Non-dopaminergic symptoms in Parkinson's disease

Velseboer, D.C.

Publication date
2019
Document Version
Final published version
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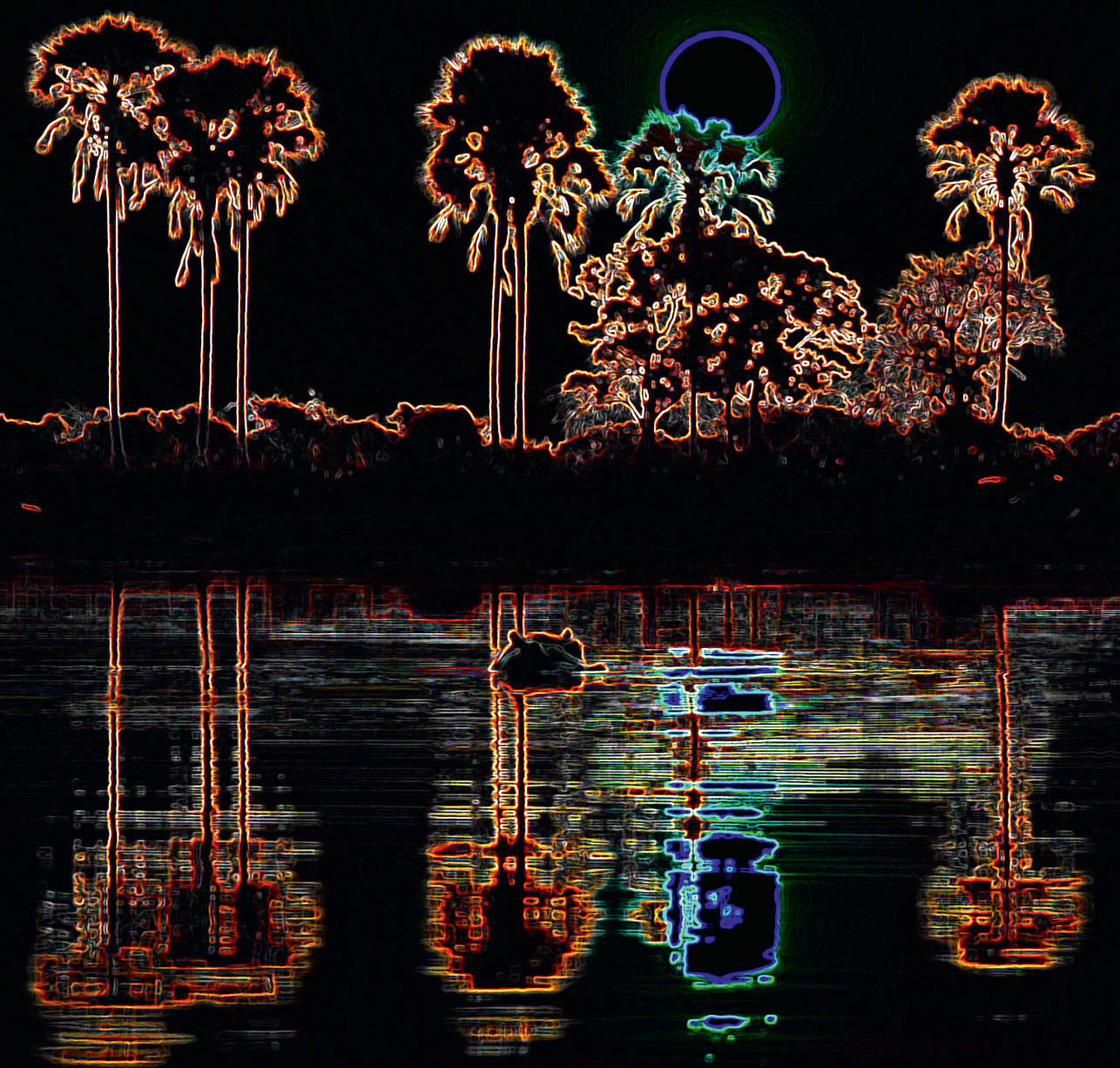

Daan Velseboer

Non-Dopaminergic Symptoms In Parkinson's Disease

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Colofon

Cover design: Daan Velseboer
Layout: Daan Velseboer & Loes Kema (GVO)
Print: GVO drukkers & vormgevers B.V., Ede, the Netherlands
ISBN: 978-94-6332-452-6

The research in this thesis was financially supported by funds from The Netherlands organisation for health research and development (ZonMw, grant 14350029) and the Prinses Beatrix Fonds (grant WAR 08-02), The Hague, The Netherlands. The research in chapter 4 was additionally supported by The Medical Research Council, Parkinson's UK, the Patrick Berthoud Trust, the Wellcome Trust, National Institutes of Health Research Biomedical Research Centre.

Printing of this thesis was made possible by the financial support of stichting Alkemade-Keuls and the Parkinson Vereniging

NON-DOPAMINERGIC SYMPTOMS IN PARKINSON'S DISEASE

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel

op vrijdag 8 maart 2019, te 10:00 uur

door

Daniël Cornelis Velseboer

geboren te Alkmaar

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	Prof. dr. J.W.R. Twisk	Vrije Universiteit Amsterdam
	Dr. N van der Velde	AMC – Universiteit van Amsterdam

Faculteit der Geneeskunde

Contents

Chapter 1

Introduction

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder and the incidence increases with higher age. It is estimated that 1% of the population aged 60 and older has PD.[1] The hallmark motor symptoms are bradykinesia, rigidity and tremor, and they are due to a loss of dopamine-producing neurons. These symptoms temporarily improve with levodopa and are therefore called levodopa responsive symptoms, or dopaminergic symptoms.[2] The neurodegenerative process in PD is not limited to the loss of dopamine-producing neurons and patients can therefore also suffer from various symptoms that do not improve with levodopa. These are called the levodopa unresponsive symptoms, or non-dopaminergic symptoms. The levodopa unresponsive symptoms include (but are not limited to) postural instability and numerous non-motor symptoms, such as hyposmia, autonomic dysfunction, sensory symptoms, psychosis and (global) cognitive dysfunction. Sleep disorders, impaired cognitive executive functioning, and anxiety and depression are probably caused by degeneration of dopaminergic as well as non-dopaminergic neurons.[3,4] The extent to which PD patients suffer from non-dopaminergic symptoms is highly variable.[5]

The pathophysiological basis for dopaminergic and non-dopaminergic symptoms

An important process in the neuropathological basis for PD is the formation of abnormal aggregates of the protein α-synuclein, which leads to the formation of Lewy bodies, Lewy neurites and neuronal cell death. This process is nowadays thought to be the result of interplay between environmental and genetic factors.[2] Though the neurodegeneration in PD can eventually affect the whole brain, the disease progression in various brain regions is not occurring simultaneously and at the same rate. Instead, the neurodegeneration in PD is initially limited, with the olfactory bulb, the lower brain stem and the enteric and peripheral autonomic nervous system most commonly affected in the earliest (often pre-symptomatic) stage.[6,7] The neurodegeneration then gradually spreads to the rostral brainstem including the pars compacta of the substantia nigra (SNc). In the SNc, degeneration of nigrostriatal dopamine-producing neurons leads to the hallmark dopaminergic motor symptoms mentioned earlier (*i.e.*, bradykinesia, rigidity and tremor). The neurodegeneration subsequently spreads to higher brain regions, consecutively involving the phylogenetically older mesocortex, followed by the associative areas in the neocortex and to finally involve the whole neocortex. The widespread pathology outside the SNc is responsible for the various non-dopaminergic symptoms in PD.

A shift in focus from dopaminergic to non-dopaminergic symptoms

Though James Parkinson already described numerous non-dopaminergic symptoms in his original paper, the focus of diagnosis, treatment and research in PD has been on the dopaminergic symptoms for decades.[9-12] In the sixties of the 20th century, levodopa became available as a symptomatic treatment for the dopaminergic symptoms. This was soon followed by the introduction of the first dopamine-agonists a decade later. For levodopa and dopamine replacement related motor response fluctuations, medical (*e.g.*, catechol-O-methyl transferase inhibitors and monoamine oxidase B inhibitors) as well as advanced treatment options (*e.g.*, deep brain stimulation, continuous intestinal levodopa-infusion, and continuous apomorphine subcutaneous infusion) became available.[13] The last decade, the initial fear for levodopa-induced acceleration of disease progression has gradually subdued.[14] It is common-practice nowadays to start levodopa or a dopamine-agonist early in the disease course, or at least when motor symptoms start to interfere with daily functioning. To summarize, symptomatic treatment for the dopaminergic symptoms is available for early to late-stage PD. The advancements in treatment of dopamine responsive symptoms have exposed the non-dopaminergic symptoms of PD, raising the interest of both researchers and clinicians.[15]

The gaps in our knowledge concerning non-dopaminergic symptoms

The scientific quest concerning the role of non-dopaminergic symptoms in PD takes place on various levels. In *fundamental research*, a major question concerning the pathophysiological mechanisms of PD is why non-dopaminergic symptoms are so variably present.[5] The high variability of the time of debut and the severity of these symptoms in PD patients suggest that the gradual uniform progression of PD pathology shown in post-mortem studies are an oversimplification of reality.[16] In *clinical research*, the major quest is to find proper ways to treat the non-dopaminergic symptoms. For some of the non-dopaminergic symptoms treatment is available, but the effect is only moderate and the side effects can worsen other non-dopaminergic symptoms. For the majority of these treatments, recommendations are based on expert opinion and there is no proper scientific evidence to recommend routine use.[17] Besides the need for proper treatment of non-dopaminergic symptoms, there is also a need for proper diagnostic instruments to improve the assessment of their presence. This is of specific interest for autonomic dysfunction (AD) in PD. The degeneration of the autonomic nervous system leads to a wide range of autonomic symptoms (AS), related to dysregulation of the cardiovascular, gastro-intestinal, pupillomotor, reproductive, thermoregulatory, and urogenital systems.[18] The wide range of reported prevalences in cohort studies suggest that

diagnosis of AD in PD might be difficult.[19] The use of proper diagnostic criteria for the various expressions of AD in PD could potentially improve this. Orthostatic Hypotension (OH) is a specific form of cardiovascular AD, for which consensus criteria have been made.[20] The use of these consensus criteria as a diagnostic test has been advocated, but validation of these criteria in the PD population has not been performed yet.[21]

In *prognostic research*, a major question is whether specific risk factors for the development of non-dopaminergic symptoms can be identified, and if they will have substantial influence on daily functioning and quality of life. Major prognostic impact of cognitive dysfunction and postural instability has already been suggested in post-mortem research, since development of these symptoms are associated with relatively short times to death.[22] However, confirmation of this in prospective prognostic studies has been difficult, mainly due to biased study populations and short times of follow-up.[23]

Aims and outline of this thesis

This thesis has two aims. 1) To investigate the role of non-dopaminergic symptoms in the clinical course and disease burden of PD patients. We aim to find sources underlying the heterogeneity of non-dopaminergic symptoms, and to assess the influence of dopaminergic symptoms on disability and quality of life. Therefore we perform observational studies with specific interest for the following non-dopaminergic symptoms: autonomic dysfunction, postural instability, and cognitive dysfunction. 2) To increase knowledge concerning one specific non-dopaminergic symptom: OH. We aim to investigate the prevalence of OH, and the clinical value of orthostatic blood pressure tests and additional autonomic function tests in relation to daily experienced orthostatic symptoms.

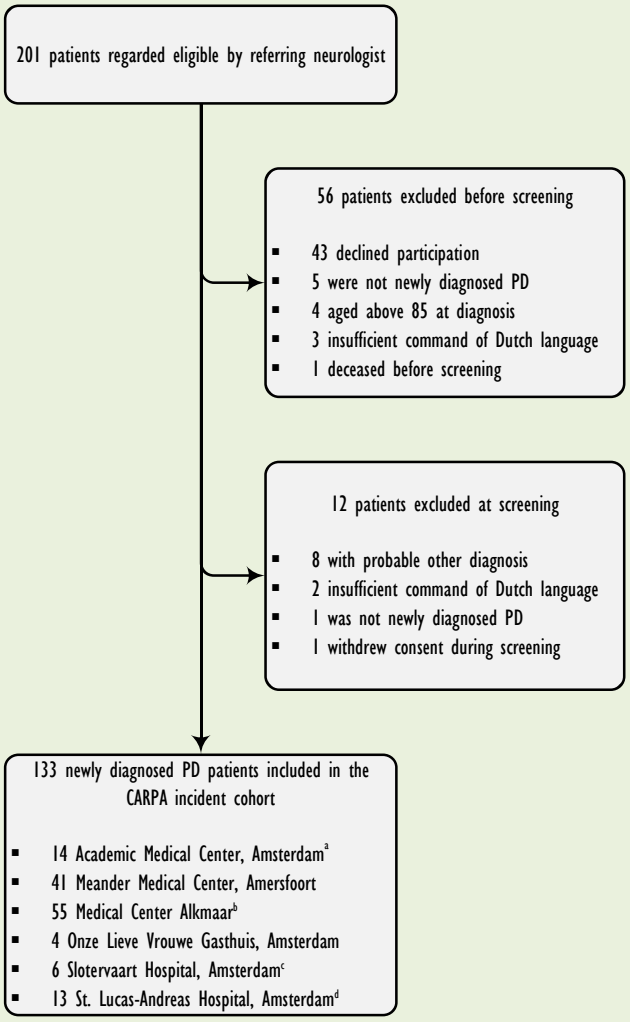
This thesis is therefore divided in two parts. In the first part of the thesis we perform prognostic studies. In **chapter two** we perform an explorative prognostic study in which we assess whether specific determinants can be identified for future motor impairments, disability, and quality of life. Besides general determinants, the PD-specific determinants include both dopaminergic and non-dopaminergic symptoms to assess their relative influence on overall PD prognosis. In **chapter three** we assess whether specific prognostic variables for the development of AS in PD can be identified, and whether AS are associated with increased disability and loss of quality of life in PD. In **chapter four** we aim to develop a prediction model to aid in detecting PD patients with unfavorable prognosis in terms of early development of dementia, postural instability or death. To facilitate future use of the model, an external validation of the model is also performed.

In the second part of this thesis we focus on OH and its related orthostatic symptoms such as light-headedness and loss of consciousness after assuming the upright position. In **chapter five** we perform a systematic review of the literature to estimate the prevalence of OH in PD. In **chapter six** we assess the relation between presence of OH as defined by diagnostic criteria and the orthostatic symptoms which PD patients suffer in daily life.[20] We also investigate whether alterations of these criteria would reflect the patient reported symptoms better. In **chapter seven** we assess whether other autonomic nervous system tests could aid in diagnosing patients suffering from orthostatic symptoms in daily life.

The CARPA cohort

Between July 2002 and March 2005, 133 consecutive patients with newly diagnosed PD were recruited from six general hospitals in the Netherlands for participation in the CARPA (Comorbitiy and Aging in Rehabilitation Patients: influence on Activities)-study.[24] Details of the selection process of the participants from the original CARPA-cohort are shown in figure 1. Activities for the CARPA PD cohort were coordinated from the Academic Medical Center, Amsterdam, and the main aim was to describe the progression of PD in terms of impairments, disability, and quality of life. The adherence to the follow-up visits of the patients in this cohort had been excellent in the first three years after diagnosis. For this reason, plans were made to extend the follow-up to assessments at 5, 8, 10 and 12 years after diagnosis. In addition, an ancillary study concerning autonomic symptoms (with specific focus on OH) in PD was planned, recruiting patients from this cohort. The studies presented in this thesis are mainly based on the results of the regular CARPA-study visits up till year 5, and the ancillary study concerning autonomic symptoms in PD.

Figure 1: Selection process of the CARPA-participants



[a] Currently Amsterdam University Medical Centers, location AMC. The Academic Medical Center is a tertiary care center, but also serves a regional function as a general hospital. For the CARPA-study only non-tertiary care referrals were included; [b] Currently Noordwest Ziekenhuisgroep; [c] Currently MC Slotervaart; [d] Currently Onze Lieve Vrouwe Gasthuis

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Part One

Prognosis in Parkinson's disease

Chapter 2

Prognostic factors of motor impairment, disability, and quality of life in newly diagnosed Parkinson's disease

Daan C. Velseboer
Mark Broeders
Bart Post
Nan van Geloven
Johannes D. Speelman
Ben Schmand
Rob J. de Haan
Rob M.A. de Bie
CARPA Study Group

Neurology 2013:80;627-633

ABSTRACT

Introduction: In Parkinson's disease, the rate of clinical progression is highly variable. To date, there are conflicting findings concerning the prognostic factors influencing the rate of progression. Methodological issues such as the use of selected patients from therapeutic trials, and short durations of follow-up probably underlie this problem. We therefore designed a prospective follow-up study of a cohort of newly diagnosed patients with Parkinson's disease.
Methods: A cohort of 129 patients with newly diagnosed Parkinson's disease was assessed at baseline, and 1, 2, 3 and 5 years later. The rate of progression and its prognostic factors on the level of motor impairments, disability and quality of life were investigated using linear mixed model analysis.
Results: Annual increase of motor impairments measured with the UPDRS-ME was estimated to be 2.46 points (95% CI: 2.05–2.88). The main determinants of faster increase of motor impairments were male sex and cognitive dysfunction at the time of diagnosis. The main determinants of faster increase of disability were higher age at onset, cognitive dysfunction and the presence of levodopa non-responsive motor symptoms at the time of diagnosis. No clinically relevant determinants were found for the decrease in quality of life.
Conclusion: This study shows the importance of non-dopaminergic symptoms at the time of diagnosis, as these symptoms are the main determinants of increased disability in the first five years of the disease.

INTRODUCTION

There is considerable variation in the clinical course of Parkinson's disease (PD).[1] In clinical practice, the heterogeneity of PD complicates adequate counseling of patients regarding prognosis of the disease and it may lead to diagnostic difficulties. In research settings, the variety in disease progression can have consequences for the external validity of study results for individual patients. There are numerous studies describing the disease progression and synthesized data from systematic reviews are available.[2-4] The most recent review showed that older age at onset and a "postural instability and gait difficulty" (PIGD) phenotype are prognostic factors for a more severe progression of disability.[2] Conflicting or limited evidence was found for other prognostic factors of motor impairments and disability. In addition, the authors concluded that the research on the progression of PD is not fulfilling present-day standards. Main critiques on available studies were short durations of follow-up, the use of prevalent cases, and the inclusion of patients that were originally enrolled in a therapeutic trial.

Therefore, we performed a 5-year follow-up study of a hospital based cohort of patients with newly diagnosed PD. We assessed progression in terms of motor impairment, disability, and quality of life. Furthermore, we searched for possible prognostic factors influencing disease progression.

METHODS

Subjects

Between July 2002 and March 2005, patients with newly diagnosed PD were recruited from six general hospitals as part of the CARPA study (Comorbidity and Aging in Rehabilitation Patients: Influence of Daily Activities). The baseline data and the data of three year follow-up from this longitudinal cohort study have been described elsewhere.[5-6] The clinical diagnosis was based upon the criteria form Gelb *et al*. (see data supplement for specification).[7] Exclusion criteria were insufficient command of the Dutch language, age of 85 years or older, and the presence of a somatic illness with a life expectancy of less than one year. The general neurologist that treated the patient made the original diagnosis. Subsequently a project neurologist (JDS) confirmed the diagnosis at baseline and reviewed the medical records at each assessment to determine whether the diagnosis had been changed. At the end of the follow-up

period, all patients still participating were approached and subsequently seen for a clinical confirmation of the diagnosis by the same project neurologist. Patients were excluded from analysis if the diagnosis was changed.

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from all participating subjects. The study was approved by the local ethics committees of the participating hospitals.

Assessments

At the entry of the study, clinical and demographic characteristics were recorded. Different dopaminergic drugs (levodopa and dopamine agonists) were pooled in a levodopa equivalent dose (LED).[8] The formula for the LED is shown in the data supplement. All assessments were done at baseline and were subsequently repeated at 1, 2, 3, and 5 years of follow-up. All assessments were done by trained research nurses and whenever possible by the same research nurse at the same time of the day.

Outcome measures

Stage of disease was measured with the Hoehn and Yahr scale.[9] The severity of motor impairment was rated with the Unified Parkinson's Disease Rating Scale motor examination section (UPDRS-ME, range 0–108).[10] Disability was measured with the Schwab and England activities of daily living scale (range 0–100)[11] and with the AMC Linear Disability Scale (ALDS).[12] The ALDS item bank was developed to quantify functional status in terms of the ability to perform activities of daily living using an item response theory framework. The original units of the ALDS scale are logistic regression coefficients, expressed in logits (theta's). The theta's can be linearly transformed into values between 10 and 90. However, since all statistical analyses are performed on the theta-values, the results are also reported as theta-values with a range of -3.86 to 3.58. Quality of life was measured with the Parkinson's Disease Quality of Life questionnaire (PDQL, range 37–185).[13]

Potential prognostic factors

Based on the potential prognostic factors in the literature a set of predefined prognostic variables was selected. These included sex, age at onset, hand preference, disease duration, comorbidity, anxiety and depression, cognitive function, and PD motor symptoms. The Cumulative Illness Rating Scale (CIRS, range 0–52)[14] was used as a measure of comorbidity

and the Hospital Anxiety and Depression Scale as a measure of anxiety and depression (HADS, range 0–42).[15,16] Cognitive functioning was assessed at baseline using an extensive neuropsychological test battery including 17 different tests with a total of 25 different measures. Cognitive dysfunction was defined as a score of -2SD below the age and educated appropriate mean on three or more of the 25 measures.[17] Finally, the baseline UPDRS-ME score was divided into two subscales representing relatively levodopa responsive symptoms (Levy score A, range 0–80) and relatively levodopa non-responsive symptoms (Levy score B, range 0–20).[18] The levy B-score contains the UPDRS-ME items for 'speech', 'rising from chair', 'posture', 'gait' and 'postural stability'. The levy A-score contains the remaining UPDRS-ME items with omission of the item 'finger taps'.

Statistical Analysis

Baseline demographic and clinical characteristics, progression of Hoehn and Yahr-scores and the outcome measures at baseline and 5 years were summarized using descriptive statistics. Progression of motor impairment, disability and quality of life, and the influence of potential prognostic factors were analyzed using linear mixed models. In these models we accounted for the correlation between repeated measurements on the same patient. To estimate the influence of the potential prognostic factors, mixed models were made in which time was used as a continuous variable. For each prognostic factor we estimated the main effect and the effect of the interaction with time on the outcome measure in a univariable mixed model. Main effects estimate the impact of a prognostic factor on the outcome measure at baseline. Interaction terms with time estimate the annual difference of progression on the outcome measure for subjects with and without the prognostic factor. All identified significant prognostic variables and their interaction with time were selected for a multivariable model with a backward selection strategy. When an interaction term was selected, the main effect of that factor was also retained in the model. For both entry and removal from the model a threshold *p*-value of 0.05 was used. Statistical uncertainties in the estimated effect sizes were expressed using the corresponding 95% confidence intervals (95% CIs). As linear mixed models are relatively robust to missing data, missing data were not imputed. The interpretation of effect sizes of interaction terms between time and a prognostic factor can be difficult, especially with continuous variables. Therefore, the data supplement includes a detailed example using one of our analyses. The original sample size was calculated to detect a clinically relevant change on the UPDRS-ME during a period of three years follow-up. Assuming a moderate correlation ($r = 0.50$) between measurements, a sample size of 135

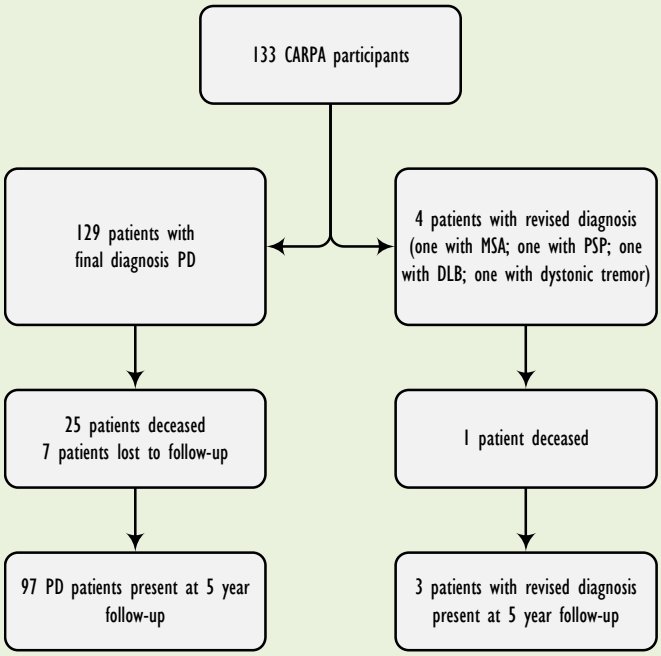
patients was calculated to detect a standardized effect size of 0.40 on the UPDRS-ME with a statistical power of 90% at a two-tailed significance level of 5%. All analyses were performed in MLWin v2.20 (Centre for Multilevel Modelling, Bristol, UK) and PASW statistics version 18 (IBM SPSS, Chicago, IL, USA).

RESULTS

Characteristics

Between July 2002 and March 2005, 145 participants were referred for inclusion in the present study. Following the screening, 12 patients were excluded (8 patients had a different diagnosis; 2 patients had insufficient command of the Dutch language; one patient was diagnosed with PD two years earlier; and one patient withdrew consent before baseline assessment). The remaining 133 patients were included in our cohort (figure 1).

Figure 1: Flowchart showing the final diagnosis and loss to follow-up of the original 133 participants



MSA: Multiple System Atrophy; DLBD: Diffuse Lewy Body Disease; PSP: Progressive Supranuclear Palsy; PD: Parkinson's Disease. The 129 patients with a final diagnosis of PD are included in the analysis.

At 5-year follow-up, in four patients the diagnosis had been revised. Of these, one patient had Multiple System Atrophy (MSA), one had Progressive Supranuclear Palsy (PSP), one had Diffuse Lewy Body Disease (DLBD), and one had dystonic tremor. These patients were excluded from the present analysis. A total of 129 patients had a diagnosis of PD at their last follow-up assessment; *i.e.* at 5-year follow-up, at the last visit before lost to follow-up, or at the last visit before death. The baseline characteristics are shown in table 1.

Table 1: Baseline characteristics

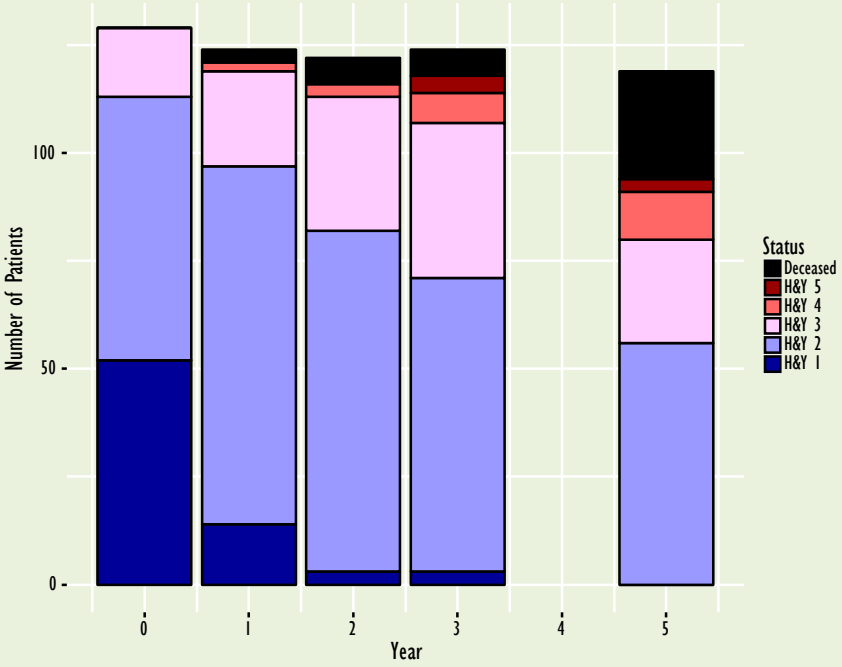
Patients and clinical variables	n = 129
Gender (male : female)	72:57
Mean age at onset in years (SD, range)	64.8 (10.5; 30.9–83.5)
Mean age at diagnosis in years (SD, range)	66.1 (10.5; 32.0–84.6)
Mean age at baseline examination in years (SD, range)	66.5 (10.5; 32.4–84.9)
Mean disease duration at baseline examination in months (SD, range)	19.8 (11.1; 4.7–83.9)
Initial symptom	
– tremor	59
– bradykinesia/rigidity	60
– tremor/bradykinesia/rigidity	10
Therapy at baseline examination	
– no medication	39
– dopaminergic	82
– non-dopaminergic (amantadine, propranolol, anticholinergic)	8
LED when receiving therapy (mean, SD, range)	238.8 (117.8; 10–600)

LED: Levodopa Equivalent Dose

Disease progression and prognostic factors

Disease progression as measured with the Hoehn and Yahr scale is shown in a bar chart in which the patients that died have also been incorporated (figure 2). For the other outcome measures the mean values at baseline and at 5-year follow-up are shown in table 2. The results of the multivariable linear mixed models estimating the impact of prognostic factors per outcome measure are shown in table 3. The results of the univariable analyses are shown in the data supplement.

Figure 2: Disease progression measured with the Hoehn and Yahr-scale.



Slight fluctuations in the total height of de bars are caused by patients that were lost to follow-up.

