LEADING ARTICLE

Newly Approved and Investigational Drugs for Motor Symptom Control in Parkinson's Disease

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Abstract

Motor symptoms are a core feature of Parkinson's disease (PD) and cause a significant burden on patients' quality of life. Oral levodopa is still the most effective treatment, however, the motor benefits are countered by inherent pharmacologic limitations of the drug. Additionally, with disease progression, chronic levodopa leads to the appearance of motor complications including motor fluctuations and dyskinesia. Furthermore, several motor abnormalities of posture, balance, and gait may become less responsive to levodopa. With these unmet needs and our evolving understanding of the neuroanatomic and pathophysiologic underpinnings of PD, several advances have been made in defining new therapies for motor symptoms. These include newer levodopa formulations and drug delivery systems, refinements in adjunctive medications, and non-dopaminergic treatment strategies. Although some are in early stages of development, these novel treatments potentially widen the available options for the management of motor symptoms allowing clinicians to provide an individually tailored care for PD patients. Here, we review the existing and emerging interventions for PD with focus on newly approved and investigational drugs for motor symptoms, motor fluctuations, dyskinesia, and balance and gait dysfunction.

Key Points

Motor symptoms are common in Parkinson's Disease, and a cause of significant health-related quality of life impairment. Although levodopa remains the most effective treatment, a range of new therapies are currently being explored for the treatment of motor symptoms.

Besides new levodopa formulations, other non-dopaminergic drugs are also being extensively evaluated for potential use in the control of motor symptoms in PD. A key feature necessary to the development of a successful therapy will involve a similar or better "ON" response, without significant side effects, as well as a reliable and long duration of benefit.

1 Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder affecting more than 6.1 million people worldwide, with an estimated prevalence of 2–3% in individuals above 65 years of age in industrialized countries [1–3]. PD presents with a broad range of manifestations, with motor symptoms being widely known to cause difficulties in movement and physical tasks [4, 5]. To date, the lack of effective disease-modifying therapies means that treatment of PD, particularly motor symptoms, relies on dopamine replacement with oral levodopa or alternative levodopa preparations, plus additional options of dopamine agonists (DAs), monoamine oxidase type B inhibitors (MAOB-Is), and adjunct catechol-O-methyl transferase inhibitors (COMT-Is) [6–9]. Surgical therapies, including deep brain stimulation, have also led to important improvements in the care of individuals with PD [10, 11], although these are beyond the scope of this review.

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Despite therapeutic advances, motor symptoms continue to negatively affect the health-related quality of life (HRQoL) of PD patients [12, 13], especially with the emergence of motor complications as a consequence of disease progression and chronic dopamine replacement therapy. These complications include motor fluctuations and levodopa-induced dyskinesia (LID). Motor fluctuations consist of oscillations between good (ON periods) and suboptimal drug response characterized by re-emergence or worsening of parkinsonian symptoms (OFF periods) [14], and generally reflect the loss of sustained medication benefit [15, 16]. With longer disease duration leading to nigrostriatal degeneration and striatal plasticity changes, the therapeutic window becomes narrow [14, 17]. This, in combination with other factors such as aberrant gastric emptying, pulsatile drug administration, and altered drug pharmacokinetics, can engender motor fluctuations even in the context of levodopa's beneficial effects on motor function, disease progression, and QoL [17].

These factors and the need for higher levodopa daily doses, dopamine agonists, and/or other adjunctive medications as the disease advances also underlie the emergence of LID, which is typically characterized by involuntary movements largely occurring in a dose-dependent manner [18, 19]. In addition to motor complications, gait and balance disturbances, which may occur throughout the disease course, can also impair mobility, increase the risk of falls, and reduce the QoL of PD patients [20].

The anatomical basis for PD motor symptoms, motor complications, and gait and balance disorders are complex and yet to be fully elucidated. For these features, there is significant evidence of diffuse impairment not only in the basal ganglia, but in other subcortical and cortical networks. Besides dopamine, other neurotransmitters have been implicated, including glutamate, adenosine, serotonin (5-HT), gamma aminobutyric acid (GABA), acetylcholine, noradrenaline, and histamine [21–25]. The complexity of symptoms and involved pathways pose challenges to pharmacological management and drug development. Nevertheless, there have been significant progress and advances in the pharmacologic treatment of PD over the recent years. In this review, we perform a comprehensive discussion of the newly approved and investigational drugs aiming to treat motor features in PD.

