Clinical Predictors of disease progression in Parkinson's disease

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Chapter 4:

Course and risk factors for excessive daytime sleepiness in Parkinson's disease

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ABSTRACT

Introduction. Excessive daytime sleepiness (EDS) is a common feature of Parkinson's disease (PD) that contributes to the disease burden and increases risk of harm. The aim of this study was to examine persistency, cross-sectional and longitudinal associations, and risk factors for EDS in patients with PD. *Methods.* Analyses were performed on data from the SCOPA-PROPARK cohort, a 5-year hospital-based longitudinal cohort of over 400 PD patients who were examined annually. Cross-sectional analyses were conducted to evaluate differences between patients with and without EDS at baseline, while linear mixed models using data of all patients were used to identify factors associated with longitudinal changes in SCOPA-SLEEP-Daytime Sleepiness (SCOPA-SLEEP-DS) scores. A survival analysis was done using data of patients without EDS at baseline to identify risk factors for future EDS. *Results.* EDS proved a non-persistent symptom, although persistency and the proportion of patients with EDS increased with longer follow-up. At baseline 43% of patients had EDS, while 46% of patients without EDS at baseline developed this symptom during follow-up. Male gender, poorer nighttime sleep, cognitive and autonomic dysfunction, hallucinations, less severe dyskinesias, dose of dopamine agonists and use of antihypertensives were associated with higher EDS scores over time, while use of benzodiazepines was associated with lower scores. Baseline SCOPA-SLEEP-DS score and PIGD phenotype were risk factors for future EDS. *Conclusions.* With longer disease duration a large proportion of patients develop EDS. Some risk factors are modifiable and patients should be monitored to improve quality of life and reduce risk of harm.

INTRODUCTION

Excessive daytime sleepiness (EDS) is a common feature of Parkinson's disease (PD), which can affect up to 50% of patients.[1] The American Academy of Sleep Medicine defines EDS as the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least three months.[2] EDS in PD contributes significantly to the disease burden, and increases the risk of harm to patients.[3] Understanding the risk factors for EDS may help to prevent, identify, and target interventions to the correct patients. Earlier studies found that the presence of EDS is associated with dopamine agonist (DA) use, higher age, male gender, advanced disease, the postural-instability-gait-difficulty (PIGD) motor phenotype, insomnia, hallucinations, cognitive decline and depression.[4,5] Information on the relation between EDS and the use of medications such as antidepressants, antihypertensives and benzodiazepines, which are known to cause sleepiness in the general population, is scarce in PD.[6,7] The results on associated variables and predictors for EDS from previous studies were often inconsistent, likely due to small sample sizes and methodological differences between these studies.[4,5] Furthermore, most previous studies on EDS in PD had a cross-sectional design and to date only two longitudinal studies have been performed.[4,5] One study (n=131) showed that 23% of patients who were free of EDS developed this feature during a four year follow-up period and that the presence of EDS was associated with more severe disability and cognitive impairment. Although this study had a longitudinal setup, data of patients with EDS at baseline were pooled with those who developed EDS during follow-up, after which they were compared to those of patients who had no EDS at both time points. This strategy therefore actually involved a cross-sectional comparison and the data provide limited information on features that are related to changes in EDS over time.[5] The other study (n=153) - performed in early, initially drug naïve patients - found that the occurrence of EDS increases with disease progression and that its presence is not a persistent feature but instead may fluctuate over time; they further found that EDS severity is associated with male gender, depression, ADL disability and DA use.[4] Large longitudinal studies on EDS in more advanced PD are lacking. The PROPARK cohort study includes over 400 PD patients who have been examined annually and followed for five years (i.e., six assessments), which makes this study very well-suited for the purpose of identifying factors associated with (the development of) EDS in PD.

