Parkinsonism and Related Disorders 59 (2019) 39–48

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

The next chapter in symptomatic Parkinson disease treatments

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ARTICLE INFO

Keywords:
Parkinson disease
Levodopa
Apomorphine
Symptomatic treatment
Motor fluctuation

ABSTRACT

Significant advances in the symptomatic treatment of Parkinson disease (PD) have occurred since the discovery of levodopa (LD). Perhaps as a testament to its unparalleled efficacy, novel formulations aiming to optimize LD delivery to obtain better bioavailability, longer duration of effect and less plasma level fluctuations remain a major focus of drug development, nearly 5 decades since it was first commercially used. In addition, alternative apomorphine delivery formulations are also in development to provide rapid-acting, needle-free agents for the management of "off" episodes in patients experiencing motor fluctuations. "Non-dopaminergic" approaches have also emerged as promising treatments targeting different pathways to enhance the modulation of dopaminergic and neuroprotective mechanisms. This paper focuses on reviewing the evidence on the latest advances in non-surgical, symptomatic motor PD treatment.

1. Novel levodopa preparations

Levodopa (LD), commonly delivered with carbidopa (CD), remains the gold-standard treatment for the control of motor symptoms of Parkinson disease (PD) since its introduction in the 1960's [1]. However, an eventual reduction in the reliability and duration of its motor benefit over time has been long observed. On average, 80% of PD patients eventually develop motor fluctuations over a period of 10 years after LD initiation [2].

Although the precise mechanisms that contribute to the development of motor fluctuations are still a matter of debate, their fundamentals still rely on LD pharmacokinetics and its delivery model [2]. The non-physiologic, pulsatile stimulation of dopamine receptors due to the intermittent and bolus delivery of immediate release (IR) LD, is thought to be one of the major contributors [2]. New formulations are thus currently being developed to improve LD formulation and delivery, in the hopes of replicating a prolonged and more physiologic striatal dopamine receptor stimulation.

1.1. Levodopa accordion pill (AP-LD/CD, Intec pharma)

The LD accordion pill (AP-LD/CD) is a gastric-retentive dosage formulation containing LD and CD in both immediate- and controlled-release (IR and CR) forms. It uses a biodegradable film designed in a planar structure, arranged in multiple layers folded inside a capsule [3]. The purpose of this formulation is to prolong its gastric retention as the layers unfold and dissolve slowly in the stomach, thereby enhancing drug absorption [3]. The results of 3 small Phase 2 studies involving AP-LD/CD have been presented primarily in abstract form [4–6]. The first one was a multicenter, open-label, randomized, crossover, two-way study that evaluated AP-LD/CD twice daily in PD patients with motor fluctuations [4]. The authors performed a 14-day (on 10 patients) and a 42-day (on 16 patients) pharmacokinetic assessment along with patient motor fluctuations diaries [3,4]. LD absorption phase increased by six-fold and achieved adequate therapeutic plasma levels with twice daily AP-LD/CD. Peak-to-trough level fluctuations reduced substantially. Higher pre-dose LD plasma levels was also observed with AP-LD/CD compared to standard of care, suggesting a longer AP-LC/CD half-life. There was also a significant reduction in total "off" time and an increased in "on" time without troublesome dyskinesias [4].

Another multi-center, open-label, two-way, randomized, crossover study compared 34 subjects receiving AP-LD/CD 375/50 mg (n = 16) or 500/50 mg (n = 18) versus IR LD/CD at an equivalent dose (187.5/18.75 mg four times per day) [5]. Similar pharmacokinetic characteristics with regards to the LD absorption phase, therapeutic level coverage throughout the day, and peak-to-trough fluctuations were noted. AP-LD/CD provided a reduction of 45% in total "off" time ($p < 0.0001$) compared to IR LD/CD, without an increase in troublesome dyskinesias [5].

Finally, a head-to-head comparison between AP-LD/CD versus IR and CR LD plus a decarboxylase inhibitor (DDCI) looked for any advantage of AP-LD/CD over currently available LD presentations by performing a multi-center, open-label, two-way randomized crossover study on AP-LD/CD 375/50 mg (N = 16) or 500/50 mg (N = 18) twice

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https://doi.org/10.1016/j.parkreldis.2019.01.002
Received 17 August 2018; Received in revised form 1 December 2018; Accepted 2 January 2019

a day [6]. The groups were compared with the subjects' standard LD/DDCI during a 2-week adjustment period, followed by a one-week test period. Patients receiving both AP-LD/CD formulations had a reduction in the number of daily LD doses needed per day compared to the LD/DDCI group, as well as an increase in the proportion of good "on" time (12% and 16% increase, respectively; $p < 0.0001$). Moreover, the Clinical Global Impression of Change (CGIC) and general satisfaction scales rated by patients and physicians were significantly improved on AP-LD/CD [6].

AP-LD/CD Phase 3 trials have yet to be published in peer-reviewed literature (ClinicalTrials.gov ID number NCT02615873). The advantage of AP-LD/CD over newer LD formulations, such as extended-release LD/CD (Rytary), has not been established. Nevertheless, its superiority over IR formulations and its potential to reduce the daily dose frequency of LD to twice per day might be advantageous for several patients.