2 Literature Search Strategy and Selection Criteria

We searched PubMed and *ClinicalTrials.gov* for studies published between January 2016 and January 2022. The following medical subject heading terms were included: (Parkinson's disease) AND (clinical trial OR early Parkinson's Disease OR symptomatic therapy OR motor fluctuations OR dyskinesia OR gait OR balance). Only articles or abstracts in English were reviewed. Surgical and non-pharmacological therapies were excluded. The review is divided into drug treatments for motor symptom control; drugs for specific motor symptoms of tremor, gait, and balance; treatments for motor fluctuations including rapid acting, longer acting, and adjunct therapies; and drugs to specifically reduce LID.

3 Symptomatic Therapy

The timing of initiation and type of symptomatic pharmacotherapy for PD is an individual choice and is determined by impact on lifestyle, degree of disability, and patients' preference. Moreover, in this shared decision-making process, patients' expectations and preferences should be extensively discussed and considered prior to deciding on the best therapy. To date, dopamine replacement in the form of levodopa is the most effective and clinically useful strategy for the control of motor symptoms including tremor, rigidity, bradykinesia, and gait impairment in the early stages of PD [7]. Alternatives include directly acting DAs, and the MAOB-Is rasagiline and selegiline. The treatment options for early PD are a balance between superior efficacy of levodopa over alternatives and eventual development of levodopa-induced motor fluctuations and LID. Oral dopamine D2/3 receptor agonists have been available for decades, with potential advantages over levodopa such as lack of interference with food, ability to bypass gastrointestinal absorption issues, and longer duration of action with potential less risk of motor fluctuations if initiated as first-line therapy. However, these benefits are counterbalanced by less robust effects on motor improvement compared with levodopa and higher risk of side effects such as hypotension, sleep disturbances, and neuropsychiatric disturbances, particularly impulse control disorders (ICDs). Indeed, the American Academy of Neurology has recently published guidelines for treating early PD, confirming the superiority of levodopa compared with DAs [9].

3.1 Dopaminergic Therapies

New dopaminergic strategies for early PD symptomatic therapy include the mixed DA/MAOB-I P2B001; D1/5 DA tavapadon, and injectable formulation of DA, rotigotine (Table 1).

P2B001 is a novel formulation containing a combination of subtherapeutic doses of the DA pramipexole (0.3 mg or 0.6 mg) with a subtherapeutic dose (0.75 mg) of the MAOB-I rasagiline, with the aim to reduce side effects that are associated with standard doses of pramipexole, particularly ICDs and hallucinations. P2B001 was compared with

placebo in a Phase 2b, 12-week multicenter, double-blind, randomized, controlled trial (DBRCT) [26]. The authors reported a significant improvement in the total Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) score with both doses in 136 study completers. MDS-UPDRS part III motor scores and Parkinson Disease Quality of Life Scale–39 scores (PDQ-39) were also significantly improved with both doses of P2B001. Adverse events were as expected from dopaminergic therapy including transient nausea, vomiting, somnolence, and fatigue; however, there were no reported cases of ICD. It is possible that the lack of this specific adverse event might be related to the relatively short duration of the study. A Phase 3 trial is ongoing with 544 early PD patients randomized in a four-way arm to P2B001 (0.6 mg pramipexole/0.75 mg rasagiline), rasagiline (0.75 mg), pramipexole (titrated to optimal dose of 1.5, 3, or 4.5 mg) or pramipexole extended-release (ER; 0.6 mg). Although formal results have not been published, P2B001 has successfully met its primary and secondary endpoints according to the manufacture's website, confirming the superiority of P2B001 over other treatment arms (NCT03329508) [27, 28]. Additional findings also included less daytime sleepiness when compared to pramipexole ER (as measured by the Epworth Sleepiness Scale). The company is now planning to file a New Drug Application to the US Food and Drug Administration (FDA) in 2022. If approved, P2B001 might be a convenient and effective symptomatic therapy for patients with early PD, with a potentially lower risk of dopaminergic complications and side effects.

Tavapadon (PF-06649751) is a highly selective D1/D5 DA. Compared to D2/3, targeting dopamine D1/D5 receptors is thought to avoid side effects such as hypotension and ICDs. A Phase 2 DBRCT involving 57 participants with early PD utilizing flexible dose titration of tavapadon between 3 to 15 mg based on optimization led to significant and clinically meaningful improvements in MDS-UPDRS III scores at week 15 and all assessment time points [29]. The drug was tolerated well with mild to moderate adverse events mostly consisting of nausea, headache, dry mouth, somnolence, and tremor. No differences in ICDs were found relative to placebo. Ongoing Phase 3 trials are investigating potential motor benefits in early PD as a fixed-dose [30] and flexible-dose regimen [31] (NCT04201093 and NCT04223193). An open-label study is also ongoing to evaluate the long-term safety and efficacy of the drug (NCT04760769) [32].