Table 2: Values at baseline and 5-year follow-up of the outcome measures

Outcome measure	Mean value at baseline ± SD	Mean value at year 5 ± SD
UPDRS-ME	17.53 ± 8.20	28.10 ± 11.32
UPDRS-ME Levy A	13.22 ± 5.77	19.59 ± 7.84
UPDRS-ME Levy B	2.32 ± 2.31	4.98 ± 3.97
Schwab & England	90.00 ± 6.85	79.37 ± 19.23
ALDS (theta-score)	2.34 ± 1.09	1.73 ± 2.10
PDQL	146.58 ± 20.90	138.62 ± 24.44

UPDRS-ME: Unified Parkinson's Disease Rating Scale - Motor Examination; ALDS: AMC Linear Disability Scale; PDQL: Parkinson's Disease Quality of Life questionnaire

Motor impairment

The annual increase of the UPDRS-ME score was estimated to be 2.46 points (95% CI: 2.05–2.88). Multivariable mixed model analysis showed male sex and cognitive dysfunction as the most important predictors for increased progression of motor impairment. Baseline UPDRS Levy A and Levy B scores were not used in the model assessing progression of the UPDRS-ME due to collinearity of these measures with the total UPDRS-ME score.

For further exploration of the influence of sex and cognitive functioning on motor progression, an additional analysis using the Levy A and Levy B subscales[18] as an outcome measure was performed, using the same multivariable mixed model strategy. The only significant prognostic factor for worse progression of levodopa responsive motor symptoms (subscale A) was male sex. In contrast, the prognostic factors for worse progression of levodopa non-responsive symptoms (subscale B) were cognitive dysfunction at baseline and higher age at onset.

Disability

The annual decrease of the Schwab and England score was estimated to be 3.33 points (95% CI: 2.40–4.26). Multivariable mixed model analysis showed cognitive dysfunction and higher Levy B score as the most important predictors for increased progression of disability. The annual decrease of ALDS-theta score was estimated to be 0.21 points (95% CI: 0.13–0.29). Multivariable mixed model analysis showed cognitive dysfunction and higher age at onset as the most important predictors for increased progression of disability.

Quality of life

The annual decrease of PDQL score was estimated to be 2.78 points (95% CI: 1.84–3.71). Multivariable mixed model analysis showed higher age at onset as a prognostic factor for a steeper decline of the PDQL. Higher HADS scores at baseline predicted a less steep decline in quality of life. However, patients with higher HADS scores had lower PDQL scores at baseline.

Table 3: Multivariable mixed models

Outcome measure	Prognostic Factor	Effect	(95% CI)	*p*-value
UPDRS-ME				
	Age at onset	0.20	(0.08; 0.32)	*p*=0.001
	Male sex	-1.72	(-4.23; 0.78)	*p*=0.176
	Cognitive dysfunction	3.09	(0.09; 6.10)	*p*=0.044
	Male sex*year	0.99	(0.17; 1.81)	*p*=0.018
	Cognitive dysfunction*year	1.33	(0.30; 2.35)	*p*=0.012
UPDRS-ME				
Levy A subscale	Age at onset	0.09	(0.00; 0.17)	*p*=0.044
	Cognitive dysfunction	2.46	(0.34; 4.58)	*p*=0.023
	Male sex	-1.34	(-3.19; 0.51)	*p*=0.153
	Male sex*year	0.78	(0.17; 1.39)	*p*=0.013
UPDRS-ME				
Levy B subscale	Levy A score	0.15	(0.09; 0.21)	*p*<0.001
	CIRS score	0.15	(0.04; 0.25)	*p*=0.007
	Age at onset	0.05	(0.02; 0.09)	*p*=0.003
	Cognitive dysfunction	0.64	(-0.13; 1.41)	*p*=0.101
	Age at onset*year	0.02	(0.01; 0.03)	*p*=0.003
	Cognitive dysfunction*year	0.55	(0.22; 0.89)	*p*=0.001
Schwab &				
England	Levy B score	-1.18	(-1.64; -0.71)	*p*<0.001
	Cognitive dysfunction	0.67	(-1.89; 3.24)	*p*=0.604
	Levy B score*year	-0.67	(-1.05; -0.29)	*p*=0.001
	Cognitive dysfunction*year	-3.05	(-5.16; -0.93)	*p*=0.005
ALDS				
(theta-score)	Levy B score	-0.202	(-0.264; -0.140)	*p*<0.001
	CIRS score	-0.095	(-0.138; -0.051)	*p*<0.001
	Age at onset	-0.006	(-0.022; 0.009)	*p*=0.428
	Cognitive dysfunction	0.220	(-0.124; 0.564)	*p*=0.207
	Age at onset*year	-0.013	(-0.021; -0.005)	*p*=0.001
	Cognitive dysfunction*year	-0.234	(-0.422; -0.045)	*p*=0.016
PDQL				
	Levy B score	-2.32	(-3.44; -1.21)	*p*<0.001
	CIRS score	-1.56	(-2.36; -0.76)	*p*<0.001
	Cognitive dysfunction	-6.13	(-11.68; -0.58)	*p*=0.031
	Age at onset	0.17	(-0.10; 0.44)	*p*=0.216
	HADS score	-1.46	(-1.80; -1.12)	*p*<0.001
	Age at onset*year	-0.09	(-0.18; -0.01)	*p*=0.035
	HADS score*year	0.16	(0.04; 0.28)	*p*=0.009

UPDRS-ME: Unified Parkinson's Disease Rating Scale - Motor Examination; ALDS: AMC Linear Disability Scale; PDQL: Parkinson's Disease Quality of Life questionnaire; CIRS: Cumulative Illness Rating Scale; HADS: Hospital Anxiety and Depression Scale

DISCUSSION

Though the presence of levodopa responsive motor symptoms is the notorious feature of PD, the levodopa non-responsive symptoms are increasingly recognized as an important part of the disease. It is already known that in an advanced stage of the disease levodopa non-responsive symptoms are the main determinants of disability.[19] Our study shows that the presence of levodopa non-responsive motor symptoms and cognitive dysfunction at the time of diagnosis, are the main determinants of faster progression of disability. The influence of cognitive dysfunction on disease progression is also reflected in a faster progression of motor impairments. The additional analysis we performed on the Levy B motor-score suggests that this is mainly an increase in levodopa non-responsive symptoms. Further follow-up of the cognitive profile of our cohort also shows that the presence of levodopa non-responsive motor symptoms predicts increased cognitive decline over time.[20] These findings indicate that the various levodopa non-responsive symptoms occur in conjunction, and that the presence of one levodopa non-responsive symptom predicts the occurrence of others. We therefore hypothesize that the occurrence of the various non-dopaminergic symptoms is a reflection of a diffuse process in which multiple extra-nigrostriatal systems are affected simultaneously.

This hypothesis is supported by the data provided by a study that investigated the occurrence of four different so-called milestones in the course of PD was investigated: frequent falls, visual hallucinations, cognitive disability, and need for residential care.[21,22] The first three of these phenomena are thought to be a reflection of non-dopaminergic pathology. They found that these milestones precede the death of patients with a relatively fixed time interval of on average 3.3 years for dementia and need for residential care, 4.1 years for falls, and 5.1 years for hallucinations. These time intervals are independent of the initial response to levodopa, the age of onset of PD, and the age of death. They also found that the age of death is not related to the initial response to levodopa. A recent study with a cohort of incident PD patients similar to ours shows that the levodopa non-responsive motor symptoms as represented by the stages on the Hoehn and Yahr scale occur earlier in patients with later disease onset. [23]

Taking this into account, we postulate that the clinical progression of PD is the result of the following two distinct processes:

1. The progression of levodopa responsive symptoms, which are associated with the degeneration of the nigrostriatal dopaminergic neurons.[24] The age of onset of this process and its rate of progression are highly variable.

2. Progression of levodopa non-responsive symptoms, which are caused by widespread degeneration of extra-nigrostriatal systems. Once started, the rate of progression of these symptoms is more homogenous among patients, and the occurrence of these symptoms precedes death by three to five years. Higher age of the patient is an important predictor for the start of this process.[23,25]

The concurrence of these two processes is highly variable and probably underlies for a large part the clinical heterogeneity of PD. This suggests that although these processes are part of the same disease, the underlying pathophysiology is at least partially different.

Though there are no other reports in the literature showing a sex difference on the rate of progression of motor impairment, there are arguments supporting the hypothesis of faster progression of PD in men. First of all, the male to female ratio of the incidence of PD is estimated to be 1.58, suggesting that men are more susceptible to PD pathology.[26] Furthermore, some studies suggest that estrogens offer protection to PD pathology. A retrospective study showed that women with later menopause had a later age of onset of their PD symptoms, which suggests a protective effect of estrogens.[27] The influence of estrogens on dopamine metabolism has also been investigated in animal studies. The bio-availability of dopamine in the striatum is higher with increasing levels of circulating estrogens.[28] Increased production, decreased re-uptake and higher levels of dopamine receptors all seem to play a role in this. Animal models have also shown that estrogens exert a neuroprotective effect on nigrostriatal dopaminergic neurons.[29] Our additional analysis using the levodopa responsive and levodopa non-responsive subscales of the UPDRS-ME as an outcome measure showed that the sex difference in progression of motor impairments is mainly due to the difference in progression of levodopa responsive symptoms. This is in agreement with the hypothesis that women have less signs and symptoms due to nigrostriatal degeneration.

The influence of the prognostic factors for disability and motor impairments were not reflected in the deterioration of quality of life. Though patients with higher age of onset had a statistically significant steeper decline of quality of life, this difference was small and not clinically relevant. The finding that patients with higher anxiety and depression scores at baseline had a less steep decline in quality of life is probably caused by their low quality of life at baseline. The original clinimetric study of the PDQL investigated discriminant validity using three groups of PD patients (group 1: independent, activities a bit slower; group 2: slightly dependent, activities considerably slower; group 3: dependent, needing help or care).[13] These groups had mean scores of 137, 118 and 98 respectively. When considering this, the 2.8 points in annual decrease of the PDQL we found indicates that there is relatively little change in quality of life

in the first few years after the diagnosis of PD. These findings are endorsed by a cohort study in which the quality of life in the first four years after diagnosis remained unchanged.[30]

One of the main strengths of this study is the use of a relatively large cohort of newly diagnosed PD patients. After five years, only seven patients were lost to follow-up. By this means we were able to assess progression and to identify prognostic factors in a representative sample of PD patients. In addition, the use of linear mixed models assures that the available data from patients that were eventually lost to follow-up are still included in the analyses. The validation of the diagnosis after 5 years by a movement disorders specialist further increases the validity of the present study. Unfortunately we were not able to explore the domains of cognitive dysfunction that determine the increase in disability over time. Overall, 24% of patients were classified as having cognitive dysfunction at baseline. Our study is underpowered to further explore the impact of individual cognitive domains on disability. One might argue that the use of a hospital-based cohort is inferior to a community-based sample. However, medical care for PD patients in the Netherlands is organized in such a way that whenever a general practitioner has the clinical suspicion of PD, the patient is almost always referred to a neurologist in a general hospital. The annual progression on the UPDRS-ME of 2.46 points we found is comparable with the annual progression of 2.24 found in a large community based cohort with unselected newly diagnosed PD patients (the CamPaIGN cohort).[23,31]

Over the last decades, the non-dopaminergic features of PD have gained interest among clinicians and scientists. Using sophisticated mixed model analyses, we were able to show that non-dopaminergic features at the time of diagnosis are the main determinants for future disability and overall prognosis.

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DATA SUPPLEMENT: "GELB-CRITERIA" FOR THE DIAGNOSIS OF PARKINSON'S DISEASE.

Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol 1999;56:33-39.

Group A Features: Characteristic of Parkinson disease
• Resting tremor
• Bradykinesia
• Rigidity
• Asymmetric onset

Group B features: suggestive of alternative diagnoses
Features unusual early in the clinical course
• Prominent postural instability in the first 3 years after symptom onset
• Freezing phenomena in the first 3 years
• Hallucinations unrelated to medications in the first 3 years
• Dementia preceding motor symptoms or in the first year
• Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades
• Severe symptomatic dysautonomia unrelated to medications
• Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

Criteria for possible diagnosis of Parkinson disease:

At least 2 of the 4 features in Group A are present; at least 1 of these is tremor or bradykinesia

And

Either none of the features in group B is present, or symptoms have been present for less than 3 years and none of the features in group B is present to date

And

Either substantial and sustained response to levodopa or a dopamine agonist has been documented, or patient has not had an adequate trial of levodopa or dopamine agonist

DATA SUPPLEMENT: LED CALCULATION

Medication	Yes	No	If yes, specify daily dose		Levodopa equivalent Dose (LED)
Regular levodopa	☐	☐	L-dopa |__|__|__|__|__.|__|__|mg	times 1.0 =	|__|__|__|__|__.|__|__|(1)
Controlled release levodopa	☐	☐	L-dopa |__|__|__|__|__.|__|__|mg	times 0.75 =	|__|__|__|__|__.|__|__|(2)
Add (1) and (2) |__|__|__|__|__.|__|__| (3)					
Entacapone	☐	☐	|__|__|__|__|__.|__|__|mg	If yes, multiply the result at (3) with 0.2 =	|__|__|__|__|__.|__|__|(4)
Tolcapone	☐	☐	|__|__|__|__|__.|__|__|mg		
Rasagiline	☐	☐	|__|__|__|.|__|__|mg	If yes, multiply the result at (3) with 0.2 =	|__|__|__|__|__.|__|__|(5)
Selegiline	☐	☐	|__|__|__|.|__|__|mg		
Ropinirole	☐	☐	|__|__|__|.|__|__|mg	times 20 =	|__|__|__|__|__.|__|__|(6)
Pramipexole	☐	☐	|__|__|__|.|__|__|mg	times 100 =	|__|__|__|__|__.|__|__|(7)
Pergolide	☐	☐	|__|__|__|.|__|__|mg	times 100 =	|__|__|__|__|__.|__|__|(8)
Bromo-criptine	☐	☐	|__|__|__|.|__|__|mg	times 10 =	|__|__|__|__|__.|__|__|(9)
Apo-morphine	☐	☐	|__|__|__|.|__|__|mg	times 10 =	|__|__|__|__|__.|__|__|(10)
Levodopa Equivalent Dose (LED): add (1), (2) and (4-10)					|__|__|__|__|__.|__|__|(11)

DATA SUPPLEMENT: EXAMPLE MIXED MODEL ANALYSIS

The multivariable mixed model for the Schwab and England score shows that the Levy B score at baseline is (among others) a significant prognostic factor (table 3, original text). The Levy B score is a continuous variable ranging from 0–20 and measures the relatively levodopa non-responsive symptoms. The figure shows the progression of the Schwab and England score for patients with a Levy B score of 2 as compared to those with a score of 5, as these are relatively common scores within the range in our dataset. The estimated main effect of the Levy B score is -1.18 which indicates that for each point increase in baseline Levy B score the baseline Schwab and England score will be 1.18 lower. In the figure, this is expressed in the difference between the two lines at the intercept. The estimated effect size of the interaction term of the Levy B score with time is -0.67. This indicates that for each point increase of the Levy B score at baseline there will be an additional 0.67 point decrease of the Schwab and England score per year follow-up. In the figure, this difference is expressed as the difference between the slopes of the two lines. The estimated Schwab and England score at baseline is 3.54 (1.18*3) lower for patients with a Levy B score of 5 as compared to patients with a Levy B score of 2. The estimated Schwab and England score after five years is 13.59 (3.54+0.67*3*5) lower for the patients with a Levy B score of 5.

Figure: Example of the effect of the Levy B score at baseline on the progression of disability using the Schwab and England scale. The estimated lines are plotted for patients without cognitive dysfunction.

SUPPLEMENTARY DATA: UNIVARIABLE MIXED MODELS

Outcome measure	Prognostic Factor	Effect	(95% CI)	*p*-value
UPDRS-ME				
	Age at onset	0.21	(0.09; 0.33)	*p*=0.001
	Age at onset*year	0.02	(-0.02; 0.06)	*p*=0.386
	Male sex	-0.69	(-3.25; 1.87)	*p*=0.594
	Male sex*year	1.16	(0.35; 1.97)	*p*=0.006
	Left-handedness	-1.86	(-6.01; 2.30)	*p*=0.378
	Left-handedness*year	0.67	(-0.75; 2.09)	*p*=0.354
	Disease duration	0.11	(0.00; 0.23)	*p*=0.052
	Disease duration*year	-0.01	(-0.05; 0.03)	*p*=0.613
	CIRS score	0.44	(0.04; 0.84)	*p*=0.031
	CIRS score*year	-0.03	(-0.17; 0.10)	*p*=0.634
	HADS score	0.09	(-0.08; 0.27)	*p*=0.298
	HADS score*year	-0.01	(-0.06; 0.05)	*p*=0.834
	Cognitive dysfunction	4.40	(1.37; 7.44)	*p*=0.005
	Cognitive dysfunction*year	1.46	(0.40; 2.52)	*p*=0.008
	Levy A score			Not applicable
	Levy A score*year			Not applicable
	Levy B score			Not applicable
	Levy B score*year			Not applicable
UPDRS-ME				
Levy A subscore	Age at onset	0.10	(0.01; 0.18)	*p*=0.027
	Age at onset*year	-0.01	(-0.04; 0.02)	*p*=0.479
	Male sex	-0.47	(-2.29; 1.36)	*p*=0.613
	Male sex*year	0.80	(0.21; 1.39)	*p*=0.008
	Left-handedness	-1.41	(-4.38; 1.56)	*p*=0.347
	Left-handedness*year	0.61	(-0.42; 1.63)	*p*=0.242
	Disease duration	0.10	(0.02; 0.18)	*p*=0.015
	Disease duration*year	-0.01	(-0.04; 0.02)	*p*=0.364
	CIRS score	0.15	(-0.13; 0.44)	*p*=0.288
	CIRS score*year	-0.07	(-0.16; 0.03)	*p*=0.159
	HADS score	0.06	(-0.07; 0.18)	*p*=0.358
	HADS score*year	0.02	(-0.06; 0.03)	*p*=0.446
	Cognitive dysfunction	2.09	(-0.10; 4.28)	*p*=0.061
	Cognitive dysfunction*year	0.79	(0.02; 1.56)	*p*=0.046
	Levy A score			Not applicable
	Levy A score*year			Not applicable
	Levy B score	1.16	(0.81; 1.50)	*p*<0.001
	Levy B score*year	-0.15	(-0.29; -0.01)	*p*=0.035

UPDRS-ME				
Levy B subscore	Age at onset	0.09	(0.06; 0.12)	$p<0.001$
	Age at onset*year	0.03	(0.01; 0.04)	$p<0.001$
	Male sex	-0.25	(-1.01; 0.50)	$p=0.658$
	Male sex*year	0.24	(-0.05; 0.53)	$p=0.098$
	Left-handedness	-0.29	(-1.57; 0.99)	$p=0.658$
	Left-handedness*year	0.03	(-0.44; 0.49)	$p=0.909$
	Disease duration	0.03	(0.00; 0.07)	$p=0.065$
	Disease duration*year	0.01	(-0.01; 0.02)	$p=0.347$
	CIRS score	0.24	(0.13; 0.35)	$p<0.001$
	CIRS score*year	0.03	(-0.02; 0.07)	$p=0.270$
	HADS score	0.02	(-0.04; 0.07)	$p=0.534$
	HADS score*year	0.00	(-0.02; 0.02)	$p=0.663$
	Cognitive dysfunction	1.34	(0.43; 2.25)	$p=0.004$
	Cognitive dysfunction*year	0.65	(0.31; 1.00)	$p<0.001$
	Levy A score	0.18	(0.12; 0.23)	$p<0.001$
	Levy A score*year	0.02	(-0.01; 0.04)	$p=0.180$
	Levy B score			Not applicable
	Levy B score*year			Not applicable
Schwab and				
England	Age at onset	-0.08	(-0.19; 0.04)	$p=0.176$
	Age at onset*year	-0.19	(-0.28; -0.10)	$p<0.001$
	Male sex	0.63	(-1.70; 2.97)	$p=0.592$
	Male sex*year	-1.08	(-2.99; 0.84)	$p=0.268$
	Left-handedness	2.93	(-0.67; 6.53)	$p=0.109$
	Left-handedness*year	-0.39	(-3.42; 2.65)	$p=0.801$
	Disease duration	-0.06	(-0.17; 0.04)	$p=0.240$
	Disease duration*year	0.01	(-0.07; 0.10)	$p=0.780$
	CIRS score	-0.30	(-0.67; 0.06)	$p=0.106$
	CIRS score*year	-0.26	(-0.56; 0.04)	$p=0.085$
	HADS score	-0.19	(-0.35; -0.03)	$p=0.020$
	HADS score*year	0.02	(-0.11; 0.15)	$p=0.797$
	Cognitive dysfunction	-1.42	(-4.20; 1.37)	$p=0.316$
	Cognitive dysfunction*year	-4.14	(-6.40; -1.88)	$p<0.001$
	Levy A score	-1.72	(-4.23; 0.78)	$p<0.001$
	Levy A score*year	3.09	(0.09; 6.10)	$p=0.026$
	Levy B score	0.99	(0.17; 1.81)	$p<0.001$
	Levy B score*year	1.33	(0.30; 2.35)	$p<0.001$
ALDS theta-score				
	Age at onset	-0.04	(-0.05; -0.02)	$p<0.001$

	Age at onset*year	-0.02	(-0.02; -0.01)	p<0.001
	Male sex	0.29	(-0.06; 0.64)	p=0.101
	Male sex*year	0.01	(-0.17; 0.16)	p=0.950
	Left-handedness	0.22	(-0.35; 0.80)	p=0.440
	Left-handedness*year	0.04	(-0.22; 0.30)	p=0.770
	Disease duration	-0.01	(-0.03; 0.00)	p=0.155
	Disease duration*year	0.00	(-0.01; 0.01)	p=0.667
	CIRS score	-0.15	(-0.20; -0.10)	p<0.001
	CIRS score*year	-0.02	(-0.05; 0.01)	p=0.140
	HADS score	-0.02	(-0.04; 0.01)	p=0.126
	HADS score*year	0.00	(-0.01; 0.01)	p=0.663
	Cognitive dysfunction	-0.25	(-0.68; 0.17)	p=0.243
	Cognitive dysfunction*year	-0.31	(-0.51; -0.10)	p=0.003
	Levy A score	-0.05	(-4.23; 0.78)	p=0.001
	Levy A score*year	-0.02	(0.09; 6.10)	p=0.016
	Levy B score	-0.24	(0.17; 1.81)	p<0.001
	Levy B score*year	-0.07	(0.30; 2.35)	p<0.001
PDQL				
	Age at onset	-0.19	(-0.54; 0.15)	p=0.268
	Age at onset*year	-0.11	(-0.19; -0.02)	p=0.019
	Male sex	-0.68	(-7.88; 6.52)	p=0.852
	Male sex*year	-1.36	(-3.22; 0.51)	p=0.152
	Left-handedness	1.06	(-10.76; 12.89)	p=0.859
	Left-handedness*year	1.58	(-1.40; 4.55)	p=0.297
	Disease duration	-0.56	(-0.87; -0.25)	p=0.001
	Disease duration*year	0.07	(-0.02; 0.16)	p=0.120
	CIRS score	-2.80	(-3.84; -1.77)	p<0.001
	CIRS score*year	0.09	(-0.20; 0.38)	p=0.540
	HADS score	-1.84	(-2.22; -1.46)	p<0.001
	HADS score*year	0.13	(0.00; 0.26)	p=0.047
	Cognitive dysfunction	-11.77	(-20.08; -3.44)	p=0.006
	Cognitive dysfunction*year	-1.08	(-3.29; 1.13)	p=0.334
	Levy A score	-1.19	(-4.23; 0.78)	p<0.001
	Levy A score*year	0.06	(0.09; 6.10)	p=0.480
	Levy B score	-3.67	(0.17; 1.81)	p<0.001
	Levy B score*year	0.13	(0.30; 2.35)	p=0.644

UPDRS-ME: Unified Parkinson's Disease Rating Scale - Motor Examination; ALDS: AMC Linear Disability Scale; PDQL: Parkinson's Disease Quality of Life questionnaire; CIRS: Cumulative Illness Rating Scale; HADS: Hospital Anxiety and Depression Scale

Chapter 3

Autonomic symptoms in Parkinson's disease: Frequency, risk factors and influence on disability and quality of life

Daan C. Velseboer
Bart Post
Ben Schmand
Rob J. de Haan
Rob M.A. de Bie

Submitted

ABSTRACT

Background: The risk factors for autonomic symptoms (AS) in Parkinson's disease (PD), and the influence of AS on disability and quality of life (QoL) have mainly been investigated in cohorts consisting of prevalent PD patients, which are susceptible to overrepresentation of patients with milder disease course.

Methods: In an ongoing longitudinal cohort study consisting of newly diagnosed PD patients (the CARPA-study) AS were assessed with the SCOPA-AUT and COMPASS-31 in patients still participating after 5 years of follow-up. Baseline data from the CARPA-study were used for prognostic modeling of AS at 5 years, whereas data from the CARPA 5-year assessment were used to assess the impact of AS on disability and QoL in a cross-sectional analysis.

Findings: A total of 72 PD patients were included. Mean patient age was 69.8 years (SD 10.4) and mean disease duration was 6.7 years (SD 0.7). In the longitudinal analysis, presence of non-levodopa responsive motor symptoms and higher anxiety and depression scores at the time of diagnosis were associated with a higher risk of developing AS. In the cross-sectional analysis, presence of AS was associated with more disability and lower QoL. Adjustment for non-levodopa responsive motor symptoms and symptoms of anxiety and depression in a multivariable analysis decreased regression coefficients of this relation by more than 50%.

Interpretation: Future development of AS is predicted by the presence of psychiatric and non-levodopa responsive motor symptoms at the time of diagnosis. Patients with AS have more disability and a lower QoL, but whether this is a causal relation or caused by concurrent presence of other non-dopaminergic symptoms remains unclear.

INTRODUCTION

Autonomic symptoms (AS) are part of the disease spectrum in Parkinson's disease (PD).[1] A study in an incident PD cohort showed that AS can be present to some extent early in the disease course.[2] To date, studies concerning AS later in the disease course all concern patients from prevalent PD cohorts. In these studies patients with a milder disease course are relatively overrepresented and the actual disease burden resulting from AS may be underestimated.[3] In addition, the lack of studies with a long follow-up duration has made the identification of specific risk factors for development of AS difficult. To investigate the prevalence, risk factors, and disease burden of AS in PD patients with longer disease duration we assessed AS in participants of an ongoing longitudinal cohort study consisting of newly diagnosed PD patients (the CARPA-study). We examined whether baseline prognostic variables could be identified that were associated with future occurrence of AS in a longitudinal analysis and whether the presence of AS is associated with higher level of disability or lower quality of life (QoL) in a cross-sectional analysis.

METHODS

Participants

Patients were recruited from the CARPA-cohort in which patients with newly diagnosed PD from six general hospitals were included between 2002 and 2005.[4] The clinical diagnosis of PD was based on standard criteria and was confirmed by a movement disorder specialist during the study.[5] All patients with a confirmed diagnosis of PD still participating at the 5 year follow-up of the CARPA-study were approached for participation.[6] The current study was part of a larger project in which patients were also assessed for the presence of orthostatic hypotension (OH) using an active standing test and a head-up-tilt test.[7] Patients unable to stand unassisted were excluded for this project and therefore also from the present study. The present study was approved by the medical ethics committees of the Free University Medical Center and the Academic Medical Center, Amsterdam (since 2018 both part of Amsterdam University Medical Centers). From all participants written informed consent was obtained.

Autonomic questionnaires

With regard to AS experienced in daily life, all participants were requested to complete the Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT) and the Composite Autonomic Symptom Score 31 (COMPASS 31).[8] The questionnaires were administered on two separate occasions. The SCOPA-AUT was mailed beforehand and the COMPASS 31 was administered during a study visit on a day patients were also assessed for the presence of OH.[7] The SCOPA-AUT is a questionnaire developed specifically for PD patients (range 0–69, higher scores indicate more symptoms).[9] It contains items rating AS in the cardiovascular, gastro-intestinal, pupillomotor, sexual, thermoregulatory, and urogenital domains. The COMPASS 31 is a shortened version of the generic Autonomic Symptom Profile (range 0–100, higher scores indicate more symptoms).[10,11] It contains items rating AS in the cardiovascular, gastro-intestinal, pupillomotor, sudomotor, urogenital and vasomotor domains. For comparability to the SCOPA-AUT the vasomotor and a sudomotor domains in the COMPASS 31 were combined into one thermoregulatory domain. Correlations between the various subdomains of both scales were estimated using Spearman's rank correlation coefficient. The correlation between the sum scores of both scales was estimated using Pearson's correlation coefficient. For the remainder of the present study, analyses were performed primarily using the SCOPA-AUT. Analyses were repeated using the COMPASS 31 for confirmation, of which detailed results are shown in the data supplement.

