Parkinson's Disease: Measurement, Monitoring, and Management - Focus on non-motor symptom treatment guidelines, sleep disturbances, and motor complications

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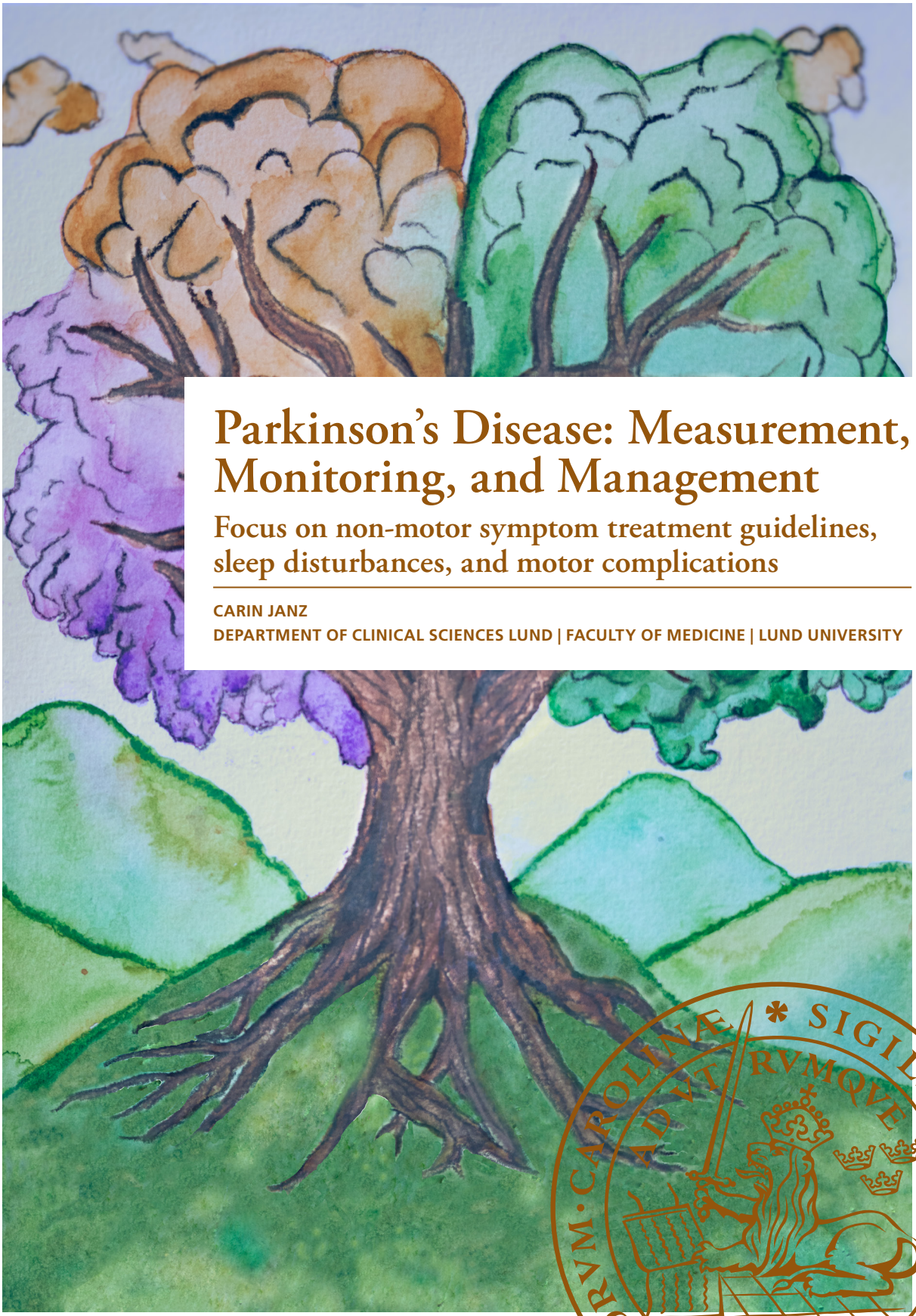

Parkinson's Disease: Measurement, Monitoring, and Management

Focus on non-motor symptom treatment guidelines, sleep disturbances, and motor complications

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Parkinson’s Disease: Measurement, Monitoring, and Management

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Carin Janz

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Abstract:

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Aims: The overarching aim of this thesis is to improve understanding of NMS management in PD and to strengthen the evidence base for tools used to measure and monitor PD symptoms and fluctuations.

Methods: A descriptive, cross-sectional study assessed adherence to national and international pharmacological NMS treatment guidelines. An open-label, observational study evaluated rotigotine's effects on sleep and daytime sleepiness, along with correlations between PKG parameters and subjective questionnaires. The HD was validated in one investigational and one observational clinical study.

Results: On average, 32% of NMS were treated according to guidelines. Rotigotine improved sleep only in dopamine agonist-naïve patients and those with severe baseline sleep disturbances. Daytime sleepiness did not worsen with rotigotine, PKG scores even indicated improvement. However, PKG-derived nocturnal sleep and daytime sleepiness metrics showed no significant correlations with corresponding questionnaires. Structured patient training on motor complications did not significantly improve overall clinical observer-patient HD agreement, although dyskinesia detection showed non-significant improvement. Temporal HD agreement was fair between relative-observer and relative-patient groups. Distributions of daily time spent in "off" and "on without dyskinesia" states differed significantly between both relative-observer and patient-observer groups, but not between relatives and patients.

Conclusions: Low adherence to NMS guidelines suggests under-recognition, underscoring the need for systematic detection and management strategies. Rotigotine may improve sleep in patients with severe baseline disturbances and warrants further study for daytime sleepiness. PKG sleep metrics require further validation against polysomnography and established questionnaires. The HD reflects subjective motor state experience and is not interchangeable with observer ratings; validated monitoring alternatives are needed.

Key words: Parkinson's disease, Motor fluctuations, Dyskinesia, Non-motor symptoms, Sleep, Parkinson's KinetiGraph, Rotigotine, and Home Diary.

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"Medicine is a science of uncertainty and an art of probability"

William Osler

Table of Contents

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Preface

I stumbled into the field of Parkinson's disease somewhat by chance while searching for a place to write my master's thesis. My boyfriend met my future supervisor, Professor Per Odin, during his neurology placement in medical school. Per mentioned that he was looking for someone to work as a junior doctor over the summer and then continue with a master's project. I sent him an email, and we arranged a meeting the following week. I vividly remember not understanding most of what was discussed in that first meeting, but I immediately had a good feeling about it.

Over the summer and autumn at the research unit, I learned an incredible amount. I was fascinated by how differently Parkinson's disease could manifest from one patient to another and how dramatically symptoms could fluctuate throughout the day. I also gained invaluable insights from both my colleagues and the patients I had the privilege of meeting and speaking with. By the end of that summer, I knew that I wanted to delve deeper into understanding Parkinson's disease. I was determined to continue the research in the hope of contributing to a better quality of life for the patients who had made such a strong impression on me.

List of Papers

Paper I

Janz C, Timpka J, Rosqvist K, Paul G, Storch A, Odin P. Non-Motor Symptom Management: Insights into Adherence to Treatment Guidelines in Parkinson's Disease Patients. *J Parkinsons Dis*. 2024;14(2):297–312. doi: 10.3233/JPD-230263

Paper II

Grigoriou S†, **Janz C**†, Horne M, Bergquist F, Dizdar N, Odin P. Effects of rotigotine on sleep in Parkinson's disease patients: a Parkinson's KinetiGraph study. *Front Neurol*. 2025;16:1591537. doi: 10.3389/fneur.2025.1591537. †These authors have contributed equally to this work and share first authorship.

Paper III

Janz C, Timpka J, Löhle M, Bremer A, Gandor F, Ebersbach G, Storch A, Odin P. Agreement between Parkinson Disease Home Diary and Observer Assessments before and after Structured Patient Training. *Acta Neurol Scand*. 2023;2023:8667591. doi: 10.1155/2023/8667591.

Paper IV

Janz C, Timpka J, Storch A, Paul G, Odin P. Agreement between relatives of Parkinson's patients and clinical observer in Home Diary assessments. *Unpublished, submitted.*

Author's contribution to the Papers

Paper I, III and IV

Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - Original Draft, Writing -Review and editing.

Paper II

Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - Original Draft, Writing - Review and editing.

Thesis at a glance

Table 1. Summary of the included papers

Paper	Aim	Results and conclusions
I	To investigate the adherence to national and international pharmacological NMS[a] treatment guidelines in patients with mild to severe PD[b], who were able to walk or stand unassisted (Hoehn and Yahr ≤ 4).	Among 165 included patients, the median number of NMS was 14, with a median of 7 symptoms identified as requiring treatment. Guideline adherence was highest for depression (79%) and constipation (77%), but lowest for dysphagia (0%) and daytime sleepiness (4%). On average, only 32% of NMS were treated according to guidelines.
II	1) To investigate the effects of rotigotine on sleep in PD patients using PDSS-2[c] and PKG[d] recordings. 2) To investigate the effect of rotigotine on daytime sleepiness, quality of life and motor symptoms in PD patients. 3) To examine correlations between PKG-derived parameters and corresponding questionnaire-based measures for sleep and daytime sleepiness.	1) Rotigotine did not significantly improve sleep based on the PDSS-2 or PKG scores in the entire study population. However, patients with PDSS-2 ≥ 18 and those naïve to dopamine agonists showed improvements in PDSS-2 (p = 0.009, r = 0.33 and p = 0.013, r = 0.31, respectively). 2) PKG data showed reduced PTI_D[e] with rotigotine treatment (p < 0.001, r = 0.56), possibly reflecting reduced daytime sleepiness. Motor symptoms and health-related quality of life improved significantly with rotigotine, as shown by questionnaires and PKG data. 3) No significant correlations were observed between the PTI_D and the ESS[f] (ρ = -0.046, p = 0.718) or between the CSS[g] and the PDSS-2 (ρ = -0.065, p = 0.612).
III	To investigate the effect of structured patient training regarding motor fluctuations and dyskinesia on the agreement between clinical observer and patient HD[h] ratings in the evaluation of the PD motor state and daily motor state times.	The observer and 20 patients completed 316 pairs of motor state assessments. The overall agreement was 68% before training and 76% after (p = 0.093, r = 0.27). Structured patient training did not significantly improve agreement between observer and HD ratings or the correlation/reliability of daily motor state times. Before training, agreement for the "on with dyskinesia" state was 58%, which increased to 80% following training (p = 0.074, r = 0.33).
IV	1) To evaluate the agreement between a clinical observer and relatives of PD patients when assessing the patients' motor status using the HD. 2) To evaluate agreement between relatives and patients, and between patients and clinical observer, when rating PD motor state using the HD.	1) The clinical observer and 28 relative-patient pairs completed 445 sets of motor state ratings. Temporal agreement between relatives and the observer was fair (Cohen's kappa [κ] = 0.250), with agreement ranging from 26% for "off" to 71% for "on with dyskinesia". Significant differences were found in the daily time distribution for "off" and "on with dyskinesia" states when comparing relative-observer and patient-observer ratings. 2) Temporal agreement between relative-patient pairs was fair (κ = 0.230) and between patient-observer pairs slight (κ = 0.120).

[a]NMS: non-motor symptoms; [b]PD: Parkinson's disease; [c]PDSS-2: Parkinson's Disease Sleep Scale-2; [d]PKG: Parkinson's KinetiGraph; [e]PTI_D: daytime Percent Time Immobile; [f]ESS: Epworth Sleepiness Scale; [g]CSS: Combined Sleep Score; [h]HD: Home Diary.

Abbreviations

BKS	Bradykinesia Score
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CISI-PD	Clinical Impression of Severity Index for Parkinson's disease
CSS	Combined Sleep Score
COMT	Catechol-O-methyltransferase
DA	Dopamine agonist
DBS	Deep brain stimulation
DKS	Dyskinesia Score
EDS	Excessive daytime sleepiness
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level Scale
ESS	Epworth Sleepiness Scale
HADS	Hospital Anxiety and Depression Scale
HD	Home Diary
H&Y	Hoehn and Yahr
ICC	Intraclass Correlation Coefficient
LCIG	Levodopa–carbidopa intestinal gel
LECIG	Levodopa–entacapone–carbidopa intestinal gel
LEDD	Levodopa equivalent daily dose
MDS	Movement Disorder Society
MDS-NMS	Movement Disorder Society-Non-Motor Rating Scale
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NMS	Non-motor symptoms
NMSS	Non-Motor Symptoms Scale
NMSQ	Non-Motor Symptoms Questionnaire

ParkReg	Swedish National Quality Registry for Parkinson's Disease
PD	Parkinson's Disease
PDQ-8	Parkinson's Disease Questionnaire (8 items)
PDSS-2	Parkinson's Disease Sleep Scale-2
PKG	Parkinson's KinetiGraph
PSG	Polysomnography
PTB	Percent Time in Bradykinesia
PTI_N	Nighttime Percent Time Immobile
PTI_D	Daytime Percent Time Immobile
PTT	Percent Time with Tremor
PTD	Percent Time in Dyskinesia
QoL	Quality of life
RCT	Randomised controlled trial
RBD	Rapid eye movement sleep behaviour disorder
REM	Rapid eye movement
RLS	Restless legs syndrome
SWEMODIS	Swedish Movement Disorder Society
UPDRS	Unified Parkinson's Disease Rating Scale
VALIDATE-PD	The Diagnostic Validity of the Hauser Patient Diary and Sensor Based Movement Tracking for Evaluation of Motor Fluctuations in Advanced Parkinson's Disease Study Program
VAS	Visual Analogue Scale

Introduction

Parkinson's disease in brief

Parkinson's disease (PD) was first described by James Parkinson, who in 1817 published "An Essay on the Shaking Palsy", formally establishing PD as a medical condition.[1] Despite significant progress since then, our understanding of this complex and heterogeneous disease remains incomplete.[2]

As the second most common neurodegenerative disorder, PD affects approximately 1% of the population over the age of 60.[3] Cardinal symptoms include tremor (shaking), rigidity (stiffness), bradykinesia (slowness of movement), and postural instability.[3] However, motor symptoms vary widely,[2] and the clinical picture often includes numerous non-motor symptoms (NMS).[4] These symptoms include sleep disturbances, daytime sleepiness, cognitive impairment, constipation, anxiety, and depression.[4] As the disease advances, both motor symptoms and NMS worsen, with dyskinesia and symptom fluctuations becoming more frequent.[2]

The primary pathological features of PD include the loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies.[2, 4] These are aggregates of misfolded proteins, primarily composed of α-synuclein.[2, 5] Lewy pathology can occur in the brain, peripheral nervous system, and spinal cord.[2] Additionally, disruptions in synaptic transport, neuroinflammation, mitochondrial dysfunction, and lysosomal impairment all contribute to the complex pathophysiology of PD.[5] PD is diagnosed clinically,[6] though magnetic resonance imaging (MRI) or dopaminergic imaging can facilitate differential diagnosis against, for example, atypical parkinsonism or essential tremor.[4]

Treatment is symptomatic, primarily targeting the dopaminergic system.[4] Levodopa is often the first-line therapy and can be combined with other agents, such as dopamine agonists (DAs), catechol-O-methyltransferase (COMT) inhibitors, and monoamine oxidase type B (MAO-B) inhibitors. Furthermore, some medications target the glutamate, adenosine, or acetylcholine pathways.[5] Device-aided therapies, including deep brain stimulation (DBS), levodopa infusion pumps, and subcutaneous apomorphine, can also be employed. Although treatment for NMS varies,[7] dopaminergic drugs can alleviate some of these symptoms.[5] Beyond pharmacological treatments, physiotherapy, occupational therapy, and exercise are crucial in managing PD symptoms.[5]

Epidemiology and pathophysiology

As the second most prevalent neurodegenerative disorder, PD impacts approximately 1% of the population aged over 60.[3] By 2019, global prevalence reached approximately 8.5 million individuals.[8] Over the last two decades, both incidence and prevalence have risen sharply. While an aging global population partly explains this trend,[5] age-standardised prevalence rates have increased by nearly 22%.[9] Other potentially contributing factors include improved diagnostic accuracy, prolonged survival, and environmental neurotoxin exposure.[5]

Pathophysiology in PD stems from a complex interplay of factors, including α-synuclein aggregation into Lewy Bodies, neuronal destruction, dysfunction in lysosomal and mitochondrial processes, neuroinflammation, and impairments in vesicle and synaptic transport. These processes lead to the progressive loss of both dopaminergic neurons and broader motor and non-motor circuits.[5] Although most cases are idiopathic, identifiable genetic risk factors are present in 5–10% of patients.[3] The **Braak hypothesis** posits that PD is initiated by an external agent entering the central nervous system, likely through the vagus nerve from the gastrointestinal tract. This theory suggests that the earliest lesions appear in the olfactory bulb, anterior olfactory nucleus, and dorsal motor nucleus of the vagus nerve.[10] This anatomical progression explains why constipation and olfactory deficits are frequent prodromal symptoms of PD.[5]

An alternative hypothesis proposes two distinct PD subtypes based on the site of pathological origin. In the **body-first** subtype, α-synuclein pathology originates in the enteric or peripheral nervous system. It then ascends through the sympathetic connectome to the heart and via the vagus nerve to the dorsal motor nucleus, in line with the Braak hypothesis. Conversely, in the **brain-first** subtype, pathology begins within the central nervous system or olfactory bulb before descending to the peripheral autonomic nervous system. In this model, prodromal rapid eye movement (REM) sleep behaviour disorder (RBD) indicates a body-first subtype, whereas RBD onset following motor symptoms suggests the brain-first subtype.[11] It's hypothesised that the brain-first phenotype is linked to genetic predisposition, while the body-first phenotype is driven by alterations in gut microbiota.[5]

Overview of antiparkinsonian treatments

The sites of action for various antiparkinsonian drugs are displayed in **Figure 1**.

Levodopa

Levodopa is a precursor to dopamine that can cross the blood-brain barrier, unlike dopamine itself. Once in the brain, it is converted to dopamine and relieves PD

symptoms.[4, 12] However, this conversion also occurs in the peripheral nervous system.[13] Therefore, levodopa is given together with carbidopa or benserazide. These are both decarboxylase inhibitors that block peripheral conversion, ensuring that as much levodopa as possible reaches the brain. For optimal absorption, patients are advised to take levodopa one hour before or two hours after protein-containing meals. Levodopa is available in multiple formulations, including capsules, inhalations, and infusions. Common side effects include nausea, dizziness, headache, and somnolence.[12]

Dopamine agonists

DAs mimic dopamine by binding to and activating dopaminergic receptors.[5] They tend to cause fewer dyskinesias compared to levodopa but are associated with other side effects, such as impulse control disorders, nausea, excessive daytime sleepiness (EDS), and hallucinations.[5, 14] Examples of DAs include ropinirole, pramipexole, rotigotine, and apomorphine. Ropinirole and pramipexole are administered as oral tablets, rotigotine is administered via a transdermal patch, and apomorphine through injection, sublingual film, or infusion.[14] An advantage is that several DAs can be dosed once daily.[15]

COMT inhibitors

The metabolism of levodopa into 3-O-methyldopa limits its cerebral bioavailability. This methylation is catalysed by the enzyme COMT, which exists both peripherally and centrally. COMT inhibitors (such as entacapone, opicapone, or tolcapone) reduce the plasma elimination of levodopa, increasing its availability in the brain.[14]

MAO-B inhibitors

The MAO-B enzyme is responsible for the metabolism of dopamine within the synapse. By utilising MAO-B inhibitors (selegiline, rasagiline, or safinamide), this degradation is reduced, increasing the dopamine availability locally within the synapse.[14]

Amantadine

Amantadine demonstrates both antiparkinsonian and antidyskinetic effects.[16, 17] Although its exact mechanisms remain incompletely understood, the drug exhibits multiple pharmacodynamic properties.[17] It acts as a non-selective glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist.[14, 17] This antiglutamatergic property is hypothesised to be central to its antidyskinetic efficacy, as dysregulation of glutamatergic signalling is a key driver of dyskinesia development. Additionally, amantadine appears to enhance dopamine transmission through both pre- and post-synaptic mechanisms.[17] Specifically, amantadine stimulates dopamine release and prevents its reuptake.[18]

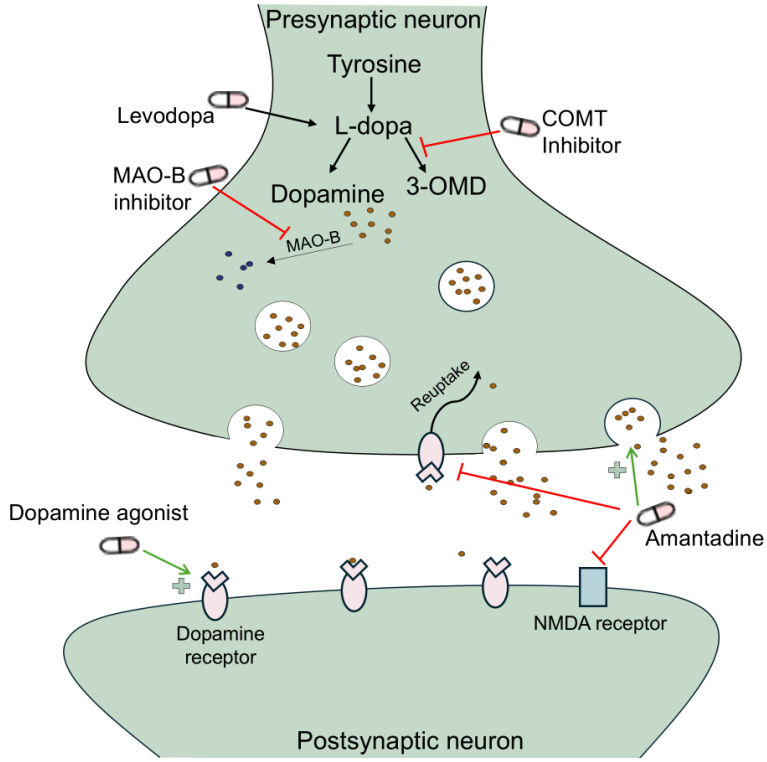

Figure 1: Antiparkinsonian drugs and their sites of action
MAO-B: monoamine oxidase type B; COMT: catechol-O-methyltransferase; 3-OMD: 3-O-methyldopa; NMDA: N-methyl-D-aspartate. Figure created in Microsoft PowerPoint but modified after Bloem et al.[5]

Motor symptoms and complications

Motor symptoms in PD typically present asymmetrically.[4] While patients frequently report resting tremor, family members may observe a stooped posture or a reduced arm swing during gait. A clinical PD diagnosis requires bradykinesia combined with resting tremor, rigidity, or both.[6] Initial treatment typically provides significant relief, sometimes causing symptoms to disappear.[14] Over time, symptoms become bilateral,[19] more severe, and increasingly complex to manage.[14] Long-term dopaminergic treatment is often complicated by the emergence of motor complications (**Figure 2**). These include motor fluctuations, where patients alternate between the "on" state and the "off" state, as well as dyskinesias.[16] The "on" state indicates that the patient receives sufficient benefit from their antiparkinsonian treatment, resulting in reduced parkinsonian signs and improved functional status.[14] *Papers III* and *IV* validate a patient diary as a tool for monitoring these motor complications.

