Clinical Predictors of disease progression in Parkinson's disease

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Chapter 7:

Onset and evolution of anxiety in Parkinson's disease

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Published in *European Journal of Neurology* 2017;24:404-411

ABSTRACT

Background. Anxiety is common in Parkinson's disease (PD) and has great influence on quality of life. However, little is known about risk factors for development of anxiety in PD.

Objectives. To investigate which factors are associated with longitudinal changes in severity of anxiety symptoms and development of future anxiety in non-anxious patients at baseline.

Methods. Analyses were performed in data of the SCOPA-PROPARK cohort, a 5-year hospital-based longitudinal cohort of over 400 PD patients who have been examined annually. Linear mixed models was used to identify factors associated with longitudinal changes in Hospital Anxiety and Depression Scale – Anxiety (HADS-A) scores. Survival analysis using data of non-anxious patients at baseline was performed to identify predictors for future anxiety (i.e. HADS-A ≥11).

Results. Of 409 patients included at baseline, 67 (16%) had anxiety, whereas 64 (19%) of the remaining 342 non-anxious patients developed anxiety after a mean (SD) follow-up of 2.6 (1.3) years. Seventy percent of the patients with anxiety were also depressed. Female gender, cognitive impairment, depressive symptoms, dysautonomia, insomnia and excessive daytime sleepiness (EDS) at baseline were associated with higher HADS-A scores over time and, except for female gender and EDS, all these variables were independent predictors of development of anxiety in non-anxious patients at baseline. *Conclusions.* Anxiety is highly prevalent in PD. Higher anxiety scores over time and future development of anxiety are associated with female gender, cognitive impairment, autonomic dysfunction, insomnia and EDS. Anxiety and depression usually co-exist and share similar determinants, suggesting a common pathophysiological mechanism.

INTRODUCTION

Anxiety and depression are common in Parkinson's disease (PD) and these features have profound consequences for a patient's health and mental well-being over the disease course.[1] A recent systematic review found an average point prevalence of anxiety disorders in PD of 31%.[2] Anxiety may be non-episodic and episodic in nature; it may vary with the severity of motor fluctuations and situational anxiety may be related to motor deficits caused by, for example, fear of falling due to freezing [3]. Anxiety and depression often co-occur in PD, and even though anxiety has a greater influence on the quality of life of PD patients,[1,4] studies in the past have mainly focused on depression and little is known about risk factors for anxiety in PD.

Most research on anxiety in PD has been cross-sectional in nature.[3,4,6-9] Similar to findings in the general population, these studies reported a more frequent occurrence of anxiety symptoms in female patients.[5] PD-specific factors found associated with anxiety include longer disease duration, younger age-at-onset, dysautonomia, motor fluctuations and impairment in activities of daily living.[3,4,6-8] Due to the heterogeneity of factors examined and the inconsistent findings across studies, definite conclusions regarding the role of some factors (e.g. disease severity, motor fluctuations) remain difficult.[3,4,6-8] Another disadvantage of cross-sectional studies is that the time relation between potential risk factors and emergence of anxiety is obscured. Hitherto, only one longitudinal study on anxiety in PD has been performed.[9] In this study, 89 mildly affected patients were followed over a relatively short period of 1.5 years. However, identification of risk factors ideally requires a large cohort that is followed up long enough until a sufficient number of anxiety cases has developed. The PROPARK cohort includes over 400 PD patients who have been examined annually and followed for five years.[10] This cohort is therefore well-suited to investigate which factors are associated with: 1) longitudinal changes in severity of anxiety symptoms; and 2) development of future anxiety in patients who are free of this symptom at baseline.

