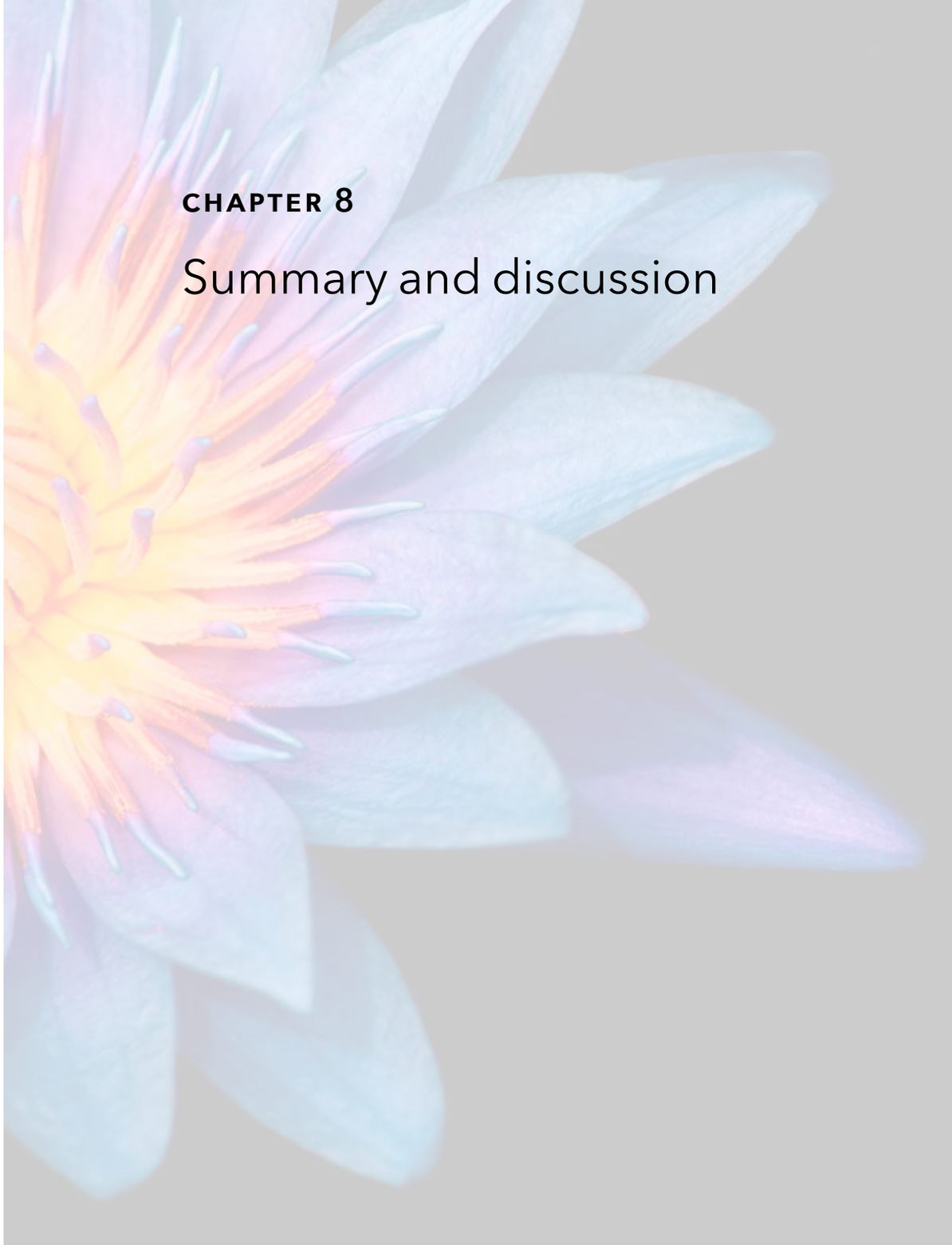
Clinical pharmacology studies investigating novel formulations of dopaminergic drugs

Thijssen, E.



CHAPTER 8

Summary and discussion

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects millions of people worldwide. Despite all research efforts, there is currently no disease-modifying treatment available and the main treatment avenue remains symptomatic treatment. As the disease progresses, patients develop motor and non-motor fluctuations that significantly impact activities of daily living and quality of life. Patients alternate between periods of favorable response to medication (*ON*) and periods of inadequate response (*OFF*). Apomorphine is a dopamine agonist that has been used to treat *OFF* episodes for three decades. It is available both as subcutaneous intermittent injections and subcutaneous continuous infusion. The intermittent injections are especially suited for patients with only a few *OFF* episodes per day, which is the focus of this thesis. Despite the well-known efficacy of apomorphine in treating *OFF* episodes, its administration route has several impracticalities. For instance, patients must self-administer injections during their *OFF* periods. This can be inconvenient, especially since the injection site is often covered by clothing. Additionally, the occurrence of injection site reactions and the fear of needles may serve as further limitations to its use.

APOMORPHINE

In this thesis, we evaluated two new administration routes of apomorphine that are expected to be more user-friendly. In **chapter 2 and 3**, a breath-actuated, oral inhalation device was investigated in healthy volunteers and PD patients. Staccato apomorphine (AZ-009) reached maximum plasma concentrations 1-2 minutes after inhalation and improved mean motor function (MDS-UPDRS III) in PD patients during an induced morning *OFF* state from the first measurement at 10 minutes post-dose. Its systemic absorption was significantly faster than that of the subcutaneous apomorphine injection for which maximum plasma concentrations were reached only after 30 minutes. This suggests the potential for a quicker transition from *OFF* to *ON* following treatment. To establish this conclusively, a direct head-to-head comparison is necessary. Additionally, it is important to assess and compare the duration of effect of both formulations in this study.