1.2. XP21279 (XenoPort, Inc.)

XP212779 is an ester-conjugate LD *prodrug*, with the ability to be absorbed from the small *and* large intestines due to a high capacity nutrient transporter expressed through the gastrointestinal tract. Once absorbed, it is metabolized into LD by carboxylesterases [3,7]. XP21279 had an overall levodopa mean bioavailability measured by the area under the concentration versus time curve (%Frel AUC) of 89–91% compared to IR LD/CD in Phase 1 and 2 trials [7–9] An open-label trial, multiple-dose, multicenter, 2-period, sequential-treatment study on XP212779 plus CD randomized 10 PD patients with motor fluctuations [8]. Patients received IR LD/CD three times daily for two weeks, followed by XP212779 plus CD three times daily for two weeks. XP21279 provided less variability in LD concentration compared with IR LD/CD. Also, the subjects reported an average of 4.2 h/day spent "off" by the last four days with XP21279, as opposed to 7.09 h/day with IR LD/CD. This constituted a mean reduction in daily "off" time of about 2.88 h compared to IR LD/CD ($p = 0.0315$). XP21279 also increased the time spent "on" without troublesome dyskinesias, and shortened the mean time to "on" after the first morning dose [8].

Despite these initial results, a subsequent Phase 2 double-blind, double-dummy, crossover, randomized trial on 28 PD patients failed to show a reduction in total daily "off" time between XP21279 three times daily and immediate release LD/CD four to five times daily (3.0 h/day vs. 2.7 h/day; $p = 0.49$) [7,9]. Both treatments had a similar incidence of new or worsening dyskinesias.

The medication's potential to increase LD bioavailability by enhancing its absorption capability represents a novel approach. Unfortunately, likely due to the conflicting Phase 2 results, the company has not announced plans for any future development of XP1279.

1.3. Subcutaneous levodopa (ND0612 NeuroDerm)

ND0612 is a liquid form of LD/CD administered subcutaneously through a small pump-patch to maintain LD plasma levels over a 24 h period [3,10]. ND0612 is usually available as LD/CD 60/7.5 mg/ml in two formulations: the high dose form (ND0612H) delivering 0.64 ml/h; the low dose (ND0612L), delivering 0.24 ml/h. The approximate total LD dose administered after an 8-h infusion is approximately 115 mg for ND0612L and 307 mg for ND0612H. Both presentations have undergone extensive pre-pivotal trial testing including six Phase 1, seven Phase 2 and it is currently undergoing Phase 3 studies worldwide [11–20]. We selected for review four phase two studies showing the most relevant data of ND0612 used either as adjunctive therapy to LD/CD IR or as monotherapy in comparison with LD/CD IR or levodopa infusions forms such as Levodopa/Carbidopa intestinal gel (LCIG). To the date, the results from both Phase 1 and 2 trials have been released in the form of poster presentations only. Results of Phase 3 have not been publish in peer-reviewed form.

The first Phase 2 study was a double-blind, placebo-controlled trial that recruited 30 PD patients with motor fluctuations [13]. Subjects were randomized to receive ND0612L versus placebo as an adjunct to their optimized therapy for two weeks, followed by a one-week open-label extension of ND0612L with or without entacapone. ND0612L was given on continuous infusion for 24 h with a nighttime rate reduction. The total daily dose of ND0612L/CD infusion was 270/63 mg. A reduction in the fluctuations of LD concentration with ND0612L compared to placebo, as well as a decreased peak-to-trough ratio (4.8 versus 59.4) was noted. ND0612L reduced the mean "off" time by 2.42 h in clinic and 2.13 h using home diaries, compared to 0.41 h and 1.39 h, respectively, with placebo. Good tolerance and safety were observed during the study with only local infusion site reactions and no systemic side effects [13].

Another Phase 2 study randomized 16 PD patients to ND0612L or ND0612H. On day one, groups received their usual IR LD/CD; on day two, they were treated with ND0612L or ND0612H with 7.5 mg/mL of carbidopa; on day three, patients received their allocated ND0612 regimen with 14 mg/mL of carbidopa; finally, on day 4, subjects received an optional evaluation on ND0612 plus carbidopa *and* entacapone. After the 4th day, patients then entered into a safety follow-up phase. ND0612 caused less LD plasma fluctuations compared to baseline oral LD/CD ($p < 0.001$ for both high and low dose). Both ND0612L and ND0612H achieved stable therapeutic dose proportional LD plasma concentrations without relevant differences in bioavailability. Co-administration of entacapone increased the mean LD plasma levels to 604 ng/ml and 1844 ng/ml in the low and high dose groups, respectively. Finally, both regimens were well-tolerated. Nevertheless, mild and delayed-onset infusion site skin reactions were noted in nearly all subjects (15/16). All patients developed at least one injection site nodule by six months. These nodules were considered a delayed reaction with a peak severity at week 3, typically resolving by 4–6 months [15,21].

A third Phase 2 randomized, parallel-group, open-label, rater-blinded study evaluated two regimens of continuous ND0612H [22]. Thirty-eight subjects were randomized to receive either regimen 1 (24-h infusion with 720/90 mg LD/CD) or regimen 2 (14-h "waking-day" infusion with 538/68 mg LD/CD + morning oral LD/CD 150/15 mg). Supplemental oral IR LD/CD was used as needed. Both regimens were well tolerated. However, mild to moderate infusion site reactions were common especially with the high dose (nodules 58%, bruising 21% and erythema 26%). Regimen 1 had a mean reduction in "off" time of −2.8 h ($p = 0.004$), with 8/19 subjects reporting zero "off" time per day. Good "on" time also increased (+3.7 h; $p < 0.001$). Regimen 2 showed an increase in good "on" time by +2.8 h ($p < 0.003$) and a non-significant mean reduction in "off" time of 1.3 h ($p = 0.158$).

