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DAYTIME SLEEPINESS IN PARKINSON'S DISEASE IN RELATION TO OTHER SYMPTOMS, DISEASE PROGRESSION AND DAILY LIFE

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Daytime sleepiness in Parkinson's disease in relation to other symptoms, disease progression and daily life

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To my mother and the other women in my family who appreciate knowledge.

ABSTRACT

The aim of this doctoral thesis is to explore daytime sleepiness (DS) in Parkinson's disease (PD). The Papers will evaluate how DS is connected to both motor and non-motor symptoms in PD, changes in DS over time, and the consequences of DS for the daily life of people with PD.

Paper I is a multicentre study with 118 participants from four university movement disorder clinics in Sweden. The aims of this study were to (1) explore the relationship between excessive daytime sleepiness (EDS) and other symptoms of PD, and (2) to discover if there are PD symptoms that can predict the prevalence of EDS. Our results showed a weak correlation between EDS and the following: fatigue, depressive and anxiety symptoms, non-specific pain and, axial/postural/gait-related motor symptoms (PIGD phenotype) for people with PD. The factor analysis showed no interrelationship with other symptoms of PD; therefore, EDS seems to be a separate manifestation in PD.

Paper II is a longitudinal study with 30 participants younger than 65, from an outpatient hospital clinic in Stockholm, Sweden. The participants were followed for up to 10 years depending on the progression of PD symptoms, especially EDS and other non-motor features. Seventeen participants completed the study. EDS was stable during the follow-up period at the group level but showed variation for individuals from year to year. EDS did not deteriorate in parallel with motor symptoms and disease severity in PD.

Paper III is a study about daytime sleepiness and motor and non-motor fluctuations in PD. Fifty-three people with PD who had been investigated with DaTSCAN to verify the PD diagnosis participated in this study. The three-day patient home diary and a six-day actigraphy Parkinson's KinetiGraphTM (PKG) were used for data collection. The items in the patient home diary were: feeling sleepy; low mood; anxiety and motor symptoms. These conditions correlated with each other and indicated that daytime sleepiness fluctuates with motor and non-motor symptoms in PD, but not with the PKG data.

Paper IV is a qualitative study of people with PD and their unique experience of daytime sleepiness and the consequences in their daily life. Twelve people participated in this face-to-face interview study. The impact of daytime sleepiness was not a constant experience but depended on the resilience of the individual and their ability to handle and resist sleepiness. DS could interfere with their daily life by reducing their self-compassion and need to struggle against it. Napping could also be a powerful method for recovery and refreshing the body and brain.

In summary, daytime sleepiness is a multi-factorial and multi-dimensional feature in PD. Excessive daytime sleepiness is not a stable phenomenon over time but can vary greatly for individuals from year to year, and did not deteriorate as motor symptoms in PD did. Daytime sleepiness fluctuates with motor and other non-motor symptoms like low mood

and anxiety. Personal resilience can affect how people with PD can resist the sleepiness or use the recovery effect of napping to refresh the body and brain during the daytime.

SAMMANFATTNING

Syftet med denna doktorsavhandling är att undersöka dagsömnighet hos personer med Parkinsons sjukdom (PS) och hur dagsömnighet är kopplad till andra motoriska och icke-motoriska Parkinsonsymtom, förändringar över tid och dess konsekvenser i det dagliga livet för personer med PS.

Delstudie I är en multicenterstudie med 118 personer med PS från fyra universitetskliniker i Sverige (Karolinska Huddinge, Linköping, Lund och Sahlgrenska i Göteborg). Syftet med denna studie var att (1) undersöka sambanden mellan besvärande dagsömnighet (EDS) och andra Parkinsonsymtom och (2) om det fanns Parkinsonsymtom som skulle kunna förutsäga förekomsten av besvärande dagsömnighet vid PS. Våra resultat påvisade ett svagt samband mellan EDS och trötthet (fatigue), depressiva och ångestsymtom, ospecifik smärta och med axiala/posturala/gångstörningsrelaterade symtom (PIGD-fenotyp) för personer med PS. Faktoranalys påvisade ingen koppling till andra PS symptom vilket indikerar att EDS kan betraktas som fristående fenomen vid Parkinsons sjukdom.

Delstudie II är en långtidsuppföljning av 30 personer som var yngre är 65 år vid studiestart. Deltagarna följdes under 10 års tid gällande symtomutveckling, speciellt dagsömnighet och andra icke-motoriska symtom. Sjutton deltagare genomförde hela studien. På gruppnivå var utvecklingen av dagsömnighet stabil under uppföljningsperioden i jämförelse med individnivå där större variation kunde påvisas från ett år till annat. Dagsömnighet försämrades inte parallellt med motoriska försämringen vid PS.

Delstudie III är om dagsömnighet och motoriska och icke-motoriska fluktuationer vid Parkinsons sjukdom. Syftet var att undersöka om dagsömnighet fluktuerar beroende och oberoende av andra symtom vid PS. Femtiotre personer med isotopundersökningsverifierad (DaTSCAN) Parkinsondiagnos ingick i studien. Deltagarna fyllde i dagbok om dagsömnighet, nedstämdhet, oro och motoriska symtom under tre dagar, samtidigt med en bärbar rörelsemätare kallad Parkinson's KinetiGraph™ (PKG). PKG-mätning gjordes under sex dagar. Dagboksdata korrelerade med varandra och detta är en indikation att dagsömnighet fluktuerar med andra Parkinsonsymtom, men inte med PKG-data.

Delstudie IV är en kvalitativ intervjustudie med tolv personer med dagsömnighet. Individuella intervjuer genomfördes för att få fördjupad kunskap om deltagarnas unika erfarenhet av dagsömnighet och dess konsekvenser i deras dagliga liv. Dagsömnigheten är inte ett konstant tillstånd utan var beroende på individens förmåga att både stå emot och stå ut med sömnigheten. Dagsömnigheten kunde påverka personens dagliga liv dels genom minskad självkänsla, dels något som måste kämpas emot, hanteras med, eller ses som en positiv kraft. En kort sovstund på dagen kunde används som en metod för återhämtning och något att omstarta både kropp och hjärna med.

Sammanfattningsvis är dagsömnighet både multifaktoriellt och mångsidigt fenomen vid Parkinsons sjukdom. Besvärande dagsömnighet är inte stabil över tid utan kan variera för

personer med PS. Dagsömnighet försämrades inte parallellt med motoriska symtomen vid PS. Dagsömnighet kan fluktuera med andra Parkinsonsymtom som nedsatt motorik, nedstämdhet och oro. Individens motståndskraft kan avgöra hur denne kan stå ut, stå emot eller hantera dagsömnigheten eller använda den för en tupplur för återhämtning och omstart av både kropp och hjärna under dagen.

LIST OF SCIENTIFIC PAPERS

I. Höglund A, Broman J-E, Pålhagen S, Fredrikson S, Hagell P.
Is excessive daytime sleepiness a separate manifestation in Parkinson's disease?
Acta Neurologica Scandinavica, 2015: 132: 97–104.
https://doi.org/10.1111/ane.12378

II. Höglund A, Hagell P, Broman J-E, Pålhagen S, Sorjonen K, Fredrikson S.
A 10-year Follow-Up of Excessive Daytime Sleepiness in Parkinson's Disease.
Parkinson's Disease Volume 2019, Article ID 5708515, 7 pages.
https://doi.org/10.1155/2019/5708515

III. Höglund A, Hagell P, Broman J-E, Pålhagen S, Sorjonen K, Fredrikson S, Svenningsson P.
Associations Between Fluctuations in Daytime Sleepiness and Motor and Non-motor Symptoms in Parkinson's Disease.
Movement Disorders Clinical Practice 2020
https://doi.org/10.1002/mdc3.13102

IV. Höglund A, Fredrikson S, Hagell P, Sandlund C
Like a wave in its sharpe, breath, and depth: A qualitative interview study of experiences of daytime sleepiness in people with Parkinson's disease.
(manuscript).

CONTENTS

LIST OF ABBREVIATIONS

BKS	Bradykinesia score
CAPSIT-PD	Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease
COMT	Catechol-O-Methyltransferase inhibitor
DA-agonist	Dopamine agonist
DaTSCAN	Dopamine transporter (DAT) SPECT
DBS	Deep Brain Stimulation
DKS	Dyskinesia Score
EDS	Excessive Daytime Sleepiness
ESS	Epworth Sleepiness Scale
FACIT-F	The Functional Assessment of Chronic Illness Therapy—Fatigue Scale
FDS	Fluctuation Score
HADS	The Hospital Anxiety and Depression Scale
HADS-A	The Hospital Anxiety and Depression Scale – Anxiety
HADS-D	The Hospital Anxiety and Depression Scale – Depression
HY	Hoehn and Yahr Staging
KSS	Karolinska Sleepiness Scale
LCIG	Levocopa-Carbidopa Intestinal Gel
LED	Levodopa Equivalent Dose
MADRS	Montgomery-Asberg Depression Self Rating Scale
MMSE	Mini Mental State Examination
MS	Motor symptoms
NHP	The Nottingham Health Profile
NHP-Pain	The Nottingham Health Profile - Pain
NMF	Non-Motor Fluctuations
NMS	Non-Motor Symptoms
PCA	Principal Component Analysis
PD	Parkinson's Disease
PIGD	Postural Instability-Gait Difficulties

PKG	Parkinson’s KinetiGraph™
PS	Parkinsons sjukdom
PSQI	The Pittsburgh Sleep Quality Index
PTI	The proportion of time as immobile
RBDQ1	Rapid Eye Movement Sleep Behavior Disorder Questionnare
SCOPA-sleep	SCales for Outcomes in PArkinson’s disease – sleep
SD	Daytime sleepiness
SD	Standard Deviation
TD	Tremor Dominant
UPDRS	Unified Parkinson’s Disease Rating Scale
WIM	Within-individual mean
WIRS	Within-individual correlation Spearman’s rho
WISD	Within-individual standard deviation

1 INTRODUCTION

Parkinson's disease (PD) is an incurable disease, which is caused by loss of dopamine neurons in the midbrain, and it can cause a huge variety of symptoms. It is fascinating that similar brain damage can cause such different symptoms. People with PD need to handle the disease and its consequences in their daily life. Some cope well whereas others struggle with the disease symptoms every day.