METHODS

The PROPARK cohort

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.[8] The majority of patients were evaluated at the Leiden University Medical Center, but more severely affected patients were offered the possibility to be examined at their homes to prevent selective drop-out. In view of the fact 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. We intended to recruit at least 100 patients in each of the four strata.[9] The medical ethical committee of the Leiden University Medical Center approved the PROPARK study and written informed consent was obtained from all patients.[9]

Measures and assessments

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. The total LDE is the sum of the levodopa dosage equivalent (LDE-Dopa) and the dopamine agonist dosage equivalent (LDE-DA).[10] Diagnosis and Hoehn & Yahr (H&Y) stages of the patients were ascertained at every assessment.[11] The following instruments were administered by qualified examiners: the SPES/SCOPA (including sections on motor examination, activities of daily living and motor complications),[12] the SCOPA-COG (cognitive function),[9] and the SCOPA-PC[13] (psychotic symptoms; items 1-5). Over the years, there were in total five examiners, who all regularly attended retraining and recalibration sessions to prevent inter-rater variability. All patients who used dopaminergic medication were assessed during “on’’. Patients completed the following instruments themselves: the SCOPA-AUT (three autonomic domains: gastrointestinal, urinary tract and cardiovascular),[14] the SCOPA-SLEEP (with sections on nighttime sleep problems [NS] and daytime sleepiness [DS]),[15] and the Beck Depression Inventory (BDI).[16] For all instruments except the SCOPA-COG, higher scores reflect poorer functioning. Patients were classified according to motor subtype using a ratio of tremor score (SPES/SCOPA) over PIGD score (SPES/SCOPA).[9,17] A total tremor or PIGD score of 0 was replaced by 0.5. Patients with a ratio value <1.0 were classified as PIGD dominant, whereas those with values from 1.0 were classified as non-PIGD dominant.[9,17]

Ascertainment of excessive daytime sleepiness

EDS was assessed using the daytime sleepiness (DS) section of the SCOPA-SLEEP questionnaire.[15] The SCOPA-SLEEP-DS evaluates daytime sleepiness in the past month, and includes six items with four response options [0 (never) to 3 (often)], with a maximum score of 18 and mainly focuses on falling asleep in unexpected or unwanted situations. Patients were considered to suffer from EDS if they scored 5, according to earlier suggested cut-offs.[15]

Statistical analysis

The objectives of the analyses of this study are: 1) to examine which factors are associated with the presence of EDS; 2) to evaluate which variables are associated with longitudinal variation in EDS scores; and 3) to identify risk factors for future development of EDS. To this end we first evaluated which features were associated with the presence of EDS in the baseline data of our population (objective 1). For objective 2 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 variation in SCOPA-SLEEP DS scores over time. LMM takes into account that repeated measures in the same subject are not independent but correlated. Baseline variables that have been found associated with EDS in earlier studies were considered in the LMM. These included: age, gender, disease duration, sumscore of motor impairment and activities of daily living (SPES/SCOPA), motor phenotype, presence of hallucinations (score 1 on item 1 of the SCOPA-PC), scores on autonomic dysfunction (gastro-intestinal, urinary tract and cardiovascular domains), sumscore for nighttime sleep problems, sumscore of BDI, sumscore of cognitive dysfunction (SCOPA-COG) and dosage of antiparkinsonian medication (LDE-Dopa, LDE-DA). A few other variables were added because a relation with development of EDS could be presumed: sumscore of dyskinesias, sumscore of motor fluctuations and the use of benzodiazepines or antihypertensives. The LMM was first executed with only one independent variable at a time (unadjusted model). Hereafter an adjusted model that considers the main effects of all baseline variables was performed. The final model only includes the variables that were significant from the unadjusted and the adjusted model. To examine which characteristics were associated with future development of EDS (objective 3), we performed a survival analysis in the data of patients who had no EDS at baseline, using the same variables that were considered in the LMM. We also added the baseline SCOPA-SLEEP DS score in this analysis, since it may be an important determinant for developing EDS.[4] For each variable a hazard ratio (HR) with 95% confidence intervals (CI) was calculated, with a HR > 1 indicating that this variable is associated with a higher risk of developing EDS. If for a particular patient 25% or more of the items of a scale was missing,

the patient was excluded from statistical analyses (this occurred in 1 patient). If less than 25% of the items were missing, missing values were replaced by the average score of the non-missing items on that scale of that particular patient. Analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 21.0.