Finally, in a Phase 2 open-label cross-over study on ND0612H versus LCIG, 15 subjects were randomized into three groups, receiving 2 of 3 possible doses of LCIG followed by a washout period of 24 h [23]. ND0612H infusion was then administered using an equivalent total LD dose. ND0612 infusion resulted in higher total plasma LD which translated into higher LD bioavailability compared to LCIG. There was also less inter- and intra-subject variability in LD plasma levels with ND0612H compared to LCIG [23].

A Phase 3 multicenter, randomized, double-blind placebo-controlled trial on ND0612 (INDIGO trial) is currently ongoing (ClinicalTrials.gov ID: NCT2726386) [24].

While a true "continuous delivery" form of levodopa has been elusive, preliminary evidence from ND0612 trials suggest a less cumbersome and less invasive alternative to LCIG in advanced PD patients experiencing motor fluctuations. Nonetheless, the total LD dose delivered through this mechanism may still require a maintenance dose of oral LD and/or co-administration of other agents such as CD or entacapone. In addition, injection site skin reactions such nodules and erythema were commonly reported. It is unclear whether these side effects become a limiting factor for long-term use. Therefore, continued vigilance is required throughout its development lifecycle. On top of

this, other issues will need to be addressed, such as the ability (or lack thereof) to adjust doses and ease of incorporating it with other PD medications.

1.4. Inhaled levodopa (CVT 301, Acorda Therapeutics)

Currently, apomorphine via subcutaneous injection is the only available FDA-approved "rescue therapy" for "off" episodes. Although it is well known to be efficacious in reversing "off" periods, its use is primarily limited by its subcutaneous administration, which can often be an off-putting option for patients [25].

CVT-103 is a potential alternative to apomorphine for the management of "off" periods [7,26]. It is a self-administered LD inhalation powder developed as an adjunct to oral LD/CD [27]. The device consists of a LD powder formulation placed in capsules which are then inserted in a breath-actuated inhaler, providing a precise LD dose via intrapulmonary delivery, avoiding first-pass metabolism [10], inducing a rapid return to the "on" state [6,7].

During a Phase 1, single ascending dose, cross-over study in 18 healthy volunteers, CVT-301 produced rapidly increasing, dose-proportional plasma LD concentrations, achieving therapeutic levels within 5 min [26,28]. Moreover, when compared with oral LD/CD administration, CVT-103 showed less plasma concentration variability [28].

A subsequent Phase 2, placebo-controlled, dose-finding study randomized 24 PD patients experiencing wearing "off" to single doses of CVT-301 [29]. Open-label IR LD/CD was given as the first treatment, followed by blinded administration of CVT-301 (25 mg or 50 mg) or placebo. LD plasma concentrations (400 ng/ml) increased more rapidly after CVT-301 50 mg versus oral LD/CD (80% vs 20% of the subjects within 10 min, respectively). In addition, plasma concentration variability was lower over the next 60 min following CVT-301 when compared to oral LD/CD. Improvement in motor response, measured by the Unified Parkinson Disease Scale (UPDRS) part III scores, was noted within 5–15 min. These motor benefits lasted throughout the entire 90-min evaluation [29].

On a subsequent Phase 2b study, 89 PD patients were randomized to CVT-301 or placebo for 4 weeks [27]. After two weeks, CVT-301 dose was escalated from 35 to 50 mg. The active arm had an average use frequency of 2.1 times per day, and an onset of effect within 10 min. By the end of the 4th week, the least-squares mean improvement in the UPDRS part III was 10 points for 50 mg of CVT-301 versus 3.1 points for placebo ($p < 0.001$). CVT-301 was also superior to placebo in reducing the daily "off" time by 1.6 h/day compared to 0.8 h/day with placebo ($p = 0.045$) [7,10,27]. No severe adverse effects were noticed, although some patients reported nausea and dizziness [7,27].

The most recent Phase 3 trial, SPAN-PD, evaluated CVT-301 on 339 PD patients using a three-arm design: CVT-301 84 mg, 60 mg or placebo [30]. After 12 weeks, the mean improvement in the UPDRS part III at 30 min was 9.83 points with CVT-301 84 mg compared to 5.91 points with placebo ($p = 0.009$). This motor improvement was noted as early as 10 min and sustained for 1 h. A higher proportion of patients taking CVT-301 compared to placebo achieved an "on" state within 60 min ($p < 0.05$). Pulmonary safety profiles remained unchanged [31]. A subsequent long-term study demonstrated that CVT-301 84 mg exposure for up to 12 months did not alter pulmonary function [30].

Based on the evidence presented above, CVT-301 may provide an upgrade, especially in terms of drug delivery, when compared to SC apomorphine as a rescue therapy for motor fluctuations in patients with advanced PD. However, the lack of head-to-head comparison between subcutaneous apomorphine and CVT-301 makes it challenging to determine which one provides better efficacy and longer duration of effect.

1.5. Levodopa methylester (V1512, Melevodopa, Sirio®; Chiesi pharmaceuticals)

Melevodopa is a liquid effervescent tablet formulation of LD methyl ester. It is a highly soluble *prodrug* designed to allow for rapid, complete dissolution, faster delivery and consistent absorption at the small intestines [32]. Melevodopa has a higher absorption across the intestinal wall because it is non-ionized at physiological pH compared to LD which maintains its ionized form [32]. Because of this, melevodopa has a higher bioavailability without significant changes in half-life. Melevodopa is approved for treatment of PD patients in Italy under the brand name of Sirio®. However, clinical trials on melevodopa/CD are conflicting.