One strategy thought to reduce development of motor fluctuations is the concept of "continuous dopaminergic stimulation" (CDS) with longer-acting dopaminergic receptor stimulation. One prior attempt evaluated levodopa (as the most effective anti-parkinsonian drug) combined with the COMT-I entacapone to extend the duration of action of each dose of levodopa in early PD subjects; however, the study failed to reach its primary endpoint [33]. A similar option is being investigated with opicapone, a third-generation COMT-I with high enzyme-binding affinity [34], the aim being that CDS may be better with opicapone due to the improved potency compared to entacapone. The EPSILON study (Early ParkinSon wIth L-DOPA/DDCI and OpicapoNe) will investigate the benefits opicapone as an add-on therapy to levodopa in the early stages of disease (NCT04978597) [35, 36]. Individuals with PD on stable doses of levodopa and no signs of motor complications will be randomized to either opicapone 50 mg daily or placebo (1:1 ratio). The primary endpoint will be the change in MDS-UPDRS Part III at 24 weeks from baseline, and an open-label period of opicapone 50 mg daily for 1 year with the end point of MDS-UPDRS part IV and motor fluctuations. Thus, the risk of motor fluctuations will be evaluated in the open-label phase but may give insights into potential benefit of combined levodopa and COMT-I in early PD as a strategy to prevent long-term complications.

One longer-acting dopaminergic formulation currently available is the DA rotigotine, as a once-daily patch. A novel delivery system using rotigotine ER microspheres has been developed (LY03003), which combines rotigotine with polyoxazolines, a stable biodegradable polymer, thus allowing weekly drug injections [37]. A Phase 1 trial has been successfully completed in Japan (NCT NCT03589066) [38, 39]. A Phase 3 trial comparing weekly injection of LY03003 versus placebo in levodopa-naïve patients in China is actively recruiting patients (NCT04571164) [40]. If proven safe and effective, this new therapy might provide a convenient, more reliable, and steadier delivery of dopaminergic therapy, while reducing the development of dopaminergic side effects.

3.2 Non-Dopaminergic Therapies

To date, non-dopaminergic drugs as monotherapy in early PD have not shown strong evidence for effectiveness [41, 42]. Three further agents identified were also ineffective: the selective A_{2A} adenosine receptor ($A_{2A}R$) antagonist preladenant; the non-selective adenosine antagonist caffeine, and nicotine (see sections 3.2.1 and 3.2.2). Novel interventions currently being investigated for motor symptoms in early and more advanced PD include low doses of the $GABA_A$ receptor agonist zolpidem.

3.2.1 Adenosine Receptor Antagonists

Preladenant is a highly selective adenosine $A_{2A}R$ antagonist that was shown to improve motor function in animal models of PD possibly via a selective action on indirect striatopallidal pathways to potentially reduce motor symptoms without

Table 1 Newly approved or investigational drugs for symptomatic motor symptoms in Parkinson's disease