Longitudinal analysis with baseline variables to identify risk factors for autonomic symptoms

A set of predefined prognostic variables was selected, comparable with our earlier prognostic study.[6] Besides age at onset and sex we used the following variables from the baseline visit of the CARPA-study: dopaminergic treatment, motor symptoms, comorbidity, anxiety and depression, and cognitive function. Medication use was assessed with an interview and a Levodopa Equivalent Dosage (LED) was calculated.[12] Motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale - Motor Examination (UPDRS-ME, range 0–108, higher scores indicate more severe symptoms)[13] which was divided into two subscales representing relatively levodopa responsive symptoms (Levy score A, range 0–80) and relatively non-levodopa responsive symptoms (Levy score B, range 0–20). The Levy B score contains the UPDRS-ME items for "speech", "rising from chair", "posture", "gait", and "postural stability". The Levy A score contains the remaining UPDRS-ME items with omission of the item "finger taps".[14] Comorbidity was assessed with the Cumulative Illness Rating Scale (CIRS, range 0–52, higher scores indicate more comorbidity).[15] Anxiety and depression were

assessed with the Hospital Anxiety and Depression Scale (HADS, range 0–42, higher scores indicate more symptoms of anxiety and depression).[16] Cognitive functioning was assessed at baseline using an extensive neuropsychological test battery, after which established PD-MCI criteria were applied.[17] Univariable linear regression was performed using the potential prognostic variables as determinants and SCOPA-AUT as outcome measure. Prognostic factors with a significant ($p < 0.05$) association with the SCOPA-AUT score were evaluated in a multivariable model. Strength and direction of associations were expressed by the regression coefficients from the regression analyses.

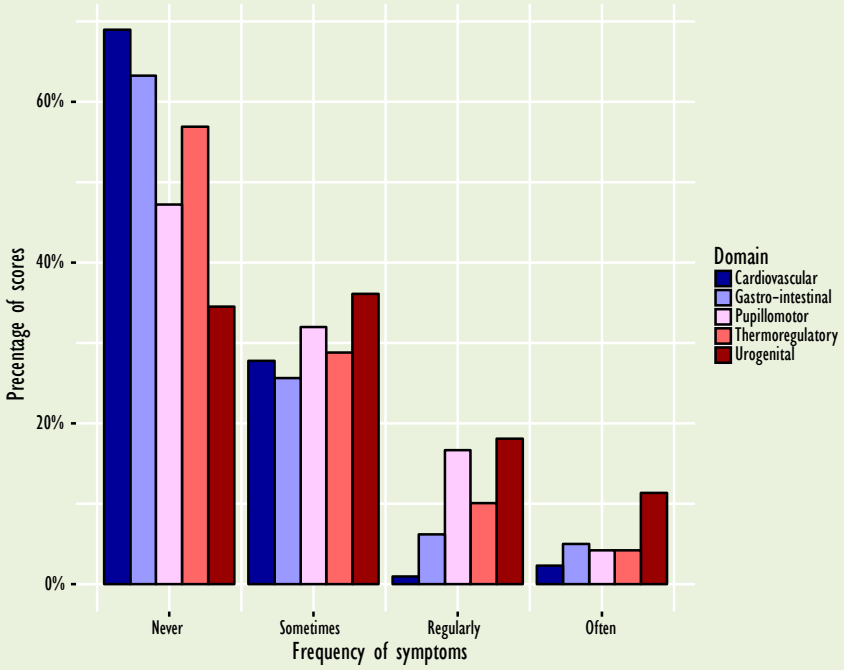
Cross-sectional relation of autonomic symptoms to disability and quality of life (QoL)

To investigate the influence of AS on disability and quality of life we used linear regression in which SCOPA-AUT scores were used as determinant and data on disability and quality of life from the regular CARPA-year 5 visit were used as outcome measure.[6] There was an interval of 1.3 years between the regular CARPA-year 5 visit and the assessment of the SCOPA-AUT for the present study. By this means this analysis is not strictly cross-sectional, but set against the slow progressive nature of PD, it was considered as such. From the CARPA-year 5 visit the Schwab and England was used to assess disability (SE, range 0–100, lower scores indicate more disability) and the Short Form (36) Health Survey (SF-36) Mental and Physical Components Summaries were used to assess quality of life (MCS and PCS, where the averages of the healthy population are 50 with an SD of 10 and higher scores indicate better QoL).[18,19] Since the Parkinsons Disease Quality of Life scale contains overlapping items with the autonomic questionnaires it was not used as an outcome measure.[20] Associations between AS and disability and QoL were first investigated with univariable linear regression. To investigate whether associations between AS and disability or QoL were caused by a causal relationship or caused by confounding variables additional multivariable regression analysis was performed. For this analysis, from the determinants identified as prognostic factors for AS in the prognostic model, the scores from the CARPA 5-year visit were included in the multivariable regression analyses. A change of > 10% in regression coefficients of the SCOPA-AUT score between univariable and multivariable analyses was classified as potential relevant confounding. For all analyses a threshold of $p < 0.05$ was used for statistical significance. Statistical uncertainties were expressed using 95% Confidence intervals (CI). All analyses were performed in IBM SPSS version 23.

RESULTS

Of the original 133 patients from the CARPA-cohort 72 participated in the present study. Thirty-seven patients were deceased, three had a revised diagnosis, six were unable to stand unassisted and 15 declined participation for the present study or had already declined further follow-up earlier during the CARPA-study. A flowchart showing details on the selection process can be found in the data supplement. Mean patient age was 69.8 years (SD 10.4). Mean disease duration since diagnosis was 6.7 years (SD 0.7). Thirty-seven (51.4%) participants were men. All patients were using dopaminergic treatment. Patients with a final PD diagnosis that declined participation, or were excluded because they were unable to stand unassisted (n = 21) were compared with study participants and no substantial differences in baseline variables were found (supplementary table 1).

Figure 1: Distributions of rated frequency of autonomic symptoms in the different domains of the SCOPA-AUT



The barchart shows the distribution of responses for the cardiovascular (3 items); Gastro-intestinal (7 items); Pupillomotor (1 item); Thermoregulatory (4 items); and Urogenital (6 items) domains of the SCOPA-AUT.

Autonomic symptom scores

Data in the sexual domain of the SCOPA-AUT was missing in 37 of the 72 participants. For calculation of sum scores of the SCOPA-AUT, missing values in the sexual domain were imputed by averaging the scores from the other domains.[9] Because of the frequent missing data the results of the sexual domain are not presented separately. There were no missing data in all other domains of both autonomic questionnaires. Analyzing the different domains of AS, the urogenital symptoms are most frequent and the cardiovascular symptoms are the least frequent (Figure 1). Correlation coefficients of sum scores and subdomains between the two autonomic scales were relatively low for the pupillomotor and thermoregulatory domains. For all other subdomains and for the sum scores of the two questionnaires the correlation-coefficients were between 0.70–0.79 (Table 1).

Longitudinal analysis with baseline variables to identify risk factors for autonomic symptoms

Univariable linear regression showed that higher Levy B-scores and higher HADS-scores at baseline were associated with the presence of more AS later in the disease (Table 2). In multivariable analysis the regression coefficients of both prognostic variables decreased by ±15% and statistical significance was lost. Repeated analyses using the COMPASS 31 as outcome measure showed comparable results, with the exception of Levy B scores remaining borderline statistically significant in multivariable analysis (supplementary table 2). AS are known side-effects of antidepressant and antipsychotic medication. We therefore repeated multivariable regression in which the association between the HADS-scores and the SCOPA-AUT was corrected for use of antidepressant or antipsychotic medication (at the time of the SCOPA-AUT assessment). In this analysis no relevant change in the association between the HADS-scores and SCOPA-AUT was found (supplementary table 3).

Cross-sectional relation of autonomic symptoms to disability and quality of life (QoL)

Univariable linear regression showed that presence of more AS was associated with more disability and lower physical and mental QoL (Table 3). Multivariable analysis with correction for Levy B-scores and HADS-scores from the 5-year follow-up visit showed changes of the effect size of > 50% for all analyses. This indicates that a causal relationship between AS and more disability and lower QoL could not be established, since more disability and lower QoL in patients with AS could also be caused by non-dopaminergic motor symptoms or psychiatric symptoms. Repeated analyses using the COMPASS 31 as outcome measure showed comparable results (supplementary table 4).

Table 1: Means and correlations between SCOPA-AUT and COMPASS 31 scores

Domain[a]	SCOPA-AUT	COMPASS 31	Correlation coefficient
Cardiovascular (Orthostatic Intolerance)	1.1 (1.4)	2.4 (2.9)	0.78[b]
Gastro-intestinal (Gastro-intestinal)	3.7 (2.7)	5.0 (4.7)	0.74[b]
Pupillomotor (Pupillomotor)	0.8 (0.9)	3.3 (3.1)	0.47[b]
Thermoregulatory (Vasomotor + Secretomotor)	2.4 (2.0)	1.8 (1.9)	0.31[b]
Urogenital (Bladder)	6.4 (3.4)	1.9 (1.9)	0.79[b]
Sumscores	16.1 (7.6)	20.8 (15.4)	0.70[c]

SCOPA-AUT: Scales for Outcomes in Parkinson's Disease - Autonomic questionnaire; COMPASS 31: Composite Autonomic Symptom Score 31. [a] The names of the corresponding domains differ slightly between the two questionnaires; the names of the COMPASS 31 domains are shown in parentheses; [b] Spearman's rank correlation coefficient, all correlations $p < 0.05$; [c] Pearson's correlation coefficient, $p < 0.05$

Table 2: Prognostic model with the SCOPA-AUT as outcome measure

	Prognostic Factor	Effect	(95% CI)	*p*-value
Univariable linear regression				
	Age at onset	0.02	(-0.16; 0.20)	p=0.79
	Male sex	-1.25	(-4.83; 2.34)	p=0.49
	LED	0.01	(-0.01; 0.02)	p=0.29
	UPDRS-ME Levy A	0.16	(-0.13; 0.45)	p=0.28
	UPDRS-ME Levy B	0.96	(0.11; 1.81)	p=0.03
	CIRS	0.38	(-0.18; 0.93)	p=0.18
	MCI	1.19	(-3.00; 5.38)	p=0.58
	HADS	0.28	(0.03; 0.54)	p=0.03
Multivariable linear regression				
	UPDRS-ME Levy B	0.81	(-0.03; 1.66)	p=0.06
	HADS	0.24	(-0.01; 0.49)	p=0.06

SCOPA-AUT: Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire; LED: Levodopa Equivalent Dosage; UPDRS-ME: Unified Parkinson's Disease Rating Scale - Motor Examination; CIRS: Cumulative Illness Rating Scale; MCI: Mild Cognitive Impairment; HADS: Hospital Anxiety and Depression Scale

Table 3: Relation of autonomic symptoms (SCOPA-AUT) to disability and quality of life

Outcome measure	Determinant	Effect	(95% CI)	*p*-value
Schwab and England univariable linear regression				
	SCOPA-AUT	-0.56	(-0.91; -0.21)	p=0.002
Schwab and England multivariable linear regression				
	SCOPA-AUT	-0.26	(-0.55; 0.04)	p=0.09
	UPDRS-ME Levy B	-1.60	(-2.39; -0.81)	p<0.001
	HADS	-0.17	(-0.47; 0.13)	p=0.26
SF-36 PCS univariable linear regression				
	SCOPA-AUT	-0.30	(-0.60; 0.00)	p=0.05
SF-36 PCS multivariable linear regression				
	SCOPA-AUT	-0.12	(-0.41; 0.17)	p=0.42
	UPDRS-ME Levy B	-1.11	(-1.90; -0.33)	p=0.01
	HADS	-0.22	(-0.52; 0.08)	p=0.14
SF-36 MCS univariable linear regression				
	SCOPA-AUT	-0.41	(-0.73; -0.08)	p=0.01
SF-36 MCS multivariable linear regression				
	SCOPA-AUT	-0.08	(-0.33; 0.17)	p=0.54
	UPDRS-ME Levy B	0.57	(-0.10; 1.25)	p=0.09
	HADS	-1.10	(-1.36; -0.85)	p<0.001

SCOPA-AUT: Scales for Outcomes in Parkinson's Disease - Autonomic questionnaire; UPDRS-ME: Unified Parkinson's Disease Rating Scale - Motor Examination; HADS: Hospital Anxiety and Depression Scale; SF-36: Short Form (36) Health Survey; PCS: Physical Components Summary; MCS Mental Components Summary

DISCUSSION

In the present study we show the frequency of AS in a representative cohort of PD patients with disease duration of more than 5 years. We found that anxiety and depression and non-levodopa responsive motor symptoms at the time of PD diagnosis to be main determinants for the presence of AS later in disease. In previous cross-sectional studies, age, disease duration and disease severity were important determinants for the presence and severity of AS.[21,22] In longitudinal studies the relatively low patient numbers and short follow-up length has made the identification of other risk factors difficult.[23,24]

Though this is the first study to show the presence of anxiety and depressive symptoms early in the disease to be predictive of future development of AS, the reverse relationship of AS predicting anxiety and depressive symptoms later in the disease was recently described.[25,26] The relationship between symptoms of anxiety and depression and AS in PD patients could be a reflection of concurrent disease progression in the brain stem. Though AS in PD are largely ascribed to degeneration of neurons in the peripheral autonomic nervous system, degeneration of the dorsal motor nucleus of the vagus nerve; the nucleus of the solitary tract; and the C1 layer of the rostral ventrolateral medulla also seem to play a role.[27] These brain stem nuclei share a close anatomical relationship to the serotonergic and noradrenergic neurons in the raphe nuclei and locus coeruleus of which degeneration could play a role in the development of symptoms of anxiety and depression in PD.[28] On the other hand, the concurrent progression of symptoms of anxiety and depression and AS in PD does not necessarily reflect their close anatomical relation. Previous prognostic studies repeatedly demonstrate that development of non-levodopa responsive symptom in PD are best predicted by the presence of other non-levodopa responsive symptoms irrespective of their anatomical location.[6,29] Lastly, the association could also be caused by contamination of the HADS questionnaire with somatic items. Review of this questionnaire however, identifies only one out of 13 items that could be regarded as 'somatic' (the item: "I get a sort of frightened feeling like butterflies in the stomach"), making substantial contamination explaining the association unlikely.[16] Unfortunately, the autonomic questionnaires were not administered at the time of diagnosis, making a correction for baseline AS-scores in our prognostic model impossible.

The results of our study suggest that AS are associated with more disability and lower QoL, but due to considerable confounding of non-levodopa responsive motor symptoms and symptoms of anxiety and depression we were unable to show a causal relationship. Various

studies have already indicated the presence of an association between AS and lower QoL in PD patients.[30-33] In the only other study with a multivariable regression analysis the significant association between AS and QoL was lost, comparable to our results.[33] This is probably caused by the associated presence of non-levodopa responsive motor symptoms which were already known to have impact on disability and symptoms of anxiety and depression which were already known to have impact on QoL.[6]

Our present exploratory analyses tentatively provide insight into the risk profile and burden of AS in PD. This could be useful for selecting subgroups of PD patients and for selecting outcome measures when investigating new therapies for AS in PD. However, more robust data are needed first. As mentioned earlier, the use of a cohort with newly diagnosed PD patients has the major advantage of providing results with a high external validity. The major drawback of selecting participants solely from an incident cohort is the relatively low number of included patients. In addition, the relatively small proportion of patients in our cohort experiencing AS regularly or often makes investigation of the impact of AS on disability and QoL difficult. Hopefully, data from other incident cohorts will follow in the upcoming years. In addition, researchers responsible for different incident PD cohorts are increasingly collaborating and hopefully more detailed analyses concerning AS in PD will be possible by pooling data.[34,35]

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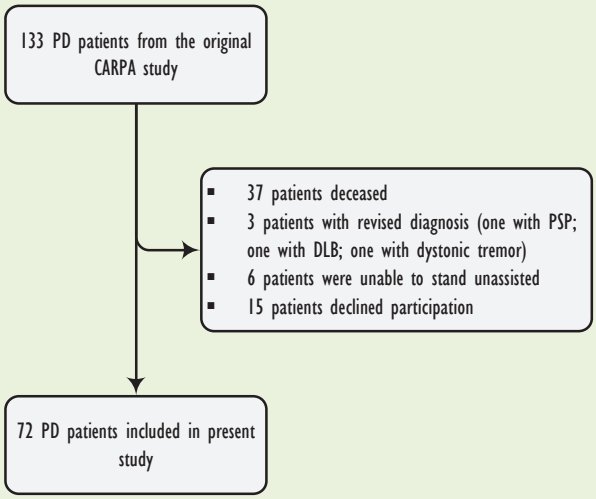
SUPPLEMENTARY DATA

Supplementary figure: Selection of participants



PSP: progressive Supranuclear Palsy; DLB: Dementia with Lewy Bodies

Supplementary table 1. Baseline comparison of PD patients that participated in the present study with PD patients that declined participation, or were excluded because they were unable to stand unassisted

	Participants (n = 72)	Non-participants (n = 21)	*p*-value[a]
Age at diagnosis; mean (SD)	63.1 (10.1)	65.2 (10.8)	0.41
Number of males (%)	37 (51%)	10 (48%)	0.76
Baseline UPDRS-ME; mean (SD)	16.6 (8.3)	17.0 (7.0)	0.84
Baseline UPDRS-ME Levy A; mean (SD)	12.9 (6.2)	13.2 (4.7)	0.83
Baseline UPDRS-ME Levy B; mean (SD)	1.8 (2.1)	1.9 (2.1)	0.86
Baseline Hoehn & Yahr; mean (SD)	1.7 (0.7)	1.7 (0.7)	0.80
Baseline Schwab and England; mean (SD)	90.8 (6.4)	91.4 (6.5)	0.71
Baseline CIRS; mean (SD)	4.7 (3.2)	4.7(3.2)	0.96
Frequency of MCI (%)[b]	17 (24%)	6 (33%)	0.42
Baseline HADS; mean (SD)	9.8 (6.9)	10.7 (9.5)	0.67

[a] Independent sample t-tests for continuous variables and chi-square test for dichotomous variables;
[b] data on baseline classification of MCI were missing in one patient in the group of participants and in three patients in the group of non-participants.

Supplementary table 2: Prognostic model with the COMPASS 31 as outcome measure

	Prognostic Factor	Effect	(95% CI)	*p*-value
Univariable linear regression				
	Age at onset	0.03	(-0.33; 0.39)	*p*=0.87
	Male sex	-1.09	(-8.37; 6.19)	*p*=0.77
	LED	0.02	(-0.01; 0.04)	*P*=0.23
	UPDRS-ME Levy A	0.43	(-0.15; 1.01)	*P*=0.15
	UPDRS-ME Levy B	2.08	(0.37; 3.79)	*P*=0.02
	CIRS	0.77	(-0.35; 1.89)	*p*=0.17
	MCI	8.15	(-0.03; 16.33)	*p*=0.05
	HADS	0.58	(0.07; 1.09)	*p*=0.03
Multivariable linear regression				
	UPDRS-ME Levy B	1.79	(0.09; 3.50)	*p*=0.04
	HADS	0.48	(-0.02; 0.99)	*p*=0.06

COMPASS 31: Composite Autonomic Symptom Score 31; LED: Levodopa Equivalent Dosage; UPDRS-ME: Unified Parkinson's Disease Rating Scale - Motor Examination; CIRS: Cumulative Illness Rating Scale; MCI: Mild Cognitive Impairment; HADS: Hospital Anxiety and Depression Scale

Supplementary table 3: Prognostic model with baseline HADS as determinant and SCOPA-AUT as outcome measure, with and without correction for use of antidepressant and antipsychotic medication

	Prognostic Factor	Effect	(95% CI)	*p*-value
Univariable linear regression				
	HADS	0.28	(0.03; 0.54)	*p*=0.03
Multivariable linear regression				
	HADS	0.27	(-0.01; 0.55)	*p*=0.05
	Use of antidepressants or antipsychotic medication	0.47	(-4.68; 5.62)	*p*=0.86

SCOPA-AUT: Scales for Outcomes in Parkinson's Disease - Autonomic questionnaire; HADS: Hospital Anxiety and Depression Scale

Supplementary table 4: Relation of autonomic symptoms (COMPASS 31) to disability and quality of life

Outcome measure	Determinant	Effect	(95% CI)	*p*-value
Schwab and England univariable linear regression				
	COMPASS 31	-0.30	(-0.47; -0.13)	*p*=0.001
Schwab and England multivariable linear regression				
	COMPASS 31	-0.15	(-0.30; 0.00)	*p*=0.05
	UPDRS-ME Levy B	-1.48	(-2.30; -0.67)	*p*=0.001
	HADS	-0.16	(-0.45; 0.14)	*p*=0.30
SF-36 PCS univariable linear regression				
	COMPASS 31	-0.13	(-0.28; 0.02)	*p*=0.09
SF-36 PCS multivariable linear regression				
	COMPASS 31	0.18	(-0.13; 0.17)	*p*=0.81
	UPDRS-ME Levy B	-1.22	(-2.04; -0.41)	*p*=0.004
	HADS	-0.27	(-0.57; 0.03)	*p*=0.08
SF-36 MCS univariable linear regression				
	COMPASS 31	-0.21	(-0.37; -0.05)	*p*=0.01
SF-36 MCS multivariable linear regression				
	COMPASS 31	-0.07	(-0.20; 0.06)	*p*=0.26
	UPDRS-ME Levy B	0.66	(-0.29; 1.35)	*p*=0.06
	HADS	-1.08	(-1.33; -0.83)	*p*<0.001

COMPASS 31: Composite Autonomic Symptom Score 31; UPDRS-ME: Unified Parkinson's Disease Rating Scale - Motor Examination; HADS: Hospital Anxiety and Depression Scale; SF-36: Short Form (36) Health Survey; PCS: Physical Components Summary; MCS Mental Components Summary

Chapter 4

Development and external validation of a prognostic model in newly diagnosed Parkinson disease

Daan C. Velseboer
Rob M.A. de Bie
Luuk Wieske
Jonathan R. Evans
Sarah L. Mason
Thomas Foltynie
Ben Schmand
Rob J. de Haan
Bart Post
Roger A. Barker
Caroline H. Williams-Gray

Neurology 2016;86:986-993

ABSTRACT

Objective: To develop a prognostic model to predict disease outcomes in individual PD patients, and perform an external validation study in an independent cohort.

Methods: Model development was done in the CARPA cohort (Netherlands). External validation was performed using the CamPaIGN cohort (UK). Both are longitudinal incident cohort studies that prospectively followed up PD patients from the time of diagnosis. A composite outcome measure was made in which patients were classified as having an unfavorable prognosis when they had postural instability or dementia at the five-year assessment (or at the last assessment before loss to follow-up), or had deceased before this time. The final model was derived with a backward selection strategy from candidate predictor variables that were measured at baseline.

Results: In the resulting model, higher patient age, higher UPDRS-ME axial-score, and a lower animal fluency score were all associated with a higher probability of an unfavorable outcome. External validation confirmed good discriminative ability between favorable and unfavorable outcomes with an area under the ROC-curve of 0.85 (95% CI: 0.77–0.93), and a well calibrated model with a calibration slope of 1.13 and no significant lack of fit (Hosmer-Lemeshow test: $p = 0.39$).

Conclusion: We have constructed a model that allows individual patient prognostication at five years from diagnosis, using a small set of predictor variables that can easily be obtained by clinicians or research nurses.

INTRODUCTION

Disease progression in Parkinson's disease (PD) is highly heterogeneous. Disability is mainly determined by the onset of postural instability and dementia.[1] The time to reach these irreversible milestones varies considerably among PD patients.[2] In clinical research, disease heterogeneity generally leads to a higher variance in outcomes, which in turn results in larger sample sizes needed to demonstrate possible treatment effects. This can be a problem especially in trials investigating neuroprotective therapies in PD, as these trials already have high costs due to their need for lengthy follow-up to show effects.[3]

Through longitudinal follow-up of our incident PD cohorts in the Netherlands and the UK, we have previously identified a number of baseline clinical characteristics associated with poor outcomes including older age, non-levodopa responsive motor symptoms, and deficits on semantic fluency and pentagon copying tests.[2,4-6] However, these previous analyses have mainly been explorative in nature and whilst they may allow subgroups of patients at higher or lower risk of a poor outcome to be defined, they do not allow prognostication on an individual basis. The latter would be of considerable use in selecting patients for clinical trials. We therefore developed a prognostic model to predict five-year outcomes for patients with newly-diagnosed PD and validated the model in an independent cohort.

METHODS

Study Populations

Model development was performed using data from the CARPA study.[6-8] The CARPA study is a clinic-based longitudinal prospective cohort study of newly-diagnosed PD patients from outpatient clinics in six general hospitals in the Netherlands, recruited between July 2002 and April 2005. Clinical diagnoses of PD were based on the criteria from Gelb and colleagues, and were re-evaluated at the five-year assessment by a movement disorder specialist.[9] Patients with a revision of their diagnosis during follow-up were retained in the dataset. Model validation was performed in data from the CamPaIGN study.[2,4,5,10] The CamPaIGN study is a community-based longitudinal prospective study of a population-representative cohort of newly-diagnosed PD patients from the county of Cambridgeshire, UK, recruited between December 2000 and December 2002. Clinical diagnosis was based on the UK Parkinson's Disease Society Brain Bank criteria.[11] Diagnosis was re-evaluated by a movement disorder specialist at 3.5 years and

five years of follow-up. Baseline differences between development and validation datasets were evaluated using independent sample t-tests and chi-square tests where appropriate.

Outcome measure

A composite binary outcome measure was made in which patients were classified as having an unfavorable prognosis when they had postural instability or dementia at the five-year assessment (or at the last assessment before loss to follow-up), or had deceased before this time. All other patients were classified as having a favorable prognosis. The presence of postural instability was assessed on the basis of a modified Hoehn and Yahr score of three or higher.[12] Patients were classified as having dementia using level 1 criteria from the Movement Disorder Society Task Force, operationalized using the Mini Mental State Examination (MMSE) in addition to the clock drawing test in het CARPA study and a phonemic fluency test in the CamPaIGN study.[13-18] Patients that already met the criteria of an unfavorable outcome at baseline were excluded from further analyses in both datasets.

Candidate predictors

The set of candidate predictors consisted of demographic variables including age, gender and symptom duration; and clinical characteristics that were assessed at baseline in both cohort studies. Motor impairment was assessed with the Unified Parkinson's Disease Rating Scale motor examination (UPDRS-ME) section and tremor-, bradykinesia-, rigidity-, and axial-subscores were calculated using established methods.[19,20] Equivalent levodopa doses were calculated using our previously published formula.[4] The Cumulative Illness Rating Scale was used to count the number of organ systems with comorbid disease (CIRS, range 0–13).[21] Presence of depressive symptoms was assessed with the Hospital Anxiety and Depression Scale (HADS) in the development dataset and by the Beck Depression Inventory (BDI) in the validation dataset.[22,23] To overcome differences between development and validation datasets, both scales were dichotomized using recently suggested cut-off values for screening for depression in PD.[24] Phonemic fluency was assessed by the Controlled Oral Word Association Test (COWAT) in which patients are asked to produce as many words as possible starting with the same letter in a one-minute timeframe for a total of three individual letters.[17] Semantic fluency was assessed with the animal fluency test in which patients are asked to name as many animals as possible in a one-minute timeframe.[25] Global cognitive function was assessed by the MMSE.[15]

Model development

Missing candidate predictors were imputed using multiple imputation (MI), by which fifty different imputed datasets were generated. Regression coefficients and standard errors were averaged using Rubin's rules.[26] Missing outcomes were not imputed.[27] All candidate predictors were entered into a multivariable logistic regression analysis with stepwise backward selection strategy for each imputed dataset. The Akaike Information Criterion (AIC) was used as a stopping rule. Candidate predictors that appeared in 50% or more of the multivariable models from the different imputed datasets were retained in the final model.[28]

Parameters of model performance and model validation

Model performance is divided into two main categories: discriminative ability and model calibration. The discriminative ability assesses whether the model is able to differentiate between patients with a favorable and an unfavorable outcome. It is expressed by Harrel's c-statistic, which is similar to the area under the curve (AUC) of a receiver operator characteristic (ROC) curve.[29] The c-statistic ranges from 0.50 (indicating a non-informative model) to 1.00 (indicating a model with perfect discrimination between patients with and without an unfavorable outcome). Model calibration assesses to what extent predicted values agree with observed outcomes. It is visualized by the calibration plot in which the calibration curve is estimated by local regression (LOESS).[27] The calibration slope has an ideal value of 1. A slope < 1 reflects overfitting, meaning that low predictions are too low and high predictions are too high. A slope > 1 reflects underfitting, meaning that the predictions are not sufficiently extreme. Overall agreement between predicted and observed outcomes is tested using the Hosmer-Lemeshow goodness-of-fit test in which a p-value < 0.05 indicates significant disagreement between predicted and observed outcomes.

Validation of the final model was divided into three stages: apparent validation, internal validation, and external validation. For apparent validation, performance parameters were estimated directly in the dataset in which the model was developed. For internal validation, the final model was validated with ($n = 1000$) bootstrap samples from the development dataset, after which the optimism corrected c-statistic and calibration slope were estimated. The use of MI-datasets automatically results in model performance parameters for each individual MI-dataset at apparent and internal validation. Therefore for each parameter at the apparent and internal validation stage the median value is shown.[30] Missing predictor variables and missing outcomes were not imputed in the external validation dataset. Since patients from the CamPaIGN study whose diagnosis was revised to non-PD were excluded from further

follow-up after 3.5 years, only patients meeting diagnostic criteria at the baseline and 3.5-year visits were used for the primary external validation. To investigate whether the missing data on patients with a revised diagnosis could have had a large influence on the external validity of the model, an additional sensitivity analysis was performed where patients with a revised diagnosis were assigned a favorable or unfavorable outcome based on their final diagnosis on the consensus of three authors (DCV, RMdB, and CHWG).
Statistical uncertainties were expressed using 95% confidence intervals (95% CI). Statistical analyses were performed in R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/).