METHODS

Study design and participants

The study design has been described in detail elsewhere.[10] In brief, patients were recruited from neurology clinics of university and regional hospitals in the western part of The Netherlands and all fulfilled the United Kingdom Parkinson's disease Society Brain Bank criteria for idiopathic PD.[11] In view of the fact that we aimed to obtain information on the full spectrum of the disease, a recruitment strategy based on age-at-onset (< or ≥50 years) and disease duration (< or ≥10 years) was applied, which resulted in four different strata that were aimed at containing at least 100 patients each.[10] In view of the fact that we aimed to obtain information on the full spectrum of the disease, a recruitment strategy based on age-at-onset (< or ≥50 years) and disease duration (< or ≥10 years) was applied, which resulted in four different strata that were aimed at containing at least 100 patients each.[10]

Assessment of baseline variables

At baseline (2003-2005) and the five subsequent annual visits all patients received standardized assessments. These included an evaluation of demographic and clinical characteristics, family history of PD, and registration of antiparkinsonian medication. A levodopa dose equivalent (LDE) of daily levodopa and dopamine agonists dose was calculated for each patient at baseline.[11] Diagnosis of PD and the patient's Hoehn & Yahr (H&Y) stage were ascertained at every assessment.[12]

The following instruments were administered by qualified examiners: the SPES/SCOPA[13] (including sections on motor examination, activities of daily living (ADL) and motor complications), SCOPA-COG (cognition),[14] and SCOPA-PC (psychotic symptoms).[15] All patients with dopaminergic medication were assessed during "on''. Motor subtype was determined by calculating a ratio of tremor score (SPES/SCOPA)[13] over PIGD score (SPES/SCOPA).[14] Patients with a ratio <1.0 were classified as PIGD-dominant, whereas those with values of ≥1.0 were classified as non-PIGD-dominant.[16]

Patients completed the following instruments: the SCOPA-AUT (autonomic domains: gastrointestinal, urinary tract and cardiovascular),[17] SCOPA-SLEEP (nighttime sleep [NS] and daytime sleepiness [DS])[18] and Beck Depression Inventory (BDI).[19] For all instruments except SCOPA-COG, higher scores reflect poorer functioning.

Ascertainment of anxiety

Anxiety was assessed using the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS).[20] This scale focusses on the non-somatic features of anxiety and its clinimetric properties for use in PD are very satisfactory.[21] The HADS-A includes 7 items that measure severity of anxiety symptoms over the previous 2 weeks; all items are rated on a 4-

point scale (0-3), with higher scores indicating more severe anxiety. To minimize the number of false-positive cases and obtaining maximum certainty regarding the anxiety cases, a score of ≥11 was considered as 'having anxiety'.[21] To verify robustness of this method, all analyses have been repeated with a cut-off score of ≥8.

Statistical analysis

For objective 1 a linear mixed models (LMM) analysis was performed using data of all patients included in the follow-up. This method allows for the identification of variables that are associated with variations in HADS-anxiety scores over time. A restricted maximum likelihood model with an autoregressive (heterogeneous) covariance structure type was used in all LMM analyses and since heterogeneity between patients was expected in baseline levels and in change over time, random intercepts and random slopes were used. Variables that have been found associated with anxiety in earlier studies were considered in the LMM. H&Y stage was not included because it is partly determined by motor phenotype. BDI scores were not included in the primary LMM analysis due to the strong correlation with anxiety as found in earlier studies;[22] inclusion of such a strongly associated variable could obscure the relationship of anxiety with other potentially interesting variables. In addition, to determine the degree of correlation between anxiety and depression, depression rates were determined in patients with anxiety at baseline and in patients who developed anxiety during follow-up. In a secondary analysis, however, the effect of including the BDI score on the model was examined.[23] The relationship between variables that are associated with variation in HADS-anxiety scores over time were first analyzed including one variable at a time (unadjusted model). Subsequently an adjusted model was performed in which the main effects of all significant baseline variables from the unadjusted model were entered. The final model only includes variables that were significant from the adjusted model.