Sleep is essential for our well-being and we need to sleep, e.g. for recovery. Chronic disorders like PD can have a negative impact on sleep and alertness. Many people with PD have different kinds of sleep-related problems caused by PD, its treatment and the consequences of these.

One of the sleep related problems is daytime sleepiness (DS), which is a reason for dissatisfaction among people with PD. There are several studies about the prevalence and severity of excessive daytime sleepiness (EDS) in PD. Results from these studies are conflicting regarding associations between EDS and other PD symptoms, disease duration and treatment. Previous studies had used a medical definition of EDS and there may be a gap between this definition and how people with PD perceive this phenomenon. This can lead to underestimation of EDS, which thus may be a greater problem for people with PD than has been shown in previous studies, So, there is still little evidence about the relationship of EDS to other symptoms and fluctuations in PD, changes over time, and people with PD's experience of daytime sleepiness and its impact on their daily life.

2. BACKGROUND

2.1 PARKINSON'S DISEASE

Parkinson' disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. The estimated prevalence of PD is approximately 1 % of people above 60 years of age in industrialised countries [1], and in Sweden approximately 22 000 people are living with PD [2]. The mean age of diagnosis is around 60 with an increasing prevalence with higher age [1].

2.1.1 Aetiology

The aetiology of PD is still unknown, but it is considered to be a disease with a multi-factorial background with both genetic and environmental factors [3]. There is a degeneration of dopaminergic neurons in the midbrain and especially in the pars compacta substania nigra, which leads to loss of dopamine in the striatum [4]. There is a hypothesis about a sequential disease progression in the brain starting from the cerebellum, and ultimately the whole brain is affected [5].

2.1.2 Motor and non-motor symptoms

The symptoms in PD are divided into motor and non-motor symptoms. The motor symptoms include bradykinesia, resting tremor, rigidity and postural impairment, of which bradykinesia and one or two other symptoms are required for a clinical PD diagnosis [6].

The motor symptoms of PD can be divided into different kinds of phenotypes according to motor symptoms scored with the Unified Parkinson's Disease Rating Scale (UPDRS; [7]. These phenotypes are postural instability-gait difficulties (PIGD), tremor dominant (TD) or mixed [8]. The PIGD phenotype has been connected to more severe parkinsonism and is considered a risk factor for developing cognitive decline and dementia in PD [9-11].

Non-motor symptoms (NMS) are numerous and include symptoms related to mood changes, gastrointestinal symptoms, cognitive impairment, sleep and vigilance disturbances, dysautonomia and difficulties in communication [12]. NMS such as constipation, depression, sleep disturbances like REM sleep behavior (RBD) disorder can precede the motor symptoms of PD [12], which could support the Braak hypothesis [5]. The NMS are more common for people with PD with the PIGD phenotype, even in early PD [13].

There is evidence that NMS can be a greater burden than motor symptoms for people with PD, because symptoms like depression, anxiety and sleep problems can impair quality of life more than motor symptoms [14].

2.1.3 Treatment

The treatment of PD is symptomatic. The basic treatment is oral medication with levodopa with or without COMT-inhibitor, dopamine agonists or MAO-B inhibitors. The choice of treatment is individual and depends on the patient's symptomatology, age, symptom burden

and tolerability of the treatment [6]. The medication needs to be modified over time in relation to the progression of PD symptoms. The more advanced PD can be treated with continued dopaminergic treatment with liquid levodopa (LCIG), apomorphine infusion or with deep brain stimulation (DBS) as a complement to medical treatment [15, 16].

2.1.4 Fluctuations in PD

There is no neuroprotective treatment, and therefore disease progression is independent of symptomatic treatment [15, 17]. The pre-phase of fluctuations is "wearing off" and can occur randomly before the next intake of medication. The fluctuations in PD are categorised as ON-OFF phenomena. The ON phase is characterised as a benefit of treatment with or without dyskinesia, involuntary movements, contrary to the OFF phase with the presence of parkinsonian motor symptoms [15, 17]. Previously, fluctuations were considered to be related to motor symptoms, but during the last decade there has been an increasing interest in non-motor fluctuations in PD. For example, the burden of non-motor symptoms has been related to motor fluctuations already in early PD [18]. Non-motor symptoms as well as non-motor fluctuations (NMF) in PD are more subtle and therefore not as easy as motor symptoms to detect. Scales such as the Non-Motor Symptoms Scale (NMSS; [19]) have been used to identify NMS in PD. This scale has been used to categorise NMS into neuropsychiatric, autonomic and sensory fluctuations [20]. Sleep and sleep-related problems were not included in NMF because these can be caused by other factors than PD symptoms [21]. Motor and non-motor fluctuations are not isolated from each other, but their associations have not been fully explored.

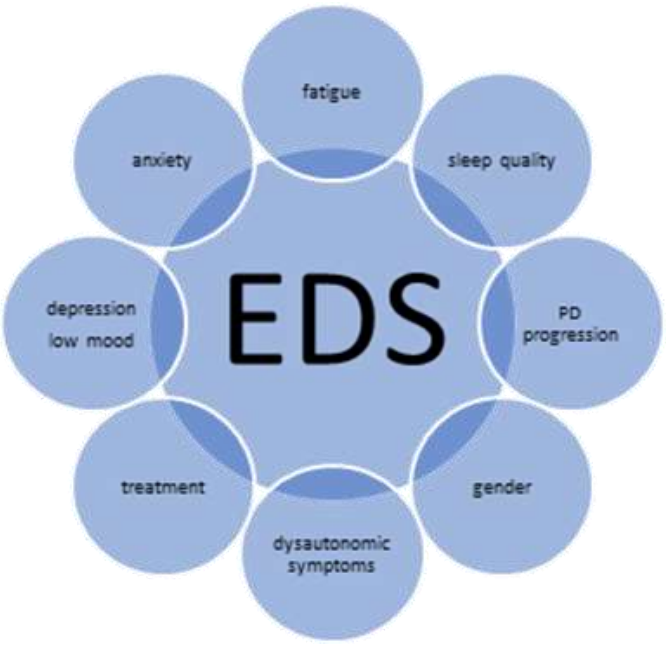
The most used evaluation of motor fluctuations is patient diaries, like the Parkinson's disease home diary [22]. Another recommended validated diary is Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD; [23]). These diaries categorise different motor stages, e.g. ON with, and without dyskinesias, and OFF. Ossig et al. [24] used a six-day diary with a visual analogue scale for assessment of both motor and non-motor fluctuations. The NMF were categorised according to NMSS, and these categories showed a low concordance with motor fluctuations. The participant needs to be educated in differences in motor stages as ON/OFF to be aware of their motor status [25]. Even non-motor symptoms have been recorded by diaries for several decades e.g. Richard et al. [26] studied mood and anxiety along with motor fluctuations in PD using a seven-day home diary. Thirty-five percent of people with PD had fluctuations. The most common fluctuating symptom was anxiety (29 %), followed by motor (24 %) and mood (21%) fluctuations. And about a third of participants reported fluctuations in all three symptoms. There are both pros and cons of a home diary. For example, it is a cost-effective method to collect data about participants' experience of both motor and non-motor symptoms in PD, but there is a risk for incomplete data, missing and duplicate diary entries due to diary fatigue [22, 25], and poor compliance.

2.2 SLEEP DISORDERS IN PD

Sleep disturbances are well-known in PD and were described by James Parkinson in 1817 [27]. Sleep-related problems cover a large range of issues such as insomnia, unsatisfied sleep quality, vivid dreaming, nightmares, REM sleep behavior disorder, and restless legs syndrome [28, 29]. The main hypothesis of disturbed sleep in PD is that it is the disease itself that affects areas in the brain that are involved in sleep and wakefulness [30]. A longitudinal cohort study of community-dwelling men from the USA showed that reduced circadian rhythmicity was a factor for increasing risk to develop PD [31]. However, both motor and non-motor symptoms can disturb sleep, and treatment can play a role [30].

2.3 EXCESSIVE DAYTIME SLEEPINESS IN PD

The common definition of EDS is "the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep. Sleepiness may vary in severity and is more likely to occur in sedentary, boring, and monotonous situations that require little active participation." [32]. Excessive daytime sleepiness (EDS) is more common among people with PD (up to 55 %; [33-35]) compared with the normal population (around 20%; [36, 37]). EDS in PD seems to be related to several features such as PD severity, disease progression, PD symptoms, pharmacological treatment of PD, and gender (Figure 1), but these results are conflicting [34, 38-47]. Sleep problems and EDS have even reduced quality of life for people with PD [34, 38, 47, 48].



Excessive daytime sleepiness (EDS) in Parkinson's disease (PD) has been connected to both motor and non-motor symptoms, as well as progression of the disease, dopamine replacement therapy and male gender.

Figure 1 Excessive Daytime Sleepiness in PD

There are some longitudinal studies about EDS in PD. Most of the studies show a progression of EDS during the PD progression [45-47, 49, 50]. For example, Erro et al. [44] showed a more than 300 % increase of EDS in the novo PD patients from years 2 to 4 during the PD duration. These results are conflicting about the role of medication, motor and non-motor symptoms, so further studies are needed of the long-term effects and progression of EDS in PD.

The most severe form of EDS is sudden onset of sleepiness, which is defined as suddenly falling asleep without prior signs of sleepiness [51]. Sleep attacks have been connected to medical treatment of PD [52-55], but these results are conflicting e.g. role of dopamine agonist in sleep attacks.

Daytime sleepiness and fatigue are often interrelated and are often used as interchangeable features named as “tired” [56]. Fatigue is a common NMS in PD with a prevalence of 40-65% ([57-59]. Fatigue has been defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion with an association with physical and cognitive impairment [56]. EDS and fatigue can coexist in PD, and can be perceived as similar symptoms by people with PD, and these phenomena overlap [60]. Despite these similarities they seem to have different aetiologies in PD [61]. It can therefore be difficult to distinguish between EDS and fatigue due to similar expressions such as overwhelming tiredness, need to rest, and not feeling recovered after rest or sleep.