Different types of motor complications

"Off" state

The "off" state occurs when levodopa's therapeutic effect diminishes, causing symptoms to return toward untreated levels.[14] Symptoms in the "off" state include tremor, bradykinesia, rigidity, muscle cramps, balance issues, dysphagia, and hypophonia. Some NMS can worsen in the "off" state, such as depression, anxiety, fatigue, apathy, concentration difficulties, and cognitive impairment. Despite involving NMS, the "off" state is still classified as a motor fluctuation due to the historical prioritisation of motor symptoms in Parkinson's research.[20]

Various "off" periods exist in PD. "**Wearing-off"**, or **end-of-dose deterioration**, refers to the gradual decline of symptomatic response to levodopa. This means that the dose benefit lasts four hours or less, causing symptoms to return before the next scheduled dose.[14, 16, 21] During advanced PD stages, patients may experience "**on-off" fluctuations**, characterised by rapid transitions between "on" and "off" states. When these transitions occur unexpectedly and independently of levodopa intake, they are termed "**sudden-off"** periods. "**Delayed-on"** describes a situation where the time for levodopa to take effect is prolonged, while a **dose failure** occurs when no symptomatic improvement follows a levodopa dose. "Off" symptoms in the morning, prior to the first dose, are referred to as "**early-morning off"**.[14]

Dyskinesia

Levodopa treatment is frequently complicated by the development of levodopa-induced dyskinesias.[14] These involuntary, choreiform, and often writhing movements affect the face, neck, or limbs, typically occurring during "on" periods.[16] The most common form is **peak-dose dyskinesia**, which occurs when levodopa's effects on parkinsonism are strongest.[16, 22] While not always directly related to systemic blood levels, these movements are thought to result from peak levodopa concentrations within the brain.[16] Approximately 15–20% of levodopa-treated patients develop **diphasic dyskinesias**,[22] characterised by dyskinesias at the onset of the "on" period and when the patient starts to turn "off" again. These dyskinesias are more prevalent in individuals with advanced disease.[16]

Dystonia

Dystonia manifests as a sustained muscular contraction, frequently causing abnormal movements or postures. In young-onset PD (diagnosed before age 40), dystonia is more prevalent, affecting approximately 14–50% of patients. Dystonia often occurs as a complication of dopaminergic therapy. The most frequent manifestation, "**off"-period dystonia**, affects approximately 30% of long-term levodopa users. Dystonia may further present as **peak-dose dystonia** or **diphasic dystonia**.[23] While "off"-period dystonia typically occurs in the morning and affects the foot,[16, 23] peak-dose dystonia usually involves the neck or face. Diphasic dystonia

often affects both proximal and distal parts of the lower limb, as well as the ipsilateral arm.[23]

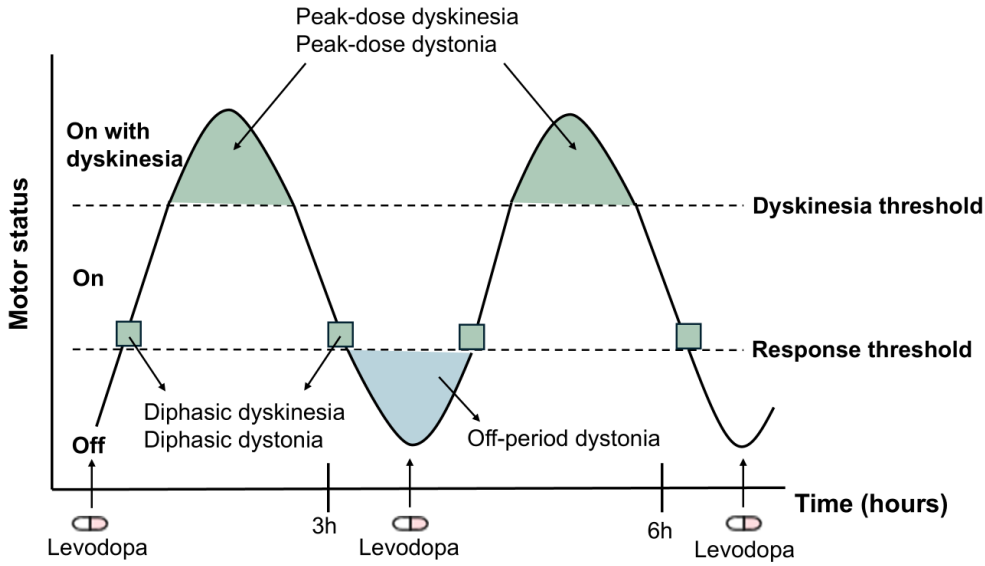

Figure 2: Dyskinesia and dystonia in relation to levodopa administration
Figure created in Microsoft PowerPoint but modified from Bhidayasiri and Truong.[16]

Onset of motor fluctuations and dyskinesia

In early stages of PD, most patients experience a consistent treatment effect, which leads to significant symptomatic improvement.[16] This stable response to levodopa is defined as enhanced motor function without motor fluctuations while requiring four or fewer daily doses.[21] This period is referred to as the **levodopa honeymoon**.[16] Following four to six years of levodopa treatment, up to 75% of patients with PD experience motor fluctuations,[24] while approximately 40% develop dyskinesias.[25] Risk factors for developing motor complications include female sex, greater disease severity, longer levodopa treatment duration, and younger age.[26] Higher doses of levodopa are associated with more dyskinesias.[27]

The development of these complications is thought to be driven by the striatum's declining capacity to store dopamine.[20] In early stages of the disease, the therapeutic response to levodopa includes both short-duration and long-duration responses.[20, 28] Over time, the long-duration response progressively diminishes, leading to a loss of the smooth drug effects and an increase in the magnitude of the short-duration response. This is hypothesised to result in fluctuations, as the effectiveness of levodopa becomes increasingly reliant on the short-duration response. The loss of the long-duration response is likely due to the depletion of presynaptic

dopaminergic terminals, which reduces the striatum's capacity to store dopamine and buffer fluctuations in plasma levodopa levels.[20] This storage failure causes elevated synaptic dopamine concentrations that overstimulate receptors, triggering peak-dose dyskinesias. Additionally, alterations in striatal dopamine receptor levels are thought to contribute to dyskinesia induction and may partly explain diphasic dyskinesias. However, the mechanisms behind dyskinesia remain complex.[29] For instance, the dysregulation of glutamatergic transmission within the basal ganglia also plays a critical role in dyskinesia development.[17, 29]

Clinically, initial motor fluctuations often present as "**wearing-off"** or "**early-morning off"**.[16, 21] As PD progresses, the therapeutic window for the "on" state narrows (**Figure 3**). The dyskinesia threshold decreases while the threshold for achieving an "on" state increases. This makes optimisation difficult, as reducing levodopa to avoid dyskinesia often results in "off" periods. Management can be further complicated by unpredictable **"on-off" fluctuations**. In addition, patients may experience **dose failures**, or "**delayed-on"**, which can arise from inadequate dosing, slowed gastrointestinal transit, or competition from dietary protein.[16]

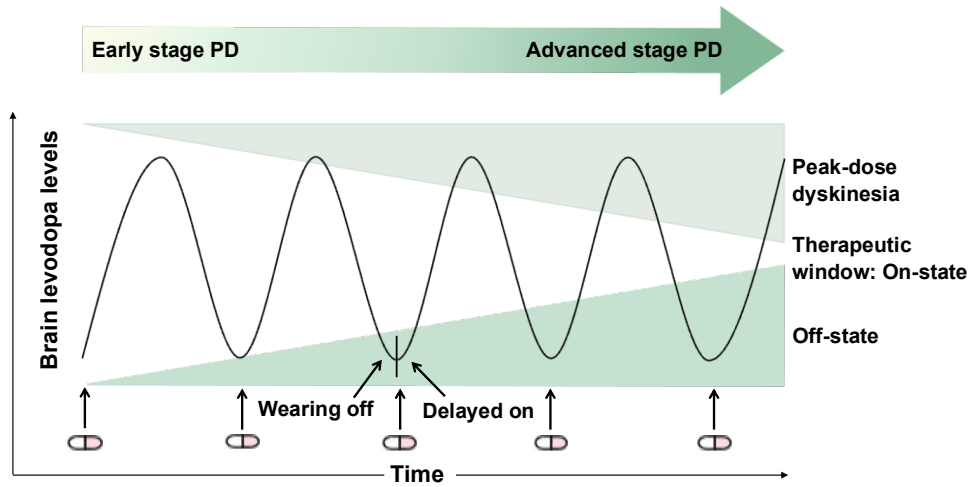

Figure 3: **Motor fluctuations in Parkinson's disease**
Schematic representation of how the therapeutic window for levodopa narrows over time in Parkinson's disease, leading to the development of motor fluctuations. Figure created in Microsoft PowerPoint but modified from Fabbri et al.[30]

Pharmacological approaches in managing motor complications

To avoid complications, levodopa levels must remain within the therapeutic window to maintain the "on" state.[14] As this window narrows over time, achieving symptom control without triggering dyskinesias becomes increasingly difficult.[16]

The levodopa sparing strategy

Because long-term use and higher doses of levodopa are linked to motor complications,[26, 27] a levodopa-sparing strategy is sometimes proposed. This involves initiating treatment with non-levodopa medications and subsequently adding levodopa when these agents fail to manage symptoms adequately.[14, 31] Clinical studies demonstrate that initiating treatment with a DA instead of levodopa can lower the incidence of dyskinesia and motor fluctuations for several years.[14] However, this strategy increases the risk of adverse effects and may result in lower mobility scores compared to levodopa.[14, 32] Moreover, levodopa-sparing strategies do not improve long-term disability rates.[14] Most experts recommend initiating levodopa treatment when needed for functional and symptomatic benefits,[14] emphasising that it should not be withheld from patients.[5] To minimise the risk of motor fluctuations and dyskinesias, clinicians generally aim to use the lowest effective dose and avoid unnecessary escalation.[14]

Reducing "off" time

To prevent "off" periods, the primary goal is to maintain a stable plasma dopamine concentration within the therapeutic "on" window.[14] Achieving this may involve adding a COMT or MAO-B inhibitor,[16, 33] shortening levodopa dosing intervals, or utilising sustained-release levodopa formulations.[14, 16] Also, the introduction of a DA can facilitate stable levels, as these agents degrade more slowly than levodopa.[16, 33] "Early-morning off" periods can be managed with nocturnal long-acting DAs, sustained-release levodopa, or COMT inhibitors. For occasional "off" symptoms, an apomorphine pen is a viable option.[33] To address dose failure or "delayed-on", clinicians should first exclude drug interactions. Moreover, these issues frequently stem from inadequate levodopa absorption, necessitating strategies to enhance bioavailability. Key interventions include treating constipation and ensuring levodopa is taken well before high-protein meals, as amino acids compete with levodopa for transport across the intestinal mucosa and blood-brain barrier. Utilising immediate-release or water-soluble levodopa can also reduce "delayed-on".[16] For patients with severe "off" periods and "delayed-on", intermittent subcutaneous apomorphine or inhaled levodopa serve as alternatives.[16, 28]

Reducing dyskinesias

Identifying the timing and pattern of dyskinesia is vital for effective reduction. Clinicians must ensure the patient correctly distinguishes dyskinesia from symptoms like tremor or dystonia to ensure appropriate treatment.[16] To manage **peak-dose dyskinesias**, the primary objectives include lowering individual levodopa doses and pursuing stable dopaminergic stimulation.[33] Reviewing the medication regimen is necessary to remove any drugs that exacerbate dyskinesia without providing substantial antiparkinsonian benefits.[16] Common strategies include reducing levodopa while adding a DA,[16, 33] or administering smaller, more

frequent levodopa doses.[14, 16] Switching from sustained-release to immediate-release formulations may be effective, though this approach can sometimes worsen end-of-dose "wearing-off".[16] Amantadine is currently the only medication proven to reduce dyskinesias.[16, 17] However, its duration of effect remains debated. While some evidence suggests a limited window of three to eight months,[34] other studies report effectiveness lasting several years.[35, 36] For patients with diphasic dyskinesias, reducing the levodopa dose is typically ineffective. The most successful intervention is subthalamic nucleus DBS. Interventions to consider before surgery include adding a DA or administering larger, more frequent levodopa doses. This strategy aims to sustain a continuous "on" state, preventing cycling through diphasic phases. However, it may result in development of peak-dose dyskinesias.[16]

Treatment of dystonia

Bedtime administration of sustained-release levodopa, long-acting DA, or a rotigotine patch can reduce "early-morning off" periods and associated "off"-period dystonia. Alternatively, patients may take a levodopa dose before rising from bed in the morning.[16] For localised relief, botulinum toxin injections in the affected muscles demonstrate effectiveness in reducing dystonic contractions.[16, 33]

Device-aided therapies in the management of motor complications

Advanced treatment options for patients with severe motor complications refractory to oral medication encompass DBS, MRI-guided focused ultrasound, continuous infusions of subcutaneous apomorphine, levodopa–carbidopa intestinal gel (LCIG), levodopa–entacapone–carbidopa intestinal gel (LECIG), and subcutaneous foslevodopa–foscarbidopa.[28, 37-39] The primary objective of continuous infusions is to maintain stable plasma concentrations, thus minimising motor complications.[28] To identify candidates for these device-aided therapies, clinicians may apply the 5-2-1 criteria. According to these criteria, a patient has suspected advanced PD if they require five or more oral levodopa doses daily, experiencing at least two hours of "off" symptoms, or having at least one hour of troublesome dyskinesia during the waking day.[40]

Deep brain stimulation

DBS involves the surgical implantation of leads into the basal ganglia, which are connected to a chest-implanted pacemaker that is programmed to deliver optimal stimulation to these brain regions.[28, 33] While its precise mechanism remains unknown,[37] DBS improves both "on" and "off" motor scores on the Unified PD Rating Scale (UPDRS) compared to best medical therapy. Furthermore, DBS has demonstrated effectiveness in reducing medication-refractory tremor.[28] Factors such as cognitive impairment, age $\geq$ 75 years, and levodopa-unresponsive symptoms, such as balance disturbances, can diminish DBS efficacy.[28] Potential surgical

complications include intracerebral haemorrhage and pulmonary embolism, while hardware-related complications involve electrode fracture, extension wire failure, or lead migration. Stimulation-induced side effects, such as dysarthria, paraesthesia, postural instability, and involuntary muscle contractions may occur, but are typically reversible through reprogramming.[37]

Focused ultrasound

MRI-guided focused ultrasound utilises high-frequency ultrasound beams to create precise thermal lesions in targeted brain regions. Due to risks of impaired speech or balance, the procedure is currently performed only unilaterally. Thalamic focused ultrasound has demonstrated a 62% improvement in tremor scores during the "on" state.[28] Results from a randomised controlled trial (RCT) suggest that it can improve motor symptoms in patients with asymmetrical signs.[41] Focused ultrasound is approved for severe tremor in both PD and essential tremor, serving as an alternative for patients ineligible for surgery.[33, 41] Recently, low-frequency ultrasound has emerged as a less invasive alternative. Preclinical studies suggest it may improve motor symptoms in PD, but further clinical trials are necessary to evaluate its safety and optimise its use.[42]

Continuous subcutaneous apomorphine

Apomorphine is a DA and an antagonist for α-adrenergic and 5-HT2 serotonergic receptors. Continuous subcutaneous apomorphine infusion is delivered through a small subcutaneous pump, typically paused at night. Doses are normally divided into a morning bolus dose, a continuous dose, and a bolus dose. While the therapeutic goal is monotherapy, most patients require supplemental oral treatment.[37] Continuous subcutaneous apomorphine is indicated for severe motor fluctuations,[33] and enhances health-related quality of life (QoL), particularly when it reduces the need for oral therapies.[37] The treatment is suggested to reduce "off" time by 40–60% and decrease troublesome dyskinesias.[33, 37, 43, 44] Additionally, it may benefit certain NMS, including sleep/fatigue, attention/memory and gastrointestinal problems. Subcutaneous nodules represent the most common adverse effect, affecting approximately 50% of patients.[37]

LCIG (Duodopa)

LCIG is a levodopa–carbidopa intestinal gel administered continuously via a portable pump connected through a percutaneous endoscopic transgastric jejunostomy.[28, 37] Typically, the patient receives a morning bolus dose, a continuous dose, and an on-demand bolus dose. Most patients pause the infusion overnight. Although monotherapy is the goal, many patients require supplemental oral medications. LCIG has been shown to improve both motor symptoms and health-related QoL.[37] In an RCT, it reduced the mean "off" time by 4 hours compared to placebo and significantly decreased the time spent in "on with troublesome

dyskinesia".[45] LCIG also appears to have positive effects on certain NMS, including sleep, gastrointestinal issues, cardiovascular health, and sexual functioning.[46] Common adverse effects include abdominal pain, tube dislocation, and knotting.[28]

LECIG (Lecigon)

LECIG is an intestinal gel approved in Sweden in 2018.[38] Like LCIG, it is administered continuously via a pump connected to a percutaneous endoscopic transgastric jejunostomy. While both formulations contain levodopa and carbidopa, LECIG also includes the COMT inhibitor entacapone. The addition of entacapone increases the bioavailability of levodopa, allowing for reduced levodopa doses.[47]

Subcutaneous foslevodopa–foscarbidopa (Produodopa)

In early 2024, foslevodopa–foscarbidopa was approved as the first subcutaneous levodopa treatment, offering a less invasive option for managing PD symptoms.[48, 49] A phase 3 trial demonstrated a significant increase in "on without troublesome dyskinesia" time and a reduction of "off" time compared to LCIG.[49] Subcutaneous administration is advantageous because absorption is not affected by delayed pharyngeal, gastric, or intestinal motility.[50] Common side effects include infusion site reactions, such as subcutaneous nodules and localised infections.[48, 49]

Motor complications and life quality

QoL is significantly lower in PD patients compared to healthy controls. Demographic factors, including age, gender, education level, and marital status, are associated with this reduction. These are further compounded by clinical characteristics, such as disease stage, severity, and duration.[51] A review concluded that motor complications significantly affect PD patients' health-related QoL.[52] Hechtner et al.[53] investigated the effects of motor complications on QoL in PD patients across five European countries and found that while "on-off" fluctuations deteriorated QoL, "off"-period dystonia did not. Another study demonstrates that "early-morning off", nocturnal akinesias, end-of-dose "off", paradoxical fluctuations, and unpredictable "off" periods all significantly worsen QoL. They particularly affect mobility, activities of daily living, communication, and stigma.[54] Hjalte et al.[55] found that patients fulfilling the 5-2-1 criteria had significantly lower health-related QoL, with "off" time having the most substantial effect.

A study demonstrated that during the first four years of treatment, motor complications did not significantly diminish overall QoL. In fact, the presence of dyskinesias was associated with improved QoL scores. This positive effect disappeared after the initial four-year period.[56] Hechtner et al.[53] similarly identified no significant QoL decline among patients experiencing peak-dose or diphasic dyskinesias. Conversely, Péchevis et al.[57] demonstrated that increasing dyskinesia severity was associated with reduced QoL, and Hjalte et al.[55] found that more time

spent with troublesome dyskinesias reduced health-related QoL. This discrepancy is hypothesised to reflect the wide clinical spectrum of dyskinesia. Mild dyskinesia does not compromise QoL, whereas pronounced dyskinesia adversely does.[58]

Non-motor symptoms

Papers I and *II* both address NMS management. NMS involve a broad spectrum of approximately 30 identified symptoms,[59] including sleep disturbances, pain, cognitive dysfunction, depression, anxiety, and sexual dysfunction (**Figure 4**).[60]

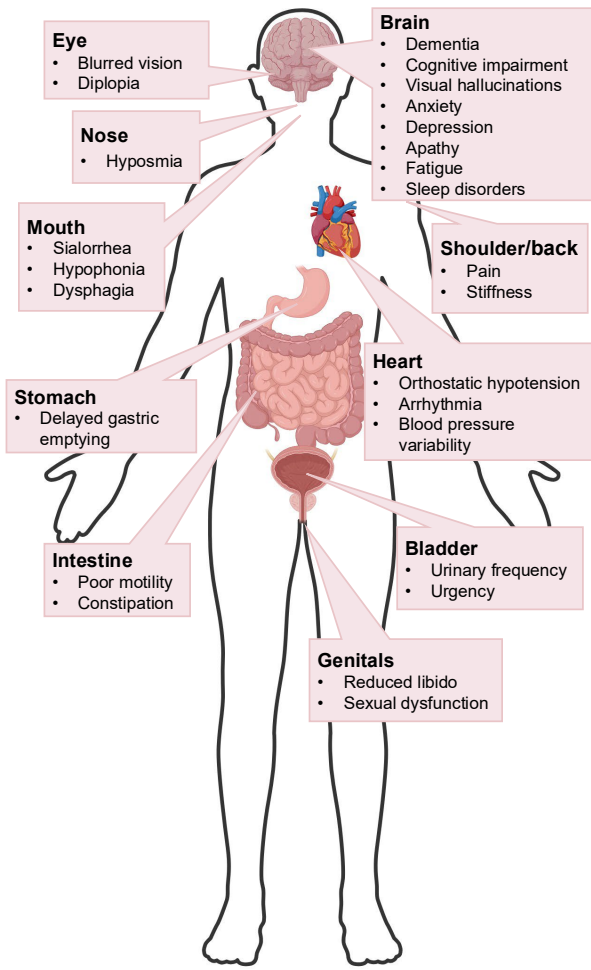

Figure 4: Potential non-motor symptoms in Parkinson's disease
The figure is created using BioRender and Microsoft PowerPoint, but is modified from Schapira et al.[60]

Research indicates that 98% of individuals with PD experience at least one NMS,[61] reporting an average of eight symptoms on the NMS questionnaire. This is three times more than age-matched controls.[62] Clinical diagnosis follows the onset of motor symptoms but is often preceded by a prodromal stage sometimes lasting 20 years or more.[2] Examples of prodromal NMS include hyposmia, RBD, depression, and constipation (**Figure 5**). While these symptoms can also manifest later, other symptoms such as dementia, hallucinations, and orthostatic dysfunction become more prevalent in advanced stages of PD. Ultimately, the progression, timing, and specific NMS profile vary widely among patients.[2, 60] NMS can fluctuate throughout the day, with symptoms such as depression, anxiety, fatigue, apathy, concentration difficulties, and cognitive impairment often intensifying during "off" periods.[20]

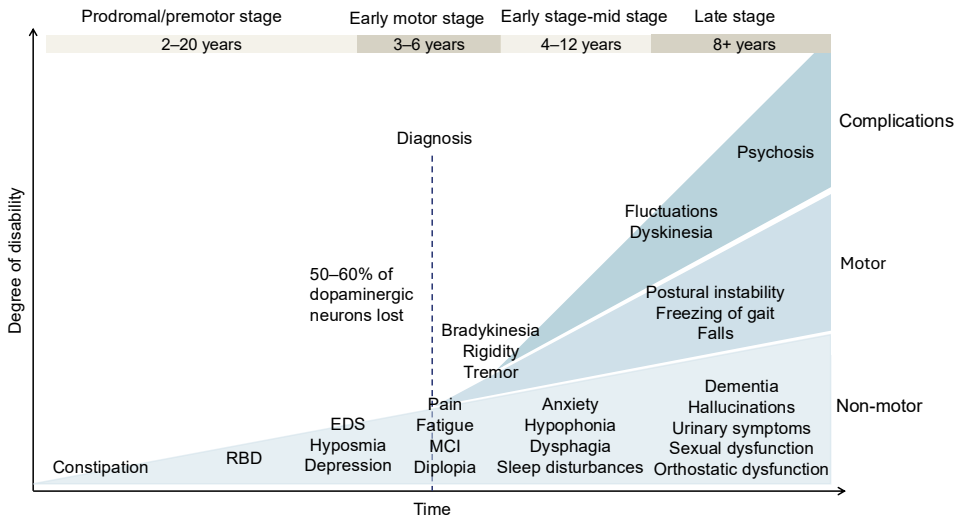

Figure 5: Symptoms and potential timeline in Parkinson's disease
This figure illustrates the symptomatic progression of Parkinson's disease. The specific symptoms, as well as the sequence and timing of their manifestation, vary significantly between individuals. RBD: rapid eye movement sleep behaviour disorder; EDS: excessive daytime sleepiness; MCI: mild cognitive impairment. Created in Microsoft PowerPoint but modified after Kalia and Lang[2] and Schapira et al.[60]

Pathophysiology of non-motor symptoms

Sensory features

Olfactory deficits affect approximately 90% of PD patients, often preceding motor symptoms by years.[59, 60] The Braak hypothesis suggests this reflects α-synuclein deposition in olfactory structures prior to substantia nigra involvement.[10, 59] In later PD stages, olfactory dysfunction may also be related to cholinergic denervation and

cognitive decline. Visual manifestations, such as hallucinations and diplopia, are prevalent. Hallucinations sometimes worsen with DA treatment.[60]

Pain is prevalent in PD and is often categorised into five types: musculoskeletal, neuropathic, dystonia related, central parkinsonian, and akathitic discomfort.[60, 63] It involves both dopaminergic and non-dopaminergic pathways, often intensifying during "off" states. While motor symptoms such as dystonia and stiffness cause musculoskeletal pain, neuropathic pain is often linked directly to the neurodegenerative process. The loss of dopaminergic input to the basal ganglia alters sensory perception and lowers pain thresholds. Also, dopamine modulates pain signalling in the thalamus, spinal cord, and cingulate cortex. The serotonergic raphe nuclei and noradrenergic locus coeruleus, both involved in pain pathways, are also affected in PD. While dopaminergic therapy can alleviate pain by improving motor symptoms and raising pain thresholds, pain does not completely resolve.[60]

Neuropsychiatric features

Anxiety and depression are prevalent in PD, occurring both as prodromal symptoms and throughout the course of the disease. Anxiety frequently intensifies during "off" periods, although its underlying biochemical basis remains poorly understood.[60] Approximately 17% of PD patients experience major depression, while 22% exhibit minor depression.[64] Depression is linked to motor fluctuations, symptom severity, disease duration, and dopaminergic dose. Similar to endogenous depression, it involves alterations in dopaminergic, noradrenergic, and serotonergic systems, potentially compounded by the loss of cholinergic neurons.[60] Apathy affects approximately 60% of individuals with PD, occurring independently or alongside depression and dementia. While the exact cause remains unclear, it is linked to atrophy of the nucleus accumbens and dysfunction within ventral and striatal regions. Evidence suggests that apathy subtypes are associated with either cholinergic or dopaminergic pathways.[60] Fatigue, characterised by mental and physical exhaustion, affects around 50% of patients and can emerge at any disease stage.[60, 65] While fatigue may result from motor dysfunction or specific neuropathology, it often improves when "off" periods are reduced.[60]

