Clinical pharmacology studies investigating novel formulations of dopaminergic drugs

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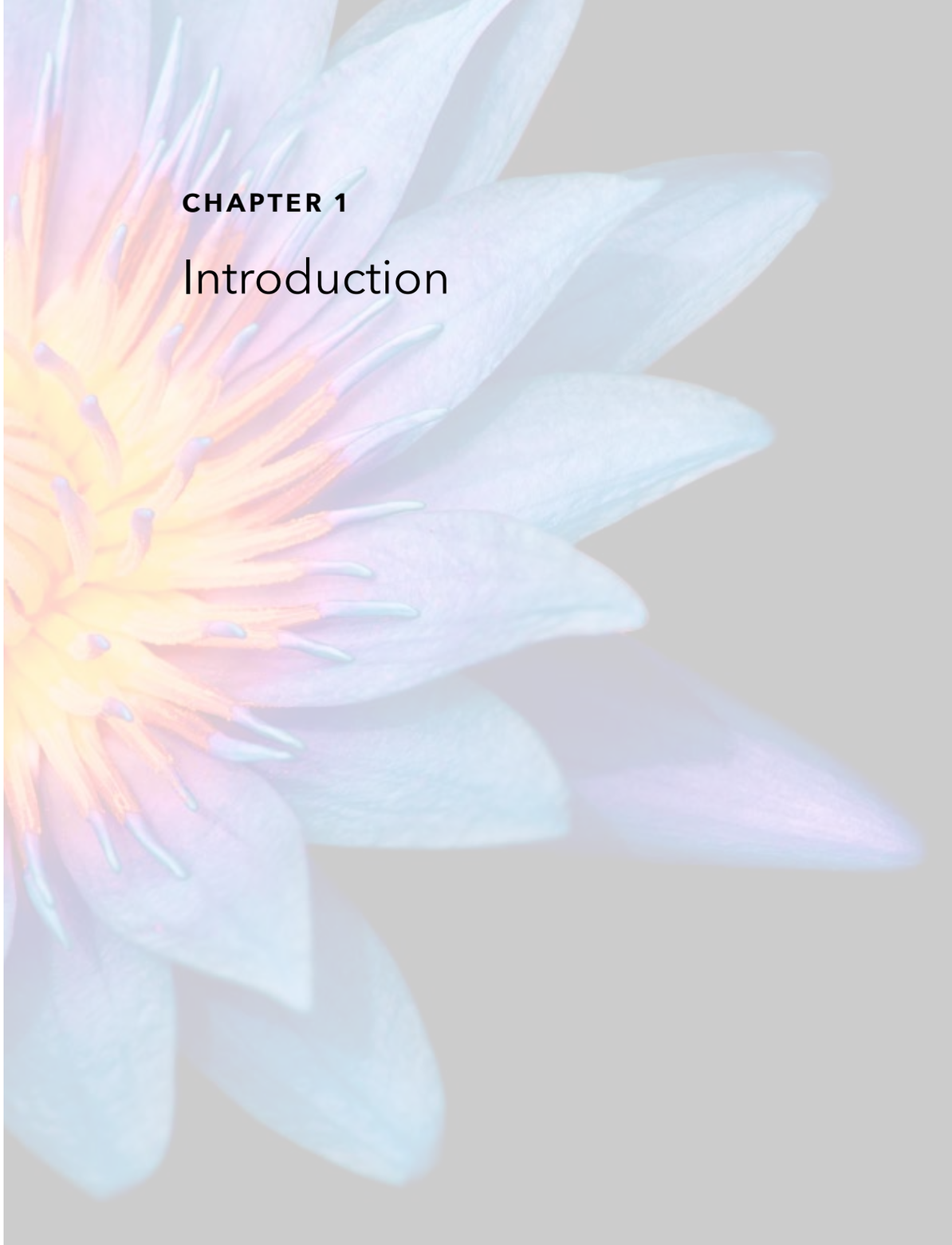