For objective 2 we performed a survival analysis in data of patients without anxiety at baseline using the same variables that were included in the LMM. Survival time was calculated as the difference in years between the date on which anxiety was first reported and the date of the patient's baseline assessment. Patients were considered to have an event ('uncensored') if they scored ≥11 on the HADS-anxiety scale. If a patient did not have an event during follow-up, he or she was 'withdrawn alive' and classified as 'censored'. In case a patient had missed one year and had no anxiety in the previous and following year, we assumed that the patient had not developed anxiety in that year. A similar approach as used for the LMM was employed to adjust for the potential influence of confounders. As before, the effect of including the baseline BDI score on the model was examined in a secondary analysis. Risk factors were calculated as hazard ratios (HR) with 95% confidence

intervals (CI), with a HR >1 indicating that a baseline variable was associated with a higher risk of developing anxiety.
Since antidepressant or benzodiazepine use might have a potential effect on anxiety severity, these variables were included as covariates in the LMM and survival analysis. Analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 21.0.

RESULTS

Of the 409 patients at baseline, 67 (16%) were classified as suffering from anxiety, whereas 342 (84%) were not (figure 1). Of those not suffering from anxiety at baseline, 64 (19%) developed this symptom after a mean (SD) follow-up of 2.6 (1.3) years.

Study Sample

For details on the baseline study sample, see Table 7.1.

Co-existing anxiety and depression

Seventy percent of patients with anxiety at baseline also fulfilled the criteria for depression (BDI≥15). During follow-up of patients without anxiety at baseline (N=342), 43 of 64 (67%) patients who subsequently developed anxiety also qualified for depression. No additional survival analysis was performed on this group due to insufficient power.

