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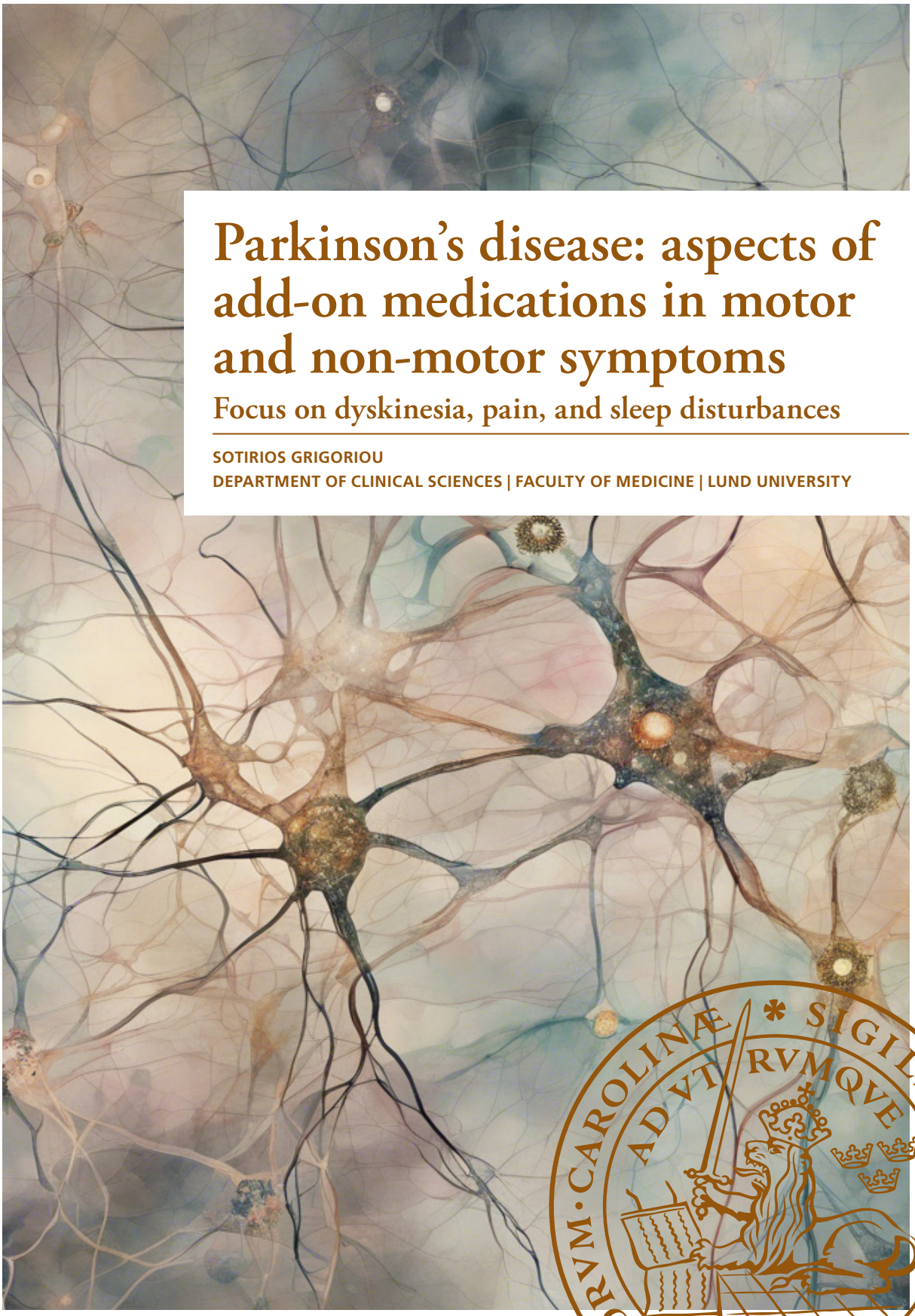

Parkinson's disease: aspects of add-on medications in motor and non-motor symptoms

Focus on dyskinesia, pain, and sleep disturbances

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SOTIRIOS GRIGORIOU was born in Alexandroupolis, Greece in 1989. He received his medical degree from the Aristotle University of Thessaloniki in 2012 and completed his specialization in neurology in 2018 after training in the University Hospitals in Linköping and Lund. He has worked as a specialist in neurology in Lund and Malmö. The research projects in this thesis were conducted at the Neurology Research Center in Lund, Sweden and explore the effects of add-on treatments in Parkinson's Disease.

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DOCTORAL DISSERTATION

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Abstract:

Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by a spectrum of motor and non-motor symptoms (NMS). NMS are often overseen but have a negative impact on patients' quality of life (QoL). There is currently no curative treatment for PD and identifying symptomatic treatments that can address both motor symptoms and NMS is crucial.
Aims: The overarching aim of this thesis is to look into how different, commonly used, add-on treatments affect patients with PD, with a focus on NMS and motor complications, mainly dyskinesias.
Methods: Two open-label, observational, prospective studies (*Papers I & III*) and one interventional study with a randomised crossover design (*Paper II*) are included in the thesis. *Paper I* investigates the effects of safinamide in different NMS with a focus on pain; in *Paper II* we investigate how coadministration of the dopamine agonist (DA) ropinirole affects dyskinesia phenomenology compared to levodopa (L-dopa) alone; *Paper III* focuses on the effects of rotigotine on sleep and daytime sleepiness. Evaluations were conducted using patient-completed questionnaires, clinician-completed rating scales and objective measurements using accelerometer data.
Results: Adding safinamide, while maintaining an otherwise stable dopaminergic treatment, in patients with fluctuating PD led to pain alleviation 6 months after treatment. Motor complications improved also, but other NMS, including sleep and depression remained unchanged. Coadministration of DA ropinirole produced different temporal and topographical dyskinesia patterns. We observed lower peak-phase dyskinesias and generally a smoother dyskinesia curve over time. After L-dopa challenge, dyskinesia scores were higher in the legs compared to all other body parts, while adding ropinirole resulted in comparable scores in legs and arms. Arm dystonia during end-phase was significantly higher after DA coadministration. Furthermore, we developed a model that could accurately predict trunk hyperkinesia based on accelerometer data. Finally, rotigotine treatment did not exacerbate daytime sleepiness and improved sleep disturbances only in patients with more severe baseline sleep problems and those that had not previously received other DA treatment. Motor improvements, as well as improvement in QoL were noticed at approximately one month after treatment initiation. Daytime and nighttime scores produced by actigraphy did not show a strong correlation with patient reported outcomes.
Conclusion: Different add-on treatments have distinctive effects on a variety of motor symptoms and NMS that should be considered in decision-making aimed at personalized, precision treatment in PD.

Key words:

Parkinson's disease, Non-motor symptoms, Pain, Sleep, Safinamide, Rotigotine, Ropinirole, PKG

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"Ἐν ὀλιγίστοις κεῖται τὸ εὐδαιμόνως βιῶσαι."

"Very little is needed to make a happy life."

Marcus Aurelius, Meditations

Table of Contents

Abstract

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List of Papers

Paper I

Grigoriou S, Martínez-Martín P, Ray Chaudhuri K, et al. Effects of safinamide on pain in patients with fluctuating Parkinson's disease. Brain Behav. 2021;11(10):**esq2336**. doi:10.1002/brb3.2336

Paper II

Grigoriou S, Espa E, Odin P, et al. Comparison of dyskinesia profiles after L-DOPA dose challenges with or without dopamine agonist coadministration. Neuropharmacology. 2023;237:109630. doi:10.1016/j.neuropharm.2023.109630

Paper III

Grigoriou S, Janz C, Horne M, et al. Effects of rotigotine on sleep in Parkinson's disease patients: A Parkinson's Kinetigraph study *Unpublished, submitted*

Author's contribution to the papers

Paper I

Conceptualization, Supervision, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing

Paper II

Conceptualization, Supervision, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing

Paper III

Conceptualization, Supervision, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing

Abbreviations

AADC	Aromatic amino acid decarboxylase
ADL	Activities of daily living
AIMs	Abnormal involuntary movements
BBB	Blood-brain barrier
BKS	Bradykinesia score
CDRS	Clinical Dyskinesia Rating Scale
CNS	Central nervous system
CGI-I	Clinical global impression - Improvement
CGI-S	Clinical global impression - Severity
CISI-PD	Clinical Impression of Severity Index for Parkinson's Disease
CSAI	Continuous subcutaneous apomorphine infusion
CSS	Combined sleep score
COMT	Catechol-O-methyltransferase
DA	Dopamine agonist
DAT	Dopamine transporter
DBS	Deep brain stimulation
DDCI	Dopa-decarboxylase inhibitors
DKS	Dyskinesia score
EDS	Excessive daytime sleepiness
EQ-5D-3L	EuroQol-5D 3 level version
EQ-5D-5L	EuroQol-5D 5 level version
ESS	Epworth sleepiness scale
ICD	Impulse control disorder
FoG	Freezing of gait
GPi	Internal globus pallidus
HADS	Hospital Anxiety and Depression Scale
H&Y	Hoehn & Yahr

IQR	Interquartile range
KPPS	King's Parkinson's Disease Pain Scale
LCIG	Levodopa-carbidopa intestinal gel
LECIG	Levodopa-entacapone-carbidopa intestinal gel
LEDD	Levodopa equivalent daily dose
LID	Levodopa induced dyskinesia
LD	Levodopa
LD+R	Levodopa + ropinirole
L-dopa	Levodopa
MAO-B	Monoamine Oxidase-B
MDS	Movement Disorders Society
NMS	Non-motor symptoms
NMSS	Non-motor symptoms scale
PD	Parkinson’s disease
PDD	Parkinson’s disease dementia
PDQ-8	Parkinson’s disease questionnaire (8 items)
PDQ-39	Parkinson’s disease questionnaire (39 items)
PDSS	Parkinson's disease sleep scale
PDSS-2	Parkinson's disease sleep scale - 2
PGI-I	Patient global impression - Improvement
PGI-S	Patient global impression - Severity
PKG	Parkinson’s KinetiGraph
PLMD	Periodic limb movement disorder
PSG	Polysomnography
PTI	Percentage time immobile
PTI_D	Percentage time immobile during the day
PTT	Percentage time tremor
PTD	Percentage time dyskinesia
QoL	Quality of life

RBD	Rapid eye movement sleep behavior disorder
REM	Rapid eye movement
RCT	Randomized controlled trial
RLS	Restless legs syndrome
SNpc	Substantia nigra pars compacta
SNRI	Serotonin–norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
STN	Subthalamic nucleus
SWEPAR-net	Swedish Parkinson’s Network
TCAs	Tricyclic antidepressants
UPDRS	Unified Parkinson's Disease Rating Scale
ViM	Thalamic ventral intermediate nucleus

Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder, characterized by a spectrum of motor and non-motor symptoms. First identified by James Parkinson in 1817, its impact extends beyond its widely recognized motor manifestations, delving into the realm of various non-motor symptoms (NMS) that affect patients and their quality of life. This introduction aims to look into the multifaceted nature of Parkinson's disease, exploring its diverse symptoms, the vital significance of managing both motor and non-motor manifestations, and the evolving landscape of add-on medications and their effects.

Background

PD is the second most common neurodegenerative disorder behind Alzheimer's disease, with an estimated prevalence of over 8.5 million patients worldwide in 2019 and increasing incidence.[1] Neurological disorders are the leading source of worldwide disability, and Parkinson's disease is considered the fastest growing of these disorders, mainly, but not exclusively, due to an ageing population.[2] This results in a rapidly growing socioeconomic and disability burden,[3] especially as the duration of the disease can span decades.

PD pathophysiology is a result of complex mechanisms involving mainly α-synuclein aggregation, while neuroinflammation, lysosomal and mitochondrial dysfunction seem to also hold a significant role.[4] These disease mechanisms lead to neuronal death of dopaminergic neurons and consequently dopamine deficiency in the basal ganglia, resulting in the classic triad of motor symptoms: bradykinesia, tremor, and rigidity.[5] The neuropathological mechanisms underlying NMS are poorly understood and arise due to dysfunction in dopaminergic and nondopaminergic systems.[6]

PD symptomatology is notoriously heterogeneous,[7] as different neurotransmitters other than dopamine and brain regions outside the basal ganglia are involved, and often a quite unique combination of motor symptoms and NMS with variable severity is present in each patient. NMS can precede the debut of motor symptoms by many years or develop during the course of the disease. They are common, with virtually all patients reporting at least one, and most experiencing multiple NMS.[8-

[10] They may often, though, remain undeclared to health-care professionals. Patients may forget to report them or be unaware that the symptoms are linked to PD, while clinicians may neglect asking due to unawareness or lack of time.[11] During recent years, though, research interest and awareness on NMS has grown, **Figure 1**.

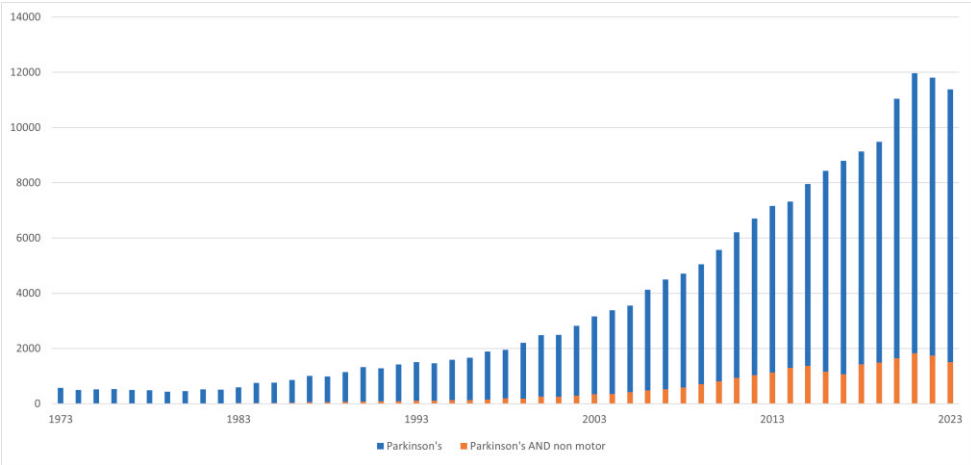


Figure 1
Number of PubMed publications, by year, for search terms "Parkinson's" (blue) and " Parkinson's AND non-motor" (orange).

Sleep disorders, neuropsychiatric symptoms (most commonly depression and anxiety), fatigue, gastrointestinal and urinary symptoms, pain, and cognitive symptoms are often reported as the most common NMS.[8, 9, 12] Olfactory dysfunction, apathy, sexual difficulties, hypotension, dysphagia, drooling, visual dysfunction, and many more can also be present through different stages of the disease, **Figure 2**.

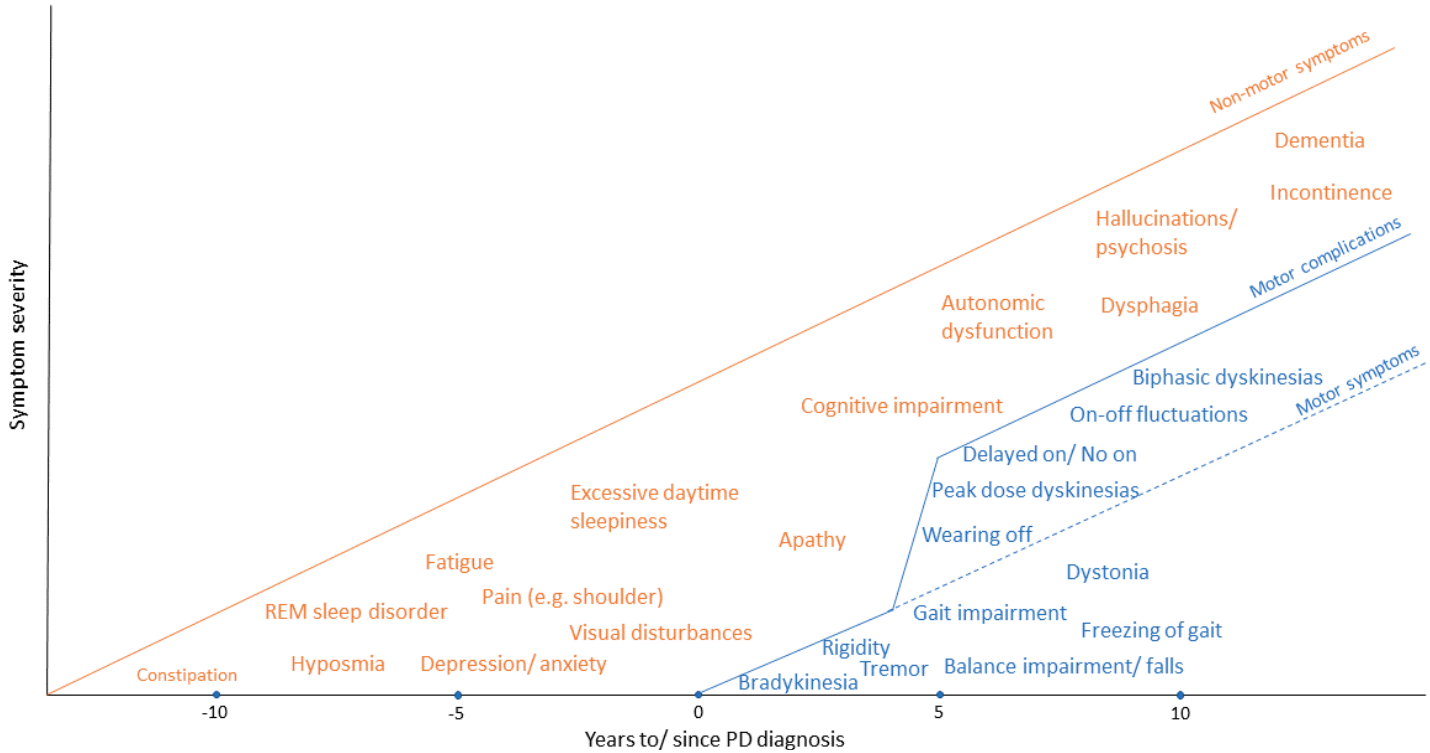


Figure 2
Development of motor and non-motor symptoms during PD progress (not to scale).

To complicate things further, many NMS, such as sleep disturbances, excessive daytime sleepiness, impulse control disorders (ICD) and cognitive impairment can be at least partially caused or exacerbated by antiparkinsonian or other concomitant medications.

PD and sleep

The regulation of sleep and wakefulness is dependent on the interplay of multiple brain regions and different neurotransmitters that can be affected in PD, leading to a wide range of disturbances.[13] Sleep disturbances and excessive daytime sleepiness (EDS) are common in PD affecting up to 60-90% of patients[14, 15] and have a substantial negative impact on quality of life.[15, 16] Different PD patients may display a different constellation of sleep and sleep-related disturbances.