CHAPTER 1

Introduction

PARKINSON'S DISEASE

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects millions of people worldwide, significantly impacting their quality of life. It is the fastest growing neurological disorder.[1] Whereas in 1990, 2.5 million people were affected by PD worldwide, this number had increased to 6.1 million in 2016.[1] Projections indicate that this will further increase to 13-14 million people in 2040.[2] This increase can be attributed to the aging worldwide population but environmental factors linked to industrialization are expected to contribute as well.[1]

Early motor symptoms of PD can be subtle and may go unnoticed. As the condition progresses, more pronounced motor signs become apparent, such as slowness of movement (bradykinesia), tremors, rigidity, and impaired balance. Before the appearance of these characteristic motor symptoms, patients may have already experienced non-motor symptoms like hyposmia, sleep disturbance (e.g., rapid eye movement (REM) sleep behavior disorder (RBD)), depression and constipation for several years.[3] Similar to the motor symptoms, the non-motor symptoms will progress as the disease advances, and cognitive impairment and autonomic dysfunction will become more common in the later disease stage.[3]

The exact cause of PD is unknown, but it is believed to result from an interplay between genetic, environmental and lifestyle factors. The two most common genetic risk factors linked to PD are mutations in the glucocerebrosidase (*GBA1*) and the leucine-rich repeat kinase 2 (*LRRK2*) genes. Ongoing research continues to unveil a growing number of common and rare genetic variants linked to the disease.[4] Exposure to pesticides has been linked to a higher likelihood of developing PD, while smoking, caffeine intake, and physical activity have been associated with a decreased risk.[5]

Neuropathologically, PD is characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta. At the time of diagnosis, it is estimated that approximately 30% of the dopaminergic neurons of the substantia nigra and 50-60% of their axon terminals have degenerated.[6] This degeneration causes striatal dopamine deficiency resulting in the cardinal PD motor symptoms. The second pathological hallmark of PD is the accumulation of alpha-synuclein aggregates in neurons, called Lewy bodies and Lewy neurites. Under physiological circumstances, alpha synuclein is thought to play a role in synaptic vesicle dynamics, mitochondrial function and intracellular trafficking. However, upon its misfolding and aggregation, it becomes neurotoxic. It has been hypothesized that the initial misfolding and aggregation of alpha-synuclein may start in the gut enteric nerves and the olfactory bulb, and from there spread in a prion-like fashion to other areas, ultimately affecting the dopaminergic neurons in the substantia nigra.[7] Despite the importance of nigrostriatal neurodegeneration in the clinical motor presentation, degeneration is certainly not limited to dopaminergic neurons, but also affects for example GABAergic, glutamatergic, and cholinergic neurons.[8] The pathophysiological mechanisms underlying the abovementioned PD hallmarks involve a complex interplay of alpha-synuclein aggregation and spreading, mitochondrial dysfunction and oxidative stress, lysosomal dysfunction, and neuroinflammation.[7]

To date, no disease-modifying therapies for PD are on the market yet. Available treatment options are focused on symptom control to improve the quality of life for patients. This is typically achieved by either indirectly boosting dopamine levels in the brain or mimicking dopamine's effects through medications such as levodopa, dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, and monoamine oxidase B (MAO-B) inhibitors. Moreover, some non-dopaminergic and non-pharmacological treatment options are available, such as anticholinergics, amantadine, physiotherapy, occupational therapy, and speech and language therapy.[9]

SYMPTOM FLUCTUATIONS

A large proportion of patients develop motor complications within a few years after disease onset and dopaminergic therapy initiation.[10,11] Complications consist of motor fluctuations and abnormal involuntary movements (dyskinesias). Motor fluctuations cause the

patient to alternate between periods of favorable response to medication (*ON* phase) and periods of inadequate response (*OFF* phase). These fluctuations in therapeutic effects can be predictable (e.g., end of dose 'wearing *OFF*') or unpredictable, and do not only involve fluctuations in motor symptoms but also in non-motor symptoms like anxiety, panic attacks, mood changes, slowness of thinking, and pain.[12] Fluctuating symptoms impact activities of daily living and worsen quality of life.[11,13]