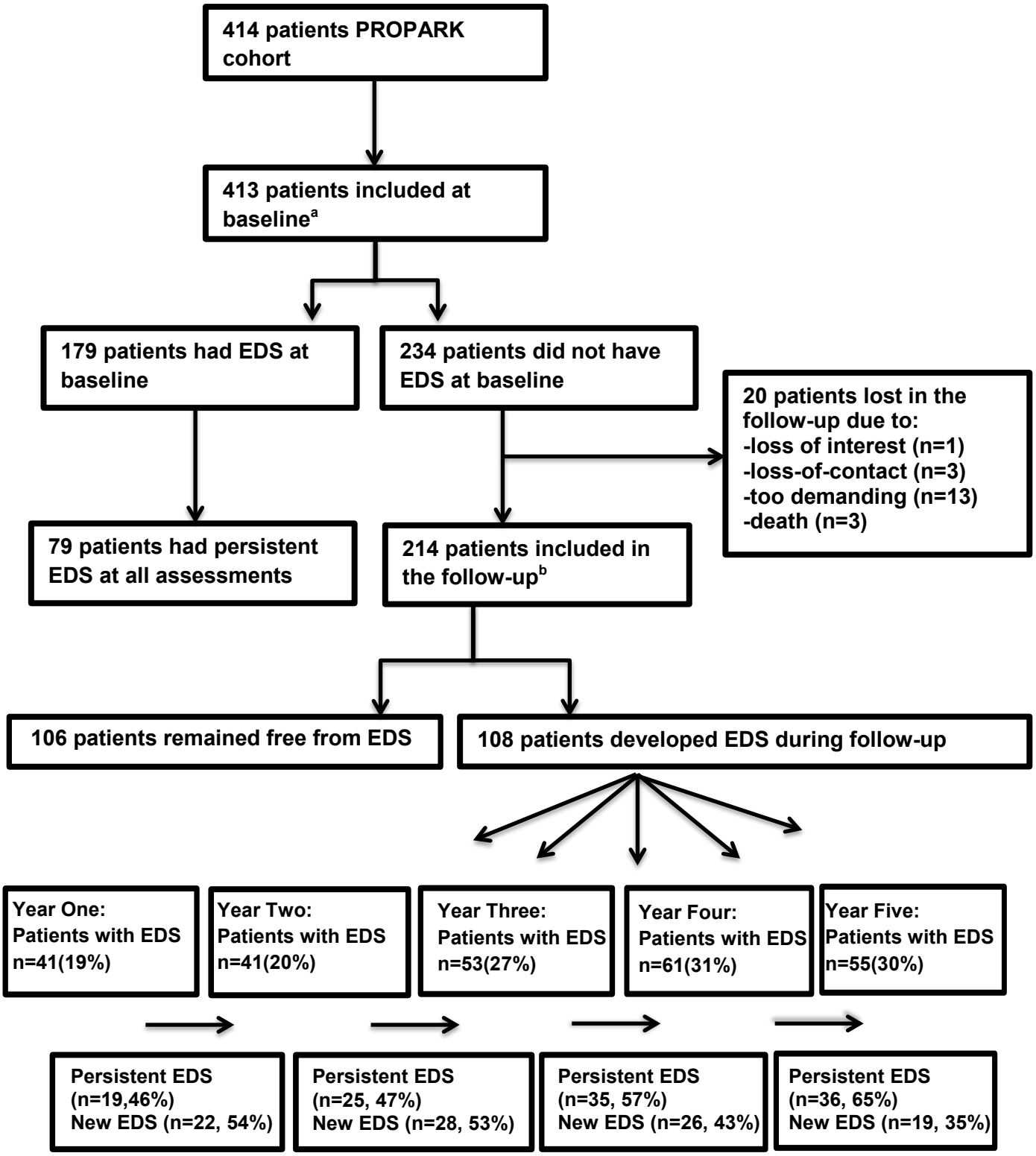
RESULTS

Of the 413 patients of whom an EDS score was available at baseline, 179 (43%) were classified as having EDS and 234 patients were classified as not having EDS (see for details Figure 4.1). Of the 234 patients without EDS at baseline, 108 patients (46%) developed this symptom during the follow-up period. During the 5-year follow-up period (Figure 4.1), EDS proved a non-persistent symptom, although the proportion of patients with EDS increased over time. In addition, with longer follow-up and disease duration, persistency of EDS increased: from 46% from year 1 to 2, to 65% from year 4 to 5.