In healthy volunteers, apomorphine inhalation was not well tolerated with nausea, vomiting and hypotension being the most troublesome AEs. In contrast, PD patients tolerated apomorphine inhalation up to 4 mg reasonably well with AEs most often related to the inhalation: coughing and throat irritation. These AEs were mild and transient, usually resolving within minutes. No apparent accumulation and changes in safety profile were observed when AZ-009 was dosed three times daily with 2 hours between doses. In clinical practice, subcutaneous apomorphine is initiated at a low dose (1 or 2 mg) and titrated up until an optimal balance between side effects and efficacy is reached. In contrast, in the studies described in chapter 2 and 3, patients received a fixed dose. This likely led to suboptimal dosing, where for some the dose was too high and therefore resulted in AEs preventing the conduct of MDS-UPDRS III, and for others might have been too low to reach optimal efficacy. While these initial studies show that AZ-009 improves motor function, the described effects are likely an underestimation. Hence, future studies should investigate AZ-009's efficacy when administered at a patient's individually optimized dose. Currently, a phase 2 study is ongoing including an open-label titration phase followed by a double-blind at-home treatment period with an in-clinic visit.[1] Therefore, this study will provide more information on the efficacy of a titrated dose, as well as the usability of the device by patients during an *OFF* state in an at-home setting. Future studies should also investigate the long-term (pulmonary) safety and tolerability.

Overall, the data provided in chapter 2 and 3 provide confidence for the further development of Staccato apomorphine (AZ-009) in larger scale trials.

In **chapter 4**, buccal administration of an oromucosal apomorphine solution was evaluated. Its safety, tolerability and PK were compared to a subcutaneous apomorphine injection and a sublingual apomorphine film. Both comparator formulations were marketed at the time of study execution. However, in 2023, the sublingual apomorphine film was retracted from the market by the company (Sunovion) due to limited utilization. The company gave no further information on the reason for retracting, but it might have been related to the relatively high incidence of oropharyngeal side

effects upon repeated exposure.[2] The side effects are likely the result of apomorphine undergoing autooxidation in the saliva,[3] resulting in the formation of quinone derivatives and reactive oxygen species which have been associated with cytotoxicity.[4,5] It is hypothesized that this will occur less when apomorphine is administered as a solution, but this requires confirmation in future studies. Nonetheless, we showed that short-term treatment with oromucosal apomorphine was generally well-tolerated without oropharyngeal side effects and buccal mucosa abnormalities. Although relevant and reproducible plasma concentrations were reached, the exposures are not expected to be sufficient to treat all PD patients. Currently, the maximum dose that can be administered is 14 mg (0.2 mL). Administering a higher volume is not recommended so as to prevent saliva production and the induction of a swallowing reflex. Separating the administration of sprays by a few minutes instead of administering them sequentially was shown to not increase dose-normalized exposure. Therefore, future administrations are suggested to be administered as consecutive sprays. This is also more user-friendly. To make the oromucosal solution useful for the entire PD population, it is recommended to investigate other options to increase its exposure. Increasing the apomorphine concentration is unfortunately not possible due to apomorphine's limited solubility. However, an option could be to increase the surface area over which apomorphine solution is dispersed. This could be facilitated by using a different spray nozzle capable of dispersing the solution across a wider buccal area. Another potential avenue is to change the solvent composition. Adding/increasing for example ethanol might improve apomorphine's solubility, increase buccal absorption and enhance the dispersibility of the solution (thereby again increasing the surface area).[6,7] Lastly, the addition of a permeation enhancer to the formulation can theoretically increase buccal absorption.[8,9] However, due to the risk of local tolerability issues during prolonged daily use, this is considered a less suitable option.

Median t_{max} of oromucosal apomorphine ranged between 32 and 53 minutes over different dose groups with an overall range between 15 and 120 minutes. Therefore, absorption was slower than for subcutaneous injection in the abdomen (19 minutes (range: 8-40 minutes), and more comparable (although on the low end) to subcutaneous injection in the thigh described in chapter 2 (30 min (20-60 minutes)). Moreover, it was also considerably slower than apomorphine inhalation described in chapter 2. Future studies should therefore assess how this t_{max} relates to onset of effect of the oromucosal apomorphine formulation in order to confirm its usefulness as a rescue medication for *OFF* episodes.

A limitation of the apomorphine studies outlined in this thesis is the lack of an investigation into the usability of the devices. Given that the development of new apomorphine formulations is aimed at delivering a less invasive and easier to use formulation for PD patients, it is imperative that future studies verify that PD patients can independently use the breath-actuated inhaler and the spray pump device during an *OFF* state. Encouraging results have been published though on the use of dry powder inhalers by PD patients. Others have shown that most PD patients could handle a dry powder inhaler, had sufficiently high inspiratory flow rates and were able to hold their breath for up to 5 seconds after inhalation.[10] Moreover, a breath-actuated inhaler of levodopa dry powder has been approved for the treatment of *OFF* episodes. In a phase 2b study with this inhaler, patients were able to prepare and self-administer the treatment, even though some indicated concerns about inhaler system use during telephone contact (7% placebo, 14% levodopa).[11] Overall, this provides evidence that a breath-actuated inhaler can be used by PD patients.

ACUTE DOPAMINERGIC TREATMENT EFFECTS

To assess the effects of new fast-acting compounds, objective, quantitative and fast measurements are ideal. Especially for the treatment of *OFF* episodes, the onset of effect is crucial to evaluate whether the drug is suitable for this indication. Currently, the rather extensive MDS-UPDRS part III scale is often used to evaluate drug efficacy. Even though it is useful, it requires a trained rater, takes relatively long to complete (approximately 15 minutes) and is subject

to inter- and intra-rater variability. In **chapter 5, 6 and 7** of this thesis, multiple finger tapping tasks were evaluated for their use as objective, quantitative and fast pharmacodynamic measurements.