Model presentation
For future users, the regression formula to calculate the probability of an unfavorable outcome is given. In addition, appendix e-1 to the original publication contains an electronic calculator in Microsoft Excel in which probabilities are automatically calculated when values of predictor variables are entered. This electronic appendix also contains a table showing model sensitivity and specificity to detect an unfavorable outcome for different cut-off values. The present study is reported in compliance with standard guidelines.[31]

Standard Protocol Approvals, Registrations, and Patient Consents
All patients gave written informed consent. The study was approved by the medical ethical committees of the participating hospitals (Netherlands) and the local research ethics committee (UK).

RESULTS

Details on patient selection and missing data for both cohorts are shown in Figure 1. A total of 111 patients were included in the model development dataset, whereas 108 patients were included in the model validation dataset. Patient characteristics for both cohorts are shown in Table 1. Patients from the CamPaIGN cohort were on average 3.4 years older at baseline than patients from the CARPA cohort. The risk of an unfavorable was also higher in the CamPaIGN cohort (absolute risk difference 11.6%).

Table 1: Cohort characteristics

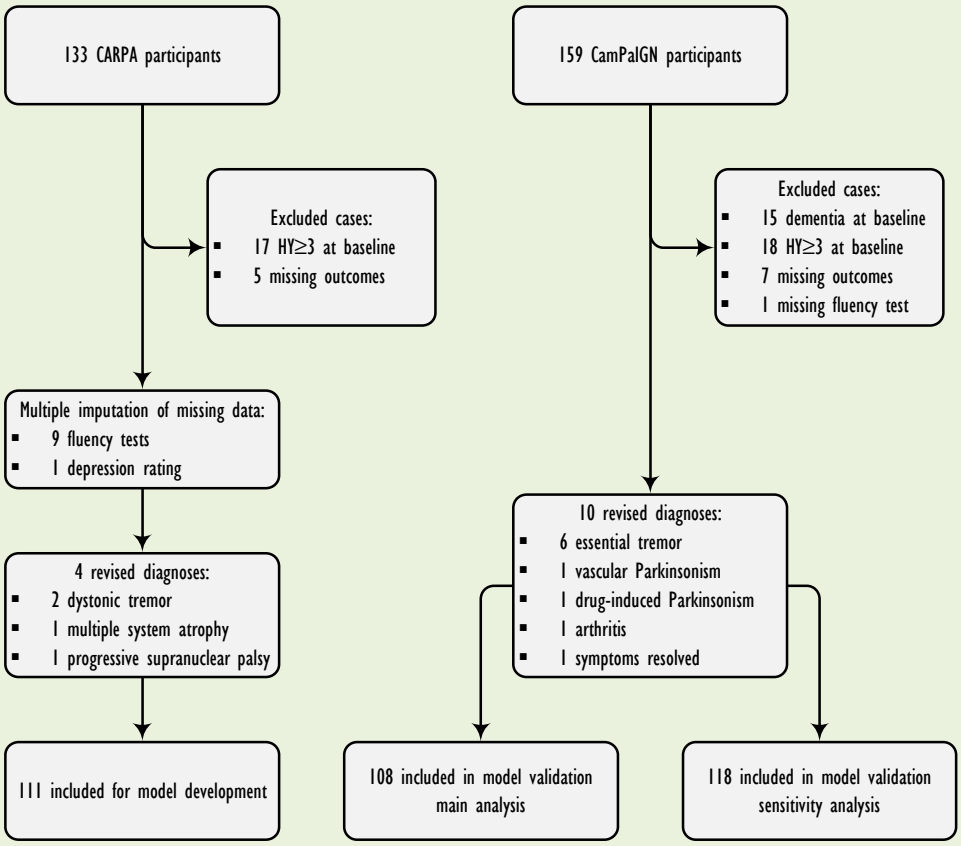
	Development set (CARPA, n = 111)	Validation set (CamPaIGN, n = 108)	Validation set (CamPaIGN, sensitivity analysis, n = 118)	*p*-value[a]
Mean age at baseline (SD)	65.6 (10.1)	69.0 (9.8)	68.7 (9.9)	0.01
Mean age at diagnosis (SD)	65.2 (10.1)	68.7 (9.8)	68.4 (9.9)	0.01
Mean symptom duration at baseline (years, SD)	1.6 (0.9)	2.2 (1.8)	2.3 (2.4)	<0.01
Mean duration from diagnosis to baseline assessment (years, SD)	0.3(0.2)	0.3 (0.4)	0.3 (0.4)	0.43
Mean duration from baseline assessment to outcome at 5 year assessment (years, SD)	5.1 (0.3)	5.0 (0.5)	5.0 (0.5)	0.47
Number of males (%)	66 (59.5%)	62 (57.4%)	65 (55.1%)	0.76
UPDRS-ME axial score (SD)	1.3 (1.4)	2.8 (2.3)	2.6 (2.3)	<0.01
Animal fluency score (SD)	19.2 (5.5)	16.6 (5.7)	16.7 (5.7)	<0.01
Number with unfavorable outcome (%)	54 (48.6%)	65 (60.2%)	66 (55.9%)	0.09
Number deceased at year 5 (%)	18 (16.2%)	23 (21.3%)	23 (19.5%)	0.34
Number HY ≥ 3 at year 5 (without dementia) (%)	25 (22.5%)	27 (25.0%)	–	0.67
Number demented at year 5 (with HY < 3) (%)	3 (2.7%)	2 (1.9%)	–	0.67
Number HY ≥ 3 & demented at year 5 (%)	8 (7.2%)	13 (12.0%)	–	0.28

[a] Independent sample t-test or chi-square test for comparisons between development set and main analysis validation set (n = 108); SD: Standard Deviation; HY: Hoehn and Yahr

Model development

The final model is a three-predictor variable model with higher patient age, higher UPDRS-ME axial-score and lower animal fluency score all giving a higher probability of an unfavorable outcome. The predictor variables and their corresponding regression coefficients in the final model are shown in Table 2. Details on model development from the set of candidate predictors are shown in data supplement.

Figure 1: Patient selection



MMSE: Mini Mental State Examination; HY: Hoehn and Yahr

Table 2: Regression coefficients of the final model

	Estimate	Standard error	*p*-value
Intercept	-3.1246	2.2335	–
Age	0.0590	0.0273	0.033
UPDRS-ME axial-score	0.3794	0.1804	0.038
Animal names-score	-0.0684	0.0477	0.155

The three predictor variables appeared in more than 50% of the multivariable models generated in the different imputed datasets (see data supplement for more details). Regression coefficients and standard errors were averaged using Rubin's rules.[26]

Model validation

Parameters of model performance are shown in Table 3. ROC-curves and calibration plots are shown in Figures 2 and 3. During external validation, considerable miscalibration was initially found, with patients in the validation set getting probabilities of an unfavorable outcome that were systematically too high. Since we suspected that this could be caused by the influence of language differences on the results of the animal fluency test, we calculated a correction factor based on normative scores for healthy controls from the same age range.[7,32] Comparison of model calibration with and without the correction factor is shown in the data supplement. After correction for language, the resulting formula for the prediction rule is shown below.

$$P_{\text{unfavorable outcome}} = \frac{1}{1+e^{-(\text{age}*0.059+\text{UPDRS-ME axial score}*0.3794+\text{animal names}*\text{language correction factor}*-0.0684-3.1246)}}$$

For Dutch, the language correction factor = 1; for English, the correction factor = 1.267. For all other languages the correction factor can be calculated if a mean score is available for healthy controls aged 60–70. The correction factor then is equal to 22.3/(mean score).

Sensitivity analysis including patients with a revised diagnosis

By consensus, the patient in whom the diagnosis was revised to vascular Parkinsonism was assigned an unfavorable outcome. The other nine patients whose diagnosis was revised away from PD in the validation dataset were assigned a favorable outcome. Repeated validation of the model in the dataset that included the patients with a revised diagnosis (n = 118) did not substantially change model performance parameters (Table 3). The calibration plot showed slight overestimation of the probability of an unfavorable outcome compared to the main analysis (Figure 3).

DISCUSSION

The present study shows that a relatively simple equation based on three clinical parameters measured at diagnosis can give reliable predictions concerning the prognosis of PD over the next five years. The UPDRS-ME and the animal fluency test can be administered by clinicians and research nurses in a short timeframe without specialist equipment, thus this predictive

Table 3: Model performance parameters

Validation stage	Performance parameter	Estimate
Apparent validation	c-statistic (95% CI)[a]	0.765 (0.677–0.854)
	Hosmer-Lemeshow-test[a]	p=0.339
Internal validation	bootstrap corrected c-statistic[a]	0.748
	calibration slope[a]	0.914
External validation (main analysis)	c-statistic (95% CI)	0.848 (0.770–0.926)
	calibration slope	1.134
	Hosmer-Lemeshow-test	p=0.389
External validation (sensitivity analysis)	c-statistic (95% CI)	0.842 (0.769–0.916)
	calibration slope	1.130
	Hosmer-Lemeshow-test	p=0.523

[a] During apparent and internal validation, these parameters are generated in 50 imputed datasets. Therefore, for each parameter the median is shown. CI: confidence interval

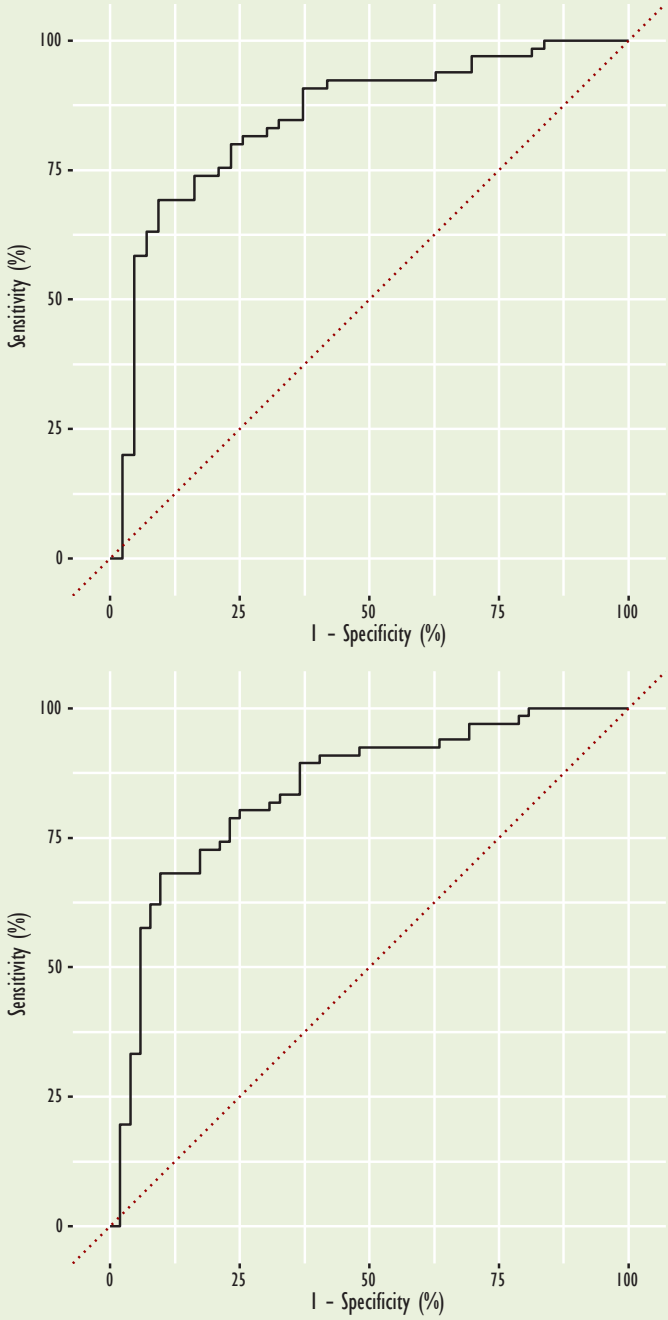
model is easily translatable to the clinic.

The main purpose of this study was to develop a model that could aid in patient selection and stratification in clinical trials. We specifically chose a composite outcome including the presence of postural instability or dementia because these are important determinants of disability in PD that are both non-levodopa responsive.[5,6] In future clinical trials investigating disease-modifying effects of dopaminergic cell-based therapies, PD patients that are likely to develop one of these non-levodopa responsive symptoms within five years can be selectively excluded. Conversely this 'high risk' group can be positively selected for trials of other types of disease-modifying therapies, to enable changes in outcome to be assessed within a shorter time period.

Whilst the primary purpose of developing the prognostic model was for use in patient selection and stratification for clinical research, it may also be useful to counsel individual patients regarding their prognosis, and enable the clinician to better plan their management. The upper and lower boundaries of the 95% CI of the calibration curve indicate that systematic misclassification of more than 15% is unlikely, making the model acceptable for patient counselling.

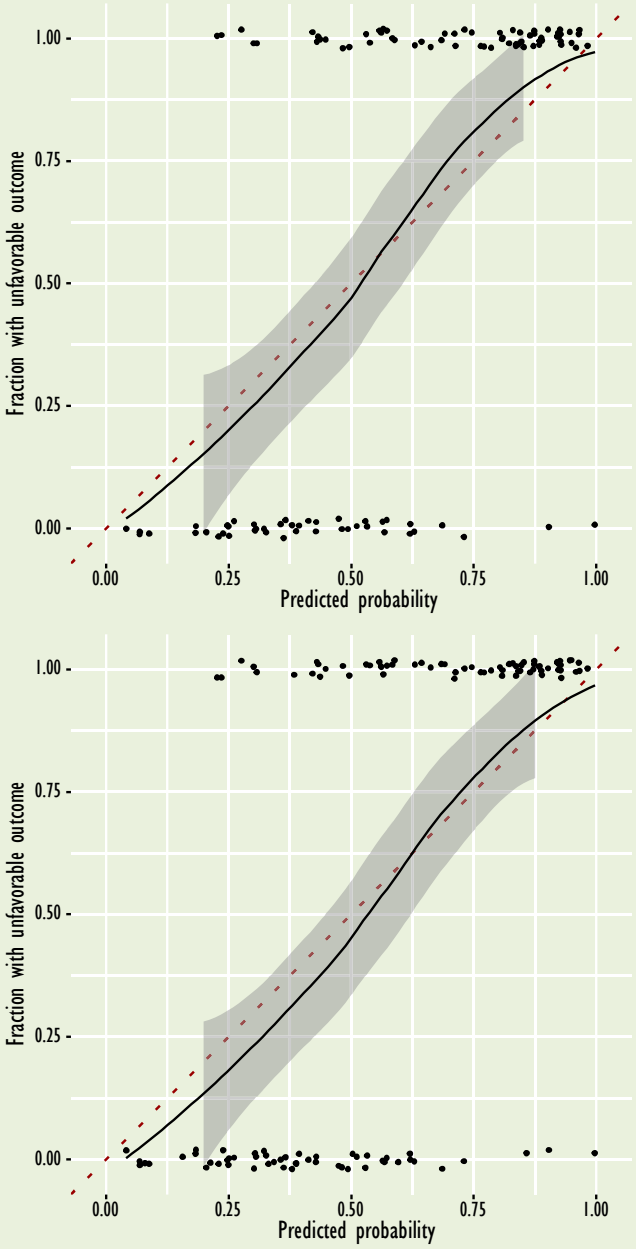
In addition, the sensitivity analysis showed that the model can robustly cope with patients in which the diagnosis is eventually revised. This is important as approximately 8% of the patients diagnosed with PD will eventually be given another diagnosis.[33]

Figure 2: ROC-curves at external validation



Upper panel: ROC-curve main analysis. Lower panel: ROC-curve sensitivity analysis. The dotted red reference line corresponds to a c-statistic of 0.50, indicating a non-informative model. Tabulated sensitivity and specificity values for different cut-off values of predicted probabilities can be found in data appendix e-1 of the online publication.

Figure 3: Calibration plots at external validation



Upper panel: Calibration plot main analysis. Lower panel: Calibration plot sensitivity analysis. The calibration curve is estimated by local regression (LOESS).[27] The 95% CI of the curve is represented by the shaded area. The dotted red reference line corresponds to prefect calibration with a calibration slope of 1. When the calibration curve is above the reference line the probabilities of an unfavorable outcome are underestimated, when it is beneath reference line the probabilities are overestimated. The black dots represent the individual patients in the external validation dataset.

When using the model for patient counselling, an important caveat is that patients with a high probability of an unfavorable outcome will still not know whether this is because of impending balance disorders, dementia or death. On the other hand the model is able to reliably identify patients with a good prognosis.

One of the major strengths of the present study is that the model is developed and validated in two completely independent cohorts of newly-diagnosed PD patients. This is important as the majority of clinical trials investigating disease-modifying therapies in PD will include patients shortly after diagnosis. In addition, the period around the time of diagnosis is typically when patients seek counselling regarding their prognosis. Though the clinical diagnosis of PD was based on different criteria in both cohorts, both criteria are well-established in PD research, and re-evaluation of the clinical diagnosis during follow-up has shown that the proportion of revised diagnoses is comparable to earlier studies.[9,11,33] Furthermore, the model proved to be robust across the two cohorts in spite of these differences in diagnostic methods and the differences in age and symptom duration at baseline.

Another major strength is that both cohorts consist of unselected PD patients who did not participate in clinical trials and are representative of the general PD population. Though the CARPA-study is a clinic-based cohort study rather than a strictly population-based one, selection bias is likely to be negligible as general practitioners in the Netherlands nearly always refer patients with a clinical suspicion of PD to a neurologist. Furthermore, the model has been shown to be valid in the CamPaIGN cohort, which is a community-based population-representative cohort.[10] The use of unselected cohorts has the drawback that the total number of included patients is relatively low causing some imprecision in estimating model performance parameters. In addition, during a backward selection the first model is fit with a relatively large number of potential predictors considering the number of participants. In theory this could have led to model instability. However, the selected predictor variables are largely in line with those found in our earlier reports.[2,4-6] Future validation in a third independent cohort might still increase the robustness of the present study. Since the present model is only validated for newly diagnosed PD patients, additional independent validation in a cohort with prevalent PD patients is also needed to investigate whether predictions also hold true for patients that already have a PD diagnosis for a longer time.

Another important issue with the current model is that for future use in non-Dutch or non-English speaking countries, normative values for the animal fluency test are needed. Use of the model in another language without correcting for language differences might lead to miscalibration. Unfortunately, we were not able to correct for the influence of educational

level and potential cultural differences, although available evidence suggests that the latter do not have a relevant effect on fluency scores.[34] If normative animal fluency values are unavailable, we would recommend administration of the animal fluency test in an age matched control group (of ± 70 healthy controls) to allow the appropriate correction factor to be applied.

We have developed a predictive model allowing prognostication of outcome in individuals with newly-diagnosed PD, and demonstrated that this model is valid in two independent PD populations. This model is easily translatable to the clinic, requiring only basic clinical information, and has potential value in aiding the selection of patients for clinical trials.

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DATA SUPPLEMENT

This data appendix provides more detailed insight into the selection of the predictor variables during the model development stage and the influence of a language correction factor during the model validation stage.

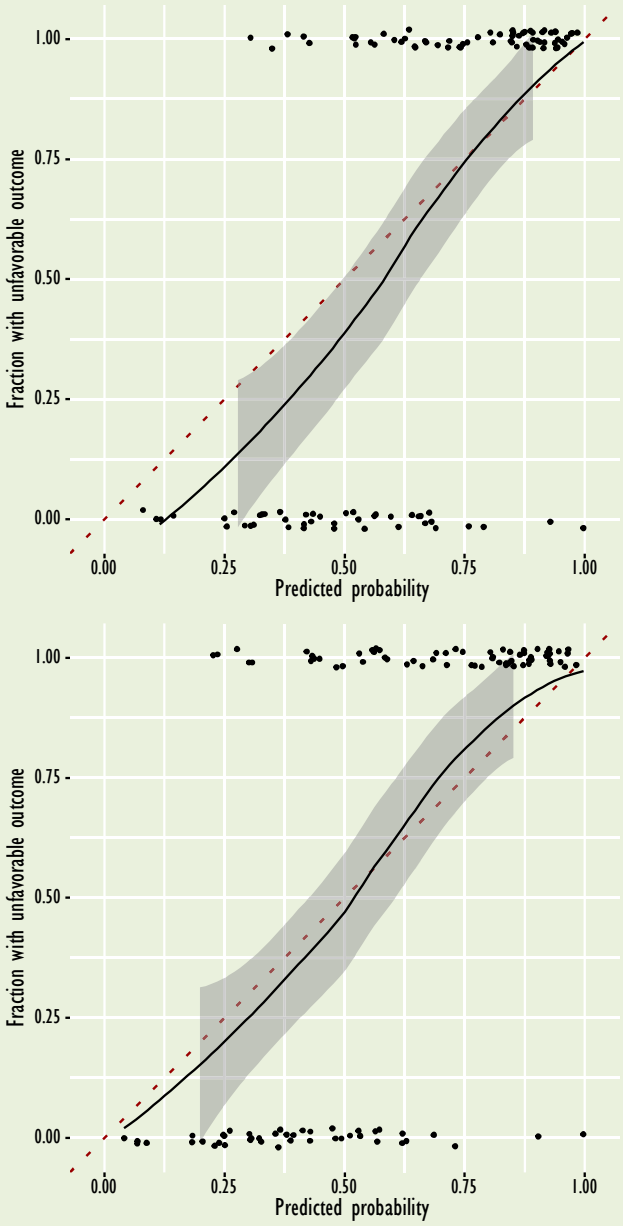
Model development

Supplementary Table 1 shows the full set of candidate predictors including summary statistics. The backward selection process was repeated in each individual multiple imputed dataset (n = 50). The variation in imputed data can result in selection of different predictors in each individual imputed dataset. Based on recommendations in the literature we chose to include variables in the final model when they were selected in at least 25 out of the 50 datasets.[1]

Model validation

The initial external model validation showed miscalibration with generated probabilities for an unfavorable outcome that were systematically too high (Supplementary Figure 1). To identify the potential source of miscalibration, univariable logistic regression analyses with the three selected predictor variables were performed separately in the development and validation datasets (Supplementary Table 2). The effect sizes of patient age and animal fluency score both showed moderate differences between development set and validation set. Since no biologically plausible reason for a difference in the effect size of patient age between two countries could be thought of, we identified language difference on the animal fluency test as the most likely source of miscalibration. A correction factor for language was then calculated in which the mean number of animal names for a Dutch control population was divided by norm scores for English controls from the same age range.[2,3] Comparison of the calibration plot with and without the use of the language correction factor is shown in Supplementary Figure 1.

Supplementary Figure 1: External validation calibration plot with and without correction for language on the animal fluency test



Calibration plot without (upper plot) and with (lower plot) correction for language. The calibration curve is estimated by local regression (LOESS). The 95% CI of the curve is represented by the shaded area. The dotted red reference line corresponds to prefect calibration with a calibration slope of 1. When the calibration curve is above the reference line the probabilities of an unfavorable outcome are underestimated, when it is beneath reference line the probabilities are overestimated. The black dots represent the individual patients in the external validation dataset.

Supplementary Table 1: Set of candidate predictors including summary statistics from the development dataset, and the number of selections from the 50 imputed datasets

Candidate Predictor	Mean (SD) or proportion	Times selected
Patient age (years)	65.6 (10.1)	50
Male sex	59.5%	–
Symptom duration (months)	1.6 (0.9)	1
Modified Hoehn and Yahr stage	1.7 (0.6)	–
UPDRS-ME tremor score (item 20-21)	2.5 (2.0)	–
UPDRS-ME rigidity score (item 22)	3.0 (2.1)	–
UPDRS-ME bradykinesia score (item 23-26 + 31)	6.0 (3.2)	–
UPDRS-ME axial score (item 27-30)	1.3 (1.4)	50
Levodopa Equivalent dosage (mg)	253 (392)	–
Number of comorbid organ systems on CIRS	2.3 (1.7)	–
Presence of depression (HADS score above 23)	42.7%	–
COWAT score	29.5 (10.9)	1
Animal fluency score	19.2 (5.5)	31
MMSE score	27.8 (1.8)	1

UPDRS-ME: Unified Parkinson's Disease Rating Scale - Motor Examination; CIRS: Cumulative Illness Rating Scale; HADS: Hospital Anxiety and Depression Scale; COWAT: Controlled Oral Word Association Test; MMSE: Mini Mental State Examination

Supplementary Table 2: Effect sizes (*B*) of the three selected predictor variables in development and validation datasets (univariable logistic regression)

Predictor variable	*B* (development set)	*B* (validation set)	Percentage difference
Patient age	0.114	0.091	20.1%
UPDRS-ME axial score	0.557	0.560	0.5%
Animal fluency score	-0.118	-0.138	16.9%

UPDRS-ME: Unified Parkinson's Disease Rating Scale - Motor Examination

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Part Two

Orthostatic hypotension in Parkinson's disease

Chapter 5

Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis.

Daan C. Velseboer
Rob J. de Haan
Wouter Wieling
David S. Goldstein
Rob M.A. de Bie

Parkinsonism & Related Disorders 2011;17:724-729

ABSTRACT

Background: Although orthostatic hypotension (OH) is recognized as one of the main non-motor symptoms of Parkinson's disease (PD), there is inconsistent evidence about the prevalence of OH in PD. To estimate the prevalence of OH in PD more precisely we conducted a systematic review of the literature.

Methods: From PubMed and Embase searches with predefined inclusion criteria, we identified studies published up till December 2009. Prevalence numbers from studies were pooled using a non-linear random-effects meta-analysis.

Results: We found 25 studies from which the prevalence of OH could be calculated. The pooled estimate of the point prevalence of OH in PD was 30.1% (95% CI: 22.9–38.4). We found a large statistical heterogeneity between studies which could not be reduced by several subgroup analyses.

Conclusions: The estimated prevalence of OH in PD is 30%. However, due to the large heterogeneity between studies this pooled estimate should be interpreted with caution. More data from unselected population-based cohorts are needed.

INTRODUCTION

In advanced Parkinson's disease (PD), non-motor symptoms may be the major determinant of disability.[1] Orthostatic hypotension (OH) is one of the non-motor features in PD. It is thought to be the result of degeneration of the peripheral autonomic nervous system as part of the disease progress.[2] These abnormalities lead to an inadequate response to the gravitational force on the effective circulatory volume during standing due to defective vasoconstriction and excess venous pooling of blood.[3] Symptoms of OH mainly result from cerebral and retinal hypoperfusion and include dizziness, faintness, seeing black spots, and may even be accompanied by a transient loss of consciousness.[4] The occurrence of symptoms is directly related to the extent of the blood pressure drop, but autoregulation of the cerebral vasculature and baseline supine blood pressure probably also play a role. This hypothesis is supported by data showing that about one-third of patients with a systolic blood pressure drop of 60 mmHg or more during tilt-table testing are completely asymptomatic during the test.[5]

By consensus, OH has been defined as a fall of ≥ 20 mm Hg systolic or ≥ 10 mm Hg diastolic blood pressure by three minutes of active standing or head up tilt.[6] Recently, the consensus-statement has been revised and a systolic fall of 30 mm Hg was suggested for patients with an abnormally high supine blood pressure.[7] OH can be a debilitating problem and an association with increased mortality was shown for the general population.[8] Over recent decades, awareness of the impact of OH in PD has increased and consequently more research on this topic has come available. Furthermore, comprehensive reviews have been published concerning pathophysiology, diagnosis, and management of OH in PD.[2,9] Despite the increasing amount of research concerning this subject, the prevalence of OH in PD stated in the literature has a wide range; *i.e.*, 10 to 58%.[10-12] Accordingly, we conducted a systematic review of the literature in order to estimate the prevalence of OH in PD more precisely.

METHODS

Literature Search

We searched the electronic databases Medline and Embase using the entire time scale up to December 2009. The terms "Parkinson's disease", "Parkinson disease", and "parkinsonism" were combined with "orthostatic hypotension" and "orthostatic intolerance". The full search strategy is available in the data supplement.

Study Selection

After combining the search results, a list of titles and abstracts was evaluated by two independent reviewers (DCV and RMAdB) for eligible studies. Studies were selected according to the following inclusion criteria: (1) the study was written in English, French, German or Spanish; (2) the study investigated the number or proportion of subjects with OH in a sample of PD patients, either as a primary objective or a secondary objective; and (3) the study reported original data which were derived from retrospective, cross-sectional, or prospective cohort research. For inclusion of a paper, it was necessary that the diagnosis of OH was based on blood pressure measurements. Papers were not selected if the diagnosis was made by history taking solely. The studies that investigated the presence of OH in more than one underlying disorder (*e.g.,* idiopathic PD, Multiple System Atrophy and Progressive Supranuclear Palsy), were only included if the results for the subgroup of PD patients were described separately. In that case, we only used the results for the PD patients. Papers that used the term Parkinsonism to describe the patient population without further specifying whether the patients had idiopathic PD were excluded.

A study was excluded if it concerned a case-report, a drug trial or if it was designed in a case-control manner, where PD patients were included on the basis of presence or absence of autonomic symptoms. In studies with overlapping data sets, we selected the study with the largest sample size. In case of doubt or disagreement between the reviewers, the full paper was retrieved.