Figure 7.1: Flow Chart of follow-up for anxiety

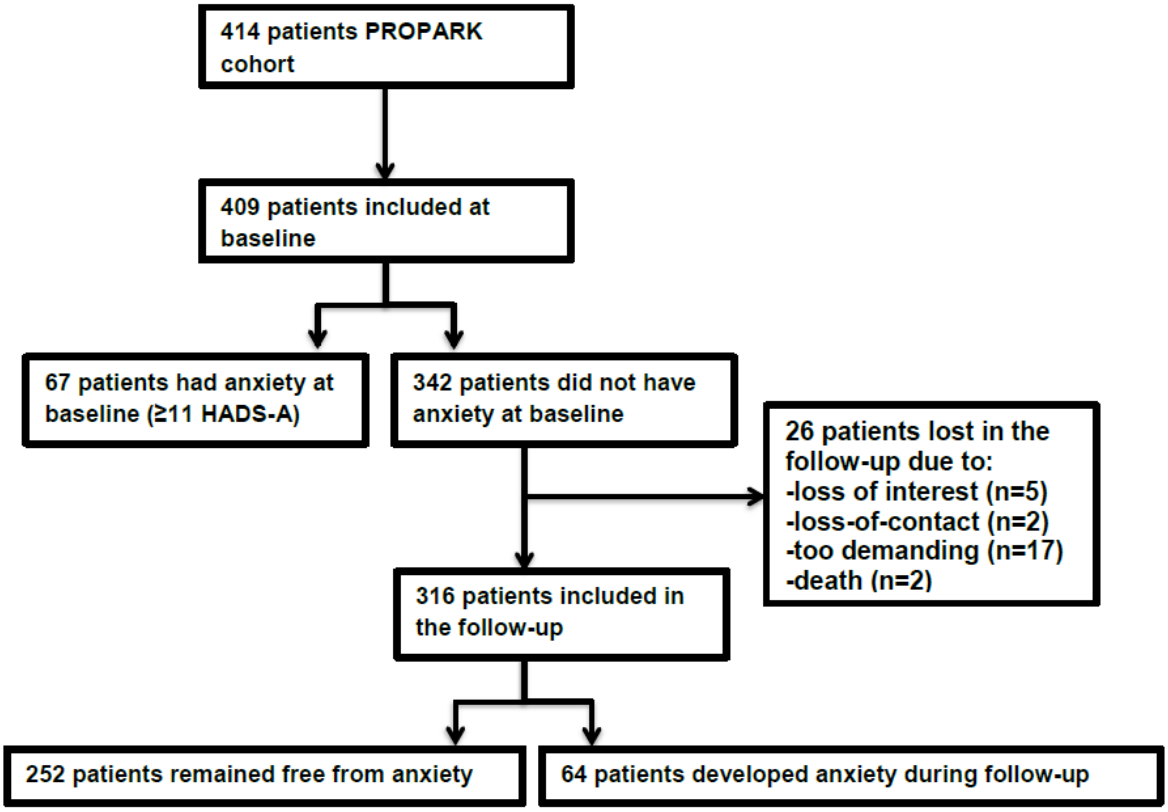

Table 7.1: Baseline data of patients with and without anxiety

	Total	With anxiety	Without anxiety	p-values
N	409	67	342	
Age, yr	61.14 (11.37)	62.38 (12.85)	60.86 (11.07)	.32
Sex, % female	35.9	55.2	32.2	<.001[a]
Age at onset, yr	50.53 (11.89)	51.56 (12.08)	50.35 (11.89)	.45
Disease duration, yr	10.62 (6.53)	10.82 (5.94)	10.50 (6.62)	.71
Hoehn & Yahr, stage	2 (2,3)	3 (2,4)	2 (2,3)	<.001[b]
SPES/SCOPA-Motor Impairment	13.49 (4.95)	15.10 (5.42)	13.16 (4.79)	.004
SPES/SCOPA-Dyskinesia	0.94 (1.62)	0.94 (1.52)	0.93 (1.62)	.96
SPES/SCOPA-Motor Fluctuations	0.78 (1.26)	1.09 (1.47)	0.70 (1.19)	.04
SPES/SCOPA-ADL	8.92 (3.56)	9.75 (3.97)	8.71 (3.45)	.03
PIGD dominant phenotype, %	44.2	58.1	39.9	.008[a]
BDI score	10.21 (6.57)	18.17 (7.25)	8.64 (5.22)	<.001
No. (%) meeting depression criteria	86 (21.0)	46 (68.7)	40 (11.7)	<.001[a]
HADS Anxiety score	6.54 (3.63)	12.73 (1.68)	5.33 (2.49)	<.001
SCOPA-COG score[c]	25.71 (6.21)	23.41 (5.63)	26.21 (6.21)	.001
SCOPA-SLEEP-NS score[d]	4.51 (3.77)	6.15 (4.30)	4.17 (3.57)	.001
SCOPA-SLEEP-DS score[d]	4.87 (3.73)	6.20 (3.70)	4.62 (3.70)	.002
SCOPA-AUT, GI score[e]	2.72 (2.20)	3.79 (2.36)	2.50 (2.11)	<.001
SCOPA-AUT, CV score[e]	1.16 (1.19)	1.76 (1.30)	1.02 (1.10)	<.001
SCOPA-AUT, UR score[e]	6.72 (4.02)	8.39 (4.48)	6.36 (3.81)	.001
Hallucinations, % with	16.5	29.0	14.2	.004[a]
Antidepressants, % with	14.7	23.9	12.9	.02[a]
Benzodiazepine, % with	22.1	44.8	17.6	<.001[a]
Total LDE, mg/day	608 (463)	575 (395)	609 (475)	.54
LDE-Dopa, mg/day	380 (375)	367 (342)	378 (381)	.82
LDE-DA dose, mg/day	231 (226)	208 (218)	233 (227)	.42

Variables are expressed as means (standard deviations), except for gender (percentages), motor subtype (percentages), Hoehn and Yahr stage (median ((interquartile range)). All differences are calculated with the independent-samples t-tests, except for
a Chi-square test and b Mann-Whitney U test.
c SCOPA-COG: cognitive function, higher scores reflect better functioning.
d SCOPA-SLEEP, NS score: nighttime sleep problems; DS score: daytime sleepiness
e SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).
Abbreviations: DBS, Deep Brain Surgery; ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; LDE, Levodopa dosage equivalent; DA, dopamine agonists.