One of the most common sleep disorders is insomnia, with difficulties initiating sleep (sleep-onset insomnia), difficulty maintaining sleep (sleep-maintenance insomnia) and early awakenings. Long disease duration, cognitive impairment, female sex, depression, and use of dopamine agonists are associated with increased incidence of insomnia in PD.[17] Insomnia can arise due to nocturnal symptoms related to hypodopaminergic state (e.g., rigidity, hypokinesia, dystonia, pain) or hyperdopaminergic state at night (e.g., dyskinesia, delusions, hallucinations), disease related changes (e.g., disturbance of sleep-wake cycle and changes in sleep architecture), neuropsychiatric symptoms such as depression, anxiety, dementia, or other primary sleep related disorders that are related to/ overrepresented in PD such as rapid eye movement sleep behavior disorder (RBD), restless legs syndrome (RLS), and periodic limb movement disorder (PLMD).[14]

EDS in Parkinson's disease is often multifactorial in nature, stemming from the disease pathology itself, alterations in neurotransmitter systems, medication side effects (mainly dopamine agonists), and disruptions in sleep architecture. The underlying mechanisms contributing to EDS in Parkinson's disease involve dysfunction in the wake-promoting and sleep-regulating circuits within the brain, including the degeneration of nuclei involved in the sleep-wake cycle, such as the locus coeruleus and the orexinergic system. Furthermore, disturbances in the circadian rhythm, sleep fragmentation, and nocturnal sleep disturbances commonly coexist with EDS in Parkinson's disease and may exacerbate daytime sleepiness.[18-20]

PD and pain

Pain is a highly prevalent NMS in PD and may be more disabling than the motor symptoms. Pain can be present already in the early stages of the disease, even in the

prodromal phase.[21] Research indicates that approximately 40% to 85% of people with Parkinson's experience pain at some point during the disease.[22] The prevalence of pain tends to increase with disease duration and severity, with studies suggesting that it may be more common in advanced stages of PD.[23, 24] Pain in PD can be heterogeneous, encompassing various types such as musculoskeletal, central, dystonic, orofacial, and radicular/ neuropathic pain.[21, 24] Risk factors for pain in PD include disease onset in early age, female sex, genetic polymorphisms, motor complications, and medical conditions other than PD that predispose to painful symptoms, while pain has been also associated with NMS, mainly sleep disturbances and depression.[24-28]

The mechanisms underlying pain in PD are multifactorial and complex. While the exact pathophysiology remains incompletely understood, several hypotheses have been proposed. Dysfunction within the central nervous system, particularly alterations in nociceptive processing, seem to play a crucial role in the manifestation of pain.[26] PD is characterized by neurodegeneration primarily affecting dopaminergic pathways, but it also involves non-dopaminergic systems, including those implicated in pain processing, while changes in the peripheral nervous system may also contribute to the development of pain in PD.[29] Furthermore, motor symptoms such as rigidity, bradykinesia, and dystonia can cause or exacerbate pain.

Comprehending the significance and underlying mechanisms of pain in PD is crucial for devising efficacious management approaches. A comprehensive approach to managing pain should entail a multidisciplinary strategy, incorporating pharmacological treatments, physical therapy, psychological assistance, and patient education.

Motor complications and dyskinesias

Treatment options used to address motor symptoms in PD include levodopa (L-dopa), dopamine agonists (DA), anticholinergics, amantadine, COMT- and MAO-B inhibitors.

Although response to dopaminergic treatment is often initially satisfactory, continued treatment along with disease progress results in motor complications, including reduced duration of motor response, wearing-off, dose failures and dyskinesia, in many patients within 3–5 years from levodopa initiation.[30-32]

The term dyskinesia refers to a variety of involuntary movements including chorea, dystonia, ballism, and myoclonus, that can affect every body part. The three main clinical presentations, defined based on their relationship to the timing of L-dopa administration, are peak-dose dyskinesia, diphasic dyskinesia, and off-period dystonia.[33, 34] A higher cumulative incidence of dyskinesias occurs in patients of female gender, low body weight, and earlier disease onset.[35, 36]

The mechanisms underlying dyskinesia are complex, involving all basal ganglia nuclei, and stem from an imbalance in the functionality of the direct and indirect striatal efferent pathways containing D1 and D2 dopamine receptors respectively, together with the loss of bidirectional synaptic plasticity.[37]

Levodopa induced dyskinesia (LID) can be non-bothersome for patients especially when mild, and poor self-awareness is one of the hallmarks of LID in PD patients.[38] Strategies to ameliorate bothersome dyskinesias include avoiding high L-dopa doses, initiating amantadine, and introducing continuous dopaminergic treatment or deep brain stimulation (DBS).

Quality of life

Motor symptoms, motor complications and dyskinesias

PD patients have generally lower health-related quality of life (QoL) compared with age-matched healthy controls in most domains, especially in physical function and mental health.[39] Demographic factors like age, sex, education and living status should be considered when investigating questions associated to QoL.[40] Motor symptoms, such as tremor and bradykinesia, especially when they are profound, are widely recognised as key factors influencing QoL in PD patients.[41] Gait disturbances and complications arising from medication have also a substantial effect.[40]

Research indicates that PD patients experiencing motor fluctuations exhibit markedly greater disruptions in psychological, social, physical, and economic functions when compared to those without fluctuations. Furthermore, even during their best ON-state, those with motor fluctuations perceive a more pronounced impact on their social well-being compared to those without fluctuations.[42] Early-morning and nocturnal akinesias, end-of-dose and paradoxical fluctuations, as well as "unpredictable offs," seem to notably deteriorate QoL.[43, 44] Most, but not all, studies seem to also agree that LIDs have a negative impact on QoL as a whole and more specifically in aspects of emotional well-being, communication, and bodily discomfort (with some differences between the studies on the exact subunits of QoL affected), while some studies also indicate an increased social stigma. [43, 45-49]

Non-motor symptoms

NMS have a negative cumulative effect on patients' daily activities and QoL.[50, 51] Some studies even suggest greater impact compared to motor symptoms and that NMS progression contributes to further decline in QoL.[52, 53] There is also evidence

that NMS are perceived as more important for health-related QoL than motor symptoms even in the early disease phase,[54] while a recent study highlighted the importance of non-motor fluctuations as a negative factor in respect to QoL, when present.[55] Different studies have identified different NMS as the main drivers of the impact on QoL; those most often reported are depression and other mood disorders, sleep problems, EDS, nocturia, cognitive decline/ memory difficulties, neuropsychiatric disorders such as ICD, apathy, fatigue, autonomic dysfunction, and gastrointestinal issues.[51, 56-59]

The heterogeneity of motor and non-motor symptoms and their different relative impact in different PD patients, highlights the need for precision medicine in which the various treatment decisions should be to be customized to align with each individual's requirements.

Literature review

Traditional classifications in Parkinson's disease (PD) have typically revolved around motor milestones. They focus on the topography and severity of motor symptoms, progressing from unilateral to bilateral involvement and finally the appearance of gait disturbances, postural impairment, and eventually bedridden immobility.[60] The first period after PD diagnosis prior to development of postural impairment is generally considered as early-stage PD; mid-stage PD with postural instability and the appearance of motor complication follows, and eventually develops to advanced stage PD with severe disability. While such classifications offer valuable insights into motor symptom severity over time, they often overlook the comprehensive spectrum of both motor and non-motor symptoms.

L-dopa is the most effective and widely used treatment during all PD-stages and is often the first choice of treatment from the beginning. However, DAs and MAO-B inhibitors can be chosen as initial treatment,[61] mainly in patients of younger age or in patients with non-disabling symptoms respectively,[62] or as add-on treatments. COMT-inhibitors, amantadine, and anticholinergics (in a lesser degree due to their side-effect profile) can also be added to address different symptoms and motor complications. Besides dopaminergic treatment, a wide arsenal of non-dopaminergic agents can be used to address NMS, while methods of continuous dopaminergic stimulation are reserved for patients in more advanced stages facing motor fluctuations and unstable motor response. In the following part I aim to provide a concise review of the literature, with the focus being on add-on treatments, mainly DA and MAO-B inhibitors, and their effect on dyskinesias, sleep and pain.

Treatment approaches in early PD

L-dopa

Parkinson's disease is characterized by degeneration of the substantia nigra, disruption in the nigrostriatal pathway and reduced levels of dopamine in the striatum. Levodopa is a dopamine precursor that has the ability to penetrate the blood-brain barrier (BBB). Levodopa undergoes conversion to dopamine both centrally within the central nervous system (CNS) and peripherally. It is

administered alongside dopa-decarboxylase inhibitors (DDCI) such as carbidopa and benserazide, to prevent the conversion of levodopa to dopamine outside the CNS. This reduces treatment complications, extending L-dopa half-life and increasing L-dopa availability in the brain. L-dopa is then decarboxylated to dopamine by aromatic amino acid decarboxylase (AADC) present within neurons and glia and activates postsynaptic dopaminergic receptors, compensating for the diminished levels of endogenous dopamine.[63-66]

It is recommended to initiate L-dopa in early-stage PD, when motor symptoms impact QoL.[67] Side effects that can occur include nausea, dizziness, postural hypotension, somnolence, headache, and neuropsychiatric side effects, mainly in older patients.[64] The need for multiple doses during the day, due to the drug's relatively short half-life, can also be problematic for some patients.

DAs and MAO-B inhibitors can, as mentioned, be used as initial monotherapy or as add-on treatment in a L-dopa sparing strategy in early PD.

Dopamine agonists

DAs mimic the effect of dopamine at the dopamine receptors level. The most commonly used oral DAs are pramipexole, ropinirole and rotigotine. Apomorphine is used parenterally either as continuous subcutaneous infusion in later PD stages or as rescue medication for OFF periods and is described in detail below. Older DAs, such as bromocriptine, cabergoline, lisuride, and pergolide are rarely used due to the risk of valvular and lung fibrosis.[68] DAs have the benefit of less frequent dosing; pramipexole and ropinirole can be administered once daily if the long-acting preparation is used. Rotigotine comes in a patch formulation for continuous release transdermally, that is changed once daily. DAs, although less potent than L-dopa in ameliorating motor symptoms,[69] are effective in early PD, as monotherapy or combined with L-dopa. Nausea, vomiting, orthostatic hypotension, headache, dizziness, and cardiac arrhythmia are the most common side effect of dopamine agonists.[70] Hallucinations, delusions, confusion, sleep attacks, and particularly ICDs such as hypersexuality, excessive gambling or shopping, hyperphagia and obsessive hobbying may arise.[71] Compared to L-dopa, DAs seem to carry a higher risk of peripheral oedema, somnolence, constipation, dizziness, and hallucinations.[72] DAs should be used cautiously in patients with cognitive impairment and orthostatic hypotension and should be avoided when there is a history or risk of psychosis or ICDs.[73]

MAO-B inhibitors

Monoamine Oxidase-B (MAO-B) metabolizes dopamine released in the synaptic cleft and taken up by glial cells. MAO-B inhibitors inhibit MAO-B activity in the

brain, block dopamine catabolism and increase thus the amount of dopamine in the synaptic cleft, enhancing dopamine signaling.[74] MAO-B inhibitors used in PD treatment include selegiline, rasagiline, and most recently safinamide, which is approved only as an add-on treatment to L-dopa in Sweden, while the first two can also be used as monotherapy. They are recommended as first-line monotherapy for patients with early PD, whose motor symptoms are not affecting their quality of life[67] and are often better tolerated than DAs with fewer patients withdrawing treatment due to side effects,[75] while also offering the advantage of once daily administration. Common side effects include nausea, headache, xerostomia, orthostatic hypotension, and sleep difficulties. In older patients, confusion might be an issue, and caution should be taken with the concomitant use of antidepressants or other serotonergic drugs due to a higher risk of developing serotonin syndrome, that can manifest with severe high blood pressure, fast heart rate, fever, and muscle rigidity, among other symptoms.[76] However, this complication is extremely rare in early PD.[77] When it comes to efficacy compared to DAs, recent meta-analyses indicate a weaker effect of MAO-B inhibitors both as monotherapy and adjunct treatment to L-dopa.[75, 78, 79]

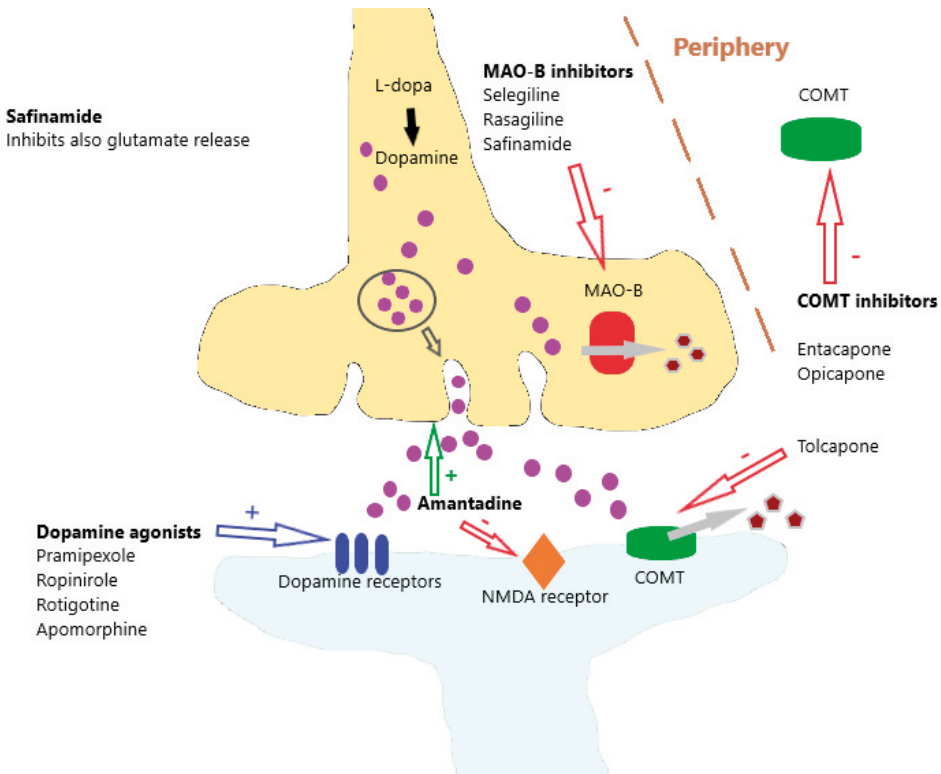
Anticholinergics and other treatments

Anticholinergics, the first drug utilized in treating PD symptoms, remain in use today, either alone or in combination with other treatments, but their use has decreased due to a less desirable side effect profile compared to alternative medications, especially concerning neuropsychiatric and cognitive issues. They are primarily considered in the treatment of tremor, mainly in younger patients that are cognitively intact.[80] Beta-blockers, otherwise used in treating essential tremor, can also contribute to tremor reduction in some patients.[81]

Treatment initiation and long-term outcomes

The development of neuroprotective, disease-modifying treatment is an unmet need in PD and treatment remains symptomatic. Primary treatment options center around pharmacological dopamine replacement, aiming to alleviate symptoms and enhance QoL. There might sometimes be a hesitancy to initiate dopaminergic therapy early due to concerns regarding potential adverse effects on disease progression or the premature emergence of side effects, such as dyskinesias. Despite increasing evidence contradicting these worries, the precise impact of dopaminergic treatment on the long-term progression of the disease remains incompletely understood.[82-84] None of the large studies looking into early treatment initiation have found clinical evidence of accelerated PD progression, with some reporting potential long-term benefits but others not able to confirm this finding. [85-89] DAs are less likely than levodopa to cause dopaminergic motor complications, particularly dyskinesia, in the

short term.[90, 91] Because younger age at disease onset is a risk factor for dyskinesia,[92] DAs are usually introduced as initial treatment in younger patients. However, there is increasing evidence that the development of motor fluctuations over time depends mainly on the progressive degeneration of the nigrostriatal dopamine terminals, rather than the timing and type of medication used as initial treatment.[87, 93] MAO-B inhibitors have shown neurotrophic and neuroprotective properties in preclinical studies, but how this finding translates into clinical studies and practice needs to be investigated further, as early positive signals have not been verified in follow-up studies.[94] The proportion of patients who later discontinue treatment based on a combination of side-effects and absence of efficacy is higher for a MAO-B inhibitors than dopamine agonists.[87] Irrespective of the treatment initiation strategy, the vast majority of patients is eventually prescribed L-dopa treatment. Finally, there seems to be no advantage in delaying L-dopa treatment when symptoms warrant therapy; this delay might only result progressive worsening of QoL and a shorter period free of motor complications.[77]



Picture 1
Antiparkinsonian drugs and their mechanism of action

Treatment approaches in mid- and advanced stage PD

Motor complications

The progression of PD with increasing degeneration of dopamine terminals in the nigrostriatal system and fluctuating in L-dopa levels, stemming from both central and peripheral mechanisms, contribute to the development of motor complications. Initially, patients typically experience a robust response to dopaminergic therapy, characterized by consistent effectiveness without noticeable fluctuations. However, as the disease and time progresses, typically after 2 to 5 years, patients often begin to notice shorter periods of symptom relief and experience less reliable and effective response to medication, marking the onset of motor fluctuations. The vast majority of patients will develop motor complications by 10 years of dopaminergic treatment.[31] Younger age at disease onset, higher levodopa equivalent daily dose (LEDD) and the akinetic-rigid dominant phenotype of PD are considered risk factors for fluctuation development.[95, 96] Another study has also linked the risk to developing motor complications to NMS burden and particularly low mood and anxiety.[97]

The most common, and usually earliest sign of motor complications is **predictable wearing-off**. Patients develop a shorter response to L-dopa doses with the desirable effect waning out and transitioning from ON (state with medication effect and symptom control) to OFF (worsening of parkinsonian symptoms), before taking the next dose. This is linked to the decrease in the quantity of dopaminergic nerve terminals within the striatum that leads to a diminished capacity for dopamine storage and an increased dependency on pulsatile, externally administered L-dopa in order to produce sufficient dopamine levels.[98] Sustained-release L-dopa is usually not an efficient alternative due to its unreliable absorption but is sometimes tried. A strategy used to address wearing-off consists of utilizing lower L-dopa doses administered in shorter intervals or added doses if needed (gastrointestinal factors that may affect levodopa absorption, especially in patients reporting worse effect after eating, should also be considered). Adding a DA or MAO-B inhibitor can also reduce OFF time.[99-103]. Caution needs to be taken when increasing the total LEDD, particularly regarding the possible development of dyskinesias and other side effects. Immediate release L-dopa formulations can also be prescribed and taken as needed between doses, with vigilance to avoid overconsumption and dyskinesias.