In one Phase 2 open-label naturalistic study, PD patients with motor fluctuations were recruited [33]. Group A included 75 subjects who completely switched their LD/CD to melevodopa. Group B consistent of 119 subjects who only partially replaced their LD/CD with melevodopa while continuing LC/CD/entacapone (Stalevo) four times per day. While group A showed a reduction in "off" hours in the *afternoon period* after 6 months when compared to baseline (0.75 h vs 0.84 h; $p < 0.005$), no difference in *total* daily "off" time was observed. The mean dyskinesia scale score remained unchanged at six months. Group B showed a decrease in daily "off" periods at six months when compared to baseline (1.97 h versus 2.35 h; $p < 0.05$). No differences compared to baseline on UPDRS part III scores were found in both groups [33].

Another Phase 2 randomized, double-blind, double-dummy, parallel group study compared oral melevodopa/CD with IR LD/CD in reducing total daily "off" time [34]. A total of 221 PD patients, after a 2-week IR LD/CD optimization period, were randomized into melevodopa/CD or IR LD/CD in a 2:1 ratio for 12 weeks. No significant differences in total daily "off" time were observed between the groups, although there was a trend toward superiority of melevodopa/CD ($p < 0.07$). While a reduction in daily "off" time in both groups was noted during the first eight weeks of treatment, this benefit persisted after 12 weeks only on the melevodopa group (mean change −40 min $p = 0.005$) [34].

The most recent Phase 4 study tested the efficacy of melevodopa in PD patients with small intestinal bacterial overgrowth (SIBO), based on the hypothesis that SIBO might potentially interfere with the LD absorption in PD patients, thereby worsening motor fluctuations [2,35]. Thirty-three patients with PD experiencing motor fluctuations and SIBO were challenged with 250 mg of IR LD/CD and 314 mg of melevodopa before and after SIBO eradication. At baseline, the onset of motor effect was significantly shorter on melevodopa when compared to IR LD/CD (28.8 ± 11.5 versus 55.5 ± 40.2 min; $p = 0.0004$). However, the duration of "on" time or area under the curve (AUC) was not significantly different [35]. According to clinicaltrials.gov, no further studies testing melevodopa have been registered since 2011.

Despite the hypothetical pharmacokinetic advantage proposed for melevodopa as a prodrug with capability to increase LD absorption across the small intestinal wall, the evidence available regarding its efficacy and duration of effect is conflicting. More evidence is needed to determine its advantage over the current standard of care. Nevertheless, its proposed faster delivery method might possess a potential benefit in the management of PD with SIBO. These findings warrant further study.

2. Novel apomorphine preparations

Since its use in clinical practice 30 years ago, apomorphine has never generated as much interest until the present time with the emergence of new delivery formulations including sublingual, subcutaneous infusion and inhaled presentations [36]. Apomorphine is a potent non-ergoline dopamine receptor agonist with very high D2, D3, and D4 affinity [37]. It has a rapid onset but short duration of action. It is absorbed entirely from the subcutaneous tissue with a bioavailability of 100% [37]. For many years apomorphine has been used as an

intermittent, self-administered subcutaneous injection, as a rescue therapy for the rapid relief of motor fluctuations [36]. Overall, apomorphine has generally been viewed as a drug with a shorter duration of effect compared to LD, but with the same quality of motor response [36].

2.1. Sublingual apomorphine (APL-130277 Sunovion pharmaceuticals)

APL-130277 is a sublingually administered form of apomorphine composed of a bilayer film that disintegrates when in contact with mucosal tissue. The first layer is composed of the actual drug, while the second layer neutralizes the acid generated following absorption, and helps lessen local mucosal irritation. Although apomorphine is extensively inactivated during first-pass metabolism, the sublingual administration bypasses the liver [10].

An open-label study recruited 20 PD patients [38]. Subjects were instructed to skip their morning LD dose and received 10 mg of APL-130277 during their "off" state. MDS-UPDRS part III was administered at pre-dose, 15, 30, 45, 60 and 90 min after APL-130277. Fifteen out of 19 (79%) patients reached full "on" within 30 min. Non-responders appeared to have swallowed the medication. MDS-UPDRS part III scores improved by 30% on each assessment reaching a maximum of 51.3% improvement among responders. The duration of "on" time was 50 min. Nausea and dizziness were the most common adverse events [38].

The preliminary results of an open-label Phase 3 dose titration study on APL-130277 were presented recently at a scientific meeting [39,40]. The APL-130277 titration sequence of was 10, 15, 20, 25, 30 and 35 mg. Subjects who reached their full "on" state entered into the maintenance treatment phase, whereas those who did not, returned to clinic for the next dose, until the full "on" state was achieved. MDS-UPDRS part-III was obtained every 15 min, up to 90 min with each dose. The preliminary data on 76 PD subjects reported that 83% of subjects achieved full "on" state (median APL-130277 dose of 20 mg). The onset of clinical benefit was 5–12 min for responders, with a 22-point improvement in MDS-UPDRS part III within 30 min and 16 points at 90 min [39]. The same protocol was also used to determine the safety of APL-130277 [40]. Nineteen subjects did not complete the titration phase. There was no evidence of local mucosal irritation. Mild to moderate nausea occurred in 16%, and vomiting occurred in 8% [39].

Finally, the preliminary results of a Phase 3 trial of APL-130277 were published as a late-breaking abstract [41]. This double-blind, placebo-controlled trial recruited 141 PD patients to undergo a dose titration phase, followed by a maintenance phase in which subjects were randomized to receive their previously titrated APL-130277 dose or placebo for 12 weeks. Only 89 out of 109 randomized patients completed the study, mostly due to side effects that led to discontinuation. The least square mean change in MDS-UPDRS part III from pre-to 30 min post-dose was −11.1 for APL-130277 compared to −3.5 for placebo ($p = 0.0002$), with similar results on weeks 1, 4 and 8. The duration of benefit persisted up to 90 min. There was a significant difference in the percentage of patients taking APL-130277 who rated themselves as full "on" within 30 min compared to placebo at 12 weeks ($p = 0.04$). The most frequent side effects were nausea (27.8%), somnolence (13%), and dizziness (9.3%) and local oral side effects (31.5%) [41] (ClinicalTrials.gov ID: NCT02542696).