Variables associated with longitudinal changes in HADS-anxiety score (LMM analysis)
The final model of the LMM analysis showed that female gender, more cognitive impairment, and more severe insomnia, EDS and dysautonomia at baseline were associated with higher HADS-anxiety scores over time (Table 7.2). The secondary analysis including the BDI-score showed that baseline BDI-score was associated with higher anxiety scores over time in the final analysis (B (95%CI)=0.28 (0.24-0.32), p<.001). Female gender, cognitive dysfunction and the cardiovascular domain of autonomic dysfunction remained significant, while insomnia and the gastrointestinal domain of autonomic dysfunction did not, suggesting a strong shared covariance between these two factors and depression.

Risk factors for future development of anxiety (survival analysis)
The multivariate Cox proportional hazards' model showed that more cognitive impairment, insomnia and autonomic dysfunction (cardiovascular domain) were independent predictors for future development of anxiety in patients not suffering from anxiety at baseline (Table 7.3).
The secondary analysis including the baseline BDI-score showed that baseline BDI-score was an independent predictor of anxiety (HR(95%CI)=1.12 (1.07-1.17), p<.001). Insomnia and the cardiovascular domain of autonomic dysfunction remained significant, while cognitive impairment did not. Repeating the analysis with a cut-off score of ≥8 showed that the same variables emerged as significant in the final model (Table 7.4).

Table 7.2: Factors associated with higher HADS-A scores over time in patients with PD

	Unadjusted Model		Adjusted Model		Final Model	
Variable	**B (95%CI)**	**P**	**B (95%CI)**	**P**	**B (95%CI)**	**P**
Age	0.04 (0.01-0.06)	.01[d]	-0.03 (-0.06-0.01)	.04[d]	-0.03 (-0.05-0.01)	.05
Female gender	1.37 (0.73-2.02)	<.001[d]	0.72 (0.10-1.34)	.02[d]	0.67 (0.12-1.22)	.02[d]
Disease duration in years	0.05 (0.01-0.10)	.04[d]	-0.07(-0.12- -0.02)	.01[d]	-0.04 (-0.08-0.01)	.05
SPES/SCOPA–Motor Impairment	0.18 (0.12-0.24)	<.001[d]	0.07 (-0.01- 0.15)	.10		
SPES/SCOPA – ADL	0.29 (0.20-0.37)	<.001[d]	0.01 (-0.12-0.15)	.85		
SPES/SCOPA – Dyskinesia	0.28 (0.09-0.48)	.01[d]	0.01 (-0.20-0.23)	.89		
SPES/SCOPA – Motor Fluctuations	0.51 (0.26-0.76)	<.001[d]	0.20 (-0.07-0.47)	.15		
PIGD dominant phenotype	1.49 (0.85-2.13)	<.001[d]	0.23 (-0.39-0.86)	.47		
SCOPA-COG score[a]	-0.16 (-0.21--0.11)	<.001[d]	-0.11(-0.16- -0.05)	<.001[d]	-0.11(-0.16- -0.06)	<.001[d]
Presence of hallucinations	1.92 (1.09-2.75)	<.001[d]	0.66 (-0.13-1.44)	.10		
SCOPA-SLEEP-NS score[b]	0.28 (0.21-0.36)	<.001[d]	0.10 (0.02-0.19)	.02[d]	0.15 (0.07-0.22)	<.001[d]
SCOPA-SLEEP-DS score[b]	0.26 (0.16-0.33)	<.001[d]	0.09 (0.01-0.18)	.03[d]	0.13 (0.05-0.20)	.001[d]
SCOPA-AUT[c] GI score	0.52 (0.38-0.66)	<.001[d]	0.17 (0.01-0.32)	.03[d]	0.18 (0.05-0.31)	.01[d]
SCOPA-AUT[c] CV score	1.16 (0.92-1.41)	<.001[d]	0.61 (0.34-0.89)	<.001[d]	0.66 (0.42-0.90)	<.001[d]
SCOPA-AUT[c] UR score	0.27 (0.20-0.35)	<.001[d]	0.06 (-0.02-0.15)	.13		
Daily levodopa dose, p/100mg	0.15 (0.06-0.23)	.001[d]	-0.01 (-0.01-0.01)	.88		
Daily DA dose, p/100 mg	-0.03 (-0.17-0.11)	.71				
Use of benzodiazepines, yes/no[e]	2.44 (1.71-3.16)	<.001[d]	0.94 (0.21-1.67)	.01[d]	1.15 (0.47-1.84)	.001[d]
Use of antidepressants, yes/no[e]	1.89 (1.02-2.76)	<.001[d]	1.47 (0.67-2.28)	<.001[d]	1.22 (0.47-1.98)	.002[d]

