1049.
25. Uc EY, McDermott MP, Marder KS, et al. Incidence of and risk factors for cognitive impairment in an early Parkinson disease clinical trial cohort. *Neurology* 2009;73:1469-1477.
26. Chaudhuri KR, Healy DG, Schapira AH; National Institute for Clinical Excellence. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol* 2006;5:235-245.
27. Barone P, Poewe W, Albrecht S, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2010;9:573-580.
28. Leentjens AF. The role of dopamine agonists in the treatment of depression in patients with Parkinson's disease: a systematic review. *Drugs* 2011;71:273-286.
29. Frucht S, Rogers JD, Greene PE, et al. Falling asleep at the wheel: Motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* 1999; 52:1908–1910.
30. Fenelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: Prevalence, phenomenology and risk factors. *Brain* 2000; 123:733–745.
31. Calne DB, Brennan J, Spiers ASD, Stern GM. Hypotension caused by levodopa. *BMJ* 1960; 1:474–475.
32. Dodd ML, Klos JH, Bower JH, et al. Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 2005; 63:1377–1384.
33. Voon V, Hassan K, Zurowski M, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. *Neurology* 2006; 67:1254–1257.
34. Goetz CG, Ouyang B, Negron A, Stebbins GT. Hallucinations and sleep disorders in PD: ten-year prospective longitudinal study. *Neurology* 2010;75:1773-1779.
35. Rodrigues TM, Castro Caldas A, Ferreira JJ. Pharmacological interventions for daytime sleepiness and sleep disorders in Parkinson's disease: Systematic review and meta-analysis. *Parkinsonism Relat Disord* 2016;27:25-34.

36. Evans AH, Pavese N, Lawrence AD, et al. Compulsive drug use linked to sensitized ventral striatal dopamine transmission. *Ann Neurol* 2006; 59:852–858.
37. van der Heeden JF, Marinus J, Martinez-Martin P, et al. Importance of nondopaminergic features in evaluating disease severity of Parkinson disease. *Neurology* 2014;82:412-418.
38. Calabresi P, Mercuri NB, Di Filippo M. Synaptic plasticity, dopamine and Parkinson's disease: one step ahead. *Brain* 2009;132:285–287.
39. Cheng HC, Ulane CM, Burke RE. Clinical progression in Parkinson disease and the neurobiology of axons. Ann Neurol 2010;67:715–725.
40. Schulz-Schaeffer WJ. The synaptic pathology of alpha-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. *Acta Neuropathol* 2010;120:131–143.
41. Levy G, Tang MX, Cote LJ, et al. Motor impairment in PD: Relationship to incident dementia and age. *Neurology* 2000; 55:539–544.
42. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 2015; 30: 1591-1601.
43. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord* 2015; 30: 1600-1611.
44. Medicine, A.A.O. The International Classification of Sleep Disorders, 2nd ed.: Diagnostic and coding manual. Journal. 2005.
45. Białecka M, Droz´dzik M, Kłodowska-Duda G et al. The effect of monoamine oxidase B (MAOB) and catechol-O-methyltransferase (COMT) polymorphisms on levodopa therapy in patients with sporadic Parkinson's disease. *Acta Neurol Scand* 2004; 110: 260–266.
46. Liu YZ, Tang BS, Yan XX et al. Association of the DRD2 and DRD3 polymorphisms with response to pramipexole in Parkinson's disease patients. *Eur J Clin Pharmacol* 2009; 65: 679–683.
47. Salisbury BA, Pungliya M, Choi JY, Jiang R, Sun XJ, Stephens JC. SNP and haplotype variation in the human genome. *Mutat Res* 2003; 526: 53–61.
48. Kalinderi K, Fidani L, Katsarou Z, Bostantjopoulou S. Pharmacological treatment and the prospect of pharmacogenetics in Parkinson's disease. *Int J Clin Pract* 2011;65:1289-1294.
49. Oliveri RL, Annesi G, Zappia M et al. Dopamine D2 receptor gene polymorphism and the risk of levodopa induced dyskinesias in PD. *Neurology* 1999; 53: 1425–1430.
50. Makoff AJ, Graham JM, Arranz MJ et al. Association study of dopamine receptor gene polymorphisms with drug-induced hallucinations in patients with idiopathic Parkinson's disease. *Pharmacogenetics* 2000; 10: 43–48.
51. Rissling I, Geller F, Bandmann O et al. Dopamine receptor gene polymorphisms in Parkinson's disease patients reporting "sleep attacks." *Mov Disord* 2004; 19: 1279–1284.