Current evidence is promising for APL-130277 as a less invasive alternative to subcutaneous apomorphine in PD patients with "off" episodes including morning "off", unpredictable "off" and end-of-dose wearing "off". Nevertheless, nausea was the most common limiting factor for trial completion in 27% of patients according to the latest Phase 3 trial, which may be similar to its older subcutaneous formulation. While no head-to-head comparisons have been performed against subcutaneous apomorphine, early evidence suggests that APL-130277's onset of action may be similar to, or just slightly delayed, and its duration of action slightly longer, compared to its older predecessor. It will be, however, more challenging to compare APL 130277 with CVT-301.

2.2. Continuous subcutaneous apomorphine infusion (CSAI; Britannia pharmaceuticals LTD; USWorldMeds)

Continuous subcutaneous apomorphine infusion (CSAI) is a reversible, device-aided, minimally-invasive therapy for advanced PD [42]. The drug is delivered subcutaneously, typically in the abdominal region, by using a needle connected to an infusion pump [42–44]. In general, patients on CSAI still take oral LD, albeit often at a lower dose [36]. CSAI has been approved in several countries in Europe; however, it has yet to be approved in the United States. Nevertheless, over the last two years, randomized controlled studies have been started to re-evaluate the efficacy, tolerability, and safety of CSAI in the US [45].

From the motor standpoint, a large number of short- and long-term uncontrolled studies evaluating the efficacy of CSAI both as monotherapy or add-on therapy to LD in patients with advanced PD and motor fluctuations have been performed since the late 1980's [46–68]. In addition, three review papers have performed pooled analyses of these studies to determine the strength of the evidence and clinical utility of CSAI [37,69,70]. Overall, there was a great variability in methodology, sample size (N from 6 to 82), follow up duration (3–60 months) and outcome measures [69]. These open-label studies have consistently reported substantial reductions in daily "off" time ranging from 50 to 72%. However, there is significant variability with regards to dyskinesia reduction as some studies report improvement in severity, frequency, and duration [50,52,53,56,58,59,71]; while others report no significant improvement [57,60,70]. A potential confounding factor was the marked reduction in LD dose requirements experienced on some patients receiving CSAI [70,71].

A six-month follow up of patients receiving CSAI showed an improvement of mean Non-Motor Symptoms Scale (NMSS) sub-scores on attention/memory, gastrointestinal, perceptual/hallucination, sleep/fatigue and urinary symptoms [36,72]. Several studies have also reported an overall improvement in the quality of life [36,42,73].

With regards to safety profile, 89% of the patients treated with CSAI report at least one side effect [74]. It is estimated that 1 in 10 patients decide to discontinue the medication due to side effects [75]. The most common adverse reaction is subcutaneous nodules (50%) [42,76]. From the neuropsychiatric standpoint, apomorphine is considered to be better tolerated than oral dopamine agonists. Nevertheless, mild hallucinations (20%), as well as severe visual hallucinations (10%), have been reported, although likely less common than intermittent apomorphine delivery [42]. Furthermore, a recent long-term observational study reported cognitive decline 15 months after receiving CSAI, and hallucinations after 39.8 months [77]. Other side effects resulting in discontinuation include orthostatic hypotension and hemolytic anemia [45].

Although most of the evidence supporting the use of CSAI have come from open-label studies, the results of a Phase 3 randomized, double-blind, placebo-controlled trial of CSAI (TOLEDO trial) were recently published [78]. The study enrolled 106 PD patients who were randomized to receive 3–8 mg/h apomorphine infusion or placebo during waking hours for 12 weeks. The flow rate of the infusion was adjusted in the first four weeks, followed by an 8-week maintenance period, then a 52-week open-label phase. CSAI (mean final dose of 4.68 mg/h) significantly reduced daily "off" time compared to placebo after 12 weeks (−2.47 h vs −0.58 h; $p = 0.0025$). CSAI increased "on" time without troublesome dyskinesia (+2.77 h/day with CSAI versus + 0.88 h/day with placebo; $p = 0.0008$). No significant difference in oral LD dose from baseline to week 12 were observed between groups. Patients receiving CSAI reported higher scores on Patient Global Impression of Change at 12 weeks. CSAI was generally well-tolerated. However, adverse effects including skin nodules (44%), nausea (22%), somnolence (22%), and infusion site erythema (17%). Only six patients withdrew from the study due to adverse events.

CSAI is undergoing Phase 3 testing in the United States (ClinicalTrials.gov ID: NCT02339064).

Apomorphine infusion is a reasonable option for the management of "off" episodes in advanced PD supported by a lengthy "real world" experience, and finally a recently published large randomized controlled trial. It provides a less invasive and painless delivery mode, with the potential to allow a reduction in the LD dose. Nevertheless, there are still unanswered questions about its long-term tolerability given the significant rate for skin adverse effects, and, more importantly, its place amongst advanced therapies such as LCIG and deep brain stimulation surgery. Head-to-head comparisons comparing CSAI with LCIG are ideal (although unlikely to be embarked) because of the significant overlap in their indicated patient population.