Estimates are presented as B with 95% confidence intervals (CI), where a positive value is associated with a positive relationship between the baseline variable and HADS-A scores.
Abbreviations: HADS-A, Hospital Anxiety and Depression Scale-Anxiety; ADL, activities of daily living; PIGD, postural instability gait difficulty; DA, dopamine agonists.

[a] *SCOPA-COG: cognitive function, higher scores reflect better functioning.*
[b] *SCOPA-SLEEP, NS score: nighttime sleep problems. DS score: daytime sleepiness*
[c] *SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
[d] *significant values*
[e] *these variables were only included as a covariate in a secondary LMM analysis to correct for possible confounding effect of medication use. exact same variables were significant from the final analysis.*

Table 7.3: Longitudinal risk factor analysis of the development of anxiety (≥11 HADS-A) in patients without anxiety at baseline

	Unadjusted Model		Adjusted Model		Final Model	
	HR (95%CI)	**P**	**HR (95%CI)**	**P**	**HR(95%CI)**	**P**
Age, p/yr increase	1.03 (1.01-1.05)	.01[d]	1.01 (0.98-1.04)	.68		
Gender, HR for females	1.54 (0.94-2.52)	.09				
Disease duration, p/yr increase	1.03 (0.99-1.07)	.11				
SPES/SCOPA – Motor Impairment	1.09 (1.04-1.15)	.001[d]	1.01 (0.94-1.09)	.77		
SPES/SCOPA – ADL	1.16 (1.08-1.25)	<.001[d]	1.10 (0.95-1.27)	.22		
SPES/SCOPA – Dyskinesia	1.23 (1.09-1.40)	.001[d]	0.99 (0.83-1.17)	.89		
SPES/SCOPA – Motor Fluctuations	1.20 (1.00-1.45)	.05				
Motor phenotype, HR for PIGD dominant	1.68 (0.99-2.84)	.05				
SCOPA-COG[a], p/point increase	0.93 (0.89-0.97)	.001[d]	0.94 (0.89-0.99)	.03[d]	0.93 (0.89-0.97)	.002[d]
Presence of hallucinations, yes/no	2.25 (1.24-4.09)	.008[d]	1.34 (0.68-2.64)	.40		
SCOPA-SLEEP-NS[b], p/point increase	1.17 (1.10-1.24)	<.001[d]	1.11 (1.03-1.20)	.006[d]	1.15 (1.08-1.23)	<.001[d]
SCOPA-SLEEP-DS[b], p/point increase	1.09 (1.03-1.16)	.003[d]	1.00 (0.93-1.07)	.92		
SCOPA-AUT, GI[c] score p/point increase	1.27 (1.15-1.41)	<.001[d]	1.07 (0.96-1.21)	.24		
SCOPA-AUT, CV[c] score p/point increase	1.72 (1.43-2.08)	<.001[d]	1.35 (1.06-1.72)	.02[d]	1.45 (1.18-1.79)	<.001[d]
SCOPA-AUT, UR[c] score p/point increase	1.13 (1.07-1.20)	<.001[d]	1.05 (0.96-1.11)	.37		
Daily levodopa dose, p/100mg increase	1.10 (1.03-1.16)	.003[d]	0.96 (0.89-1.04)	.29		
Daily DA dose, p/100 mg increase	1.04 (0.94-1.16)	.43				
Use of benzodiazepines, yes/no[e]	2.00 (1.14-3.49)	.02[d]	1.09 (0.56-2.13)	.80		
Use of antidepressants, yes/no[e]	1.65 (0.88-3.01)	.12				