Variables associated with EDS at baseline (cross-sectional analysis)

Patients with EDS at baseline were older, had a longer disease duration and higher Hoehn and Yahr stage, and performed worse with respect to motor function, activities of daily living and autonomic function (Table 4.1). A significant higher proportion of patients with EDS had a PIGD phenotype. They also presented with more severe cognitive impairment, depressive symptoms, nighttime sleep problems and more often suffered from hallucinations. Patients with EDS had a higher dopamine agonist and levodopa equivalent dose.

Figure 4.1: Flow Chart of follow-up for excessive daytime sleepiness



[a]*Data of these patients were used in the cross sectional analysis (objective 1) and the Linear Mixed Models (LMM) analysis (objective 2), n=413.*

[b]*Data of these patients were used in the survival analysis (objective 3), n=214.*

Table 4.1: Baseline data of patients with and without excessive daytime sleepiness (EDS)

	Total	With EDS	Without EDS	p-values
N	413	179	234	
Age, yr	61.14 (11.37)	63.46 (10.47)	59.37 (11.76)	<.001
Sex, % male	64.2	64.8	63.7	.813[a]
DBS at baseline, %	9.2	7.3	10.7	.233[a]
Education, yr	11.95 (4.11)	11.74 (4.09)	12.10 (4.13)	.377
Age at onset, yr	50.53 (11.89)	51.26 (11.47)	49.95 (12.22)	.266
Disease duration, yr	10.62 (6.53)	12.20 (6.93)	9.42 (5.96)	<.001
Hoehn & Yahr, stage	2 (2,3)	3 (2,4)	2 (2,3)	<.001[b]
SPES/SCOPA-Motor Impairment	13.31 (4.90)	14.82 (4.99)	12.23 (4.55)	<.001
SPES/SCOPA-Dyskinesia	0.94 (1.62)	0.98 (1.65)	0.91 (1.60)	.635
SPES/SCOPA-Motor Fluctuations	0.78 (1.26)	0.80 (1.22)	0.77 (1.29)	.823
SPES/SCOPA-ADL	8.92 (3.56)	10.26 (3.48)	7.91 (3.29)	<.001
PIGD dominant phenotype, %	45.4	55.0	38.2	.001[a]
BDI score	10.21 (6.57)	12.34 (6.72)	8.57 (5.97)	<.001
SCOPA-COG score[c]	25.27 (6.68)	23.31 (7.11)	26.79 (5.92)	<.001
MMSE score	26.65 (2.82)	25.98 (3.17)	27.15 (2.41)	<.001
SCOPA-SLEEP-NS score[d]	4.51 (3.77)	5.29 (3.80)	3.92 (3.64)	<.001
SCOPA-SLEEP-DS score[d]	4.87 (3.73)	8.39 (2.76)	2.18 (1.43)	<.001
SCOPA-AUT, total score[e]	10.55 (5.71)	12.87 (5.56)	8.82 (5.20)	<.001
SCOPA-AUT, GI score[e]	2.72 (2.20)	3.45 (2.26)	2.16 (1.98)	<.001
SCOPA-AUT, CV score[e]	1.16 (1.19)	1.42 (1.26)	0.96 (1.10)	<.001
SCOPA-AUT, UR score[e]	6.72 (4.03)	7.97 (4.08)	5.77 (3.72)	<.001
Hallucinations, % with	16.9	25.1	10.6	<.001
Antidepressants, % with	15.3	15.1	15.5	.918[a]
Antihypertensives, % with	20.8	24.6	17.9	.100[a]
Benzodiazepine, % with	22.3	24.0	21.0	.470[a]
Total LDE, mg/day	608 (463)	729 (423)	517 (473)	<.001
LDE-Dopa, mg/day	380 (375)	454 (360)	324 (377)	<.001
LDE-DA dose, mg/day	231 (226)	275 (218)	197 (227)	<.001

Variables are expressed as means (standard deviations), except for gender (percentages), motor subtype (percentages) and 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; MMSE, Mini-mental state examination; LDE, Levodopa dosage equivalent; DA, dopamine agonists.