In late-stage PD, cognitive dysfunction and dementia are prevalent. Patients presenting with bradykinesia and rigidity face a higher risk than those with tremor-dominant PD.[60] Early executive dysfunction may relate to dopaminergic denervation in the striatum, whereas progression to dementia is primarily associated with cholinergic denervation.[20] Psychosis, including visual hallucinations and delusions, can occur in late-stage PD. Dopaminergic therapy can trigger these symptoms, and other contributing factors include sleep dysfunction, abnormal visual processing, and neurochemical or pathological changes.[60]

Autonomic dysfunction

Autonomic dysfunction becomes increasingly prevalent as PD progresses.[60] The pathology involves neuronal degeneration encompassing nerve fibre loss, synaptic damage, and cell death alongside α-synuclein accumulation in Lewy bodies. These pathological changes affect key central control centres including the cortex, insula, hypothalamus, brainstem, and spinal cord. In the peripheral autonomic nervous system, degeneration is observed in structures such as the vagus nerve and the enteric neural plexus.[66]

Gastrointestinal symptoms affect 60–80% of PD patients and include sialorrhea, dysphagia, delayed gastric emptying, weight loss, and constipation.[59, 67] Normally, the parasympathetic system promotes motility via the vagus nerve, while the sympathetic system inhibits it.[66] According to the Braak hypothesis, the dorsal motor nucleus of the vagus is affected early in PD, which explains that constipation is a common prodromal symptom.[10, 60] Furthermore, Lewy bodies are distributed throughout the gastrointestinal tract, disrupting local function.[60, 67] Oropharyngeal dysphagia is often attributed to bradykinesia and rigidity, though peripheral motor and sensory nerve involvement may also contribute.[67] Urinary symptoms stem primarily from central mechanisms, manifesting as increased frequency, urgency, and nocturia.[60, 66] Bladder hyperreflexia, characterised by heightened frequency and urgency, is thought to result from the diminished inhibitory role of the basal ganglia.[60] Furthermore, degenerative changes in lower brainstem nuclei, such as the pontine micturition and continence centres, may contribute to impaired bladder storage.[66] No morphological, pathological, or biochemical changes have been identified within the bladder itself.[60]

Orthostatic dysfunction, heart-rate variability, and labile hypertension are common NMS in PD. [60, 66] These issues are attributed to the degeneration of the sympathetic and parasympathetic nervous systems, though central mechanisms may also contribute. [66] Orthostatic hypotension affects 30–58% of patients, resulting from an abnormal cardiovascular response to blood pressure drops triggered by postural changes.[60, 66] Furthermore, "off" periods often exacerbate resting tachycardia, hypertension, and orthostatic hypotension.[60] Sexual dysfunction is prevalent in both men and women. In men, it frequently manifests as erectile dysfunction, premature ejaculation, or orgasmic dysfunction. In women, it typically involves low desire, arousal difficulties, and challenges in reaching orgasm.[63] While the specific neurobiological impacts of PD on sexual function remain unclear, lower testosterone levels observed in patients may be a contributing factor.[66]

Sleep disturbances and daytime sleepiness in Parkinson's disease

Paper II addresses treatment and measurement of sleep disturbances and daytime sleepiness in PD. Sleep disturbances affect up to 90% of patients, with prevalence

increasing alongside disease progression. Sleep disorders include insomnia, RBD, periodic limb movements, restless legs syndrome (RLS), and akathisia.[68] Up to 50% of patients exhibit EDS.[69]

The hypothalamus regulates sleep and wakefulness, and hypocretin (orexin) is a neuropeptide expressed by specific neurons in the hypothalamus. Hypocretin levels rise during wakefulness, and the peptide is hypothesised to be crucial for consolidating sleep–wake cycles into distinct daily episodes and for suppressing motor activity during REM sleep. While the loss of hypocretin-producing neurons leads to narcolepsy,[70] hypocretin has also been found to be nearly undetectable in patients with PD.[60] This is thought to be linked to the development of both sleep disorders and sleep attacks in PD patients.[71] Serotonin, noradrenaline, and dopamine are also involved in sleep regulation, and these neurotransmitters are all compromised in PD.[60]

Insomnia

Insomnia is defined as the subjective perception of non-restorative sleep leading to impaired daytime function, caused by difficulties in initiating and/or maintaining sleep and/or early-morning awakening. Reported prevalence in PD ranges from 37% to 80%. PD-related insomnia manifests predominantly as sleep fragmentation rather than onset difficulties. This fragmentation is driven by neurodegeneration in sleep–wake regulatory centres, alongside motor complications such as nighttime akinesia, dyskinesia, and fluctuations. Neuropsychiatric and autonomic symptoms, such as nocturia and blood pressure abnormalities, further contribute to insomnia. While dopaminergic agents and amantadine improve motor symptoms and thus aid sleep, higher doses can worsen sleep quality and aggravate insomnia.[68]

REM sleep behaviour disorder

Descending motor pathways are normally inhibited during REM sleep to ensure muscle atonia, but in RBD, this inhibition fails.[60, 72] RBD manifests as vigorous motor activity during REM sleep, wherein individuals act out their dreams.[70] This dysfunction involves several brain structures, including the subcoeruleus nucleus, where glutamatergic neurons normally promote skeletal muscle atonia during REM sleep by inhibiting the ventral medial medulla.[72] Impaired cholinergic circuits and the loss of dopaminergic neurons are also believed to contribute to RBD.[70, 72] Frequently appearing as a prodromal symptom, the early onset of RBD may be explained by either the Braak hypothesis or the "body-first" subtype.[10, 11]

Sleep-disordered breathing

Sleep-disordered breathing in PD encompasses obstructive sleep apnoea, hypoventilation, and isolated hypoxaemia. Obstructive sleep apnoea is the most common, affecting 20–60% of patients.[72] Sleep-disordered breathing can lead to sleep fragmentation and non-restorative sleep.[68] Dopaminergic neurons are involved

in respiratory control, and their degeneration may impair ventilation. Moreover, the degeneration of other brainstem structures responsible for regulating respiration may further contribute to these breathing disorders.[72]

Circadian rhythm disorders

PD-related circadian rhythm disturbances drive non-restorative sleep, EDS, early awakenings, and delayed bedtimes. They may also worsen neuropsychiatric complications such as anxiety and hallucinations. Circadian rhythm disorders are often accompanied by alterations in physiological functions, including blood pressure, heart rate, and body temperature. The circadian clock is centred in the suprachiasmatic nucleus. It receives retinal inputs and communicates with the pineal gland to regulate melatonin secretion. In PD, circadian rhythm disorders are believed to stem from the neurodegeneration of retinal dopaminergic cells and decreased mobility, which reduces exposure to bright light and physical exercise. This compromises the regulation by the suprachiasmatic nucleus.[68]

Restless legs syndrome

RLS is characterised by unpleasant sensations, typically in the legs, accompanied by an uncontrollable urge to move. Symptoms primarily occur in the evening or at night. The prevalence of RLS in PD patients compared to the general population is debated, and the exact relationship between RLS and PD remains unclear.[68, 72] RLS can lead to difficulties with sleep initiation, sleep fragmentation, and daytime sleepiness.[68] The problems often improve with dopaminergic medications, and PD patients with RLS may benefit from nighttime dopaminergic treatment.[72]

Periodic limb movements

Periodic limb movements are repetitive, stereotyped limb movements primarily affecting the lower extremity during sleep. The exact pathophysiology is not fully understood, but it is thought to involve dysfunction within a network comprising the spinal cord, brainstem, and supratentorial structures. This leads to an overactive bilateral spinal pattern generator, affecting spinal motor neurons. Approximately 80% of individuals with RLS also exhibit periodic limb movements.[68]

Excessive daytime sleepiness

EDS is defined as an increased tendency to fall asleep, particularly in monotonous situations, despite getting an adequate amount of total sleep. Individuals with EDS may experience sudden sleep attacks, where they unexpectedly fall asleep without warning. Its prevalence in PD ranges from 20% to 60%. EDS in PD is associated with factors such as male sex, advanced disease stages, faster motor progression, and the presence of autonomic, cognitive, and neuropsychiatric complications.[68] Proposed mechanisms include reduced hypocretin levels,[71, 72] the loss of wake-

promoting mesencephalic dopaminergic neurons,[70] and alterations in serotonergic and GABAergic systems. Also, DAs may exacerbate EDS.[60, 68]

Treatment of non-motor symptoms

Several NMS respond to dopaminergic therapy, particularly symptoms associated with motor fluctuations, such as musculoskeletal pain, anxiety, and depression during "off" periods.[33, 73, 74] Other symptoms, such as dementia, sweating, and dysphagia, are unresponsive to dopamine. Furthermore, dopaminergic therapy can exacerbate or cause certain NMS, including psychosis, dopamine dysregulation syndrome, nausea, EDS, and orthostatic hypotension.[74]

NMS treatment guidelines

National treatment guidelines for NMS are provided by the Swedish National Board of Health and Welfare (Socialstyrelsen). The guidelines prioritise treatment strategies on a scale from 1 to 10, with 1 being the highest priority and 10 being the lowest. Ranks 1 to 4 indicate that the treatment should be offered, 5 to 7 that it can be offered, and 8 to 10 that it should only be offered in exceptional cases. The designation "FoU" restricts treatment to a research context. The guidelines were last updated in 2022.[75] The Swedish Movement Disorder Society (SWEMODIS) also provides national treatment recommendations that are harmonised with the Swedish National Board of Health and Welfare guidelines where appropriate. Developed by an expert group, the SWEMODIS recommendations integrate both scientific evidence and clinical experience.[33] International treatment guidelines are provided by the Movement Disorder Society (MDS). The MDS guidelines were last updated by the MDS Evidence-Based Medicine Committee in 2019. These guidelines incorporate only high-quality research, requiring all included studies to meet a quality score of 75% or higher. Based on this evidence, treatments for various NMS are categorised as clinically useful, possibly useful, unlikely useful, not useful, or investigational.[7]

A recent study evaluated adherence to NMS treatment guidelines in late-stage PD. The study utilised MDS and SWEMODIS guidelines from 2019, as well as the 2016 Swedish National Board of Health and Welfare and SWEMODIS guidelines. The findings revealed poor adherence to pharmacological guidelines within this cohort.[76] However, guideline adherence across the full spectrum of disease severity remained unknown, a knowledge gap addressed in *Paper I*.

Management of sleep disturbances and daytime sleepiness

Evidence for PD-related insomnia treatment remains limited. Non-pharmacological strategies include improved sleep hygiene and regular physical exercise. For

insomnia secondary to nocturnal akinesia or tremor, extended-release DA or long-acting levodopa in the evening may provide relief.[33, 68] International guidelines categorise the DA rotigotine patch as "possibly useful" for treatment of insomnia.[7] Additionally, hypnotics and melatonin may be used to alleviate insomnia.[7, 33] Mirtazapine is another option, as it may alleviate both sleep problems and depressive symptoms. Regarding RBD, while no international recommendations exist, SWEMODIS guidelines suggest clonazepam. For RLS, DA administered prior to sleep is recommended. If symptoms persist, antiepileptic drugs such as pregabalin can be considered. Other alternatives include hypnotics like zopiclone to aid in sleep initiation.[33] If the patient suffers from sleep apnoea, treatment with continuous positive airway pressure is indicated.[7]

There is limited evidence for treating EDS in PD, with no medications currently recommended for this indication in Sweden.[33, 75] While modafinil is labelled "possibly useful" internationally,[7] Swedish guidelines restrict its use to research contexts.[75] Modafinil is primarily indicated for narcolepsy, and three RCTs investigating modafinil for PD-related EDS yielded inconclusive results. However, a systematic review suggested modafinil to reduce daytime somnolence in PD patients.[77] Non-pharmacological strategies include structured daytime napping, increased physical activity, and light therapy.[68] While EDS can be associated with nocturnal sleep disturbances,[78] in which case sleep optimising is essential,[68] evidence suggests these symptoms often occur independently. Specifically, Klingelhoefer et al.[79] observed that nighttime Parkinson's KinetiGraph (PKG) variables do not differentiate between patients with and without EDS, and Liguori et al.[80] found no correlation between nocturnal sleep quality and daytime sleepiness.

Rotigotine

Rotigotine is a DA administered via a transdermal patch, providing stable drug release over 24 hours. While other DAs like pramipexole and ropinirole lack activity at D1 and D5 receptors, rotigotine possesses high affinity for D1, D2, and D3 receptors, with a lower affinity for D4 and D5 receptor subtypes.[81] The patch is generally well tolerated, with the most common side effect being application site reactions. Other side effects include nausea, vomiting, and dizziness, particularly during the up-titration phase.[82]

Beyond alleviating motor symptoms and reducing motor fluctuations,[83] rotigotine may improve various sleep-related issues including night-time pain,[84] nocturnal motor impairment, sleep fragmentation,[85] and overall sleep quality.[86] While international NMS guidelines categorise rotigotine as "possibly useful" for treating insomnia,[7] it remains excluded from national guidelines.[33, 75] Recent meta-analyses conclude that rotigotine improves both motor symptoms and sleep quality in individuals with PD, while also being well-tolerated.[87-89] Rotigotine's potential beneficial effects on sleep disturbances are hypothesised to stem from its non-oral transdermal route, which provides stable continuous dopaminergic stimulation.

Moreover, its specific affinity for various dopamine receptor subtypes may further contribute to these potential improvements in sleep architecture.[90]

The RECOVER study, a four-week RCT, demonstrated significant positive effects of rotigotine on sleep, showing improvements in 10 of 15 PD Sleep Scale-2 (PDSS-2) items.[84] Long-term benefits were further observed in a one-year follow-up study.[91] Positive effects on sleep with rotigotine have been shown using actigraphy,[86, 92] polysomnography (PSG), PDSS,[93] PDSS-2,[85, 91, 94, 95], and axial inertial sensor.[94] Although Mizuno et al.[95] observed significant improvements on the PDSS-2 with rotigotine compared to placebo, there were no significant differences between rotigotine and ropinirole. However, results are not universally positive. One study failed to show any differences between rotigotine and placebo on the PDSS-2.[96] Furthermore, an RCT evaluating rotigotine using the Non-Motor Symptoms Scale (NMSS) found no significant sleep improvements, though notably, sleep disturbances were not an inclusion criterion for that study.[97] While antiparkinsonian treatment, especially DA, can worsen EDS,[68] some studies have shown that rotigotine does not exacerbate daytime sleepiness.[80, 90, 96, 98] Others demonstrate that rotigotine decreases daytime sleepiness, as indicated by actigraphy and the Epworth Sleepiness Scale (ESS).[86, 99] Calandra-Buonaura et al.[86] found that rotigotine positively influenced diurnal sleep disturbances via actigraphy, though these improvements were not reflected in ESS scores. *Paper II* further investigates the effect of rotigotine on sleep and daytime sleepiness in PD patients.

Non-motor symptoms and life quality

Individual NMS such as pain, apathy, and depression markedly affect health-related QoL both among PD patients and their caregivers.[100] Research indicates that the breadth and severity of NMS are primary determinants of health-related QoL,[100-103] often exerting a greater impact than motor symptoms,[104] even in early disease stages.[63] Furthermore, non-motor fluctuations have been shown to negatively affect QoL independently of motor fluctuations.[105]

A meta-analysis concluded that individuals with PD have significantly poorer QoL compared to healthy controls. NMS, particularly anxiety, pain, and apathy, were more strongly associated with reduced QoL than motor symptoms. Depression was frequently identified as the most influential factor. Also, neuropsychiatric symptoms have been demonstrated to significantly exacerbate caregiver burden.[63] Evidence regarding the effect of sleep disturbances on life quality is mixed. While some studies report a significant link between sleep problems and lower QoL, others do not.[51] A recent study identified reduced health-related QoL in individuals with RBD, independent of emerging motor symptoms. Moreover, sleep–wake disorders, depression, and fatigue correlated with poorer QoL.[106] Both EDS and RLS have been associated with impaired QoL.[72] The profound impact of NMS on QoL underscores the necessity of identifying and treating these symptoms.

Symptom monitoring and measurement

Optimising and evaluating PD treatment relies on accurate symptom assessment. Regarding motor complications, this requires precise data on the timing, duration, and pattern of motor fluctuations and dyskinesia.[16] Consequently, reliable motor state monitoring is essential. Clinically, sleep disturbances are prevalent and significant, requiring systematic assessment to characterise and identify treatable sleep disorders.[68] Collectively, robust symptom measurement and monitoring provide the foundation for optimising PD management and evaluating interventions aimed at reducing motor complications, sleep disturbances, and daytime sleepiness. *Paper II* evaluates the PKG for monitoring sleep and daytime sleepiness, whereas *Papers III* and *IV* validate the Home Diary (HD) for assessing motor fluctuations and dyskinesia.

Measure and monitor motor complications

UPDRS and MDS-UPDRS scale

To standardise clinical assessment and improve comparability between studies, the UPDRS was developed in the 1980s to replace various inconsistent questionnaires.[107] Its updated version, the MDS-UPDRS, was designed to offer improvements over the original scale while maintaining a similar four-part structure. This structure covers non-motor and motor experiences of daily living, a clinical motor examination, and motor complications.[108] Both the MDS-UPDRS and the UPDRS assess the patient's motor state at a specific moment but do not capture fluctuations in motor state throughout the day. To address this limitation, PD diaries were developed.[109]

Parkinson's disease Home Diary

The HD was developed by Hauser et al.[110] in the early 2000s to monitor motor symptoms. It requires patients to categorise their motor status every 30 minutes into one of four distinct states: "off", "on without dyskinesia", "on with non-troublesome dyskinesia", and "on with troublesome dyskinesia".[111] Clinically, the HD is used for routine monitoring and frequently serves as a primary endpoint in clinical trials evaluating therapies for motor symptoms and motor complications.[112]

In an initial validation study, Hauser et al.[110] found that HD-derived "off" time and "on with troublesome dyskinesia" correlated with patient-rated "bad time". Conversely, "on" status without or with non-troublesome dyskinesia correlated with "good time". Subsequent research confirmed the diary's predictive reliability against Visual Analogue Scales (VAS) and demonstrated good test–retest reliability.[111] Although ratings by experienced clinical observers remain the gold standard for assessing motor status, the HD was not validated against this measure until a recent

collaborative project between Sweden and Germany. Both countries conducted similarly designed studies and consistently found that the agreement between clinical observer assessments and patient HD ratings was only fair, displaying poor temporal agreement.[113, 114]

Accurate HD completion requires patients to have a comprehensive understanding of motor fluctuations. To address this challenge, several studies have validated the use of educational videos. Hauser et al.[115] reported that 95% of participants found a training video helpful for clarifying diary items. Similarly, Goetz et al.[116] demonstrated that using a video designed to educate patients about motor fluctuation significantly improved agreement between patients and observers when completing an on–off diary. In the German study by Löhle et al.[113], an educational video was utilised to enhance patient understanding of motor states prior to rating. However, the Swedish study by Timpka et al.[114] provided only oral and written instructions before completing the HD. Consequently, it remained unknown whether a structured training in motor complications could improve the agreement between patients and observers, a knowledge gap addressed in *Paper III*. Furthermore, clinical experience suggests that patients and their relatives frequently evaluate motor states differently. *Paper IV* therefore investigates the agreement between relatives and a clinical observer when completing the HD.

Technical solutions

The inherent subjectivity of questionnaires and diaries necessitates the need for objective methods to monitor motor complications. Consequently, various technological solutions have emerged to record motor fluctuations, primarily utilising accelerometer-based wearables that quantify body acceleration across one or multiple axes. By capturing data on movement orientation, amplitude, frequency, and speed at the site of placement, these devices enable the objective assessment of tremor, bradykinesia, and dyskinesia.[109]

Wearable devices for assessing PD motor function include the STAT-ON,[117] Sense4Care/REMPARK,[118] PERFORM,[119] Kinesia system, and PKG.[109] Also, smartwatch applications such as StrivePD and Verily smartwatch have been developed.[120, 121] While some technologies, such as the PKG, utilise a single sensor on the most affected wrist, others employ multiple sensors or different anatomical placements. For instance, the STAT-ON is worn on a belt and utilises real-time machine learning algorithms to analyse inertial signals.[117] The Kinesia system can be positioned on the index finger or heel to detect bradykinesia or utilise one or multiple bilateral sensors to monitor dyskinesia.[109] In real-world settings, distinguishing involuntary movements from voluntary activities, such as exercise, remains a challenge for continuous monitoring. This difficulty is frequently mitigated by recording data over several days to increase sample size and by excluding periods of inactivity. Subsequently, the data are averaged and smoothed to enhance accuracy.[120, 122, 123]

Digital health technologies have demonstrated feasibility in measuring motor function and fluctuations. Clinical evidence suggests that continuous, objective monitoring via wearable sensors can enhance clinical decision-making and improve therapeutic outcomes for PD patients.[124, 125] Nevertheless, research indicates poor temporal agreement between actigraphy and the HD, even when a clinical observer completes the diary.[121] Importantly, many wearable devices have been validated primarily by their developers, necessitating independent external validation.[109]

Measure and monitor sleep and daytime sleepiness

Accurate sleep characterisation is vital to identify treatable conditions and to evaluate therapeutic efficacy.[68] Within the context of PD, sleep disturbances and daytime sleepiness are assessed through both subjective and objective measures.[126] Nevertheless, frequent discrepancies between these modalities necessitate access to reliable objective measurement tools.[68] Although PSG remains the gold standard for sleep assessment,[126, 127] its high cost, limited availability,[128] and typical requirement for hospitalisation make longitudinal monitoring difficult.[129] Furthermore, the hospital setting itself may disrupt patients' habitual sleep patterns.[129] Such limitations underscore the need for reliable, home-based objective methods for longitudinal assessment. This gap is addressed in *Paper II*, which evaluates the PKG as a tool for monitoring sleep and daytime sleepiness as a secondary endpoint. **Figure 6** illustrates various sleep disturbances in PD, alongside strategies for their monitoring and management.

Questionnaires and diaries

Several scales quantify sleep quality in PD, with the PDSS being among the most widely used.[130] Its revised version, the PDSS-2,[131] covers a broader range of PD-related nocturnal disturbances.[130] Other questionnaires include the Scales for Outcomes in PD - Sleep, the Pittsburgh Sleep Quality Index, the Insomnia Severity Index, and the RBD screening questionnaire.[126] Additionally, sleep diaries completed by the patient are sometimes used.[126, 132] These require patients to record parameters such as bedtime, sleep interruptions, daytime naps, and perceived sleep quality each morning.[126] To evaluate daytime sleepiness, the ESS is frequently administered. This self-reported instrument measures a patient’s general level of sleepiness during daily activities.[133] Moreover, the Inappropriate Sleep Composite Score is used to specifically investigate the occurrence of sleep attacks.[126]

Polysomnography

Video-PSG remains the gold standard for sleep assessment.[126, 127] This modality utilises surface electrodes to monitor physiological parameters, including brain, muscular, and ocular activity. Additionally, it records respiratory patterns, oxygen saturation, and heart rate. PSG provides data on for instance sleep latency, total sleep

time, sleep efficiency, time spent in different sleep stages, periodic leg movements, RBD, and wake time after sleep onset.[126, 127] While typically performed in a controlled hospital setting, home-based alternatives are also available.[129, 134]

Respiratory polygraphy

Respiratory polygraphy uses a nasal cannula or thermistor, along with thoracic and abdominal belts, to monitor body position and oxygen saturation. These parameters facilitate the identification of obstructive sleep apnoea.[126]

Actigraphy

Actigraphy utilises sensors to quantify activity and rest. Since immobility is a primary characteristic of sleep, these devices can assess sleep and wakefulness parameters.[126, 127] A significant advantage of actigraphy is the ability to monitor sleep longitudinally within a home environment.[68] However, compared to PSG, actigraphy tends to overestimate sleep duration and underestimate wake time.[127] The PKG, an actigraph primarily used to assess motor symptoms in PD, also provides insights into sleep and daytime sleepiness.[78] McGregor et al.[78] demonstrated that PKG scores distinguish between normal and abnormal PSG findings with good sensitivity and specificity. They also identified an inverse correlation between the Combined Sleep Score (CSS) on the PKG and the PDSS-2. These findings suggest that PKG offers a reasonably accurate estimation of wakefulness, sleep duration, sleep quality, and sleep fragmentation. Another study proposed that PKG can be used as a rough evaluation of night-time sleep and as a tool to determine whether PSG is needed.[79] Kotschet et al.[135] found a correlation between daytime Percent Time Immobile (PTI_D) measured with PKG and the ESS, suggesting that PTI_D is a useful measure of daytime sleep, or at least somnolence in PD patients. Conversely, Höglund et al.[136] failed to detect any significant correlations between PTI_D and diary-reported daytime sleepiness.

Suggested immobilisation test

The suggested immobilisation test is designed to detect periodic leg movements during wakefulness as a marker for RLS. During the procedure, the patient remains seated in bed during the evening or nocturnal hours with their legs outstretched. Meanwhile, electromyographic electrodes are positioned on the tibial muscles to detect movement.[126]

Multiple sleep latency test

The multiple sleep latency test utilises electroencephalography, electrooculography, and electromyography to identify EDS and the premature intrusion of REM sleep. Conducted on the day following video-PSG, the protocol involves five nap opportunities during which the patient attempts to initiate sleep. The participant's mean sleep onset latency and sleep architecture are evaluated.[126]

Maintenance of wakefulness test

The maintenance of wakefulness test assesses the ability to remain awake by instructing the patient to resist sleep during the day under soporific conditions. The test is conducted the day after a video-PSG.