COMT-inhibitors

Catechol-O-methyl transferase (COMT) degrades catecholamines, including dopamine. COMT inhibitors prevent peripheral degradation of levodopa (tolcapone has also central action in the CNS), allowing higher concentrations to cross the BBB.[104] They are one of the recommended first-line L-dopa add-on medications prescribed to alleviate wearing-off symptoms as they increase plasma and brain levels of L-dopa.[105] COMT-inhibitors used in PD include tolcapone (limited use due to hepatotoxicity), entacapone and recently the long-acting, potent COMT-inhibitor opicapone.[106] Entacapone is the most widely used agent and is also available as combination pill with L-dopa/ carbidopa. It can cause discoloration of urine and sweat and may cause diarrhea, nausea, anorexia, vomiting, orthostatic hypotension and sleep disorders. L-dopa dose may need adjustment when initiating treatment with a COMT-inhibitor due to risk of dyskinesia development or worsening.[107]

Unpredictable off / sudden-off consist of unanticipated instances of pronounced parkinsonism that occur less frequently than predictable wearing-off and are more prevalent in the later stages of PD. Patients experience a sudden return of symptoms, which may not correlate with medication timing and can manifest at any point during the day. This rapid deterioration in parkinsonian symptoms, occurring within seconds, can lead to the development of sudden and severe akinesia. **On-Off fluctuations** refer to a combination of predictable or unpredictable rapid transitions between ON and OFF state, can be abrupt, and are also observed in later stage PD.[31, 108] Patients may also encounter an extended delay between ingesting a medication dose and experiencing its intended effect, termed as **delayed on**, or may observe a partial or complete lack of benefit from a dose of L-dopa, referred to as **dose-failure** or **no-on.**[109] These complications are frequently linked to gastrointestinal factors, such as variations in L-dopa absorption due to competition with dietary amino acids or delayed/ irregular gastric emptying. The role of H. pylori has also attracted interest.[108] Fast-acting medications, such as immediate release L-dopa or "rescue" administration of subcutaneous apomorphine have the potential to address unpredictable off periods and dose failures. Their reliability may though vary (especially with oral preparations), or logistical/ practical challenges may be an issue (subcutaneous apomorphine). Additionally, clinicians should exercise caution when considering the regular use of these options due to concerns about potent pulsatile dopaminergic stimulation. Patients who use these agents regularly should therefore be evaluated for continuous, device-assisted treatments.[110]

Freezing of gait (**FoG**) can often affect PD patients at a later stage of the disease, but milder forms can occur early on. It is characterized by a difficulty in stepping forward, which appears either in gait initiation or during gait, especially when turning or going through narrow spaces, with the inability to lift the feet from the floor and trembling of the legs. FoG is closely linked with motor fluctuations and is usually observed in the OFF phase.[111] Rasagiline has shown positive effect on

FoG.[103, 112] Besides MAO-B inhibitors, there are also indications that amantadine can have a beneficial effect,[113] while visual and auditory cues may also be helpful.[114] FoG can also be present in the ON state and is usually in that case not responsive to dopaminergic treatment.

Dyskinesias

The term refers to abnormal, involuntary movements that can be phenomenologically characterized as chorea, dystonia, ballism, myoclonus or athetosis. Chorea is the more prevalent phenotype but different combinations of the above can be present. These movements typically occur in a repetitive and stereotyped manner (or as fixed, sometimes painful, abnormal, postures in the case of dystonia) and can range from mild to violent that disrupt voluntary motor control. Dyskinesias are notoriously underreported by PD patients,[115] partly because many patients prefer an ON state with moderate or even severe dyskinesias opposed to a severe OFF, hypokinetic state. Dyskinesias are strongly associated with the use of L-dopa[116] and three main clinical presentations are defined based on their relationship to the timing of L-dopa administration: **peak-dose dyskinesia**, **diphasic dyskinesia**, and **off-period dystonia**.[34]

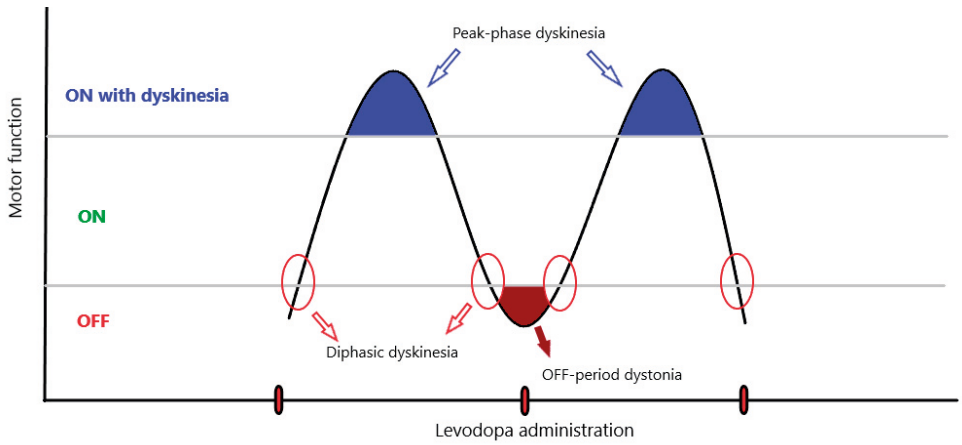


Figure 3
Types of dyskinesia related to L-dopa timing

Peak dose dyskinesia coincides with the period of maximum L-dopa effect and can consist of a combination of chorea, dystonia and ballism. **Diphasic dyskinesias** are less common than peak dose dyskinesias and occur when L-dopa levels rise or fall. Compared to peak dose dyskinesias they more frequently present as repetitive lower limb movements of mainly dystonic nature (chorea and ballism may also be present). **Dystonia** is a movement disorder characterized by sustained or

intermittent muscle contractions that result in abnormal, movements, postures, or both and can affect the limbs, the axial parts of the body and the face. While it can be a component of a more complex dyskinesia pattern in the ON-phase, dystonia mainly appears during OFF-phase. Another stereotypical motor behavior related to L-dopa treatment and characterized by repetitive, non-goal oriented, motor behaviors such as handling and examining, or sorting, lining, and arranging objects, is **punding**. It is not considered a dyskinesia but often coincides with dyskinesia and ICDs.[117]

The prevalence of dyskinesia is believed to be around 40% after 5 years on L-dopa treatment,[118] with earlier disease onset and high LEDD being significant risk factors for developing dyskinesias.[119, 120] Other predisposing factors are, as mentioned above, female sex, and low body weight, while the duration of L-dopa treatment has also been considered as a risk factor.

The complex mechanisms of LID pathogenesis involve the striatum, cerebellum, cortex, and brain stem nuclei that show aberrant activity in LID, and the chronic loss of dopamine that alters cortico-striatal, thalamo-striatal, and striato-striatal connectivity.[121] Recent studies in parkinsonian rodent models have highlighted that dystonic and hyperkinetic forms of LID may differentially rely on the stimulation of D2 vs D1 receptors, and that D2 receptors mediate predominantly dystonic components,[122] while D3 receptors have also been implicated in LID pathogenesis.[123] This is especially interesting as oral DAs are mainly acting as D2/3 agonists. Different patterns of striatal neuroplasticity have been observed upon treatment with DA and L-dopa compared to L-dopa alone, including a marked inhibition of angiogenic, endothelial and immunological responses[124-127] and adjunct treatment with ropinirole has been observed to alter the response to known antidyskinetic drug principles.[124] All in all, there is mounting evidence from animal studies that treatment with DA can affect the topographical, chronological, and morphological characteristics of LIDs.

Despite the growing interest in investigating the underlying mechanisms and the efforts to discover new antidyskinetic agents the current treatment arsenal is limited.

Amantadine

Amantadine's mechanism of action involves multiple sites. It enhances dopamine transmission and has also anti-glutamatergic properties acting as an antagonist of NMDA receptors.[128] It has the ability to ameliorate dyskinesias (via NMDA-antagonism),[129] without aggravating but often improving hypokinetic PD symptoms. It has shown promising effect in addressing OFF periods[130] and FoG[113]. It is mainly, though, used as antidyskinetic as the dysregulation of glutamatergic transmission in the basal ganglia is a key mechanism underlying LID,[128] and is more effective in peak-dose dyskinesias. It is often well tolerated but may cause nausea and anticholinergic side effects. Livedo reticularis is an uncommon side effect

connected to amantadine. Caution should be also taken regarding the onset or worsening of existing neuropsychiatric symptoms and kidney function should be taken into account, as dose may need to be adjusted in older patients or those with pre-existing renal impairment.[131]

Other strategies to address peak-phase dyskinesias include reviewing treatments that may exacerbate dyskinesia without providing meaningful PD symptom alleviation (e.g., anticholinergics or MAO-B inhibitors), consider lowering L-dopa dose by adding adjunct treatment (e.g., COMT-inhibitors) or keeping the same daily L-dopa dose given more often in lower doses in an effort to keep L-dopa plasma concentrations within the narrow therapeutic window. It should though be noted that the decision to treat peak phase dyskinesias should be taken after discussion with the patient, as mild, non-troublesome dyskinesias do not necessarily need to be treated. Avoiding on-off fluctuations can be a strategy to prevent or improve diphasic dyskinesias, while adding a DA may also provide some benefit. Off-period dystonia can be treated with Botulinum toxin injections when reducing off-time is not sufficient on its own. Sustained release L-dopa at night or transdermal rotigotine patch may prevent or improve early morning OFF and should be considered in patients with OFF dystonia after waking up.[132]

Device-assisted therapies, which are presented below, are effective in addressing motor complications in patients not adequately controlled with the treatments mentioned above while also showing positive effects on NMS. Other oral treatments, with lower evidence grade on treating dyskinesias (memantine, zonisamide, clozapine) or not in routine clinical use in Europe for treating motor complications (istradefylline), are not mentioned in detail.

Device aided therapies

Despite the various treatment strategies that have been analyzed above, some PD patients continue to experience severe motor complications. Device-aided therapies, termed also advanced PD treatments, have a crucial role in the management of these patients. These treatments focus on delivering continuous dopaminergic or electrical stimulation and have a more invasive nature. While the optimal timing for their introduction remains debated, the rule of 5-2-1 (5 times oral L-dopa taken/day, 2 hours of OFF time/day, 1 hour/day of troublesome dyskinesia) can be useful for identifying patients in need of PD treatment optimization and suitable for device aided therapies.[133, 134]

Infusion Therapies

Infusion therapies include Levodopa-carbidopa intestinal gel (**LCIG**) and Levodopa-entacapone-carbidopa intestinal gel (**LECIG**), where the treatment is

delivered via an external pump into the upper jejunum through a percutaneous endoscopic gastrostomy tube with a jejunal extension (PEG-J). The continuous jejunal infusion bypasses gastric emptying issues, ensuring stable L-dopa plasma levels throughout the day. This is shown to significantly decrease OFF time, increase ON time without troublesome dyskinesia and improve QoL,[135, 136] but device-related complications may limit their use. Continuous subcutaneous apomorphine infusion (**CSAI**) and the recently approved **foslevodopa/ foscarbidopa** continuous subcutaneous infusion offer a less invasive alternative. They are also effective in reducing OFF and increasing ON time, however local adverse effects such as skin nodules and infections can occur, and long-term tolerability is variable.[110, 137]

Neurosurgical Approaches

DBS is another advanced treatment for addressing motor complications and treatment-resistant tremor in PD.[138] It involves surgical implantation of electrodes and a pulse generator device to provide continuous electrical stimulation. The subthalamic nucleus (STN) and internal globus pallidus (GPi) are commonly targeted structures for DBS, each with unique benefits and risks. While STN DBS may reduce medication requirements, it poses higher risks of cognitive and psychiatric complications. GPi stimulation offers fewer mood and cognitive side effects, can be more effective in addressing dyskinesias but may not significantly reduce medication requirements. The thalamic ventral intermediate nucleus (ViM) can also be a DBS target in cases of treatment-resistant tremor in PD.[139] DBS improves OFF time, tremor and reduces dyskinesias and while these effects can last for a long time, its positive impact on quality of life may diminish over time due to the progress of axial symptoms with walking difficulties and falls, dysarthria and cognitive decline.[140]

The selection of device-aided therapy depends on various factors including indications, contraindications, each patient's symptom profile, and the patients' personal preferences. It is crucial to initiate discussions about these treatments early, while both motor symptoms and NMS are still more treatment responsive.[141]

Treatment of non-motor symptoms

As mentioned in the introduction, NMS are often not reported by patients or neglected by clinicians, despite their detrimental effect on patients' QoL. Current treatment strategies involve the utilization of symptomatic treatments for different NMS with evidence or indication for use in PD, dopaminergic agents that can also have a positive effect on NMS or introducing device-aided therapies that can

improve NMS in addition to motor symptoms. A concise review with focus on pain management and the latest evidence regarding safinamide, as well as sleep disorders and the role of rotigotine, is presented below. The role of non-pharmacologic interventions (that can be useful for different NMS) is not reviewed here.

Dopaminergic replacement therapies may have contrasting effects on NMS. DAs for example may be useful for the treatment of depression, apathy, and fatigue but can also increase EDS and induce ICDs. Therefore, reviewing the antiparkinsonian drug regime is always an important first step in addressing NMS.[142] It should also be highlighted that NMS can also fluctuate in accordance with motor symptoms which can indicate a dopaminergic origin. Thus, providing a more stable dopaminergic effect may improve NMS that coincide with motor fluctuations, e.g neuropsychiatric, autonomic, and sensory symptoms.[143]

Depressive symptoms can be treated with antidepressants e.g SSRIs, SNRIs or tricyclic antidepressants (TCAs), while dopaminergic medications, mainly DAs pramipexole[144] and rotigotine,[145] have also demonstrated positive effects on depression in PD patients. Quetiapine, clozapine and pimavanserin can be used when an antipsychotic agent is deemed necessary, and adjustment of dopaminergic treatment is not sufficient or leads to unacceptable worsening of motor symptom control.[142] Botulinum toxin injections in the salivary glands or administration of muscarinic antagonists (e.g glycopyrrolate) can improve drooling/ sialorrhea, the risk of anticholinergic side effects should though be considered especially regarding older patients.[146] Symptomatic orthostatic hypotension can be a part of PD-related dysautonomia, but also manifest as a side effect of dopaminergic treatment. Pharmacological agents used to address orthostatic hypotension include midodrine, fludrocortisone, etilefrine and droxidopa.[147] Rivastigmine has the highest evidence grade among cholinesterase inhibitors for use in Parkinson's disease dementia (PDD) and has also the potential to improve apathy in non-demented patients.[142, 148] Rotigotine can also improve apathy,[145] and piribedil can be helpful in apathy after STN-DBS.[149] Constipation can be treated with laxatives[150] and probiotics[151], while opicapone has shown improvements in gastrointestinal and urinary domain scores of the Non-Motor Symptoms Scale (NMSS).[152]

NMS should be considered when deciding the choice of advanced PD treatment; some NMS constitute absolute or relative contraindications for all or some device-aided therapies, while a patient's NMS profile may advocate the preferential use of a specific treatment. For example, pronounced dementia is considered a contraindication for all device-aided treatments; severe depression for DBS; severe ICD, or hallucinations for CSAI; and the presence of severe orthostatic hypotension can favor the use of DBS over infusion treatments.[153] Treatment with LCIG, CSAI and DBS decreased total NMS burden in the EuroInf-2 study,[154] but their direct comparison revealed distinct effect profiles. STN-DBS improved mainly urinary/sexual functions, mood/cognition, sleep/fatigue, and the miscellaneous domain of NMSS. LCIG improved the three latter domains and gastrointestinal

symptoms. CSAI improved mood/cognition, perceptual problems/hallucinations, attention/memory, and the miscellaneous domain. Studies on the effect of the newer device aided treatments (LECIG and foslevodopa/ foscarbidopa) on NMS are still lacking but the latter demonstrated a positive effect on sleep in a phase 3 study.[155]

Pain

The origin and phenomenology of pain in PD patients is complex, typically involving multiple factors. Even in instances where it seems unrelated to PD, such as pain related to arthritis, pain can be intensified by PD symptoms like akinesia, rigidity, or NMS like depression and anxiety.[156] Pain is common, being reported by up to 85% of PD patients and has a wide spectrum of manifestations that include (but are not limited to, depending on different classifications) musculoskeletal, radicular/neuropathic, dystonia-related, and central pain.[24] PD-related pain results from a complex and poorly understood interplay of different neurotransmitter pathways. Degeneration of nigrostriatal dopaminergic pathways and alterations of extra-striatal dopaminergic, noradrenergic, serotoninergic, glutamatergic, opioid and endocannabinoid circuits may lead to an increased sensitivity to pain in PD patients.[157]

When pain is confined to OFF states or significantly increased in OFF, adjusting the dopaminergic treatment aiming a more stable dopaminergic state is a logical first step. Only three drugs (rotigotine, oxycodone/naloxone and duloxetine) have been investigated specifically for their analgesic efficacy in PD-related pain in double-blind randomized controlled trials (RCTs), but the primary endpoint was not met in any of them; evidence-based pharmacological treatment strategies for PD-related pain remain an unmet need.[158] The only medication that has received a "possibly useful" status by the Movement Disorder Society (MDS) for PD patients with chronic pain is prolonged release oxycodone/naloxone.[142]

Safinamide

Due to the lack of evidence-based, specific pain treatments, studies have investigated the effects of different antiparkinsonian drugs on pain. Safinamide has gathered a significant amount of interest during recent years, due to its unique mechanism of action, that includes both dopaminergic and non-dopaminergic properties, as it leads to an inhibition of glutamate release by modulation of calcium and sodium ion channels.[159] This is especially interesting, as the role of glutamate in central pain processing and the development of chronic pain is well established.[160] Numerous studies have previously shown that safinamide as add-on treatment improves motor symptom control, ON-time, and fluctuations in both early and advanced PD, having a dopamine-sparing effect and being generally well tolerated.[161-164] Studies looking into its effect on NMS though and especially pain have only emerged recently.

Before 2018, when we started recruiting patients for the study that led to *Paper I,*[165] very little was known about safinamide and its effect on pain. A multicenter RCT comparing safinamide (50 & 100 mg daily) to placebo in patients with mid- to late-stage PD with motor fluctuations showed that safinamide at 100 mg daily improved bodily discomfort compared to placebo at 24 weeks,[166] as assessed by domain 3 of Parkinson's disease questionnaire (PDQ-39).[167] The post-hoc analysis by Cattaneo et al. combining the 016 study[162] the SETTLE study,[168] reported reduction of pain medications by 24% in PD patients using safinamide 100 mg, six months after initiating treatment, and improvements in two out of three PDQ-39 pain-related items.[169] Similar results were found in the post hoc analysis of 018 study[166] by the same group looking in more long-term effects, two years after initiating safinamide treatment.[170] However, no studies focusing on pain, using specific PD pain scales were performed by then.