Variables associated with longitudinal changes in EDS (LMM analysis)

The assumptions for LMM were met and residuals from the LMM analysis were normally distributed. The final model of the LMM analysis showed that male gender, poorer nighttime sleep, presence of hallucinations, and cognitive and autonomic dysfunction at baseline were associated with higher EDS scores over time, whereas the motor impairment score was marginally significant (Table 4.2). In addition, less severe dyskinesias were also significantly related to higher EDS scores. The dose of DA agonists - but not the levodopa dose - and use of antihypertensive drugs were associated with higher EDS scores as well, whereas use of benzodiazepines was associated with lower EDS scores. There were no significant differences between the different classes of antihypertensive medication and the risk for the development of EDS (40% beta-antagonists vs 35% diuretics, p=0.63).

Risk factors for future development of EDS (survival analysis)

The multivariate Cox proportional hazards' model showed that a higher baseline EDS score, a PIGD phenotype, urinary tract symptoms and the use of antihypertensives were independent predictors of the future development of EDS in patients without this symptom at baseline (Table 4.3).

Table 4.2: Factors associated with higher SCOPA SLEEP DS scores over time in patients with PD

	Unadjusted Model		Adjusted Model		Final Model	
	B (95%CI)	**p**	**B (95%CI)**	**p**	**B (95%CI)**	**p**
Age	0.056 (0.041-0.072)	<.001[d]	0.010 (-0.024-0.045)	.55	0.011 (-0.022-0.044)	.51
Male gender	0.540 (0.192-0.889)	.002[d]	0.761 (0.055-1.466)	.04[d]	0.781 (0.091-1.471)	.03[d]
Disease duration in years	0.092 (0.066-0.117)	<.001[d]	0.046 (-0.016-0.108)	.15	0.043 (-0.018-0.104)	.17
SPES/SCOPA – Motor Impairment	0.205 (0.167-0.242)	<.001[d]	0.092 (-0.001-0.184)	.05	0.088 (-0.004-0.180)	.06
SPES/SCOPA – ADL	0.310 (0.262-0.358)	<.001[d]	0.056 (-0.095-0.207)	.46	0.060 (-0.089-0.208)	.43
SPES/SCOPA – Dyskinesia	0.032 (-0.075-0.138)	.56	-0.353 (-0.597- -0.109)	.005[d]	-0.394 (-0.632- -0.157)	.001[d]
SPES/SCOPA – Motor Fluctuations	0.052 (-0.084-0.189)	.45	-0.185 (-0.492-0.121)	.24		
PIGD dominant phenotype	0.858 (0.515-1.201)	<.001[d]	-0.424 (-1.159 -0.310)	.26	-0.392 (-1.118-0.333)	.29
SCOPA-COG score[a]	-0.133(-0.160- -0.107)	<.001[d]	-0.090 (-0.150- -0.030)	.003[d]	-0.089(0.148- -0.029)	.004[d]
BDI score	0.138 (0.113-0.164)	<.001[d]	0.048 (-0.016-0.112)	.14	0.046 (-0.017-0.108)	.15
Presence of hallucinations	2.120 (1.653-2.588)	<.001[d]	0.823 (-0.096-1.742)	.08	0.924 (0.026-1.823)	.04[d]
SCOPA-SLEEP-NS score[b]	0.128 (0.084-0.172)	<.001[d]	0.117 (0.016-0.217)	.02[d]	0.109 (0.012-0.206)	.03[d]
SCOPA-AUT[c] GI score	0.363 (0.287-0.439)	<.001[d]	0.174 (0.002-0.347)	.05[d]	0.179 (0.012-0.346)	.04[d]
SCOPA-AUT[c] CV score	0.535 (0.390-0.679)	<.001[d]	0.106 (-0.200-0.412)	.50	0.170 (-0.127-0.466)	.26
SCOPA-AUT[c] UR score	0.241 (0.199-0.284)	<.001[d]	0.112 (0.019-0.206)	.02[d]	0.108 (0.015-0.200)	.02[d]
Daily levodopa dose, p/100mg	0.149 (0.103-0.196)	<.001[d]	0.025 (-0.087-0.137)	.67	0.002 (-0.103-0.107)	.97
Daily DA dose, p/100 mg	0.264 (0.192-0.336)	<.001[d]	0.348 (0.194-0.502)	<.001[d]	0.336 (0.184-0.487)	<.001[d]
Use of anti-hypertensives	0.803 (0.379-1.226)	<.001[d]	1.241 (0.445-2.038)	.002[d]	1.264 (0.475-2.053)	.002[d]
Use of benzodiazepines	-0.248 (-0.656-0.159)	.23	-1.313 (-2.143- -0.484)	.002[d]	-1.444 (-2.246- -0.641)	<.001[d]
Use of antidepressants	0.051 (-0.428-0.530)	.84	-0.412 (-1.319-0.494)	.37		