In **chapter 5**, four different touchscreen-based finger tapping tasks were evaluated in a technical validation study in healthy volunteers. Configurations included alternate index and middle finger tapping (IMFT) with 2.5 cm between targets and repetitive alternate index finger tapping (IFT) with 20 cm between targets. Both tasks were assessed with and without a visual cue. The results indicated that the visual cue, rather than signaling the next target, provided immediate visual feedback. When participants tapped outside the target area, the next circle did not appear, prompting participants to pause and correct the error. This resulted in a reduced tapping speed and lower fatigue in both tasks. If and how these data would translate to a PD population was uncertain and would have required further validation in a PD population. This uncertainty combined with the good performance of the uncued tasks, led to the decision to only validate the uncued tasks further in chapter 6.

No significant differences were observed in tapping measurements within a day, but these were observed between days. It appeared that participants changed their tapping strategy during the second visit, prioritizing speed over accuracy, possibly due to familiarity with the task. The absence of a learning effect within a day supported the further evaluation of these tasks in response to fast-acting medication, without the need for extensive training sessions. Considering the observed changes between days, the next study was conducted using a balanced crossover design (chapter 6). Overall, this technical validation study provided evidence that the uncued IMFT and IFT tasks functioned well and were repeatable, and that speed, accuracy and rhythm parameters showed good potential sensitivity in healthy volunteers.

Hence, in **chapter 6**, these two touchscreen-based finger tapping tasks, together with a thumb-index finger tapping (TIFT) task, were further evaluated in a follow up study in PD patients during an induced *OFF* state. This randomized, double-blind, placebo-controlled crossover study assessed their ability to detect and quantify dopaminergic medication effects.

Of the three tapping tasks, the alternate IMFT task performed the worst, that is, had the lowest effect sizes. Its effect sizes were also below that of the gold standard MDS-UPDRS III. Moreover, the task was sometimes difficult to perform for the patients with PD, resulting in a high percentage of same-sided double taps. These problems with correctly performing/recording the IMFT task, combined with the relatively small effect sizes, make the task in its current configuration the least suitable for efficacy studies in PD patients. In contrast, PD patients were able to perform the IFT and TIFT tasks without difficulties. The IFT task showed significantly faster tapping (total taps), improved rhythm (inter-tap interval SD), and decreased accuracy (total spatial error) in response to levodopa/carbidopa compared to placebo. Total number of taps and total spatial error had the largest standardized effect sizes, and these were comparable to MDS-UPDRS III. That speed- and accuracy-related parameters had the largest effect sizes was consistent with expectations based on the potential sensitivities calculated in chapter 5. In the TIFT task, levodopa/carbidopa compared with placebo resulted in faster tapping (opening and closing velocity) with a bigger amplitude and improved rhythm (inter-tap interval SD). Mean opening and closing velocity had the largest effect sizes, and were comparable to the effect size of the MDS-UPDRS III. The speed-related parameters in both tasks showed a moderate-to-strong correlation with the MDS-UPDRS III ($r = 0.45–0.70$). Moreover, the inter-tap interval SD showed a strong correlation with the MDS-UPDRS III in the levodopa/carbidopa group ($r = 0.66$) and a trend toward a moderate correlation ($r = 0.45$) in the placebo group. In conclusion, the alternate IFT and TIFT tasks provided short, rater-independent measurements sensitive to dopaminergic medication effects with similar effect sizes as the MDS-UPDRS III.

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 parameters ('composite biomarker') to predict the treatment effect (i.e., did the patient receive active or placebo treatment?) and estimate the disease severity (i.e., MDS-UPDRS III score). A composite biomarker was created for each tapping task individually, for the three tapping tasks combined

and for the MDS-UPDRS III. Overall, the baseline corrected models performed better than the uncorrected models. The baseline-corrected IFT composite biomarker had the best classification performance (83.50% accuracy, 93.95% precision, effect size 2.58 ± 0.90)) and outperformed the MDS-UPDRS III composite biomarker (75.75% accuracy, 73.93% precision, effect size 2.12 ± 1.25). The IFT composite biomarker included total number of taps and total spatial error, which was in line with expectations based on the effect sizes reported in chapter 6. The baseline-corrected IFT composite biomarker also achieved the best performance when the MDS-UPDRS III total score was estimated (mean absolute error: 7.87, Pearson's correlation: 0.69).

Overall, we demonstrated that the IFT composite biomarker outperformed the combined tapping tasks and the MDS-UPDRS III composite biomarkers in detecting treatment effects. Combining the most relevant parameters instead of using a single parameter, improves the ability to detect medication effects. Therefore, this provides evidence to include the IFT composite biomarker in future clinical trials for the detection of medication effects. Despite these positive outcomes, it is essential to note that these conclusions are based on a relatively small sample size. To address this limitation, chapter 7 employed nested cross-validation. Nevertheless, the generalizability of the findings from this specific group of PD patients to the broader and heterogeneous PD population remains uncertain. While finger tapping tasks are good at detecting bradykinesia in forearm and fine finger movements, they may not provide a comprehensive measure of overall motor function. Consequently, certain subsets of PD patients might not show improvement in finger tapping, even if their overall motor function has improved. Therefore, it is imperative to confirm the validity, reliability, and generalizability of our methods using an independent dataset. Therefore, we propose to conduct a follow-up study with a larger cohort of PD patients with diverse MDS-UDPRS III scores, in which both akinetic-rigid dominant and tremor-dominant PD subtypes are represented.