Geroin et al.[171] reported in 2020 the results of an open label study, recruiting 13 PD patients with chronic pain, that found a significant reduction in total pain score measured by King's Parkinson's Disease Pain Scale (KPPS), at 12 weeks after safinamide initiation. Our study[165] found that safinamide resulted in improvements of total KPPS score and fluctuation-related pain at 6 months after treatment, while Santos Garcia et al.[172] reported, additionally, improvements in KPPS domains for musculoskeletal and nocturnal pain, discoloration and/or edema/swelling and radicular pain, also at 6 months after treatment. A post-hoc analysis of the Japanese phase 2/3 study reported in 2021, positive effects on PDQ-39 domain 3 ("bodily discomfort") and UPDRS item 17 ("sensory symptoms") during the OFF phase, 6 months after treatment, but no pain-specific scale was used.[173] In 2022, De Masi et al.[174] found only improvement in the "discoloration, oedema/swelling" domain of KPPS at 6 months but could not detect any statistically significant changes in total KPPS score. De Micco et al.[175] looked instead into the efficacy of safinamide 50 mg on different NMS. While they reported improvements in other NMS domains, no significant improvement in KPPS was reported, suggesting that the effect of safinamide in pain may be dose dependent. Interestingly, a recent animal study reported analgesic effect of safinamide in neuropathic pain.[176] Another recent study on a PD mouse model, published earlier this year,[177] compared the analgesic effects of safinamide and rasagiline. The study found that only safinamide counteracted, in a concentration-dependent manner, the hyperexcitability of dorsal root ganglion neurons leading to alleviated hyperalgesia.

All in all, many studies have found positive effects of safinamide on NMS, but results differ between the studies regarding to specific NMS areas improved. It is also shown that safinamide may have a positive effect on QoL.[178] A recent review suggested that MAO-B inhibitors (mainly rasagiline and safinamide) may potentially improve depression, sleep disturbances, and pain, with a more unclear effect on other NMS.[179] When it comes to pain specifically, there is mounting evidence that safinamide has a positive effect, primarily at a dose of 100 mg daily,

but the reported improvements regarding specific pain subtypes differ in the studies mentioned above.

Sleep

Sleep disturbances are one of the most common NMS in PD and have a significant impact on patients' QoL.[14-16]. Sleep architecture alterations are present early on in PD, are multifactorial, and progress with disease duration. Studies registering sleep with polysomnography (PSG) have shown a negative correlation of disease duration with total sleep time, deep sleep time, REM sleep time and sleep efficiency and a positive correlation with sleep latency. This sleep destructuring seems to evolve independently from other major disease parameters (age, degree of motor impairment, dose of dopaminergic medications), suggesting that the PD-related neurodegenerative process itself may be responsible for disrupting sleep architecture.[180] On the other way around, sleep disruption in general and obstructive sleep apnea in particular may exacerbate neurodegenerative processes.[16] Sleep fragmentation has been associated with accumulation of Lewy bodies and neuronal loss in substantia nigra (that are hallmarks of PD pathology) in older adults without PD.[181]

Common sleep or sleep-related disturbances often seen in PD include RBD, RLS, insomnia and disturbed breathing during sleep. Insomnia may be the most common sleep disorder in PD and is associated with long disease duration, depression, use of DAs, and female sex.[17] The pattern of insomnia seems to differ depending on disease duration, with sleep initiation insomnia being more common in the early stage with decreasing rate later, while sleep maintenance difficulties, such as fragmented sleep and early awakening increase with disease progression.[182] RBD consists of loss of muscle atonia during REM sleep that results in abnormal dream enactment with complex motor behaviors or vocalization during REM sleep.[183] RBD is strongly associated with PD and synucleinopathies in general and can be present in the prodromal phase, long before the development of motor symptoms. RBD in PD is associated with older age, longer disease duration, rigid-akinetic form of PD and more severe parkinsonian symptoms.[184] RLS can underly insomnia and cause sleep fragmentation, while PD patients with RLS may also manifest PLMD. PD patients with RLS suffer more often from worse sleep quality and QoL, depression, anxiety, and autonomic disturbances.[185] EDS can affect over 50% of PD patients at some point during the disease course, and has been associated with i.a. male gender, poor nighttime sleep (although not necessarily), depression, cognitive impairment, and the use of DAs.[186] Additionally, other motor and non-motor symptoms, like nighttime OFF, pain and nocturia can negatively affect sleep in PD.[180]

Reviewing the patients' antiparkinsonian and concomitant treatments should always be a part of addressing sleep and sleep-related disturbances. Antidepressants can for example cause or exacerbate insomnia, while amantadine and selegiline can have a

similar effect when taken late during the day. Reducing dopaminergic treatment and especially DAs, when possible, can prove to be useful in addressing EDS. When this is not sufficient, adding amantadine or modafinil may improve EDS. Melatonin, mirtazapine, clonazepam, and extended-release L-dopa before nighttime can improve sleep-onset and sleep-maintenance insomnia. Other hypnotics and sedatives may also be tried, while melatonin and clonazepam may be used to alleviate RBD.[158] Rotigotine transdermal patch is the only medication that has received both *likely efficacious* and *possibly useful* status in improving sleep quality and maintenance by the MDS Evidence-Based Medicine Committee.[142]

Rotigotine

Rotigotine is a unique DA in regards of dopamine receptor profile, as it demonstrates high affinity for binding to D1, D2 and D3 receptors, resembling more apomorphine than pramipexole and ropinirole that bind primarily to D2 and D3 receptors;[187] as well as regarding its mode of administration, consisting of a transdermal patch.[188] The drug is delivered over a 24-h period and the patch is changed once daily. It is usually well tolerated by patients, with side effects such as nausea and dizziness in alignment with other DAs and others like local skin reactions unique for rotigotine. The RECOVER study reported a relatively low incidence of ICDs following treatment with rotigotine (4%).[189] It was also the first study to report a significant positive effect of rotigotine on sleep compared to placebo, as measured by Parkinson's disease sleep scale (PDSS-2). Improvements were observed in total score and in all sub-domains (disturbed sleep, motor symptoms at night, PD symptoms at night). In 2014, Mizuno et al[190] reported significant improvements in PDSS-2 after treatment with rotigotine compared to placebo, but not compared to ropinirole. Another study though conducted the same year by and Nicholas et al[191] could not detect any significant differences. Positive effects of rotigotine in sleep were demonstrated in a double-blind, placebo-controlled study utilizing PSG.[192] Improvement in REM sleep quantity, increased sleep efficiency and reduced sleep latency and wakefulness after sleep onset were observed compared to placebo. The improvement of PSG parameters corresponded to improvements noticed also in PDSS. Bhidayasiri et al reported improvements in sleep and nocturnal motor symptoms, verified by data collected by an axial inertial sensor.[193] Interestingly, rotigotine does not seem to induce or exacerbate EDS, an otherwise common side-effect of DA treatment,[194] with open label studies even showing EDS improvement following rotigotine treatment, according to Epworth sleepiness scale (ESS)[195] and actigraphic data.[196] However, in contrast to these studies, an RCT evaluating rotigotine effectiveness using the non-motor symptoms scale (NMSS) found no significant improvements in the sleep/ fatigue domain.[197] The recent meta-analyses on rotigotine converge to the conclusion that rotigotine has a positive impact on sleep-related disturbances and improves sleep quality in PD, while also providing improvement of motor symptoms and being generally well-tolerated.[145, 198, 199]

Aims

The overall aim of this thesis is to increase our knowledge on how different add-on treatments affect patients with PD, with a focus on NMS and motor complications, mainly dyskinesias.

In *Paper I* we set out to investigate how add-on treatment with safinamide in fluctuating PD patients affects motor complications and different NMS. We looked more extensively into anxiety/ depression, sleep, and pain and how changes in motor symptoms correlate to changes observed in pain.

In *Paper II* we looked into differences in abnormal involuntary movements (AIMs) phenomenology in PD patients affected by LID upon challenge test with either L-dopa alone or a combination of L-dopa and the D2/3 agonist ropinirole. We assessed dyskinesias by using clinical ratings of the patients by physicians and by using accelerometer data and developing an algorithm for predicting the presence and severity of dyskinesias.

In *Paper III*, the primary objective was to investigate the effects of rotigotine on sleep in PD patients, using rating scales and recordings from Parkinson's KinetiGraph (PKG). Secondarily, we aimed to assess the impact of rotigotine treatment on daytime sleepiness, quality of life and motor symptoms. Furthermore, the study aimed to explore the correlations between PKG parameters used to evaluate sleep and daytime sleepiness, and corresponding questionnaires that evaluate the same parameters.

Ethical considerations

All three studies included in this dissertation had an open-label, prospective design. Ethics Committee applications were submitted for all studies and approvals were received before study initiation. The study resulting *Paper I* received approval with DNR 2017/579 in Sweden and approval from the German authority for the other participating center. The Swedish Ethical Review Authority approved the studies resulting in *Paper II* and *Paper III* with DNR 2019-04047 and DNR 2019-01294 respectively. The patients were informed verbally and in writing about the study procedures and were given the opportunity to discuss any questions with study personnel, ensuring that they had completely understood the nature of the studies. All patients were recruited voluntarily and could discontinue their participation at any point if they chose to do so. Written informed consent was obtained from all patients participating in the studies. All study evaluations were performed by participating physicians and research nurses, that were trained and certified on the rating scales used for the studies. All studies were conducted according to Good Clinical Practice rules (GCP) and to the Declaration of Helsinki with respect to General Data Protection Regulation (GDPR).

Methods

Study design & participants

All studies had an open-label, prospective design with PD patients being recruited from the neurology outpatient clinics at each site.

Paper I

In this multicenter study [165], investigating the effects of add-on safinamide in motor complications and NMS, participants were recruited in Skane University Hospital in Lund, Sweden and Dresden University Hospital, Germany. King's College Hospital, London, United Kingdom was also a collaborating center, but did not contribute to patient recruitment as safinamide availability in UK was an issue at the time. The study was observational, meaning that the patients' clinicians were responsible for taking the decision of initiating safinamide treatment with the indication of motor symptom improvement/ off time reduction. Other dopaminergic treatment was maintained stable if possible, and patients already on other MAO-B inhibitors discontinued their previous treatment and went through a 4-week wash-out period before initiating safinamide.

We enrolled 38 PD patients who met the following criteria: age between 30 and 90, Hoehn and Yahr stage I-IV during OFF, and history of motor fluctuations with more than 1.5 hours of OFF time per day. We excluded patients with severe neuropsychiatric symptoms, such as psychosis, severe depression, dementia or other significant cognitive impairment, history of drug abuse, previous safinamide use, patients with DBS or continuous infusion treatment, late-stage PD with severe unpredictable fluctuations, symptomatic orthostatic hypotension, and those with concurrent medications and conditions regarded as contraindications for safinamide use.

Of the 38 patients recruited, 5 were excluded during screening and 4 withdrew prematurely from the study, while 2 patients that completed the study were excluded from the final statistical analysis due to changes in their antiparkinsonian medications during the study. The final analysis included 27 patients with one of them on safinamide 50 mg and the rest on 100 mg daily. The patients completed a

series of evaluations at two timepoints: before treatment initiation and after at least 6 months with safinamide treatment.

Paper II

This was a single center, open-label study conducted in Lund, Sweden that compared two sequential dose challenges with L-dopa, given alone, or combined with ropinirole[200]. The study was conducted in a randomized crossover design, meaning that all patients received both challenge doses in a random order. Immediate-release oral formulations of L-dopa-benserazide and ropinirole were used for the challenge tests, comprising 150% of the patients' usual morning L-dopa dose, capped at a maximum of 250 mg L-dopa, or a combination of equivalent doses of L-dopa and ropinirole to achieve the same LEDD, calculated according to Schade et al [201]. Patients with PD experiencing dyskinesias were enrolled, and their PD medication was tapered off before each challenge dose: amantadine was stopped one week prior; all PD medications (except amantadine and L-dopa) were halted 24 hours before; L-dopa preparations were discontinued at 10 p.m. the night before. All patients received the challenge doses in OFF, early in the morning. The patients were also instructed to consume consistent food categories before both evaluation days and abstain from breakfast and other beverages except water before and during the study visit. They maintained a stable treatment regime during study duration and the challenge tests were performed within a 2-week window. Evaluations were conducted at baseline in OFF and every 30 minutes for up to 5 hours after each challenge test, in order to capture the topographical and temporal profiles of dyskinesia and to then be able to compare the presence and characteristics of dyskinesias between the two challenges.

Patient selection adhered to the following inclusion criteria: patients with idiopathic PD with clinical evidence of classical, predominantly hyperkinetic LIDs and/or suspected treatment-related dyskinesia/dystonia as evaluated by MDS-UPDRS or patient history, age between 40 and 85 and being capable of performing medication washout as described above. Patients with dementia or neuropsychiatric conditions hindering study completion, non-ambulatory patients during OFF, patients receiving advanced PD treatment and pregnant patients were excluded. In total, 34 patients were enrolled in the study. Eight patients withdrew during the treatment washout phase before the first visit due to severe motor impairment during medication withdrawal, and one additional patient dropped out shortly after the start of the first visit due to feeling unwell. Consequently, 25 patients were included in the final analysis.

Paper III

This investigator-initiated, multicenter, observational, prospective study was a collaboration within the Swedish Parkinson's Network (SWEPAR-net). We enrolled PD patients aged 18 to 85 who were experiencing sleep disturbances (Clinical Global Impression-Severity (CGI-S) score ≥ 3). Participants were required to maintain a steady PD treatment regimen, with the exception of adding rotigotine. Patients were excluded based on the following criteria: advanced PD therapies; patients on oral DAs; dementia or notable cognitive impairment; severe prostate issues, sleep apnea syndrome, or other diagnosed non-PD-related conditions significantly affecting nocturnal sleep. Introduction or alteration of sedatives or hypnotics during the study period was prohibited. 40 patients were included in the study and 32 patients completed the study. 5 patients dropped out before the first visit mainly due to worsening in OFF periods during washout of oral DA and 1 patient was excluded after study inclusion due to major orthopedic surgery that affected sleep and overall well-being. 1 patient dropped out after initiating rotigotine treatment due to worsening of motor symptoms and 1 patient due to side effects. Patients were evaluated before starting treatment and at least 1 week after up-titration to rotigotine maintenance dose (the dose that provided adequate motor improvement without bothersome side effects). The mean follow-up time was approximately 1 month after treatment initiation.

Outcome assessments

Rating scales

Well-known, validated rating scales were used in all studies to capture and evaluate motor symptoms and NMS. The scales used in the studies are presented below and consist of both clinical rating scales, where study personnel assess different kinds of symptoms by interview or clinical examination and self-rating patient scales.

Motor symptom assessment

The Unified Parkinson's Disease Rating Scale (**UPDRS**)[202] and Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (**MDS-UPDRS**)[203] scales were used in *Paper I* and *Paper II* respectively. UPDRS serves as a widely accepted tool for assessing impairment and disability related to Parkinson's Disease (PD). It comprises four key sections: Part I Evaluation of mentation, behavior, and mood; Part II Assessment of Activities of Daily Living (ADLs); Part III Examination of motor functions; and Part IV Identification of complications. Different questions are rated based on symptom severity in a scale from 0-4. Scores on this scale range from 0 to 199, with higher scores indicating

increased disability levels. Administering the UPDRS typically takes between 10 to 20 minutes when conducted by a clinician or researcher, although certain sections, such as mentation, behavior, mood, and ADLs, may be suitable for patients or caregivers to complete independently. In *Paper I* we evaluated Part III of the scale to follow motor symptoms and Part IV to evaluate treatment complications before and after safinamide treatment. MDS-UPDRS is a further development and more detailed version of the UPDRS that follows the same basic principles and was used in *Paper II*, when the validated Swedish version of the scale was available. We utilized item 4.1, that assesses the presence and degree of LIDs during the day, in the inclusion phase of patient enrollment to ensure the inclusion of patients experiencing LIDs. Items 3.3 (evaluation of rigidity) and 3.6 (evaluation of hand bradykinesia) were assessed before the challenge doses and every 30 minutes up to 5 hours after the challenge tests to ensure that patients transitioned from OFF to ON. In this study we have also utilized the Clinical Dyskinesia Rating Scale (**CDRS**)[204] that provides evaluations of dyskinesia presence and severity, distinguishing between hyperkinesia and dystonia, for each specific body part separately. This was a crucial distinction needed to describe dyskinesias as detailed as possible. The scale scores range from 0 to 4, where 0 signifies no hyperkinesia/ dystonia, 1 indicates questionable or mild hyperkinesia/ dystonia, 2 moderate hyperkinesia/ dystonia, 3 severe hyperkinesia/dystonia and 4 incapacitating hyperkinesia/ dystonia. Patients were video recorded at 30-minute intervals for up to 5 hours after a drug challenge while performing a series of tasks: (i) describing a picture while sitting; (ii) drinking from a cup; (iii) putting on and removing a lab coat; and (iv) standing up, walking 4.5 meters forward, turning 180 degrees, walking back, and sitting down again. Most patients completed each sequence in 2 to 4 minutes. Videos were reviewed independently by raters experienced in movement disorders and dyskinesia assessment after receiving training on CDRS. The raters were blinded as to which challenge dose was given in each video series. The highest severity score observed during each video recording session was documented for each body part (face, neck, trunk, arms, and legs) and the data were used to produce curves of hyperkinesia/ dystonia over time.

Assessment of NMS

Different rating scales that evaluate the presence and severity of NMS were utilized in *Paper I* and *III.* **NMSS**[205] is a comprehensive assessment tool utilized in PD to evaluate a broad range of NMS and was used in *Paper I*. It comprises of nine domains including questions about cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal tract, urinary, sexual function, and miscellaneous symptoms. The scale consists of 30 questions in total, allowing clinicians to systematically assess the frequency and severity of non-motor symptoms experienced by PD patients. **KPPS**[206] was used in *Paper I* in its English version, as it was not available in Swedish at the time. It is a specialized tool designed to assess pain in PD and consists of seven subdomains:

musculoskeletal pain, chronic pain, fluctuation-related pain, nocturnal pain, orofacial pain, discoloration and oedema, and finally radicular pain, and dystonic pain. The scale utilizes a rating system ranging from 0 to 3 for pain severity, with 0 indicating no pain, 1 representing mild pain, 2 indicating moderate pain, and 3 representing severe pain. This score is then multiplied by a frequency score (rated from 0-4 depending on how often the symptoms occur during a week) with a total score that can range from 0 to 168. The Hospital Anxiety and Depression Scale (**HADS**)[207] is a self-assessment questionnaire designed to measure the levels of anxiety and depression, and was used in *Paper I*. It consists of 14 items, with seven items targeting anxiety symptoms and the other seven focusing on depressive symptoms. Each item is scored on a scale from 0 to 3, yielding separate scores for anxiety and depression ranging from 0 to 21 for each subscale. Higher scores indicate higher levels of anxiety or depression. The HADS is widely used in clinical settings due to its brevity, ease of administration, and effectiveness in screening for anxiety and depression, including studies focused on PD. **PDSS-2**[208] is a patient completed rating scale that evaluates the frequency of sleep disturbances experienced over the previous week. It consists of 15 questions graded on a scale from 0 ("never") to 4 ("very often"), resulting in a score of 0-60, with scores ≥ 18 indicating clinically significant/ relevant sleep problems.[209] Subdomains can be derived summing different questions in groups: “motor problems at night” that combines items 4–6, 12 and 13, “PD symptoms at night” combining items 7, 9–11 and 15, and “disturbed sleep” with items 1–3, 8 and 14. The scale was applied in *Paper I* and *III* in order to follow-up the patients’ subjective experience of change in sleep parameters. **ESS** is a self-administered questionnaire designed to measure the level of daytime sleepiness and was used in *Paper III*. It consists of eight items that assess the likelihood of dozing off or falling asleep during different everyday situations that require passive observation. These situations include sitting and reading, watching television, sitting inactive in a public place, being a passenger in a car for an hour without a break, lying down to rest in the afternoon, sitting and talking to someone, sitting quietly after a lunch without alcohol, and being in a car stopped for a few minutes in traffic. For each situation, respondents rate their likelihood of dozing off on a scale from 0 to 3, with 0 indicating no chance of dozing, 1 suggesting a slight chance, 2 indicating a moderate chance, and 3 suggesting a high chance. After rating each situation, the scores are summed to obtain a total score, which can range from 0 to 24. Higher scores indicate greater daytime sleepiness and a total score of ≥ 10 is considered pathologic.