All variables are expressed as hazard ratio (HR) with 95% confidence interval (CI).
Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; DA, dopamine agonists.

a SCOPA-COG: cognitive function, higher scores reflect better functioning.
b SCOPA-SLEEP, NS score: nighttime sleep problems. DS score: daytime sleepiness.
c SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).
d significant values
[e] these variables were only included as a covariate to correct for possible confounding effect of medication use

Table 7.4: Longitudinal risk factor analysis of the development of anxiety (≥8 HADS-A)* in patients without anxiety at baseline

	Unadjusted Model		Adjusted Model		Final Model	
	HR (95%CI)	**P**	**HR (95%CI)**	**P**	**HR(95%CI)**	**P**
Age, p/yr increase	1.02 (1.01-1.04)	.01[d]	1.00 (0.97-1.02)	.86		
Gender, HR for females	1.08 (0.71-1.64)	.74				
Disease duration, p/yr increase	1.01 (0.98-1.04)	.44				
SPES/SCOPA – Motor Impairment	1.06 (1.01-1.11)	.02[d]	1.04 (0.97-1.11)	.34		
SPES/SCOPA – ADL	1.08 (1.02-1.15)	.01[d]	0.98 (0.88-1.10)	.75		
SPES/SCOPA – Dyskinesia	1.12 (1.00-1.26)	.06				
SPES/SCOPA – Motor Fluctuations	1.01 (0.84-1.21)	.96				
Motor phenotype, HR for PIGD dominant	1.01 (0.64-1.59)	.97				
SCOPA-COG[a], p/point increase	0.94 (0.91-0.97)	.001[d]	0.95 (0.91-0.99)	.03[d]	0.94 (0.91-0.98)	.001[d]
Presence of hallucinations, yes/no	1.65 (0.92-2.97)	.10				
SCOPA-SLEEP-NS[b], p/point increase	1.09 (1.03-1.14)	.002[d]	1.08 (1.02-1.15)	.008[d]	1.09 (1.04-1.15)	.001[d]
SCOPA-SLEEP-DS[b], p/point increase	1.10 (1.05-1.16)	<.001[d]	1.06 (1.00-1.12)	.06		
SCOPA-AUT, GI[c] score p/point increase	1.19 (1.08-1.30)	<.001[d]	1.07 (0.96-1.18)	.24		
SCOPA-AUT, CV[c] score p/point increase	1.41 (1.18-1.69)	<.001[d]	1.33 (1.07-1.64)	.01[d]	1.30 (1.07-1.59)	.008[d]
SCOPA-AUT, UR[c] score p/point increase	1.09 (1.03-1.15)	.002[d]	1.00 (0.94-1.07)	.96		
Daily levodopa dose, p/100mg increase	1.08 (1.03-1.14)	.004[d]	1.04 (0.98-1.11)	.20		
Daily DA dose, p/100 mg increase	0.97 (0.89-1.06)	.55				
Use of benzodiazepines, yes/no[e]	1.58 (0.94-2.64)	.08				
Use of antidepressants, yes/no[e]	0.95 (0.51-1.79)	.88				

All variables are expressed as hazard ratio (HR) with 95% confidence interval (CI).
Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; DA, dopamine agonists.