While completion of the MDS-UPDRS III scale typically requires about 15 minutes, the finger tapping tasks take only 15 to 30 seconds. This makes the finger tapping tasks less burdensome for patients

but also allows for more frequent and closely spaced assessments compared to the MDS-UPDRS III. This enables a better detection of the onset of effect and the time to reach maximum effect. This is especially useful for drugs with an anticipated fast onset of effect, like apomorphine for the treatment of *OFF* episodes. Hence, it is advised to include (at a minimum) the IFT task in future trials with inhaled apomorphine and apomorphine oromucosal solution to determine their precise onset of efficacy.

Since the IFT task is a touchscreen tapping task and does not require a trained rater like the MDS-UPDRS III, it could also be suitable for testing medication effects or monitoring disease progression in a home setting. However, this would require further validation of the tapping tasks' variability over a longer time period when performed without study staff supervision. The advantage of performing the IFT task at home would be the ability of the investigator to monitor the patient in their real-life environment and reduce the number of in-clinic visits required, thereby reducing patient burden.

LOOKING TOWARDS THE FUTURE

The Parkinson 'pandemic' and the search for a disease-modifying therapy

PD is the fastest growing neurological disorder.[12] Whereas in 1990, 2.5 million people were affected by PD worldwide, this number had increased to 6.1 million in 2016.[12] Projections estimate that this will increase further to 13-14 million people by 2040.[13] This substantial rise has led some to call Parkinson's disease a pandemic. The increase in incidence can be attributed to the aging of the worldwide population. Environmental factors linked to industrialization are thought to contribute as well.[12] Population-based incident PD cohorts have shown that motor fluctuations manifest in 22.8-54.3% of patients within 5 years after diagnosis, and increase to 100% 10 years after diagnosis (Table 1).[14–16] For levodopa-induced dyskinesia this was 14.5-29.6% within 5 years, and 55.7% within 10 years. This means that within 5-10 years after disease onset, the majority of PD patients suffer from motor complications. With the aging of the worldwide population, more

patients will live long enough to fall victim to motor complications. This adds significant disease burden but also economic costs. Hence, the need for disease-modifying therapies is high.

Our knowledge about the pathology of PD is expanding and shows that it is a complex interplay of alpha-synuclein aggregation and spreading, mitochondrial dysfunction, oxidative stress, lysosomal dysfunction, and neuroinflammation.[17] Therapies targeting these dysfunctional processes are currently undergoing extensive research.[18] For alpha synuclein, multiple options are being investigated, aiming either for the inhibition of its aggregation (stabilizing small molecule blockers, autophagy induction with ABL1 inhibitors), reducing its synthesis (antisense oligonucleotides, small interfering RNAs), preventing its cell-to-cell transmission (monoclonal antibodies, active immunization), or reducing its gene transcription (beta2 adrenergic receptor agonists).[18] Improving mitochondrial function has shown promise in preclinical models by preventing neurodegeneration. Thus far, however, these results have not translated into a slower disease progression in PD patients in clinical trials. To improve lysosomal function, various strategies targeting the beta glucocerebrosidase (GCase) enzyme have been investigated.[18] These include increasing GCase activity (GCase modulators), reducing accumulated GCase substrate (glucosylceramide synthase inhibitors) and GBA1 gene therapy. LRRK2 inhibitors and LRRK2 antisense oligonucleotides are in clinical development aiming to decrease LRRK2 activity in PD patients with a LRRK2 mutation, but might also be useful for patients without a mutation but with elevated LRRK2 activity.[18] Targeting neuroinflammation is another strategy that is being investigated, for example by inhibiting the NLRP3 inflammasome.[18] Lastly, stem cell-based therapies are in early phase clinical development. Studies investigate transplantation of dopamine neurons derived from embryonic stem cells or induced pluripotent stem cells to replace lost dopaminergic cells.[19] In addition, mesenchymal stem cells are investigated for their neuroprotective and immunomodulatory effects.[20,21]

Despite all efforts, no disease-modifying drug has reached the market yet. When it does, it is expected to slow disease progression but not cure the disease. Therefore, the need for symptomatic treatment of response fluctuations in Parkinson's disease remains high. In the next section, an overview of drugs that are currently in clinical development is provided.

Symptomatic treatments in clinical development for response fluctuations

INTERMITTENT OFF

For sudden unpredictable *OFF* periods, there are currently only two treatment options available, i.e., subcutaneous apomorphine injection (APO-go, APOKYN) and levodopa dry powder inhalation (Inbrija). Between 2020 and 2023, apomorphine sublingual film (KYNMOBI) was shortly available in the US and Canada, but it was discontinued, again reducing the number of treatment options. Currently, there are only a few alternatives in development, of which two are described in this thesis: 1) Staccato apomorphine inhalation, 2) oromucosal apomorphine solution for buccal delivery, and 3) levodopa dry powder inhalation (Cyclops). Staccato apomorphine is further investigated in an ongoing phase 2 clinical trial expected to complete in March 2024.[22] The Cyclops dry powder inhaler has completed a phase 2 clinical trial,[23] and recently in 2023, a pilot comparative bioavailability study investigating levodopa Cyclops and Inbrija.[24] Between November 2023 and December 2024, a study will be conducted to investigate and compare the usability of both inhalation devices.[25] According to pureIMS, the developer of levodopa Cyclops, these studies are undertaken to support a marketing authorization in the US.[26] Although both Inbrija and Cyclops deliver levodopa as a dry powder for inhalation, differences between the devices exist. For Inbrija, patients must complete multiple steps to inhale a full dose (2 capsules). This involves removing a capsule from its blister immediately before use, loading it into the inhaler, inhaling and holding the breath for 5 seconds, removing the capsule, loading a second one, and repeating the process. Following the second inhalation, the inhaler's mouthpiece must be cleaned.[27] So even though the administration route is more user-friendly than a subcutaneous injection, it does require patients

to complete multiple fine finger movements during an *OFF* state. On the other hand, the levodopa Cyclops inhaler requires fewer steps. Opening the pouch containing the inhaler and pulling out a cover foil readies it for use.[28] These steps are fewer than those for Inbrija because the Cyclops inhaler comes prefilled with levodopa. Additionally, being a single-use inhaler eliminates the need for cleaning. These differences suggest that the levodopa Cyclops inhaler may offer an even more straightforward administration route, although this hypothesis requires confirmation in the planned study comparing the usability of both devices.