In previous studies EDS has been defined according to the classification of EDS [32], and therefore is seen more as a medical problem than experience of daytime sleepiness. There may be a gap between the medical definition of EDS and how people with PD interpret and perceive this symptom. Probably their experience is more like daytime sleepiness than EDS, but this has not been studied before.

2.4 RATIONALE

EDS in PD has been explored in several studies, but there is still no consensus about the role of EDS in PD, both regarding the association with PD symptoms, or PD severity and treatment. Despite a large number of studies about EDS in PD, there is still a lack of data in several fields about this disabling non-motor symptom in PD. First, the relationship between EDS and other both motor and non-motors symptoms is still unclear. Moreover, the evidence about PD symptoms as a predictive factor to develop EDS in PD is insufficient. Longitudinal studies of EDS in PD are few and therefore the changes of EDS over time are poorly studied. There is also a lack of evidence about the relationship between daytime sleepiness and fluctuations in PD, because EDS has not been included in non-motor fluctuations in PD.

Many people with PD suffer from daytime sleepiness, which can affect their daily life. There are no studies about how people with PD experience EDS or DS in their daily life, and their descriptions of the phenomena are lacking. So, more research is needed about the multi-dimensionality of EDS and DS for people with PD.

3. AIMS

3.1 GENERAL AIM

The overall aim for this thesis were to explore how daytime sleepiness in PD is connected to other motor and non-motor symptoms, to explore progression over time and to increase understanding of the experiences of daytime sleepiness among people in PD.

3.2 SPECIFIC AIMS

Paper I

To investigate potential predictors of EDS in PD and to explore how EDS relates to other motor and non-motor PD features.

Paper II

To investigate EDS over time and in relation to other PD symptoms among people with PD.

Paper III

To evaluate whether daytime sleepiness is associated with other motor and/or non-motor fluctuations in PD.

Paper IV

To explore the experiences of daytime sleepiness in people with PD.

4. MATERIAL AND METHODS

4.1 SAMPLE

The participants in Paper I were recruited from four movement disorders university outpatient clinics in Sweden (Karolinska Huddinge; Linköping, Lund, and Sahlgrenska). In Papers II, III and IV the participants were recruited from the movement disorders outpatient clinic at Karolinska University Hospital, Stockholm, Sweden.

All participants had been diagnosed as having clinical PD by a neurologist. The patient records were checked for exclusion criteria such as a diagnosis of dementia, severe depression or active cancer disease, because these conditions could lead to daytime sleepiness and therefore could have an impact on the study results. Every participant was Swedish-speaking and able to complete self-reported instruments.

In Paper I every participant was screened for cognitive impairment with the Mini-Mental-State-Examination (MMSE;[62]), and scores less than 24 points were used as an exclusion criterion. In Paper II, all participants were younger than 65 at the baseline visit. In Paper III, the participants' PD diagnosis had been verified by DaTSCAN [63], and the MMSE was used to describe the participants' cognitive status, but not as an exclusion criterion. In Paper IV the participants had been selected from Paper III. The inclusion criterion was the presence of EDS according to Epworth Sleepiness Scale (ESS) > 10 points.

An overview of the papers is provided in Table 1.

Table 1 Overview of Papers

	Aim	Design	Participants	Data analysis
Paper I	Investigate potential predictors of EDS in PD and to explore how EDS relates to other motor and non-motor PD features	Prospective	118 consecutive selected PD patients from four hospital outpatient movement disorders clinic in Sweden	Descriptive Multiple linear regression model Principal component analysis (PCA)
Paper II	Investigate EDS over time and in relation to other PD symptoms among people with PD	Prospective	30 randomly selected PD patients > 65 years age from hospital movement disorders outpatient clinic, Sweden	Descriptive Linear mixed models
Paper III	Evaluate whether daytime sleepiness is associated with other motor and/or non-motor fluctuations in PD	Observational	53 consecutive selected PD patients with DaTSCAN verified PD diagnosis from hospital movement disorders outpatient clinic, Sweden	Descriptive Correlations Spearman's rho
Paper IV	To explore the experiences of daytime sleepiness in people with PD	Qualitative	12 participants selected from study III populations based by ESS score > 10	Qualitative Content analysis

EDS Excessive Daytime Sleepiness; ESS, Epworth Sleepiness Scale; PD Parkinson's Disease

4.2 ASSESSMENTS

Several standardised generic and PD-specific scales and assessments were used to get a broad coverage of symptoms and features related to PD (Table 2).

Table 2 Assessments, both self-rated instruments and clinical assessments

Assessments	Paper I	Paper II	Paper III	Paper IV
ESS	X	X	X	
FACIT-F	X	X[1]	X	
HADS-A	X	X[1]	X	
HADS-D	X	X[1]	X	
Home diary			X	
HY	X	X	X	
Interview				X
MADRS-S		X		
MMSE	X		X	
NHP	X			
PKG			X	
PSQI	X	X	X	
RBDQ1			X	
UPDRS	X	X	X	

[1] from year 1

ESS, Epworth Sleepiness Scale; FACIT-F, The Functional Assessment of Chronic Illness Therapy—Fatigue scale; HADS, The Hospital Anxiety and Depression Scale; HY, Hoehn and Yahr-staging; MADRS-S, Montgomery-Asberg Depression Rating Scale Self rating scale; MMSE, Mini-Mental-State Examination; NHP, The Nottingham Health Profile; PKG Parkinson's KinetiGraph™ ; PSQI, the Pittsburgh Sleep Quality Index; RBDQ1, REM sleep behavior disorder questionnaire; UPDRS, The Unified Parkinson's Disease Rating Scale

Every participant, except one person in Paper I, was treated with antiparkinsonian medication. Some participants had more advanced PD and were therefore treated with apomorphine infusion (n= 2), levodopa-carbidopa intestinal gel (n= 10) or DBS (n=12). Antiparkinsonian medications were expressed as daily levodopa equivalent (LED) doses [64] for the total medication as well as for levodopa and dopamine agonists separately.

The data about demographics, PD duration, overall medication, and comorbidity were collected by interviewing participants and from medical records and were verified by the participants. The participants' characteristics are presented in Table 3.

Table 3 Participant characteristics

	Gender Male/ female	Age (yrs)[a]	PD dur (yrs)[a]	Total LED[a]	L-dopa LED[a]	DA-agonist LED[a]	UPDRS III	HY "on"/ "off"	MMSE	ESS	PSQI	MADRS-S	FACIT-F	HADS-D	HADS-A
Paper I n= 118	64/54	63.9 (9.6)	8.4 (5.7)	891.8 (489.4)	704.8 (438.4)	131.6 (187.3)	17 (10.5–27)	II (II-III) / III (II-III)	29 (28–30)	10 (0–21)	7 (4–10)		35.5 (26.75–42.0)	5 (3–7)	5 (3–8)
Paper II n = 30 (baseline)	24/6	58.2 (6.6)	6.2 (4.8)	937.8 (480.0)	772.3 (480.0)	123.3 (140.2)	12.5 (9.5–17.5)	II (II-III) / ND		10.5 (6.75–13.25)	7.0 (4.0–9.25)	10 (6–15)	34 (29 – 41)[b]	5.0 (2.5–8.0)[b]	5.0 (2.0–7.5)[b]
n= 17 (end of study)	12/5	67.2 (6.4)	15.3 (3.7)	1276.4 (824.2)	1037.3 (734.7)	60.8 (79.7)	28 (18–27)	III (III-IV) / ND		8 (4.75–15.75)	9 (4.0–10.75)	11 (7–17)	23.0 (10.25–30.5)	6.0 (2.0–8.0)	7.0 (1.25–9.75)
Paper III n = 28 fluctuators	15/13	63.8 (11.6)	11.9 (8.2)	1195,6 (611.0)	1122.4 (627.0)	73.2 (118.2)	21 (15-27.75)	III (II-III) / III (III-IV)	28 (27-30)	11 (7-14)	11 (10-13)		29.5 (24.0 - 43.25)	9.0 (8.0-10.0)	13.0 (10.0-14.0)
n = 24 non-fluctuators	17/7	67.0 (8.9)	4.0 (4.3)	598.9 (298.7)	459.8 (231.9)	139.1 (133.1)	16 (11.5-22.75)	II (II-III)	29 (28-30)	9 (6-13)	9 (9-10.75)		41.5 (35.5-44.75)	9.0 (8.0-10.0)	14 (12.25-15.0)
Paper IV n=12*)	7/5	65.2 (11.9)	8.2 (6.7)	612.4 (232.2)	446.8 (269.9)	115.6 (153.8)	18.5 (11.5–26.25)	II (I-III) / III (III-IV) (n=7)	29 (28-30)	14 (13-19)	10 (9.25-13)		34.0 (26.75-44.75)	9.0 (7.25-12.25)	13 (10.25-15.0)

Data are median (q1 – q 3) unless otherwise noted.
[a] Mean (standard deviation, SD)
[b] From Year 1.
*) Selected from Paper III sample.
yrs, years; PD dur, Parkinson's disease duration; Total LED, total Levodopa equivalent dose; L-dopa LED, total levodopa equivalent dose; DA-agonist LED. Total dopamine agonist equivalent dose; UPDRS III, Unified Parkinson's disease rating scale (motor score); HY "on"/"off", Hoehn & Yahr staging in ON-phase and OFF phase of parkinsonism; MADRS-S, Montgomery-Asberg Depression Rating Scale Self rating scale; MMSE, Mini Mental State Exam.; ESS, Epworth Sleepiness Scale; PSQI, The Pittsburgh Sleep Quality Index; FACIT-F, The Functional Assessment of Chronic Illness Therapy—Fatigue scale; HADS-D, The Hospital Anxiety and Depression Scale – depression; HADS-A, The Hospital Anxiety and Depression Scale – Anxiety; ND, not done

4.2.1 Daytime sleepiness, sleep and fatigue

The *Epworth Sleepiness Scale* (ESS; [65, 66]) is a generic eight-item self-rated questionnaire regarding the risk of dozing off or falling asleep during various day-to-day activities during the past month. Scores can range between 0 and 24 (higher scores = more daytime sleepiness) and scores >10 suggest abnormal levels of daytime sleepiness.