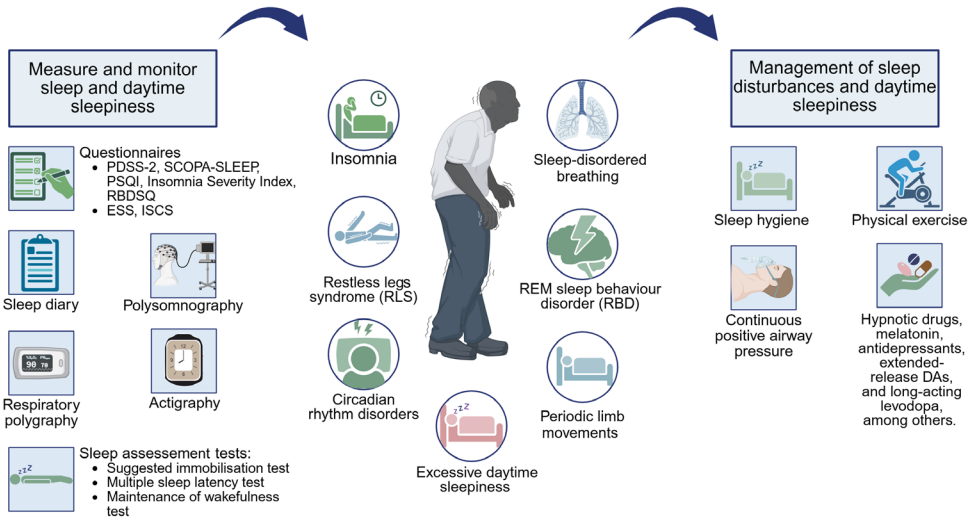

Figure 6: Sleep disturbances and daytime sleepiness in Parkinson's disease

PDSS-2: Parkinson's Disease Sleep Scale-2; SCOPA SLEEP: Scales for Outcomes in Parkinson's Disease - Sleep; PSQI: Pittsburgh Sleep Quality Index; RBDSQ: Rapid eye movement sleep Behaviour Disorder Screening Questionnaire; ISCS: Inappropriate Sleep Composite Score. The figure is created in BioRender.

Rationale

In the absence of curative therapies, optimising symptomatic treatment remains essential to improve QoL in PD patients. This thesis primarily addresses two gaps: the limited understanding of how NMS are identified and managed in clinical practice (*Papers I* and *II*) and the need for validated tools to measure and monitor both non-motor and motor PD symptoms and fluctuations to support treatment optimisation (*Papers II–IV*).

NMS often impair QoL to a greater extent than motor symptoms,[104] yet remain frequently overlooked in clinical practice.[137] Prior research demonstrated poor NMS guideline adherence in advanced PD, but adherence across all disease stages remained uncharacterised.[76] *Paper I* investigates adherence to pharmacological NMS guidelines to inform improved patient care and future guideline development.

Sleep disturbances represent some of the most prevalent and burdensome NMS,[68] necessitating effective management and reliable assessment methods. The DA rotigotine has shown potential sleep-enhancing effects,[87-89] yet it is not included in the Swedish guidelines.[33] While PSG is the gold standard for sleep assessment,[126, 127] it is resource-intensive and typically requires overnight hospitalisation. This may disrupt habitual sleep and limits feasibility for repeated or long-term monitoring.[128, 129] Actigraphy-based approaches, including the PKG, offer a practical alternative. However, PKG-derived sleep metrics remain insufficiently validated. *Paper II* addresses these gaps by evaluating rotigotine's effects on sleep and daytime sleepiness using both questionnaires and PKG recordings, and by examining correlations between PKG parameters and corresponding subjective questionnaires.

Beyond NMS, reliable tools are essential to assess motor fluctuations and dyskinesia, complications that frequently emerge during disease progression and substantially impair QoL.[24, 25, 52, 54, 55] The HD is widely used in clinical practice and as a primary endpoint in trials.[112] However, studies have demonstrated only fair temporal agreement between patient and clinical observer diary entries.[113, 114] Consequently, *Papers III* and *IV* examine whether structured patient education on motor complications and the involvement of relatives enhance HD accuracy and reliability.

Aims

The overarching aim of this thesis is to improve understanding of NMS management in PD and to strengthen the evidence base for tools used to measure and monitor PD symptoms and fluctuations.

Specifically, the thesis addresses (i) the adherence to pharmacological NMS treatment guidelines (*Paper I*), (ii) the effects of rotigotine on sleep disturbances and daytime sleepiness, and the utility of the PKG when monitoring these symptoms (*Paper II*), and (iii) the validity of the HD for assessing motor fluctuations and dyskinesia (*Papers III* and *IV*).

Paper-specific aims:

Paper I: To assess adherence to pharmacological NMS treatment guidelines among PD patients with a disease severity spanning from mild to severe stages, who were able to walk or stand unassisted (Hoehn and Yahr [H&Y] stage ≤ 4).

Paper II: To evaluate the effects of rotigotine on sleep in PD patients using well-established rating scales and PKG recordings. Secondary aims are to assess the impact of rotigotine on daytime sleepiness, motor symptoms, and health-related QoL, and to examine correlations between PKG-derived parameters and corresponding questionnaire-based measures for sleep and daytime sleepiness.

Paper III: To investigate the effect of structured patient training regarding motor fluctuations and dyskinesia on the agreement between clinical observer and patient HD ratings in the evaluation of the PD motor state and daily motor state times.

Paper IV: To evaluate the agreement between a clinical observer and relatives of PD patients when assessing the patients' motor status using the HD. Secondary aims are to assess agreement between relatives and patients, and between patients and the clinical observer.

Methods

Overview of methods

Paper I evaluated adherence to pharmacological treatment guidelines for NMS in patients randomly selected from the Swedish National Quality Registry for PD (ParkReg). NMS were mapped using investigator- and self-administered questionnaires, with treatments verified via medical records. Treatment was then compared with Swedish national treatment guidelines and international MDS Evidence-Based Medicine Committee guidelines.[7, 33, 75] *Paper II* included patients with sleep disturbances scheduled for rotigotine initiation. The study utilised the PKG alongside patient- and investigator-reported outcomes to evaluate rotigotine's effects on sleep, daytime sleepiness, motor symptoms, and QoL. Additionally, correlations between PKG parameters and corresponding questionnaires were examined. *Papers III* and *IV* were validation studies within the international VALIDATE-PD collaboration, assessing agreement between HD entries and gold standard clinical observer ratings. While *Paper III* focused on the impact of structured patient training, *Paper IV* examined the agreement between relatives of PD patients and a clinical observer when assessing the patient's motor state in the HD. An overview of study designs is displayed in **Table 2.**

Table 2. Overview of the study designs used in the papers included in this thesis.

Paper	Study design	Recruitment	n[a]
I: Adherence to pharmacological NMS[b] treatment guidelines	Clinical, cross-sectional, descriptive	ParkReg[c]	165
II: Rotigotine, sleep and PKG[d]	Clinical, multicenter, prospective, open-label observation	Outpatient clinic	32
III: Diary validation with structured patient training	Clinical, prospective, open-label investigational	Re-invited cohort (initially recruited outpatient clinic)	20
IV: Diary validation with relatives	Clinical, prospective, open-label observation	ParkReg	56 (28 patient-relative pairs)

[a]n: Number of included participants; [b]NMS: non-motor symptoms; [c]ParkReg: Swedish National Quality Registry for Parkinson's Disease; [d]PKG: Parkinson's KinetiGraph.

Participants and study design

Paper I

This descriptive study utilised ParkReg, a Swedish national quality register with PD patients in specialist care, to identify potential participants. As of 2023, ParkReg achieved 66% national coverage, with 79% coverage in the Lund and Malmö regions.[138] A total of 220 patients with a H&Y stage ≤ 4 and ≥ 1 point on the Non-Motor Symptoms Questionnaire (NMSQ) were randomly selected from neurology departments in Scania. The selection aimed for equal gender distribution. For study inclusion, patients also had to be able to provide informed consent and complete questionnaires. Patients were excluded if they exhibited clinical signs of secondary or atypical parkinsonism, severe dementia, or other conditions impairing protocol adherence. Eligible participants were mailed study information and questionnaires (ESS, PDSS-2, and HADS [Hospital Anxiety and Depression Scale]). Following written informed consent, participants completed the questionnaires and the MDS-Non-Motor Rating Scale (MDS-NMS) was administered via telephone by a rater. The MDS-NMS evaluates the frequency and severity of 52 items across 13 domains. Finally, treatment data were extracted from medical records. To determine whether a patient was symptomatic and thus was defined to require treatment for a specific symptom, the following criteria were applied:

- **Specific treatment available for an item within a domain**: ≥ 6 points on that specific item in the MDS-NMS domain.
- **No specific treatment for the item, but for the entire domain**: ≥ 6 points on any of the items within that MDS-NMS domain.
- **Insomnia**: ≥ 6 points on the insomnia item (domain K question 1) in the MDS-NMS and ≥ 15 points on the PDSS-2.
- **Daytime sleepiness:** ≥ 6 points on the daytime sleepiness item (domain K question 3) in the MDS-NMS and ≥ 13 points on the ESS.
- **Depression**: ≥ 6 points on any item within the depression domain (A) in the MDS-NMS and ≥ 8 points on the HADS for depression.
- **Anxiety**: ≥ 6 points on any item within the anxiety domain (B) in the MDS-NMS and ≥ 8 points on the HADS for anxiety.

Adherence was assessed against the 2022 SWEMODIS guidelines,[33] the 2022 Swedish National Board of Health and Welfare guidelines,[75] and the 2019 MDS guidelines.[7] Analysis was restricted to NMS covered by the MDS-NMS for which treatment recommendations existed in at least one of these guidelines. Regarding national guidelines, treatments with priorities 1–7 (“should” or “can” be used) or

unspecified priorities were considered appropriate. MDS recommendations were considered followed if treatments were rated as "clinically" or "possibly useful". As specific indications for prescribed medications were not always available in medical records, adherence was defined as the use of any recommended medication for a documented symptomatic NMS. The study design is illustrated in **Figure 7.**

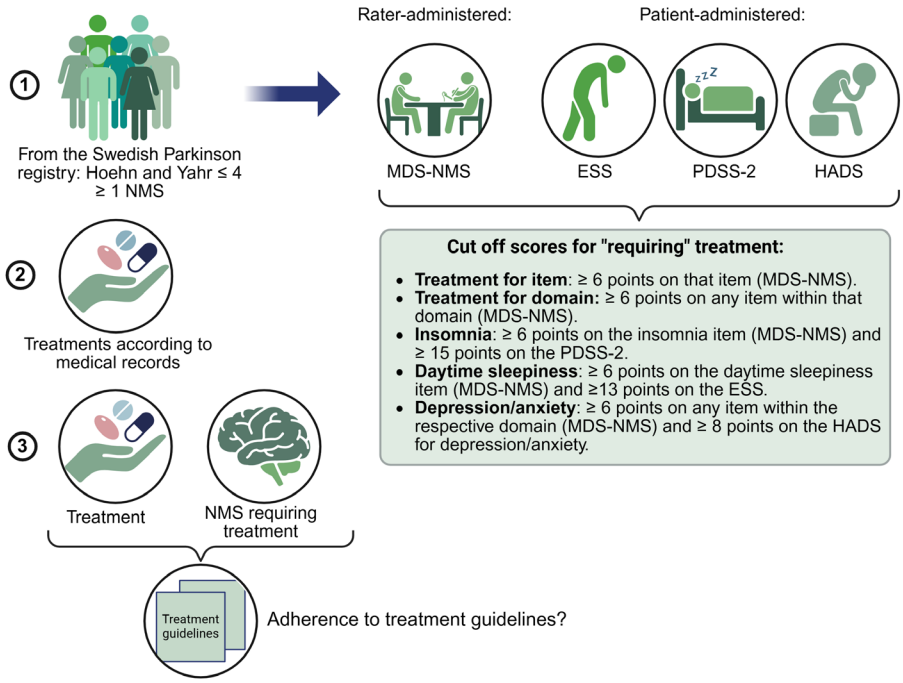

Figure 7: Study design of Paper I
NMS: non-motor symptoms; MDS-NMS: Movement Disorder Society-Non-Motor Rating Scale; ESS: Epworth Sleepiness Scale; PDSS-2: Parkinson's Disease Sleep Scale-2; HADS: Hospital Anxiety and Depression Scale. The figure is created in BioRender.

Paper II

This prospective observational study was conducted within the Swedish Parkinson Research Network. *Paper II* is also included in the doctoral thesis of Sotirios Grigoriou, 2024, Lund University.[139] Inclusion criteria targeted patients with PD aged 18–85 who experienced sleep disturbances (Clinical Global Impression-Severity [CGI-S] ≥ 3) and were scheduled to initiate rotigotine treatment. A stable PD medication regimen for at least 28 days was required for enrolment. Exclusion criteria comprised: device-aided therapies such as DBS, apomorphine infusion, or levodopa infusion; current oral DA administration; dementia or significant cognitive impairment; and non-PD-related conditions significantly impacting nocturnal sleep

such as clinically significant prostate problems causing sleep disturbances or sleep apnoea syndrome. The initiation or modification of sedatives or hypnotics during the study period was prohibited.

Following screening, patients underwent a baseline assessment. This involved a six-day continuous PKG recording (24 hours/day) alongside the completion of the PDSS-2, the ESS, the 8-item PD Questionnaire (PDQ-8), and the European Quality of Life Five-Dimension Five-Level Scale (EQ-5D-5L). Study clinicians evaluated sleep disturbances using the CGI-S and disease severity via the Clinical Impression of Severity Index for PD (CISI-PD). Rotigotine was subsequently titrated from an initial 2 mg/24 h, with weekly 2 mg increments, to a target dose of 4–16 mg. Doses were optimised based on motor relief and tolerability through weekly in-person or telephone follow-ups. Following at least a one-week maintenance phase at the stable dose, a second PKG recording was performed. All baseline assessments were then repeated and supplemented by the CGI-Improvement (CGI-I) scale. Final analyses compared outcomes before and during treatment. Additionally, the study examined correlations between PKG parameters used to evaluate sleep and daytime sleepiness and corresponding questionnaires. The study design is summarised in **Figure 8**.

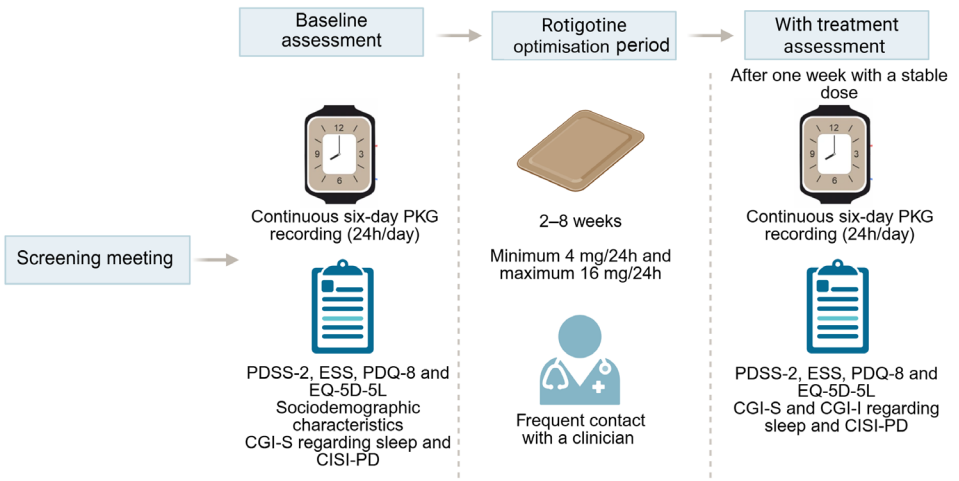

Figure 8: Study design of Paper II

PKG: Parkinson's KinetiGraph. PDSS-2: Parkinson's Disease Sleep Scale-2; ESS: Epworth Sleepiness Scale; PDQ-8: 8-item Parkinson's Disease Questionnaire; EQ-5D-5L: European Quality of Life Five-Dimension Five-Level Scale; CGI-S: Clinical Global Impression-Severity; CISI-PD: Clinical Impression of Severity Index for Parkinson's Disease; CGI-I: Clinical Global Impression-Improvement. The figure is created in BioRender.

Paper III

This study is a part of the international VALIDATE-PD collaboration, which aims to validate the HD for assessing motor fluctuations and dyskinesia in PD. Similar protocols have previously been implemented in Sweden and Germany.[113, 114] **Figure 9** illustrates the study design. This study re-enrolled participants from the previous Swedish validation cohort,[114] who still met the inclusion criteria. Eligible patients had a diagnosis of PD, were over 30 years old, had motor fluctuations confirmed by a neurologist or MDS-UPDRS Part IV, and were able to complete diaries and provide informed consent. Exclusion criteria included signs of dementia (Montreal Cognitive Assessment (MoCA) < 21), psychotic symptoms, inability to complete diaries or questionnaires, or any condition impairing cooperation, clinical evaluation, or study participation.

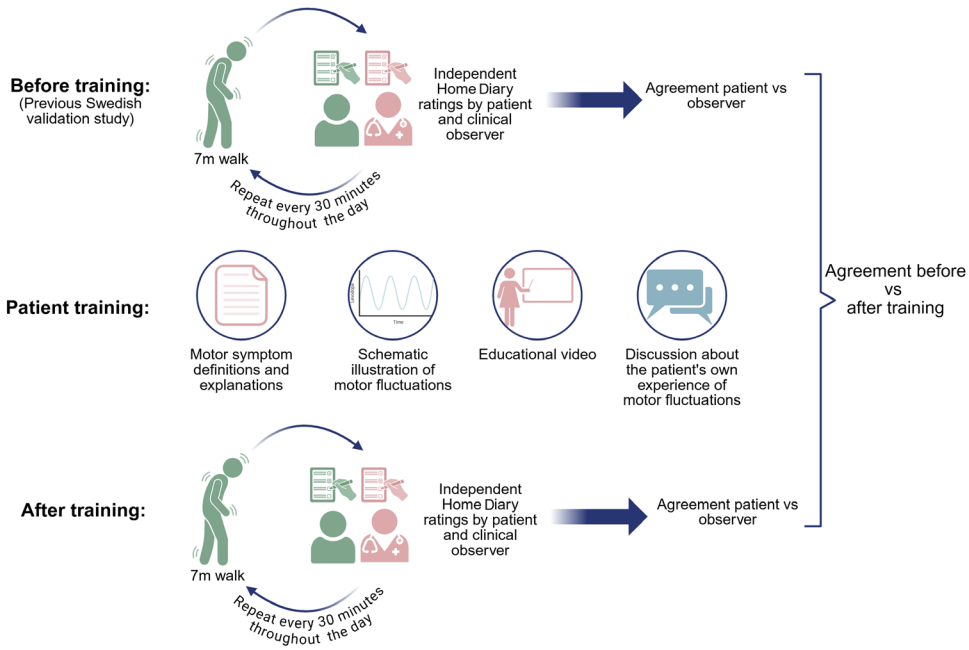

Figure 9: Study design of Paper III
The figure is created in BioRender.

Potential participants received study information via mail and a follow-up phone call. Interested individuals attended a screening visit to confirm eligibility. If included, they underwent a 50-minute training session on motor complications. This session began with an explanation of motor symptom nomenclature. Thereafter, patients were shown an illustration describing the occurrence of motor fluctuations and dyskinesia in relation to plasma levodopa levels. Participants then viewed a

training video, translated into Swedish, on motor fluctuations and diaries.[116] During the video, participants actively engaged by identifying the motor states of the individuals shown. The session concluded with a discussion of the patient's motor complications and specific instructions on completing the HD.

During the full-day visit (8:30 AM–4:00 PM), participants completed the HD at 30-minute intervals. Each assessment included a standardised task: walking seven meters, sitting, and returning. Immediately following the task, patients recorded their current motor state in the HD. Simultaneously, a clinical observer independently recorded their evaluation in a separate HD. Participants were instructed to base their motor state assessment on a global evaluation rather than gait function alone. Observations encompassed the entire interval, including periods of rest before the task, the walking session itself, and time spent in conversation. Finally, pre-training ratings from the previous study were compared with post-training ratings to evaluate the intervention's impact.

Paper IV

This observational study was conducted within the VALIDATE-PD collaboration,[113, 114] utilising the same core study protocol as *Paper III*. Eligibility criteria remained identical, with one additional requirement. To be included, patients needed a close relative who spent significant time with them, was willing to participate, and achieved a MoCA score ≥ 21. **Figure 10** summarises the study design.

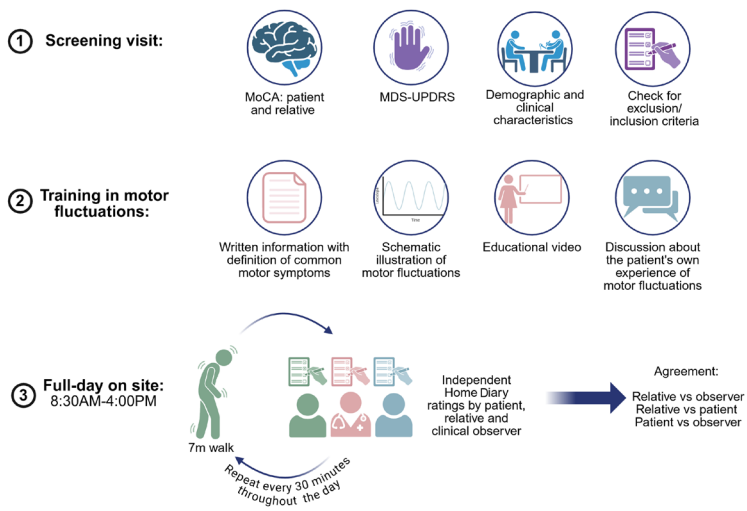

Figure 10: Study design of Paper IV
MoCA: Montreal Cognitive Assessment; MDS-UPDRS: Unified Parkinson's Disease Rating scale. The figure is created in BioRender.

Potential participants were identified via ParkReg, targeting patients in Scania Country with PD, motor fluctuations, and preserved cognition. Following initial contact, interested participants (patient and relative) attended a screening visit. If eligible, they participated in the structured training session previously described for *Paper III*. During the clinical observation day (8:30 AM–4:00 PM), patients performed a 7-metre Timed Up and Go test every 30 minutes.[140] After each walk, the patient, relative, and observer independently assessed the patient's motor state in the HD. Participants were instructed to base their motor state assessment on a global evaluation rather than gait function alone. Agreement between the relative-observer, patient-observer, and relative-patient assessments was investigated.

Outcome measures

Rating scales

Parkinson's disease staging and global assessment

The **H&Y scale** (**Figure 11**) is a widely utilised rater-administered instrument for staging PD severity based on motor involvement and postural stability. Originally developed as a five-point scale in 1967,[19] it was later modified to include 0.5-point increments to enhance sensitivity.[141] The scale is valued for its simplicity and alignment with typical disease progression. However, it primarily captures motor disability and excludes other PD dimensions. Consequently, the MDS recommends its use mainly for research eligibility and general staging.[141] In this thesis, an H&Y stage ≤ 4 was an inclusion criterion for *Paper I*, and the scale was utilised across all four papers to characterise the study cohorts.

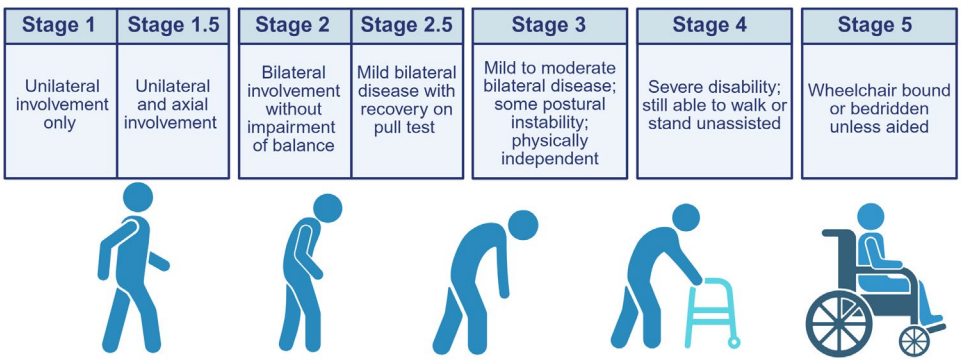

Figure 11: The Hoehn and Yahr scale
The figure is created in BioRender.

The CGI scale provides a brief, clinician-rated summary of the patient's global functioning over the past seven days, based on all available clinical information.[142] In *Paper II*, a **CGI-S** score ≥ 3 regarding sleep was required for inclusion, while the **CGI-I** scale was utilised to evaluate treatment effects. To provide a more detailed clinical profile, *Paper II* also employed the **CISI-PD**. Developed by Martínez-Martín et al.[143] in 2006 to refine global assessments, the CISI-PD evaluates four domains: motor signs, disability, motor complications, and cognitive impairment. Each domain is rated from 0 to 6, offering greater insight into patient impairment than the broader CGI-S alone.