CONTINUOUS DELIVERY

Another avenue to decrease symptom fluctuations (*OFF* episodes and dyskinesia) is to provide a more continuous stimulation of the (dopaminergic) neuronal system. A few treatment options are already available, namely DBS, continuous subcutaneous apomorphine infusion and continuous levodopa-carbidopa intestinal infusion.[29] However, research is ongoing to develop other drugs/formulations. Currently, there are three subcutaneous formulations in development for continuous infusion of (fos)levodopa/(fos)carbidopa. Two are in late stage development (ND0612, ABBV-951), and one is in early stage development (DIZ102).[30,31] The advantage of continuous subcutaneous levodopa/carbidopa administration, as opposed to intestinal administration, is that no surgery to insert a permanent percutaneous endoscopic gastro-jejunal (PEG-J) tube is needed. This is considered an invasive procedure and there is a considerable risk for device complications.[29] Continuous subcutaneous levodopa/carbidopa infusion has been shown to result in stable drug plasma concentrations.[30,32,33] For ABBV-951, the product that is furthest in its development, *ON* time without troublesome dyskinesia has been shown to increase with 2.72 ± 0.52 hours/day, compared to 0.97 ± 0.50 hours for oral immediate-release levodopa/carbidopa.[34] ABBV-951 can be used as a monotherapy, but ND0612 should be combined with oral levodopa/carbidopa to reach therapeutic concentrations, which might be a disadvantage of the latter pump.[31] Moreover, continuous subcutaneous therapies can result in infusion site reactions.[31] Another continuous therapy being investigated is the DopaFuse, which provides continuous oral delivery of levodopa/carbidopa to the back of the mouth via a specialized mouthpiece. It is a non-invasive delivery system, but it does not bypass the gastric dysmotility or the challenges related to erratic gastric emptying prevalent in PD patients. However, phase 2 results published in the EU Clinical Trials Register do show that it leads to less fluctuating plasma levels than oral immediate-release levodopa/carbidopa tablets.[35] In addition, *OFF* time was 1.51 ± 1.44 hours/day when DopaFuse was combined with a morning oral levodopa/carbidopa dose, compared to 3.23 ± 2.18 hours/day for oral levodopa/carbidopa tablets alone. One should note that this was a single arm non-randomized study, so future studies should address its efficacy further. Complications associated with the oral device occurred in 31.25% of the patients.

EXTENDED RELEASE

Another way to achieve more stable levodopa plasma concentrations, is the use of extended release formulations. Three extended-release levodopa/carbidopa capsules are in clinical development: IPX203, DM-1992 and the Accordion Pill. IPX203 is a capsule containing immediate-release levodopa/carbidopa granules and extended-release levodopa beads with an enteric coating to prevent early disintegration in the stomach. In a phase 3 trial, IPX203 resulted in 0.53 more hours of *ON* time without troublesome dyskinesia per day compared to immediate-release levodopa/carbidopa, while it had to be dosed less often (3 versus 5 times/day).[36] The New Drug Application (NDA) that was submitted to the FDA was rejected in July 2023. The FDA requested additional safety information on carbidopa in the formulation. The company will resubmit the NDA with additional information when available.[36] The other two formulations, DM-1992 and the Accordion Pill, are both gastric retentive formulations including immediate and extended release components. DM-1992 swells when exposed to gastric fluid and the Accordion Pill consists of folded sheets in a capsule that extend while in the stomach. As a result, both formulations remain in the stomach longer, where they dissolve slowly and provide controlled release of levodopa to the small intestine.[37] Phase 2 results comparing DM-1992 with immediate-release levodopa/carbidopa were positive for DM-1992,

demonstrating steadier levodopa plasma concentrations and reduced *OFF* time despite a lower dosing frequency.[36] However, no follow up studies with DM-1992 have been reported in study registries after this publication in 2015. The same is observed for the Accordion Pill. This formulation was investigated in a phase 3 clinical trial that completed in 2019. Topline results shared in July 2019 indicated that the Accordion Pill was not superior to immediate-release levodopa/carbidopa in reducing daily *OFF* time.[38] Nevertheless, in 2020, the company suggested that this lack of superiority might be attributed to the administration of doses that were too low to reach optimal efficacy. This idea was supported by the fact that patients who did not reach the maximum dose during the dose titration phase did show a relevant reduction in *OFF* time. Consequently, the pharmaceutical company expressed the intention to seek a strategic partner capable of advancing the levodopa Accordion Pill through a final phase 3 pivotal trial and progressing it towards marketing authorization.[39] However, results of this trial have not been published to date and no follow up studies have been registered in the registries. Given the lack of recent updates on the clinical development progress of DM-1992 and the Accordion Pill, the main hope is for IPX203 to reach the market.