The *Pittsburgh Sleep Quality Index* (PSQI; [67]) is a generic self-rated questionnaire regarding sleep quality during the past month. Scores can range between 0 and 21 (higher scores = poorer sleep quality), and scores >5 indicate abnormally poor sleep quality.

The *Karolinska Sleepiness Scale* (KSS; [68]) is a single-item generic self-rated scale regarding the subjective level of sleepiness during the last ten minutes. The KSS assesses

situational drowsiness and is sensitive to fluctuations. Scores range between 1 (extremely alert) and 9 (extremely sleepy – fighting sleep).

The *REM sleep behavior disorder single-question screen* (RBDQ1; [69]) is a single Yes/No-question about the presence of Rapid eye Movement Behavior Disorder (RBD).

The *Functional Assessment of Chronic Illness Therapy—Fatigue scale* (FACIT-F; [70, 71]) is a self-rated questionnaire originally developed to assess anemia-associated fatigue but has been validated for use in a range of disorders, including PD. FACIT-F yields scores that ranges from 0 to 52 (higher scores = less fatigue).

4.2.2 Depression and anxiety

The *Hospital Anxiety and Depression Scale* (HADS; [72, 73]) is a self-rated questionnaire for detecting depression and anxiety in non-psychiatric patients during the past week. HADS consists of 14 items, of which seven represent anxiety (HADS-A) and seven represent depression (HADS-D). Each subscale score can range between 0 and 21 (higher scores = more anxiety/depression symptoms).

Montgomery-Asberg Depression Rating Scale Self rating scale (MADRS; [74]) is a self-rating questionnaire with nine items expressing different levels of discomfort regarding depressive symptoms during the past three days. The total score can range between 0 and 54 (higher scores = more severe depression). Scores 0 – 12 = no or very mild depression, 13 - 19 = mild, 20 – 34 = moderate and >34 indicate depression.

4.2.3 Parkinsonian symptoms

The *Unified Parkinson's Disease Rating Scale* (UPDRS; [7]) consists of four parts: (I) Mental functions; (II) Activities of daily living; (III) Motor examination, and (IV) Complications of therapy. Parts I, II and IV are based on interviews regarding the patient's situation during the past week, whereas part III is a clinical examination of motor symptoms at the time of examination. All items in parts I – III can generate 0-4 points, and part IV is a mixture of "yes/no"-questions (0–1 point) and items which generate 0-4 points. Part I: 0-16 points; part II: 0 – 52 points; part III: 0 – 56 points and part IV: 0 – 23 points with a total maximum score of 147 points. The higher scores indicate more severe problems.

For all participants the motor symptom profile scores were calculated [75] according to the UPDRS motor score (part III): axial/postural/gait impairments (items 18, 19, 27–31), rest tremor (item 20), postural tremor (item 21), rigidity (item 22), and limb bradykinesia (items 23–26). The UPDRS part IV (complications of therapy) was used to derive scores of dyskinesias (items 32–35) and motor fluctuations (items 36–39).

The *Hoehn and Yahr-staging* (HY;[76]) describes overall disease severity based on natural PD history. It defines five stages of PD: I = unilateral disease, II = bilateral disease, without impairment of balance, III = mild to moderate disease, some postural instability; physically

independent, IV = severe disability; still able to walk or stand unassisted, and V = wheelchair bound or bedridden unless aided.

A study-specific patient-reported *home diary* of the severity motor and non-motor symptoms was devised based on previously available diaries [22, 26]. Participants are asked to rate their perceived severity ("not at all", "somewhat", "pretty much" or "very much") of motor (bradykinesia, tremor, and rigidity) and non-motor symptoms (worrying/nervousness/anxiety, mood, and sleepiness) every second hour from awakening to bed time.

The *Parkinson's KinetiGraph*™ (PKG; [77]), is an accelerometer with algorithms that provide continuous registration of movements. The PKG logger collects data every two minutes from 9:00 to 18:00 for six days, from whom bradykinesia (BKS) and dyskinesia (DKS) scores are calculated Detailed information on immobility (the proportion of time as immobile, PTI), variation in dyskinesia and bradykinesia (fluctuation score, FDS) and percentage of time above the threshold for "off" (proportion of time that an individual's BKS is >26) is also provided.

4.2.4 Others

The *Mini-Mental-State-Examination* (MMSE, [62]) is a screening instrument for the purpose of evaluating cognitive impairment in older adults. The MMSE covers a range of domains such as orientation, registration, attention, recall, memory, language and visual-spatial skills. MMSE scores can range between 0 and 30, and levels <24 indicate cognitive impairment. The Swedish version of the MMSE has been modified by Svensk Förening för Kognitiva Sjukdomar (2000).

The *Nottingham Health Profile* (NHP; [78]) is a generic patient-reported health status questionnaire covering six aspects of health (energy; pain; emotional reactions; sleep; social isolation and physical mobility); in total 24 statements with Yes (presence) or No (1-0 point) alternatives. NHP-Pain was used here to assess non-specific pain.

A study-specific *semi-structured interview guide* was developed and used to guide qualitative face-to-face interviews. The questions included: (1) Can you describe your experience of daytime sleepiness? (2) Can you tell me how daytime sleepiness affects your daily life? (3) Can you tell me if daytime sleepiness affects your Parkinson's symptoms? (4) Can you tell me how you cope with daytime sleepiness? (5) Can you tell me what words you use to describe this sleepiness? If the participant found it difficult to describe his or her experience of daytime sleepiness, the interviewer asked the participant to describe a situation when he or she felt sleepy during the day.

4.3 PROCEDURE

All clinical assessments were performed by a registered nurse specialised in PD. For Paper I all raters underwent standardised video-based training [79, 80] regarding clinical assessments

according to the UPDRS and HY-staging of PD. The training included independent ratings of patient video sequences to reach a similarity in ratings. This was followed by independent ratings of patient video sequences where all assessors rated the same sequences. Inter-rater concordance was ≥0.85 (Kendall's coefficient of concordance) for all scores.

For Papers II-IV all data collection was done by the same PD nurse (A.H.). All assessments were done during the "ON-phase" of PD when possible. HY stages were also estimated for the "off" phase from the patient-reported history and medical records.

Paper I

The participants (n = 118) underwent a single outpatient visit. After signed informed consent the PD nurse collected the data about demographics, medication, and comorbidity, followed by clinical assessment of parkinsonian symptoms (UPDRS), disease severity (HY) and cognitive status (MMSE). At the end of the visit the participants completed the ESS, FACIT-F, PSQI, and HADS.

Paper II

To investigate EDS over time and in relation to other PD symptoms among people with PD. Thirty participants younger than 65 with PD were randomly selected. The participants made annual visits up to year 8 and a final study visit at year 10 (Figure 2). At baseline the participants signed an informed consent form. There was the same procedure at each visit. First, a PD nurse (A.H.) interviewed the participant about their present PD symptoms, comorbidity, and medication, and asked questions about sleep habits, the presence of dreams, nightmares, hallucinations and EDS. From year 1, questions about changes since the last visit were included. The clinical assessments (UPDRS and HY) were performed after the clinical interview. At the end of the visit the participant completed the ESS, PSQI, and MARDS-s. From year 1, the FACIT-F and HADS were added to the protocol.

Flow chart showing number of participants with and without excessive daytime sleepiness (EDS) from year 0 (baseline) to year 10. ESS, Epworth Sleepiness Scale

Figure 2

Paper III

The participants (n = 53) made a single outpatient visit. After they have given their signed informed consent the PD nurse (A.H.) interviewed them about demographics, the presence of fluctuations, the burden of PD, overall health, medication and comorbidity. PD symptoms and severity were assessed by the UPDRS and HY, followed by assessment of cognitive status (MMSE), measurement of weight, height, and orthostatic blood pressure. The participants completed the self-estimated questionnaires ESS, PQSI, FACIT-F, HADS, and RBDQ1. The visit ended with practical training in using the home diary and the PKG logger. The PKG logger was placed on the participant's most affected wrist and was worn for six days. The PKG logger was activated after training at the clinic. The oral levodopa treatment dosage times were pre-programmed for participants (n=41) on their PKG logger. The home diary and PKG were later returned by mail to the data collector (A.H.).

Paper IV

Twelve participants were interviewed face-to-face. Eleven interviews were conducted at the clinic during office hours in a separate room. One participant was interviewed in her home. Before the start of each interview, the interviewer (A.H.) repeated the aim of the study and confirmed the subject's willingness to participate. The interviewer also explained the definition of "tiredness" (trötthet) and "sleepiness" (sömnighet) to clarify the differences between these phenomena, and these definitions were available in written form during the interview. Participants could contact the interviewer afterwards if they wanted to add or clarify something. All interviews were recorded and transcribed verbatim, and the interviewer compared the text to the audio files to verify that they were consistent with each other.

5 DATA ANALYSIS

5.1 Statistical analysis

Statistical analysis in this thesis was conducted by using IBM SPSS for Windows, versions 20 to 26 (IBM Corp., Armonk, NY, USA), LISREL 8.8 (Scientific Software International, Inc., Skokie, IL, USA) and R version 3.5.0 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2018) employing the lme4 [81], lmerTest [82], weights [83] and beanplot [84] packages. The level of statistical significance was set to $p < 0.05$ (2-tailed) for all analyses.

The description of continued variables means, standard deviation (SD) and median (q1 - q3) and minimum and maximum were used. For categorical variables frequency and percentage were used.

Specific analyses in the respective papers are described below.