The development of motor complications results from pre- and postsynaptic dopaminergic changes, as well as secondary changes to non-dopaminergic systems.[14] As the disease progresses an increasing number of dopaminergic nigrostriatal neurons degenerate, resulting in reduced endogenous dopamine synthesis, presynaptic dopamine storage capacity and dopamine release.[15] Due to the loss of the presynaptic dopaminergic terminals, there is a reduced capacity to regulate the fluctuations in plasma levodopa levels.[15,16] Moreover, dopamine release is further dysregulated by serotonergic neurons taking over the function of dopaminergic neurons in the striatum.[14] Whereas serotonergic neurons can store and release dopamine, they do so in an uncontrollable manner since they lack presynaptic autoreceptors and the ability for dopamine reuptake.[14] This leads to unphysiological fluctuations in extracellular dopamine and hence in unphysiological postsynaptic dopamine receptor stimulation. Similarly, dopaminergic treatment leads to non-physiological, pulsatile stimulation of post-synaptic dopamine receptors.[17–19] This non-physiological stimulation results in post-synaptic changes affecting receptor sensitivity and intracellular signal processing, ultimately affecting the postsynaptic response to dopamine and the striatal output activity.[7,15] Lastly, the combined impact of dopaminergic neurodegeneration and pulsatile receptor stimulation leads to pathophysiological changes to non-dopaminergic systems, such as the glutamatergic and serotonergic system.[14] Together these changes result in impaired dopaminergic control leading to *ON-OFF* fluctuations and/or dyskinesia.

When a patient is using levodopa but motor complications persist despite optimized oral levodopa therapy, other treatments can be chosen or added. First options are adding oral or transdermal drugs, like non-ergot dopamine agonists and enzyme inhibitors that prolong the effect of levodopa, i.e., COMT and MAO-B inhibitors.[20] If dyskinesia is the main problem, then if possible, dopaminergic medication should be reduced and amantadine or clozapine can be added.[20] If the abovementioned adjustments are insufficient, advanced device-aided treatments are available, i.e., deep brain stimulation (DBS), continuous subcutaneous apomorphine infusion and levodopa-carbidopa intestinal infusion.[21–23] The infusion pump therapies provide continuous drug administration resulting in fewer fluctuations in drug plasma levels and hence more continuous dopaminergic stimulation. However, if a patient has less than five *OFF* periods per day, intermittent treatment is often preferred over a continuous therapy. For relief of these sudden and intermittent *OFF* periods, subcutaneous apomorphine injections have long been the only treatment option. Its onset of action has been reported to be between 5-15 minutes,[24–26] with maximum motor improvements as assessed by part III of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) after 20-40 minutes.[25,27,28] Despite its efficacy and fast onset of action, the use of intermittent injections is often limited by injection site reactions, pain and difficulty self-administering the injection during an *OFF* period.[29] With the FDA approval in 2018 of Inbrija, a breath-actuated inhaler of levodopa powder, and in 2020 of KYNMOBI, an apomorphine sublingual film, the treatment options for on-demand therapy of *OFF* periods increased.[30] Inhalable levodopa and sublingual apomorphine have an initial onset of effect based on MDS-UPDRS III reduction around 10 minutes and 15 minutes respectively, and show maximum MDS-UPDRS III improvements at 30 and 60 minutes respectively.[31–33] Both are considered less invasive treatment options than subcutaneous apomorphine injections. Unfortunately, only three years after sublingual apomorphine was introduced to the market, Sunovion announced its discontinuation in the US and Canada due to "limited utilization" and "business reasons". As of September 2023, it is no longer available, and hence the treatment options for *OFF* periods remain limited.