LEVODOPA-INDUCED DYSKINESIA

The focus of this thesis was the treatment of sudden intermittent *OFF* periods. However, most patients with advanced PD also experience dyskinesia which has a major impact on their quality of life. To reduce dyskinesia, one can change the treatment regimen (timing, dose), have DBS surgery, or use the abovementioned continuous therapies that provide lower peak-trough oscillations. Moreover, amantadine, a non-selective N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, has shown benefit in reducing dyskinesia by reducing glutamatergic activation. However, it can result in neuropsychological side effects which limit its use. Several other more selective glutamatergic drugs have been evaluated but clinical development has been stopped due to insufficient anti-dyskinetic effect.[35] Another glutamatergic drug, dipraglurant, an mGluR5-negative allosteric modulator, was already in phase 2b/3 clinical trials, when the study was terminated in mid-2022.[40,41] According to

Addex Therapeutics this was due to the slow recruitment of patients. Only AV-101, a selective NMDA receptor antagonist, seems to be still in development targeting the glutamatergic system.[42] Not only the glutamatergic system is expected to play a role in dyskinesia, but also the serotonergic system. It is known that serotonergic neurons can take over the function of striatal dopaminergic neurons, but since they lack autoreceptors and dopamine reuptake abilities, they release dopamine in an uncontrolled manner.[43] Therefore, inhibition of serotonin neurons (via G_i-coupled 5-HT_1 receptors) might prove beneficial in reducing dyskinesia.[37] Various drugs are in development to test this hypothesis and initial results are positive. Drugs in clinical development include 5-hydroxytryptophan (5-HTP), buspirone/zolmitriptan (JM-010), eltoprazine, and befiradol.[37,44] In addition, the D3 antagonist, mesdopetam has shown benefit in phase 2 clinical trials and is therefore expected to progress to phase 3 clinical trials.[45,46] Lastly, two phosphodiesterase inhibitors are in development. CPL500036, a phosphodiesterase 10A (PDE10A) inhibitor, has shown anti-dyskinetic effects without reducing the effect of levodopa in an animal PD model,[47] and is expected to complete its phase 2 trial in PD patients with levodopa-induced dyskinesia at the end of 2023.[48] Lenrisopodun, a PDE1 inhibitor, is currently also in phase 2 clinical trials, where it is investigated as an adjunctive therapy for PD patients with wearing *OFF* symptoms and levodopa-induced dyskinesia.[49]

INITIAL TREATMENT WITH NOVEL (MORE PHYSIOLOGICAL) DOPAMINE AGONISTS

The abovementioned treatments in development are all focused on treating patients that already experience motor fluctuations and/or dyskinesia. However, ideally, we are able to at least delay the onset of these complications. Previously, it was thought that delaying the initiation of levodopa might help delay the onset of motor fluctuations and dyskinesia. The LEAP study has shown that this is not the case, and that starting levodopa later in early PD patients does not reduce or delay response fluctuations. In contrast, the group that started levodopa earlier had fewer patients experiencing motor response fluctuations after 80 weeks, underscoring the importance of timely intervention.[50]

Another option that has been contemplated is to start treatment in early PD patients with a levodopa-sparing therapy instead of levodopa. The PD-MED study has shown that patients that started on levodopa compared to a levodopa-sparing therapy (dopamine agonist or MAO-B inhibitor) were more likely to develop dyskinesia, but showed no differences in motor fluctuations. Despite the higher likelihood of developing dyskinesia, patients initially treated with levodopa had small but persistent higher patient-rated mobility scores and had less side effects (mainly psychological, sleep disturbance, and gastrointestinal). Hence, levodopa was, and still is, considered the preferred initial treatment in most patients.[51] However, if a dopamine agonist with a better risk-benefit profile would become available, this preference might shift. Tavapadon might be such a dopamine agonist. It is a novel selective D1/D5 partial agonist.[52] Preclinical studies have shown that it improves motor function as effectively as levodopa but with a longer duration of effect. Moreover, animal studies have shown that D1/5- but not D2/3-selective dopamine agonists can improve motor symptoms in animals with progressive neurodegeneration that are unresponsive to levodopa.[52] This indicates that D1/5 agonism could be useful both in early as well as advanced PD. Tavapadon is currently indeed investigated in multiple phase 3 clinical trials as a monotherapy in treatment-naïve early PD patients, as well as an adjunctive treatment in levodopa-treated patients with motor fluctuations.[53-56] Due to its partial D1/5 agonism, tavapadon is hoped to result in fewer D2/3-associated side effects (e.g. impulse control disorder, sleep disturbance) and less D1/5 full agonism-associated side effects (e.g. cardiovascular and dyskinetic side effects). Its partial agonism is also expected to provide a more physiological stimulation, since the likelihood of receptor overstimulation and hence desensitization and tolerance is lower. A final added benefit of D1 stimulation is that D1 is not only involved in motor control but also in cognition, and hence might have a beneficial effect on cognition. Results from phase 1 and phase 2 clinical trials are encouraging with significant improvements in motor function and MDS-UPDRS I-III combined scores, a substantially longer half-life (~24 hours) than levodopa and available D2/3 agonists, and only mild cardiovascular changes (e.g. decreases in blood pressure, increases in heart rate).[52] The phase 3 clinical trials will have to confirm whether tavapadon will live up to its potential.

The development of response fluctuations is largely due to the progressive degeneration of dopaminergic neurons, but also partly due to non-physiological pulsatile stimulation by dopaminergic drugs. By developing drugs that provide a more physiological stimulation, we may be able to delay the development of response fluctuations and dyskinesia. Positive allosteric modulators (PAMs) have been implicated to provide such a more physiological stimulation. They do not directly activate the dopamine receptor, but enhance the effects of endogenously available dopamine. Therefore, they have the potential to prevent excessive stimulation and resulting receptor desensitization and the development of tolerance, as well as contribute to a better tolerability profile. D1 PAMs are already in development for PD. A phase 1b study in PD patients has been completed with mevidalen (LY3154207) showing improved motor function in all patients receiving mevidalen and in some receiving placebo.[57] However, the compound is further being developed for symptomatic Lewy body dementia.[58] Another D1 PAM, UCB0022, has shown preclinically to improve motor function similar to levodopa but with less dyskinesia.[58] It will be investigated in a phase 2 clinical trial starting at the end of 2023. The trial will evaluate the effect on *OFF* time when UCB0022 is given as an adjunctive therapy to advanced PD patients.[59] UCB0022 has not yet been investigated as a monotherapy and compared to the efficacy of levodopa in PD patients, but this will be an interesting next step. Similarly, D2 PAMs hold promise for progressing the treatment of PD by offering a more physiological stimulation compared to existing dopamine agonists. However, its development is still in the preclinical stage.[60]