Paper I

The data were analysed in several steps. First, bivariate analyses were conducted (Spearman's rho) to assess associations between ESS scores and other variables. Second, clinical PD features and symptoms that were significantly associated with ESS scores (dependent variable) were entered into a multiple linear regression model. All included scores were adjusted to the same direction (higher scores = more problems). After that, two principal component analyses (PCA) with varimax rotation were conducted to explore the interrelationships among EDS and other motor and non-motor aspects of PD. The first PCA used the total UPDRS III (motor score) as an indicator of parkinsonism, and one used for the five UPDRS III derived motor symptom profile scores instead. Other variables entered into the PCAs were EDS (ESS), fatigue (FACIT-F), depressive symptoms (HADS-D), anxiety (HADS-A), sleep quality (PSQI), pain (NHP-Pain), cognition (MMSE), symptomatic orthostatism (UPDRS IV), motivation (UPDRS I), thought disorder (UPDRS I), dyskinesias (UPDRS IV), and motor fluctuations (UPDRS IV). Since most variables were no more than ordinal, the PCAs were based on matrices of Pearson, polychoric, and polyserial correlations, as appropriate [85].

Paper II

Spearman correlations were estimated between baseline and year 10 for those who completed follow-up period. The data was analysed according as linear mixed models in different settings: (1) the outcomes were predicted from time, and the intercept and effect of time (i.e., slope) were allowed to vary between individuals (i.e., defined as random). (2) the outcomes were standardised within individuals and used as predictors (effects allowed to vary between individuals) of ESS, that also was standardised within individuals. These analyses indicate how many intraindividual standard deviations ESS is predicted to change for PD an increase in the predictor by one intraindividual standard deviation.

Paper III

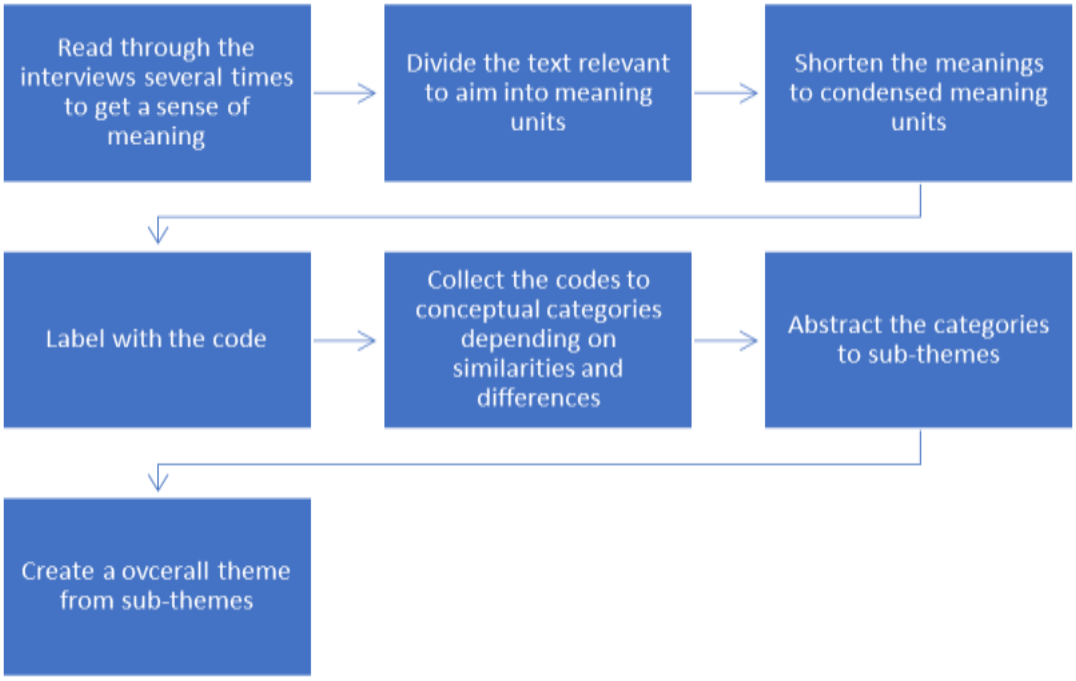
The data was shared into two groups fluctuators vs. non-fluctuators according to UPDRS part IV (item 36-39) and interview about presence of the motor and non-motor fluctuations. Comparisons between groups were made by using Chi-square, Mann-Whitney U- and t-tests, as appropriate. We also calculated the within-individual mean (WIM) which indicates the participant's average level of self-rated symptoms, and the within-individual standard deviation (WISD), which is a measure of how much these ratings fluctuate within each person during the study period. As well as the within-individual correlation Spearman's r, (WIRS) between all diary variables for each participant. WIRS indicates how each person's ratings tend to covary, with a positive value showing that a high rating on one variable tends to coincide with a high rating on the other variable, and a negative value indicating that a high value on one variable tends to coincide with a low value on the other variable.

Collected PKG-logger data were transferred to a server where the results were analysed using a proprietary algorithm to calculate and graph the respective variables to obtain an objective and quantitative picture of the variations in the patient's motor state [77].

5.2 Qualitative analyses

Paper IV

Interviews were analysed by qualitative content analysis, as described by Graneheim and Lundman [86, 87]. The process started with the reading of interviews several times to get a sense of them, followed by use of the stepwise method to create meaning units, which were converted to shorter meaning units and labelled code. The codes were sorted into conceptual categories according to similarities and differences. These categories were abstracted to sub-teams and at the end, if possible, to an overall theme. This dynamic process moved back and forth from the original text to the overall theme to maintain the essence of the participants' unique experience of their daytime sleepiness (Figure 3). The inductive approach was used as a method to describe daytime sleepiness from the perspective of people with PD.



The analytic process moves back and forth between the text, meaning units, codes, categories, and subthemes not to lose the essence of the participants experiences of the phenomena.

Figure 3 The working process for the content analysis

6 ETHICAL CONSIDERATIONS

The work in this thesis was approved by the ethical review board and conducted in accordance with the Helsinki declaration. Paper I was based on a multicentre study (KI 03-054) with the main centre in Lund, Sweden. Papers II, III and IV were based on studies approved by the ethical review board at Karolinska Institutet, Sweden (Dnr. 500/02, 2011/1866-31/4 and 2015/761-32). First, all participants were sent written study information, and were then given oral information at an outpatient visit. In the longitudinal study (Paper II) participants were asked the participation before the start of data collection at each annual visit. All participants signed a written informed consent form and received a copy of it.

There may be a risk that participation in a study can be a burden for the participant, especially in longitudinal studies. To minimise this risk the participants were carefully informed about their right to withdraw at any time during the study. Some participants became cognitively impaired during the study, and the data collector (A.H.) was aware of the problem this could cause for participation. If an individual was uncomfortable with participating, she or he was excluded from the study. If the participant had problems with reading the self-estimated questionnaires, the data collector (A.H.) read the questionnaires for the participant without changing or explaining the text.

7 RESULTS

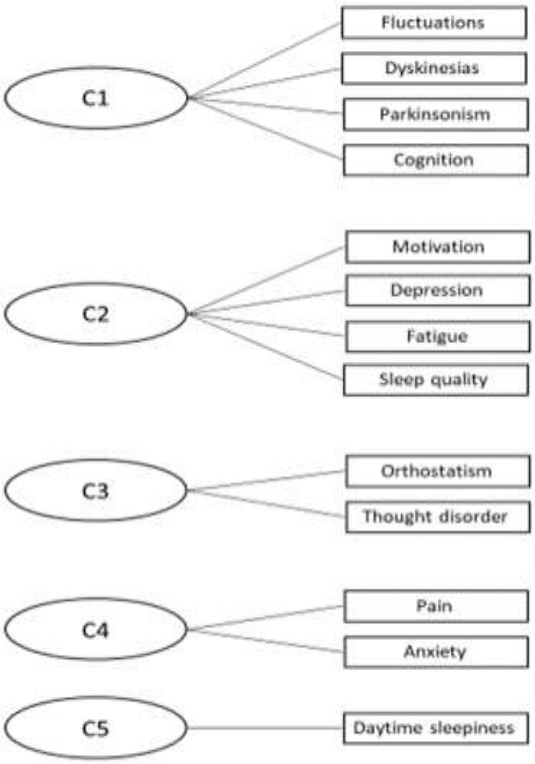
7.1 STUDY SUMMARY AND MAIN FINDINGS

Paper I *Is excessive daytime sleepiness a separate manifestation in Parkinson's disease?*

One hundred and fourteen of 118 people with PD were included in the analysis. Four people were excluded due to an incomplete ESS score. A median (q1–q3) ESS score was 10 (6– 13), and 53 participants (46.5%) scored above 10 and were therefore classified as having EDS. A median (q1 – q 3) for ESS scores vs. gender (female/male scores, 9 (6–13)/10 (6–13); P = 0.989; Mann-Whitney test), presence of orthostatic blood pressure or not (10 (4–13)/10 (6–14); P = 0.367; Mann-Whitney test) , or across disease severity in both the "on" or "off" phases (P = 0.703; Kruskal-Wallis' test) showed no differences.

Significant bivariate associations were found between ESS scores and fatigue (FACIT-F), depressive symptoms (HADS-D), anxiety (HADS-A), pain (NHP-Pain), and the axial/postural/gait impairment score of the UPDRS III, as well as total daily LDE dose. Regression analysis with ESS scores as the dependent variable (controlling for age and gender) showed significant independent associations with axial/postural/gait impairment, depressive symptoms, and pain. This model was able to account for about 20% of the variation in ESS scores. The analysis was repeated including total daily LDE dose as an additional independent variable without any changes in the results. EDS did not load

significantly together with any other of the PD features entered into the principal component analysis (PCA; Figure 4). Another PCA was conducted including the total UPDRS III motor score as an indicator of parkinsonism. Additional PCA with the five UPDRS III derived motor symptom profile scores were conducted (Table 4). These analyses did not change the result and therefore this finding was consistent.



Principal Content Analysis (PCA) results of five components, C1 – C5. The symptoms/variables within each component loaded significantly. In component C5, the excessive daytime sleepiness (EDS) was the only component with significant loading.