Indication/drug	Mechanism of action	Clinical benefit	References
PD Symptomatic			
P2B001 (pramipexole (0.3 mg or 0.6 mg) with 0.75 mg of rasagiline)	D2, D3, and D4 dopamine receptor agonist and MAO-B inhibitor	Phase 2 DBRCT ($n = 136$, untreated PD) demonstrated safety and tolerability over 12 weeks and significant improvement in MDS-UPDRS III (mean adjusted change from baseline to the end of the study versus placebo: $- 4.67 \pm 1.28$ and $- 3.84 \pm 1.25$ points for higher and lower dose, respectively). A Phase 3 trial has been completed –results pending	[26–28]
Tavapadon	D1/D5 dopamine agonist	Phase 2 DBRCT ($n = 57$, untreated PD) significant improvement of MDS-UPDRS III scores at week 15 (mean change $- 9 \pm 1.54$ for the drug group versus $- 4.3 \pm 1.65$ for placebo). Phase 3 trials – ongoing	[29]
Opicapone	Third-generation COMT-inhibitor	Phase 3 trial ($n = 324$, PD on optimized levodopa) evaluating opicapone as an add-on to levodopa in patients with early PD – results pending	[35, 36]
Rotigotine extended-release microspheres for injection (LY03003)	D1–D5 dopamine agonist	Phase 1 trial completed – results pending. Phase 3 trial – ongoing	[40]
Preladenant	Adenosine A_{2A} receptor antagonist	Phase 3 RCT ($n = 1,007$, untreated PD) – no significant benefit of preladenant given as monotherapy compared to placebo over 26 weeks (combined MDS-UPDRS part II and III scores difference from placebo was 2.60, CI 0.86, 4.30 for preladenant 2 mg, 1.30, CI $- 0.41$, 2.94 for preladenant 5 mg, 0.40, CI $- 1.29$, 2.11 for preladenant 10 mg, and 0.30, CI $- 1.35$, 2.03 for rasagiline 1 mg).	[45–47]
Caffeine	Non-selective Adenosine-receptor antagonist	Phase 2 ($n = 121$, PD treated), No difference in MDS-UPDRS part III scores caffeine versus placebo in 6–18 months (0.16 ± 7.68 for the caffeine group and 0.57 ± 7.25 for the placebo group)	[52]
Nicotine	Cholinergic receptor agonist	Phase 2 ($n = 40$, treated PD) randomized open-label trial of transdermal nicotine 90 mg daily versus control in 40 patients. No significant improvement in motor symptom baseline to week 39 when comparing the nicotine-treated versus control groups (MDS-UPRS part III scores 19.4 ± 9.3 vs. 21.5 ± 14.2)	[53]
Zolpidem	GABA$_A$ receptor agonist	Phase 2 DBRCT ($n = 28$, treated PD) low-dose Zolpidem (5 mg daily) – results pending	[54]
PD Symptomatic – Tremor			
Zuranolone	Positive allosteric modulator of the GABA$_A$ receptor	Exploratory study ($n = 14$, treated PD) significant improvement MDS-UPDRS part 2/3 tremor total score of 40% with vs placebo over 7 days (19.1 ± 3.8 at baseline followed by 11.4 ± 4.5 with drug)	[59]
Cannabidiol (CBD)	Cannabinoid receptors agonists	Phase 2 open label ($n = 15$, treated PD) demonstrated safety and tolerability of different CBD doses and improvement in motor scores (baseline mean 24.70 ± 8.93 and 18.60 ± 9.66 following intervention; 24.7% improvement in MDS-UPDRS III scores)	[60]
CX-8998	Selective T-type calcium channel modulator	Phase 2 study was recently withdrawn for unclear reasons with no preliminary results reported. The drug is now being evaluated in essential tremor	[61]

RCT randomized controlled trial, *DBRCT* double-blind randomized, controlled trial, *PD* Parkinson's disease, *CBD* cannabidiol, *CI* confidence interval, *mg* milligram, *MDS-UPDRS* Movement Disorders Society -Unified Parkinson's Disease Rating Scale

inducing dyskinesia [43, 44]. Whereas most investigation has focused on safety and tolerability as an add-on for motor fluctuations (section 4.3) [45, 46], preladenant was also evaluated as a monotherapy in the control of motor symptoms in early PD. In a large Phase 3 DBRCT, patients were randomized to preladenant 2.5 or 10 mg twice daily, rasagiline 1 mg daily (active comparator), or placebo in a 1:1:1:1 ratio. Although the drug was deemed safe and well tolerated, no differences were found in the primary efficacy outcome (total decrease in MDS-UPDRS part II and III scores in 26 weeks) [47]. The lack of benefit of the rasagiline as a positive comparator meant that interpretation of the results is uncertain and the clinical effectiveness of preladenant for early PD remains unclear.

Caffeine, the non-selective adenosine antagonist, ingested as coffee drinking, has been linked with lower risk of PD in several large epidemiological studies [48, 49], therefore suggesting its potential role as a neuroprotective agent (likely via adenosine receptors) [50, 51]. In Café-PD, Postuma et al. performed a multicenter parallel-group controlled trial demonstrating no differences in the MDS-UPDRS part III scores between patients given caffeine 200 mg twice daily (BID) and placebo [52]. The inclusion criteria were relatively broad, enrolling patients with H&Y stages I–III and a disease duration of 1–8 years. Following this study, the use of caffeine as a symptomatic therapy for the control of PD motor symptoms was considered ineffective.