Data Extraction and Assessment of Methodological Quality

Full reports were evaluated independently by two reviewers (DCV and RMAdB) using a standard checklist. From eligible studies the number of patients with PD and the number of PD patients with OH was extracted, as were the mean age at examination and mean duration of disease. If mean disease duration was not stated, we calculated it by subtracting the age at onset from the age at examination, where possible. For potential subgroup analyses we extracted data on type of patient population (tertiary *vs*. non-tertiary care) and definition of OH used, as we hypothesized that these factors would influence the prevalence of OH. We performed an assessment of study quality using a predefined set of eight criteria concerning the internal and external validity of the study. The criteria were based upon general recommendations for reporting on observational studies,[13] and several methodological instruments developed for systematic reviews of prevalence studies.[14-16] Criteria were adapted and modified for the purpose of this review. If a study fulfilled the item, one point was

awarded. If it was unclear whether the study fulfilled the item, no point was awarded. All items were assumed to be of equal importance and were not weighted. Studies with a score of 0 to 3 were classified as "low quality" reports and those with a methodological score of 4 to 8 as "high quality". The exact checklist with criteria is given in the data supplement. We used two of the eight items for separate subgroup analyses. The first item assessed whether the primary objective of the study was to investigate the prevalence of OH in PD, the second item assessed the risk of selection bias. Studies in which the patient sample was stated as random or consecutive, without the use of stringent inclusion or exclusion criteria were judged as having a low risk of selection bias. These criteria were used for separate subgroup analyses, as we hypothesized that heterogeneity between studies would be lower in unselected patient groups. Results were compared and discrepancies between the two reviewers were resolved in a meeting.

Statistical Analysis

For each study, patient and study characteristics and prevalence of OH were summarized using descriptive statistics. Heterogeneity between the studies was estimated by calculating the I^2-statistic. The I^2 index reflects the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and values of 25%, 50%, and 75% suggest low, moderate, and high degrees of heterogeneity.[17,18] Pooled prevalence rates accounting for interstudy variation were analyzed using a nonlinear random effects model, implemented (proc nlmixed) in SAS version 9.1 (SAS Institute Inc, Cary, NC). Statistical uncertainties were expressed in 95% confidence intervals (CIs).

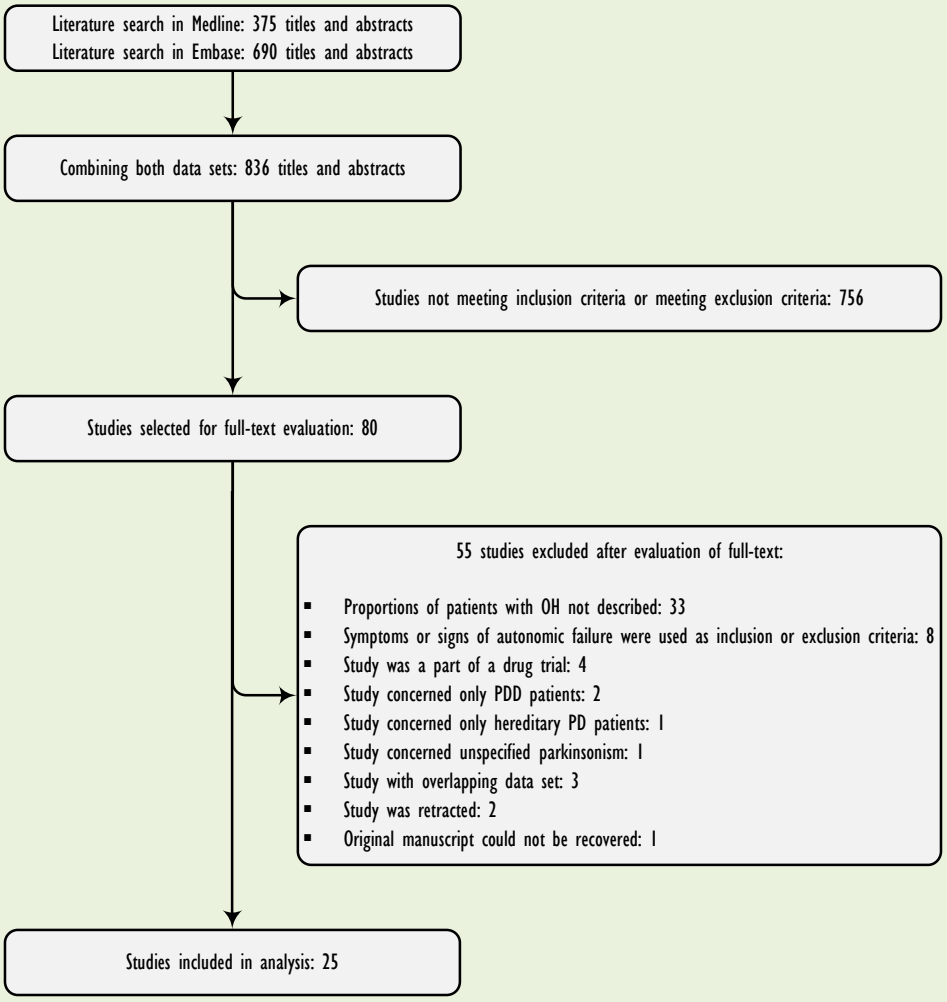
RESULTS

Literature Search and Study Selection

Combining both the lists of titles and abstracts resulted in 836 records. Figure 1 shows the results of the search and the study selection. A total of 80 full-text articles were selected for further review. Of these, 25 fulfilled our selection criteria. The other 55 articles were excluded for the following reasons: 33 studies reported a mean change of blood pressure after standing for the total patient group instead of the number of patients with OH; 8 studies used the presence or absence of autonomic symptoms as inclusion criteria; 4 studies were part of a

drug trial; 4 studies did not include idiopathic PD patients; 3 studies had partially overlapping data sets; 2 studies were retracted; and 1 manuscript could not be retrieved.

Figure 1: Search results and study selection



PDD: Parkinson's Disease Dementia

Study Characteristics

Table 1 summarizes the characteristics and methodological quality of the included studies. The 25 studies involved a total of 5070 PD patients. Mean age at examination ranged from 54.2 to

81.6. Mean disease duration ranged from 1.9 to 11.3 years. In eight of the 25 studies the primary objective was to report on the prevalence of OH,[10,11,20,23,28,30,32,34] while in the remaining 17 studies the proportion of patients with OH was investigated as a secondary objective. In 18 studies the study population consisted of tertiary care patients. In six studies the population consisted of non-tertiary care or mixed tertiary and non-tertiary care patients. One study did not state the origin of the patient sample. The definition used to diagnose OH varied highly between studies. Only five studies[21,35,38-40] used the criteria as stated in the consensus agreement from 1996.[6] Using the arbitrary cut-off value of four points on our quality assessment checklist, 12 studies were defined as being of high quality and 13 of low quality. There were only five studies in which the risk of selection bias was judged to be low.[20,26,31,38,39]

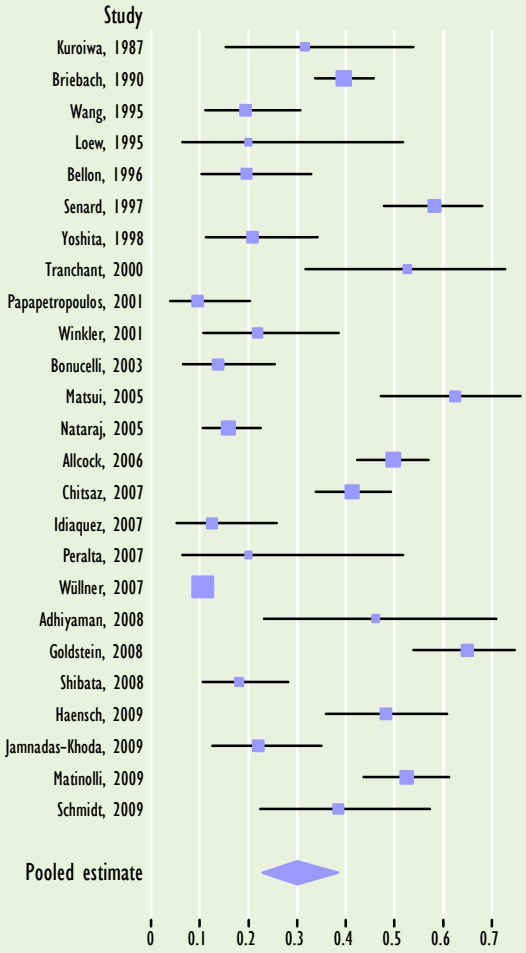
Prevalence of OH in PD

The prevalence rate across studies ranged from 9.6% to 64.9% with an estimated pooled prevalence of 30.1% (95% CI: 22.9–38.4). Figure 2 shows the forest plot for these studies. The I^2-value was about 96%, indicating a large heterogeneity between the studies.

Subgroup Analyses

Several subgroup analyses were performed in order to search for sources introducing heterogeneity between the studies and as such to explore for factors that have an impact on the prevalence of OH (table 2). In all the subgroups the heterogeneity between studies remained high (I^2-value ranged from 79.7% to 98.3%). The estimated prevalence in the different subgroups ranged from 25.1% to 37.6%. To assess if the study with the largest sample size (of n = 3414) had a significant effect on the pooled estimate, we repeated the meta-analysis leaving the study from Wüllner and colleagues out.[11] The pooled point prevalence was estimated to be 31.5% (95% CI: 24.2–39.9), indicating that the impact of the study on the total estimate is small.

Figure 2: Forest plot



Point prevalences of OH in PD per study and pooled prevalence rate (with their corresponding 95% Confidence Intervals)

Table 2: Prevalence rates of OH in PD and heterogeneity between studies in relation to subgroups

Subgroup	Number of studies	Estimated prevalence (%; 95 CIs)	I^2-value (%)
Estimation of prevalence was primary objective	8	25.1 (13.9–41.0)	96.9
Other primary objective	17	32.9 (23.7–43.7)	90.1
High quality studies	12	33.2 (21.3–47.7)	97.6
Low quality studies	13	26.9 (18.5–37.5)	85.7
Risk of selection bias judged to be low	5	32.2 (14.9–56.3)	93.8
Risk of selection bias judged to be high	20	29.5 (21.4–39.2)	95.1
Sample size larger than 70	9	36.2 (21.8–53.6)	98.3
Sample size smaller than 70	16	26.3 (18.7–35.7)	79.7
Definition OH: drop of systolic BP 20 mmHg in 3 minutes	8	37.6 (23.4–54.2)	91.2
Other definition for OH	17	26.3 (18.7–35.6)	95.3
Tertiary care population studies	18	29.6 (21.6–39.1)	91.2
Non-tertiary care or mixed population studies	6	35.8 (16.8–60.7)	95.3

BP: Blood pressure

DISCUSSION

This is the first systematic review investigating the prevalence of OH in PD. The prevalence we found lies in the range stated in previous non-systematic reviews concerning this subject. We found a large heterogeneity between studies. In addition, repeated analyses for several subgroups of studies with specific characteristics — *e.g.*, sample size above 70, less risk for selection bias — also showed large heterogeneity between studies.

Though there was a large variety between studies, this is the first time a meta-analysis concerning the prevalence of OH in PD is performed, and the estimated point prevalence of 30% is the best estimate currently available in the literature. Furthermore, though subgroup analyses did not lead to a reduction of heterogeneity, the calculated prevalence in individual subgroups was always in the range of 25% to 38%.

From the 25 studies in the meta-analysis, 19 gave detailed descriptions about the use of standardized criteria for the diagnosis of PD. Considering this, and given the low prevalence of MSA compared to PD, the number of MSA patients that mistakenly entered the meta-analysis is negligible.

We did not find subgroup factors that could clearly explain the large variety in results between the studies. The occurrence of OH is known to be influenced by various factors, such as medication use (*e.g.* for PD and hypertension), deconditioning, time of the day and time after meals, ambient temperature, and comorbidity.[42] Only six of the studies in our review gave detailed information about the circumstances during the blood pressure measurements.[10,22,25,31,38,39] Furthermore, in seven studies patients with concurrent treatment for diabetes mellitus or hypertension were excluded.[21,23,32,33,35,37,41] Other important factors to consider are the role of age and disease duration. Several individual studies have shown that the risk of OH in PD patients increases with higher age and longer disease duration.[10-12,20] As our systematic review lacks individual patient data, we could not analyze the impact of age and disease duration on the presence of OH.

These factors, in combination with the different definitions of OH used throughout the studies have probably caused the large variety in our results. Our review shows that data regarding the occurrence of OH in PD comes mainly from studies in tertiary care centers. Furthermore, in only five out of the 25 studies, the authors have tried to minimize the risk of selection bias. One can imagine that on one hand, this could lead to an underestimation of the prevalence, as patients with concurrent illness were often excluded from analysis. On the other hand it could lead to an overestimation, as non-consecutive patient samples might include more patients with symptoms of OH, as they are more likely to volunteer is such research. Therefore, there is still a need for studies investigating this problem in an unbiased population-based cohort, as the extent of this problem in the general PD population is still not well known.

Table 1: Characteristics of the 25 studies included in the analysis

Study	Methodological quality Score	Sample size	Study Design	Setting	Definition of OH	Mean age at assessment	Disease duration (years)	Prevalence (95% CIs)
Kuroiwa, 1987[19]	2	19	Cross-sectional	Tertiary Care	A drop of at least 15 mmHg in mean arterial pressure in 21 minutes.	59.0	NS	31.6% (15.4–54.0)
Briebach, 1990[20]	5	250	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP in 9 minutes.	65.9	7.3	39.6% (33.7–45.8)
Wang, 1993[21]	3	62	Cross-sectional	General Hospital	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 3 minutes.	65.6	4.7	19.4% (11.4–30.9)
Loew, 1995[22]	2	10	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP in 1 minute.	81.6	NS	20.0% (5.7–51.0)
Bellon, 1996[23]	3	46	Cross-sectional	Tertiary Care	A drop of at least 30 mmHg systolic BP in 9 minutes.	64.3	NS	19.6% (10.7–33.2)
Senard, 1997[10]	4	91	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP in 10 minutes.	66.0	8.0	58.2% (48.1–68.3)
Yoshita, 1998[24]	2	48	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 10 minutes.	69.9	10.0	20.8% (11.7–34.3)

Tranchant, 2000[25]	3	19	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP. No information on standing time.	70.7	11.3	52.7% (31.7–72.7)
Papapetropoulos, 2001[26]	4	52	Cross-sectional	Tertiary Care	No information on definition used.	65.4	6.1	9.6% (4.2–20.6)
Winkler, 2001[27]	3	32	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP in 5 minutes.	63.1	7.2	21.9% (11.0–38.8)
Bonucelli, 2003[28]	4	51	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP in 3 minutes.	54.2	1.9	13.7% (6.8–25.8)
Matsui, 2005[29]	4	40	Cross-sectional	General Hospital	A drop of at least 20 mmHg systolic BP in 3 minutes.	71.2	9.7	62.5% (47.0–75.8)
Nataraj, 2005[30]	2	145	Retrospective cohort	Tertiary Care	A drop of at least 30 mmHg systolic BP or 10 mmHg diastolic BP in 3 minutes.	NS	NS	15.9% (10.8–22.7)
Allcock, 2006[31]	6	175	88 patients from a prospective cohort, 87 patients cross-sectional	General Hospital	A drop of at least 20 or a fall below 90 mmHg systolic BP in 3 minutes.	70.8	NS	49.7% (42.4–57.1)
Chitsaz, 2007[32]	4	150	Cross-sectional	Tertiary Care	A drop of at least 20 or a fall below 90 mmHg systolic BP in 2 minutes.	NS	NS	41.3% (33.8–49.3)

Idiaquez, 2007[33]	3	40	Cross-sectional	No information on setting	A drop of at least 20 mmHg systolic BP in 10 minutes.	69.0	11.2	12.5% (5.5–26.1)
Peralta, 2007[34]	4	10	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 10 minutes.	74.1	6.4	20.0% (5.7–51.0)
Wüllner, 2007[11]	4	3414	Retrospective cohort	Community	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP. No information on standing time.	66.1	9.0	10.6% (9.6–11.7)
Adhiyaman, 2008[35]	2	13	Cross-sectional	General Hospital	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 3 minutes.	69.5	5.2	46.2% (23.2–70.9)
Goldstein, 2008[36]	2	77	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 5 minutes.	65.0	9.0	64.9% (53.8–74.7)
Shibata, 2008[37]	2	72	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP. No information on standing time.	73.4	3.5	18.1% (10.9–28.5)
Haensch, 2009[38]	5	58	Cross-sectional	General Hospital	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 3 minutes.	70.9	5.1	48.3% (35.9–60.8)

Jamnadas-Khoda, 2009[39]	5	50	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic or 10 mmHg diastolic in 3 minutes.	57.3	NS	22.0% (12.8–35.2)
Matinolli, 2009[40]	4	120	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 3 minutes.	68.2	5.8	52.5% (43.6–61.2)
Schmidt, 2009[41]	2	26	Cross-sectional	Tertiary Care	No information on definition used.	65.0	7.0	38.0% (22.1–57.0)

BP: Blood pressure; NS: Not stated

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DATA SUPPLEMENT: SEARCH STRATEGY

Medline Executed on 02-12-2009: 375 results
(exp "hypotension, orthostatic"/
OR
(orthostatic adj2 (hypotension* OR intolerance)).ti,ab.
)
AND
(
exp parkinson's disease/
OR
parkinson*.ti,ab.
)
NOT
(Case report.tw. or Letter/ or Historical article/ or Review of reported cases.pt. or Review, multicase.pt. or Review.pt.) not (exp Animals/ not (exp animals/ and exp humans/))

Embase Executed on 02-12-2009: 690 results
((exp orthostatic hypotension/
OR
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OR
parkinson*.ti,ab.
)
)
NOT
(
Case study/
OR
review.pt.
OR
Case report.tw.
OR
Abstract report/
or
letter/
OR
(exp animal/ not (exp animal/ and exp human/)))

DATA SUPPLEMENT: QUALITY ASSESSMENT

Assessor: _____ Ref |__|__|__|

City: _____ Year |__|__|__|__|

Reporting & Methodological quality:

	YES	NO
Was one of the stated aims to study the prevalence of OH in PD?	☐	☐
Defined diagnosis of PD according to Gelb 1999, UKPDS brain Bank criteria (Hughes 1992), in older studies description of signs (tremor/bradykinesia/rigidity/ postural reflex abnormality) in the absence of red flags?	☐	☐
Is there a clear description of the methods used to recruit PD patients?	☐	☐
Is there a description of the patients that refused to participate?	☐	☐
Is there a clear description of demographic and clinical characteristics of the PD patients (age, gender, disease duration/age at onset, and disease stage e.g. H&Y)?	☐	☐
Is there a clear description of the definition of OH used?	☐	☐
Are the circumstances in which the patients are tested for OH clearly specified (time of the day, with/without medication, standardized or normal breakfast)?	☐	☐
Have the authors tried to minimize the risk of selection bias? 1) The authors have used an unselected patient sample,(i.e the description of sample selection states words such as "random" or "consecutive"), 2) without stringent exclusion-criteria (e.g. for patients with co-morbid disease or for patients using antihypertensive agents)	☐	☐

If there is a potential risk of selection bias, state why:

_____

_____

Chapter 6

Orthostatic hypotension in Parkinson's disease: The relation of blood pressure tests and symptoms in daily life.

Daan C. Velseboer
Rob J. de Haan
Bart Post
C.T. Paul Krediet
Hein J. Verberne
Rob M.A. de Bie

Movement Disorders Clinical Practice 2016;4:329-334

ABSTRACT

Background: Orthostatic Hypotension (OH) is common in Parkinson's disease (PD), but the relation between the results of orthostatic blood pressure tests and orthostatic symptoms in daily life is not clear.

Methods: We performed a cross-sectional study in an incident non-tertiary care cohort of PD patients with additional recruitment of PD patients from our own outpatient clinic. We recruited sex and age matched controls. All participants underwent orthostatic blood pressure tests using continuous blood pressure measurements. Orthostatic symptoms experienced in daily life were assessed using autonomic symptom questionnaires (SCOPA-AUT and COMPASS-31).

Results: A total of 83 PD patients and 35 controls were included. Mean patient age was 69.2 years (SD 10.0). Mean disease duration was 6.6 years (SD 0.8). The estimated prevalence of OH in PD was 24.1% (95% CI: 16.2–34.3). There was no significant difference between PD patients with and without OH regarding reported daily orthostatic symptoms. Alternative OH criteria did not substantially improve this.

Conclusion: Perceived orthostatic symptoms in daily life have no clear association with the results of a single orthostatic blood pressure test. Better diagnostic strategies are needed.

INTRODUCTION

Orthostatic Hypotension (OH) is one of the non-motor features in Parkinson's disease (PD). It is the result of degeneration of the peripheral autonomic nervous system as part of the disease.[1] Failure of the autonomic nervous system leads to an inadequate response to the gravitational force on the effective circulatory volume during standing by means of a lack of peripheral vasoconstriction and an inadequate rise in heart frequency.[2] Symptoms of OH are due to organ hypoperfusion and include, but are not limited to, light-headedness, dizziness, feeling about to faint, and syncope in response to sudden postural change. The disease burden caused by OH is highly variable, ranging from asymptomatic to severely disabling with increased risk of falls.[3,4] In 1996, a consensus committee stated that OH is a clinical sign, defined as a fall of at least 20 mmHg systolic or 10 mmHg diastolic blood pressure in 3 minutes after standing up or head-up-tilt.[5,6] Since then, it is common-practice to use these criteria as a diagnostic test for clinicians when encountering patients complaining of typical symptoms of OH.[5] The last decade, alterations of the original consensus criteria for OH have been proposed in order to increase the clinical value of orthostatic blood pressure testing. Examples are the use of different cut-off values for patients with a relatively high or low supine blood pressure, an extension of the 3-minute timeframe using a prolonged head-up tilt test (HUT), and recently the fall of the mean arterial blood pressure below the absolute threshold of 75 mmHg during standing.[8-10]

In a systematic review concerning the prevalence of OH in PD, we concluded that the majority of studies are potentially biased by investigating selected patients recruited solely in tertiary care clinics.[11] In most studies the relation between the results of orthostatic blood pressure tests with perceived orthostatic symptoms was not investigated. The few studies that did so, only investigated the relation of orthostatic blood pressure tests results with the orthostatic symptoms that patients experience during testing, and not with orthostatic symptoms they experience in daily life. It is therefore not known if the application of a single orthostatic blood pressure test (using either the original OH-criteria or the recently suggested revisions) is sufficient to identify PD patients experiencing symptoms of OH in daily life. This could potentially lead to misdiagnosis of OH.

We therefore performed a cross-sectional study in a representative group of PD patients to investigate the relation between the presence of OH during orthostatic blood pressure testing and the orthostatic symptoms patients experience in daily life, and whether this relation could be improved by using one of the recently proposed alterations of the criteria for OH. Because

results of prolonged HUT tests are not available for healthy subjects in this age category, we also included a control population matched for sex and age.

METHODS

Study Participants

The CARPA study is a longitudinal prospective cohort study in which patients with newly diagnosed PD from six general hospitals were included between July 2002 and April 2005.[12] The clinical diagnosis of PD was based on standard criteria.[13] All patients with a confirmed diagnosis of PD still participating at the 5-year follow-up of the CARPA study were approached and asked for participation. Patients unable to stand unassisted were excluded from the present study. During the current project, the number of patients from the CARPA-cohort that were ineligible or declined participation was higher than anticipated. For this reason, additional PD patients from the Academic Medical Center outpatient clinic were recruited. To ensure that the demographic profile of these additional patients was comparable to the patients from the CARPA-project, only patients with disease duration of 5 to 8 years were selected. In addition, patients that were treated in our clinic as a result of a tertiary care referral were excluded. Healthy control subjects matched for age and sex were recruited from a cohort that had already participated as a control group in the neuropsychological follow-up of the CARPA study.[14] Controls underwent the same research protocol. This study was approved by the medical ethics committees of the Free University Medical Center and the Academic Medical Center (Amsterdam, the Netherlands). All participants gave written informed consent.

Blood pressure measurements

Continuous non-invasive blood pressure measurements were performed using a Nexfin HD monitor (Edwards Lifesciences BMEYE, Amsterdam, the Netherlands). The Nexfin HD monitor uses finger-cuff technology and reconstructs the blood pressure to the brachial artery. Changes in blood pressure as measured with this technique have a good correlation with changes in blood pressure measured with the conventional Riva-Rocci method.[15,16] All measurements were performed between 10 and 11 am. All participants used their regular medication. For the active standing test (AST), participants were requested to remain standing for 3 minutes after a period of 5 minutes supine rest. After a new period of 5 minutes supine

rest, participants were positioned to 60 degrees HUT for 45 minutes using a tilt table. Participants were positioned back if they were unable to sustain the total duration of the test (either due to imminent syncope or due to other complaints). Supine blood pressure was calculated by averaging the last minute before standing up. Upright blood pressure was calculated for each minute by averaging the continuous registration with intervals of one minute. If patients with a long travel distance or more advanced PD deemed the protocol to burdensome, a shortened version was offered in which patients were visited at home. In this protocol, the HUT was not included.

Questionnaires

With regard to symptoms experienced in daily life, all participants were requested to complete the COMPASS 31 and the SCOPA-AUT.[17] The COMPASS 31 is a shortened version of the generic Autonomic Symptom Profile.[18,19] The SCOPA-AUT is a questionnaire developed specifically for PD patients.[20] Symptoms of generalized autonomic nervous system degeneration were rated by using the sum scores of these questionnaires (COMPASS 31, range 0–100 and SCOPA-AUT, range 0–69). Orthostatic symptoms in daily life were rated by the orthostatic symptom domains of these questionnaires (COMPASS 31-OI, 4 items, range 0–10 and SCOPA-AUT-CV, 3 items, range 0–9). Comorbidity was rated with the Cumulative Illness Rating Scale (CIRS, range 0–52).[21] In PD patients, the severity of motor impairment was rated with the Unified Parkinson's Disease Rating Scale motor examination section (UPDRS-ME, range 0–108).[22] For all questionnaires higher scores indicate more symptoms. Medication use was assessed with a semi-structured interview.

Statistical analysis

Demographic characteristics and the prevalence of OH were reported using descriptive statistics. Group differences between PD patients and controls and between PD patients with and without OH were analyzed with independent samples t-test and chi-square test or Fisher's exact test, when appropriate. To evaluate the diagnostic value of the original OH criteria and the recently proposed alterations for the OH criteria, the orthostatic symptom domain score of the COMPASS 31 was dichotomized (0 = having no orthostatic symptoms in daily life: ≥ 1 = having orthostatic symptoms in daily life) after which sensitivity and specificity were calculated using the perceived orthostatic symptoms in daily life as reference standard. Statistical uncertainties were expressed using 95% confidence intervals (CI). All analyses were performed in IBM SPSS version 20.

RESULTS

A total number of 83 PD patients (72 from the CARPA-cohort, and 11 from the AMC outpatient clinic) participated in the present study of which 47 patients participated in the full research protocol including HUT. The remaining 36 patients were assessed at home. A total of 35 age and sex matched controls were recruited. A flowchart with details of the selection process is shown in figure 1. Group comparisons for PD patients and controls are shown in Table 1.