3. Catechol-O-methyltransferase (COMT) inhibitors

3.1. Opicapone (BIA-91067, BIAL)

Opicapone is a third generation COMT inhibitor approved in 2016 in Europe as adjunctive therapy to LD/CD in PD patients with motor fluctuations [79]. Unlike entacapone that needs to be administered with each levodopa dose, opicapone has a high binding affinity, resulting in a slow complex dissociation rate constant and a long duration of action, which allows once-daily dosing [10].

Opicapone has been reported to have good tolerability with doses ranging from 10 to 1200 mg [79–82]. Its COMT inhibitory effect, as well as its duration of action, are dose dependent [80]. Two Phase 3 studies served as the groundwork for its European approval (BIPARK I and BIPARK II) [81,83]. In both studies, opicapone given once a day reduced "off" time compared to placebo. BIPARK I was a randomized, double-blind, placebo- and active-controlled trial of opicapone as an adjunct to LD for end-of-dose deterioration [81]. The study enrolled approximately 600 patients assigned to either opicapone (5 mg, 25 mg, or 50 mg), placebo, or entacapone (200 mg with each LD) for 14–15 weeks. Opicapone 50 mg was better than placebo (mean difference in change from baseline −60·8 min; p = 0.0015) and non-inferior to entacapone (−26·2 min). The most common adverse events were dyskinesia, insomnia, and constipation [81].

Subsequently, a multicenter randomized, double-blind placebo-controlled Phase 3 study (BIPARK II) enrolled 427 PD patients, who were randomized to 25 mg/day or 50 mg/day opicapone or placebo for 14–15 weeks [83]. This was followed by a 1 year open-label trial. The mean change in "off" time was −64.5 min for placebo versus −101.7 min for 25 mg opicapone and −118.8 min for the 50 mg opicapone. The adjusted treatment difference compared to placebo was significant for 50 mg/day (p = 0.08) but not for 25 mg/day (p = 0.11). This "off" time reduction was sustained throughout the open-label phase (−126.3 min at one year). The most common adverse events were dyskinesia, constipation and dry mouth [83].

In addition, another open-label study was offered to patients completing BIPARK I, enrolling 495 patients for 1 year [84]. Patients started with 25 mg opicapone for one week, followed by individually adjusted LD/opicapone doses. Patients who were initially treated with opicapone 50 mg in BIPARK I, maintained their efficacy whereas patients who switched from entacapone led to a further decrease in "off" time (−39.9 min). Dyskinesia was the most frequent adverse event (14.5%) but was generally managed by adjusting dopaminergic therapy [10,84].

Opicapone has emerged as an alternative to entacapone for the management of motor fluctuations. Although its longer duration of action with once-daily dosing represents an attractive and practical option to improve medication adherence, evidence for superiority to entacapone in terms of efficacy and side effect profile is wanting. It is likely that further differentiation between these COMT inhibitors may come from other sources outside randomized clinical trials.

4. Adenosine 2A antagonists

Dopaminergic depletion has been thought to be the primary neurochemical basis for the development of the motor symptoms in PD [85]. However, new neurotransmitters and neuromodulation systems have been found to influence the extrapyramidal function as well as the neurodegenerative process itself, paving the way for novel "non-dopaminergic" alternatives in the management of motor fluctuations.

A2A adenosine receptors in striatal spiny neurons have been found to influence and regulate neuronal signaling from the striatum to the globus pallidus pars externa as well as its projections towards the subthalamic nucleus and substantia nigra–the striatopallidal output (or "indirect") pathway [86]. The A2A antagonism translates into enhanced striatal gamma-aminobutyric acid (GABA) release, resulting in reduction of the overactive striatopallidal output. This outcome is somewhat similar to the one achieved with high-frequency electrical stimulation of the subthalamic nuclei. As a result, A2A antagonists are developed for the treatment of motor fluctuations [2,87,88]. Interestingly, studies on the clinical efficacy of A2A antagonist have mixed results, resulting in an unusually long drug development journey [89–95].

4.1. Istradefylline (KW-6002, Kyowa Hakko & Kirin pharma)

Istradefylline is a selective first-in-class adenosine A2A receptor antagonist, approved in some countries for the treatment of motor fluctuations in PD [86,89–94,96–102]. It has been under development since the early 2000's, with a portfolio that spans three Phase 1, thirteen Phase 2, ten Phase 3 and several Phase 4 trials.

In the first Phase 3 trial in the early to mid-2000's that recruited 231 PD patients experiencing wearing off, istradefylline (20 mg/day) reduced "off" time [103]. The mean absolute reduction in the percentage of the daily "off" time was 9.3% with istradefylline and 5.0% with placebo, with a mean difference between groups of 4.6% (p = 0.03). The mean reduction from baseline in "off" time per day was 1.6 h for the former and 0.9 h for the latter, with a mean difference between groups of 0.7 h (p = 0.03) [103].

In contrast, a larger, 12-week trial with a similar design that recruited 584 PD patients showed that istradefylline (doses of 10, 20 or 40 mg/day) provided no significant benefit when compared to placebo in reducing "off" state, although an improvement in motor function (as measured by the UPDRS part III) was noted with istradefylline 40 mg when compared to placebo [98]. Similarly, in another 16-week Phase 3 trial, istradefylline 40 mg/day did not reduce the percentage of "off" state, compared with placebo [104]. A subsequent 52-week, long-term, open-label Phase 2/3 trial that included 496 patients previously enrolled from another 12-week controlled trial, showed sustained improvement with istradefylline. Subjects who previously received placebo reported mean reductions in daily "off" time of 3.8–7.4% over 52 weeks [99]. Because of these conflicting results, in 2008 the United States FDA issued a "non-approvable" letter on istradefylline.