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 SCOPA-SLEEP DS scores.
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.
[c] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).
[d] significant values

Table 4.3: Longitudinal risk factor analysis for the development of excessive daytime sleepiness (EDS) in patients without EDS at baseline

	Unadjusted Model		Adjusted Model		Final Model	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**	**HR (95%CI)**	**p**
Age, p/yr increase	1.012 (0.995-1.029)	.16	0.990 (0.963-1.017)	.47		
Gender, HR for males	1.071 (0.718-1.596)	.74	1.265 (0.736-2.173)	.40		
Baseline EDS score, p/point increase	1.367 (1.191-1.569)	<.001[d]	1.400 (1.178-1.664)	<.001[d]	1.361 (1.182-1.569)	<.001[d]
Disease duration, p/yr increase	1.011 (0.981-1.042)	.47	0.984 (0.937-1.033)	.51		
SPES/SCOPA – Motor Impairment	1.041 (0.996-1.088)	.07	1.003 (0.935-1.076)	.94		
SPES/SCOPA – ADL	1.063 (1.003-1.125)	.04[d]	1.012 (0.901-1.138)	.84	0.998 (0.934-1.066)	.95
SPES/SCOPA – Dyskinesia	1.000 (0.889-1.126)	.99	0.902 (0.746-1.091)	.29		
SPES/SCOPA – Motor Fluctuations	1.017 (0.881-1.193)	.82	0.865 (0.660-1.133)	.29		
Motor phenotype, HR for PIGD dominant	1.244 (0.998-1.550)	.07	1.882 (1.041-3.402)	.04[d]	1.520 (1.003-2.303)	.05[d]
SCOPA-COG[a], p/point increase	0.979 (0.945-1.014)	.24	1.012 (0.958-1.070)	.67		
BDI, p/point increase	1.011 (0.980-1.043)	.50	1.016 (0.970-1.064)	.50		
Presence of hallucinations	1.538 (0.859-2.752)	.15	0.818 (0.382-1.753)	.61		
SCOPA-SLEEP-NS[b], p/point increase	1.005 (0.955-1.057)	.84	1.026 (0.949-1.108)	.52		
SCOPA-AUT[c], GI score p/point increase	1.071 (0.973-1.178)	.16	1.035 (0.888-1.207)	.66		
SCOPA-AUT[c], CV score p/point increase	1.145 (0.980-1.337)	.09	1.243 (0.970-1.594)	.09		
SCOPA-AUT[c], UR score p/point increase	1.093 (1.041-1.147)	<.001[d]	1.039 (0.960-1.125)	.34	1.070 (1.015-1.127)	.01[d]
Daily levodopa dose, p/100mg increase	1.065 (1.014-1.117)	.01[d]	1.077 (0.987-1.176)	.10	1.014 (0.959-1.073)	.61
Daily DA dose, p/100 mg increase	1.041 (0.962-1.127)	.32	1.048 (0.946-1.161)	.37		
Use of antihypertensives,	1.780 (1.136-2.788)	.01[d]	1.460 (0.835-2.551)	.18	1.624 (1.026-2.572)	.04[d]
Use of benzodiazepines	0.701 (0.417-1.179)	.70	0.613 (0.297-1.263)	.18		
Use of antidepressants	1.268 (0.763-2.107)	.36	1.207 (0.619-2.353)	.58		