APOMORPHINE

The historical use of apomorphine is believed to have its origins in ancient cultures like that of the Maya civilization and ancient Egyptians. Depictions in tombs and papyrus scrolls dating back to 1400 BC portray the Nymphaea caerulea flower. Based on the drawings, it seems these civilizations used Nymphaea plants in religious-magical ceremonies, likely because of their aphrodisiac and hallucinogenic properties, as well as in purifying rituals because of their emetic effects. We now know that the bulbs and roots of this water lily species contains various aporphins, including apomorphine.[34] The synthesis of apomorphine did not occur until 1868 when Matthiessen and Wright produced apomorphine by heating morphine with concentrated hydrochloric acid.[35] This advanced and intensified the research into the effects of apomorphine. In 1884, it was suggested by Weil for the first time that apomorphine might be a potential treatment for PD.[36] Nonetheless, it took until 1951 for apomorphine to be administered to PD patients for the first time by Schwab et al.[37] They demonstrated that subcutaneous injections had positive effects on PD motor symptoms, but also resulted in side effects like nausea, vomiting and hypotension. These peripheral side effects impeded its broader use. Therefore, the discovery that a peripheral dopamine receptor antagonist (domperidone) could reduce apomorphine-induced side effects like nausea, drowsiness, sedation and hypotension, was a major breakthrough in 1979.[38] More years of research followed, resulting in apomorphine's first European marketing authorization in the UK in 1993.[39] It was approved for use as subcutaneous intermittent injections (APO-go) to treat *OFF* episodes in PD patients. Approval in other EU countries followed in the subsequent years. In the US, intermittent subcutaneous apomorphine injections (APOKYN) earned FDA approval in 2004.[40] In the EU, apomorphine is also available as a continuous subcutaneous infusion via a percutaneous pump. Again, this formulation received its first marketing approval in the UK in 2004 and was approved in other EU countries in the following years.[41] This formulation is currently not (yet) authorized by the FDA. The FDA did authorize the use of apomorphine sublingual film (KYNMOBI) in 2020.[30] Unfortunately, the drug was discontinued about three years later due to "limited utilization".

Apomorphine is a potent broad spectrum dopamine agonist, activating both D1-like (D1, D5) and D2-like (D2, D3, D4) receptor subtypes.[42] Moreover, based on in vitro studies, it was demonstrated to have modest agonistic activity at 5-HT_{1A} receptors, and acts as an antagonist at α2-adrenergic, 5-HT_{2A} and 5-HT_{2C} receptors.[43,44] The potential influence of apomorphine on the adrenergic system has not yet been well explored.[45] As for the serotonergic system, apomorphine might have a lower tendency to induce visual hallucinations compared to other dopamine agonists due to its 5-HT_{2A} antagonism.[46] Apomorphine's molecular formula is $C_{17}H_{17}NO_2$ and it has a molecular weight of 267.32 g/mol.[45] In clinical practice, apomorphine is used as its hydrochloride salt. It is a chiral molecule, meaning it exists in two distinct mirror-image forms called R- and S-enantiomers. The R-enantiomer is the biologically active form responsible for its pharmacological effects.[45] Therefore, the R-enantiomer is utilized in clinical practice.[47] In vivo, there is no interconversion to the S-form.[48] Apomorphine's polycyclic structure makes it highly lipophilic, allowing apomorphine to easily cross the blood-brain barrier. Its ortho-catechol group has less favorable effects since it renders apomorphine sensitive to oxidation, making it unstable in aqueous solutions. Exposure to light and air triggers this spontaneous oxidation, turning apomorphine solutions green. Apomorphine oxidation results in a loss of pharmacological activity and the formation of quinones and reactive oxygen species.[45] These molecules can be cytotoxic due to the induction of oxidative stress and damage to lipids, proteins, and DNA.[49,50] Therefore, antioxidants like sodium bisulfite and L-ascorbic acid are often part of apomorphine formulations to enhance apomorphine's stability in solution. Moreover, it is protected from light.[45]

Apomorphine has a poor oral bioavailability (<4%) due to its nearly complete first-pass hepatic metabolism.[51] Hence, apomorphine formulations are administered subcutaneously or sublingually (recently discontinued), thereby effectively bypassing the first-pass effect. The bioavailability of subcutaneous apomorphine is approximately

100%,[52,53] and the relative bioavailability of sublingual to subcutaneous apomorphine is 17.2 (13.7–21.6)%.[54] For subcutaneous and sublingual apomorphine, median time to reach maximum plasma concentrations (T_{max}) varies across studies, but usually ranges between 15-23 and 38-51 minutes respectively.[54–56] Maximum concentrations in cerebrospinal fluid lag approximately 10-20 minutes behind, and correlate with the onset of clinical effect.[57] Apomorphine is rapidly cleared from the body with a terminal elimination half-life ($T_{½}$) ranging between 30-60 minutes.[58] This rapid clearance results in a short duration of effect, making apomorphine a suitable rescue medication that can be used in addition to standard PD medication.