Table 1: Comparison PD patients and controls

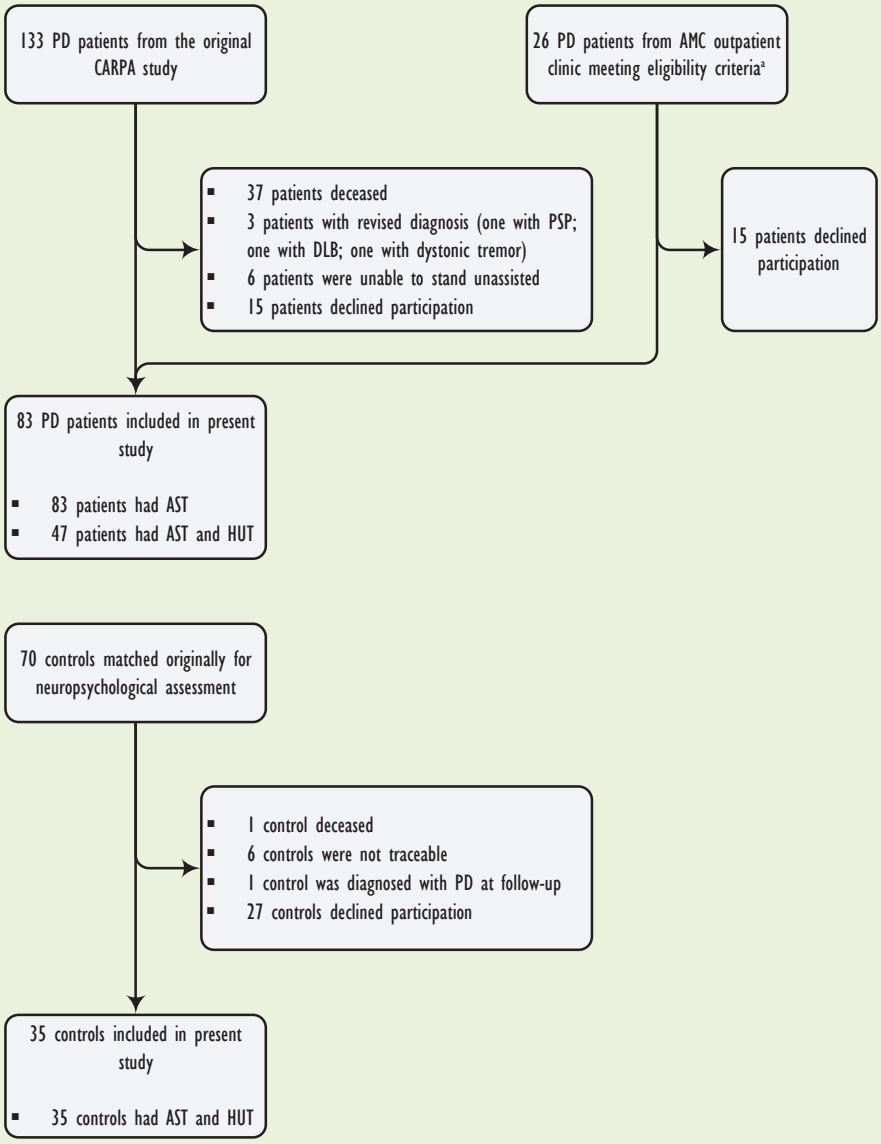
	PD patients (n = 83)	Controls (n = 35)	*p*-value[b]
Mean Age (SD)	69.2 (10.0)	68.3 (6.7)	0.54
Number of males (%)	44 (53.0%)	20 (57.1%)	0.68
Mean age at diagnosis (SD)	62.7 (9.8)	–	–
Mean disease duration, years (SD)	6.6 (0.8)	–	–
Mean CIRS score (SD)	4.84 (3.00)	4.09 (3.07)	0.22
Prevalence of OH on 3 minutes AST	20 (24.1%)	3 (8.6%)	0.05
Prevalence of OH on 3 minutes HUT	22 (46.8%)[a]	11 (31.4%)	0.16
Prevalence of OH on 45 minutes HUT	34 (72.3%)[a]	22 (62.9%)	0.36
Mean COMPASS 31-OI domain (SD)	2.51 (2.79)	0.69 (1.57)	<0.001
Mean COMPASS 31 sumscore (SD)	21.66 (15.00)	9.04 (10.53)	<0.001
Mean SCOPA-AUT-CV domain (SD)	1.08 (1.35)	0.26 (0.56)	<0.001
Mean SCOPA-AUT sumscore (SD)	17.05 (8.68)	9.66 (6.25)	<0.001

CIRS: Cumulative Illness Rating Scale; AST: Active standing test; HUT: Head up tilt; [a] total number of participants is 47 instead of 83; [b] independent t-test for continuous variables and chi-square test for dichotomous variables

Active standing test

Using the original consensus criteria for OH, 20 out of 83 PD patients had OH during the AST, giving an estimated prevalence of 24.1% (95% CI: 16.2–34.3). Group comparisons for PD patients with and without OH are shown in Table 2. Higher age, male sex, alpha-blocker and rivastigmine use were associated with the presence of OH in PD. Two patients with OH were taking antihypotensive medication. No significant group differences were found for other clinical characteristics and medication groups. Only three control subjects had OH during the AST (8.6%; 95% CI: 2.5–21.1). Two of these three control subjects used an alpha-blocker.

Figure 1: Selection of study participants



[a] Patients from the Academic Medical Center were eligible if they had a disease duration between five and eight years, and if they were not under treatment in our center as a result of a tertiary referral. AST: Active standing test; HUT: Head up tilt; PSP: Progressive supranuclear palsy; DLB: Dementia with Levy bodies; PD: Parkinson's disease

Tilt table testing

Thirty-four out of 47 patients (72.3%; 95% CI: 58.2–83.1) had OH at some time during the 45-minute tilt table test. Twenty-two had OH during the first three minutes of the test and 12 patients had OH in the remaining duration of the test (delayed OH). Five patients experienced symptoms during HUT. No patient required a tilt-back because of imminent syncope. In total, 22 out of 35 control subjects (62.9%; 95% CI: 46.4–77.3) had OH at some time during the 45-minute tilt table test. Eleven control subjects had OH during the first three minutes of the test and 11 controls had delayed OH. Five controls experienced symptoms during HUT. In two, symptoms arose directly after HUT and were self-limiting. In three, they arose later and these control subjects had to be tilted back because of imminent syncope. The latter three control subjects reported no orthostatic symptoms of OH in daily life.

Table 2: Comparison of PD patients with and without OH

	Patients with OH (n = 20)	Patients without OH (n = 63)	*p*-value[a]
Mean age	73.4	67.9	0.01
Mean age at diagnosis	66.8	61.3	0.01
Mean disease duration	6.5	6.6	0.80
Number of males (%)	15 (75.0%)	29 (46.0%)	0.02
Mean UPDRS-ME score	25.6	23.2	0.41
Mean CIRS score	4.90	4.83	0.91
Mean LED[b]	740.3	663.3	0.31
Number using rivastigmine (%)[b]	4 (20.0%)	3 (4.8%)	0.05
Number using alpha-blocker (%)[b]	5 (25.0%)	2 (3.2%)	0.002
Number using antihypertensive medication (%)[b]	11 (55.0%)	30 (47.6%)	0.57
Number using antihypotensive medication (%)[b]	2 (10.0%)	0 (0%)	0.06
Mean COMPASS 31-OI domain	2.85	2.40	0.53
Mean COMPASS 31 sumscore	23.23	21.17	0.60
Mean SCOPA-AUT-CV domain	1.00	1.11	0.75
Mean SCOPA-AUT sumscore	17.90	16.78	0.62
Number reporting loss of consciousness in previous 6 months (SCOPA-AUT item 16) (%)	2 (10.0%)	7 (11.1%)	0.88

UPDRS-ME: Unified Parkinson's Disease Rating Scale - Motor Examination; CIRS: Cumulative Illness Rating Scale; LED Levodopa Equivalent Dosage; [a] independent t-test for continuous variables and chi-square test or Fisher's exact test for dichotomous variables; [b] no significant differences were found for other groups of medication.

Symptoms of OH in daily life

Patients had significantly higher sum scores and orthostatic symptom domain scores on both the COMPASS-31 and the SCOPA-AUT than controls (Table 1). No significant differences in symptom scores were found between PD patients with and without OH (Table 2). The relation between different criteria for OH and the orthostatic symptoms PD patients experience in daily life are shown in Table 3.

Table 3: Relation between the different criteria for OH and orthostatic symptoms in daily life in PD patients

Presence of OH		Symptoms of OH in daily life	No symptoms of OH in daily life	*p*-value[f]	sensitivity (95% CI)	specificity (95% CI)
Original OH	Yes	12	8	0.28	29%	81%
criteria (AST)[a]	No	29	34		(18%–44%)	(67%–90%)
OH 30/15 systolic	Yes	13	9	0.29	32%	79%
(AST)[b]	No	28	33		(20%–47%)	(64%–88%)
OH mean < 75	Yes	9	6	0.36	22%	86%
(AST)[c]	No	32	36		(12%–37%)	(72%–93%)
OH 20/10 – 3	Yes	10	12	0.86	48%	55%
minutes (HUT)[d]	No	12	13		(30%–67%)	(35%–73%)
OH 20/10 – 45	Yes	19	15	0.55	76%	32%
minutes (HUT)[e]	No	6	7		(57%–89%)	(16%–53%)

[a] blood pressure drop of at least 20 mmHg systolic or 10 mmHg diastolic on the first three minutes of the active standing test; [b] when the supine systolic pressure is above 160 mmHg, a systolic drop of at least 30 mmHg is required, and when the supine systolic pressure is under 115 mmHg, a systolic drop of at least 15 mmHg is required; [c] a drop of the mean blood pressure below the absolute level of 75 mmHg in the first three minutes after active standing up; [d] blood pressure drop of at least 20 mmHg systolic or 10 mmHg diastolic on the first three minutes after head up tilt; [e] blood pressure drop of at least 20 mmHg systolic or 10 mmHg diastolic at any time during the 45 minutes head up tilt; [f] chi-square test

DISCUSSION

The present study shows the lack of a clear association between the results of a single orthostatic blood pressure test and perceived orthostatic symptoms in the daily life of PD

patients. The exploration of recently proposed alterations of the original OH criteria did not change this.

One of the major strengths of this study is the use of an incident PD cohort with patients from general hospitals. This is of special importance since most studies on OH in PD have been performed in selected tertiary care populations in which patients with more severe symptoms of autonomic degeneration are likely to be overrepresented.[11] To investigate the relation between test results and perceived orthostatic symptoms, we specifically focused on symptoms that patients experience in daily life, instead of symptoms experienced during the orthostatic blood pressure tests. We did this because the orthostatic symptoms experienced in daily life are more directly related to disease burden. In addition, the blood pressure threshold to experience symptoms may not always be reached during each individual orthostatic test, and therefore patients could incorrectly be classified as asymptomatic based solely on the symptoms reported during a single test. To further increase external validity, participants in our study continued their regular medication during the blood pressure tests because this resembles best the condition during a regular outpatient consultation. The use of an incident cohort has resulted in a relatively small number of participants and is a drawback of the present study.

The use of HUT instead of AST increased the sensitivity to detect PD patients suffering from orthostatic symptoms in daily life, but only at the cost of a large drop in specificity. The use of a control population in the present study corroborates the findings that the results of HUT in the elderly population lack specificity, because abnormal test results and even near syncope were found in a substantial number of control subjects who did not experience any orthostatic symptoms in daily life.

A likely explanation for the lack of an association between daily orthostatic symptoms and the results of orthostatic blood pressure tests might be the low reproducibility of the latter, as this has already been shown in the general population.[23] The most likely cause for this is that the blood pressure reaction to orthostatic stress is highly variable and dependent on various factors such as the time since the last meal, composition of the last meal, amount of fluid intake, extent of ambulation during the day and ambient temperature.[24] Besides this, sympathetic denervation in PD is generally less pronounced compared to other disorders with severe autonomic degeneration such as Multiple System Atrophy and Pure Autonomic Failure where more consistent results of orthostatic blood pressure tests might be expected.[25] Lastly, specific for the PD population is the additional use of dopaminergic treatment, which might also impede the orthostatic blood pressure response highly dependent on the plasma levels of

dopaminergic drugs from one moment to the other. The opposite explanation would be that the symptoms reported on the questionnaires are non-specific and caused by other medical conditions such as orthostatic tremor, vestibular disorders or impaired propriocepsis due to myelopathy or polyneuropathy. The low prevalence of these conditions makes it unlikely that they can explain the substantial number of patients experiencing orthostatic symptoms in daily life in which a single orthostatic blood pressure test failed to demonstrate OH. In addition, the groups with and without OH had a comparable proportion of patients reporting a loss of consciousness in the previous six months. Unfortunately we were not able to use the more recently developed Orthostatic Hypotension Questionnaire, because the present study was ongoing at the time of publication.[26]

The main conclusion of the present study is that in PD patients complaining from typical orthostatic symptoms in daily life, the diagnosis of OH cannot be excluded after a normal orthostatic blood pressure test. A potential diagnostic strategy might be to repeat an AST during a second visit. However, the extent to which the sensitivity of orthostatic blood pressure tests are increased by repeating them on separate occasions is not known and repeated testing may also lead to a decrease of specificity. Therefore, it may still be worthwhile to counsel patients complaining of typical orthostatic symptoms about simple lifestyle changes such as adequate fluid intake and physiological counter maneuvers to prevent OH during the day, even in the absence of confirmation of OH during an orthostatic blood pressure test. In addition, it is important to check whether a patient uses an alpha-blocker, as this is the most important reversible risk factor for OH in PD.[27] Meanwhile, the need to find a better diagnostic test to confirm the presence of OH in daily life remains. A potential strategy might be to investigate the clinical test characteristics of other markers of autonomic degeneration that have been shown to be abnormal in selected PD patients with confirmed OH.[1] Besides this, whether PD patients have an additional impairment of cerebrovascular auto-regulation during hypotensive episodes also needs to be investigated in larger patient groups.[28,29] Finally, another strategy may be to investigate the use of ambulatory continuous blood pressure measurements, including an alarm button which the patient can press while experiencing orthostatic symptoms.[30] A similar strategy for detecting cardiac arrhythmias in ambulatory settings is already available in patient care.[31]

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Chapter 7

The relation between autonomic nervous system tests and reported daily orthostatic symptoms in Parkinson's disease

Daan C.Velseboer
Hein J. Verberne
Bart Post
C.T. Paul Krediet
Rob J. de Haan
Rob M.A. de Bie

Submitted

ABSTRACT

Background: Routine orthostatic blood pressure tests in the outpatient clinic may be insufficient to determine whether a patient with Parkinson's disease (PD) suffers from symptomatic Orthostatic Hypotension (OH) in daily life.

Objectives: To investigate whether additional tests of autonomic nervous system integrity could aid in diagnosing OH in PD patients.

Methods: We performed a cross-sectional study in a group of non-selected PD patients. Participants underwent orthostatic blood pressure tests and a Valsalva maneuver using continuous blood pressure measurements, ambulatory 24-hour blood pressure measurements, and cardiac ^{123}I-*meta*-iodobenzylguanidine (^{123}I-*m*IBG) scintigraphy. Orthostatic symptoms in daily life were assessed with the COMPASS 31 questionnaire.

Results: A total of 47 PD patients were included. No association was found between orthostatic symptoms in daily life and the absolute blood pressure drop during orthostatic blood pressure testing. Orthostatic symptoms in daily life were associated with a prolonged systolic blood pressure recovery time and decreased systolic overshoot during phase IV of the Valsalva maneuver (*p*-values 0.03 and 0.04 respectively) and with an increased ^{123}I-*m*IBG late heart-to-mediastinum ratio with decreased myocardial wash-out (*p*-values 0.02 and 0.04 respectively). Discriminative value of these variables remained low (AUC-ROC: range 0.59–0.71).

Conclusion: When suspecting symptomatic OH in a PD patient, the blood pressure response to a Valsalva maneuver and the results of ^{123}I-*m*IBG scintigraphy may have more diagnostic value than the results of an orthostatic blood pressure test. However, the discriminative ability of these tests is also limited.

INTRODUCTION

Orthostatic hypotension (OH) is a common phenomenon in Parkinson's disease (PD).[1,2] It is caused by degeneration of the autonomic nervous system.[3] When there is a clinical suspicion of OH, orthostatic blood pressure tests such as the active standing test (AST) or the head-up-tilt test (HUT) have been recommended, and a systolic drop of 20 mmHg or diastolic drop of 10 mmHg in the first three minutes of AST or HUT are considered diagnostic for OH.[4,5] However, different studies have shown that in PD patients there is no clear association between the orthostatic symptoms patients experience in daily life and the results of these tests.[2,6,7] This is possibly explained by variability in the blood pressure response on standing up, dependent on the time of the day, ambient temperature, fluid intake, extent of ambulation, and use of antihypertensive drugs.[8,9] Blood plasma fluctuations of dopaminergic drugs may further increase the daily variability in orthostatic blood pressure responses in PD patients. Since OH can have a significant impact on the daily functioning of a PD patient, a better diagnostic test is therefore needed.[10]

Abnormal results on several tests of autonomic nervous system integrity have been described in PD patients. Examples are diminished cardiac ^{123}I-*meta*-iodobenzylguanidine (^{123}I-*m*IBG) uptake, diminished supine norepinephrine plasma concentrations, presence of nighttime supine hypertension, and an abnormal blood pressure and heart rate response during a Valsalva maneuver.[11-17] With the exemption of cardiac ^{123}I-*m*IBG scintigraphy, for all these tests an association with the presence of OH in PD patients has been reported previously. However, the association of these tests with reported daily symptoms of OH has not been systematically investigated in a non-selected population of PD patients. Previous studies adhered to strict research protocols in which patients had an overnight fast and standardized meal, and had to abstain from any dopaminergic and/or anti-hypertensive medication that might influence test results. In the day-to-day care this can be impractical, especially in patients with more advanced disease. We therefore performed a pragmatic study in a representative cohort of non-selected PD patients to investigate whether various tests of autonomic nervous system integrity could be of aid in detecting patients suffering from orthostatic symptoms in daily life.

METHODS

Study Participants

Participants for the present study were recruited from the CARPA-cohort and our own outpatient clinic. The CARPA study is a prospective cohort study in which patients with newly diagnosed PD from six general hospitals were included between 2002 and 2005. The clinical diagnosis of PD was based on standard criteria and was confirmed by a movement disorder specialist throughout the study.[18] All participants with a confirmed diagnosis of PD still participating at the 5 year follow-up of the CARPA-study were asked for participation.[19] During the project, the number of PD patients from the CARPA-cohort that only wanted to participate in a shortened protocol at home was higher than anticipated.[2] In addition, some of the participants who were willing to visit the hospital deemed the full research protocol too extensive, and were only willing to participate with the omission of the cardiac ^{123}I-*m*IBG scintigraphy. For this reason, additional participants from our own outpatient clinic (Academic Medical Center, Amsterdam) were recruited. To ensure a similar demographic profile of the additional PD patients, only patients with disease duration of 5-8 years were selected. In addition, patients who were treated in our outpatient clinic as a result of a tertiary care referral were excluded. All PD patients used their regular medication throughout the study. This study was done in accord with the Helsinki declaration of 1975 and was approved by the medical ethics committees of the Free University Medical Center and the Academic Medical Center (Amsterdam, the Netherlands). All participants gave written informed consent.

Orthostatic symptoms in daily life

To assess orthostatic symptoms in daily life, all PD patients were requested to complete the COMPASS 31. This is a shortened version of the generic Autonomic Symptom Profile, which has been recommended for use in PD patients.[20-22] This questionnaire was completed by the PD patients in the presence of a research clinician on the day of testing. Orthostatic symptoms in daily life were rated by the orthostatic symptom domain of this questionnaire (COMPASS 31-OI, 4 items, range 0–10, with higher scores indicating more symptoms). The items in this domain concern orthostatic symptoms that patients may have experienced in the timespan of the preceding year. For the present study, participants were arbitrarily classified as having orthostatic symptoms in daily life if they scored one or more points on the COMPASS 31-OI.

Continuous blood pressure measurements

Continuous blood pressure measurements were performed using a Nexfin HD monitor (Edwards Lifesciences BMEYE, Amsterdam, the Netherlands). The Nexfin HD monitor uses non-invasive finger-cuff technology and reconstructs the blood pressure to the brachial artery. Alterations in blood pressure measured with this technique have a good correlation with alterations in blood pressure measured with the conventional Riva-Rocci method measured at the brachial artery.[23,24] Measurements were started at 10 a.m. After a period of 5 minutes rest with the headrest of the bed at a 20 degree upright position the Valsalva maneuver was performed. The participant was then instructed to forcibly strain by blowing into a mouthpiece with a high resistance for flow of expired air. The mouthpiece contained a digital pressure monitor, and participants were instructed to maintain the air pressure during expiration at a constant 40 mmHg during 15 seconds after which they were allowed to continue normal breathing. From the Valsalva maneuver three sympathetic and one parasympathetic variables were derived. The variables reflecting the sympathetic part of the baroreflex response were: the presence or absence of a partial recovery of systolic blood pressure during the active straining part (phase II partial recovery); the duration between the release of the strain and the recovery of the systolic blood pressure to the baseline systolic pressure (phase IV full recovery time); and the extent of the overshoot of the systolic blood pressure after the Valsalva maneuver compared to the baseline systolic blood pressure (phase IV systolic overshoot). The variable reflecting the parasympathetic part of the baroreflex response is the Valsalva-ratio obtained by dividing the maximum heart frequency by the minimum heart frequency that are measured in the first 30 seconds after the release of the strain.[25] A more detailed explanation of the different components of the Valsalva maneuver is shown using data from two representative participants in figure 1.

A Valsalva-maneuver was deemed unsuccessful if the total duration of the strain could not be maintained for longer than 10 seconds, the pressure during forced expiration could not be maintained above 30 mmHg, or when a flat-top response occurred.[25] A flat-top response occurs when the amount of effective circulation volume within the chest wall during a Valsalva maneuver is still relatively high. As a result, there is no sufficient drop in cardiac output during the active straining phase of the Valsalva maneuver, and the resulting parameters of the baroreflex response cannot be assessed. When the first Valsalva maneuver was unsuccessful, participants made one more attempt after an additional 5 minutes resting period.

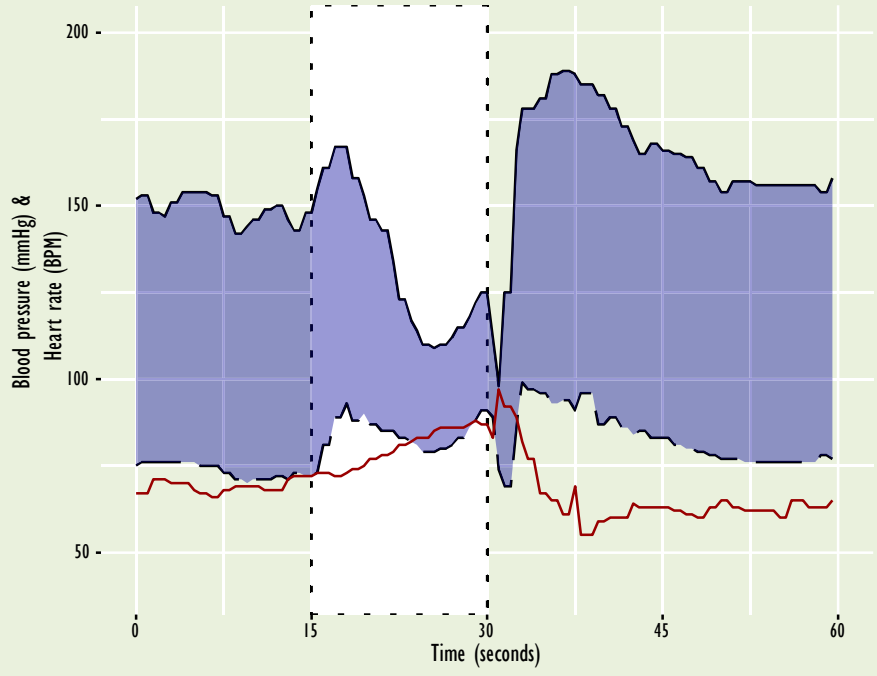
After the Valsalva maneuver participants performed the AST and the HUT. For the AST, participants were instructed to remain standing for 10 minutes after a period of 5 minutes

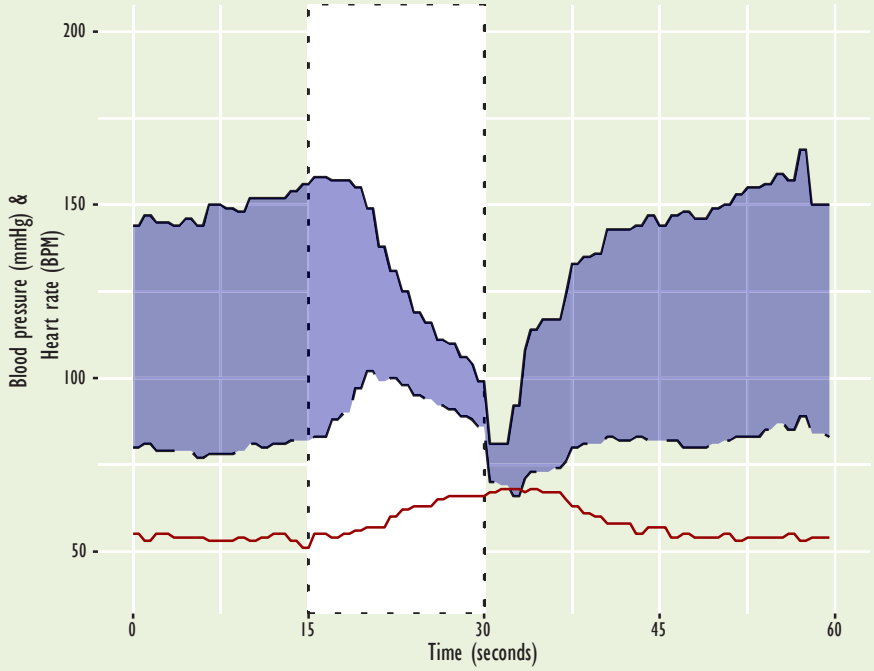
supine rest. After the AST, participants had a new period of 5 minutes supine rest, after which they were positioned to 60 degrees HUT for 45 minutes using a tilt table. Supine blood pressure was calculated by averaging the last minute of the supine resting periods. Upright blood pressure was calculated for each minute by averaging the continuous registration with intervals of one minute. Presence of OH was defined as a systolic blood pressure decline > 20 mmHg or diastolic > 10 mmHg in the first three minutes of AST. In addition for both the AST and the HUT, the maximal systolic blood pressure drops for the total duration of the tests were calculated.

Ambulatory 24-hour blood pressure measurements

After the continuous blood pressure measurements, participants were connected to an ambulatory blood pressure monitor for 24 hours (Spacelabs Healthcare, Snoqualmie, WA, United States). The ambulatory blood pressure monitor assessed the blood pressure at 15-minute intervals during daytime and 30 minute intervals during nighttime.

Figure 1: Normal and abnormal response to the Valsalva Maneuver





Left panel: normal response to the Valsalva maneuver. Right panel: typical response to the Valsalva maneuver in patients with autonomic nervous system failure. Solid black line: systolic blood pressure; dashed black line: diastolic blood pressure; red line: heart rate; white rectangle: duration of the Valsalva-maneuver. The Valsalva maneuver consists of four phases: During phase I the active straining causes a short rise in blood pressure; During early phase II there is a progressive decline in blood pressure due to a preload reduction maintained by the raised intrathoracic pressure. The baroreflex leads to a compensatory rise in heart rate and peripheral vasoconstriction. In healthy subjects this leads to a partial recovery of the blood pressure during late phase II. Phase III is initiated by release of the strain and is characterized by a short-lasting further fall of the blood pressure. Phase IV is characterized by recovery of the blood pressure, normally including an overshoot of the blood pressure compared to the baseline supine blood pressure. In patients with autonomic nervous system failure there generally is an absence of the blood pressure recovery during late phase II, a diminished (or absent) systolic blood pressure overshoot during phase IV, and an increased systolic blood pressure recovery time. In addition the Valsalva-ratio is diminished (maximum heart rate divided by the minimum heart rate in the 30 seconds after release of the strain).[25]

Participants recorded the time of going to sleep and getting up again. Presence of nocturnal hypertension was defined as an average nocturnal systolic pressure above 120 mmHg and/or a diastolic pressure above 75 mmHg. In addition, the nocturnal blood pressure fall was

calculated by subtracting the average daytime systolic blood pressure with the average nighttime systolic blood pressure.[26,27]

Cardiac ^{123}I-mIBG scintigraphy

Participants returned one week later for the second part of the study protocol. Between 9:30 and 10:30 a.m. an indwelling venous cannula was placed in the cubital fossa. After 30 minutes of supine rest 185 MBq of ^{123}I-*m*IBG was injected. Anterior planar images of the chest were acquired 15 minutes and 4 hours after injection. The myocardial region of interest (ROI) was drawn manually to include both ventricles and any atrial activity that was clearly visible. The mediastinal ROI was drawn in the upper mediastinum, using the apices of the lungs as anatomic landmarks. The heart to mediastinal (H/M) ratio was calculated as the ratio of the counts/pixel in the two ROIs. Early and late H/M were calculated and myocardial washout of ^{123}I-*m*IBG was determined ([early H/M - late H/M]/ early H/M). The H/M ratio reflects presynaptic myocardial uptake of the tracer. The early H/M ratio reflects predominantly the integrity of sympathetic nerve terminals (*i.e.*, number of functioning nerve terminals and intact uptake mechanism). The late H/M ratio and myocardial ^{123}I-*m*IBG washout offer predominantly information about neuronal function resulting from uptake, storage and release mediated by sympathetic tone or adrenergic drive.[28]

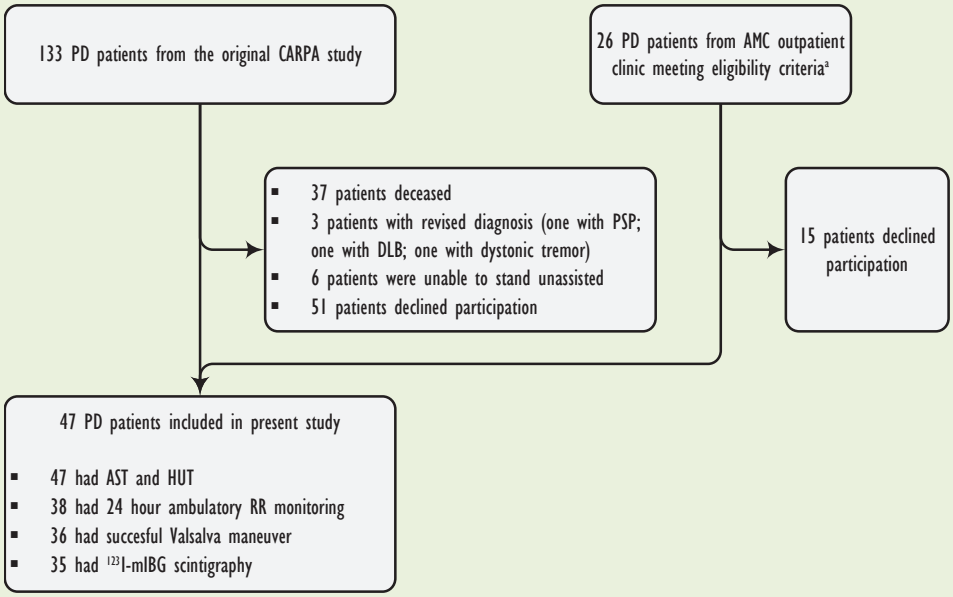
Statistical Analysis

Group differences between PD patients with and without orthostatic symptoms in daily life, and between PD patients with and without OH during the AST were estimated using independent sample t-tests and chi-square or Fisher's exact tests, where appropriate. A *p*-value of < 0.05 was considered significant. For test variables with a significant association with the presence of orthostatic symptoms in daily life, the area under the curve of the receiver operator characteristics curve (AUC-ROC) was estimated to assess discriminative value (where an AUC-ROC of 0.5 indicates a non-informative test and an AUC-ROC value of 1 indicates a test with perfect discriminative ability). Statistical uncertainty was expressed in a 95% confidence interval (CI). Due to the explorative nature of this analysis, no corrections for multiple testing were made.[29] Analyses were performed in IBM SPSS version 23.