Quality of life

PDQ-8[210] is an 8-item, shortened version of the 39-item Parkinson’s Disease Questionnaire (**PDQ-39**)[167], that was developed to reduce the respondent burden and increase convenience for PD patients. The PDQ-39 comprises 39 questions from 8 dimensions which include mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort, and

PDQ-8 was developed by using only 1 question from each domain. It is a self-administered, PD-specific questionnaire, used to measure QoL, where patients have to answer on how often PD affected different aspects of their life during the last month assigning points from 0 (never) to 4 (always). The PDQ-8 was used in *Papers I & III* to assess QoL with higher total scores representing poorer quality of life. EuroQol-5D 3 level version (**EQ-5D-3L**)[211] and 5 level version (**EQ-5D-5L**)[212] were used in *Paper I* and *Paper III* respectively as instruments for assessing health-related QoL. They include five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels of severity in EQ-5D-3L (no problems, some problems, and extreme/ incapacitating problems) and five levels of severity in EQ-5D-5L (no, slight, moderate, severe, incapacitating problems). Respondents are asked to indicate their health state by selecting the most appropriate level for each dimension. The responses can then be converted into time trade-off index value (TTO) using specific value sets developed for each country. TTO index can take values between 0-1 with lower values indicating more severely affected QoL due to health issues.

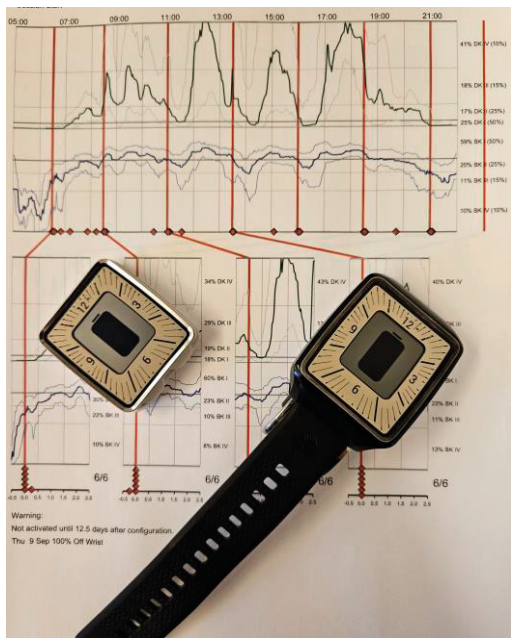
PD staging

The Hoehn & Yahr staging system (**H&Y**)[213] used in *Papers I & III* is a widely used method for assessing the progression of Parkinson's disease based on clinical features. It categorizes patients into five stages based on motor symptoms and impairment. Stage 0 corresponds to no clinical signs; in stage 1, symptoms affect only one side of the body and are mild; stage 2 involves bilateral involvement but with preserved postural reflexes; stage 3 marks the onset of impaired balance and coordination; stage 4 indicates severe disability but with the ability to walk and stand without assistance; and stage 5 represents a state of severe disability, often rendering patients wheelchair-bound or bedridden. This staging system provides clinicians with a simple and effective tool to measure disease severity and progression, aiding in treatment planning and prognosis assessment in PD patients. The Clinical Impression of Severity Index for Parkinson's Disease (**CISI-PD**)[214] is a scale used by clinicians to assess global severity in PD. The CISI-PD has been shown to be valid, reliable, and precise for assessing clinical impressions of PD severity in clinical practice and research. It includes various aspects such as motor signs, disability due to PD symptoms, motor complications (dyskinesia and fluctuations), and cognitive status. The scale is rated by a healthcare professional based on their clinical judgment and observations. Each item is scored on a scale from 0 to 6, with higher scores indicating greater severity. The total score ranges from 0 to 24 and PD severity can be classified as mild (1–7), moderate (8–14), and severe (≥15). The CISI-PD provides a comprehensive evaluation of the overall impact of Parkinson's disease on an individual's daily functioning and quality of life and has good correlations with both disease-specific (PDQ-8) and generic (EQ-5D) health related QoL assessments.[215] It was used in *Paper III* of this dissertation. The Clinical Global Impression (**CGI**) scale and Patient Global Impression (**PGI**) scales

capture clinician and patient impression about illness/symptom severity (**CGI-S** & **PGI-S**) using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients) and about change/improvement (**CGI-I** & **PGI-I**) after a treatment using again a range of responses from 1 (very much improved) to 7 (very much worse) and 4 corresponding to “no change”.

Parkinson’s KinetiGraph – PKG

The Parkinson's KinetiGraph (**PKG**) is a wearable device designed to objectively monitor motor symptoms in PD patients. It consists of a small, wrist-worn sensor that collects data on movement patterns continuously throughout the day. It utilizes accelerometry to measure and analyze various aspects of movement, including tremor, dyskinesia, bradykinesia, and fluctuations in motor function. Patients wear the device during their regular daily activities, and clinicians are provided with quantitative data on motor symptoms over an extended period of days (typically 6 days). The PKG report gives a measure of symptom severity and proportion of time spent at different levels of dyskinesia and bradykinesia, as well as an estimation of time with tremor and time that is spent in immobile state during the day.



Picture 2
PKG with wristband and PKG report from a patient with peak dose dyskinesia (photo by author)

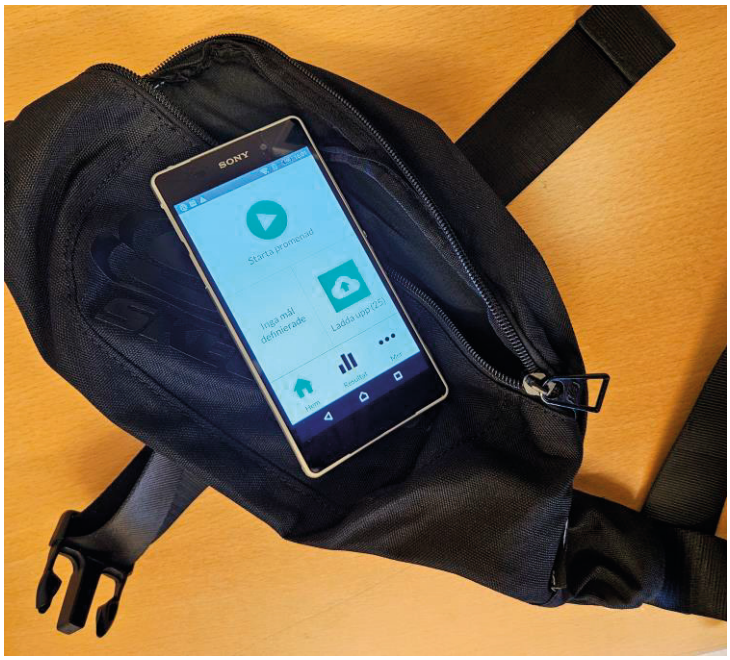
The main plot of the PKG report shows the median, 25% and 75% percentile of the bradykinesia score (BKS) and dyskinesia score (DKS) of the patient over all days of recording, while also depicting the medication timing. Fluctuation and dyskinesia score (FDS) is a summary score combining variations in bradykinesia and dyskinesia scores and is representative of motor complications. Percent Time with Tremor (PTT) is a summary score for the assessment of tremor and the Percent Time Immobile (PTI) represents the percentage of time the patient was totally immobile, helping to describe sustained immobility. This score has also been corelated with daytime sleep and somnolence.[216] Additionally, PKG has been utilized to provide an evaluation of night-time sleep in PD patients.[217] Combined sleep score (CSS) consists of a combination of other PKG sleep subscores and has been shown to correlate with PSG findings in regards of differentiating between normal or abnormal sleep.[218]

When it comes to daytime recording, the PKG produces a score every 2 minutes, and fifteen consecutive 2-minute periods are used to produce a smoothed moving average of bradykinesia and dyskinesia which is then averaged again over the same period from all registration days. While this design reduces the likelihood of atypical physical activity or inactivity biasing the scores produced, it limits the utility of the recording during short periods of time (few minutes) or when trying to look into specific timepoints. A recent study looking into the temporal agreement of PKG recordings using 30-minute periods and evaluation of motor status by clinical observers during the same time periods showed incongruous results.[219] PKG was utilized in *Paper II* to assess dyskinesia in connection to challenge tests with L-dopa and L-dopa/ ropinirole (but the data could not be utilized due to the limitations mentioned above) and in *Paper III* to assess sleep and daytime sleepiness.

Dyskinesia assessment by MedoClinic app

Several studies have tried to develop methods of assessing different aspects of PD symptoms such as bradykinesia, tremor, and dyskinesia using wearable sensors.[220-225] Furthermore, a set of different systems for monitoring PD motor patterns over longer time periods are commercially available, like PKG mentioned above. Capturing, though, reliable data that accurately represent the presence and degree of dyskinesia at specific, short, timepoints remains a challenge. In *Paper II,* sensor measurements were performed by using the "MedoClinic App" for mobile phones (MedoTemic, released 2018), that was developed in Lund, Sweden. The app collects accelerometer and gyroscope data captured by mobile phone sensors. A mobile phone, with the app installed, was placed in a waist bag that was fastened around the patients' trunk with a belt. A model for predicting and grading trunk hyperkinesia was developed with supervised machine learning. 3/4 of the patients were chosen as training data and the model was fed with the clinicians' ratings of

trunk hyperkinesia measured by CDRS and 1/4 of the patients were used as testing subjects for the model.



Picture 3
MedoClinic app on smartphone and waist bag (photo by author)

Statistical methods

All statistical analyses were performed using IBM SPSS Statistics for Windows, versions 26.0, 28.0 and 29.0. Armonk, NY: IBM Corp and GraphPad Prism, version 9.5.1. Descriptive statistics in the papers were presented with median and interquartile ranges (IQR) or mean and range or standard deviation. The statistical methods used in the papers are described below.

The ***Shapiro-Wilk*** *test* was used to test if the data followed a normal distribution. It is a hypothesis test used to assess whether a sample originates from a normally distributed population. By comparing the obtained p-value to a significance level, (typically 0.05), if the p-value is below this threshold, we reject the null hypothesis (being that the population follows a normal distribution), indicating that the sample does not stem from a normal distribution. The ***paired samples t-test*** was used to

compare means of variables with normal distribution (parametric test). It is a statistical method that can be used to compare the means of two related groups or conditions, in our case the same group of patients under two different conditions (before and after treatment intervention). The test determines whether there is a statistically significant difference between the means of these paired observations. For data without normal distribution the ***Wilcoxon signed-rank test*** was selected instead. It is a non-parametric statistical test used to compare two related samples, in this case, different variables before and after treatment in the same study group. It assesses whether there is a significant difference between the medians of paired observations. In *Paper III*, we have calculated the ***effect size "r"*** that provides information about the strength and direction of the relationship between the paired observations. It ranges from -1 to 1, where 1 indicates a perfect positive relationship, -1 indicates a perfect negative relationship, and 0 indicates no relationship. The significance level was usually set at 0.05 except when it needed to be adjusted to lower levels due to multiple comparisons. In that case the ***Bonferroni correction*** was applied. It is a method used to adjust the significance threshold for multiple comparisons in statistical analyses and is applied by dividing the desired significance level (usually 0.05) by the number of comparisons being made. This adjustment helps maintain a lower probability of committing a Type I error (false positive) when conducting multiple tests simultaneously.

Spearman rank correlation is a non-parametric measure of statistical dependence between two variables. It assesses the strength and direction of the monotonic relationship between two variables, which may not necessarily follow a linear pattern. Spearman's rank correlation coefficient is calculated based on the ranks (ordinal positions) of the data points. It ranges from -1 to 1, where 1 indicates a perfect positive monotonic relationship, -1 indicates a perfect negative monotonic relationship, and 0 indicates no monotonic relationship. It was used in *Paper I* to investigate the correlations between the baseline and follow-up differences in KPPS scores and UPDRS item 39 (percentage time in OFF) to see if the changes depended on change in OFF time or not. It was also used in *Paper III* to investigate correlations between PKG parameters and rating scales, more specifically PTI_D (percentage time immobile during the day) and ESS, as well as between PDSS-2 and CSS.

The more demanding statistical analysis was the one conducted for *Paper II*. The patients participating in the study received two different challenge doses (one with L-dopa alone and an equipotent dose of L-dopa/ ropinirole on a different day) and we recorded videos at different timepoints while the patients performed different predetermined motor tasks. The video recordings were then reviewed by two clinicians that rated the presence and degree of hyperkinesia and dystonia in different body parts. Both raters were trained on CDRS (the scale used for the rating), but some disparity is always to be expected. To investigate the consistency of the ratings between the two raters we used the ***Intraclass correlation coefficient (ICC)***. It is a descriptive statistical measure used to assess the reliability of

measurements taken by different raters/ observers on the same subjects. It quantifies the proportion of total variance in the data that is due to differences between the subjects, as opposed to differences between the measurements themselves and reflects both the degree of correlation and agreement between measurements. ICC values range from 0 to 1, where higher values indicate greater agreement among the measurements. In order to investigate differences in the time course of dyskinesia between the challenge tests a ***two-way mixed effect ANOVA*** was applied. It is a statistical method used to analyze the effects of two independent variables (in our case time and treatment, two-way) on an outcome variable - CDRS score, while also considering both within-subject and between-subject variability. The "mixed effects" part indicates that the model includes both fixed effects (which represent systematic differences due to the experimental design, e.g., timing of evaluation and medication type) and random effects (which account for variability between participants, e.g., demographic characteristics, baseline dyskinesia severity, factors that can affect response to medication). This type of ANOVA is particularly useful for study designs where there are both within-subject and between-subject factors, such as repeated measures designs. It allows the examination of the overall impact of each factor as well as interaction effects (how the combination of factors influences the outcome). When we looked into differences in the total CDRS score for hyperkinesia and dystonia as a sum of all timepoints after the two challenge tests, we used the ***Kruskal-Wallis test***. Without the need to investigate repeated measures we could use this non-parametric test that performs a rank variance analysis and is the equivalent of the parametric one-way analysis of variance (ANOVA). ***Dunn's test for multiple comparisons*** was then used to compare scores in different body parts to each other after finding a significant result in the Kruskal-Wallis test. This test calculates adjusted p-values for each pair compared to determine whether the differences observed are statistically significant.

Results

Effects of safinamide on pain in patients with fluctuating Parkinson's disease (Paper I)

The demographic and clinical characteristics of patients included in the final analysis of the study are presented below (**Table 1**).

Table 1
Patient demographic and clinical characteristics

Patient characteristic			Range
Age (years)	Mean:	65	38-87
Gender	Male:	22	
	Female:	5	
PD duration (years)	Mean:	6.8	1-20
H&Y	Median:	2.5	1-4
LEDD, mean (mg)	Baseline:	963	400-1890
	Follow-up:	955	

Most study participants were male (22 of 27), which is partly explained by the fact that PD prevalence is higher in males,[226] and it was a result of the recruitment of consecutive patients at the outpatient clinics. The results should therefore be interpreted cautiously in that aspect. LEDD remained virtually unchanged through the study (mean follow-up time was 6.6 months) and patients that were initially recruited but had major medication changes during the study (e.g., addition of new antiparkinsonian medication besides safinamide) were excluded. We can thus assume that the results reflect effects of safinamide treatment.

As a first step we investigated the effects of treatment on NMSS, a scale that encompasses a wide variety of NMS and is described in detail in "Methods" above. The total NMSS score reduced slightly from 60.6 at baseline to 57.1 at follow-up, and this improvement was not statistically significant (p=0.29), nor could we detect a significant change in any of the scale's subdomains or separate items. A slight numerical improvement from 14.8 to 13.8 was noted in the total score of PDSS-2 that assesses sleep disturbances, but the change was not statistically significant either (p=0.35). HADS score for depression and anxiety, PDQ-8 and EQ-5D-3L did not exhibit any significant changes.

In the next step we looked into the effects on pain measured by KPPS. The total KPPS score improved by approximately one third at follow-up (31.1%) from 18.0 at baseline to 12.4 (p=0.02). Looking more closely into the different subdomains of the scale, the improvement in total score seemed to be driven primarily from changes in domain 1 (musculoskeletal pain), domain 3 (fluctuation-related pain) and domain 4 (nocturnal pain). Of these, domain 3 showed a statistically significant improvement from a mean of 5.1 to 2.1 (p= 0.02). Looking into all KPPS items separately, revealed trends of improvement in most items, but only item 5 (OFF dystonia in a specific region) improved significantly. **Figure 4** displays the baseline (blue) and follow-up (red) scores of the different KPPPS domains and total score.