Motor symptoms and motor state assessment

In *Papers III* and *IV*, motor symptoms and complications were assessed using the Swedish version of the **MDS-UPDRS**. Participants completed Parts I and II (experiences of daily living) independently or with a caregiver, whereas Part III (motor examination) and Part IV (motor complications) were rater-administered.[108] For these specific studies, eligibility required the presence of motor fluctuations, either confirmed by a neurologist or reflected in Part IV of the scale. The MDS-UPDRS comprises 65 items, of which 48 are rated on a 0 to 4 scale, while 7 items are binary (yes/no).[108] The maximum total score is 272, with higher scores indicating more severe symptoms.[144] In *Papers III* and *IV*, the **HD** was validated by having participants and a clinical observer concurrently and independently record motor states every 30 minutes. Ratings were categorised into one of the following states: “off”, “on without dyskinesia”, “on with non-troublesome dyskinesia”, and “on with troublesome dyskinesia”.[111]

Non-motor symptom assessment

In *Paper I*, participant eligibility required the presence of at least one NMS as identified by the **NMSQ**. The NMSQ is a 30-item self-report questionnaire, with each item answered using “yes”, “no”, or “I don’t know”.[145] To further characterise NMS frequency and severity, the **MDS-NMS** scale was employed. This rater-administered update of the original NMSS evaluates 52 items across 13 domains. Each item is scored by multiplying frequency (0–4) and severity (0–4).[146]

In *Papers I* and *II*, daytime sleepiness and sleep disturbances were evaluated utilising the ESS and the PDSS-2. The **ESS** is a self-administered, 8-item questionnaire that rates the likelihood of dozing off or falling asleep during common daytime activities. Each item is scored from 0 (would never doze) to 3 (high chance of dozing), with a total score range of 0–24.[133] Clinically, an ESS score of 13–15 indicates moderate EDS, while a score ≥ 16 is considered severe EDS.[147] The **PDSS-2** is a 15-item self-administered scale assessing PD-specific nocturnal disturbances across three domains: disturbed sleep, motor symptoms at night, and PD symptoms at night. Each item is rated from 0 (“never”) to 4 (“very often”), yielding a total score of 60, with higher scores indicating poorer sleep quality.[131] Proposed

thresholds for sleep disturbances vary across studies. One study recommended a threshold of ≥ 15 for detecting poor sleepers,[148] while another suggested a cutoff of ≥ 18 for clinically significant sleep disturbances.[130]

In *Paper I* anxiety and depression were assessed via the **HADS**. This tool comprises two 7-item subscales: HADS-A (anxiety) and HADS-D (depression).[149] For both subscales, a score of ≥ 8 is the commonly accepted threshold for identifying clinically significant symptoms.[150] For *Papers III* and *IV*, the **MoCA** was utilised as a screening tool for cognitive impairment. The MoCA evaluates 30 points across eight cognitive domains, including visuospatial/executive function, memory, and orientation. A score of ≥ 26 is generally considered normal.[151]

Quality of life assessment

In *Paper II*, the EQ-5D-5L and PDQ-8 assessed health-related QoL. The **EQ-5D-5L** is an evolution of the original 3L version designed to increase sensitivity to changes in health status. It evaluates health across five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has five response levels ranging from "no problems" to "unable to". Respondents also rate their global health on a VAS (EQ-VAS) from 0 to 100.[152] The EQ-5D-5L is summarised using an index based on the Time Trade-Off (TTO) method, reflecting how a country's population values different health states. This index ranges from 0 (death) to 1 (full health) and is calculated by subtracting dimension-specific weights from 1. These weights are derived from value sets where representative populations rank health states using a standard protocol.[153] In Sweden, Anxiety/Depression has the strongest impact on both TTO and VAS scores.[154]

The **PDQ-8** is a shortened version of the PDQ-39. The PDQ-39 evaluates eight discrete dimensions of QoL: mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort. Each dimension is scored from 0 (best) to 100 (worst).[155] The PDQ-8 utilises one representative item from each of these domains,[155] using the standardised prompt: "Due to having PD, how often during the last month have you…".[156] The PDQ-8 demonstrates a strong correlation with the PDQ-39,[157] and possesses an excellent convergent and concurrent validity.[158]

PKG

The PKG (Global Kinetics Corporation) is a wrist-worn actigraphy used on the most affected side for up to 10 days (**Figure 12**).[78] It utilises specialised algorithms to convert accelerometer data into continuous variables,[118] including scores for bradykinesia, dyskinesia, tremor, sleep, and daytime immobility.[78, 118] Data are recorded in 2-minute epochs and averaged over at least five days to generate severity

scores.[118, 159] The wearable produces a graphical representation of the patient's median Bradykinesia Score (**mBKS**) and median Dyskinesia Score (**mDKS**) score, alongside their 25th and 75th percentiles.[159, 160] These metrics are mapped against medication timing. Information about other scores is also provided. Daytime scores are calculated from 09:00 to 18:00, while nighttime scores cover the period from 23:00 to 06:00.[78] In *Paper II*, the PKG was used to evaluate rotigotine's effect on sleep, daytime sleepiness, and motor symptoms. Correlations between ESS and PTI_D as well as between PDSS-2 and CSS, were also examined.

Figure 12: PKG device and report
PKG: Parkinson's KinetiGraph. Photo by the author.

The **BKS** is calculated per epoch, and higher values indicate more severe bradykinesia.[161] Daytime mBKS excludes scores above 80, as these are associated with daytime sleep.[78] Controlled bradykinesia is defined as BKS ≤ 25.[162, 163] The Percent Time in Bradykinesia (**PTB**) represents the proportion of time exceeding this threshold.[159] Similarly, higher **DKS** values indicate more severe dyskinesia, with scores above 9 considered uncontrolled.[161-163] The Percent Time in Dyskinesia (**PTD**) is the proportion of time with DKS > 9, excluding periods where walking, or tremor is detected.[159] Percent Time with Tremor (**PTT**) > 1% indicates the presence of tremor.[163] **PTI_D** is defined as daytime immobility episodes (BKS > 80) lasting at least 2 minutes.[78, 161] This metric has shown concordance with daytime sleep detection via PSG and elevated PTI_D scores have been associated with higher ESS scores. PTI_D is thus suggested to represent daytime sleepiness.[135] The target score is ≤ 10%.[160]

Nighttime PTI (**PTI_N**) is the percentage of the nocturnal period with a BKS > 80. Higher values indicate better sleep efficiency. However, PTI_N may underestimate actual sleep by misclassifying periodic limb movements and microarousals as

wakefulness. To address this, the Percent of Time Sleeping (**PTS**) uses a smoothing function to enhance the accuracy of sleep efficiency assessments. Sleep Quality (**SQ**) is defined as the percentage of the nocturnal period with a BKS above 110, a threshold that correlates with deep sleep in 80% of instances. A higher score indicates superior sleep quality and in healthy controls the median SQ is 77%. PTI_N, PTS, and SQ are normalised into percentile-based scores (0–9) and summed to derive the **CSS**. The resulting total CSS ranges from 0 to 27, where higher values reflect superior overall sleep. The CSS has been shown to correlate with PDSS-2, particularly PDSS-2 subscores related to sleep quality and quantity.[78]

Statistical methods

Data were analysed using IBM SPSS Statistics (versions 27.0 and 29.0), Microsoft Excel 365, and RStudio (version 4.2.0). Descriptive statistics are reported as mean ± standard deviation (SD) for normally distributed data, median (interquartile range [IQR]) for non-parametric data, or frequencies (percentages). GraphPad Prism (versions 9.4.0, 9.5.1, and 10.4.2) was used to create graphs. **Levodopa equivalent daily dose (LEDD)** was calculated according to Jost et al.[164] or Tomlinson et al.[165] to standardise dopaminergic treatment intensity across patients. Data distribution was assessed through visual inspections of **histograms** and **Q–Q plots**, followed by **Shapiro–Wilk** testing. This evaluates the null hypothesis that data follow a normal distribution. For *Papers II–IV*, multiple comparisons were accounted for using **Bonferroni correction**. This method reduces the risk of false positives by dividing the significance level (0.05) by the total number of comparisons.

The **Wilcoxon signed–rank test**, a non-parametric method for comparing two related groups, was used in *Paper II* to assess changes following rotigotine treatment. It was also employed in *Paper III* to evaluate differences in percentage agreement before and after structured training and served as a post hoc analysis in *Papers III* and *IV*. To determine the magnitude of differences between paired observations in *Paper II* and *III*, the **effect size (*r*)** was calculated from Wilcoxon signed–rank test using the formula $r = |Z|/\sqrt{N}$. Absolute effect sizes are reported. Following Cohen's criteria,[166] *r* values were interpreted as small (0.1–0.3), moderate (0.3–0.49), or large (≥ 0.5). For sub-analyses in *Paper I*, the **Mann–Whitney U test** was employed. This non-parametric test evaluates differences between two independent samples by comparing the ranks of their values. In *Papers III* and *IV*, the **McNemar–Bowker test** was used to assess the symmetry of disagreements between rating procedures. This method is applied to paired nominal data with more than two categories. Where appropriate, post hoc **McNemar tests** were used for pairwise comparisons of binary categories. Additionally, the **Friedman test** was employed to investigate differences in distribution of daily motor state times. As a

non-parametric alternative for repeated measures across three or more related groups, this test is based on ranked data.

In *Papers III* and *IV*, **Cohen's kappa (κ)** was utilised to assess agreement between raters completing the HD. This analysis of two dependent categorical samples investigated the extent to which rater measurements aligned. Agreement strength was interpreted as: slight (< 0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), or almost perfect agreement (0.81–1.00).[167] In *Paper III*, the delta function from the R package "multiagree" was utilised to compare dependent pairwise κ coefficients via **Hotelling's T^2 statistics**. This multivariate approach, developed by Vanbelle and Albert,[168, 169] assesses whether differences between dependent κ coefficients obtained on multilevel data are statistically significant. **Spearman's rank correlation** was utilised in *Paper II* to assess relationships between variables. As a non-parametric test based on data ranks, it is appropriate for non-normally distributed or ordinal data. **Pearson's correlation** was employed in *Papers III* and *IV* to measure the strength and direction of linear relationships between continuous variables. Both methods assume independent observations. In *Papers III* and *IV*, the **Intraclass Correlation Coefficient (ICC)** was utilised to evaluate the concurrent validity of the HD by assessing the degree of absolute agreement between patient/relative and a clinical observer (gold standard). ICC estimates and their 95% confidence intervals (95% CIs) were calculated based on single-rating, absolute-agreement, 2-way mixed-effects models. According to the guidelines by Cicchetti,[170] reliability was interpreted as follows: < 0.40 (poor), 0.40–0.59 (moderate), 0.60–0.74 (good), and 0.75–1.00 as (excellent).

Ethical considerations

All research in this thesis was approved by the Swedish Ethical Review Authority (Etikprövningsmyndigheten; *Paper I*: Dnr 2022-05274-01; *Paper II*: Dnr 2019-01294; *Paper III*: Dnr 2022-00550-02; *Paper IV*: Dnr 2023-02986-01). A risk-benefit analysis was performed for each study to minimise potential harm and maximise patient benefit. All studies were conducted in accordance with the principles of the Declaration of Helsinki. Prior to study inclusion, participants received oral and written information and were provided the opportunity to ask questions to ensure a full understanding of the study and its implications. Written informed consent was obtained from all participants, who were informed of their right to withdraw at any time without consequence. The primary ethical concern was the handling of sensitive personal data. To ensure secure management, each participant was assigned a unique study ID number used throughout the study. Access to the key linking these IDs to personal identifiers was strictly limited to authorised study personnel.

Results

Summary of the main findings

Non-motor symptom management:

- **Adherence to guidelines**: On average, 32% of NMS requiring treatment were treated according to national or international guidelines. Adherence was highest for depression (79%) and constipation (77%), but lowest for dysphagia (0%).
- **Rotigotine and sleep**: Rotigotine did not improve sleep for the whole cohort (PDSS-2 and PKG data). However, significant PDSS-2 improvements occurred in DA-naïve patients ($p = 0.013$, $r = 0.31$) and those with severe baseline sleep disturbances (PDSS-2 ≥ 18; $p = 0.02$, $r = 0.33$).
- **Rotigotine, daytime sleepiness, motor symptoms, and QoL**: Rotigotine treatment significantly decreased the PKG measure PTI_D ($p < 0.001$, $r = 0.56$), suggesting reduced daytime sleepiness. This was not reflected in ESS scores. Improvements were observed in motor symptoms (CISI-PD, $p < 0.001$, $r = 0.45$; PTT, $p < 0.001$, $r = 0.42$) and health-related QoL (PDQ-8, $p = 0.014$, $r = 0.31$; EQ-5D-5L, $p = 0.002$, $r = 0.38$).

Evaluating symptom measurement and monitoring tools:

- **PKG vs questionnaires**: No correlations were found between PKG measures and corresponding questionnaires (CSS vs PDSS-2; ESS vs PTI_D).
- **Diary validation with structured patient training**: Structured training on motor fluctuations did not significantly improve temporal agreement between clinical observer and patient HD ratings, nor the correlation/reliability of HD-recorded daily motor state times when compared to observer ratings. Agreement for "on with dyskinesia" rose from 58% to 80% post-training, although this change remained non-significant ($p = 0.074$, $r = 0.33$).
- **Diary validation with relatives**: Temporal agreement in HD motor state ratings was fair for relative-observer ($\kappa = 0.250$) and relative-patient ($\kappa = 0.230$) pairs, but slight for patient-observer pairs ($\kappa = 0.120$). Significant differences existed in daily time distribution for "off" and "on without dyskinesia" states between the clinical observer and both relatives ($p = 0.027$ and $p = 0.012$, respectively) and patients ($p = 0.006$ and $p = 0.012$).

Non-motor symptom management

A limited understanding of how NMS are identified and managed in clinical practice was noted. Therefore, *Paper I* and *II* address this knowledge gap from different perspectives. *Paper I* provides a comprehensive assessment of clinical adherence to national and international pharmacological NMS guidelines, while *Paper II* evaluates rotigotine's effect on sleep and daytime sleepiness in PD patients.

Adherence to pharmacological non-motor symptom guidelines

In *Paper I*, 165 patients were included. **Table 3** summarises their clinical and demographic characteristics.

Table 3. Clinical and demographic characteristics of Paper I

Patient characteristics	
Gender (n, %)	Male: 80 (48%) Female: 85 (52%)
Age, years (mean ± SD)	71 ± 9
PD[a] duration, years since diagnosis (mean ± SD)	11 ± 7
LEDD[b], mg/day (mean ± SD)	890 ± 490
NMSQ[c] total score (median, IQR)	10 (6–14)
Hoehn and Yahr stage (median, IQR)	2 (2-3)
Stage 1 (n,%)	24 (15%)
Stage 2 (n,%)	61 (37%)
Stage 3 (n,%)	58 (35%)
Stage 4 (n,%)	22 (13%)
ESS[d] total score (median, IQR)	8 (5–13)
≥ 13 (n, %)	47 (28%)
PDSS-2[e] total score (median, IQR)	17 (11–26)
≥ 15 (n, %)	92 (56%)
HADS[f] total score (median, IQR)	10 (5–15)
Anxiety total score (median, IQR)	6 (3–9)
≥ 8 (n,%)	55 (33%)
Depression total score (median, IQR)	4 (2–7)
≥ 8 (n,%)	38 (23%)
MDS-NMS[g] total score (median, IQR)	98 (71–140)

[a]PD: Parkinson's disease; [b]LEDD: Levodopa equivalent daily dose; [c]NMSQ: Non-Motor Symptom Questionnaire; [d]ESS: Epworth Sleepiness Scale. Total score (score ≥ 13 indicates moderate daytime sleepiness); [e]PDSS-2: Parkinson's Disease Sleep Scale-2 (score ≥ 15 indicates insomnia); [f]HADS: Hospital Anxiety and Depression Scale (score ≥ 8 points on respective subscales indicates depression/anxiety); [g]MDS-NMS: Movement Disorder Society-Non-Motor Rating Scale.

First, the prevalence of NMS was investigated. Participants reported a minimum of five and a median of 14 different NMS. They had a median of seven symptoms that were classified as "symptomatic" (defined in the Methods section), indicating a need for intervention. The most prevalent symptomatic NMS were muscle joint or back pain (65%), hyposmia (59%), and urinary urgency (49%). Conversely, the

lowest prevalence was observed for impulse control disorders (0–2% scoring ≥ 6 on any item within the domain on MDS-NMS), snoring or breathing difficulties (3%), and delusions (4%).

The second phase of the analysis focused on adherence to pharmacological treatment guidelines. On average, 32% (± 23%) of NMS identified as requiring intervention were treated according to national or international pharmacological guidelines. Adherence to guidelines was 26% (± 21%) for mild PD (H&Y 1–2), 35% (± 26%) for moderate severe PD (H&Y 3), and 39% (± 34%) for severe PD (H&Y 4). Adherence was highest for depression (79%, n = 29, where n indicates number of symptomatic patients), constipation (77%, n = 66), and insomnia (62%, n = 55). Conversely, the lowest adherence was observed for dysphagia (0%, n = 22), EDS (4%, n = 28), cognitive impairment (7%, n = 91), and apathy (7%, n = 58).

Third, the specific treatments prescribed for NMS were examined. For cognitive impairment, 7% received the recommended rivastigmine. In contrast, 8% were prescribed memantine, which is priority 9 (for exceptional cases only) in Sweden and not recommended according to international guidelines. Among patients with symptomatic depression, 72% received antidepressants. Of these, 62% were prescribed venlafaxine (priority 3), 48% mirtazapine, 14% selective serotonin reuptake inhibitors (SSRIs, priority 8), and 5% tricyclic antidepressants (priority 4).

Rotigotine's effect on sleep and daytime sleepiness

Paper II investigated the effects of rotigotine, with sleep as the primary endpoint. Secondary endpoints included daytime sleepiness, motor symptoms, and health-related QoL. Of the 40 patients included, 32 completed the study. Within this final cohort, 16 patients were DA-naïve and 16 had discontinued prior DA treatment before inclusion. Clinical and demographic characteristics are presented in **Table 4**.

Table 4. Clinical and demographic characteristics of Paper II

Patient characteristics		
Gender (n, %)	Male: 21 (34%)	Female: 11 (34%)
Age, years (mean, range)	67 (50–82)	
PD[a] duration, years since diagnosis (mean, range)	5 (0–14)	
LEDD[b], mg/day (mean, range)	783 (120-1,983)	
Hoehn and Yahr stage (median, IQR)	2 (2–2)	
CGI-S[c] for sleep at baseline (median, IQR)	4 (4-5)	
PDSS-2[d] total score at baseline (median, IQR)	17 (13–24)	
Rotigotine maintenance dose, mg/24 h (mean, range)	5 (4–8)	
Days with rotigotine treatment[e] (mean, range)	29 (16–49)	
Days with rotigotine maintenance dose[f] (mean, range)	16 (13–32)	

[a]PD: Parkinson's disease; [b]LEDD: Levodopa equivalent daily dose; [c]CGI-S: Clinical Global Impression-Severity (regarding sleep); [d]PDSS-2: Parkinson's Disease Sleep Scale-2; [e]Total duration from initiation of rotigotine to completion of the second Parkinson's KinetiGraph (PKG) registration; [f]Duration of rotigotine maintenance dose (optimal dose) until completion of the second PKG registration.

The primary outcomes were changes in PDSS-2 and CSS, evaluated using a Bonferroni-adjusted threshold of $p < 0.025$. Secondary and post hoc analyses were exploratory and not corrected for multiple comparisons.

The effects of rotigotine on sleep

Nighttime sleep was assessed using the PDSS-2, CGI-S, and PKG monitoring. In the total cohort, median PDSS-2 scores decreased from 17 (IQR: 13–24) to 13 (IQR: 11–24) during rotigotine treatment, though this change was not statistically significant ($p = 0.13$, $r = 0.19$; **Figure 13**). Similarly, PKG nighttime scores, including the CSS, showed no significant change. However, CGI-S improved significantly from a median of 4 (IQR: 4–5) to 3 (IQR: 2–4) ($p < 0.001$, $r = 0.51$). Also, item 14 on the PDSS-2 (sleepiness after waking) improved, with median scores decreasing from 2 (IQR: 1–3) to 1 (IQR: 1–3) ($p = 0.02$, $r = 0.29$; **Figure 13**).

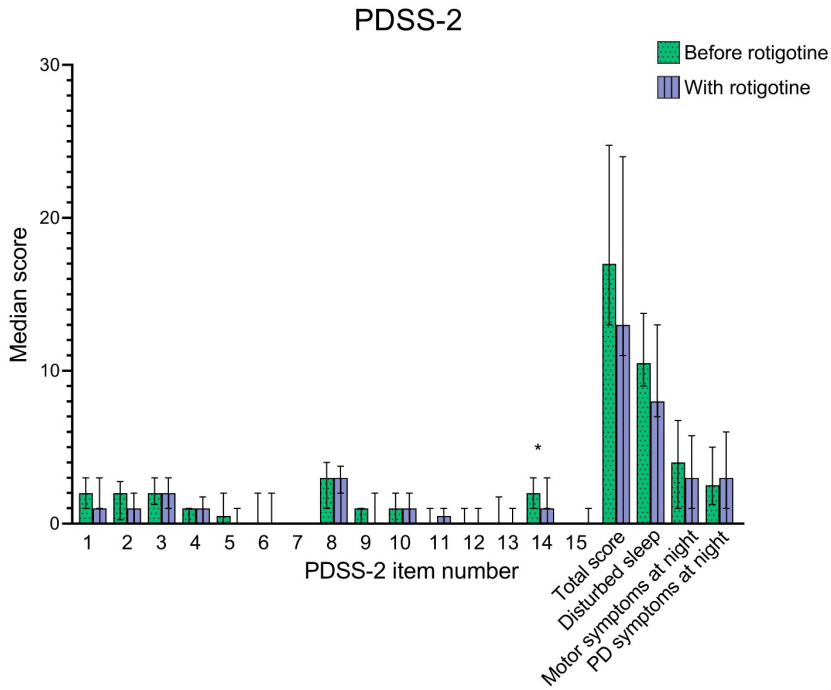

Figure 13: Median PDSS-2 scores before and with rotigotine treatment

Error bars represent IQR. Statistical significance was assessed using the Wilcoxon signed–rank test; *$p \leq 0.05$). PDSS-2: Parkinson's Disease Sleep Scale-2. PD: Parkinson's disease. "Disturbed sleep" comprises items 1, 2, 3, 8 and 14; "Motor symptoms at night" comprises items 4, 5, 6, 12 and 13; "PD symptoms at night" comprises items 7, 9, 10, 11 and 15.

Subgroup analyses revealed significant benefits for specific patient subgroups. Among those with severe baseline sleep disturbances (PDSS-2 ≥ 18, n = 15), median

scores improved from 25 (IQR: 21–27.5) to 20 (IQR: 12–25) ($p = 0.009$, $r = 0.33$) with treatment. In DA-naïve patients (n = 16), PDSS-2 scores improved from a median of 17.5 (IQR: 13–25) to 12.5 (IQR: 10–23) ($p = 0.013$, $r = 0.31$), whereas no significant change was observed in those previously treated with oral DAs.

The effects of rotigotine on daytime sleepiness

Daytime sleepiness measured by the ESS showed no significant change, with a stable median score of 7.5 (IQR: 5–11 at baseline vs 3–10 during treatment; $p = 0.358$, $r = 0.11$). However, the PKG-derived score PTI_D improved significantly, decreasing from a median score of 10 (IQR: 5–14) to 6 (IQR: 3–7) ($p < 0.001$, $r = 0.56$; **Figure 14**). With a target PTI_D threshold of ≤ 10%, 12 patients shifted from elevated to normal PTI_D scores during the treatment period.