Figure 4 Results of PCA with varimax rotation

Table 4. Principal component analysis (varimax rotation) using the five symptomatic profile scores from the UPDRS III [a]

	Component [b]							
	1	2	3	4	5	6	7	Communalities
Motivation (UPDRS I)	**0.925***	0.076	-0.089	0.055	0.016	-0.098	-0.115	0.812
Depression (HADS)	**0.654***	0.102	0.118	-0.016	0.317	0.063	0.167	0.879
Fatigue (FACIT-F)	**0.599***	0.316	-0.005	-0.001	0.367	0.360	0.241	0.822
Axial/postural/gait impairment (UPDRS III)	0.196	**0.827***	0.123	-0.113	0.158	0.055	0.182	0.661
Limb bradykinesia (UPDRS III)	0.132	**0.754***	0.079	0.223	-0.071	0.113	-0.042	0.701
Cognition (MMSE)	-0.079	**0.618***	0.260	-0.028	0.332	0.104	-0.227	0.818
Fluctuations (UPDRS IV)	0.087	0.164	**0.866***	-0.038	0.012	0.091	-0.038	0.795
Dyskinesias (UPDRS IV)	-0.159	0.235	**0.787***	-0.125	0.261	0.158	-0.095	0.630
Rigidity (UPDRS III)	0.161	-0.031	**0.598***	0.258	-0.224	-0.325	0.307	0.781
Resting tremor (UPDRS III)	0.007	0.027	-0.031	**0.910***	-0.106	-0.174	-0.086	0.812
Action tremor (UPDRS III)	-0.007	0.049	-0.007	**0.875***	0.219	0.043	0.060	0.585
Symptomatic orthostism (UPDRS IV)	0.230	0.067	-0.061	0.118	**0.804***	-0.050	-0.097	0.710
Thought disorder (UPDRS I)	0.054	0.360	0.275	-0.040	**0.577***	-0.065	0.290	0.767
Pain (NHP-Pain)	-0.124	0.275	-0.024	-0.102	-0.153	**0.770***	0.222	0.800
Anxiety (HADS)	0.238	-0.029	0.135	0.075	0.503	**0.595***	0.146	0.631
Sleep quality (PSQI)	0.500*	-0.004	0.274	-0.294	-0.100	**0.571***	-0.229	0.896
Daytime sleepiness (ESS)	0.022	-0.005	-0.023	-0.023	0.043	0.161	**0.884***	0.733

[a] Kaiser-Meyer-Olkin measure of sampling adequacy, 0.461; Bartlet's test, P<0.001.
Bold loadings indicate the strongest loading for each variable; significant loadings (>0.481; Norman & Streiner 2008) are indicated with *.
UPDRS, The Unified Parkinson's Disease Rating Scale; HADS, The Hospital Anxiety and Depression Scale; FACIT-F, The Functional Assessment of Chronic Illness Therapy - Fatigue scale; PSQI, The Pittsburgh Sleep Quality Index; MMSE, Mini-Mental State Exam; NHP, The Nottingham Health Profile; ESS, Epworth Sleepiness Scale.

Paper II *A 10-year Follow-up of Excessive Daytime Sleepiness in Parkinson's Disease*

Fifteen of 30 participants were classified as having EDS (ESS > 10) at inclusion, and at the end of the follow-up period seven participants scored above 10 in ESS. At the group level, EDS remained stable over 10 years and did not deteriorate in parallel with worsening of motor symptoms. The mean ESS scores varied between 7.5 (year 5) and 10.5 (baseline) and were slightly lower at the end of the study than at inclusion.

EDS assessed by ESS was not stable during the follow-up at individual level. One participant scored >10 at every visit, three participants developed EDS during the follow-up period, and three participants scored >10 at most of the visits. Four people who scored for EDS at baseline scored 10 or less at the end of the study. So, at the individual level, ESS scores fluctuated from year to year.

Seventeen participants completed the 10-year follow-up. The mean (SD) disease duration was 15.3 (3.7) years, the median disease severity had deteriorated from HY mild (II) to moderate (III), and UPDRS motor scores deteriorated from 14 at baseline to 28 at the end of the study.

During the follow-up period a significant increase of daily levodopa doses, neuropsychiatric impairment, motor symptoms (specific axial/postural/ gait impairment and limb bradykinesia), dyskinesias, depression, and fatigue was found. Daily dopamine agonist, however decreased during the study period.

Intraindividual associations between ESS and sleep quality, depression, anxiety, and axial/postural/gait impairments (PIGD phenotype) were found, but not in the overall motor state scored by UPDRS III (Table 5; effect on ESS). There was no association between ESS scores and the dopaminergic medication for participants who completed the whole study.

There were 13 dropouts during the follow-up: severe cognitive deterioration (n = 3), deaths (n = 6), withdrawal of informed consent (n = 2, one after baseline and another after five years), and two were lost to follow-up: one after five years and another after seven years.

Table 5.

Longitudinal changes in variables as well as standardized intra-individual associations with ESS.

	Effect of Time		Effect on ESS
Variable	Intercept (*SE*)[a]	Slope (*SE*)[b]	Beta (*SE*)[c]
LDE (mg)	994.2 (83.86)***	56.36 (16.62)**	-0.141 (0.099)
DAag (mg)	97.01 (16.50)***	-5.469 (2.161)*	0.060 (0.117)
UPDRS_I	2.878 (0.301)***	0.092 (0.032)**	0.162 (0.081)†
UPDRS_II	7.290 (0.624)***	0.704 (0.141)***	0.132 (0.082)
UPDRS_III	16.05 (1.438)***	1.308 (0.204)***	-0.020 (0.095)
UPDRS_IV	3.717 (0.356)***	0.161 (0.062)*	0.113 (0.073)
HY	2.178 (0.066)***	0.122 (0.017)***	-0.021 (0.092)
ESS	9.916 (0.839)***	-0.076 (0.137)	-
PSQI	6.834 (0.581)***	0.071 (0.086)	0.226 (0.079)**
MADRS	10.84 (1.355)***	0.136 (0.123)	0.178 (0.069)*
HADS-A	5.417 (0.758)***	0.129 (0.093)	0.249 (0.077)**
HADS-D	4.947 (0.615)***	0.175 (0.075)*	0.127 (0.068)†
HADS-T	10.36 (1.278)***	0.305 (0.156)†	0.245 (0.072)**
FACIT-F	31.49 (1.663)***	-1.022 (0.322)**	0.108 (0.068)
UPDRS_IIIapg	4.687 (0.390)***	0.590 (0.114)***	0.182 (0.079)*
UPDRS_IIIrt	1.559 (0.310)***	-0.057 (0.031)†	0.013 (0.082)
UPDRS_IIIpt	0.124 (0.045)**	0.002 (0.008)	0.017 (0.125)
UPDRS_IIIrig	2.511 (0.509)***	0.083 (0.053)	-0.077 (0.079)
UPDRS_IIIbrad	7.046 (0.649)***	0.791 (0.111)***	-0.081 (0.091)

[a] Predicted value on variable at baseline; [b] Predicted change in variable score per year; [c] Standardized intra-individual association between variable and ESS;

*** $p < .001$; ** $p < .01$; * $p < .05$; † $p < .10$

DA-agonist, dopamine agonist; ESS, Epworth Sleepiness Scale; ; FACIT-F, Functional Assessment of Chronic Illness Therapy - Fatigue scale; HADS, The Hospital Anxiety and Depression Scale, A- anxiety, D-depression, T-total; HY, Hoehn and Yahr staging; LDE, Levodopa Equivalent Dose; MADRS, Montgomery Asberg Depression Rating Scale; PSQI, Pittsburgh Sleep Quality Index; UPDRS, Unified Parkinson's Disease Rating Scale: I = Mentation, Behavior and Mood, II = Activities of Daily Living, III = Motor examination, IV = Complications of therapy; UPDRS_III, motor symptom profile scores UPDRSIIIapg, axial/postural/gait impairments (items 18, 19, 27–31); UPDRSIIIrt, rest tremor (item 20); UPDRSIIIpt, postural tremor (item 21); UPDRSIIIrig, rigidity (item 22), UPDRSIIIbrad, limb bradykinesia (items 23–26).

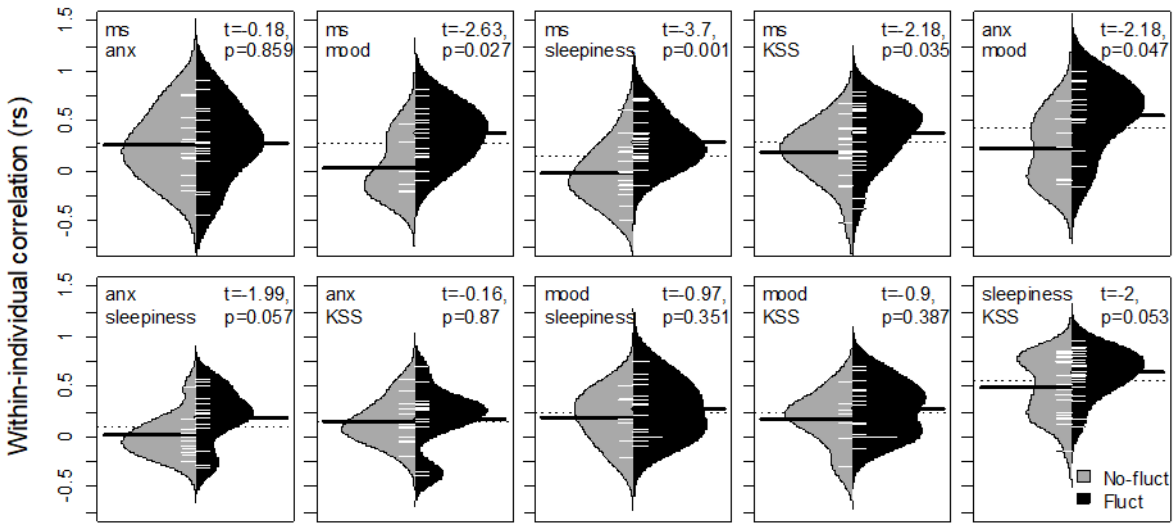
Paper III *Associations between Fluctuations in Daytime Sleepiness and Motor and Non-motor Symptoms in Parkinson's Disease*

Fifty-three people with PD were included in the study. One participant was excluded from the analysis due to an incomplete study protocol. The remaining 52 participants were divided into fluctuators (n=28) and non-fluctuators (n=24). Forty-nine persons completed the home diary for three (n=42), 2-2.5 (n=5) and 0.5-1.5 (n=2) days, and 52 PKG registrations were included in the analysis.