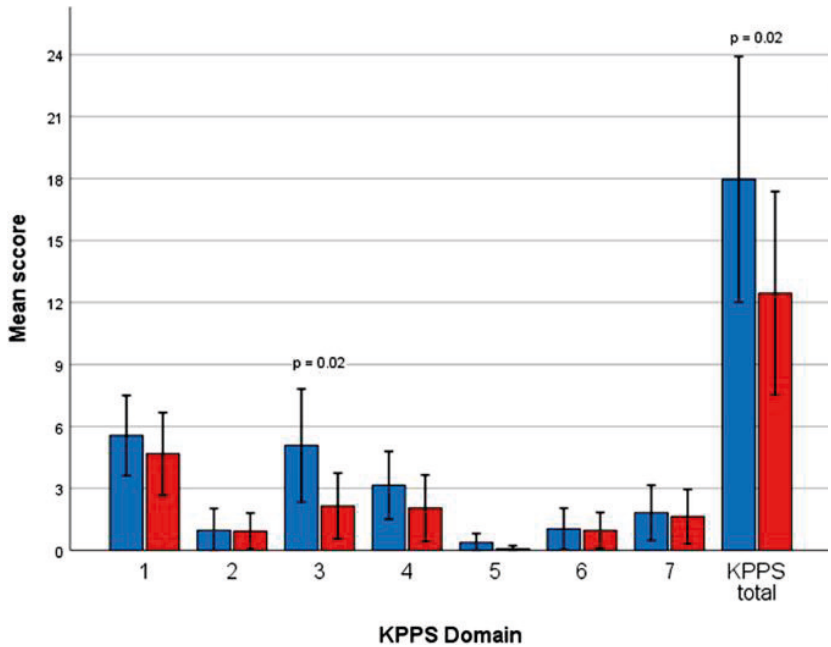


Figure 4
Changes in KPPS domains and total score. Error bars represent 95% confidence interval

UPDRS part III (motor examination) was performed in ON state at baseline and follow-up and no changes were apparent. On the other hand, UPDRS part IV (complications of therapy) improved significantly from 5.0 to 4.1 (p=0.04), with improvements noted in all 3 subdomains of part IV, but not reaching statistical significance in any subdomain separately. Next, we wanted to explore whether the improvements seen in KPPS item 5, KPPS domain 3 and total KPPS score were correlated to the difference in UPDRS item 39 that represents improvement in OFF

time. All pair analyses performed showed low levels of correlation with Spearman's correlation coefficients between 0.16 - 0.23. Lastly, when looking into clinicians' (CGI-C) and patients' (PGI-C) general perspective of change in patients' condition after treatment, positive trends were also noted. Improvement was experienced by both clinician and patient in ten cases, worsening in five cases, and no change in seven, while discrepant results were found for the rest. To summarize, total pain improved significantly, and this effect did not seem to exclusively arise by the reduction of OFF time. While the other NMS did not improve and remained mostly stable, it could be seen in a positive light, considering that PD is a progressive neurodegenerative condition with disease burden accumulating over time.

Comparison of dyskinesia profiles after L-DOPA dose challenges with or without dopamine agonist coadministration (Paper II)

This was probably the paper with the most strenuous data analysis, as we utilized the big amount of generated data in many different ways leading to the results described below. We started by analyzing the results from the CDRS evaluations on the video recordings of the 25 patients included in the final analysis. The patients were filmed as mentioned above before each challenge dose and at 30-minute intervals up to 5 hours, by two raters that were blinded in regard to given medication. The most severe dyskinesias during all motor tasks in each video recording were registered. A high degree of reliability was found between the two raters' measurements with an ICC at 0.801 ± 0.01 ($p < 0.001$). We could thus use the mean CDRS score of the two raters for each body part and timepoint for the final statistical analysis. Data on participants' demographic and clinical characteristics are shown in **Table 2**.

Table 2
Patient demographic and clinical characteristics

Patient characteristic			Range
Age (years)	Mean:	68.2	48-81
Gender	Male:	13	
	Female:	12	
PD duration (years)	Mean:	10.6	5-23
Dyskinesia duration (years)	Mean:	4	0.5-9
LEDD (mg)	Mean:	1115	486-2218
L-dopa, daily dose (mg)	Mean:	736	250-1400

Before the analysis of dyskinesias we wanted to confirm that the two equipotent challenge doses of L-dopa (LD) and L-dopa + ropinirole (LD+R) resulted in similar motor improvement. To ensure this study personnel performed on site MDS-UPDRS assessments on items 3.3 (rigidity) and 3.6 (hand pronation-supination) through all timepoints at both challenges. The mixed effect ANOVA analysis did not reveal any significant difference between the two challenges regarding the time course or degree of improvement of rigidity and bradykinesia (**Figure 5**). Maximal improvement was observed at 60- and 90-minutes post dose for both LD and LD+R.

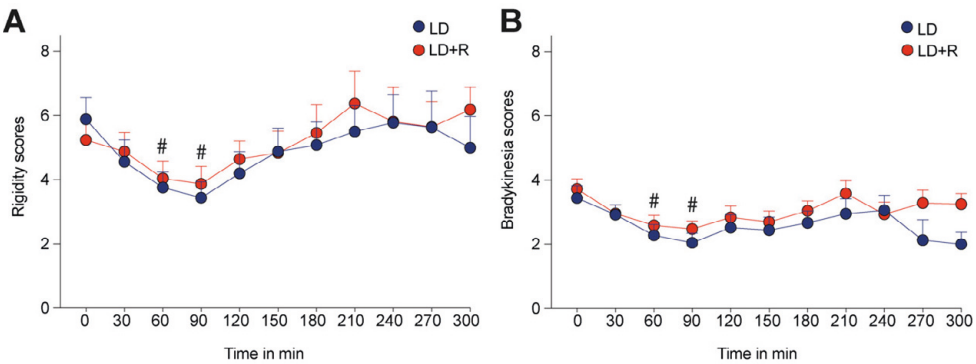


Figure 5
Time course of rigidity (A) and bradykinesia(B) after LD challenge (blue) and LD+R challenge (red). # p<0.05 vs 0 min for both LD & LD+R.

As a next step, we looked separately into the time courses of dystonia and hyperkinesia after the two challenge tests, using the sum of CDRS scores for all body parts at each timepoint. Mixed effect ANOVA revealed different time courses (time-treatment interaction) for the two challenges for both hyperkinesia, F(interaction)= 2.911, p = 0.002, and dystonia, F(interaction)= 2.275, p = 0.0152. Inspection of the time curves shows a sharper, higher peak phase (60-120 min) after LD with a blunter peak with slower decline after LD+R and a higher level of end phase (240-270 min) dyskinesias (**Figure 6 A, B**). Based on Wilcoxon test the peak phase hyperkinesia (sum of CDRS scores of 60-120 min) after LD was significantly higher than after LD+R, with a median CDRS value of 18 for LD *vs.* 13 for LD + R, p = 0.026 (**Figure 6 A´**). The trend of higher dystonia scores in the end phase after LD+R was not statistically significant, p = 0.0605 (**Figure 6 B´´**).

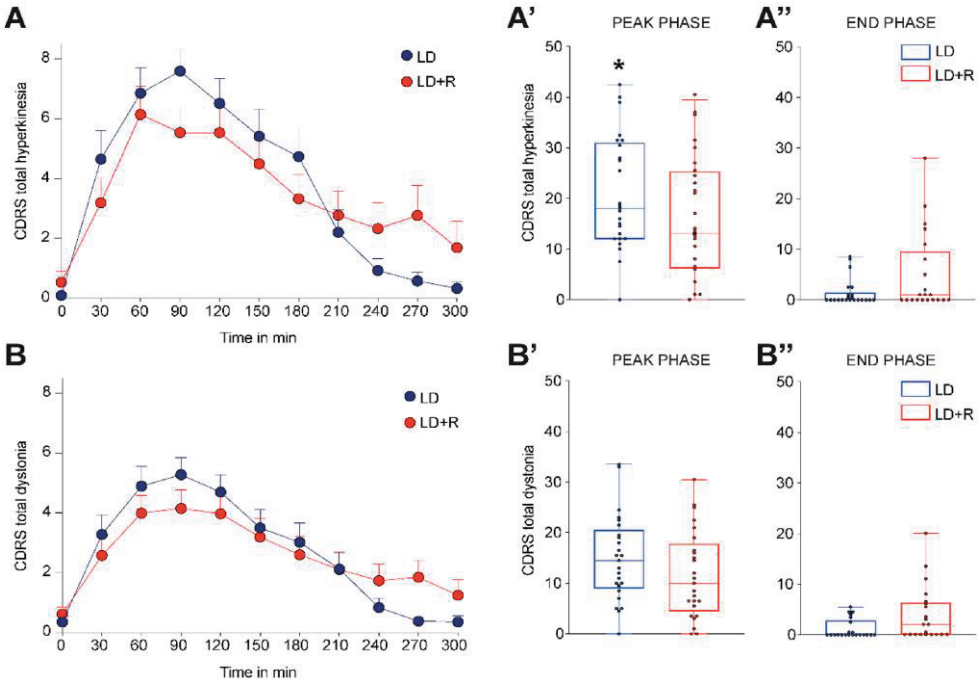


Figure 6
Time course of hyperkinesia (A) and dystonia (B). Scores on Y-axis represent sum of scores for all body parts (total CDRS). Peak phase (A´, B´) represents the sum of total CDRS score through 60-120 min and end phase (A´´,B´´) the sum of total CDRS score through 240-270 min. * p< 0.05.

Subanalyses for the temporal profiles of hyperkinesia and dystonia were then conducted using the same methodology for each body part separately. The time curves produced represented closely those of total hyperkinesia and dyskinesia presented above, with more severe peak phase dyskinesias for LD and more pronounced end phase dyskinesias after LD+R. The comparisons of peak and end phases between the two challenges revealed significantly higher levels of peak phase hyperkinesia and dystonia in the legs after LD compared to LD+R, $p = 0.0305$ & $p = 0.0181$ respectively. On the other hand, end phase dystonia was significantly higher in the arms after LD+R compared to LD. No significant differences in peak or end phase were noted in the temporal analyses of hyperkinesia and dystonia in the neck and trunk, but significant differences in the temporal profiles of dyskinesias between LD and LD+R were noted, except for neck dystonia.

Following these results, we looked into the topographic profile of dyskinesias by summing the CDRS score for each body part through all timepoints and comparing the results between different body parts after each challenge. Both challenge doses resulted in more severe dyskinesias in the extremities compared to trunk and neck. The difference reached statistical significance after administration of LD for leg

hyperkinesia (Kruskal-Wallis test: KW = 88.98, $p < 0.0001$ & Dunn's multiple comparison test $p < 0.05$ vs each hyperkinesia in trunk and neck) and for leg dystonia ($p < 0.05$ vs each dystonia neck, trunk, and arms). After LD+R administration, dystonia scores in arms and legs were significantly higher compared to dystonia in the trunk and neck (Kruskal-Wallis test: KW = 63.98, $p < 0.0001$ & Dunn's multiple comparison test $p < 0.05$ vs each dystonia trunk and neck). We conclude, thus, that LD resulted mainly in leg dyskinesias compared to other body parts while LD+R resulted in more comparable dystonias in the legs and arms that were significantly more severe than axial dystonias.

Finally, we conducted an analysis based on the accelerometer/ gyroscope data registered by the MedoClinic app. Using machine learning, we developed a model that could accurately predict the presence and severity of trunk hyperkinesia, with a high level of correlation with the raters' CDRS evaluations (mean Pearson correlation coefficient 0.829; p-value <0.001). The model could, after the initial training, provide accurate assessments based on very short periods of registration, of about 20-30 seconds, while the patients were sitting in a chair and described a picture and pretended drinking from a cup (2 of the 4 motor tasks performed during the video recordings of the patients), **Figure 7**.

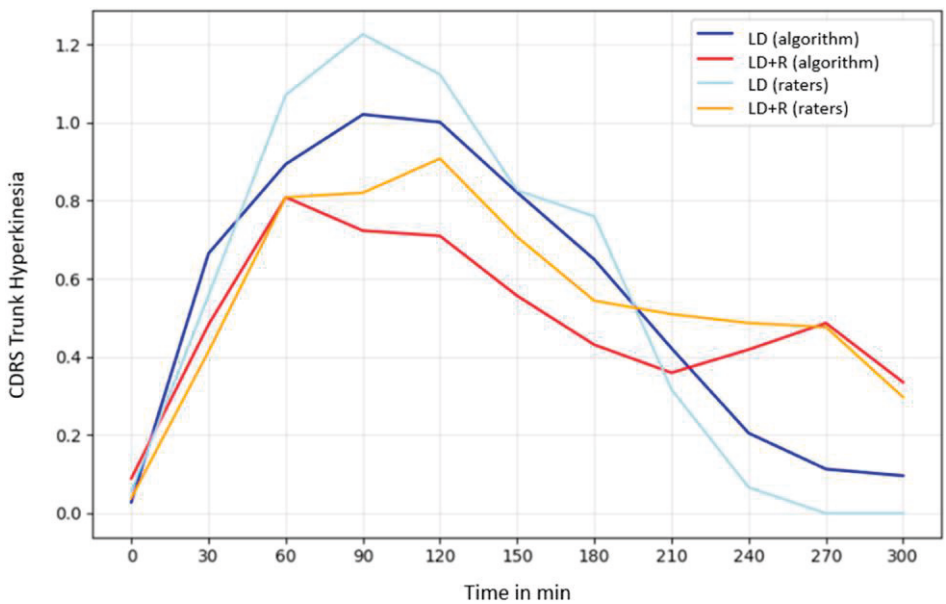


Figure 7
Trunk hyperkinesia assessed by raters according to CDRS and by the developed model/ algorithm after the two challenge doses (LD & LD+R).

Finally, both challenge doses were well-tolerated but resulted in more pronounced dyskinesias compared to the patients' routine dyskinesia levels. This is to be expected as the challenge doses were designed to be 1.5 times more potent than the patients' usual morning L-dopa dose. 3 patients could not complete the evaluations after 210 min following L-dopa (LD) administration and 4 patients following L-dopa/ ropinirole (LD+R) due to severe OFF. Additionally, 2 DA naïve patients experienced nausea after LD+R challenge and could not perform the evaluations at 60 and 90 min.

Effects of rotigotine on sleep in Parkinson's disease patients: A Parkinson's Kinetigraph study (Paper III)

The demographic and clinical characteristics of patients included in the final analysis of the study are presented below, **Table 3**. The different parameters are presented as mean with range of values in parentheses, or median with interquartile range (IQR). 32 patients were included in the final analysis.

Table 3
Patient demographic and clinical characteristics

Patient characteristic	
Age, years (mean, range)	67 (50-82)
Gender	Male: 21 Female: 11
PD duration, years (mean, range)	5 (0-14)
LEDD, mg (mean, range)	783 (120-1983)
H&Y stage (median, IQR)	2 (2-2)
CGI-S for sleep at baseline (median, IQR)	4 (4-5)
PDSS-2 total score at baseline (median, IQR)	17 (13-24)
Rotigotine maintenance dose, mg (mean, range)	5 (4-8)
Total time on rotigotine, days (mean, range)	29 (16-49)

Nighttime sleep was first assessed by PDSS-2 before and after treatment. A trend for numerical improvement was observed, from a median score of 17 (IQR:13-24) to 13 (IQR:11-24) post treatment, but the difference was not statistically significant ($p= 0.13$, $r= -0.19$). Looking separately on the PDSS-2 questions, the only item that improved significantly ($p= 0.02$, $r= -0.29$) was PDSS-2 item 14 that represents sleepiness after waking up, which improved from a median of 2 (IQR:1-3) to 1 (IQR:1-3). No significant change was noted for any PKG nighttime parameters, more importantly CSS that is reported to reflect sleep quality. While most patients experienced at least moderate sleep problems at baseline, CGI-S ≥ 4 (29 patients, 91%), median PDSS-2 total score was measured at 17 at baseline, which lies below the suggested cut-off (PDSS-2 ≥ 18) for clinically significant sleep problems (15

patients with PDSS-2 ≥ 18 at baseline) [209]. Next, we tried to see if statistically significant changes could be noticed in the patients with clinically relevant sleep disturbance according to PDSS-2. Within this subgroup, there was notable improvement in PDSS-2 sub score for disrupted sleep (sum of items 1, 2, 3, 8, and 14), with the median decreasing from 13 (IQR:11.5-14.5) to 8 (IQR:8-13), p= 0.013. Similarly, PDSS-2 subscore for PD symptoms during nighttime (sum of items 7, 9, 10, 11, and 15) also showed a significant improvement, with the median decreasing from 5 (IQR:4-8.5) to 4 (IQR:2.5-7), p=0.041. An explorative subgroup analysis showed of DA-naive patients revealed a significant improvement in total PDSS-2 from a median of 17.5 (IQR:13-25) to 12.5 (IQR:10-23), p=0.013. We did not observe any significant change for patients with a previous history of oral DA use. The median score on CGI-S regarding sleep improved though from 4 to 3, p<0.001, r = -0.51 after treatment with rotigotine. Daytime sleepiness was firstly evaluated by using ESS; the total ESS score remained unchanged after rotigotine treatment. Baseline and follow-up values of PDSS-2 and ESS are shown in **Figure 8**.

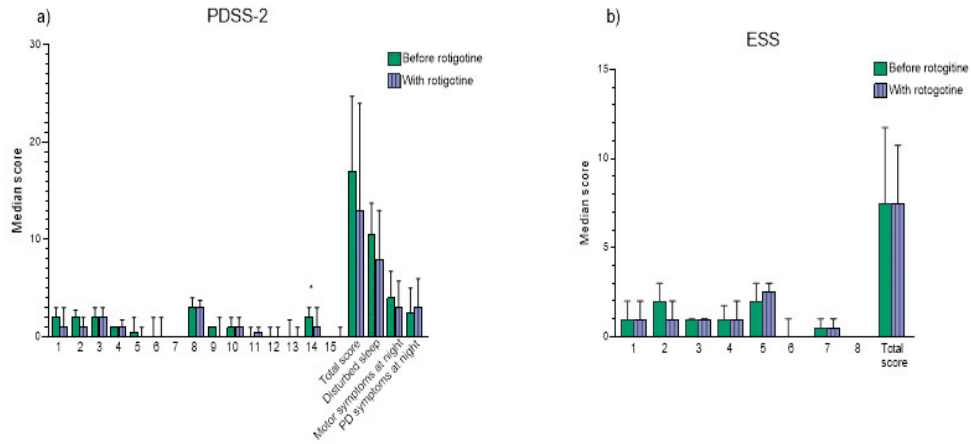


Figure 8
Median PDSS-2 and ESS scores of all patients, before (green) and after (purple) treatment with rotigotine. Error bars represent IQR. * p< 0.05

Based on Wilcoxon signed rank test of PKG data, PTI_D (Percentage time immobile during the day), showed a significant improvement from baseline (median PTI_D score 10, IQR:5-14) to follow-up (median PTI_D score 6, IQR:3-7), p< 0.001 r= -0.56. 12 patients transitioned from abnormal to normal PTI_D score (target score ≤10). PTI_D and other daytime PKG scores before and after rotigotine treatment are depicted in **Figure 9**. PTT (Percentage time tremor) improved after treatment; baseline median score of 2.1 (IQR:0.9-9.2) reduced to 1.7 (IQR:0.7-4.8), p<0.001,

r = -0.42. Median dyskinesia score (mDKS) and percent time in dyskinesia (PTD) increased after rotigotine treatment; mDKS from 0.95 (IQR:0.5-2) to 1.6 (IQR:0.7-2.7), p = 0.001, r = -0.40, and PTD from 1.7 (IQR:0-6.7) to 3.7 (IQR:0.6-12.7), p = 0.016, r = -0.30. Both parameters, though, remained in in very low, not clinically significant levels.