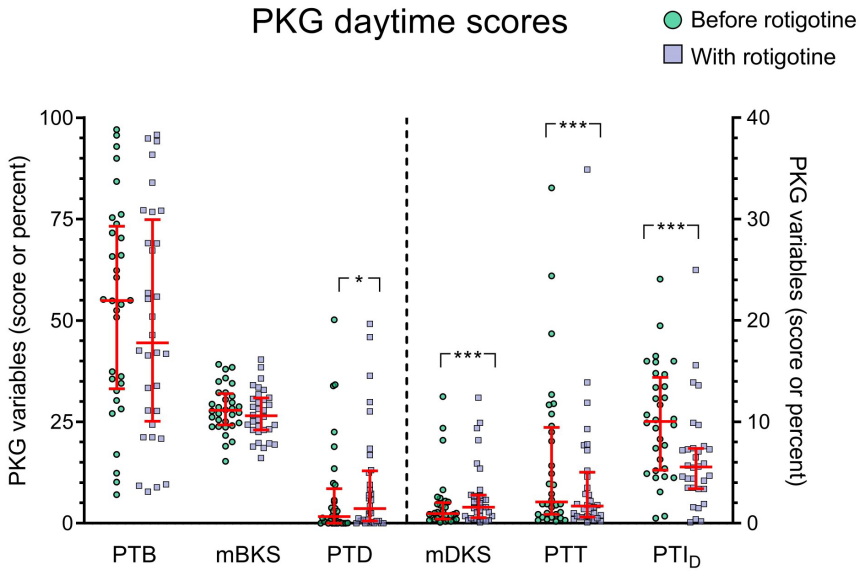

Figure 14: PKG daytime scores before and during rotigotine treatment
Error bars show median values with IQR. The left side of the figure (separated by the dotted line) corresponds to the left Y-axis and the right side corresponds to the right Y-axis. Statistical significance was assessed via Wilcoxon signed–rank test (* $p \leq 0.05$, ** $p \leq 0.01$, ***$p \leq 0.001$). Daytime scores reflect data from 09:00–18:00. Abbreviations: PKG: Parkinson's KinetiGraph; PTB: Percent Time in Bradykinesia; mBKS: median Bradykinesia Score; PTD: Percent Time in Dyskinesia; mDKS: median Dyskinesia Score; PTT: Percent Time in Tremor; PTI_D: daytime Percent Time Immobile.

The effects of rotigotine on motor symptoms and complications

Rotigotine's effect on motor symptoms was assessed using the CISI-PD and PKG scores. The median CISI-PD score improved from 7 (IQR: 4–9) to 5.5 (IQR: 4–7) with treatment ($p < 0.001$, $r = 0.45$). Specifically, significant improvements were

noted in motor signs (item 1; $p = 0.001$, $r = 0.41$) and motor complications (item 3; $p < 0.001$, $r = 0.43$). This is in line with PKG scores that showed reduced tremor during treatment, with median PTT scores decreasing from 2.1 (IQR: 0.9–9.2) to 1.7 (IQR: 0.7–4.8) ($p < 0.001$, $r = 0.42$). Consequently, the number of patients within the target range (PTT ≤ 1%) increased from 10 to 13. Regarding bradykinesia, median mBKS decreased from 27.9 (IQR: 24.6–31.6) at baseline to 26.5 (IQR: 23–30.8) during treatment ($p = 0.106$, $r = 0.20$). Of the 23 patients with uncontrolled bradykinesia at baseline (mBKS > 25), four achieved the target range (mBKS ≤ 25) during treatment.

Patients experienced increased dyskinesia during rotigotine treatment according to PKG scores. The median mDKS increased from 0.95 (IQR: 0.5–2) at baseline to 1.6 (IQR: 0.7–2.7) during treatment ($p = 0.001$, $r = 0.40$), and the median PTD increased from 1.7 (IQR: 0–6.7) to 3.7 (IQR: 0.6–12.7) ($p = 0.016$, $r = 0.30$). While these increases were statistically significant, both parameters remained relatively low. Only one patient's mDKS exceeded the threshold of 9 during treatment, representing the emergence of previously absent, uncontrolled dyskinesia. Daytime PKG scores are illustrated in **Figure 14**.

The effects of rotigotine on health-related life quality

Rotigotine's effect on health-related QoL was assessed using the PDQ-8 and the EQ-5D-5L. Median PDQ-8 scores improved from 9.5 (IQR: 6–13) to 7.5 (IQR: 3–12) ($p = 0.014$, $r = 0.31$) with treatment. The most pronounced improvement was observed in the depression item (item 3; $p = 0.007$, $r = 0.33$). Similarly, health-related QoL measured with the EQ-5D-5L showed significant improvement. The median TTO index increased from 0.79 (IQR: 0.7–0.9) to 0.84 (IQR: 0.8–0.9) ($p = 0.002$; $r = 0.38$), while the median VAS score improved from 60 (IQR: 45–70) to 67.5 (IQR: 52–76) ($p = 0.002$, $r = 0.39$) during treatment.

Evaluating symptom measurement and monitoring tools

There is a need for validated tools to measure and monitor both non-motor and motor PD symptoms and fluctuations to support treatment optimisation. Thus, *Papers II–IV* addressed this knowledge gap. A secondary outcome in *Paper II* was to examine correlations between objective PKG-derived parameters and subjective questionnaire-based measures for sleep and sleepiness. *Papers III* and *IV* focused on validating the HD for assessment of motor fluctuations and dyskinesia.

PKG for the assessment of sleep and daytime sleepiness

Correlations between PKG-derived parameters and corresponding questionnaire-based measures were examined (**Figure 15**). No correlation was observed between the PDSS-2 total score and the CSS (ρ = -0.065, p = 0.612). However, a weak negative correlation was found between the CSS and the PDSS-2 item 2 (difficulty falling asleep; ρ = -0.325, p = 0.009). Moreover, no significant correlation was found between the ESS and the PTI_D (ρ = 0.046, p = 0.718). While Kotschet et al.[135] previously reported a significant association between ESS scores ≥ 10 and elevated PTI_D scores, data from *Paper II* showed no significant difference in PTI_D between patients with a ESS score ≥ 10 and those with an ESS score < 10 (Mann Whitney U Test; p = 0.967). Similarly, patients with a PTI_D over the target score (> 10%) did not exhibit significantly higher ESS scores compared to those with a $PTI_D \leq 10$ (Mann Whitney U Test; p = 0.873).

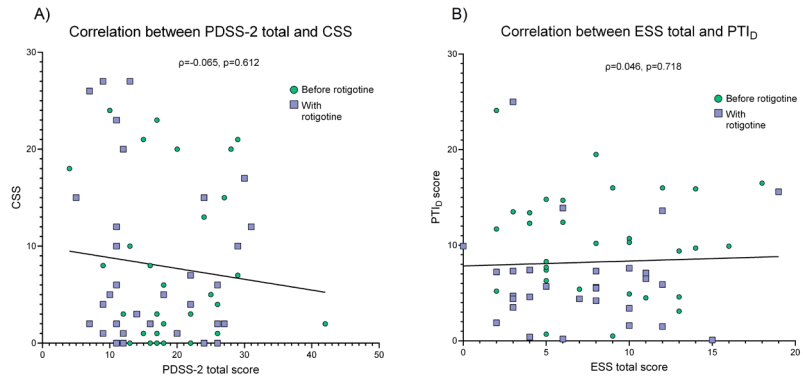

Figure 15: Correlations between PKG and questionnaires
Lines represent simple linear regressions. Statistical analysis was performed using Spearman's rank correlation test. PKG: Parkinson's KinetiGraph. PDSS-2: Parkinson's Disease Sleep Scale-2; CSS: Combined Sleep Score; ESS: Epworth Sleepiness Scale; PTI_D: daytime Percent Time Immobile **A)** Correlation between PDSS-2 total score and CSS **B)** Correlation between ESS total score and PTI_D.

Validation of the Home Diary

Structured training's impact on agreement between patients and clinical observer

Paper III investigated whether structured patient training on motor fluctuations and dyskinesia improved the agreement between a clinical observer and patients when completing the HD. The study included 20 patients and 316 pairs of motor state assessments. Ratings were distributed across "off", "on without dyskinesia", and "on with dyskinesia". Before training, ratings were obtained from the previous Swedish validation study.[114] Consequently, a median of 36 months had elapsed between the initial screening visit of that study and the screening visit for the current study. Clinical and demographic data are presented in **Table 5**.

Table 5: Clinical and demographic characteristics of Paper III

Patient characteristics	
Gender (n, %)	Male: 10 (50%) Female: 10 (50%)
Age, years (median, IQR)	70 (65–77)
PD[a] duration, years since diagnosis (median, IQR)	13 (10–16)
Months since initial screening visit (median, IQR)	36 (34–39)
LEDD[b] before training, mg/day (median, IQR)	929 (751–1,154)
LEDD after training, mg/day (median, IQR)	1058 (737–1,233)
Hoehn and Yahr stage (median, IQR)	2 (1–3)
MDS-UPDRS[c] total score before training (median, IQR)	38 (26–55)
MDS-UPDRS total score after training (median, IQR)	55 (43–78)
Duration of motor fluctuations, months (median, IQR)	68 (52–111)
Hypokinetic fluctuations	68 (51–101)
Hyperkinetic fluctuations	63 (56–93)
MoCA[d] total score before training (median, IQR)	26 (25–28)
MoCA total score after training (median, IQR)	27 (25–28)

[a]PD: Parkinson's disease; [b]LEDD: Levodopa equivalent daily dose; [c]MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; [d]MoCA: Montreal Cognitive Assessment (> 25: normal cognition; 21–25: mild cognitive impairment; < 21: dementia).

No significant differences in motor state distribution were found between patients and the clinical observer either before ($p = 0.459$) or after training ($p = 0.236$). Post-training, both groups reported fewer "on without dyskinesia" ratings and more "on with dyskinesia" ratings.

Temporal agreement between the clinical observer and patient HD ratings (utilising the observer as the reference) before and after structured training is illustrated in **Figure 16**. Following training, overall agreement increased from 68% to 76%, though this was not statistically significant ($p = 0.093$, $r = 0.27$). This trend was mirrored by a non-significant improvement in Cohen's κ, which rose from 0.438 to 0.559 ($p = 0.320$). Consequently, overall agreement remained moderate after training. Temporal agreement for "off" and "on without dyskinesia" states remained stable. In contrast, agreement for "on with dyskinesia" improved non-significantly from 58% to 80% after training ($p = 0.074$, $r = 0.33$). This trend was also reflected by a non-significant rise in Cohen's κ from fair ($\kappa = 0.388$) to moderate ($\kappa = 0.543$, $p = 0.299$). Notably, before training, agreement was significantly higher in the current cohort compared to non-recruited participants from the initial VALIDATE-PD study ($p < 0.001$).

When observed in the "off" state, the most common misclassification shifted from "on without dyskinesia" pre-training to "on with dyskinesia" post-training. Total observations by motor state (before/after training) were: "off" (n = 84/28), "on without dyskinesia" (n = 362/109), and "on with dyskinesia" (n = 204/179).

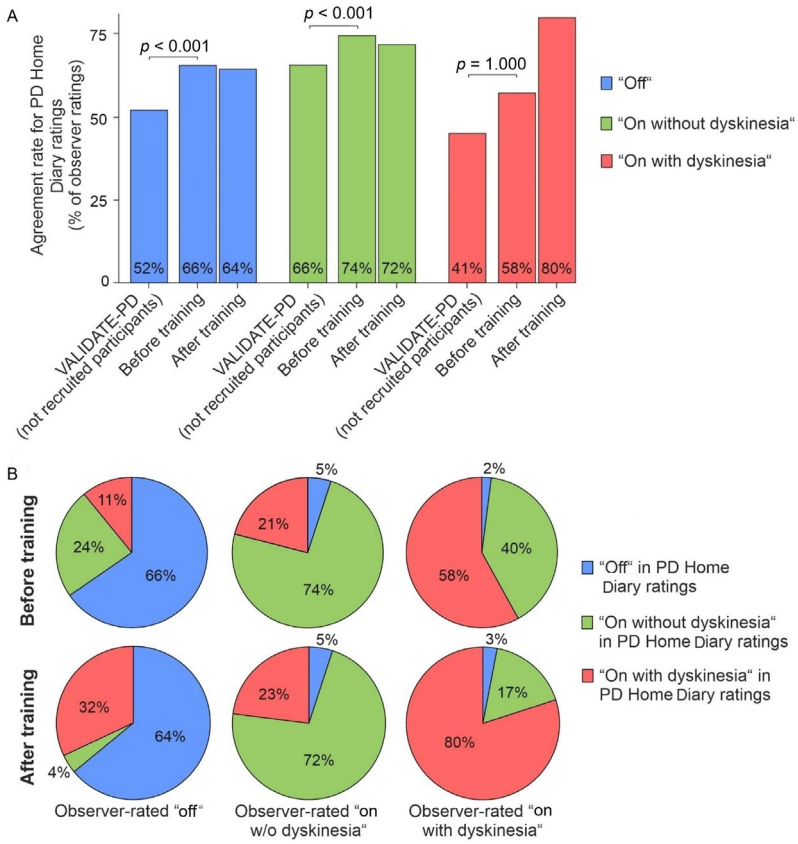

Figure 16: Temporal agreement of motor state ratings between observer and patient diaries. **A)** Comparison of temporal agreement rates (%) across motor states, using the clinical observer ratings as the reference. Bars compare: (1) the non-recruited Swedish VALIDATE-PD cohort (2) the study subcohort before training, and (3) the same subcohort after training. *P*-values are derived from McNemar's tests. **B)** Patient diary entries by observed motor state before and after training.

Daily time distribution (8:30 AM–4:00 PM) across motor states was analysed before and after training (**Figure 17**). Both clinical observer and patient diaries showed similar daily time distributions, with no significant differences between them. Following training, both the observer and patients reported significantly less time in "on without dyskinesia" and more time in "on with dyskinesia". Pearson correlation analysis confirmed strong correlations in individual daily percentage times across all three motor states before ("off": $r = 0.849$; "on without dyskinesia": $r = 0.756$; "on with dyskinesia": $r = 0.692$) and after training ("off": $r = 0.752$; "on without dyskinesia": $r = 0.841$; "on with dyskinesia": $r = 0.763$), with all reaching statistical significance ($p < 0.001$). Furthermore, ICC calculations demonstrated good-to-excellent reliability for patient HD data across all motor states compared to the clinical observer, independent of the training intervention ($p < 0.001$).

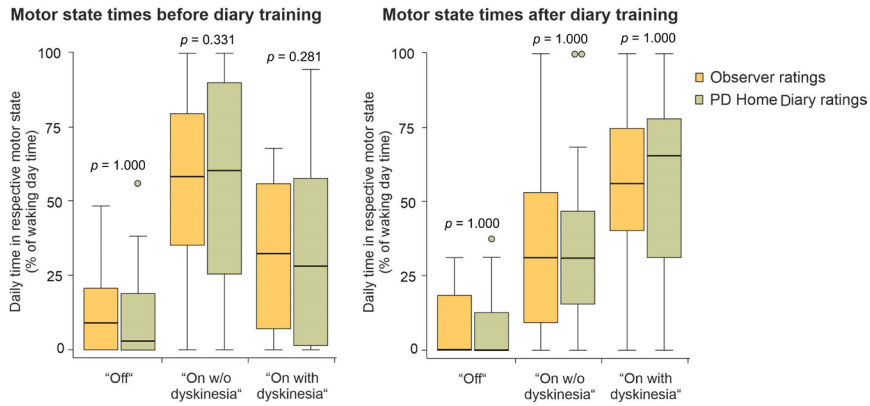

Figure 17. Proportions of time spent in motor states before and after training as assessed by observer and patient diaries

Boxplots illustrate the daily time distribution (8:30 AM–4:00 PM) across motor states before and after structured training. Central lines represent medians, boxes indicate the IQR, and whiskers extend to 1.5 times the IQR. Comparison of observer ratings (yellow) and patient ratings (green) revealed no significant differences in daily time distribution for any motor state. *P*-values are derived from Friedman tests with Bonferroni-corrected post hoc Wilcoxon signed–rank tests.

Agreement on the Home Diary between relatives, patients, and a clinical observer

Paper IV evaluated motor state agreement in the HD between PD patients, their relatives, and a clinical observer. Of 82 invited patients, 29 patient-relative pairs were recruited, and 28 pairs were included in the study. Most relatives were partners to the patient (n = 25; 89%), while three (11%) were their adult children. Clinical and demographic characteristics are summarised in **Table 6**.

Table 6: Clinical and demographic characteristics of Paper IV

Patient characteristics		
Gender patient (n, %)	Male: 17 (61%)	Female: 11 (39%)
Gender relative (n, %)	Male: 9 (32%)	Female: 19 (68%)
Patient age, years (median, IQR)	74 (70–80)	
Relative age, years (median, IQR)	71 (64–75)	
PD[a] duration, years since diagnosis (median, IQR)	11 (9–16)	
LEDD[b], mg/day (median, IQR)	900 (600-–1,179)	
Hoehn and Yahr stage (median, IQR)	2.5 (2–3)	
MDS-UPDRS[c] total score (median, IQR)	65 (52–78)	
Duration of motor fluctuations, months (median, IQR)	59 (45–91)	
Hypokinetic fluctuations	65 (47–72)	
Hyperkinetic fluctuations	46 (34–83)	
MoCA[d] total score patient (median, IQR)	25 (23–27)	
MoCA total score relative (median, IQR)	26 (24–28)	

[a]PD: Parkinson's disease; [b]LEDD: Levodopa equivalent daily dose; [c]MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; [d]MoCA: Montreal Cognitive Assessment (> 25: normal cognition; 21–25: mild cognitive impairment; < 21: dementia).

Out of the expected 448 sets of HD ratings, 445 were completed (99%). The observer's distribution of motor state ratings differed significantly from both relatives and patients for "off" and "on without dyskinesia" ($p < 0.001$). In contrast, no significant differences were found for "on with dyskinesia" compared to either relatives or patients ($p = 0.321$; $p = 0.612$, respectively). No differences were observed between patients and relatives for any motor state ("off": $p = 0.423$; "on without dyskinesia": $p = 1.000$; "on with dyskinesia": $p = 1.000$).

Overall temporal agreement was highest between relatives and patients (56%), followed by relatives and the observer (52%), with lowest agreement between patients and the observer (44%). This corresponded to Cohen's κ values indicating fair agreement between relative-patient pairs ($\kappa = 0.230$) and relative-observer pairs ($\kappa = 0.250$), but slight agreement between patients and the observer ($\kappa = 0.120$).

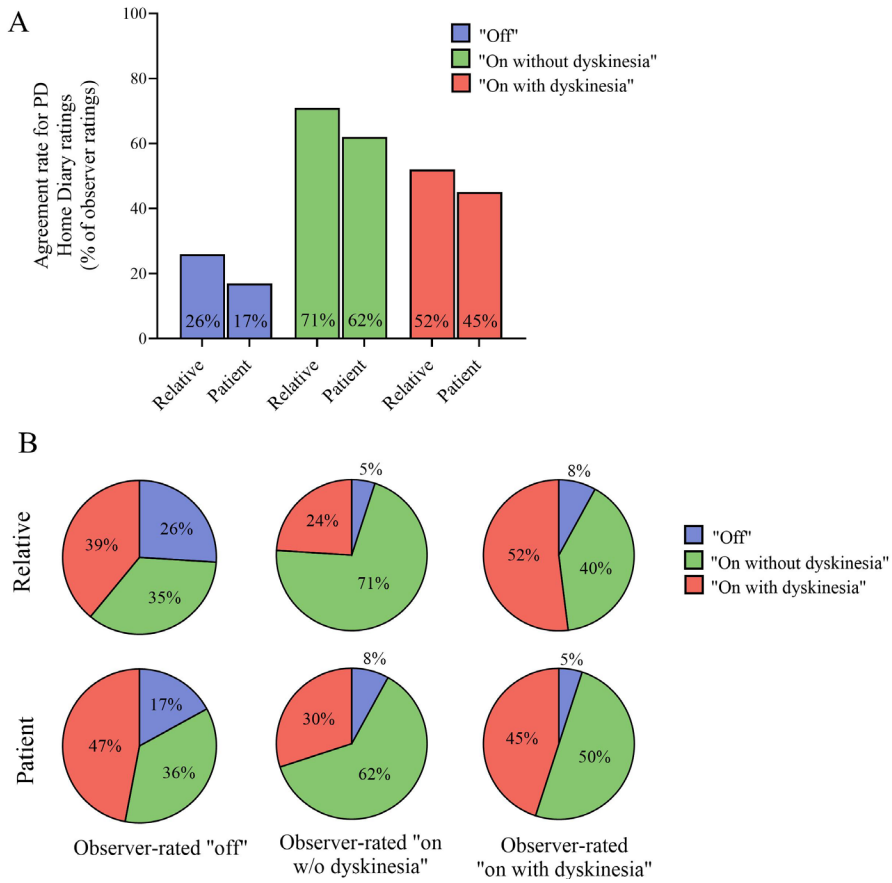

Figure 18. Temporal agreement of motor state ratings between observer, patient, and relative diaries

A) Comparison of temporal agreement rates (%) across motor states, using clinical observer ratings as the reference. **B)** Participants' diary entries by observed motor state.

When examining agreement across the specific motor states (**Figure 18A**), temporal agreement was highest for the "on without dyskinesia" state (71% for relatives; 62% for patients). Conversely, agreement was lowest for the "off" state (26% for relatives; 17% for patients). Both relatives and patients frequently misidentified the observed "off" state as "on with dyskinesia". This misclassification occurred in 39% of ratings for relatives and 47% for patients (**Figure 18B**). The total number of observations per motor state were: "off" (n = 106), "on without dyskinesia" (n = 138), and "on with dyskinesia" (n = 201).

Significant differences were found in daily time distribution (8:30 AM–4:00 PM) between raters (**Figure 19**). Specifically, differences existed between relatives and the observer for the "off" state ($p = 0.027$) and the "on without dyskinesia" state ($p = 0.012$), though no difference was observed for the "on with dyskinesia" state ($p = 1.000$). A similar pattern emerged between patients and the observer, with significant differences for the "off" ($p = 0.006$) and "on without dyskinesia" states ($p = 0.012$), but not for the "on with dyskinesia" state ($p = 1.000$). There were no significant differences between relatives and patients across any of the motor states (all $p = 1.000$).

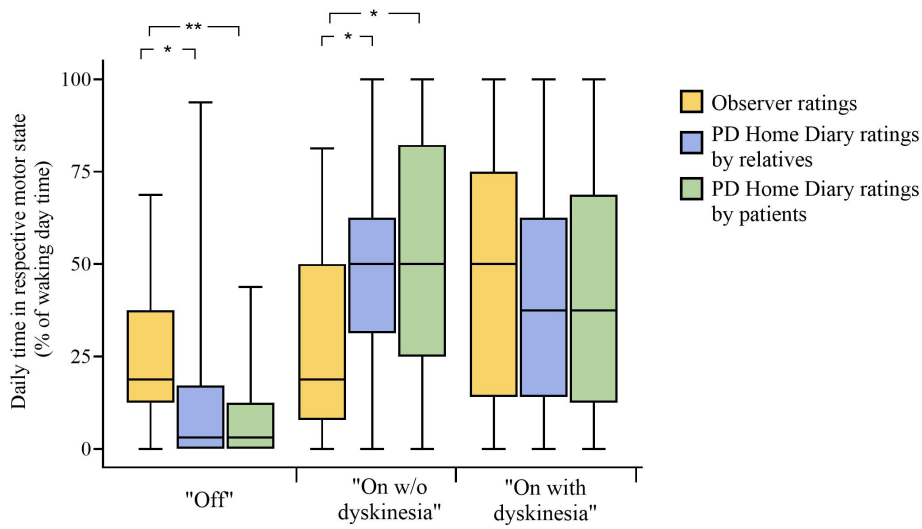

Figure 19: Proportions for time spent in motor states as assessed by clinical observer, relative and patient diaries

Boxplots illustrate the daily time distribution (8:30 AM–4:00 PM) across motor states. Central lines represent medians, boxes indicate the IQR, and whiskers extend to the extreme values. *P*-values are derived from Friedman tests with Bonferroni-corrected post hoc Wilcoxon signed–rank tests; *$p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

Pearson correlation analysis of the individual times spent in the three motor states revealed a moderate correlation between relatives and the observer for “on without dyskinesia” ($r = 0.544$, $p < 0.001$) and “on with dyskinesia” ($r = 0.380$, $p = 0.023$), but no significant correlation for “off” ($r = 0.260$, $p = 0.091$). In contrast, no significant correlations were observed between patient and observer diary data for any motor state. Reliability analysis using the ICC showed moderate reliability for relative diary data compared with the clinical observer for the “on without dyskinesia” state [ICC = 0.45 (95% CI: 0.06–0.71), $p = 0.001$], and poor reliability for the “on with dyskinesia” state [ICC = 0.38 (95% CI: 0.01–0.66), $p = 0.022$]. No significant reliability was found for the “off” state [ICC = 0.22 (95% CI: -0.10–0.52), $p = 0.087$]. Patient diary ratings demonstrated no significant reliability for any motor state when compared to observer ratings.

Discussion

Results in brief

This thesis aimed to improve the understanding of NMS management in PD and to strengthen the evidence base for tools used to measure and monitor PD symptoms and fluctuations. Regarding NMS management, adherence to national and international pharmacological guidelines was limited. Adherence was highest for depression and constipation, but lowest for dysphagia. Investigation of the DA rotigotine demonstrated that sleep improvements were restricted to DA-naïve patients and those with the most severe baseline sleep disturbances. Concerning secondary outcomes, PKG measures demonstrated reduced daytime immobility with rotigotine treatment, suggesting a potential decrease in daytime sleepiness.