In general, fluctuators showed more severe PD than non-fluctuators. They also reported more sleep-related problems and fatigue, but less anxiety compared to non-fluctuators. Fluctuators also tended to have higher values for diary variables (motor symptoms, low mood, anxiety, feeling sleepy), PKG scores DKS and FDS compared to the non-fluctuators, except for sleepiness according to KSS, PKG scores BKS and the proportion of time as immobile (PTI).

Fluctuators showed stronger positive correlations between the individual average KSS and sleepiness scores and diary variables (motor symptoms, low mood, and anxiety) compared to non-fluctuators. And overall diary variables (motor symptoms, low mood, anxiety, and feeling sleepy) within-individual standard deviations (WISD) were stronger for fluctuators than for non-fluctuators. The correlations between WISD for the diary variables and the PKG variables were generally weak and non-significant. However, higher fluctuation scores (FDS) covaried with low WISD on sleepiness among fluctuators, whereas high dyskinesia scores (DKS) and FDS tended to coincide with a low WISD on anxiety ratings among non-fluctuators.

The within-individual correlations (WIRS) indicated that high ratings on one diary variable tended to coincide with high ratings on the other variables. However, for each pair of variables at least some participants exhibited negative WIRS as well. WIRS tended to be stronger among fluctuators compared to non-fluctuators (Figure 5). For example, the WIRS between self-rated motor symptoms and sleepiness was markedly stronger among fluctuators.



MS, motor symptoms; KSS, Karolinska Sleepiness Scale; Anx, anxiety

Density of observations of within-individual correlations (WIRS) for fluctuators (black) and non-fluctuators (grey). In each panel, the dotted line indicates the grand mean of the WIRS, the two solid black lines indicate the mean WIRS in each subgroup, and the small white lines indicate individual values. The differences in WIRS between fluctuators and non-fluctuators have been analysed with weighted (for within-individual number of observation) two sample t-tests (see the panels for t- and p-values).

Figure 5

Paper IV *Like a wave in its shape, breadth, and depth: A qualitative interview study of experiences of daytime sleepiness in people with Parkinson's disease*

The content analysis that illuminate experiences of daytime sleepiness in the daily lives of people with PD, revealed four subthemes.

Daytime sleepiness was not a uni-dimensional experience but was seen *as a part of something bigger*. For example, participants considered poor nighttime sleep, antiparkinsonian treatment, and PD as parts of their experience of sleepiness. Some places and situations, such as monotonous activities, could prompt sleepiness, which was more difficult to resist than before their PD onset. However, similar activities might not lead to sleepiness if the people enjoyed them.

Daytime sleepiness was also expressed *as something to struggle against or accept*. Some people had to struggle with sleepiness several times a day and expressed feelings of being paralysed, fatigued, and an overwhelming need to sleep; something that took over their life and was nearly impossible to fight against. Several participants felt that daytime sleepiness limited their daily life, but physical activity and planning of activities could help control sleepiness. However, active participants could also fall asleep unexpectedly when they sat down. Others had accepted their sleepiness and were not disturbed by it in their daily life, although feelings of losing control and potential danger (e.g., while driving) persisted.

However, taking a nap could also be seen as something positive, a way to feel refreshed and to restart the body and brain.

Participants felt that daytime sleepiness led to *reduced self-compassion* with feelings of laziness, being less valuable in the eyes of others, shame, and worrying about what other people might notice and think. All these negative, shameful feelings about sleepiness could diminish their self-compassion. At the same time, they felt entitled to the right to rest or sleep because of their progressive disease.

Participants found it difficult to describe their sensations of sleepiness. It was more than only feeling sleepy, but a combination of sleepiness, tiredness, and fatigue. It could give both physical sensations such as pain, and also affect mental functions and the ability to think clearly *as something beyond sleepiness.*

Taken together, the experiences expressed during the interviews suggest that daytime sleepiness in PD may be expressed like *a wave in its variable shape, breadth, and depth*; a wave that looks very similar for everyone but is experienced differently depending on its content and how it affects the individual's daily life.

Table 6 Example of the analysis process, including examples of meaning units, codes, categories and subthemes that lay behind the overall theme

Meaning units	Condensed meaning units	Codes	Categories	Sub-themes	Overall theme
I see tiredness as a larger concept that has different facets. […] as being tired and sleepy – sleepy-tired. […]and this tiredness manifests itself as sleepiness (Participant 11).	Sleepiness is a larger concept than only sleepiness.	Larger concept	More than sleepiness	Something beyond sleepiness	Like a wave in its variable shape, breadth, and depth
Some days, it [daytime sleepiness] feels like it's like a big bird taking its powerful claws and hugging my body so hard. Hugging and not letting go. (Participant 1).	Sleepiness is a like a big bird hugging my body. It won't let go.	Persistent	Physical sensations		
No matter how much I rest, it doesn't go away (Participant 5).	Resist despite rest.	Irrestible	Overwhelming		

8 DISCUSSION

8.1 SUMMARY OF FINDINGS

EDS in PD is one of the most described non-motor features in PD. The present Papers provide additional knowledge about this disabling symptom of PD. EDS is not easy to understand and characterise because it has several facets and it is not the same for each person with PD. EDS in PD showed a weak relation to motor and other non-motor symptoms such as depression, anxiety, fatigue, poor sleep quality and pain, as well as total levodopa equivalent dose (LED), but not with the other PD symptoms. The changes over time of EDS can vary greatly for the individual from year to year, and, is not a stable, progressive phenomenon in PD as deterioration of motor symptoms and disease progression are. Daytime sleepiness, both for fluctuators and non-fluctuators, fluctuates with PD symptoms such as impaired motor function, anxiety and low mood. The individual experience of daytime sleepiness varies greatly depending on the person's capacity to resist or handle sleepiness.

Paper I

This paper investigated EDS in relation to a large number of motor and non-motor PD symptoms. EDS was independently associated with axial/postural/gait impairment, pain and depressive symptoms but did not covary with other PD symptoms. Associations were generally weak and EDS did not load with other motor or non-motor aspects of PD in exploratory PCA. PD duration and disease severity assessed by HY stages, as well as total levodopa equivalent dose were not associated with EDS. Our observations suggest that EDS is a separate manifestation in PD, differing from, poor sleep quality and fatigue.

EDS showed an independent association with motor sub-score categorised as PIGD phenotype. PIGD phenotype has been associated with more severe PD [8]. This phenotype has also been associated with the development of cognitive impairment and dementia in PD [9, 11], and EDS can predict the cognitive decline in elderly people [88]. We could not see a relationship between cognitive function and EDS, but we excluded participants with cognitive impairment. Our participants represented a population with mostly mild to moderate PD and their PD symptoms were not so severe, and this may have influenced our results. However, depression, anxiety, fatigue, and pain can be early, prodromal symptoms of PD [12], and despite their weak correlation with EDS, it is important to screen for EDS even in early PD. Our results are in line with Junho et al. [89] who studied clinical predictors of EDS in PD.

Paper II

This longitudinal observation of younger people with PD showed at the group lever a slightly lower progression of EDS over time. EDS did not deteriorate during follow-up, in contrast to PD progression and motor symptoms. Total levodopa equivalent dose increased, and dopamine agonist decreased during the study period, but these findings were not associated with EDS. For the individuals the EDS varied from one year to another, and was not a stable,

progressive phenomenon. There were a few participants with more persistent EDS. For the others, EDS could be present in some years and then disappear or could develop during the follow-up period.

Our findings are not in line with previous studies [45-47] which have shown that EDS is persistent and progressive over time despite different stages of PD. Both Tholfsen et al. [46] and Amara et al. [45] studied de novo patients. Zhu et al. [47] had patients with different disease durations and stages, but they used another instrument, SCOPA-sleep [90], to detect EDS. We had a small sample size covering different stages of PD, and this may have influenced our results. On the other hand, maybe the EDS progress can vary in different stages of PD.

As mentioned before, EDS is a risk factor for developing dementia. Some participants developed cognitive impairment and dementia during the study, but these participants were not classified as having EDS. Again, our sample size is a limitation, and these observations are few.

EDS is not a permanent, progressive phenomenon in PD, and therefore it is important to investigate this disabling symptom continuously during the disease progression.

Paper III

This paper investigated the role of daytime sleepiness in fluctuations in PD. Our patient diary data showed that episodes of daytime sleepiness were associated with fluctuations in mood, anxiety and motor symptoms, both for fluctuators and non-fluctuators. The fluctuators showed a stronger correlation between sleepiness, motor symptoms and low mood, but less anxiety than non-fluctuators. They also had a more severe PD both in terms of symptoms and disease severity, and this can be a sign of more severe disease progression due to longer PD duration and higher total levodopa doses than for non-fluctuators. The PD symptoms deteriorate during the disease progression and therefore it is not surprising that fluctuators showed a higher association between diary variables, except anxiety, than non-fluctuators.

The patient diaries for both fluctuators and non-fluctuators showed an association between diary items. There was a tendency for higher values in one variable, followed by higher values even in other values or vice versa. This is not surprising because people with PD can assess their symptoms as a whole rather than independent features. The symptoms of PD can be related to each other e.g. sleepiness and fatigue [60, 61], and therefore may be difficult to distinguish.

We used a patient home diary to collect the participants' subjective experience of the presence of motor symptoms, low mood, anxiety, and overall sleepiness as feeling sleepy. There is much criticism of patient diaries [22], but we obtained a high response rate from our patient diary, probably due to the brief training before the initiation which led to good compliance. An alternative to home diaries is electronic diaries, but their use is associated with additional challenges, such as technical problems, and need of support from relatives

[91]. Despite its shortcomings we chose to use the patient diary because it was an easy way to collect the data about participants' experience of motor and non-motor features in this real-life study.