Other applications of Staccato inhalation and buccal drug delivery

The Staccato technology is designed to administer drug aerosol particles into the deep lung with a single breath. The Staccato device holds a distinct advantage over other inhalation devices due to its

excipient-free composition. Unlike pressurized metered dose inhalers (pMDIs), it does not require coordination between device actuation and inhalation.[62] Moreover, unlike most dry powder inhalers that require a moderate-to-high inspiratory flow rate (usually at least 30 L/min) to separate the drug from the carrier particles and aerosolize it, the Staccato device requires only a low inspiratory flow rate of about 15 L/min for device actuatation.[62,63] But above all, inhalation of a drug with the Staccato device results in rapid systemic absorption, mimicking that of an intravenous administration. In this thesis, we indeed showed that maximum apomorphine plasma concentrations were reached within 1-2 minutes after inhalation and that motor symptoms in PD patients were improved at the first measurement time point 10 minutes post administration. This rapid absorption, and consequently, quick onset of action, provides opportunities to use the Staccato device in other indications that require quick resolution of complaints. Indeed, Staccato loxapine has already been approved for the acute treatment of agitation associated with schizophrenia or bipolar I disorder.[64-66] The phase 3 trials showed improvements in agitation at the first assessment at 10 minutes post administration, which is significantly earlier than for oral or intramuscular loxapine.[67] Moreover, ongoing research is exploring other therapeutic indications. A currently ongoing phase 3 trial in epilepsy patients investigates the safety and tolerability of Staccato alprazolam which is intended for the rapid termination of epileptic seizures.[68,69] The phase 2b study showed promising results, i.e., Staccato alprazolam resulted in a significantly greater proportion of patients with seizure cessation within 2 minutes and no recurrence within 2 hours, compared to placebo.[70] In addition, Staccato granisetron is being investigated for the acute treatment of sudden, repeated episodes of severe nausea and vomiting (cyclic vomiting syndrome). The phase 2 study has been completed in 2022, but results are pending.[71] In addition to these therapeutic indications, many others that require acute treatment can be explored, for example acute allergic reactions.

Buccal drug administration can be used both for local and systemic treatment. The focus of this thesis was on achieving systemic exposure through buccal drug delivery. Small lipophilic drugs can be easily absorbed through the buccal mucosa while avoiding first-pass hepatic metabolism and enzymatic degradation in the gastrointestinal tract. Moreover, buccal drug administration is considered more user-friendly than e.g. intravenous, subcutaneous or rectal administration. Hence, it provides an administration route that is not only interesting for the treatment of *OFF* episodes (this thesis), but also for various other indications. However, despite this potential, only a limited number of buccal formulations are on the market. Available formulations include oromucosal solutions (e.g. midazolam),[72] buccal films (e.g. buprenorphine/naloxone, and fentanyl),[73,74] and buccal tablets (e.g. fentanyl, prochlorperazine, and testosterone).[75-77] The development of buccal formulations has many challenges, including the residence time of the drug in the buccal cavity. This time is usually limited due to insufficient adhesion of the formulation to the wet buccal mucosa and swallowing of the drug with the saliva. Another challenge, especially for larger and hydrophilic drugs, is crossing the mucosal barrier that consists of multiple epithelial cell layers and a mucus layer. To overcome these challenges, current research is focused on the development of mucoadhesive films and patches that strongly adhere to the buccal cavity.[78,79] This increases the drug's residence time and hence the time available for drug absorption. Also significant research efforts are targeted at using nanoparticles as drug carriers in buccal formulations.[80] These nanocarriers can increase the permeability of the drug through the mucus layer and protect the drug from enzymatic degradation. Moreover, the nanoparticles can be adjusted to have controlled or sustained release characteristics. To increase bioavailability, researchers are also exploring permeation enhancers that can effectively increase the permeability of the buccal mucosa without toxicity.[78] For protein and peptide delivery, protease inhibitors may also be added to buccal formulations to protect the drug from degradation.

Taken together, extensive research is being conducted on buccal drug delivery systems to enhance systemic exposure and to expand the range of drugs that can be delivered via the buccal route beyond that of small lipophilic compounds. In this pursuit, mucoadhesive buccal films and patches containing drug-loaded nanoparticles, possibly with permeation enhancers and protease inhibitors, hold promise for the future.