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.
[c] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).
[d] significant values

DISCUSSION

We examined persistency, cross-sectional and longitudinal associations, and risk factors for EDS in a cohort of over 400 patients with PD who have been followed for up to five years. The analysis showed that EDS is not a stable feature but that its presence fluctuates. With longer follow-up, however, the proportion of patients with EDS increases and the feature becomes more persistent, indicating the relevance of evaluating its presence, particularly in patients who are at risk. We found that 69% of patients had EDS at some point during follow-up and that approximately 50% of patients who had no EDS at baseline reported this symptom at least once in the course of this study (Figure 4.1).

Our study is the largest longitudinal study on this subject so far.[4,5] The setup of our study is somewhat similar to a recent study conducted in a smaller population of de novo PD patients.[4] Interestingly, in spite of substantial differences between both studies concerning cohort composition, the results with respect to persistency, and identified associations and risk factors for EDS are remarkably similar. On account of this specific sampling strategy in our cohort, prevalence rates of EDS in our study are not representative of the population at large.

EDS in PD is assumed to be caused by the infestation of brain areas involved in the control of sleep and wakefulness.[18] In addition, dopaminergic treatment plays an important role as well, although the risk for EDS is significantly lower for levodopa compared to dopamine agonists, a finding that was replicated in our longitudinal analysis.

Previously reported variables that are associated with EDS and which emerged in our longitudinal analysis included male gender, dopamine agonist dosage, cognitive dysfunction, the presence of hallucinations, autonomic dysfunction, nighttime sleep problems, a higher baseline EDS score and a PIGD dominant motor phenotype. Age was only found associated with EDS in cross-sectional studies.[4,5]

Interestingly, the variables related to EDS that emerged from this study such as cognitive dysfunction, psychotic symptoms, autonomic dysfunction and PIGD were identified earlier as components of a coherent clinical predominant nondopaminergic (PND) symptom complex.[19] Notably, recent studies show that this symptom complex is prevalent early in the disease, and worsens with disease progression, which in turn plays an important role in characterizing subtypes of PD.[19,20] Hence, in accordance with the development and worsening of the aforementioned symptoms of nondopaminergic domains, the development of EDS likely is a consequence of progressive a-synuclein aggregate-related synaptopathy and axon degeneration of the central nervous system.[21] The correlation between EDS and the PND complex also raises the question whether the two could cancel each other out in the LMM analysis. After performing a more straightforward LMM analysis (only correcting for

age, disease duration and gender), the same variables were significant that were initially presented in Table 4.2. Another factor that is generally assumed to be associated with the occurrence of EDS in PD patients is an impaired nocturnal sleep.[22] Our results confirm this relationship. Additionally, we found that the use of night-time benzodiazepines was negatively associated with EDS severity, a finding corroborating with those of another study showing that PD patients treated with night-time clonazepam for nocturnal sleep disturbances, reported less EDS than those patients who were untreated.[22] In fact, post-hoc analysis showed that the nocturnal sleep disturbances and the use of night-time benzodiazepines shared the largest covariance with each other in the LMM. Both variables showed a large significant response when LMM analysis was only run with these two as variables. However, it must be noted that nocturnal sleep disturbances may not be the only responsible factor for EDS, since other studies did not confirm a relation between EDS and nocturnal sleep disturbances.[23]

In line with findings of a previous study, male gender emerged as a risk factor for EDS in our study.[4] Interestingly, such a relation has not yet been found in the general population, likely indicating a differential susceptibility for males with PD.[24]