RESULTS

A total number of 47 participated in the present study (36 from the CARPA-cohort and 11 from our own outpatient clinic). A flowchart with details of the selection process is shown in figure 2. A comparison of participants from the CARPA-cohort and the AMC outpatient clinic are shown in the supplementary appendix.

Figure 2: Selection of participants



[a] Patients from the Academic Medical Center were eligible if they had a disease duration between five and eight years, and if they were not under treatment in our center as a result of a tertiary referral.
AST: Active Standing Test; HUT: Head-up-tilt

Twenty-five of the 47 participants were men (53.2%). Mean age was 65.4 years (SD 8.1) and participants had a mean disease duration of 6.3 years (SD 0.9). All participants received dopaminergic treatment, 20 participants (42.5%) used one or more antihypertensive drugs (five patients used propranolol, eight other beta-blocking drugs, three alpha-blocking drugs and 13 antihypertensive drugs from other groups). Mean COMPASS 31-OI score was 2.49 (SD 2.53). Twenty-five participants (53.2%) were classified as having orthostatic symptoms in daily life (as defined by a COMPASS 31-OI score of one or higher).

Orthostatic blood pressure testing

All participants underwent the AST and HUT. Presence of orthostatic symptoms in daily life was not associated with the extent of the maximal systolic blood pressure drop during either the 10-minute AST or the 45-minute HUT (Table 1). Seven out of 47 patients had OH during the AST as defined by the original consensus criteria (*i.e.* a systolic drop of 20 mmHg or diastolic drop of 10 mmHg in the first three minutes of the AST).[4] No significant associations were found between presence of OH during the AST and the additional autonomic nervous system integrity tests (Table 2).

Valsalva maneuver

A total of 36 patients performed a successful Valsalva maneuver. In 11 patients results were missing (in four because of difficulties blowing into the mouth-piece without air leakage, in three because of flat-top responses, in two because the total duration of the strain was shorter than 10 seconds, in one because of inability to maintain the pressure of expired air above 30 mmHg, and in one because of device failure). Patients with orthostatic symptoms in daily life had a longer mean phase IV blood pressure recovery time and a lower mean phase IV systolic blood pressure overshoot (Table 1). Discriminative value of these tests remained relatively low (AUC-ROC 0.59 and 0.70, respectively).

Ambulatory 24-hour blood pressure measurements

A total of 38 patients underwent ambulatory 24-hour blood pressure measurements. Results were missing in nine patients (five patients because they found the device too inconvenient, two patients were unable to wear the cuff because of obesity, and two patients had too many measurement errors due to dyskinesias). Presence of orthostatic symptoms in daily life was not associated with the presence of nighttime supine hypertension or the extent of the nocturnal blood pressure fall (Table 1).

Cardiac ^{123}I-mIBG scintigraphy

A total of 35 patients had cardiac ^{123}I-*m*IBG scintigraphy. In 12 patients results were missing because of patient refusal (either because of fear of radiation exposure, or because of the preference to participate in a one-day research protocol only). Presence of orthostatic symptoms in daily life was associated with higher late H/M ratio and decreased myocardial washout (Table 1). Discriminative value of these tests remained relatively low (AUC-ROC 0.71 and 0.69, respectively). Repeated analysis with exclusion of patients using alpha- and/or

Table 1: Patients with and without orthostatic symptoms in daily life in relation to autonomic nervous system integrity test results

	Symptoms on COMPASS 31-OI	No symptoms on COMPASS 31-OI	*p*-value[a]	AUC-ROC (95% CI)
Maximum fall of the systolic blood pressure during the AST in mmHg (n = 47); mean (SD)	10.9 (19.8)	7.4 (12.5)	0.47	
Maximum fall of the systolic blood pressure during the HUT in mmHg (n = 47); mean (SD)	36.1 (21.0)	30.6 (20.5)	0.37	
Valsalva: Absence of phase II partial recovery (n = 36); number (%)	6/20 (30.0%)	2/16 (13%)	0.26	
Valsalva: Phase IV full recovery time in seconds (n = 36); mean (SD)	13.9 (16.0)	5.6 (3.1)	0.03	0.59 (0.40–0.78)
Valsalva: Phase IV systolic overshoot in mmHg (n = 36); mean (SD)	35.1 (19.1)	49.9 (22.1)	0.04	0.70 (0.53–0.88)
Valsalva-ratio (n = 36); mean (SD)	1.45 (0.39)	1.49 (0.31)	0.77	
Presence of nighttime supine hypertension (n = 38); number (%)	14/21 (67%)	8/17 (47%)	0.22	
Nocturnal blood pressure fall in mmHg (n = 38); mean (SD)	5.5 (10.1)	6.7 (8.2)	0.70	
^{123}I-*m*IBG early H/M-ratio (n = 35); mean (SD)	1.83 (0.43)	1.61 (0.22)	0.07	
^{123}I-*m*IBG late H/M-ratio (n = 35); mean (SD)	1.55 (0.37)	1.29 (0.18)	0.02	0.71 (0.53–0.89)
^{123}I-*m*IBG myocardial washout (n = 35); mean (SD)	0.15 (0.04)	0.19 (0.07)	0.04	0.69 (0.51–0.87)

[a] Independent sample t-tests for continuous variables and chi-square or Fisher's exact tests for dichotomous variables. AUC-ROC: area under the curve of the receiver operator characteristics curve; AST: Active Standing Test; HUT: Head-up-tilt; ^{123}I-*m*IBG: ^{123}I-*meta*-iodobenzylguanidine; H/M: Heart to Mediastinal

beta-blocking drugs still showed a higher late H/M ratio in patients with daily symptoms of OH (n = 24, 1.63 vs. 1.31, *p*-value 0.01), and a decreased myocardial washout in patients with daily symptoms of OH (0.15 vs. 0.20, *p*-value 0.04).

Table 2: Patients with and without OH during the active standing test in relation to autonomic nervous system integrity test results

	OH during AST	No OH during AST	*p*-value[a]
Valsalva: Absence of phase II partial recovery (n = 36); number (%)	2/6 (30%)	6/30 (20%)	0.60
Valsalva: Phase IV full recovery time in seconds. (n = 36); mean (SD)	13.0 (10.7)	9.6 (13.1)	0.57
Valsalva: Phase IV systolic overshoot in mmHg (n = 36); mean (SD)	51.2 (30.6)	39.7 (19.1)	0.24
Valsalva-ratio (n = 36); mean (SD)	1.27 (0.08)	1.51 (0.37)	0.13
Presence of nighttime supine hypertension (n = 38); number (%)	2/7 (29%)	14/31 (45%)	0.68
Nocturnal blood pressure fall in mmHg (n = 38); mean (SD)	1.3 (6.6)	7.2 (9.4)	0.13
^{123}I-*m*IBG early H/M-ratio (n = 35); mean (SD)	1.55 (0.14)	1.75 (0.37)	0.26
^{123}I-*m*IBG late H/M-ratio (n = 35); mean (SD)	1.27 (0.18)	1.49 (0.33)	0.25
^{123}I-*m*IBG myocardial washout (n = 35); mean (SD)	0.19 (0.05)	0.17 (0.06)	0.61

[a] Independent sample t-tests for continuous variables and Fisher's exact tests for dichotomous variables.
OH: Orthostatic Hypotension as defined by the consensus criteria[4] AST: Active Standing Test; ^{123}I-*m*IBG: ^{123}I-*meta*-iodobenzylguanidine; H/M: Heart to Mediastinal

DISCUSSION

In the present study, we found the presence of orthostatic symptoms in daily life to be associated with abnormal blood pressure recovery during the Valsalva maneuver and also with increased late ^{123}I-*m*IBG H/M ratio and decreased myocardial ^{123}I-*m*IBG washout. The sympathetic components of the Valsalva-maneuver are known to be stable parameters of sympathetic autonomic degeneration.[25] For PD patients, we show that they are more closely

related to the orthostatic symptoms in daily life than the actual results of orthostatic stress tests. This suggests that the blood pressure response during the Valsalva maneuver is less affected by the extrinsic factors that are known to influence the blood pressure response during orthostatic stress.[8,9] Despite the association, the discriminative values of the Valsalva-parameters were relatively low, precluding a direct translation of this test to clinical practice. In addition, a substantial number of patients were unable to perform the maneuver, or the estimation of the Valsalva variables was impossible due to a flat-top response, which further impedes the practical usability of this test.

For the total group of PD patients we found low early and late H/M ratios with ^{123}I-*m*IBG cardiac scintigraphy in line with earlier reports.[30] Surprisingly, we found that patients with symptoms of OH in daily life have a slightly higher late H/M ratio with decreased myocardial washout. This could possibly be explained by a compensatory increase of the norepinephrine transporter in the cardiac sympathetic presynapse in patients with mild to moderate peripheral autonomic degeneration. Repeated analysis with exclusion of patients using alpha or beta-blocking drugs did not substantially change our results. However, the lack of earlier studies showing comparable results necessitates more studies showing results in the same directions before any definite conclusions can be drawn.[15-17]

One of the strengths of this study is the selection of patients that are likely to represent an average PD population. The original design of the CARPA cohort study guarantees that included patients are representative of the general PD population.[19] We have ensured that the clinical profile of the additional patients from our own outpatient clinic is comparable to those from the CARPA cohort. This is important since most studies concerning OH in PD are performed in a population solely consisting of patients from tertiary care referrals resulting in an overrepresentation of patients with more severe autonomic degeneration.[1]

This study also has limitations. First, the number of patients was lower than expected because we originally planned to let all patients from the original CARPA-cohort participate in this research protocol. In addition, some patients only wanted to participate in the first part of the protocol (because they wanted to visit the hospital on only one day, or because they found the ^{123}I-*m*IBG scintigraphy too inconvenient). Despite this, the number of patients tested is comparable to earlier reports.[11-15,17] The proportion of patients having OH on the AST in the present study is lower than our previous study (14.9% in the present study versus 24.1% in our previous study), suggesting selection bias with inclusion of PD patients with relatively less severe autonomic degeneration. However, the mean COMPASS 31-OI score was more or less comparable (2.49 in the present study versus 2.51 in our previous study).[2]

In conclusion, the study shows that in PD patients, results from the Valsalva maneuver and cardiac ^{123}I-*m*IBG scintigraphy are more closely related to the presence of patient reported orthostatic symptoms in daily life than the results of single orthostatic blood pressure tests. Low discriminative ability of these tests may impede their use in the daily care for PD patients. However, since the modest sample size in our study caused the 95% CI's for the AUC-ROC values to be rather broad, it is worthwhile investigating the diagnostic value in a larger sample size.

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SUPPLEMENTARY DATA

Supplementary table: Comparison of patients from the CARPA cohort and the AMC outpatient clinic

	CARPA-cohort (n = 36)	AMC outpatient clinic (n = 11)	*p*-value[a]
Age; mean (SD)	65.2 (8.5)	65.9 (6.8)	0.80
Number of males (%)	18 (50%)	7 (64%)	0.43
Disease duration in years; mean (SD)	6.4 (0.7)	6.0 (1.1)	0.20
COMPASS-31-OI score; mean (SD)	2.3 (2.6)	3.0 (2.2)	0.41
COMPASS-31 total score; mean (SD)	20.8 (13.3)	27.6 (10.9)	0.13

[a] Independent sample t-tests for continuous variables and chi-square test for dichotomous variables

Chapter 8

General discussion

In this general discussion the results of the studies of this thesis are described in relation to the original aims of this thesis:
1) To investigate the role of non-dopaminergic symptoms in the clinical course and disease burden of Parkinson's disease (PD) patients.
2) To investigate the prevalence of orthostatic hypotension (OH) and the diagnostic value of orthostatic blood pressure tests and additional autonomic function tests in relation to daily experienced orthostatic symptoms.
The studies in this thesis will be put into perspective of the recent literature concerning non-dopaminergic symptoms in PD and suggestions for future research are given.

Part one: Prognosis in Parkinson's disease.

In **chapter two** we performed an exploratory prognostic study in which we concluded that non-dopaminergic symptoms at the moment of diagnosis are major determinants for faster progression of disability. In addition, higher age and presence of cognitive dysfunction at the moment of diagnosis are associated with faster progression of non-dopaminergic motor symptoms. We concluded that non-dopaminergic symptoms seem to cluster, and their uniform relation to higher age seems to contrast the progression of dopaminergic motor symptoms. For the latter we only found a weak association with patient sex, and the progression of dopaminergic symptoms seems to behave independent of the other prognostic variables. We postulated that though dopaminergic and non-dopaminergic symptoms are both the result of the same disease process, their pathophysiology is partially different.
In line with this hypothesis, we confirmed clustering of non-dopaminergic symptoms in **chapter three**. In this study we found that presence of autonomic symptoms (AS) in PD 5 to 8 years after diagnosis is associated with presence of more non-dopaminergic motor symptoms at the moment of PD diagnosis. We also found a longitudinal relationship between more AS 5 to 8 years after diagnosis and the presence of symptoms of anxiety and depression at the moment of diagnosis. In a cross-sectional analysis in this study, we also found that presence of AS is associated with more disability and lower quality of life, though this relation is confounded by the presence of non-dopaminergic motor symptoms and symptoms of anxiety and depression.
Clustering of non-dopaminergic symptoms has also been found in various other longitudinal studies. Especially the longitudinal relationship between non-dopaminergic motor symptoms and cognitive dysfunction has repeatedly been shown.[1,2] But perhaps a more striking longitudinal association between non-dopaminergic symptoms is the one between early

occurring (often pre-motor) olfactory dysfunction and an increased risk of cognitive dysfunction.[3,4] In patients with idiopathic REM-sleep behavior disorder, which like olfactory dysfunction is often a prodromal feature of PD, imaging defects are found in various regions in the central and peripheral nervous system that are related to the presence of non-dopaminergic symptoms.[5] In addition, when comparing patients with idiopathic REM-sleep behavior disorder with patients with PD, the former group shows more pronounced cardiac autonomic denervation as assessed by ^{123}I-*m*IBG scintigraphy.[6]

This increasing bulk of evidence for the clustering of non-dopaminergic symptoms supports a so called "dual-syndrome" hypothesis in PD, a term that was already proposed for the differential dopaminergic and non-dopaminergic aspects of cognitive dysfunction in PD.[7] As mentioned earlier, in this "dual-syndrome" hypothesis the pathological process (and the underlying risk factors) leading to degeneration of non-dopaminergic and dopaminergic neurons has to be partially different. In favor of this hypothesis is the existence of disorders that are closely related to idiopathic PD, but differ extremely in the extent to which patients suffer from dopaminergic and non-dopaminergic symptoms. On one end of the spectrum there are monogenic forms of PD, such as caused by homozygous mutations in the *Parkin* gene, where nigrostriatal degeneration may even develop in the absence of Lewy-body pathology.[8] On the other end of the spectrum are patients with severe widespread α-synuclein-related pathology throughout the nervous system, such as is the case in dementia with Lewy bodies (DLB) or pure autonomic failure (PAF), where the extent of dopaminergic symptoms is very minor or totally absent. A recent longitudinal study with long duration of follow-up showed that patients once diagnosed with PAF have a relatively high chance of developing DLB and only a minor chance of developing PD, which suggest there is subset of patients in which dopaminergic neurons are relatively spared despite severe widespread α-synuclein-related pathology.[9]

The question remains why despite the uniform neuropathological progression throughout the nervous system described in post-mortem studies, the extent of dopaminergic and non-dopaminergic symptoms is so variable between patients. Explanations can be found in pathophysiological models of PD. There are reasons to assume that the dopaminergic nigrostriatal cells respond differently to the ongoing progression of the α-synuclein-related neuropathological progress throughout the nervous system. Hypotheses are that their relatively long total axon length make them very susceptible for degeneration, even with only minor numbers of local Lewy-bodies. Another explanation might be that the high susceptibility is caused by chemoreactivity of dopamine and α-synuclein, leading to local neurotoxicity.[10]

With various new genetic polymorphisms identified by genome-wide association studies as risk factors for the development of PD, it is necessary to identify which polymorphisms are associated with degeneration of dopaminergic neurons, and which polymorphisms are associated with α-synuclein-related disease progression in general.[11]

In **chapter four** we developed a model that estimates the probability for patients with newly diagnosed PD of having an unfavorable outcome in the first five years after diagnosis. With the knowledge that it are the non-dopaminergic symptoms that are responsible for the highest disease burden in terms of disability we operationalized an unfavorable outcome as dementia, postural instability, or death in the first five years after diagnosis. The final model uses only three determinants (patient age, UPDRS-ME axial score, and phonemic [animal names] fluency score), which can easily be assessed during an outpatient clinic visit. The model had good performance parameters during validation in an external cohort.

Experience with prediction in neurodegenerative diseases, and more specific in PD, has until recently been limited. Prognostic studies in PD were explorative in nature, and more importantly prognostic models were never validated in independent cohorts.[12] This has recently changed, with the publication of three clinical prediction models estimating survival, progression of motor impairments, and development of cognitive dysfunction respectively.[13-15] For other neurodegenerative diseases such as Alzheimer's disease, Amyotrophic Lateral Sclerosis, Huntington's disease, and Multiple Sclerosis, prediction models have also been recently published.[16-20] An important question is whether prediction models can be used for patient counseling. Among clinicians and researchers opinions are divided.[21-23] Ultimately, with the public availability of regression formulae and risk score calculators, it will be up to the patient to decide whether they want to know their own prognosis or not. It will then be the task of researchers and clinicians to provide adequate guiding. Currently our prediction model has only been validated in one independent cohort. Substantial correction was needed for reference values of the animal fluency for the difference in Dutch and English language as otherwise considerable miscalibration occurred during external validation. For this reason, it would be advisable to perform at least one more additional validation in another independent cohort before utilizing the model for patient counseling.

Directions for future research

Since the exploratory prognostic studies have taught us that the non-dopaminergic symptoms are very important regarding prognosis in terms of disability, it is important that potential disease-modifying therapies target the whole disease progress and not just the dopaminergic

part. Though specific therapies seem promising in laboratory studies, no treatment has currently shown to alter the course of PD. Hopefully, the use of prediction scores form prognostic models can be used to increase efficiency of clinical trials.[24] First, an additional validation study needs to be performed for the prognostic model described in chapter 4. In the years after the start of the CARPA and CamPaIGN studies, other longitudinal cohort studies with newly diagnosed PD patients have started.[25-27] Their follow-up time has currently reached five years, so this generates the opportunity to start new collaborations to validate the prognostic model in new independent data. In addition, it would be interesting to see whether the prediction rule from the model also holds for cohorts with patients with non-newly diagnosed PD. Hopefully, when performance of the model is robust, it will be used for patient selection and stratification to improve the efficiency of new clinical trials.

Part two: Orthostatic Hypotension in Parkinson's disease.

In **chapter five** we estimated the prevalence of OH in PD to be 30.1% (95% CI: 22.9–38.4) using a systematic review of the literature. We concluded that research in this field is biased due to the majority of studies being performed in tertiary care settings. This limited the external validity of the estimated prevalence, and research concerning OH in PD in general. Since the publication of this review some cross-sectional studies with modest sample size have been published in which the prevalence of OH in PD was estimated in a prospective manner. Of these studies, one was performed in a population of PD patients in residential care and all others were performed in tertiary care populations.[28-32] Therefore, the need for studies concerning OH in the general PD population has not changed. In **chapter six**, we performed a cross-sectional study to estimate the prevalence of OH in PD, and to investigate the relation of OH to orthostatic symptoms in a non-tertiary care population. The estimated prevalence of OH in this non-tertiary care cohort of patients with PD for over five years was 24.1% (95% CI: 16.2–34.3). We showed that the presence of OH in a PD patient diagnosed using the consensus criteria has no clear relationship with the orthostatic symptoms patients suffer in daily life. These findings have two implications: 1) The burden of cardiovascular autonomic failure in PD patients is probably misjudged by looking solely at the prevalence of OH. 2) For individual PD patients the use of an active standing test with the OH consensus criteria is an improper diagnostic test to assess whether a patient suffers from orthostatic symptoms in daily life. We investigated whether the modification of the cut-off values of the consensus criteria for OH or the use of a head-up tilt test would improve diagnostic accuracy, but unfortunately there was no substantial improvement of test characteristics.

We speculated about two possible explanations for the lack of a relation between orthostatic test results and reported daily orthostatic symptoms. First, the orthostatic blood pressure response upon standing is highly variable (besides integrity of the peripheral autonomic nervous system, it is influenced by the time of the day, post-prandial status, ambient temperature, extent of ambulation during the day, concurrent use of medication) and a single orthostatic stress test at the outpatient clinic or at home is not sufficient. This hypothesis is supported by studies that show limited reproducibility of OH when measured at two different moments.[33,34] Second, measured changes in blood pressure after standing up during an orthostatic stress test do not adequately reflect changes in cerebral perfusion during orthostatic stress. A study that supports this hypothesis showed that impaired cerebral blood flow velocity measured by transcranial Doppler is related to orthostatic symptoms in PD patients that did not fulfill criteria for OH during orthostatic measurement.[35]

To see whether other tests of autonomic nervous system integrity could aid in detecting patients suffering from orthostatic symptoms in daily life we performed a cross-sectional study in **chapter seven** in which we investigated the diagnostic value of the cardiovascular response to a Valsalva maneuver, 24-hour ambulatory blood pressure measurement, and myocardial ^{123}I-*m*IBG-scintigraphy. We found orthostatic symptoms in daily life to be associated with a prolonged systolic blood pressure recovery time, with a decreased systolic overshoot during phase IV of the Valsalva maneuver, and with an increased ^{123}I-*m*IBG late heart-to-mediastinum ratio with decreased myocardial wash-out. When suspecting symptomatic OH in a PD patient, the blood pressure response to a Valsalva maneuver and the results of ^{123}I-*m*IBG scintigraphy may therefore have more diagnostic value than the results of an orthostatic blood pressure test. Unfortunately, the discriminative ability of the Valsalva maneuver and the results of ^{123}I-*m*IBG scintigraphy were both relatively low.

The results in our study are partially supported by a study in which PD patients with orthostatic symptoms in daily life and no OH during active standing have an abnormal blood pressure response during the Valsalva maneuver more frequently than asymptomatic patients.[36] The found association between orthostatic symptoms and ^{123}I-*m*IBG scintigraphy has not been found in other studies and needs to be confirmed before more definite conclusions can be drawn.[37,38] The increased heart-to-mediastinum ratio with decreased myocardial wash-out in symptomatic patients seems counter-intuitive, though might be explained when considering the presence of myocardial tracer in the late phase as the result of compensatory myocardial catecholamine re-uptake and preservation to counterbalance the effects of peripheral autonomic degeneration.

Directions for future research

There is still an urgent need to perform more studies on orthostatic symptoms in PD in a non-tertiary care setting. Though the results from the Valsalva test and ^{123}I-*m*IBG scintigraphy are interesting, the definitive diagnostic test for detecting patients with orthostatic symptoms has to be sought in another direction. Main reason is that in both tests the discriminative ability is still relatively low. In addition, a substantial number of patients were not able to perform a Valsalva maneuver or the blood pressure results were not assessable due to a 'flat-top'-response. ^{123}I-*m*IBG-scintigraphy is relatively costly and time-consuming, which impedes practical use.

In line with our two hypotheses for the lack of a relationship between the results from single orthostatic stress tests and the reported daily orthostatic symptoms, we suggest a two-tier research strategy:

- The first hypothesis suggests that orthostatic symptoms are directly related to OH, but the high variability in orthostatic blood pressure responses makes a single orthostatic blood pressure test insufficient as a diagnostic tool. For this reason, the potential of continuous ambulatory blood pressure monitoring needs to be investigated. By this manner, it will be possible to assess patients for a longer period throughout the day, and more importantly when they are most vulnerable for OH: early in the morning after rising from bed. This kind of blood pressure monitoring was impractical a couple of years ago, but techniques have developed rapidly, and the connection with a smart phone-app could be useful for the registration of experienced orthostatic symptoms.[36,39]
- The second strategy assumes that blood pressure measurements at the upper arm or the finger are an overall mediocre marker for cerebral circulation during orthostatic stress. The potential of trans-cranial Doppler (TCD) then needs to be investigated since this technique more directly assesses cerebrovascular hemodynamics. A potential drawback of TCD is that it is only possible to look at regional cerebral blood flow velocities. With a variable (and with TCD not assessable) diameter of the measured artery, it is still a surrogate marker for overall cerebral perfusion. It would therefore be wise to simultaneously investigate another surrogate marker of cerebral perfusion: cerebral tissue oxygen saturation using near-infrared-spectroscopy (NIRS).[40] Unfortunately, other diagnostic tests measuring cerebral perfusion more directly (such as computed tomography perfusion imaging) are not possible to perform during orthostatic stress.

Finally, if the development of both strategies does not lead to a proper diagnostic test, the possibility that orthostatic symptoms in PD patients are unrelated to cardiovascular autonomic degeneration has to be looked at. Previous reports have suggested that orthostatic symptoms could be caused by benign paroxysmal position vertigo (BPPV) or polyneuropathy.[41,42] However, the estimated prevalence of classical BPPV of 8% is still too low to explain the large group of patients experiencing orthostatic symptoms. Studies on polyneuropathy in PD are potentially biased by relying solely on neuropathy questionnaires with nervous conduction studies being confined to nerves of the lower limbs or being omitted.[43]

There is a need for studies investigating the prognostic implication of the presence of cardiovascular autonomic dysfunction in PD. The negative prognostic implication of the presence of OH has been suggested by associations with a higher frequency of falls and higher prevalence of cognitive dysfunction in cross-sectional and retrospective studies, but longitudinal follow-up studies of PD patients with cardiovascular autonomic dysfunction is lacking.[44-46] For the association between OH and cognitive dysfunction, research is needed to study whether this is merely an association (such as the simultaneous presence other non-dopaminergic symptoms described earlier) or whether cardiovascular autonomic dysfunction is a causative factor by causing cerebral hypoperfusion in the upright position, and increasing the risk of stroke by the presence of supine hypertension.[44,47] Recently, the number of small studies evaluating treatment options for orthostatic symptoms in PD is increasing.[48] With the lack of a definitive diagnostic test to detect patients with orthostatic symptoms it is important to use patient reported symptoms as primary endpoint when evaluating effectiveness of potential treatment options.

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Summary

"Non-dopaminergic symptoms in Parkinson's disease"

In the general introduction in **Chapter 1**, the dopaminergic and non-dopaminergic symptoms in Parkinson's disease (PD) are defined. Non-dopaminergic symptoms are caused by neurodegeneration outside the pars compacta of the substantia nigra as part of the disease progress. Important examples of non-dopaminergic symptoms in PD are postural instability, cognitive dysfunction and autonomic symptoms. In the last decades, the treatment of dopaminergic symptoms has improved considerably, exposing the non-dopaminergic symptoms in PD. Therefore, the non-dopaminergic symptoms have gained interest from both clinicians and researchers. The amount of non-dopaminergic symptoms from which PD patients may suffer is highly variable. Little is known about the cause of the high heterogeneity of non-dopaminergic symptoms in PD patients. For specific non-dopaminergic symptoms, proper diagnostic tests are lacking and the impact of non-dopaminergic symptoms on overall PD prognosis is unclear.

The aim of the first part of this thesis (chapters 2-4) is to gain insight in the role of non-dopaminergic symptoms in the disease course of PD patients. We investigate the underlying causes of the heterogeneity of non-dopaminergic symptoms in PD, and we evaluate the influence of non-dopaminergic symptoms on patient disability and quality of life. We focus specifically on the non-dopaminergic motor symptoms (postural instability), cognitive dysfunction, and autonomic symptoms.
The aim of the second part (chapters 5-7) of this thesis is to investigate the frequency and diagnosis of one specific non-dopaminergic symptom: orthostatic hypotension (OH). Therefore, we assess the prevalence of OH in PD, we evaluate the diagnostic value of general consensus criteria for OH in PD patients and we investigate the possible role of additional autonomic testing.

In **chapter 2** we performed an exploratory prognostic study investigating prognostic factors for the progression of motor impairments, disability and loss of quality of life in patients with newly diagnosed PD. Male sex was associated with faster progression of dopaminergic motor symptoms. Higher age and cognitive dysfunction were associated with faster progression of non-dopaminergic motor symptoms. Higher age, non-dopaminergic motor symptoms and cognitive dysfunction were associated with faster progression of disability. No relevant prognostic factors associated with loss of quality of life were found.

In **chapter 3** we performed an exploratory study to identify prognostic factors associated with the development of autonomic symptoms later in the disease. Presence of non-dopaminergic motor symptoms and symptoms of anxiety and depression at baseline were identified as prognostic factors for more autonomic symptoms later in the disease. We also investigated the influence of autonomic symptoms on disease burden in terms of disability and quality of life. Patients with more autonomic symptoms had more disability and lower quality of life. It is not sure whether there is a causal relation, or whether this is caused by the simultaneous occurrence of other non-dopaminergic symptoms.