Subsequently, in 2011 a large Japanese randomized, double-blind, controlled trial that included 373 PD patients demonstrated positive results. Istradefylline at 20 or 40 mg significantly reduced "off" time (−0.99 h and −0.96 h, respectively; p = 0.003) compared with placebo (−0.23 h) [2,100]. This trial led to istradefylline's approval in Japan as adjunctive therapy to LD/CD for motor fluctuations.

However, recent top-line data from the global, double-blind, placebo-controlled Phase 3 trial that randomized 609 PD patients to istradefylline (20 mg or 40 mg once-daily) or placebo for 12 weeks, was reported to be negative [104]. No significant difference in daily "off" time at Week 12 between the study drug versus placebo was seen. Results have not yet been published in peer-reviewed literature.

Nonetheless, because the cumulative evidence on large istradefylline trials remains positive, and it is well-tolerated, despite mixed results with individual studies, the drug is currently under US FDA re-

review for adjunctive treatment in PD patients experiencing motor fluctuations.

Istradefylline's "non-dopaminergic" mechanisms of action through A2A receptors modulating the indirect pathway of the basal ganglia, with its theoretical advantage of improving "off" periods with a lesser likelihood of worsening dyskinesias or causing other dopaminergic side effects such as sedation and hallucinations, remains intriguing. However, current clinical trial evidence suggests a consistent safety and tolerability profile, with an inconsistent (or yet to be fully understood) efficacy profile.

5. Repurposed agents

5.1. Nilotinib (Tasigna® Novartis)

Nilotinib is a tyrosine kinase inhibitor particularly of the Abelson non-receptor tyrosine kinase or c-Abl. It is currently approved for the treatment of Philadelphia chromosome-positive adult chronic myelogenous leukemia [84,105]. Studies postulate that oxidative stress activates c-Abl in PD [84,106]. Activated c-Abl phosphorylates parkin, leading to the accumulation of toxic substrates, including parkin-interacting substrates. These toxic substrates lead to downregulation of peroxisome-proliferator-activated receptor gamma-coactivator-1-alpha (PGC-1 alpha), causing mitochondrial dysfunction and eventual depletion of dopaminergic neurons. Moreover, activated c-Abl promotes the aggregation of a-syn into Lewy bodies [84,106].

Nilotinib has been shown to enhance clearance of cytosolic debris in the subtantia nigra neurons, enhances dopamine levels, mitigates neuronal loss and stabilizes motor impairment in MPTP-treated mice [84,107]. Furthermore, it also exerts effects on mitochondrial function and posttranslational modifications of a-syn [108].

In a highly controversial small, open-label, safety trial, 12 patients with PD dementia and dementia of Lewy bodies were randomized to nilotinib 150 mg or 300 mg. Nilotinib was found to be safe and well tolerated, although a high proportion of participants had some increase in psychiatric symptoms (hallucinations, paranoia, agitation, confusion, and anxiety) and dyskinesias. A decrease in the mean UPDRS scores by 3.4 points in the 150 mg group and 3.6 points in the 300 mg group compared to baseline was reported at 24 weeks. These beneficial effects were not sustained after the 12-week washout period. The authors also reported an increase in CSF homovanillic acid in both groups, and a slight decrease in CSF alpha-synuclein compared to baseline in the 150 mg group only [84,109]. Although the study received unprecedented publicity, several investigators raised strong criticism regarding the media hype, based on the fact that this small open-label study did not have the design or power to test for drug efficacy [110].

The development of nilotinib has moved forward with two Phase 2 trials, with nearly identical protocols, in the United States. (ClinicalTrials.gov identifier NCT03205488, NCT02954978).

The potential role of nilotinib as a symptomatic and/or neuroprotective agent in patients with PD remains unclear given the insufficient evidence on human trials. Although the results of phase 1 animal studies were promising it is unclear whether they will translate into the clinical setting.

5.2. Dextromethorphan HBr and quinidine sulfate (Nuedexta, AVP-923, Avanir pharmaceuticals)

AVP-923 is a combination of two compounds: dextromethorphan (an *uncompetitive* NMDA receptor antagonist and sigma-1 receptor agonist, better known as an active ingredient in over-the-counter medications for cough), and quinidine sulfate (a CYP2D6 inhibitor) [10]. Quinidine increases the bioavailability of dextromethorphan by slowing its oxidative metabolism in the liver and by inhibition of the protein pump P-glycoprotein at the blood-brain-barrier [111]. A 2-week double-blind, crossover placebo-controlled, with intervening 2-week washout study, was performed to evaluate AVP-923 for levodopa-induced dyskinesias (LID) [112]. After 14 days, a 2-h intravenous levodopa-infusion was administered, with videotaped examinations at 30-min intervals, before infusion, from their baseline "off" state, until their return to "off". The dyskinesia rating was done by a blinded expert using the Unified Dyskinesia Rating Scale part III. The study finished with 13 randomized patients (efficacy-evaluable population). While dyskinesia severity was non-significantly lower compared to placebo, there was a significant decrease in peak dyskinesia from the start of infusion to the return to "off" state ($p = 0.018$) [112]. The preliminary evidence demonstrated in the study may thus be used in designing future studies using a larger population with a longer duration of treatment.