Regarding monitoring tools, secondary analyses in *Paper II* showed no correlations between PKG metrics and corresponding sleep or daytime sleepiness scales. Building on evidence that HD motor state assessments exhibit only fair agreement with the clinical observer gold standard, structured patient training in motor complications did not significantly improve this agreement. However, a non-significant improvement in dyskinesia detection was observed. Temporal agreement in HD motor state ratings was fair between the clinical observer and relatives (52%) and between relatives and patients (56%), but slight between patients and the observer (44%). Agreement was lowest for the "off" state across all comparisons, with significant differences in the daily time distribution for "off" and "on without dyskinesia" states when comparing both patients and relatives to the clinical observer.

Non-motor symptom management

Adherence to pharmacological non-motor symptom guidelines

Previously, the extent to which NMS treatment guidelines were followed across the spectrum of disease severity remained poorly characterised. *Paper I* demonstrated that adherence to national and international pharmacological NMS treatment guidelines was limited. Despite a high NMS burden, with patients requiring

treatment for a median of seven NMS, only an average of 32% of these were managed in accordance with guidelines. Guideline adherence was highest for depression (79%) and constipation (77%), but lowest for dysphagia (0%).

These findings prompt several points for discussion: 1) Why is the adherence to pharmacological guidelines so low? 2) Is it always wrong not to follow the pharmacological guidelines? 3) Is there some critique that should be directed toward the guidelines? 4) What are the limitations of *Paper I*?

Why is the adherence to pharmacological guidelines so low?

The limited adherence to guidelines may partly reflect a clinical priority to optimise dopaminergic therapy before introducing new medications, a strategy supported by the guidelines.[7, 33, 75] Also, as *Paper I* focused exclusively on pharmacological guidelines, it does not account for the broader, non-pharmacological management approaches included in the guidelines. Interventions such as cognitive behavioural therapy for depression, Continuous Positive Airway Pressure for sleep apnoea, and DBS for dystonia are often more appropriate than drug-based alternatives.[7, 75] Swedish guidelines recommend a multiprofessional, team-based rehabilitation to collaboratively address complex issues. A comprehensive team typically includes a clinician, physiotherapist, occupational therapist, dietitian, counsellor, speech therapist, psychologist, and nurse.[75] Consequently, deviation from pharmacological guidelines does not necessarily indicate clinical neglect of NMS, as non-pharmacological interventions may have been initiated. Dysphagia serves as an example. Internationally, specific pharmacological guidelines for dysphagia are lacking. Swedish recommendations facilitate management through optimising dopaminergic treatment, providing rehabilitation assistance, and considering gastrostomy or apomorphine.[33, 75] Therefore, the observed 0% adherence possibly indicates that clinicians prioritised non-pharmacological strategies and dopaminergic optimisation over apomorphine.

In some cases, pharmacological treatment was initiated but conflicted with specific recommendations. For example, 14% of patients on antidepressants were prescribed SSRIs, and 8% of those with cognitive dysfunction received memantine, despite both being reserved for exceptional cases nationally.[33, 75] Such patterns suggest that while clinicians identified the symptoms, they intentionally or inadvertently deviated from guidelines. These deviations may stem from prior treatment failure or intolerance to the recommended medications. Alternatively, these findings may demonstrate a lack of awareness regarding specific recommendations, highlighting a need to facilitate improved knowledge dissemination regarding NMS guidelines.

Consequently, appropriate clinical judgement, guideline unawareness, prioritisation of non-pharmacological interventions, or dopaminergic optimisation may explain some of the limited guideline adherence. However, these factors may not serve as the sole explanation. A contributing factor may be that NMS are frequently

overlooked during consultations. Research indicates that 50% of consultations fail to identify NMS,[137] and that NMS often are under-recognised and undertreated.[171] In *Paper I*, adherence to guidelines appeared higher in more severe stages of PD, suggesting that NMS in early-stage disease are particularly overlooked. This trend likely reflects heightened clinical awareness fostered by longer follow-up and frequent patient contact. Furthermore, because patients with more severe PD in *Paper I* exhibited higher MDS-NMS scores, these pronounced symptoms were likely easier to identify. It is also possible that advanced disease stages naturally shift clinical attention toward the non-motor burden of the condition. Importantly, patient underreporting due to stigma or embarrassment may also drive the under-recognition of NMS. Only 20% of men in *Paper I* reported sexual dysfunction compared to a prevalence of up to 82% in literature,[172] and 0–2% reported impulse control symptoms despite literature rates of up to 20%.[173] This discrepancy emphasises the need for clinicians to normalise discussions of sensitive symptoms and build patient trust. Ultimately, this suggested under-recognition of NMS highlights the need for more effective, systematic methods to measure, monitor, and detect NMS across all stages of the disease.

Is it always wrong not to follow the pharmacological guidelines?

The clinical necessity of addressing NMS is undeniable. Non-levodopa-responsive NMS are among the most disabling disease features,[174] and NMS often impact health-related QoL more than motor symptoms.[104] Beyond the patient, NMS drive substantial caregiver burden and societal costs. Neuropsychiatric symptoms, in particular, are associated with high caregiver burden,[63] while the general severity of NMS often leads to increased nursing home placement and higher overall healthcare costs.[175-178] Recent data from 2025 demonstrates that formal care costs nearly quadruple for patients with ≥ 10 NMS compared to those with 6–9.[178] In summary, effective NMS management can simultaneously improve patients' QoL, reduce caregiver burden, and decrease healthcare costs.

However, deliberate deviation from guidelines is frequently clinically justified and may reflect sound clinical judgement. A clinician may bypass recommendations due to prior treatment failure, intolerable side effects, or professional scepticism, particularly where evidence is limited. In *Paper I*, guideline adherence was lower for symptoms with limited supporting evidence, such as apathy and daytime sleepiness.[7, 33] Furthermore, patients may be medically unsuitable for recommended treatments due to factors such as comorbidities, advanced age, impaired renal function, or the risks associated with polypharmacy and drug-drug interactions. Additionally, patients may occasionally decline additional medication.

Is there some critique that should be directed toward the guidelines?

Working with *Paper I* highlighted some areas where current guidelines warrant refinement. For example, guidelines recommend oxycodone-naloxone for reducing

pain while omitting common first-line agents like paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs). However, evidence indicates that NSAIDs are the most frequently utilised analgesics in the PD population and that they appear to be effective.[179] Given the substantial risks of opioid misuse, dependency, and addiction,[180] guidelines should prioritise non-opioid medications whenever possible. Furthermore, a significant gap exists regarding sexual dysfunction. International guidelines focus exclusively on sildenafil for men, while Swedish guidelines offer no specific recommendations. This oversight neglects the high prevalence of libido loss and orgasmic dysfunction in both sexes,[181] as well as arousal difficulties in women.[63, 181] Management options exist for the general population, including local oestrogen for women, pelvic floor physiotherapy, and psychological support.[182] Studies assessing these interventions effectiveness specifically in PD patients are needed to update current guidelines and provide comprehensive, gender-inclusive recommendations.

What are the limitations of Paper I?

Several limitations must be considered when interpreting the results from *Paper I.* Notably, the cross-sectional design makes it difficult to distinguish between patients who were successfully treated (and thus no longer symptomatic) and those who truly lacked symptoms. To address this, the paper includes treatment-specific data tables. If patients undergoing treatment have a symptom but are not symptomatic, it indicates improvement due to treatment. Additionally, reliance on medical records introduces the risk of incomplete treatment documentation. Obtaining updated medication lists directly from patients may have enhanced data accuracy. Furthermore, the low prevalence of certain symptoms in the cohort limits the statistical power to draw definitive conclusions for those NMS.

The definition of being "symptomatic" relied on a self-selected threshold of ≥ 6 points on the MDS-NMS, as no standardised cutoffs exist. Clinically, this threshold corresponds to symptoms that occur sometimes causing considerable distress, or frequent problems causing minor distress. It is contended that these levels of frequency and burden are sufficient to warrant treatment. However, applying different thresholds would alter adherence rates. Moreover, relying solely on the MDS-NMS for cognitive assessment may lead to either over- or under-reporting of impairment. Future studies should incorporate validated cognitive questionnaires to accurately determine the prevalence of cognitive dysfunction and its management.

Rotigotine's effect on sleep and daytime sleepiness

In *Paper II*, rotigotine's effect on sleep served as the primary endpoint. Although the DA rotigotine has shown potential sleep-enhancing effects in previous research,[87-89] it is currently excluded from Swedish national guidelines.[33] Consequently, a need to further evaluate its efficacy was identified. Notably,

rotigotine only improved the PDSS-2 score in DA-naïve patients and in those with the most severe baseline sleep disturbances (PDSS-2 ≥ 18). Clinician assessments (CGI-S) indicated overall sleep improvement, though PKG nighttime scores remained unchanged. Regarding secondary outcomes, no improvement in the ESS was observed. However, the PKG-derived PTI_D score decreased, suggesting a reduction in daytime sleepiness. Motor symptoms and health-related QoL appeared to improve with rotigotine, as indicated by the CISI-PD, PTT, PDQ-8, and EQ-5D-5L scores.

The effect of rotigotine on sleep

While the literature generally supports rotigotine's beneficial effects on sleep disturbances in PD,[84, 85, 87, 88] *Paper II* did not observe a significant PDSS-2 improvement in the total cohort. However, the non-significant 24% improvement on the PDSS-2 aligns with several studies that reported significant gains between 22% and 31%.[84, 93, 95, 99] These comparative studies included 15–178 patients, suggesting that the cohort of 32 patients in *Paper II* may have lacked the statistical power to reach significance. While some trials reported even larger improvements of 40–55%,[85, 86, 94, 183] Nicholas et al.[96] found no significant changes with doses of 2–8 mg. Despite the lack of significant improvement in PDSS-2 and PKG nighttime scores, the CGI-S improved significantly. This discordance may stem from the CGI-S reflecting specific benefits, such as the observed reduction in sleepiness upon waking (PDSS-2 item 14). Furthermore, the CGI-S is susceptible to reporting bias arising from patient discussion, which may have influenced the scoring. Clinically, its holistic nature may capture meaningful improvements that the linear weighting of the PDSS-2 fails to detect.

In *Paper II*, the optimal rotigotine dose was maintained for an average of 16 days (range: 13–32), with the second PKG registration during the final week of the maintenance phase. While Pierantozzi et al.[93] observed PDSS-2 improvements after a similar two-week period, most studies evaluated outcomes after at least four weeks at an optimal dose.[84, 86, 94, 95] Consequently, a longer treatment duration may be required to fully capture rotigotine's therapeutic potential. The mean rotigotine maintenance dose in *Paper II* was 5 mg, notably lower than the 8–10 mg average reported in previous sleep studies.[85, 86, 93, 94] This lower dosage reflects the recruitment of patients with relatively early-stage PD and a titration protocol based on general efficacy rather than specific sleep outcomes. This discrepancy raises the question of whether higher doses are required for optimal sleep enhancement. Nicholas et al.[96] suggested that 8 mg/24 h is the minimally effective dose for reducing "off" time in advanced PD, implying that similar levels might be necessary for clinically meaningful sleep benefits. Although some studies reported sleep improvements at 2–5 mg/24 h,[99, 183] most positive trials utilised higher rotigotine doses.[85, 86, 93, 94] Further research is warranted to elucidate the dose-response relationship of rotigotine specifically regarding nocturnal symptoms in PD.

Interestingly, significant PDSS-2 improvements were observed specifically within the subgroup exhibiting the most severe baseline sleep disturbances (PDSS-2 ≥ 18). While the entire cohort had a median PDSS-2 baseline score of 17, most studies reporting significant sleep improvements with rotigotine included patients with mean baseline scores ranging from 19 to 24.[84-86, 94, 183] This finding aligns with Vallderiola et al.,[183] who demonstrated that a higher baseline PDSS-2 score correlated with a greater magnitude of improvement with rotigotine. Similarly, Suzuki et al.[99] observed PDSS-2 improvements at low rotigotine doses (2–4mg) in a cohort with a higher mean baseline score (27.6) than that reported in most other studies. Regarding previous treatment, subgroup analysis revealed significant PDSS-2 improvement only in DA-naïve patients. This result contradicts Pagonabarraga et al.,[85] who found no difference between DA-naïve patients and those switching from other DAs. Such discrepancies likely stem from variations in sample size, patient characteristics, or the duration and dosage of previous DA therapy. In summary, while a dose of at least 8 mg/24 h may be necessary for substantial improvement in a general PD population, lower doses may still provide clinical benefit in patients with severe baseline sleep disturbances.

The effect of rotigotine on daytime sleepiness

EDS can be related to PD itself,[70-72] but it can also be exacerbated by dopaminergic treatment, particularly DAs.[60, 68, 184] Unlike other DAs, rotigotine has been suggested not to worsen daytime sleepiness.[92, 96, 98] Conversely, some studies suggest it may actually reduce it. [86, 99] Specifically, Calandra-Buonaura et al.[86] found a decrease in the number and duration of sleep episodes with rotigotine using actigraphy. This potential benefit is supported by Del Dotto et al.[184], who demonstrated that replacing a short half-life DA with an equivalent long-acting DA reduced daytime sleepiness, suggesting that continuous dopaminergic stimulation may be beneficial. Moreover, Suzuki et al.[99] reported ESS improvements after one and three months of rotigotine treatment. Some of the findings from *Paper II* align with the view that rotigotine appears to reduce daytime sleepiness. The reduction of PTI_D, together with normalisation of PTI_D in 12 patients, implies that rotigotine improves daytime immobility and potentially reduces daytime sleep episodes. However, no improvement in the ESS was demonstrated. On the other hand, a significant improvement in PDSS-2 item 14 (sleepiness after waking) was observed, suggesting that patients experienced relief from somnolence.

The discrepancy between objective PKG measures (reduced PTI_D) and the lack of ESS improvement may have several explanations. The subjective nature of the ESS relies on patient awareness of daytime naps, which can be limited.[185] Moreover, baseline severity appears influential. While Suzuki et al.[99] reported ESS improvements in a cohort with a high baseline score (mean: 13.7 points), *Paper II* and Calandra-Buonaura et al.[86] had lower baselines (median: 7.5 and 5 points, respectively) and did not observe any ESS improvement with rotigotine. This

pattern suggests that a higher baseline ESS score may be required for patients to perceive and report subjective changes, whereas objective measures may capture improvements in milder cases. Additionally, as the CISI-PD score improved, rotigotine likely reduced motor immobility. Since PTI_D measures daytime immobility, the observed reduction may partly reflect motor improvement rather than a pure decrease in sleepiness. In conclusion, these findings suggest that rotigotine is a safe DA option for EDS, potentially even offering improvement. Consequently, it may be a preferred alternative when DA therapy is indicated in patients with daytime sleepiness, or when switching treatment due to EDS exacerbation caused by another DA.

The effect of rotigotine on life quality and motor symptoms

Treatment with rotigotine led to improvements in CISI-PD and PTT scores, with four patients achieving PKG-defined bradykinesia control. These results support that rotigotine effectively alleviates motor symptoms, aligning with previous literature.[83] While both PTD and mDKS indicated an increase in dyskinesia with rotigotine, these levels remained low and clinically non-significant. Furthermore, rotigotine significantly improved health-related QoL as measured by PDQ-8 and EQ-5D-5L, aligning with previous research.[84, 183]

Limitations of Paper II

Several limitations of *Paper II* warrant consideration. Primarily, a larger sample size would have enhanced the statistical power and reliability of the results. Additionally, the absence of a placebo control group introduces potential bias, as patient or clinician expectations may have affected subjective assessments. A double-blind, randomised design would have mitigated this. Furthermore, half of the patients had previously received a DA. While a 28-day washout period was employed, this transition may have influenced baseline conditions. Moreover, the findings are limited by the treatment duration and dosage. Longer follow-up or higher doses might have produced different therapeutic outcomes. Incorporating multiple follow-up assessments, for example at 2, 4, 8 weeks, and at 3 months, would have provided a more detailed temporal view of rotigotine's effects.

Regarding assessment, using PSG would have been preferable to objectively evaluate sleep and to validate PKG-derived sleep measures. The CGI-S was chosen as a rapid screening tool to include patients with varying severities of sleep disturbance and to facilitate comparison with prior studies.[84, 85, 183] However, using the PDSS-2 for patient inclusion would have more effectively ensured clinically significant sleep disturbances. Finally, although the CISI-PD assessed motor symptoms, a more detailed scale, such as the MDS-UPDRS, would have provided more comprehensive clinical information.

Evaluating symptom measurement and monitoring tools

PKG for the assessment of sleep and daytime sleepiness

Reliable sleep assessment tools are essential to identify treatable sleep disturbances and evaluate therapeutic interventions.[68] In particular, home-based alternatives to PSG capable of longitudinal assessment are required. To address this, a secondary objective of *Paper II* was to examine the correlations between objective PKG parameters for sleep and daytime sleepiness and corresponding subjective questionnaires. No significant correlations were found between the PDSS-2 and the CSS, nor between the PTI_D and the ESS.

In *Paper II*, PKG nighttime scores showed no significant change with rotigotine treatment, consistent with PDSS-2 results. However, no significant correlation was observed between the CSS and the PDSS-2 total score. Nonetheless, a weak negative correlation was observed between the CSS and PDSS-2 item 2 (difficulties falling asleep). Since a lower CSS indicates poorer sleep quality and a higher PDSS-2 score reflects greater symptom severity, this suggests the CSS may be primarily driven by sleep-onset insomnia. These results contrast with McGregor et al.[78], who demonstrated a significant correlation between the CSS and the PDSS-2 total scores. In their study, PKG nighttime scores distinguished between normal and abnormal sleep with good selectivity and sensitivity, as evaluated with PSG. Similarly, Klingelhoefer et al.[79] reported significant correlations between the PDSS total score and objective PKG metrics, including sleep duration and quality. Furthermore, Stavitsky et al.[186] observed correlations between PDSS scores and actigraphy-measured sleep efficiency and fragmentation.

The lack of correlation between CSS and PDSS-2 may be explained by several factors. While PDSS-2 focuses on the underlying causes of sleep disturbances, CSS assesses quantitative parameters, such as sleep quality and duration of awakening. Consequently, a strong linear correlation between the two instruments is unlikely. However, to support the reliance on PKG nighttime scores, a correlation between higher PDSS-2 and lower CSS scores, as identified by McGregor et al.,[78] was expected. Furthermore, the subjective nature of PDSS-2 implies that patients with similar objective symptoms may rate problems differently, thereby weakening the correlation with an objective metric. Additionally, the limited sample size may have hindered the reproduction of previously reported findings.[78] Finally, to fully establish the reliability of PKG nighttime scores, it would have been preferable to correlate them with PSG, the gold standard for objective sleep assessment.

Kotschet et al.[135] reported a correlation between the PTI_D and both PSG findings and the ESS, supporting the PTI_D as an objective measure of daytime sleepiness. They also identified significant associations between ESS scores ≥ 10 and elevated PTI_D values. In contrast, *Paper II* observed no significant correlation between the

PTI_D and ESS scores, nor any difference in PTI_D values between patients above and below the ESS threshold of 10. These findings align with Höglund et al.,[136] who found no correlation between PKG data and self-evaluated daytime sleepiness. Similarly, Calandra-Buonaura et al.[86] observed a reduction in daytime sleep episodes via the PKG without a corresponding decrease in ESS scores.

Several factors may explain the lack of correlation between ESS and PTI_D. The subjective nature of the ESS leads to varied ratings despite comparable objective symptoms, and its reliability is further compromised by patient underreporting. Research indicates that over one-third of PD patients and healthy controls lack awareness of sleep onset during brief naps.[185] Also, as PTI_D captures immobility, it may be confounded by motor symptoms such as bradykinesia, rather than exclusively reflecting daytime sleepiness. Since rotigotine improved motor function, the observed PTI_D reduction may partly reflect this motor improvement instead of a pure decrease in daytime sleepiness. To further evaluate the efficacy of actigraphy in assessing sleep and daytime sleepiness in PD, larger studies correlating actigraphy data with subjective questionnaires and PSG are warranted.

Validation of the Home Diary

The HD is widely utilised in clinical practice and as a primary endpoint in clinical trials.[112] However, previous studies have demonstrated only fair temporal agreement between patient and clinical observer diary entries.[113, 114] Consequently, *Papers III* and *IV* evaluated the validity of the HD and explored strategies to improve agreement between raters. *Paper III* demonstrated that structured patient training did not improve temporal agreement between patient and clinical observer HD motor state ratings. Moreover, the training did not enhance the correlation or reliability of daily motor state times recorded in the HD compared with clinical observer assessments. While agreement for "on with dyskinesia" increased from 58% to 80% post-training, this improvement did not reach statistical significance. *Paper IV* demonstrated that temporal agreement between relatives of PD patients and the clinical observer was fair, whereas agreement between patients and the observer was slight. Although relative-patient agreement was higher for motor state distribution and daily time proportions in different motor states, their temporal agreement remained fair. Notably, temporal agreement was lowest for the "off" state across all comparisons. Furthermore, significant discrepancies were observed in the daily time distribution of "off" and "on without dyskinesia" when comparing both relatives and patients with the clinical observer.

Temporal agreement of motor state ratings

Paper III showed no difference in the distribution of motor state ratings between patients and the observer before or after training. In contrast, *Paper IV* identified distributional differences, with both relatives and patients reporting fewer "off"

ratings and more "on without dyskinesia" ratings than the observer. While the initial Swedish validation study reported similar discrepancies,[114] post hoc analysis indicated these were driven by the subgroup not included in *Paper III*, explaining why no such distributional differences were observed in that study. In line with these findings, ancillary analyses revealed significantly higher baseline temporal agreement in the *Paper III* subcohort compared to the non-recruited participants from the initial VALIDATE-PD study.[114] This suggests that the participants in *Paper III* were already more proficient in assessing their motor states before training. Such proficiency may stem from a greater interest in their condition or prior research experience. Thus, the structured training might have demonstrated a greater impact if the patient cohort had been less experienced at study outset.

In *Paper III*, agreement between patients and the clinical observer was moderate both before and after training. However, overall temporal agreement improved from 68% to 76% post-training, though this increase was not statistically significant. This shift was driven by the non-significant improvement in dyskinesia detection, where agreement rose from 58% (fair agreement) to 80% (moderate agreement) after training. This enhancement may partly stem from patients spending more time in dyskinetic states or experiencing more severe dyskinesia, which are generally easier to identify.[187] Alternatively, the results may be explained by an improved understanding. During structured training, several patients noted that they finally understood the definition of dyskinesia and realized they were experiencing it. Unawareness of dyskinesia is common in PD,[187-189] and Amanzio et al.[188] suggested that this relates to metacognitive deficits in the self-monitoring system. However, findings from *Paper III* suggest that another explanation could be a fundamental lack of understanding of the concept of dyskinesia.

Despite implementing the same training protocol in *Paper IV* as in *Paper III*, agreement for "on with dyskinesia" was notably lower: 52% between relatives and the observer, and 45% between patients and the observer. These discrepancies may be attributable to the clinical manifestation of symptoms. While both studies reported comparable daily time spent in "on with dyskinesia", the dyskinesias in the *Paper IV* cohort may have been less prominent and more challenging to detect. Moreover, *Paper IV* participants had a shorter median duration of dyskinesias (46 months vs. 63 months). A longer history of dyskinesia likely affords patients and relatives greater experience in identifying and distinguishing them. It is possible that without training, the agreement in *Paper IV* would have been even lower.

A key discrepancy between *Paper IV* and the findings of *Paper III* and previous validation studies is the notably lower agreement for the "off" state in *Paper IV*.[113, 114] One hypothesis is that patients and relatives base their "off" ratings on NMS, whereas clinical observers focus primarily on motor signs. However, a follow-up to the German VALIDATE-PD study demonstrated that HD validity remains unaffected by co-occurring NMS.[190] In *Paper IV*, the observer recorded more "off" time than in *Paper III* or the initial Swedish validation study.[114] This trend aligns

with the higher MDS-UPDRS scores in the *Paper IV* cohort, indicating greater disease severity. As "off" time increases, patients and relatives may gradually shift their perception of what is "normal", leading them to underreport "off" periods. Alternatively, the observer sometimes misclassified "on without dyskinesia" as "off", due to unfamiliarity with the patient. Furthermore, discrepancies may stem from variations in study populations, such as differences in prior knowledge of motor fluctuations or less pronounced motor state transitions, both of which may complicate accurate reporting.

Interestingly, the patterns of misclassification were consistent in *Papers III* and *IV*. When patients were observed in the "on without dyskinesia" state, the most common error was misclassification as "on with dyskinesia", and vice versa. Notably, a shift occurred in the "off" states. Before training, "off" was most often misclassified as "on without dyskinesia". However, after training and in *Paper IV* (using the same training), observed "off" was most often misclassified as "on with dyskinesia". This shift suggests that while training increases sensitivity to abnormal movements, participants may struggle to differentiate between them, potentially confusing tremors with dyskinesias. This is supported by previous findings of a positive correlation between HD-derived "off" and "on with troublesome dyskinesia" time, and the patient-rated term "bad time".[110] This shared negative perception may make these clinically distinct states challenging for patients and relatives to separate.