Since apomorphine's pharmacokinetics (PK) and pharmacodynamics are subject to high interindividual variability, individual dose titration under medical supervision is required.[57] A low dose is given initially (usually 1 or 2 mg for subcutaneous apomorphine,[59,60] and 10 mg for sublingual apomorphine), and increased until the 'optimal' dose is found. The 'optimal' dose is considered the dose with the shortest latency to effect and the longest effect duration while minimizing side effects. While the optimal dose differs for each patient, most patients require 3 mg apomorphine when given as a subcutaneous administration.[61] During dose titration, special focus should be on blood pressure (supine and standing) and ECGs to monitor for potential (orthostatic) hypotension and QT prolongation, respectively. Apomorphine, especially at high doses, may induce QT prolongation.[59] This risk is increased with the concomitant use of domperidone, which is often co-prescribed to prevent the peripheral side effects of apomorphine. Therefore, monitoring the QT interval prior to domperidone initiation and during apomorphine treatment initiation is recommended, and as clinically indicated thereafter.[60,62] Especially in patients that are at risk for torsades de pointes arrhythmia. Other commonly reported side effects are nausea, vomiting, yawning, drowsiness, somnolence, dizziness, and dyskinesia.[59,60,62] Also local side effects should be monitored, i.e., injection site reactions (subcutaneous apomorphine) or oropharyngeal side effects (sublingual apomorphine).

With the recent discontinuation of sublingual apomorphine (KYNMOBI), subcutaneous apomorphine remains the only available apomorphine administration route for the treatment of *OFF* episodes.

The need for a less invasive and therefore more user-friendly treatment option remains high. Over the years, other administration routes have been investigated, such as transdermal, intranasal, rectal and inhaled routes. Initial studies investigating transdermal delivery of apomorphine were hampered by poor/absent bioavailability.[63,64] However, a study in 2004 showed relevant plasma concentrations could be reached when an apomorphine microemulsion was administered.[65] Single administration of this microemulsion often caused local erythema (71.4%) and its PK (T_{max} 5.1 hours; $T_{½}$ 10.8 hours) was unfavorable for use as a treatment of acute *OFF* episodes. It might be suitable as an add on sustained-release formulation for e.g., nocturnal fluctuations. To date, no further PD patient studies using transdermal apomorphine have advanced in clinical development. Intranasal administration, although fast and efficacious,[66–71] resulted in local side effects like nasal irritation, nasal congestion, vestibulitis and nasal crusting.[67,69–71] Hence, it is no longer in development. In the 1990's, three studies investigated rectal apomorphine delivery.[72–74] While this route demonstrated clinical efficacy, its further development was halted, likely due to difficulty self-administering apomorphine rectally during an *OFF* episode, as well as its longer latency to effect compared to subcutaneous delivery. Inhalation of apomorphine dry powder (VR040) has been investigated in three studies published in 2013. It showed favorable PK with maximum plasma concentrations between 1-7 minutes post-dose,[75,76] and a mean latency to an *ON* state of 8 and 10 minutes reported in two studies.[76,77] No local side effects or effects on lung function were reported. The observed side effects were limited to dopaminergic side effects, consistent with those seen with other apomorphine formulations.[75–77] Despite these positive outcomes, no further studies on this dry powder apomorphine formulation have been reported.