5.3. Glutamate receptor antagonists: mavoglurant (AFQ056, Novartis) and dipraglurant (ADX48621, Addex Therapeutics)

Glutamate is a primary excitatory neurotransmitter that exerts its actions through ionotropic and metabotropic receptors. There are 3 ionotropic subtypes: N-Methyl-D-aspartic acid (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate. The metabotropic receptors (mGluRs) are eight G-protein coupled receptors comprised of 3 different groups in the basal ganglia: group I (mGlur1, mGlur5), group II (mGlur2, mGlur3) and group III (mGlur4, mGlur6, mGlur7, mGlur8) [111]. Pre-clinical and clinical evidence postulate that LIDs are associated with changes in the thalamo-corticostriatal glutamatergic neurotransmission. Studies on mGluR5, show beneficial effects in reducing LIDs in animal models [95]. Furthermore, MPTP-induced parkinsonism animal models also demonstrate an enhanced density of mGluR within the striatum and posterior putamen. Based on these results, clinical trials evaluating the beneficial effects of mGluR5 receptor are ongoing.

To the date, two agents have been tested in clinical trials, mavoglurant and diplagurant [95]. Mavoglurant failed to improve dyskinesia in clinical trials [95]. On the other hand, a Phase 2a double-blind, placebo-controlled, randomized, parallel-group dose-escalation multicenter clinical trial on dipraglurant that enrolled 76 PD patients with LID [113] showed promising results. A significant reduction in peak dose dyskinesia based on the Abnormal Involuntary Movement Scale was noted after a single trial of 50 mg on day 1 (20% $p = 0.04$), and after 14 days of treatment at 100 mg dose (32% $p = 0.04$) There was also a reduction in dyskinesia across a 3-h post-dose observation period on day 14 ($p = 0.04$). No worsening of parkinsonism was noted [113]. According to the manufacturer, Addex Therapeutics, incoming Phase 2b and 3 studies have been designed although their launch date has not been announced.

Although dipraglurant is on an early development phase, it represents a novel therapeutic target for the management of LID. The above promising early results should be confirmed by larger controlled studies. Head-to-head comparisons with amantadine will further clarify its role within the evolving PD treatment armamentarium.

6. Serotonergic agents

6.1. Eltoprazine (DU-28853, Elto pharma)

Eltoprazine is an agonist of serotonin 5-HT1A and 5-HT1B receptors, but an antagonist of 5-HT2C receptors. It has been shown to lessen the LD-induced hypersensitization on the D1 pathway [88,111]. Also, it inhibits the glutamate release in the striatum as well as modulates release of glutamate and GABA in the substantia nigra pars reticulata [111]. Eltoprazine is currently being studied as a novel agent to alleviate LID. In a double-blind, randomized, placebo-controlled, dose-finding Phase 1/2a trial, 22 PD patients with LID were randomized to a single oral treatment with eltoprazine at three increasing doses (2.5, 5 and 7.5 mg) or placebo, in combination with a supra-threshold LD dose.

Eltoprazine at 5 mg provided significant dyskinesia reduction without worsening parkinsonism based on the area under the curves on the Clinical Dyskinesia Rating Scale (−1.02; p = 0.004), and Rush Dyskinesia Rating Scale (0.15; p = 0.003). Maximum Clinical Dyskinesia Rating Scale score was also significantly reduced (−1.14, p = 0.005). UPDRS part III did not differ between the placebo and eltoprazine groups [114]. Currently, a Phase 2b clinical trial to evaluate the effect of eltoprazine in reducing dyskinesia severity is ongoing (ClinicalTrials.gov identifier NCT02439125).

6.2. Piclozotan (SUN-4057, Asubio pharma)

Piclozotan is a partial 5-HT1A agonist. In pre-clinical studies, it reduced LID and improved motor complications in parkinsonian rats [111]. In the initial pilot study, piclozotan increased “on” time without worsening of dyskinesia. However, Phase 2 clinical trials have been completed without significant results (ClinicalTrials.gov Identifier: NCT00623363). Therefore, after the completion of its Phase 2 trial in 2014, no subsequent trials have been started.

It is too early to project the role of serotonergic agents in the treatment for LID in PD.

In conclusion, the landscape for symptomatic motor control in PD is diverse and promising. It is impossible to predict which of these will create a bigger impact given their varied indications within PD, diverse mechanisms of action, study design, various stage of development, etc. And it is unwise, if not dangerous, to compare (and judge the efficacy and tolerability of) emerging drugs that have not been tested head-to-head, regardless of any perceived differences in their reported magnitude of effect or safety profile. Finally, as much as the emphasis of this paper focused on the analysis of available data from randomized controlled trials, this also serves as a reminder that evidence-based treatments are also contributed by other sources outside clinical trials which are harder to quantify. And the eventual utilization of these emerging drugs is likely to be more impacted by factors other than efficacy data, such as cost, ease of use, traction within the PD community, health care systems and even media influence.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.01.002.

Disclosures

Dr. Hengartner has nothing to disclose.

Dr. Fernandez has received research support from Abbvie, Biotie/Acorda Therapeutics, Michael J. Fox Foundation, Movement Disorders Society, NIH/NINDS, Parkinson Study Group, Rhythm, Sunovion, but has no owner interest in any pharmaceutical company. Dr. Fernandez has received honoraria from Prime Education Inc. International Parkinson and Movement Disorders Society, Carling Communications, Medscape, and Vindico as a speaker in CME events. Dr. Fernandez has received honoraria from AbbVie, Biogen, Blackthorn, Inventiv, Kyowa Hakko Kirin, Medscape, Voyager, Sunovion, and Pfizer Pharmaceuticals, as a consultant. Dr. Fernandez has received royalty payments from Demos Publishing and Cambridge University Press for serving as a book author/editor. The Cleveland Clinic has a contract with Teva for Dr. Fernandez’ role as a Co-Principal Investigator in SD-809 Tardive Dyskinesia global studies. Dr. Fernandez also serves as a member of the publication committee for Acorda and Biotie Pharmaceuticals but does not receive any personal compensation for these.

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