Daily motor state times

Daily motor state times measured by the HD are a common primary endpoint in clinical trials of therapeutics targeting motor complications.[112] In *Paper III*, no significant differences were found in the distribution of daily motor state times between the observer and patients, either before or after training. However, both groups reported more time in "on with dyskinesia" and less in "on without dyskinesia" post-training. This shift is likely attributable to pre-training assessments having been conducted several years earlier. By the post-training assessment, patients had longer levodopa exposure and higher LEDD, both of which increase the dyskinesia risk.[14, 191] In contrast, *Paper IV* revealed significant differences in daily motor time distributions between the observer and both relatives and patients for the "off" and "on without dyskinesia" states. Specifically, the observer recorded a higher percentage of the day in "off" and less time in "on without dyskinesia" compared to the other raters. No significant differences in daily motor state distribution were observed between relatives and patients. While the initial Swedish study found no differences in daily time distribution,[114] the German study also reported significant discrepancies between patients and observers.[113] However, unlike the results in *Paper IV*, the German cohort rated more time in "on without dyskinesia" and less time in "on with dyskinesia" compared to the observers.

In *Paper III*, aggregate measures of daily time spent in the three motor states demonstrated good to excellent reliability (ICC) when compared to observer ratings

both before and after training. Furthermore, correlation analyses of the individual times spent in each state revealed strong correlations both pre- and post-training. These reliability values and correlations were stronger than those reported in the initial Swedish validation study,[114] likely reflecting a selection bias, as the participants who continued into *Paper III* were already more proficient at motor state assessment. In contrast, reliability and correlation were markedly lower in the other cohorts. The German validation study reported poor to moderate ICC values across all motor states.[113] Similarly, in *Paper IV*, relatives' assessments of daily motor state time showed poor to moderate reliability, with no significant reliability observed for the "off" state. Additionally, moderate correlations were identified for individual times spent in "on without dyskinesia" and "on with dyskinesia" between observer and relatives, with no significant correlation for "off". Notably, daily motor state times assessed by patients in *Paper IV* showed no significant reliability or correlation for any motor state when compared to observer diary data. These discrepancies between cohorts highlight the subjective nature of the diary, and the risk of drawing erroneous conclusions from clinical trials that utilise the HD daily motor state times as a primary endpoint.

Should the clinical observer always be considered the gold standard?

Interpreting these results requires questioning whether the clinical observer should always be regarded as the gold standard. It can be argued that because patients and relatives demonstrated higher mutual agreement in daily motor state time than with the observer, they may identify subtle clinical changes missed by an unfamiliar rater. This is particularly relevant when rating "off" periods. While dyskinesias are often visually distinct, "off" manifestations can be nuanced and require knowledge of the patient's baseline "on" state for accurate detection. However, aggregate measures of daily time showed only moderate reliability for "on without dyskinesia" and failed to reach significance for other states when comparing relative with patient data. Furthermore, temporal agreement between patients and relatives remained only fair. Most notably, temporal agreement for the "off" state was only 32%. Thus, although patients and relatives reported more "on without dyskinesia" time and less "off" time than the observer, they lacked consensus regarding the exact timing of these "off" periods.

Consequently, it can be reasoned that utilising the clinical observer as the gold standard remains the most reliable approach. Despite inherent subjectivity and inter-rater variability, observers possess standardised training, absent in patients and relatives. In *Papers III* and *IV*, the observer was a physician with formal education in PD and extensive experience across a diverse patient population. Within clinical practice, the physician's assessment is the definitive benchmark for diagnosing PD and adjusting treatment. Nevertheless, no single rater, regardless of expertise, can achieve 100% accuracy in all assessments.

Is high agreement in the Home Diary essential?

Patient diaries frequently serve as the primary outcome measure in clinical trials for motor symptom therapeutics.[45, 112, 192-195] Typically, the primary readout involves the total daily duration within each motor state. Consequently, the validity of clinical trial conclusions hinges on the accuracy of these diaries. However, *Paper IV* and the initial German validation study,[113] demonstrated significant discrepancies between patients/relatives and clinical observers regarding the distribution of daily motor state times. This discrepancy introduces a risk of erroneous conclusions from clinical trials. It may lead to false-negative or false-positive results, which is a critical concern for drug development.

Initial validation studies,[113, 114] along with *Papers III* and *IV*, indicate that temporal agreement between observers and patients/relatives is insufficient, ranging only from slight to moderate. Temporal agreement is essential when optimising individual therapy to minimise motor fluctuations and dyskinesia. In clinical scenarios, the patient's subjective well-being remains the primary objective. Consequently, it may not be problematic if an observer perceives a patient as being in "off", while the patient feels they are in "on without dyskinesia". However, a risk of undertreatment exists if patients habituate to "off" states without conscious recognition. In such instances, the failure to identify "off" periods precludes the optimisation of treatment and well-being. Furthermore, sometimes effective clinical management necessitates a precise distinction between symptoms. For example, troublesome tremors typically characterise an "off" state and warrant an increased levodopa dosage. If patients misidentify dyskinesia as tremor, increasing the levodopa dose would exacerbate symptoms rather than improve motor control.

Alternatives to the Home Diary

Several alternatives to the HD have emerged. PKG measures of bradykinesia and dyskinesia have demonstrated sensitivity to treatment effects and correlate significantly with the UPDRS III and the Abnormal Involuntary Movement Scale.[122, 196] Similarly, the STAT-ON sensor has proven effective in identifying motor severity and demonstrate moderate reliability regarding daily time spent in various motor states, when compared with patient-reported HD.[197, 198] Moreover, Rodríguez-Molinero et al.[199] suggest that an internal sensor can accurately detect motor fluctuations when validated against patient diaries. A review confirmed the utility of wearables, demonstrating that most available technologies for measuring limb bradykinesia successfully differentiate PD patients from healthy controls.[200] Specialized systems like the PD-Monitor employ artificial intelligence to develop classifiers capable of recognizing bradykinesia during finger-tapping tests. Initial results indicate that the PD-Monitor can discriminate between different severities of bradykinesia and normal motor function with high accuracy, sensitivity, and specificity.[201] Beyond validation, research suggests that continuous monitoring of

motor symptoms via wearable sensors can enhance clinical decision-making, and improve therapeutic outcomes for PD patients.[124, 125]

Despite their potential, challenges persist regarding device implementation. Löhle et al.[121] compared PKG data with clinical observer and patient HD motor state assessments. They found that while the PKG demonstrated moderate validity in estimating total daily time in different motor states, temporal agreement with observer ratings was poor. PKG data aligned more closely with clinical observer ratings than with patient ratings. Similarly, Ossig et al.[202] reported moderate to high concordance for aggregate daily times in different motor states when comparing PKG assessments to patient-reported diaries, but found limited concordance on a single-hour level. A review of wearable systems further concluded that many current algorithms offer limited, clinically actionable data, with reliability varying between controlled and home settings. The authors hypothesise that the discrepancy between device data and the clinical gold standard suggests that wearables may capture additional information beyond traditional assessments. Consequently, further research is required to translate these digital signals into a meaningful clinical understanding of disease states.[118]

In summary, wearable devices demonstrate promise in detecting motor states,[122, 196-200, 202] but temporal agreement between actigraphy and observer-rated diary remains insufficient.[121] Discrepancies between device data and clinical gold standards, especially in home settings, highlight the need for further validation.[118] Furthermore, as developers currently validate many devices themselves, independent external validation is essential.[109] This reinforces the necessity of future research to validate digital health technologies against observer-completed diary data.

Limitations of Papers III and IV

Papers III and *IV* were limited by small sample sizes, reducing their statistical power. In *Paper III*, only half of the original validation cohort returned for post-training assessments. Similarly, *Paper IV* achieved only a 35% participation rate among those informed of the study. These recruitment challenges suggest a risk of selection bias, as the participants likely represented a highly motivated subgroup. Consequently, the findings may not represent the typical advanced PD population, and agreement levels in routine clinical settings may be lower than those observed here. A larger, more diverse sample would have enhanced the reliability and generalizability of the findings. In *Paper III*, the multi-year interval between pre- and post-training assessments meant that disease progression might have confounded the results. Conducting follow-up ratings sooner would have more effectively isolated the effects of the training.

Utilising detailed tools such as the MDS-UPDRS Part III to better distinguish “on without dyskinesia” from “off” states would have been preferable. However, a walking test was used to maintain comparability with previous validation studies.

Although motor state assessment was based on the entire observation period, including sitting, walking, and conversation, symptoms primarily manifesting during, for example, fine motor tasks may have been missed. Furthermore, relative and patient ratings may have been influenced by the motor status during unobserved periods, despite instructions to base ratings solely on the observation window. In *Paper IV*, while participants were instructed not to discuss their ratings, ensuring complete independence between participants was difficult and may have influenced the level of agreement. Finally, the observer was not a movement disorder specialist and could thus be considered less accurate. However, their extensive PD experience and the use of a single rater provided internal consistency.

Future perspectives

Identification and management of non-motor symptoms

The limited guideline adherence observed in *Paper I* may, in some instances, reflect sound clinical judgment and the prioritisation of individualised patient needs. However, these results suggest that NMS may be under-recognised, leading to management that diverges from established pharmacological guidelines. This diagnostic gap may stem from a reliance on unstructured clinical discussions and a lack of unified protocols for integrating both patient-completed questionnaires (like the NMSQ) and clinician-completed tools (like the NMSS or MDS-NMS) into routine assessments.[203] Patients often fail to recognise specific NMS as PD-related, and withhold information regarding sensitive topics due to perceived stigma. These barriers emphasise the need for patient education regarding NMS, proactive clinical inquiry, and the normalisation of the entire NMS spectrum.

A dual approach could potentially enhance NMS detection: **1)** Patients should complete a **comprehensive screening scale** prior to consultations to identify symptoms that require clinical discussion. If significant distress is noted in a specific domain, then targeted secondary scales can facilitate a more detailed assessment. In Sweden, ParkReg offers the ideal digital infrastructure for this. Given clinical time constraints, proactive screening is essential to prioritise the patient's most troublesome symptoms. Additionally, objective tools are needed to evaluate NMS, to supplement subjective reports. **2)** Standardised **education for patients and relatives** should be integrated into routine care. Increasing knowledge of the PD-related NMS spectrum may facilitate better communication and strengthen patient self-advocacy, empowering patients and their relatives to navigate the healthcare system and to prioritise key issues during consultations.

A fundamental pillar of NMS management involves non-pharmacological approaches and multidisciplinary, team-based rehabilitation.[75] Research indicates

that these teams improve symptom management, enhance QoL, and provide essential education to patients and their families. Nevertheless, accessibility remains challenging for patients with limited mobility or those residing far from specialised centres. Clinically, there is a lack of long-term controlled trials evaluating the sustained effectiveness and benefits of multidisciplinary teams.[204] This underscores the need to investigate long-term outcomes of multidisciplinary teams and alternative delivery models, such as inpatient rehabilitation, home visits, or telehealth. Crucially, early introduction to multidisciplinary teams facilitates proactive NMS management.

Although pharmacological treatment is sometimes necessary for NMS, a structured management strategy is essential to mitigate polypharmacy and side effects. This proposed approach consists of four steps: **1) Prioritisation:** Following NMS identification, a detailed medical history and the use of questionnaires facilitate assessing the symptomatic burden on daily life, to prioritise the most distressing symptoms. **2) Determining the management approach**: Once target symptoms are identified, clinicians must determine whether non-pharmacological interventions are appropriate, whether current treatments can be optimised, or whether a new medication should be added. **3) Treatment and evaluation**: Intervention outcomes should be systematically evaluated via patient discussion, objective measurement tools, or questionnaires. **4) Withdrawal attempts**: Withdrawal attempts should be conducted where feasible, to prevent unnecessary long-term medication.

There are areas where clinical guidelines require further refinement and updates. For instance, prioritising non-opioid medications for pain management and incorporating gender-inclusive recommendations for sexual dysfunction would be advantageous. While rotigotine is recommended in international guidelines for the treatment of insomnia,[7] it is currently omitted from national recommendations.[33, 75] Findings from *Paper II* indicate that rotigotine primarily improves sleep in DA-naïve patients and those with severe baseline sleep disturbances. Given that numerous studies have established the beneficial effects of rotigotine on sleep,[84, 85, 87, 88] its potential inclusion in national guidelines warrants further investigation. Moreover, the potential beneficial effect of rotigotine on daytime sleepiness observed in *Paper II* merit further exploration.

Measure and monitor sleep and daytime sleepiness

Accurate sleep assessment is essential to identify treatable sleep disturbances,[68] evaluate interventions, and support the development of therapies targeting sleep dysfunction and daytime sleepiness. Specifically, a requirement exists for user-friendly, cost-effective alternatives to PSG that facilitate multi-day, home-based monitoring. Although secondary analyses in *Paper II* found no correlation between the PKG-derived CSS and the PDSS-2, previous studies suggest that the PKG is a viable tool for sleep assessment.[78, 79] This discrepancy underscores the necessity for

further validation of actigraphy devices to measure sleep disturbances in PD. Future studies should ideally incorporate larger cohorts, and validate actigraphy against both subjective questionnaires and objective PSG. Once further validated, integrating these tools into clinical practice will require identifying which of the vast digital metrics provides the greatest clinical utility for optimising patient care. Moreover, *Paper II* found no correlation between the ESS and the PTI_D, mirroring inconsistencies in existing literature where findings diverge regarding this relationship.[86, 135, 136] This discrepancy highlights the need for larger studies to investigate this relationship. Should PTI_D consistently correlate with established scales, it could provide a more reliable, objective alternative for assessing daytime sleepiness in PD patients.

Monitoring motor fluctuations and dyskinesia

Results from *Papers III* and *IV*, alongside previous validation studies,[113, 114] show insufficient agreement between clinical observers and patients/relatives when assessing motor states in the HD. *Papers III* and *IV* included small cohorts of highly motivated participants. Thus, agreement may be inferior in routine clinical settings. This underscores the necessity of developing and validating objective monitoring methods to ensure clinical trial integrity and facilitate precise, personalized patient care. Transitioning toward sensor-based monitoring depends on these devices demonstrating consistent agreement with observer-rated motor state assessments across repeated studies. Hybrid models present another promising approach to enhance accuracy. For instance, the eDiary under development by the MDS Technology Task Force aims to integrate eDiaries, wearable data, NMS tracking, and input from relatives.[205, 206] Nevertheless, implementing such models requires a clear strategy for managing potential discrepancies between eDiary entries and wearable sensor data. Another ongoing project investigates the feasibility of remote motor assessment by utilising smartphone and wrist-worn sensor data. These data are collected while participants perform standardised tasks, including the Timed Up and Go test, finger tapping, and drawing, within their home environment.[207]

Future research must continue to validate digital technologies and wearables against clinical observer-rated diaries, to ensure that the generated metrics carry clear clinical significance and direct relevance to patients. Until these digital tools are fully validated and integrated into clinical research and routine practice, structured patient training before diary completion is recommended. Findings from *Paper IV* suggest that while temporal agreement remains insufficient following training, it may improve patients' ability to detect dyskinesias, thereby potentially enhancing the reliability of the HD.

Conclusions and Implications

This thesis aimed to improve the understanding of NMS management in PD and to strengthen the evidence base for tools used to measure and monitor symptoms and fluctuations. NMS management was explored by investigating adherence to national and international pharmacological guidelines and by evaluating the effects of the DA rotigotine on sleep and daytime sleepiness. The findings demonstrate that adherence to NMS guidelines is generally low. While non-adherence may, in some cases, reflect appropriate clinical judgement rather than suboptimal care, these results indicate that NMS remain frequently overlooked. This underscores the necessity for enhanced detection and management strategies. To address these gaps, the systematic use of comprehensive NMS scales prior to neurological consultations is recommended, to ensure all relevant symptoms are discussed. Furthermore, incorporating patient education into standard care may empower patients to more effectively identify and report their symptoms. Importantly, NMS management should not rely solely on adding medications. Instead, non-pharmacological interventions or the optimisation of existing dopaminergic therapy should be prioritised. Achieving this requires a multidisciplinary, team-based workflow to determine the most appropriate treatment pathway for each individual.

Beneficial effects of rotigotine on sleep were observed exclusively in the subgroup with the most severe baseline sleep disturbances and those who were DA-naïve. Secondary outcomes demonstrated that rotigotine improved health-related QoL and motor symptoms, particularly tremor. Notably, daytime sleepiness, a frequent side effect of DAs, did not worsen with rotigotine. Instead, PKG measures showed reduced daytime immobility, suggesting a potential decrease in daytime sleepiness. Confirmation through future studies is required to investigate if rotigotine can be a promising option for this indication. Furthermore, future research should continue to investigate the effect of rotigotine on sleep disturbances, focusing primarily on determining the optimal dosage for sleep enhancement and on identifying specific patient subgroups for whom this treatment is most beneficial.

Regarding symptom measurement and monitoring, the utility of the actigraphy PKG for assessing sleep and daytime sleepiness was investigated, alongside the validity of the HD for monitoring motor fluctuations and dyskinesia. Objective PKG metrics for sleep and daytime sleepiness exhibited no correlation with their corresponding subjective questionnaires. Further research involving larger cohorts is necessary to clarify the correlation between actigraphy data, PSG findings, and established rating

scales. Previous studies have shown that the HD exhibits only fair agreement with gold-standard clinical observer ratings. Findings from this thesis demonstrate that structured patient training on motor complications did not significantly improve agreement between patients and the clinical observer when completing the HD. However, a non-significant improvement in dyskinesia detection was observed following training. The temporal agreement between relatives of PD patients and the clinical observer when rating patients' motor states was also fair. Furthermore, significant differences were identified in the daily time distribution of "off" and "on without dyskinesia" when comparing both relatives and patients to the observer. Although relative-patient agreement was higher for motor state distribution and daily time proportions in different motor states, their temporal agreement remained fair. Both validation papers included small cohorts of highly motivated participants. Consequently, these findings may not be fully representative of the broader advanced PD population, and agreement levels in routine clinical practice may be even lower.

Given that the HD is frequently used in routine care and as a primary endpoint in clinical trials, this insufficient agreement between patients, their relatives, and the clinical observer is concerning. Such discrepancies carry the risk of erroneous conclusions in drug development and may lead to suboptimal individualised care. While structured training is recommended if the HD is utilised, it is not enough to overcome the tool's inherent subjectivity. While numerous technological solutions, such as wearables and eDiaries, are available or in development, rigorous validation against movement disorder specialists remains necessary to determine if these technologies offer superior reliability to the HD.

While the search for disease-modifying treatments remains the main priority in PD research, the immediate focus must remain on optimising symptomatic management and enhancing individualized care. This is particularly critical for NMS, where clinical experience, scientific evidence, and therapeutic options are more restricted. To improve NMS management, guidelines must be further refined, and more effective strategies are needed to ensure that these symptoms are systematically detected and addressed. Furthermore, to improve disease management and accurately evaluate the efficacy of interventions, the field requires reliable, validated tools to measure and monitor motor symptoms, motor complications, and NMS. Actigraphy requires further validation before it can be utilised as a standard method for assessing sleep and daytime sleepiness among PD patients. Moreover, the HD largely reflects a subjective perception of motor states, despite its frequent use as a primary endpoint in clinical trials. Consequently, validating technological solutions that offer more accurate evaluations of motor states is essential for both clinical research and patient care.

Populärvetenskaplig sammanfattning

Parkinsons sjukdom är en kronisk neurologisk sjukdom som drabbar cirka 1% av befolkningen över 60 år. Den uppstår när dopaminproducerande celler i hjärnan dör, vilket stör signaleringen mellan nervceller och ger upphov till en rad olika symptom. Sjukdomen kännetecknas av motoriska besvär såsom skakningar, stelhet, rörelsehämning och balanssvårigheter. Även icke-motoriska symptom såsom exempelvis sömnstörningar, förstoppning, ångest, depressiva besvär och dagtrötthet är vanliga. Symtombilden är högst individuell och eftersom botande behandling ännu saknas så måste vi i nuläget fokusera på att optimera och individualisera den symptomlindrande behandling som finns. Denna avhandling syftar till att förbättra kunskapen kring hur vi idag hanterar icke-motoriska symtom samt att öka förståelsen kring hur olika verktyg kan användas för att mäta både icke-motoriska och motoriska symptom samt för att registrera dessa symptom över tid.

Det finns både nationella och internationella riktlinjer för hur icke-motoriska symptom bör behandlas. För att utveckla dessa samt för att identifiera brister i dagens vård krävs kunskap om hur riktlinjerna efterlevs. I en beskrivande studie noterades det att följsamheten till de farmakologiska riktlinjerna är bristfällig. En del av förklaringen kan vara att man prioriterar icke-farmakologiska åtgärder eller optimerar befintlig behandling, men det finns också en risk att symtomen aldrig identifieras. Identifieringen skulle kunna förbättras genom att patienter fyller i frågeformulär inför läkarbesök, vilket tydliggör vilka symtom som behöver diskuteras. Dessutom kan patientutbildningar öka förståelsen hos både patienter och anhöriga kring vilka besvär som är viktiga att lyfta fram under läkarbesök. Det är också viktigt att komma ihåg att icke-motoriska besvär inte enbart bör behandlas med läkemedel, utan att även icke farmakologiska behandlingssätt samt ett multidisciplinärt arbetssätt är av största vikt.

Dopaminagonister är en läkemedelsgrupp som ofta används för att minska motoriska symptom vid Parkinsons sjukdom. I en observationsstudie undersöktes primärt hur dopaminagonisten rotigotin påverkar sömn och sekundärt hur den påverkar dagtrötthet, livskvalitet och motorik hos patienter med sömnstörningar. För att mäta effekten av behandlingen användes både frågeformulär och en rörelsesensor. Sensorn bars runt handleden som en smartklocka och registrerade kontinuerligt patientens rörelsemönster och sömn under flera dygn. Resultaten visade att rotigotin hade en positiv effekt på livskvalitet och motoriska besvär, särskilt skakningar. Sömnen förbättrades enbart hos de patienter som hade svårast

sömnbesvär vid studiestart samt hos de som aldrig tidigare hade behandlats med någon dopaminagonist. En viktig upptäckt var att rotigotin inte verkade förvärra dagtrötthet, vilket annars är en vanlig biverkan av dopaminagonister. Mätdata från rörelsesensorn tydde snarare på minskad dagtrötthet, ett lovande fynd som bör undersökas vidare. Framtida studier bör fokusera på att fastställa optimal dosering och på att identifiera de patientgrupper som har störst nytta av rotigotin i sömnförbättrande syfte.

Polysomnografi utgör guldstandarden för sömnregistrering, men metoden kräver ofta sjukhusvistelse över natten. Detta är kostsamt, gör det svårt att följa sömn över tid och riskerar att ge en missvisande bild då sjukhusmiljön i sig kan påverka sömnkvaliteten. Användning av rörelsesensorer är ett lovande alternativ för mätning över tid i hemmet, men behöver valideras ytterligare. En sekundär frågeställning i studien om rotigotin var därför att undersöka om det fanns en korrelation mellan data från en rörelsesensor och patienternas subjektiva skattningar av sömn och dagtrötthet, dock kunde ingen sådan korrelation påvisas. Framtida studier med fler deltagare och som även jämför rörelsesensorer med polysomnografi krävs för att fastställa metodens tillförlitlighet.

Efter några år med Parkinsons sjukdom så pendlar patienterna ofta mellan god medicineffekt (on), dålig medicineffekt (off) och ofrivilliga rörelser (dyskinesier). Dyskinesier uppkommer vanligtvis när koncentrationen av läkemedel i kroppen blir för hög. När man försöker optimera behandling hos en individ för att minska dessa svängningar samt vid utveckling av nya läkemedel så krävs tillförlitliga verktyg som följer motoriska svängningar över tid. Idag används ofta hemdagböcker där patienten registrerar sin motoriska status varje halvtimme, men studier visar att överensstämmelsen mellan läkares och patienters samtidiga bedömningar är låg. I en studie undersöktes huruvida en patientutbildning kring motoriska svängningar förbättrade denna överensstämmelse, utifrån teorin att kunskap saknas kring olika motoriska tillstånd och leder till låg överensstämmelse. Ingen övergripande förbättring sågs, även om patienterna tenderade att bli bättre på att identifiera just dyskinesier. I en annan studie undersöktes överensstämmelse mellan en läkare och anhöriga till parkinsonpatienter när de bedömde patientens motoriska status i dagboken men denna var också låg. Sammanfattningsvis så verkar dagboken spegla en subjektiv upplevelse snarare än en objektiv klinisk bedömning. Detta är problematiskt då det kan leda till suboptimal behandling av individer samt till att felaktiga slutsatser dras från läkemedelsstudier. I framtiden bör tekniska lösningar, såsom sensorer eller elektroniska dagböcker, valideras mot läkarbedömningar för att undersöka om dessa verktyg kan ge mer tillförlitliga resultat.

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Carin Janz initiated her research career during the final stages of medical school. After completing her medical internship and obtaining her medical license, she joined the Department of Neurology in Lund. The clinical studies presented in this thesis were conducted at the Neurology Research Center in Lund, Sweden. Outside of her professional and academic pursuits, Carin enjoys skiing, running, reading a book in the sun, and spending quality time with her family and friends.

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