Apomorphine is currently underutilized,[78] likely because the subcutaneous injection has several impracticalities like the need to inject oneself while being *OFF*, whereas also the occurrence of injection site reactions and fear for needles may play a role. The sublingual apomorphine film that was available between 2020 and 2023 in the US and Canada often caused oropharyngeal side effects and had a later T_{max} than subcutaneous apomorphine.[56] Furthermore, the administration of subcutaneous injections and

the handling of the sublingual film requires good finger dexterity and muscle coordination that is often impaired in patients with PD.[79] Therefore, there is a need for a non-invasive and easy to administer apomorphine formulation. In this thesis, we focus on two new apomorphine formulations for the management of acute *OFF* episodes. In **chapter 2 and 3**, we will evaluate AZ-009, which is a breath-actuated, oral inhalation device using the Staccato technology.[80,81] This technology was already previously approved by the FDA and EMA for the administration of loxapine.[82–84]. A single breath through the device leads to rapid heating (<0.5 second) of a metal substrate coated with a thin film of excipient-free apomorphine. As a result pure drug vapor is formed that rapidly cools and condenses into aerosol particles appropriate for deep lung delivery and subsequent systemic exposure. Consequently, AZ-009 has the potential to induce a quick transition from *OFF* to *ON*, potentially even faster than subcutaneous apomorphine. In **chapter 4**, we describe a study that evaluated APORON, an oromucosal solution that is administered to the buccal area using a dispenser. Since apomorphine is dissolved in a solution (as opposed to the sublingual film), it is hypothesized to have a reduced risk of apomorphine particles lingering in the oropharyngeal space for a prolonged time after dosing. The dose that is not buccally absorbed is anticipated to be swallowed with the saliva and become subject to first-pass metabolism. This would minimize the chance of apomorphine degradation into reactive oxygen species in the oropharyngeal space, thereby reducing toxicity.

SHOWING ACUTE DOPAMINERGIC MEDICATION EFFECTS IN CLINICAL TRIALS

To evaluate whether a drug is suitable as a rescue medication for managing acute *OFF* episodes, it should not only be efficacious, but also have a rapid onset of action. Its onset, as reflected by T_{max}, should be faster than the standard PD medication like levodopa/carbidopa immediate release tablets, which has a reported median T_{max} in advanced PD patients of 1.25 to 1.5 hours after repeat dosing.[85,86]

The Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) can be seen as the gold standard for evaluating various aspects of Parkinson's disease, and is often used in clinical trials to show medication effects. The scale is composed of four parts.[87] Part I assesses the non-motor impact on experiences of daily living, e.g., the effect of cognitive impairment, mood and sleep disturbances, pain, urinary and gastrointestinal problems, and orthostatic hypotension on daily living. Part II assesses the motor impact on experiences of daily living, e.g., the effect of problems with speech, swallowing/chewing, dressing, writing and other mobility problems on daily living. Part III is a motor examination performed by a trained rater assessing speech, facial expression, rigidity, finger/toe tapping, hand movements, gait, balance, posture, bradykinesia, and tremor. Part IV investigates the presence and functional impact of motor complications, i.e., dyskinesia, motor fluctuations and painful *OFF* state dystonia. Especially part III of the MDS-UPDRS is often used in clinical trials to show motor improvements after (dopaminergic) medication intake.[31,32,88] However, part III requires a trained rater who preferably assesses a patient throughout the entire trial to avoid inter-rater variability. Additionally, the assessment takes relatively long (approximately 15 minutes, dependent on the patient's clinical state). This makes accurate time-response assessment of fast-acting agents challenging, especially when safety and pharmacokinetic measurements also need to be performed. Hence, a short, rater-independent and quantitative measurement would be ideal for use in clinical trials.