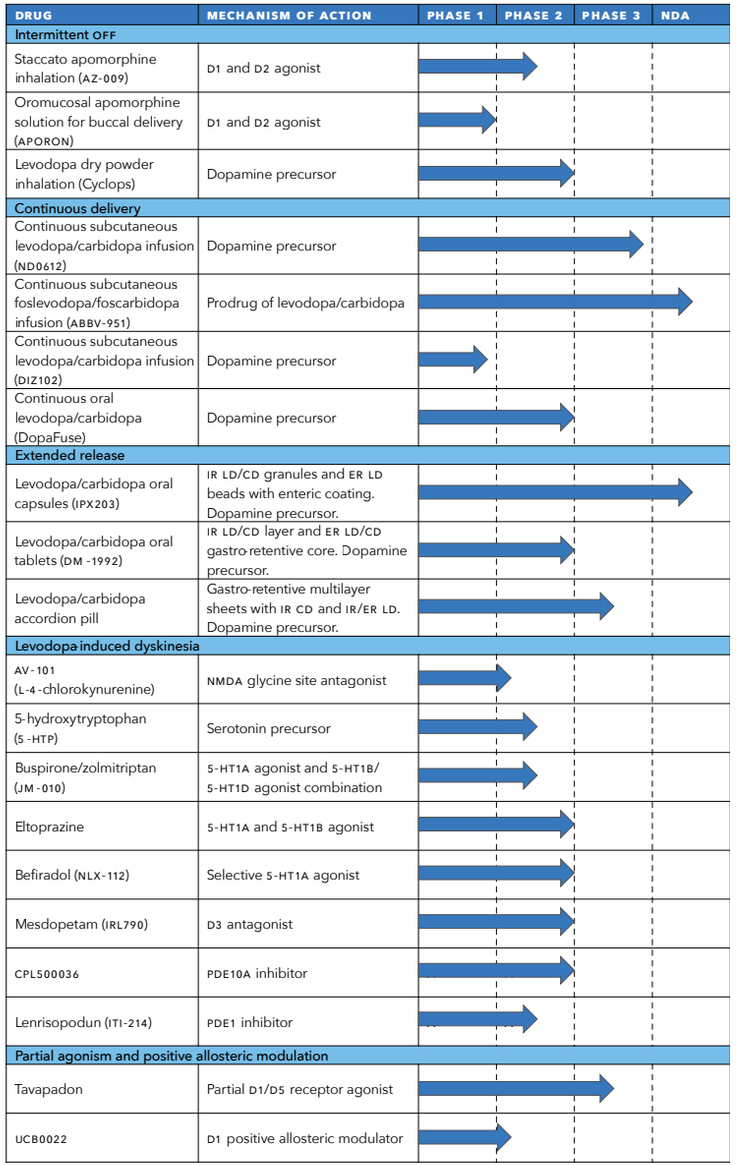
OVERALL CONCLUSION

With the aging of the worldwide population, more PD patients will live long enough to fall victim to response fluctuations. This has a significant impact on their quality of life. Although there is hope that disease-modifying drugs will enter the market, these drugs are expected to slow disease progression rather than cure the disease. Consequently, the need for symptomatic treatment is expected to remain in the future. The goal is to develop user-friendly symptomatic drugs with fewer side effects to improve patient's quality of life. Fortunately, there are several drugs in clinical development that target response fluctuations. These include novel apomorphine formulations, as discussed in this thesis, which show promise in treating sudden *OFF* episodes. To accurately assess the (onset of) efficacy of fast-acting dopaminergic drugs, future clinical trials could be improved by adding finger tapping tasks as a pharmacodynamic measurement.

TABLE 1 **Cumulative incidence of motor fluctuations and levodopa-induced dyskinesia in incident population-based Parkinson's disease cohorts from the time of diagnosis.**

Reference	Cohort size	Motor fluctuations	Levodopa-induced dyskinesia
Scott et al. 2016[14]	N=189	22.8% at 5 years	29.6% at 5 years
Bjornestad et al. 2016[15]	N=189	42.9% at 5 years	24.3% at 5 years
Kim et al. 2020[16]	N=141	54.3% at 5 years 100% at 10 years	14.5% at 5 years 55.7% at 10 years

FIGURE 1 **Symptomatic treatments in development for response fluctuations.**



DRUG	MECHANISM OF ACTION	PHASE 1	PHASE 2	PHASE 3	NDA
Intermittent OFF					
Staccato apomorphine inhalation (AZ-009)	D1 and D2 agonist				
Oromucosal apomorphine solution for buccal delivery (APORON)	D1 and D2 agonist				
Levodopa dry powder inhalation (Cyclops)	Dopamine precursor				
Continuous delivery					
Continuous subcutaneous levodopa/carbidopa infusion (ND0612)	Dopamine precursor				
Continuous subcutaneous foslevodopa/foscarbidopa infusion (ABBV-951)	Prodrug of levodopa/carbidopa				
Continuous subcutaneous levodopa/carbidopa infusion (DIZ102)	Dopamine precursor				
Continuous oral levodopa/carbidopa (DopaFuse)	Dopamine precursor				
Extended release					
Levodopa/carbidopa oral capsules (IPX203)	IR LD/CD granules and ER LD beads with enteric coating. Dopamine precursor.				
Levodopa/carbidopa oral tablets (DM -1992)	IR LD/CD layer and ER LD/CD gastro-retentive core. Dopamine precursor.				
Levodopa/carbidopa accordion pill	Gastro-retentive multilayer sheets with IR CD and IR/ER LD. Dopamine precursor.				
Levodopa-induced dyskinesia					
AV-101 (L-4-chlorokynurenine)	NMDA glycine site antagonist				
5-hydroxytryptophan (5-HTP)	Serotonin precursor				
Buspirone/zolmitriptan (JM-010)	5-HT1A agonist and 5-HT1B/5-HT1D agonist combination				
Eltoprazine	5-HT1A and 5-HT1B agonist				
Befiradol (NLX-112)	Selective 5-HT1A agonist				
Mesdopetam (IRL790)	D3 antagonist				
CPL500036	PDE10A inhibitor				
Lenrisopodun (ITI-214)	PDE1 inhibitor				
Partial agonism and positive allosteric modulation					
Tavapadon	Partial D1/D5 receptor agonist				
UCB0022	D1 positive allosteric modulator				

Based on literature reviews,[37,61] trial registries (clinicaltrialregister.eu, clinicaltrials.gov) and press releases. CD, carbidopa; ER, extended-release; IR, immediate-release; LD, levodopa; NDA, New Drug Application.

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