In **chapter 4** we developed a prediction model, which estimates the probability of having an unfavorable disease course during the first five years after PD diagnosis. An unfavorable disease course was defined as death, the development of postural instability (Hoehn and Yahr-score ≥ 3) or dementia in the first five years after diagnosis. The model was developed in data from patients with newly diagnosed PD from the CARPA-cohort. The constructed prediction model contained three prognostic factors in which higher age, more non-dopaminergic motor symptoms (UPDRS-ME axial score) and lower verbal (animal) fluency score gave a higher chance of an unfavorable outcome. The model was validated in data from patients with newly diagnosed PD from the CamPaIGN-cohort (Cambridgeshire, UK). At external validation the model had a good discriminative ability and was well calibrated. The constructed model allows individual patient prognostication five years from diagnosis, using a small set of predictor variables that can easily be obtained by clinicians or research nurses.

In **chapter 5** we performed a systematic review estimating the prevalence of OH in PD. Based on a meta-analysis of 25 studies the estimated pooled prevalence of OH in PD was 30.1% (95% CI: 22.9–38.4). We found a high heterogeneity that could not be reduced by performing several subgroup-analyses. In addition, the majority of studies was performed in populations consisting solely of patients recruited in tertiary care centers. For these reasons, the external validity of the pooled prevalence of OH in PD is low, and the results of this study have to be interpreted with caution. The review endorsed the need for new research concerning OH in a representative group of PD patients.

In **chapter 6** we investigated a non-tertiary care cohort of PD patients on the presence of OH as defined by the consensus criteria. We performed continuous blood pressure measurements

during an active standing test and a head-up-tilt test. We also investigated the daily experienced orthostatic symptoms using two questionnaires. We found that there is no clear relation between the presence of OH as defined by the consensus criteria and the orthostatic symptoms patients experience in daily life. Adjustment of cut-off values of the original criteria, or the use of the head-up-tilt test did not substantially change this. As a potential explanation for the lack of a relation between orthostatic measurements and symptoms we suggested the high variability of the orthostatic blood pressure response. An important message for general neurologists is that a single orthostatic blood pressure test during an outpatient clinic visit is probably insufficient to exclude the possibility of OH in daily life.

In **chapter 7** we investigated the diagnostic value of additional autonomic nervous system testing in PD patients. We found an abnormal blood pressure response during a Valsalva maneuver to be associated with orthostatic symptoms patients experience in daily life. We also found the results of cardiac ^{123}I-*m*IBG scintigraphy (an increased ^{123}I-*m*IBG late heart-to-mediastinum ratio and decreased ^{123}I-*m*IBG myocardial washout) to be associated with orthostatic symptoms that patients experience in daily life. Both tests had a relatively low discriminative ability, which impedes their use in clinical practice.

Chapter 8 contains a general discussion in which the results from our studies are interpreted in light of recent literature. An important finding is that dopaminergic and non-dopaminergic symptoms seem to progress differently in PD. Having a specific non-dopaminergic symptom increases the risk of acquiring other non-dopaminergic symptoms. In this respect, the prognostic factors for dopaminergic and non-dopaminergic symptoms are different and are probably caused by a partially different pathophysiology. We additionally discuss the value of our clinical prediction model and suggest additional validation in other cohorts with follow-up duration of minimally five years. We discuss potential causes of the lack of a relation between the results of orthostatic stress tests and the orthostatic symptoms that PD patients experience in daily life. We suggest that to find a better diagnostic test, the potential of continuous ambulatory blood pressure measurements has to be explored first. An alternative diagnostic test worth investigating is the use of transcranial Doppler for assessment of cerebral blood flow velocities during orthostatic stress.

Nederlandse samenvatting

"Non-dopaminerge symptomen bij de ziekte van Parkinson"

In de introductie in **Hoofdstuk 1** wordt het verschil tussen dopaminerge en non-dopaminerge symptomen bij de ziekte van Parkinson (ZvP) beschreven. Non-dopaminerge symptomen bij de ZvP worden veroorzaakt door neurodegeneratie buiten de pars compacta van de substantia nigra. Belangrijke voorbeelden van non-dopaminerge symptomen zijn houding en balansproblemen, cognitieve problemen en stoornissen van het autonome zenuwstelsel. De afgelopen decennia is de behandeling van dopaminerge symptomen bij de ZvP steeds beter geworden en hierbij zijn de behandelmogelijkheden voor non-dopaminerge symptomen achtergebleven. Hierdoor is de aanwezigheid van non-dopaminerge symptomen bij patiënten duidelijker zichtbaar geworden en daarmee toenemend onder de aandacht van artsen en wetenschappers gekomen. Er zit veel variatie tussen patiënten met de ZvP in de mate waarin zij last hebben van non-dopaminerge symptomen. De reden waarom er veel variatie is in het voorkomen van non-dopaminerge symptomen is nog niet goed bekend. Ook is er weinig bekend over goede diagnostische tests voor het vaststellen van bepaalde non-dopaminerge symptomen. Als laatste is het nog grotendeels onbekend wat de invloed van non-dopaminerge symptomen is op de prognose van patiënten met de ZvP.

Het eerste doel van dit proefschrift is om duidelijker inzicht te krijgen in de rol die non-dopaminerge symptomen hebben in het ziektebeloop van de ZvP. In het eerste deel (hoofdstuk 2-4) van dit proefschrift onderzoeken we wat er ten grondslag ligt aan de variatie van het optreden van non-dopaminerge symptomen, en wat de invloed is van non-dopaminerge symptomen op de mate van invaliditeit en de kwaliteit van leven van patiënten. We richten ons hierbij met name op non-dopaminerge motorische symptomen (houding en balansproblemen), cognitieve problemen en functiestoornissen van het autonome zenuwstelsel. Het tweede doel van dit proefschrift is om de frequentie en diagnostiek te onderzoeken van één specifiek non-dopaminerg symptoom: orthostatische hypotensie (OH). In het tweede deel (hoofdstuk 5-7) van dit proefschrift doen we daarom onderzoek naar de prevalentie van OH, onderzoeken we de diagnostische waarde van standaard criteria voor OH bij de ZvP en onderzoeken we de waarde van aanvullende diagnostische tests.

In **hoofdstuk 2** verrichtten we een exploratieve prognostische studie naar prognostische factoren voor toename van motorische symptomen, invaliditeit en afname van kwaliteit van leven bij patiënten met nieuw gediagnosticeerde ZvP. Voorspeller voor snellere toename van

dopaminerge motorische symptomen was mannelijk geslacht. Voorspellers voor snellere toename van non-dopaminerge motorische symptomen waren hogere leeftijd en de aanwezigheid van cognitieve dysfunctie. Voorspellers voor snellere toename van invaliditeit waren hogere leeftijd, aanwezigheid van non-dopaminerge motorische symptomen en aanwezigheid van cognitieve dysfunctie. Er werden geen relevante voorspellers voor afname van kwaliteit van leven gevonden.

In **hoofdstuk 3** verrichtten we een exploratieve prognostische studie naar prognostische factoren voor het optreden autonome symptomen later in het ziektebeloop. Aanwezigheid van non-dopaminerge motorische symptomen en symptomen van angst en depressie bij aanvang van de ziekte verhoogden het risico op autonome symptomen later in de ziekte. We onderzochten daarnaast wat de aanwezigheid van autonome symptomen betekent voor de ziektelast van patiënten met de ZvP. Hierbij bleek dat meer autonome symptomen gepaard ging met meer invaliditeit en lagere kwaliteit van leven. Het is in dit onderzoek niet duidelijk geworden of sprake is van een causaal verband, of dat de invloed op invaliditeit en kwaliteit van leven wordt veroorzaakt door simultaan optredende andere non-dopaminerge symptomen.

In **hoofdstuk 4** ontwikkelden we een predictie-model om de kans op een ongunstig beloop in de eerste vijf jaar na de diagnose ZvP te schatten. Dit model werd ontwikkeld in de data van het CARPA-cohort met nieuw gediagnosticeerde ZvP-patiënten. Een ongunstig beloop werd gedefinieerd als het optreden van houding & balansproblemen, dementie of het overlijden in de eerste vijf jaar na het stellen van de diagnose ZvP. Het uiteindelijke predictiemodel bevatte drie prognostische factoren, waarbij hogere leeftijd, meer non-dopaminerge motorische symptomen (de UPDRS-axiale score) en slechtere verbale fluency (aantal genoemde dierennamen in 60 seconden) allen geassocieerd waren met een hogere kans op een ongunstig beloop. Het model werd extern gevalideerd in het CamPaIGN-cohort met patiënten met nieuw gediagnosticeerde ZvP uit het graafschap Cambridgeshire (Verenigd Koninkrijk). Bij externe validatie was sprake van goede discriminerende eigenschappen en goede kalibratie. Het ontwikkelde model maakt prognosebepaling over de eerste vijf jaar na stellen van de diagnose ZvP mogelijk met een beperkte set aan variabelen welke eenvoudig door artsen of Parkinson-verpleegkundigen verkregen kunnen worden.

In **hoofdstuk 5** bepaalden we met behulp van een systematisch literatuuronderzoek de prevalentie van OH bij de ZvP. Op basis van een meta-analyse van 25 studies was de geschatte prevalentie 30,1% (95% BI: 22,9–38,4). Er werd een hoge heterogeniteit gevonden die niet verkleind kon worden middels het verrichten van diverse subgroep-analyses. Het grootste deel van de oorspronkelijke studies beschreef geïsoleerde studiepopulaties uit academische centra. Om deze redenen is de externe validiteit van de resultaten van de meta-analyse laag en dient de geschatte prevalentie met voorzichtigheid geïnterpreteerd te worden. De review onderstreept de behoefte aan wetenschappelijk onderzoek naar OH bij patiënten die representatief zijn voor de algemene populatie patiënten met de ZvP.

In **hoofdstuk 6** onderzochten wij een representatieve groep patiënten met de ZvP op de aanwezigheid van OH volgens de standaard criteria die hiervoor beschreven zijn. Dit werd gedaan middels continue bloeddrukmeting in liggende en staande positie. Tevens onderzochten wij de mate waarin patiënten in het dagelijkse leven last hebben van orthostatische symptomen met twee vragenlijsten. Hierbij bleek dat er geen goede relatie is tussen de aanwezigheid van OH volgens de standaard criteria en de klachten die patiënten in het dagelijkse leven ervaren. Aanpassing van de afkapwaarden van de standaard OH-criteria of het gebruik van een kanteltafelproef gaf geen verbetering in de relatie tussen de uitslag van de bloeddruktest en de gerapporteerde symptomen. Als belangrijkste mogelijke verklaring voor deze bevindingen opperden wij de hoge variabiliteit van de bloeddrukrespons bij verandering van liggende naar staande positie. Belangrijke boodschap voor de clinicus hierbij is dat een eenmalige orthostatische bloeddruktest in de spreekkamer onvoldoende betrouwbaar is om uit te sluiten dat een patiënt in het dagelijkse leven lijdt aan OH.

In **hoofdstuk 7** onderzochten wij de waarde van enkele andere diagnostische tests voor de integriteit van het autonome zenuwstelsel van patiënten met de ZvP. Hierbij bleek een afwijkende bloeddrukrespons bij een Valsalva manoeuvre geassocieerd met de aanwezigheid van orthostatische klachten in het dagelijkse leven. Daarnaast waren een hogere ^{123}I-*m*IBG hart-mediastinum-ratio met verminderde tracer-uitwas bij cardiale scintigrafie geassocieerd met de aanwezigheid van orthostatische klachten in het dagelijkse leven. Voor beide testen geldt dat de relatief lage discriminerende waarde en de lastige praktische uitvoerbaarheid er voor zorgen dat routinematig gebruik voor diagnostiek bij patiënten met de ZvP niet geadviseerd wordt.

In **hoofdstuk 8** worden de gevonden resultaten in onze studies bediscussieerd in het licht van de bestaande wetenschappelijke literatuur. Er valt op dat er verschil is in het beloop van de ZvP qua dopaminerge en non-dopaminerge symptomen. Het hebben van bepaalde non-dopaminerge symptomen verhoogt het risico voor het optreden van andere non-dopaminerge symptomen. De risicofactoren voor dopaminerge en non-dopaminerge symptomen zijn hiermee verschillend. Dit betekent dat hoewel ze onderdeel van de zelfde ziekte zijn, de pathofysiologie van dopaminerge en non-dopaminerge symptomen deels anders moet zijn. We bediscussiëren de waarde van het predictiemodel en adviseren aanvullende externe validatie in reeds bestaande cohorten waarvan de follow-up duur inmiddels ook langer dan vijf jaar is.
We bediscussiëren het ontbreken van een relatie tussen de aanwezigheid van OH bij een eenmalige bloeddruktest en de orthostatische klachten die patiënten in het dagelijkse leven ervaren. We opperen een strategie om een betere diagnostische test te vinden. In eerste instantie moet de mogelijkheid van continue bloeddrukmeting in de thuissituatie onderzocht worden. Indien dit geen goede test oplevert kan middels transcraniële Doppler onderzocht worden of de cerebrale bloedflow-snelheid tijdens orthostatische stress beter correleert met dagelijkse orthostatische klachten van patiënten met de ZvP.

Contributing authors

CURRENT AFFILIATIONS OF CONTRIBUTING AUTHORS

In alphabetical order

Roger A. Barker
John Van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, UK

Rob M.A. de Bie
Department of Neurology, Amsterdam University Medical Centers (location AMC) & Amsterdam Neuroscience, University of Amsterdam, The Netherlands

Mark Broeders
Stichting Warande, Zeist, the Netherlands

Jonathan R. Evans
Department of Neurology, Queens Medical Centre, Nottingham, UK

Thomas Foltynie
Department of Clinical and Movement Neurosciences, UCL Institute of Neurology, Queen Square, London, UK

Nan van Geloven
Department of Biomedical Data Sciences, Leiden University Medical Center, the Netherlands

David S. Goldstein
Clinical Neurocardiology Section, Clinical Neurosciences Program, Division of Intramural Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA

Rob J. de Haan
Clinical Research Unit, Amsterdam University Medical Centers (location AMC), University of Amsterdam, the Netherlands

C.T. Paul Krediet
Department of Internal Medicine, Amsterdam University Medical Centers (location AMC), University of Amsterdam, the Netherlands

Sarah L. Mason
John Van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, UK

Bart Post
Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands

Ben Schmand
Departments of Neurology & Medical Psychology, Amsterdam University Medical Centers (location AMC), Department of Brain and Cognition & Amsterdam Neuroscience, University of Amsterdam, the Netherlands

Johannes D. Speelman
Department of Neurology, Amsterdam University Medical Centers (location AMC), University of Amsterdam, the Netherlands

Hein J. Verberne
Department of Nuclear Medicine, Amsterdam University Medical Centers (location AMC), University of Amsterdam, the Netherlands

Wouter Wieling
Department of Internal Medicine, Amsterdam University Medical Centers (location AMC), University of Amsterdam, the Netherlands

Luuk Wieske
Department of Neurology, Amsterdam University Medical Centers (location AMC), University of Amsterdam, the Netherlands

Caroline H. Williams-Gray
John Van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, UK

AUTHOR CONTRIBUTIONS

Chapter 2

Study conception and design: B. Post, J.D. Speelman, R.J. de Haan
Acquisition of data: D.C. Velseboer, M. Broeders, B. Post, J.D. Speelman, B. Schmand
Analysis and interpretation of data: D.C. Velseboer, N. van Geloven, R.M.A. de Bie
First draft the manuscript: D.C. Velseboer. All co-authors discussed the results and commented on the manuscript.
Project supervision: R.M.A. de Bie

Chapter 3

Study conception and design: D.C. Velseboer, R.M.A de Bie
Acquisition of data: D.C. Velseboer, B. Post, B. Schmand
Analysis and interpretation of data: D.C. Velseboer, R.J. de Haan, R.M.A. de Bie
First draft the manuscript: D.C. Velseboer. All co-authors discussed the results and commented on the manuscript.
Project supervision: R.M.A. de Bie

Chapter 4

Study conception and design: D.C. Velseboer, R.M.A. de Bie, R.A. Barker, C.H. Williams-Gray
Acquisition of data: D.C. Velseboer, J.R. Evans, S.L. Mason, T. Foltynie, B. Schmand, B. Post, C.H. Williams-Gray
Analysis and interpretation of data: D.C. Velseboer, R.M.A. de Bie, L. Wieske, R.J. de Haan, C.H. Williams-Gray
First draft the manuscript: D.C. Velseboer. All co-authors discussed the results and commented on the manuscript.
Project supervision: R.M.A. de Bie, C.H. Williams-Gray

Chapter 5

Study conception and design: D.C. Velseboer, R.M.A. de Bie
Acquisition of data: D.C. Velseboer, R.M.A. de Bie
Analysis and interpretation of data: D.C. Velseboer, R.M.A. de Bie
First draft the manuscript: D.C. Velseboer. All co-authors discussed the results and commented on the manuscript.
Project supervision: R.M.A. de Bie

Chapter 6

Study conception and design: D.C. Velseboer, B. Post, H.J. Verberne, R.M.A. de Bie
Acquisition of data: D.C. Velseboer
Analysis and interpretation of data: D.C. Velseboer, R.J. de Haan, C.T.P. Krediet, R.M.A. de Bie
First draft the manuscript: D.C. Velseboer. All co-authors discussed the results and commented on the manuscript.
Project supervision: R.M.A. de Bie

Chapter 7

Study conception and design: D.C. Velseboer, H.J. Verberne, B. Post, R.M.A. de Bie
Acquisition of data: D.C. Velseboer, H.J. Verberne
Analysis and interpretation of data: D.C. Velseboer, H.J. Verberne, C.T.P. Krediet, R.J. de Haan, R.M.A. de Bie
First draft the manuscript: D.C. Velseboer. All co-authors discussed the results and commented on the manuscript.
Project supervision: R.M.A. de Bie

Dankwoord

Prof. dr. de Bie, beste Rob, dank voor de continue steun en het voortdurend aanwezige vertrouwen tijdens mijn promotietraject. Ik heb inhoudelijk veel van je geleerd, met betrekking tot wetenschappelijk onderzoek, maar ook in de zorg voor patiënten met de ziekte van Parkinson. Je bent een zeer veelzijdig wetenschapper die telkens weer de klinisch relevante vraagstukken weet aan te stippen. Daarnaast heb ik een enorm voorbeeld aan je gehad als het gaat om vastberadenheid en zorgvuldigheid. Eigenschappen die onmisbaar waren om tot dit uiteindelijke proefschrift te komen. Ik hoop dat je nog vele promovendi zult begeleiden. Ik hoop dat we gezamenlijk op ons werk en privé nog veel mooie momenten mee mogen maken.

Prof dr. van Schaik, beste Ivo, dank voor de mogelijkheden die je me de afgelopen jaren geboden hebt. Je hebt me tijdens mijn promotietraject geholpen om heldere doelen te formuleren die onmisbaar waren om stap voor stap tot dit eindresultaat te komen. Jouw pragmatische visie hierin heeft me geholpen om wat makkelijker over de teleurstellingen heen te komen die bij het promoveren horen. Het was erg fijn dat je me op dezelfde manier bleef steunen toen het allemaal wat langzamer ging.

De overige leden van mijn promotiecommissie: prof. dr. Berendse, prof. dr. Booij, prof. dr. Stam, dr. Thijs, prof. dr. Twisk, dr. van de Velde. Dank dat jullie zitting hebben genomen in mijn commissie en dank voor de tijd die jullie hebben gestoken in het beoordelen van mijn proefschrift. Beste Jan, jou wil ik natuurlijk in het bijzonder ook bedanken voor mijn opleiding tot neuroloog.

Prof. dr. Vermeulen, beste Rien, dank voor de mogelijkheid om op de afdeling neurologie te kunnen starten met dit promotieonderzoek en de opleiding tot neuroloog.

Alle deelnemende Parkinsonpatiënten uit het CARPA-cohort: Ik heb veel bewondering voor jullie trouwe inzet voor dit onderzoeksproject. Het heeft veel van jullie tijd gekost, maar jullie enthousiasme om onbaatzuchtig mee te blijven doen heeft tot mooie resultaten geleid. Ik hoop dat we de toekomstige zorg van patiënten met de ziekte van Parkinson een stukje beter hebben gemaakt. Ook alle neurologen en Parkinson-verpleegkundigen uit de deelnemende ziekenhuizen: veel dank voor jullie inzet. Hans Speelman: veel dank voor de initiatie van de CARPA-studie en de betrokkenheid bij het begin van mijn promotie-traject.

Rob de Haan, je bent bij bijna al mijn artikelen betrokken geweest. Je vond je eigen betrokkenheid vanwege mijn epidemiologie-opleiding steeds minder nodig. Je hebt me echter tot aan het laatste artikel geholpen om de methodologie gestructureerd en begrijpelijk te houden. Ik hoop dat ik het nu echt zelf kan, maar ik zal vast nog wel eens aankloppen. Ik heb erg goede herinneringen aan onze samenwerking.

Bart Post, dat ik bij het begin van dit traject in een gespreid bed ben beland is vooral aan jou te danken. Dankzij jou kon ik met starten op een lopend onderzoek bij een zeer degelijk onderzoekscohort. Je bent daarna ook goed mee blijven denken over het vervolg van het CARPA-project. Ook voor het initiëren van de samenwerking met Cambridge ben ik je veel dank verschuldigd.

Hein Verberne, dank voor de hulp bij het beoordelen van de MIBG-scans. Je bent ook erg belangrijk geweest qua support bij de rest van het orthostatische hypotensie-project.

Neuropsychologen Ben Schmand en Mark Broeders. Ben, dank voor alle hulp met betrekking tot de neuropsychologische resultaten van het onderzoek. Met name over de animal-fluency test heb ik je bij herhaling lastig gevallen. Ik heb er veel van geleerd. Mark, dank voor de fijne samenwerking aan het begin van mijn promotietraject.

Collega's van de interne geneeskunde: Wouter Wieling, dank voor de inspanningen die je hebt geleverd aan het begin van mijn project. Paul Krediet dank voor je kritische meedenken over het orthostatische hypotensie-onderzoek.

Caroline Williams-Gray, thanks for the opportunity to collaborate with your research group. You were really helpful during my stay, making it possible to do the validation-study in a short time-frame.

Alle betrokken (Parkinson-)verpleegkundigen en (oud)medewerkers van het onderzoeksbureau neurologie, in het bijzonder Dorien Standaar, Anick Gorissen, Laura Daeter, Miranda Postma, Gosia Iwan en Stefanie de Vries. Dank voor al het harde werk aan de dataverzameling van het CARPA-cohort. De uitzonderlijk goede follow-up is vooral aan jullie te danken. Annick Fransen, dank voor de secretariële ondersteuning bij de laatste fase van mijn promotie-traject.

Ingeborg Go-Schön & Marianne Cammenga dank voor jullie hulp bij het verrichten en analyseren van de bloeddrukmetingen.

Alle collega neurologen en AIOS neurologie, in het bijzonder de leden van de bewegingsstoornissen-groep: Dank voor de steun en ook de adviezen in de afgelopen jaren. Mijn kamergenoten op H2: Edo, Marc, Vincent, Constant, Sven, Daan, Henrieke en Timo: Dank voor alle gezelligheid en afleiding tijdens mijn fulltime research-tijd. Ik heb erg veel met jullie gelachen en veel geleerd over de randzaken die bij onderzoek komen kijken.

Margreeth Vroom, dank voor de mogelijkheid om een eindsprint te maken om dit proefschrift af te ronden. Alle collega-intensivisten: dank voor de mentale support bij de laatste loodjes, ik verheug me op onze gezamenlijke toekomst op de afdeling.

Jurgen en Marc, ik ben ontzettend blij met onze vriendschappen en ik kon me voor deze dag ook geen betere paranimfen voorstellen dan jullie. Ik hoop dat we nog heel veel mooie dingen gaan meemaken samen en dat we alle drie een fijne carrière tegemoet gaan (waarbij we wel en beetje bij elkaar in de buurt blijven wonen).

Lieve vrienden, familie en schoonfamilie. Dank voor alle morele steun de afgelopen jaren. Jullie bleven al die jaren vol goede moed vragen hoe het met mijn promotie ging, ook al werden mijn antwoorden steeds onbegrijpelijker. Pap en mam, jullie hebben voor mij de basis gevormd van waaruit ik uiteindelijk geneeskunde ben gaan studeren. Jullie hebben mijn vorderingen altijd met interesse gevolgd en ik ben trots om jullie te laten zien dat het nu af is.

Jonas, jouw komst is voor mij een belangrijke motivatie geweest om het boekje eindelijk eens af te maken. Nu het klaar is heb ik veel meer tijd om samen te lachen, te spelen en avonturen te beleven. Mocht je dit ooit nog eens teruglezen: Pappa zegt later misschien tegen je dat promoveren een goed idee is, maar geloof me: Doe het niet!

Lieve Nel, jij bent al die tijd mijn belangrijkste steun geweest. Je was soms in staat om de editor van een tijdschrift te bellen als er weer eens een artikel was afgewezen. Je hebt heel veel cappuccino's voor me gemaakt. Ik bewonder het geduld dat je met me hebt gehad enorm en ben je er ook heel dankbaar voor. Ik verheug me enorm op het proefschrift-vrije leven wat we hierna samen met Jonas tegemoet gaan.

Research portfolio

Name PhD student: D.C. Velseboer
PhD period: January 2009 to November 2018
PhD supervisor: Prof. Dr. R.M.A. de Bie

PhD training

	Year	ECTS
General Courses		
Better use of PubMed (AMC)	2009	0.2
Clinical data management (AMC)	2009	0.3
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2015	0.9
Specific Courses		
Developing a Cochrane systematic review (AMC)	2010	0.3
Advanced Biostatistics (AMC)	2011	2.1
Master of epidemiology (EpidM)	2012	24
Clinimetrics (EpidM)	2018	3
Presentations		
Amsterdamsche Neurologen Vereeniging "Vijf jaar follow-up van een incidentiecohort Parkinson-patiënten - resultaten van de CARPA-studie"	2011	0.5
ParkinsonNet congres "Wat is mijn prognose? Misverstanden over het beloop van de ziekte van Parkinson"	2013	0.5
Amsterdamsche Neurologen Vereeniging "De zin of onzin van bloeddrukmetingen bij de ziekte van Parkinson"	2014	0.5
International conferences		
MDS 13th international congress of Parkinson's Disease and Movement Disorders	2009	1
MDS 14th international congress of Parkinson's Disease and Movement Disorders (including poster presentation)	2010	1.5
MDS 15th international congress of Parkinson's Disease and Movement Disorders (including poster presentation)	2011	1.5
Parkinson Vereniging, Wereld Parkinson dag (including poster presentation)	2011	0.75
Other		
CARPA steering group meetings	2009-2010	1
Research meetings and journal clubs, department of neurology	2009-2016	7

Teaching

	Year	ECTS
Lecturing		
Amstel Academy post-graduate nursing courses in Neurology, Geriatrics and Emergency Medicine.	2009–2016	4
Supervising		
Research internship V. Laurent "Patient perception of deep brain stimulation hardware"	2012	1.0
Research internship J.A. Voncken "Predictors of falling and postural instability in Parkinson's disease"	2013	1.0
Research internship N. ten Den "Disease progression as a prognostic factor for motor impairment in Parkinson's disease"	2014	1.0
Research internship G.M.F.C. Balm "First choice anti-epileptic drug in pregnancy; a risk assessment"	2016	1.0

Parameters of esteem

Grants	Year
Travel stipend "Stichting het Remmert Adriaan Laan fonds"	2014

List of publications

Velseboer DC, Coutinho JM, Müller MC. Blood pressure regulation in acute neurological disorders. A & I 2017;3:20-7. (article in Dutch)

Velseboer DC, de Haan RJ, Post B, Krediet CT, Verberne HJ, de Bie RM. Orthostatic Hypotension in Parkinson's Disease: The Relation of Blood Pressure Tests and Symptoms in Daily Life. Mov Disord Clin Pract 2016;4:329-34.

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Curriculum vitae

Daan Velseboer was born on the 29th of May 1982 in Alkmaar, the Netherlands. He attended secondary school at the Jac. P. Thijsse college in Castricum, from which he graduated in 2000. He studied medicine at the University of Amsterdam and developed a fascination for both Internal Medicine and Neurology. He became a medical doctor in 2008, after which he worked as a resident (not in training) at the department of Internal Medicine of Tergooi hospitals (Hilversum) for one year. In 2009 he started his PhD-project at the department of Neurology of the Academic Medical Center (AMC) in Amsterdam under supervision of prof. dr. R.M.A. de Bie. The results of this project have led to this thesis. In 2011 he started his residency in Neurology at the department of Neurology of the AMC under direction of prof. dr. J. Stam, prof. dr. Y.B.W.E.M. Roos, prof. dr. I.N. van Schaik, and dr. J.H.T.M. Koelman. He finished a master in epidemiology (EpidM, Free University, Amsterdam) in 2012. In 2017 he became registered as a Neurologist and started a fellowship Intensive Care medicine at the AMC which he finished in July 2018. He is currently employed as a Neurologist-Intensivist at the Intensive Care department of the Amsterdam University Medical Centers (location AMC). Daan is married to Nel van Woerden and they have a one-year old son Jonas.