As technology continues to advance, we are increasingly capable of objectively and quantitatively measuring core PD motor symptoms like tremor, bradykinesia, gait disturbances and dyskinesia. These symptoms and their severity can be assessed using wearable sensors such as accelerometers, gyroscopes and inertial measurement units; with tests on tablets and mobile phones; and by using video-based movement analysis.[89] The recent advances in wearable sensors and smart devices make at-home monitoring of PD symptoms possible. At-home monitoring can be useful to monitor a patient's symptom severity over time to facilitate medication adjustments, or to evaluate whether a disease-modifying drug can slow down disease

progression. The focus of this thesis, however, is on demonstrating acute (dopaminergic) medication effects. For that, we evaluated three different finger tapping tasks while patients were confined to the clinical research unit. Finger tapping tasks are well suited for the evaluation of bradykinesia, which is one of the cardinal features of PD and defined as 'slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions'.[90] Bradykinesia, unlike tremor, usually responds well to dopaminergic treatment.[90] While quantification of finger tapping is not new, the methods available are improving and growing in numbers, ranging from rudimentary to more sophisticated methods. Described methods for the assessment of repetitive index finger tapping or alternate index-middle finger tapping include the use of arcade buttons,[91] computer keyboards,[92,93] keyboards with a musical instrument digital interface,[94] and touchscreen devices (smartphones, tablets).[23,37,71,95] An advantage of touchscreen devices is that the precise location (x, y coordinates) of each tap can be registered and hence tapping accuracy can be quantified precisely. Despite the abundance of available methods, there is a lack of standardization in task configurations. Differences between tasks include the finger(s) used for tapping (e.g., index finger tapping, or alternate index-middle finger tapping), the distance between targets (if applicable), the test duration, and whether it is given with or without a (visual) cue. Thumb-index finger tapping is part of the MDS-UPDRS III (item 3.4) and includes the evaluation of tapping rhythm, slowing of movement and tapping amplitude. These various aspects result in a combined score between 0 and 4 points. Methods for the quantification of thumb-index finger tapping are also available such as video-based motion-analysis systems,[96,97] and sensors like accelerometers,[98] gyropscopes,[99] magnetic sensors,[100] or combinations of these sensors known as inertial measurement units.[101] Electronic goniometers are angular sensors and can quantify joint movement when the end blocks of the goniometer are placed on either side of the center of the joint. It has been shown useful for this purpose in measuring for example the flexion and extension of the index finger, wrist and elbow.[102] To the best of our knowledge, an electrogoniometer has never been used to quantify thumb-index finger tapping in PD patients.

Literature has shown that finger tapping tasks can differentiate between healthy controls and PD patients[92,103–110] and between medication states (*ON*/*OFF*).[94,105,107,109–113] However, the set-up and devices used for these tapping tasks vary among studies, and it is unclear which is most suitable for the determination of (dopaminergic) medication effects in randomized placebo-controlled trials. Therefore, in this thesis we evaluate different tapping tasks alongside the gold standard MDS-UPDRS III. In **chapter 5**, we describe a study that evaluated the within- and between-day repeatability of touchscreen-based tapping tasks in different configurations in healthy volunteers. Configurations included alternate index and middle finger tapping with 2.5 cm between targets and repetitive alternate index finger tapping with 20 cm between targets. Both of these tasks were tested with and without a visual cue. In **chapter 6**, we describe a randomized, double-blind, placebo-controlled crossover study in PD patients to assess the ability of three different finger tapping tasks to detect dopaminergic medication effects. Moreover, we evaluated whether finger tapping outcomes correlate with the gold standard MDS-UPDRS III. The tapping tasks being compared include the two uncued touchscreen tasks described in chapter 5 and a thumb-index finger tapping task using an electronic goniometer. In **chapter 7**, the data from the clinical study in chapter 6 were used to train machine learning algorithms to select the optimal combination of finger tapping task features ('composite biomarker') to predict treatment effect (i.e., did the patient receive active or placebo treatment?) and estimate the disease severity (i.e., MDS-UPDRS III score).

Summarizing, this thesis investigates two novel apomorphine formulations for the acute treatment of *OFF* episodes, aiming to provide a more user-friendly alternative than the currently available subcutaneous injections. Moreover, we evaluated the usefulness of different finger tapping tasks as quick and quantitative pharmacodynamic measures for assessing the efficacy of fast-acting dopaminergic compounds. With the results described in this thesis, we hope to improve the quality of early phase clinical trials with novel fast-acting apomorphine formulations, ultimately resulting in better symptomatic treatment of PD.

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