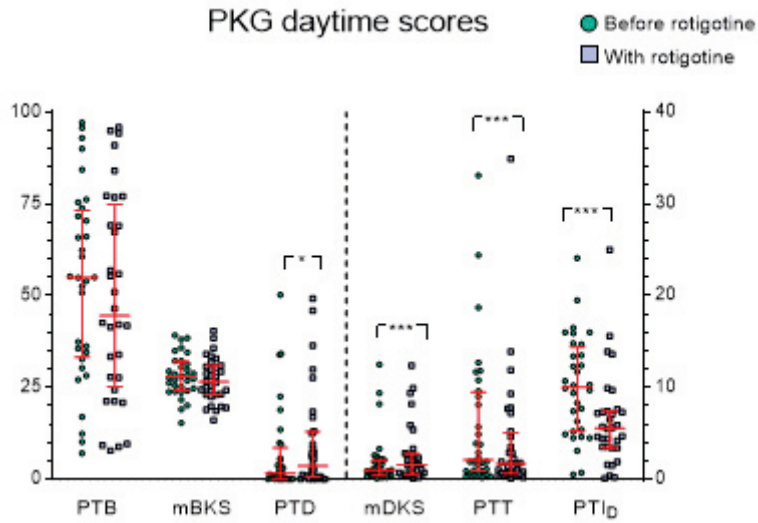


Figure 9
PKG daytime scores before and after rotigotine treatment. Median values are presented, and error bars represent IQR. Green circles indicate scores before rotigotine treatment, while purple squares indicate scores with rotigotine treatment. The left side of the figures is separated by a dotted line and corresponds to the left Y axis, while the right side relates to the right Y axis. Statistical significance is denoted as *p< 0.05, ***p< 0.001, calculated using the Wilcoxon signed rank test. r = effect size. **(a)** Daytime PKG scores, assessed from 09:00 to 18:00, include the following parameters: PTB = percent time in bradykinesia, mBKS = median bradykinesia score during daytime, PTD = percent time in dyskinesia, mDKS = median dyskinesia score, PTT = percent time in tremor, and PTI_D = percent time immobile during daytime.

Reflecting the motor improvement seen in PKG scores, median CISI-PD total score improved from 7 (IQR:4-9) to 5.5 (IQR:6-14), p<0.001, r = -0.45. More specifically, there was a reduction in motor signs according to question 1, p=0.001, r = -0.43 and in motor complications according to question 3, p<0.001, r = -0.41. Improvements were also seen in QoL. Median PDQ-8 score improved from 9.5 (IQR:6-13) to 7.5 (IQR:3-12), p= 0.014, r = -0.31, particularly in terms of decreased feeling of depression (item 3 on PDQ-8, p= 0.007, r = -0.33). The median EQ-5D-5L Time Trade Off (TTO) improved from 0.79 (IQR:0.7-0.9) to 0.84 (IQR:0.8-0.9), p=0.002, r = -0.38.

Spearman rank correlation test did not reveal any significant correlations between total PDSS-2 and CSS (ρ= -0.065, p = 0.612), but a fair negative[227] correlation (ρ = -0.325, p = 0.009) was noticed between CSS and PDSS-2 question 2 (difficulty falling asleep, sleep-onset insomnia). There was no significant correlation between ESS and PTI_D (ρ= 0.046, p = 0.718), leaving the question of whether the improvement in PTI_D represents reduced daytime somnolence or just reduced immobility during the day open.

Reported side effects of rotigotine included nausea (4, 12.5%), headache (1, 3%), tremor deterioration (1, 3%), skin irritation/rash (3, 9%), and dyskinesia (1, 3%).

Discussion

In the papers included in this thesis we have evaluated the effects of different add-on treatments in PD patients. We have looked into both motor and non-motor symptoms in *Papers I & III*, investigating the results of safinamide and rotigotine treatment, and focused on dyskinesia phenomenology in *Paper II*, where we assessed the role of ropinirole.

Effects of safinamide in motor and non-motor symptoms

The positive effect of safinamide add-on treatment in motor symptoms is well described by early[161-163, 166] and recent[228] placebo-controlled, randomized studies that included mid- to late stage, fluctuating PD patients. Recent post-hoc analyses[229-232] have reported improvements of motor symptoms and ON time after safinamide add-on. In our study we could also see a significant improvement in UPDRS part IV, that reflects motor complications, in alignment with these studies. On the other hand, we could not detect a significant improvement in UPDRS part III in our study, a finding that agrees with Bhidayasiri at al.[231] that detected UPDRS part III improvement only in Asian but not in Caucasian patients. A recent big European observational study[232] across 6 countries, with repeated follow-up evaluations during 12-month safinamide treatment, reported also stable UPDRS III scores. Most studies referenced above though, as well as a recent meta-analysis[233] reported improvements in UPDRS III for safinamide compared to placebo. It should be acknowledged that in our study, even though all UPDRS evaluations were performed with the patients in the ON state, the timing of the evaluation during the day was not always the same, which may have influenced the results. Regarding motor complications and more specifically dyskinesias, we observed a stable (slightly improved, but not statistically significant) score in UPDRS IV- part A, meaning that safinamide did not exacerbate dyskinesias. This finding is in accordance with the results reported in the recent post-hoc analyses.[229, 230, 234] Excessive glutamate signaling has been suggested as a key factor in dyskinesia pathophysiology,[235] and hyperactive glutamatergic neurotransmission, has been reported in patients with LIDs.[236] Safinamide's unique combination of action with MAO-B inhibition and antiglutamatergic properties may explain the fact that while increasing the total LEDD in our study (with other antiparkinsonian remaining

stable) by adding safinamide, no worsening of dyskinesias was observed. According to the results of the meta-analysis by Abdelalem et al.,[237] that included all randomized controlled studies on safinamide between 2004-2016, safinamide demonstrated a good safety profile and was well-tolerated, besides resulting in motor improvement. Interestingly, the Belgian safinamide study group reported in 2023 that switching from rasagiline to safinamide resulted in improvement of wearing-off fluctuations; further support, though, on this finding is lacking in the literature.[238] Safinamide seems thus to be effective in improving motor symptoms and fluctuations, with minimal risk of worsening or inducing dyskinesias and other unwanted side effects. Switching from other MAO-B inhibitors, even overnight, has been reported to be safe and well-tolerated.[239]

In *Paper I* we could not detect any significant improvements in NMSS & PDSS-2 total score, and in HADS for depression and anxiety. Prior to our study, Liguori et al.[240] reported significant improvements in sleep (PDSS-2) and daytime sleepiness (ESS), while Bianchi et al.[241] reported improvement in NMSS, but not in PDSS and HADS. Improvements in mood were reported in the meta-analysis by Abdelalem et al., mentioned above.[237] The SAFINONMOTOR study[242] published the same year as our study also reported positive results in total NMS burden, as measured by NMSS, and later the same group reported improvements in sleep and daytime sleepiness as well as in mood (measured by Beck Depression inventory, BDI).[243] One year later, the VALE-SAFI study[174] reported improvements in total NMS burden and sleep, but not daytime sleepiness and depression. A post-hoc analysis of the Japanese safinamide study that was published in 2022,[244] reported positive effect in mild depression. Most studies converge to the conclusion that safinamide has a positive effect on total NMS burden, in contrast to our findings. This can possibly be explained by the difference in baseline characteristics of the included patients, as most of the studies reporting improvement included patients with substantially higher NMSS scores at baseline compared to our study population. This can indicate that safinamide's effect on NMS may be more evident in patients with more severe baseline NMS. The results about sleep, depression, apathy, fatigue, and other NMS [175, 244-246] seem to vary more between the different studies, with some reporting improvements and other not. The positive effects of safinamide noted in NMS where the role of excess glutamatergic activity seems to be implicated, like depression[247] and sleep-wake cycle disorders,[248] might also arise from its non-dopaminergic mechanism of action.

On the other hand, all studies looking into the effect of safinamide on pain in PD seem to agree about its positive effect. Already in 2014 Borgohain et al.[166] and later Cattaneo et al[169] reported improvements in pain-related PDQ-39 items, and reduction in the use of analgesics after safinamide treatment.[169, 170] Studies looking into pain, using pain-specific rating scales, like KPPS, started to emerge later. A small study including 13 patients[171] with chronic pain reported lower (about 50%) total KPPS score 3 months after treatment initiation. In our study we report a 31%

reduction of total KPPS score, with the most evident improvement in KPPS domain 3, fluctuation related pain, after 6 months. During the same time period the results of SAFINONMOTOR study about pain were published,[172] where an almost 50% reduction of total KPPS score was seen with statistically significant improvements in almost all subdomains, excluding chronic pain (and orofacial pain, but with very low baseline pain levels). The latest studies looking into pain using KPPS,[175, 176], did not report any significant changes in total score, but the latter,[176] used safinamide at a dose of 50 mg. The post-hoc analysis of the Japanese phase 2/3 study[244] reported, in accordance with our findings, significant improvement of OFF pain after adjunct safinamide treatment, which was at least partially connected to an improvement in depressive symptoms. In our paper, we could moreover show that the improvement in fluctuation related pain did not solely depend on the reduction of OFF time.

Finally, the improvements in motor and non-motor symptoms described above can be reflected in the improvements in PDQ-39 and other QoL-related measures reported by many of the studies presented above, with metanalyses and reviews[237, 249, 250] confirming these results. Recently, a European Delphi panel consisting of movement disorder specialists from seven countries concluded with > 80% level of agreement after literature review, that safinamide can improve NMS, mainly sleep, mood, and pain and improves short- and long-term measures of QoL in PD.[251]

It should be acknowledged that most patients included in our study were male and the results should be interpreted cautiously in this regard. The patient inclusion was conducted in two sites (Lund, Sweden and Dresden, Germany) and no validated versions of the KPPS were available in Swedish and German at the time. The English version of the scale was used, which can also be considered a limitation as the raters had to translate the questions and conduct the interview, introducing thus a factor of variation that we tried to compensate by having the same rater at each visit. Lastly, every observational study has the obvious limitation of the absence of a placebo control group, and this should be acknowledged especially regarding pain that is a symptom especially prone to placebo effect.

The amounting evidence, to which our paper contributed, about the positive effects of safinamide in motor symptoms and QoL suggests that it is an attractive choice in fluctuating PD patients. Furthermore, its reversible MAO-B inhibition, that allows easier coadministration with antidepressants,[252] the favorable side-effect profile, its antiglutamatergic properties connected with NMS (and particularly pain) improvement, and the ability to switch simply (even overnight) from other MAO-B inhibitors, advocate its use; even in patients that have previously tried other MAO-B inhibitors or those who suffer from PD-related NMS.

Add-on treatments and dyskinesia

Normal dopamine transmission involves the release of dopamine from presynaptic dopaminergic terminals that then binds to postsynaptic dopamine receptors, exerting its effects on downstream neurons. Additionally, there is a process of autoregulation, where dopamine binds to presynaptic D2 autoreceptors, inhibiting further dopamine release when levels are sufficient. Excess dopamine is reuptaken by the dopamine uptake transporter (DAT), thereby maintaining a proper level of dopamine in the synapsis. In individuals without PD, striatal dopamine receptors are consistently activated. In PD on the other hand, there is progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), leading to a reduction in striatal dopamine levels. This depletion disrupts normal dopamine transmission, resulting in motor symptoms characteristic of PD. When L-dopa is administered, it serves as a precursor for dopamine synthesis, temporarily replenishing dopamine levels. In early PD, the remaining dopaminergic neurons have the capacity to store the surplus exogenous dopamine introduced by L-dopa doses, thereby reducing fluctuations in dopamine levels.[253] However, as the disease progresses, the capacity for autoregulation is impaired due to the continuing loss of dopaminergic neurons (leading to inability in properly storing and releasing dopamine). As a result, L-dopa administration leads to pulsatile stimulation of dopamine receptors, causing fluctuations in synaptic dopamine levels that resemble plasma L-dopa concentrations. Furthermore, alterations in dopamine receptor expression and sensitivity are observed due to chronic dopamine loss, mainly increased expression of D1 and D3 receptors and dopamine receptor sensitization.[254] Exogenous L-dopa is moreover metabolized in serotonergic and noradrenergic terminals that express AADC. However, these neurons lack the autoregulatory mechanisms of the dopaminergic terminals, which leads to even more abnormal and irregular dopamine release contributing to dyskinesia development. Hyperactive glutamatergic neurotransmission has also an important role dyskinesia pathophysiology as mentioned above,[235, 236] which is also supported by the fact that glutamate receptor antagonists (e.g., the NMDA-antagonist amantadine) are effective in LID treatment. These pathophysiological processes described above contribute to motor fluctuation and dyskinesia development, commonly observed in PD patients in later stages.

Dyskinesias were previously thought to be caused by chronic L-dopa administration, but this belief has been reassessed after studies[93] showing that they are more closely related to disease progression and total L-dopa dose than the duration of L-dopa treatment. Delaying use of L-dopa to prevent the development of dyskinesias may not be a justifiable treatment strategy, particularly considering its more potent antiparkinsonian effect compared for example with DAs and MAO-

B inhibitors. Avoiding high L-dopa doses, when possible, by adding DA, COMT or MAO-B inhibitors can ameliorate dyskinesias.[255]

The results of our study presented in *Paper II* support this notion. We observed a higher degree of peak-phase dyskinesias (primarily hyperkinesias) when L-dopa was administered as monotherapy and a steeper transition of dyskinesias between ON and OFF phase. Replacing 50% of L-dopa with an equipotent dose of ropinirole resulted in a smoother dyskinesia curve with lower peak-phase dyskinesias. This suggests that partially replacing dopaminergic stimulation with a D2/3 agonist could have a positive impact on the severity of peak phase dyskinesias. Adding a DA can facilitate the ability to maintain lower L-dopa doses, and consequently smoother pharmacokinetics and medication responses, which may also have a positive effect in diphasic dyskinesias, as literature suggests.[256]

As mentioned in the literature review, the importance of D2 and D3 receptors in dyskinesia has recently been highlighted in animal models of PD. While the role of D1 and D3 receptors and their interactions[123, 257-259] is widely recognized in dyskinesia development, D2 receptors were thought to be less significant. A recent study in a PD mouse model has found that D2 agonists modulate LIDs[260] and Andreoli et al. suggested that they mediate predominantly dystonic components.[122] To our knowledge, our study (*Paper II*) is the first of its kind, documenting the phenomenology of dyskinesias after L-dopa & DA coadministration in PD patients. We could indeed observe that besides the differences in time course of dyskinesias, the phenomenology and body distribution differed, with the DA add-on leading to more severe arm dystonia in the end phase and comparable dystonia levels in the arms and legs. In contrast, L-dopa resulted in more pronounced dyskinesias in the legs. A recent study[124] on 6-hydroxydopamine-lesioned rats found that cotreatment with ropinirole altered LID-related neuroplasticity and pharmacological response of LIDs to different antidyskinetic agents.

Currently, in studies aiming to develop antidyskinetic agents, it is a common practice to utilize suprathreshold L-dopa challenge tests. Considering the frequent use of adjunct DA agonist treatment in patients with motor complications, the differential expression of D1-like and D2-like dopamine receptors in the basal ganglia,[261] and the results of recent animal studies presented above as well as our own study, a drug challenge test combining a lower dose of L-dopa with a DA agonist might be better aligned with the clinical reality, possibly providing a larger chance to identify effective interventions in clinical trials. This is particularly important as dyskinesias can be debilitating and affect QoL negatively, while treatment choices are scarce and new antidyskinetic agents are much needed. We suggest that the role of add-on DAs should be accounted for when examining the underlying mechanisms of dyskinesia and potential interventions, both in clinical studies and experimental research contexts.

Dyskinesia monitoring: diary, rating scales and wearables

Dyskinesias are commonly underreported by PD patients and many factors may underly this phenomenon. Dyskinesias may be mistakenly described as other core features (mostly tremor), may not be perceived as equally bothersome to other symptoms (e.g., severe OFF) and thus not mentioned as often by patients. Self-reporting, by using patient diaries, is subject to other limitations, such as reduced compliance in registering symptoms, diary fatigue and recall bias, especially in patients with impaired cognition, which is common in advanced PD. Poor self-awareness regarding dyskinesias is associated with longer disease duration.[262] A recent study[263] recruiting 40 advanced PD patients compared motor self-assessment performed by patients versus assessment by objective observers (physicians & research nurses) and reported significant differences, more specifically regarding dyskinesia the agreement rate was slightly under 50%. It is consequently clear that self-reporting is quite unreliable, while objective measurement by structured, dyskinesia-oriented rating scales performed by objective observers and monitoring by wearable sensors are warranted.

Many different rating scales have been used for dyskinesia assessment through the years, but those mostly used recently are the Abnormal Involuntary Movement Scale - AIMS[264], the Unified Dyskinesia Rating Scale - UDysRS[265] and the Clinical Dyskinesia Rating Scale - CDRS[204]. While all scales give the ability to rate different body parts, only CDRS distinguishes between dystonia and hyperkinesia. This is important especially when studying dyskinesia phenomenology, as different medications may result in different dyskinesia patterns as we showed in *Paper II*. Furthermore, the dyskinesia patterns differ significantly between individuals, with unique combinations of dystonia and hyperkinesia, and variable degrees of dyskinesia in different body parts. CDRS could additionally be utilized for the assessment of patients through video recordings using a standardized video protocol, with excellent interrater agreement after a short training on the scale. Reproducibility and high level of inter- and intrarater reliability are of great importance when it comes to rating scales in general.