In both our cross-sectional and longitudinal analysis, autonomic dysfunction was related with EDS, a finding in line with one prior cross-sectional study in de novo PD patients.[25] To date, no longitudinal study has yet been performed which included autonomic dysfunction as a baseline variable.[4,5] Since the autonomic system plays a critical role in regulating the function of numerous organs, we evaluated if particular autonomic sub-domains were responsible for the relation with EDS. This revealed that urinary tract symptoms showed the strongest association with EDS scores over time. The autonomic nervous system exerts its control through a broad central and peripheral network, which are both involved in PD and could contribute to the development of nocturia and subsequently nocturnal sleep disruption in this disorder.[3,26,27] This relation is supported by the beneficial effect of desmopressin acetate on nocturia in PD.[28]

Dyskinesias are common in advanced disease and associated with the prolonged use of levodopa.[29] In this study, less severe dyskinesias emerged as a risk factor for EDS. An earlier actigraphy study in PD found that patients with daytime sleepiness, measured by immobility, are more bradykinetic and less dyskinetic.[30]

Notably, dyskinesias did not emerge as a risk factor for EDS in the unadjusted LMM analysis. This likely indicates that when the analysis is controlled for differences in dopaminergic medication, the protective effect of increased daily motor activity on EDS, is absent. Although EDS score itself did not differ for PD patients with different age of onsets (AO<50: 4.76 ± 3.73 versus AO≥50:4.98 ± 3.74; p=0.56), one could still argue if EDS could be a heterogeneous phenomenon, where patients have different aetiologies for developing

EDS with different age of onsets. Interestingly, the daily dopamine agonists dosage was significantly higher in patients with an age of onset PD< 50, compared to those with an age of onset of ≥50 (AO< 50: 292 mg ± 237 mg versus AO≥50:169 mg ± 196 mg; p<0.001), whereas the latter had a lower SCOPA-COG score (AO<50: 27.62 ± 5.58 versus AO≥50: 22.89 ± 6.88; p<0.001). Therefore, in addition to multifactorial origin of EDS, there seems to be a significant role of dopamine agonists to the development of EDS in PD patients with a younger age of onset, whereas in those with an older age of onset cognitive decline seems to be the culprit.

Our study also revealed a new potentially modifiable risk factor for EDS in PD, namely the use of antihypertensives. In the general population sleepiness has been described as a common effect of antihypertensives and prevalence rates of 30-75% have been reported,[6] particularly with the use of beta-antagonists.[7] It is assumed that beta-antagonists exert this effect through their action on adrenergic receptors involved in the sleep-wake regulation. In our cohort, antihypertensive drugs were related to EDS, regardless of the class of antihypertensive drugs. If the effect of antihypertensive drugs is caused by the lowering of blood pressure, possibly in conjunction with dopaminergic medication on EDS in PD, then this should be further explored in future studies.

The finding that a clinical feature demonstrates a non-persistent behaviour over time yields important consequences for the interpretation of results derived from the LMM and the Cox Proportional Hazards model. In the LMM analyses, the data of all patients are used, whereas in the survival analysis only data of patients who are free of EDS at baseline are included. Although both procedures involve analysis of longitudinal data, they provide different answers to different questions, namely: “Which factors are associated with longitudinal changes in EDS? (LMM) ” versus “Which factors are associated with an increased risk of future EDS in patients who are free of this symptom at baseline? (Cox Proportional Hazards model)”

The strengths of this study are the prospective design, the broad clinical characterization, the limited loss to follow-up and the size of the cohort of patients with more advanced PD. Limitations involve the fact that certain baseline variables such as pain and sleep disordered breathing, which were earlier described as risk factors, were not included at baseline, and the fact that our cohort is hospital-based. The latter may have resulted in some over- or underestimation of certain associations, but it is unlikely that this has resulted in major distortions. In addition, our findings largely corroborated with those of an earlier population-based study on the novo PD patients.[4]

In conclusion, EDS is not a persistent phenomenon, although frequency and persistency increase with longer disease duration. Male gender, poorer nighttime sleep, cognitive and autonomic dysfunction, presence of hallucinations, less severe dyskinesias, higher dose of

dopamine agonists and use of antihypertensives were all associated with higher daytime sleepiness scores over time, whereas use of benzodiazepines was associated with lower scores. In addition, baseline SCOPA-SLEEP-DS scores and the PIGD motor phenotype were independent risk factors for the future development of EDS.

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