**At baseline, 138 patients were classified as anxious (HADS-A≥8). 271 patients were included in the follow-up analysis, of whom 96 (35%) developed this symptom after a mean (SD) follow-up of 2.3 (1.3) years.*

[a] SCOPA-COG: cognitive function, higher scores reflect better functioning.
[b] SCOPA-SLEEP, NS score: nighttime sleep problems. DS score: daytime sleepiness.
[c] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).
[d] significant values
[e] these variables were only included as a covariate to correct for possible confounding effect of medication use

DISCUSSION

We found a baseline prevalence rate for anxiety of 16%, which is lower than earlier reported rates.[4,6,7] One potential explanation for this finding is that we used a more conservative cut-off of 10/11 ('probable anxiety') instead of 7/8 ('possible anxiety'), which could have led to an underestimation. In addition, other studies applied different tools.[7] Of note is that if we applied the lower cut-off of 7/8, the prevalence rate would have been 34%, which corresponds with those from earlier studies.[6,7]

An important strength is that our study is the largest longitudinal study on this subject so far.[6-9] Interestingly, predictors of anxiety that emerged from this study corroborate with those identified in our study on predictors of depression.[23] The finding of a common set of predictors for both conditions along with the fact these disorders co-occurred in 70% of the patients, hints at a shared pathophysiological pathway. Earlier studies also reported co-occurrence of anxiety and depression in 14-41% of PD patients.[4,6-8] In addition, our second LMM analysis with the BDI score included, showed that depressive symptoms were significantly associated with higher anxiety scores over time in the final LMM analysis and survival analysis. Together these findings support the assumption that anxiety and depression share a common pathophysiological mechanism.

Our study identified dysautonomia, i.e. cardiovascular and gastrointestinal dysfunction, as risk factors of anxiety in PD. An association between anxiety and dysautonomia in PD was found in an earlier study, in which the authors compared the prevalence of dysautonomia in 32 PD patients and healthy controls, and examined the relation with anxiety and depression.[8] Our study confirms that this relationship is also present longitudinally, which may reflect an association by environment since anxiety and certain autonomic symptoms (e.g. sweating, dizziness, palpitations) frequently co-occur.[24] Moreover, dysautonomia is a criterion for the diagnosis of panics attacks.[25] In agreement with most earlier studies, severity of motor impairment and disability were not associated with severity of anxiety over time.[3,7]

We further found that EDS and cognitive dysfunction were longitudinally associated with anxiety symptoms. Previous studies on anxiety in PD did not evaluate cognition or excluded patients with cognitive dysfunction,[26] rendering any conclusion on the relation between cognition and anxiety in PD difficult. However, findings of earlier studies show that depressive symptoms are part of a robust coherent complex of features (cognitive dysfunction, EDS, hallucinations, dysautonomia, and PIGD), which largely do not improve on dopaminergic medication. This complex of predominantly nondopaminergic (PND) features, which is present early in the disease course and worsens with advancing disease, are assumed to reflect progression of Lewy body pathology in the peripheral and central nervous system.[27,28] Against this background, the strong relation between anxiety and depression,

likely suggests that anxiety is yet another component of this PND symptom complex. Collectively, our findings suggest that patients harboring manifestations of the PND complex are more likely to develop anxiety.

Since patients in our cohort were treated with best clinical practice, it is not surprising that 45% of all patients with anxiety at baseline were treated with benzodiazepines and 24% were treated with antidepressants. Although we corrected antidepressant/benzodiazepine use in our analyses, an underestimation of anxiety symptoms still might have occurred.

Limitations of our study relate to the fact that our cohort is hospital-based, which may have resulted in some under- or overestimation, although it seems unlikely that this has led to significant distortion of our conclusions. Another limitation is that we did not establish the anxiety diagnosis according to the Diagnostic and Statistical Manual of Mental disorders criteria,[25] which precluded the identification of the subcategory of anxiety disorder (e.g. social phobia). It may also have led to misclassification of patients in the survival analysis, but we have no reasons to assume that any potential misclassification is systematic, and, given that non-differential misclassification of a dichotomous variable will always bias the effect, if there is one, towards the null value, some effects may have been underestimated, but not overestimated.

In conclusion, anxiety is highly prevalent in PD. Female patients with cognitive impairment, autonomic dysfunction, insomnia and EDS are at risk to develop more severe anxiety symptoms. Anxiety and depression usually co-exist and share similar determinants, which suggest a common pathophysiological mechanism.

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