The participants wore a PKG logger for six days. In general, correlations between diary variables and PKG scores (bradykinesias, dyskinesias, fluctuations and amount of time immobile (PTI)) were weak. Notably, the non-fluctuators showed higher bradykinesia and PTI scores than fluctuators. Non-fluctuators with bradykinesias may need to rest more due to parkinsonian symptoms. Maybe this reflects the weakness of the PKG logger, because it records all movements of the most affected wrist, which can lead to misleading results. The PKG logger is probably not so useful for detecting daytime sleepiness, even though Kotschet et al. [92] suggested PTI as a surrogate to measure daytime sleepiness in PD, because a correlation between PTI and ambulatory daytime polysomnography (PSG) was shown. PTI is not the same as daytime sleepiness or feeling sleepy, because PTI is more an indication of falling asleep rather than feeling sleepy. So far, PKG has been shown to be a complement to other instruments, like self-estimated scales or clinical interview, to detect daytime sleepiness in PD.

Paper IV

Twelve people with PD with daytime sleepiness (DS) were interviewed face-to-face. Their experience of DS was much more varied than in previous studies. DS describes as a part of something bigger than feeling sleepy. The impact of DS varied greatly among participants, from struggling with sleepiness most of time to taking a nap to get a new start for the body and brain during the day. Many participants had shameful feelings about their sleepiness and this could be expressed as reduced self-compassion. Sleepiness was not easy to describe, because it had many different layers, from tiredness to physical and mental sensations.

Some participants connected DS with PD and its treatment, especially dopamine agonist. Sleepiness had become a part of PD, expressed with comments such as "I never felt sleepy in the daytime before my Parkinson diagnosis". No one mentioned progression of sleepiness with worsening of PD, which is in line with the results from our longitudinal study [93], but in contrast to other longitudinal studies [45-47]. The dopamine replacement therapy, especially dopamine agonist has been connected with both sleepiness and sudden onset of sleep [94], but these results are inconsistent. Another interesting finding was that no one described a specific PD symptom, motor or non-motor, as a part or cause of sleepiness. As mentioned before, this may be due to seeing PD as a whole and not in terms of individual symptoms.

The individual resilience could affect how the participants handle sleepiness. Participants who described their DS as severe, and something to struggle against most of the time. Their experiences of sleepiness may be related to fatigue, even the definitions of these phenomena differ. Daytime sleepiness is more like feeling sleepy, a risk to fall asleep, and fatigue is more like feeling a lack of energy and exhaustion related to physical and cognitive impairment

[56]. These more affected participants described both physical symptoms such as pain, and difficulty in thinking during the disabling sleepiness. There is an overlap between DS and fatigue, despite the differences in their expression [60, 61], but it can be experienced as the same for people with PD who are suffering from both DS and fatigue. Physical activity and planning of daily activities were the most common ways to handle, accept and control DS.

Participants described DS with terms such as laziness, being less valuable in the eyes of others, and hiding the sleepiness from others e.g. during meetings. These shameful feelings could reduce their self-compassion, and this could secondarily lead to social isolation. PD itself is a risk factor for social isolation because of symptoms such as impaired communication, reduced facial and bodily expression [6, 12]. Sleepiness in the daytime is an additional burden for the people with PD because it can affect their PD symptoms and limit their social contacts and leads to even more isolation for both themselves and their families.

Participants found it difficult to find an adequate word to describe their sleepiness. Tiredness was the most used word for this phenomenon. Many participants did not know that DS is a symptom of PD and therefore had never discussed this symptom with their health care staff. Participants described sleepiness as more than only feeling sleepy; rather a combination of sleepiness, tiredness, and fatigue. Therefore, it is important to distinguish what the person means by "tiredness"," fatigue", "feeling sleepy", "groggy" or "drowsiness" [95].

The participants' experience of DS in PD is multi-dimensional and its impact in daily life depends on the person's ability to resist the sleepiness or find a way to accept this disabling symptom of PD.

8.2 METHODOLOGICAL CONSIDERATIONS

All assessments, both clinical and self-reported were made using validated instruments. The UPDRS, HY and some of the other instruments (HADS, MADRS, NHP) are recommended by the International Parkinson and Movement Disorder Society (www.movementdisorders.org). The MMSE was used to screen for cognitive impairment, and maybe a test such as the Montreal Cognitive Assessment (MoCA; [96]) could be more accurate in detecting cognitive impairment than the MMSE. Neither the MDS-UPDRS nor the MoCA was available at the start of the studies. The PKG logger is a rather novel method to record motor fluctuations and the proportion of time immobile (PTI) in PD, and therefore we wanted to test the device to give an objective measurement of these symptoms of PD, despite its limitations for recording PTI.

We have used self-rating assessments to reduce misunderstandings caused by interpretations of the statements between the participants and data collector (A.H.). It may also be less of a burden for the participant to fill in self-rated assessments rather than being interviewed, thus minimising both stress and tiredness. Of course, self-rating scales are not without criticism, e.g. Onen et al. [97] found that older adults > 65 years underestimated their sleepiness

compared with spouses' observations assessed by ESS. Another finding was that up to 20 % of participants who were "usually sleepy during the daytime" did not reach the mean ESS score for the cut-off level (>10) for EDS.

We used different kinds of study design and methods for data collection to get a broader knowledge of daytime sleepiness in PD in relation to both motor and non-motor symptoms, disease progression over time and consequences in daily life.

8.3 STRENGTHS AND LIMITATIONS

Our studies have both strengths and limitations. The same rater and data collector (A.H.) worked on all studies, except in centres outside Stockholm in the multicentre study (Paper I). The rater had been trained in clinical assessment of parkinsonian symptoms according to the UPDRS. So, all assessments were done similarly year by year. We also studied EDS and DS in PD from different points of view, from associations with other symptoms of PD to people with PD experience, which gives a broader picture of both EDS and DS as phenomena in PD. Another strength is our sample, since we did not exclude people with signs of cognitive impairment because we wanted to study the ordinary population with PD at the clinic.

One limitation to mention is our population. All data collections were done at the university clinic with a selected population including patients with less severe PD, and therefore it can be different from the total PD population. On the other hand, we studied a common non-motor symptom of PD, and the experiences of daytime sleepiness are probably similar in most people with PD.

Our sample size is not optimal, especially the Paper II longitudinal study with 30 including participants at the baseline, and remaining 17 participants at the end of follow-up period. We are aware of this and the deficiency has been compensated with the large number (n = 241) of observations. Thus, our results are reliable despite the small sample size.

The qualitative interview study (Paper IV) with 12 participants seems to be few, but the aim of the study was to explore the experiences of DS in PD, and not to investigate a new phenomenon in PD. The participants were selected from a larger sample (Paper III) and were defined as having EDS, and varied in age, and PD duration and severity, and were therefore representative for the PD population.

9 CLINICAL IMPLICATIONS

The participants had difficulties in describing daytime sleepiness because their experiences included a mix of sleepiness, fatigue and tiredness (Figure 6). Tiredness was the most used term for sleepiness of participants and this can be misinterpreted by health care staff as a less severe condition. It can lead to misunderstanding and even to dissatisfaction in the relationship between the patient and health care staff. Maybe it is better to talk about feeling sleepy than daytime sleepiness or excessive daytime sleepiness [98] because the word 'excessive' can be interpreted as indicating very severe sleepiness and therefore it can lead to underestimation of the burden of daytime sleepiness. Many people with PD are not aware that daytime sleepiness is a symptom of PD or see the sleepiness as an aspect of poor nighttime sleep and not as a separate feature, and therefore do not discuss it during the consultation [99].

Dopaminergic treatment of PD can cause EDS in PD, especially when dopamine agonists are used. How people with PD respond to the dopaminergic treatment is individual, and if a person responds with severe daytime sleepiness or with sleep attacks the medication should be changed [51]. There are a few studies [52-55] about treatment with modafinil with some benefit, but these studies had a limited number of participants and no long-term data are available. So, it is too early to recommend modafinil as a common treatment for EDS in PD.

Pharmacological treatment is often not an option for treating DS, and thus the people who are suffering from DS need to find a way to live with it. The patient and relatives Educational Program e.g. The Swedish National Parkinson School [100] can train the participants how to cope with symptoms of PD. Many participants used physical activity to resist and handle with daytime sleepiness. Maybe an individual training program can get in providing relief for this disabling symptom of PD. Also, light therapy was shown to improve alertness for people with PD who were suffering from EDS [101]. A short nap on daytime can also be an option to improve daytime sleepiness in PD.

The participants experience of feeling sleepy is an overlap of tiredness, sleepiness and fatigue

Figure 6

10 CONCLUSIONS

- EDS seems to be a separate phenomenon in PD, because it does not correlate with motor and other non-motor symptoms of PD, and has no interrelationship with other symptoms of PD.

- EDS is not a stable or progressive phenomenon over time but can vary greatly at the individual level, and even disappear during the PD progression. EDS remained stable over 10 years and did not deteriorate in parallel with worsening of motor symptoms and PD progression.

- The people with more severe PD (classified as the PIGD phenotype) are more likely to have EDS than the people with the tremor dominant phenotype.

- Daytime sleepiness fluctuates with motor and other non-motor symptoms, e.g. low mood and anxiety, in PD. The people with PD with motor fluctuations showed a stronger correlation between daytime sleepiness, motor symptoms and low mood, but not for anxiety, than non-fluctuators.

- The experience of DS in PD is multi-dimensional and the impact of DS in daily life depends on the person's ability to resist the sleepiness or find a way to accept this disabling symptom of PD.

- People with PD describe their sleepiness as more like feeling sleepy or as tiredness rather than DS or EDS. EDS can be interpreted as a more severe symptom than feeling sleepy or tired.

Taken together, daytime sleepiness in PD may be expressed like a wave in its variable shape, breadth, and depth. A wave that looks very similar for everyone, but is experienced differently depending on its content and how it affects the individual's daily life.

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