Wearable sensors offer the chance to measure dyskinesia remotely and objectively in a consistent way. There are currently quite a few commercially available wearables that can be used to measure dyskinesias. Among these, PDMonitor (5 sensors of which 4 are placed in the extremities and 1 axially), PKG (1 sensor placed at the wrist) and Stat-on (a single axial sensor) have reported good correlation levels with different dyskinesia rating scales (mainly AIMS).[216, 266] Other sensor systems have been used in research settings[221-223] to capture dyskinesia. In *Paper II*, we describe the development of a prototype model that utilizes smartphone generated accelerometer & gyroscope data to predict the presence and severity of axial

hyperkinesia through machine learning. Moreover, this was achieved by only using short registration periods of a few seconds while the patients were sitting in a chair. Being able to obtain so precise results in such short time is crucial to avoid the interference of usual daily activities and movements on dyskinesia measurements, which can be problematic with the commercially available systems that need registration periods of several hours or days to produce reliable reports. While this is acceptable and often useful in routine clinical praxis another level of precision may be needed in research setting, particularly in the context of antidyskinetic drug trials. The ability to quickly and reliably produce accurate results, the use of few (or single) simple sensors, or even better the utilization of data that can be collected without the need to perform any specific motor tasks or introduce dedicated devices (e.g, using an available smartwatch or smartphone), are key features of improving objective dyskinesia monitoring in the future while making it as simple and efficient as possible for the patients. Our model comes a long way to that direction. Further work should though be put on it to investigate if it is possible to, at least approximately, assess the level of total dyskinesia (primarily hyperkinesia as dystonia is probably harder to predict by accelerometry/ actigraphy) based on data collected from a single axial sensor. Ultimately, wearable devices have the potential to remove the subjectivity of patient self-assessment (e.g., patient diaries) and address discrepancies between patient and clinician/ observer assessments providing thus objective, quantifiable assessments of motor function.[219]

Sleep disorders, daytime sleepiness, and monitoring

Sleep disorders and daytime sleepiness are common problems in PD. There has been increasing interest in the effects of rotigotine on sleep and daytime sleepiness due to its unique mode of administration with continuous transdermal drug delivery over 24 hours. In *Paper III* we utilized rating scales (PDSS-2 and ESS) to look into these parameters as well as PKG. PDSS-2 showed a trend for improvement, but the difference was not statistically significant. This was surprising, as many studies have previously reported significant improvements. The degree of improvement observed in our study (approximately 25% total score improvement from baseline) corresponds numerically to the results reported by Trenkwalder et al.,[189] Mizuno et al.,[190] Pierantozzi et al.,[192] and Suzuki et al.[195] that reported significant sleep improvements. It is possible that this is a result of the relatively smaller number of participants in our study and that including more patients may have increased the statistical power of the analysis. Bhidayasiri et al.[193] and Calandra-Buonaura et al.[196] reported greater improvements by approximately 50%, while Nicholas et al.[191] reported no statistically significant differences with rotigotine treatment in doses ranging from 2 mg - 8 mg daily. Looking into these studies, besides the number of included patients, what differentiates them from our study is the mean maintenance

rotigotine dose. We maintained a dose that provided adequate motor improvement (based on patient interview) without bothersome side-effects. The mean rotigotine dose in our paper was 5 mg, much lower compared to most studies reporting significant sleep improvements[189,190,192,196] where a range of approximately 8 mg - 13 mg was used. The lower dose in our patient group is explained by the fact that we recruited patients in a relatively early phase of the disease (median H&Y stage 2 and mean PD duration of 5 years). The only other study that had a similar maintenance dose to ours was the one that did not report any significant improvements either.[191] The recent study by Suzuki et al.[195], reporting significant improvements utilized lower doses of 2 mg and 4 mg but the patient group sticks out (compared to our and previous studies mentioned above) due to a much higher baseline PDSS-2 score. Another aspect that was quite unique in our material was the quite short follow-up time. The relatively shorter treatment time was chosen to ensure that both evaluations were conducted under conditions that were as similar as possible, regarding other treatments and disease aspects (as it was an observational study). The only other study[195] presenting results after one month's follow-up, reported statistically significant PDSS-2 improvement but included patients with quite different baseline characteristics, as mentioned above. Summarizing the findings of all studies presented, it seems that doses of 8 mg and higher may be required to notice a significant positive effect on sleep, while lower doses may still be effective in patients with more severe baseline sleep disturbances as highlighted in the recent study by Suzuki et al.[195] and the analysis of our patient subgroup with baseline PDSS-2≥ 18. DA-naïve patients seem to also benefit more according to our findings. Even though we could not detect any significant improvements in total PDSS-2 in our patient group as a whole, CGI-S improved, which may correlate with the improvement noticed in item 14, with patients feeling less tired and sleepy after rotigotine treatment. It is also worth to note that there are only two randomized control trials comparing rotigotine with other DAs, namely ropinirole[190] and pramipexole,[267] showing comparable improvement between the treatments.

Excessive daytime sleepiness (EDS) may be related to PD itself, but it is recognized that dopaminergic treatments in general, and dopamine agonists in particular, may cause or aggravate of EDS in PD patients.[20, 268] We could not observe any significant changes in EDS measured by ESS, meaning that rotigotine did not cause any worsening of daytime sleepiness. This finding seems to be reported consistently by previous studies.[191, 194, 196] Antonini et al.[197] could not detect any changes in the sleep/ fatigue domain of NMSS that addresses daytime somnolence. Liguori et al.[269] also reported no change in EDS by rotigotine compared to placebo measured by ESS and by objective measurement (Multiple Sleep Latency Test), while clear improvement of sleep disturbances (evaluated PDSS-2 and PSG) was observed simultaneously. There is even one study reporting positive effect of rotigotine on EDS at one-, two- and three-month follow-up[195] but the baseline ESS of the participants was much higher compared to our and other studies presented above. These findings suggest

that rotigotine may be an attractive option when treatment with DA is warranted in patients experiencing some level of EDS and can be tried in patients that have experienced onset or worsening of EDS on other DA treatment previously.

PSG is regarded as the gold standard of objective sleep monitoring but demands significant resources and usually overnight hospital stays, which can affect sleep quality and complicate long-term monitoring. In our study we utilized PKG registrations for monitoring of sleep and daytime sleepiness at home. Nighttime scores provided by PKG have been previously shown to correlate well with patients' subjective experience of sleep problems (PDSS-2) and have been able to distinguish with good sensitivity and specificity between normal and abnormal sleep as evaluated by PSG.[218] Nighttime scores did not change significantly in our study after treatment with rotigotine, which was in accordance with the PDSS-2 results. Further analysis, though, did not show a direct correlation of the combined sleep score (CSS) measured by PKG with total PDSS-2; it correlated only with item 2 of PDSS-2 that reflects sleep onset insomnia. The lack of correlation may be attributed to the subjective nature of the questionnaire, as different patients with similar symptoms may rate themselves differently. It could also be the case that previously reported findings[269] could not be reproduced due to the small sample size of that study, which can have affected the outcome. Further studies with larger sample sizes, comparing PKG data not only with questionnaires but also with PSG measurements, are needed to further explore the usefulness of PKG in assessing sleep and daytime sleepiness in PD patients.

Another study using actigraphy (Mini Motionlogger Actigraph) after initiation of rotigotine treatment[196] reported reduction in motor activity during sleep and fewer wake episodes at night, but we could not detect any such signals.

PKG markers of dyskinesia increased but remained in very low, non-clinically significant levels. The improvements noticed on daytime PKG scores for tremor, and daytime immobility correspond well with the improvement of motor symptoms rated by the study's clinicians according to CISI-PD.

Kotschet et al.[270] reported a significant association between high ESS scores (≥10) and elevated PTI_D scores in PD patients, but we could not confirm this finding in our material. They also found a correlation between PKG's PTI_D and ambulatory daytime PSG and therefore suggested that PTI_D can be a useful surrogate measure of daytime sleepiness in PD. On the other hand, Höglund et al.[271] could not show any significant correlation between PKG scores and self-evaluated daytime sleepiness, which is in line with our findings. Similarly to our results Calandra-Buonara et al.[196] reported improvement of EDS-related actigraphic data that was not reflected on ESS scores. The subjective nature of the ESS and difficulties in recalling symptoms from the past week might affected the accuracy of the assessment. It is also shown that PD patients tend to under-report sleepiness on the ESS, as they can be unaware of daytime naps,[272] raising the question that actigraphic

data may be more reliable than self-reporting regarding the discrepancies noted above. It is though fair to note that PTI_D measures immobility, and rotigotine improved motor symptoms in our study, possibly resulting also in reduced immobility. In our analysis we could not detect any significant direct correlation between PTI_D and ESS. Hence, it is also possible that some of the disparity between ESS and PTI_D scores may be due to certain PTI_D items reflecting bradykinesia and immobility caused by motor issues rather than daytime sleepiness.

Conclusion

The general aim of this thesis was to increase the knowledge around the effects of different add-on medications in motor and non-motor symptoms (NMS) in PD.

In *Paper I* we investigated the results of safinamide treatment, 6 months after treatment initiation, in fluctuating PD patients. We observed an improvement of motor complications and pain without any significant changes in other NMS. In *Paper II* the effect of dopamine agonist (DA) treatment, more specifically ropinirole, on dyskinesias was assessed. Patients already experiencing dyskinesias performed two challenge tests using L-dopa and combination of L-dopa & ropinirole, and we analyzed the topographical and temporal profile of hyperkinesia and dystonia. We could show that DA treatment with primarily D2/3 receptor stimulation affects the phenomenology of dyskinesias, resulting generally in lower peak phase dyskinesias and more pronounced end phase dyskinesias, particularly arm dystonia. Topographically, hyperkinesia and dystonia were more prominent in the legs after L-dopa challenge, while the challenge test with ropinirole coadministration resulted in more comparable dystonia in the arms and legs. In *Paper III* we evaluated the effects of rotigotine treatment with focus on sleep, in PD patients reporting sleep disturbances. Motor symptoms, mainly tremor, improved as expected and sleep parameters improved in patients with more severe sleep disturbances at baseline and in those that have not previously received DA treatment. Daytime somnolence, a common side effect of DAs, did not worsen, with measures of daytime immobility that might reflect daytime sleepiness showing improvement after treatment. Objective measurements based on accelerometer data did not correlate with patient reported sleep problems, except for a fair correlation regarding sleep-onset insomnia.

As disease modifying treatments in PD are currently nonexistent, personalized, precision treatment choices are of utmost importance for optimized symptom control. The need for individualized and effective treatment is even more imperative in the realm of NMS where scientific evidence, clinical experience and treatment options are more limited. Reliable methods of objective measurement of both motor symptoms and NMS may reveal issues that could otherwise go unnoticed or can monitor symptoms along disease progression aiding clinicians in their tailored decision-making. Finally, careful consideration of the unique effects of different add-on treatments in motor and non-motor symptoms, with regard to each patient's unique PD phenotype, should be an integral part of clinician decision-making. I

hope that this thesis contributes to that direction by giving some novel insights on the distinctive effects of different, commonly used add-on treatments.

Populärvetenskaplig sammanfattning

Parkinsons sjukdom är en nervsjukdom som påverkar rörelseförmågan och kan orsaka motoriska symtom som förlångsamning, skakningar, stelhet och balanssvårigheter. Det kan också orsaka sömnsvårigheter, smärta, depression, kognitiv försämring och andra icke-motoriska symtom som försämrar livskvaliteten. Parkinsons sjukdom beror på att de celler i hjärnan som tillverkar signalämnet dopamin, som används för att skicka signaler mellan hjärncellerna, dör. Ungefär en av hundra personer över 60 år får Parkinsons sjukdom och det är vanligare hos män. Orsaken till sjukdomen är inte helt klarlagd och det finns ingen botande eller bromsande behandling utan behandlingar som kan bara lindra symtomatiskt.

Den mest effektiva behandlingen för Parkinsons sjukdom är levodopa. Efter ett initialt bra behandlingssvar under några år, kan många patienter uppleva fluktuationer mellan god effekt, otillräcklig effekt och dyskinesier, dvs snabba, oförutsägbara, ofrivilliga rörelser eller avvikande kroppshållningar (dystonier). När behandlingen sviktar, kan tilläggsbehandlingar, e.g. dopaminagonister och MAO-B hämmare, bidra till bättre symtomkontroll. Det övergripande målet med denna avhandling är att undersöka hur olika tilläggsbehandlingar påverkar patienter med Parkinsons sjukdom, med fokus på icke motoriska symtom och motoriska komplikationer, främst dyskinesier. Noggrann bedömning av dyskinesier och försiktig genomgång av icke motoriska symtom är en viktig del för att kunna planera behandlingen.

I denna avhandlings första del kunde vi visa att tilläggsbehandling med safinamid (MAO-B hämmare) förbättrade motoriska fluktuationer och smärta, 6 månader efter insättning. Vi märkte ingen positiv eller negativ påverkan på övriga icke motoriska symtom. I andra delen av avhandlingen, fann vi att tillägg av ropinirol (dopaminagonist) till levodopa ledde till mindre grad av dyskinesier kort efter medicinintag, jämfört med bara levodopa. Dyskinesierna var dock mer ihållande och arm-dystoni var mer uttalad när medicineffekten avtog. Levodopa orsakade dyskinesier mest i benen jämfört med övriga kroppsdelar men tillägg av ropinirol ledde till jämnare grad av dyskinesier i armar och ben. Vi har dessutom utvecklat en modell som använde data sammanställda från en mobiltelefon som patienter bar på sig, och som kunde sedan bedöma graden av dyskinesi på ett pålitligt sätt. Det är första studien med Parkinsons patienter som påvisar att dyskinesimönster kan påverkas av tilläggsbehandling med dopaminagonist och det kan vara ett viktigt

fynd vad gäller framtida studier som syftar på att utveckla behandlingar för dyskinesi. I sista arbetet visar vi att behandling med rotigotin (dopaminagonist) förbättrar motoriska symtom och försämrar inte dagsömnighet, en vanlig biverkning av andra dopaminagonister. Vi kunde också se att det har en positiv effekt på sömnen, framför allt hos patienter med svåra sömnbesvär.

Olika tilläggsbehandlingar verkar således ha distinkta effekter på en rad motoriska och icke motoriska symtom, vilket bör beaktas vid beslutsfattande för individualiserad, precisionsbehandling baserat på varje individs symtom och behov.

Περίληψη στα ελληνικά

Η νόσος του Πάρκινσον είναι μια νευρολογική νόσος που επηρεάζει την κινητικότητα και μπορεί να προκαλέσει κινητικά συμπτώματα όπως βραδυκινησία, δυσκαμψία, τρόμο (τρέμουλο) και προβλήματα ισορροπίας. Μπορεί επίσης να προκαλέσει διαταραχές ύπνου, πόνο, κατάθλιψη, έκπτωση νοητικών λειτουργιών και άλλα μη κινητικά συμπτώματα που επηρεάζουν αρνητικά την ποιότητα ζωής. Η νόσος του Πάρκινσον οφείλεται στο θάνατο κυττάρων του εγκεφάλου (νευρώνες) που παράγουν το νευροδιαβιβαστή ντοπαμίνη, η οποία χρησιμοποείται για τη μετάδοση σημάτων μεταξύ των νευρώνων. Η νόσος του Πάρκινσον είναι πιο συνηθισμένη στους άνδρες και περίπου ένας στους εκατό άνθρωπους άνω των 60 ετών πάσχει από αυτήν. Η αιτία της νόσου δεν έχει ακόμα διαλευκανθεί πλήρως και δεν υπάρχει αγωγή, που να την θεραπεύει ή να την καθυστερεί, παρά μόνο συμπτωματικές θεραπείες. Η πιο αποτελεσματική θεραπεία για τη νόσο του Πάρκινσον είναι η αγωγή με τη φαρμακευτική ουσία λεβοντόπα. Με την πάροδο του χρόνου, η αρχικά καλή απόκριση στη θεραπεία αυτή, μπορεί να εμφανίσει διακυμάνσεις, όπως περιόδους ανεπαρκούς απόκρισης με επιδείνωση των παρκινσονικών συμπτωμάτων ή/και δυσκινησίες, δηλαδή γρήγορες, απρόβλεπτες, ακούσιες κινήσεις ή ανωμαλίες στη στάση του σώματος (δυστονίες). Όταν η θεραπεία με λεβοντόπα λοιπόν δεν λειτουργεί ιδανικά, άλλες πρόσθετες θεραπείες, όπως οι αγωνιστές ντοπαμίνης και οι αναστολείς ΜΑΟ-Β, μπορεί να συμβάλλουν στον καλύτερο έλεγχο των συμπτωμάτων.

Ο γενικός στόχος αυτής της διατριβής είναι να εξετάσει πώς διάφορες πρόσθετες θεραπείες επηρεάζουν τους ασθενείς με νόσο του Πάρκινσον, με εστίαση στα μη κινητικά συμπτώματα και στις κινητικές επιπλοκές, κυρίως τις δυσκινησίες. Η λεπτομερής αξιολόγηση των δυσκινησιών και η προσεκτική εκτίμηση των μη κινητικών συμπτωμάτων είναι σημαντικό κομμάτι στον σχεδιασμό της θεραπείας.

Στο πρώτο μέρος αυτής της διατριβής, δείξαμε ότι η πρόσθετη θεραπεία με σαφιναμίδη (αναστολέας ΜΑΟ-Β) βελτίωσε τις κινητικές διακυμάνσεις και τον πόνο των ασθενών, 6 μήνες μετά την έναρξη της θεραπείας. Δεν παρατηρήσαμε κάποια θετική ή αρνητική επίδραση σε άλλα μη κινητικά συμπτώματα. Στο δεύτερο μέρος, βρήκαμε ότι η συγχορήγηση ροπινιρόλης (αγωνιστής ντοπαμίνης) με λεβοντόπα οδήγησε σε λιγότερο έντονες δυσκινησίες, σύντομα μετά τη χορήγηση της δόσης, σε σχέση με τη μονοθεραπεία με λεβοντόπα. Οι δυσκινησίες όμως είχαν μεγαλύτερη διάρκεια, και η δυστονία στα χέρια ήταν εντονότερη κατά την αποδρομή της επίδρασης του φαρμάκου. Η λεβοντόπα προκάλεσε δυσκινησίες

κυρίως στα πόδια, ενώ η συνδυασμένη χορήγηση της με ροπινιρόλη οδήγησε σε παρόμοια επίπεδα δυσκινησίας στα χέρια και τα πόδια. Επιπλέον, αναπτύξαμε ένα μοντέλο που μπορεί να αποτυπώσει με ακρίβεια το βαθμό της δυσκινησίας βασιζόμενο σε δεδομένα που συλλέγονται από ένα κινητό τηλέφωνο που φέρει ο ασθενής. Η μελέτη αυτή σε ασθενείς με Πάρκινσον, είναι η πρώτη που δείχνει ότι το μοτίβο της δυσκινησίας διαφέρει με τη συγχορήγηση αγωνιστή ντοπαμίνης κάτι που μπορεί να αποτελέσει σημαντικό εύρημα για μελλοντικές μελέτες που αποσκοπούν στην ανάπτυξη θεραπειών για τη δυσκινησία. Στο τρίτο μέρος της διατριβής, δείχνουμε ότι η προσθήκη ροτιγοτίνης (αγωνιστής ντοπαμίνης) βελτιώνει τα κινητικά συμπτώματα και δεν επιδεινώνει την υπνηλία κατά τη διάρκεια της ημέρας, μία κατα τα άλλα συνήθη παρενέργεια των αγωνιστών ντοπαμίνης. Βρήκαμε επίσης ότι βελτιώνει τον ύπνο, ειδικά σε ασθενείς με σοβαρές διαταραχές ύπνου.

Φαίνεται, λοιπόν, ότι οι πρόσθετες θεραπείες που μελετήσαμε έχουν διακριτές επιδράσεις σε μια σειρά κινητικών και μη κινητικών συμπτωμάτων, γεγονός που πρέπει να λαμβάνεται υπ' όψιν κατά τη λήψη αποφάσεων με στόχο ένα εξατομικευμένο, ακριβές θεραπευτικό σχήμα βασισμένο στα συμπτώματα και τις ανάγκες του κάθε ασθενούς.

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