3.2.2 Nicotinic Cholinergic Receptor Agonist

The interaction of nicotinic acetylcholine receptors (nAChRs) and the dopaminergic system in the basal ganglia as well as the reduced incidence of PD among smokers has led to interest in nAChR agonists as a therapeutic and possibly neuroprotective target for PD. However, to date clinical studies have reported poor tolerance of nicotine in PD. A new study was recently published further investigating nicotine in a randomized open-label Phase 2 study. A total of 40 PD patients with a disease duration longer than 3 years were enrolled to either transdermal nicotine 90 mg daily or control [53]. No significant improvement in motor symptom was observed from baseline to week 39 when comparing the nicotine-treated versus control groups. Overall side effects included nausea and dizziness, which resulted in a total drop-out of 40% in the active arm. Notably, the study lacked blinding and a placebo group, which limit the generalizability and conclusion of the study. The use of nicotine for motor symptomatic therapy appears limited due to poor tolerability likely from off target effects. Subtype selective nAChR agonists with specific basal ganglia targeting may be better tolerated and are being investigated for gait and balance, as well as LID (section 3.4).

3.2.3 Other Targets

Zolpidem is a clinically available GABA$_A$ receptor agonist that is being evaluated in a small Phase 2 RCT for motor symptoms in advanced PD (NCT03621046) (Table 1) [54]. The underlying hypothesis may be via activation of inhibitory GABAergic basal ganglia pathways and from clinical reports of sub-sedative doses of zolpidem being purported to be effective in recovery from ischemic stroke [55, 56].

3.3 Symptomatic Therapy for Tremor Control

Tremor is a common symptom that may significantly impair HRQoL in individuals with PD [57]. The response to dopaminergic therapies varies, and patients with severe and refractory tremor often require add-on therapies or consideration of surgical interventions. To date, specific therapeutic options available include anticholinergic medications such as trihexyphenidyl and benztropine but with challenging side effects of sedation, dry mouth, and cognitive dysfunction [7]. In some individuals, the tremor is non-responsive to levodopa and may require additional therapies. The mixed 5HT2A/2C receptor and cholinergic receptor antagonist clozapine has also shown efficacy, although the risk of agranulocytosis and need for frequent blood monitoring make for logistical challenges [58]. Anectodal reports of tremor improvement with amantadine have been described, although, to our knowledge, no large studies have been performed for this specific purpose. Recent drugs being evaluated for tremor include a modulator of the GABA$_A$ receptor, zuranolone; cannabidiol, and the selective T-type calcium channel modulator, CX-8998 (Table 1).

Zuranolone (SAGE-217) is a newly developed oral neuroactive steroid and positive allosteric modulator (PAM) of the GABA$_A$ receptor that has been hypothesized to be beneficial for tremor. In an open-label, exploratory study, zuranolone 20 or 30 mg was given to 14 participants as an add-on therapy for 7 days [59], and results showed a 40% significant improvement in MDS-UPDRS Part II/III tremor total score (7.7 points) compared to baseline. The most common adverse events included sedation, drowsiness, and dizziness. These findings, however, should be construed with caution in view of the lack of randomization and blinding. Future large RCTs should be performed to confirm the efficacy of zuranolone in PD tremor.

Cannabidiol (CBD) has been evaluated for tremor in PD, with duration and severity of tremor examined as a secondary outcome in an open-label, dose-escalation study of varying cannabidiol (CBD) doses in 15 individuals with PD [60]. Of note, this is the first study that provided detailed data and guidance on specific doses of CBD for this subset of patients. In this brief trial, which spanned between 10 and

15 days, the total dose of CBD was titrated by 5 mg/kg/day to target 20–25 mg/kg/day or the maximum tolerable dose. With high doses of CBD (around 1,600 mg per day and tetrahydrocannabinol (THC) concentration less than 0.15%), patients experienced mild adverse events including somnolence, diarrhea, fatigue, and transient mild elevation of liver enzymes. There was an improvement in motor scores (decrease in MDS-UPDRS part III scores by 24.7% with maximum dose compared to baseline). Nevertheless, due to the nature of this study, no robust efficacy results could be interpreted. Aside from the short duration, the trial also suffers from a small sample size and lack of a placebo arm. Given these limitations, as well as contradictory findings from the limited body of evidence, the establishment of firm conclusions regarding the clinical usefulness of CBD in PD remains a significant challenge.

CX-8998 is a selective T-type calcium channel modulator that has been considered for the symptomatic treatment of tremor. A Phase 2 DBRCT was planned to enroll patients starting in 2020, although based on recent updates on clinicaltrial.gov, the study has been withdrawn prior to patient recruitment (NCT03436953) [61]. The drug is now being evaluated for the treatment of essential tremor and it remains unclear if the potential use in PD will be explored in the near future [62].

3.4 Pharmacologic Therapies for Gait and Balance Dysfunction

With disease progression, PD patients may develop abnormalities in posture, balance, and gait, which stem from complex interrelated mechanisms involving cortical and brainstem motor circuitry and cognitive dysfunction. Such symptoms cause cumulative impaired mobility, functional deterioration, and poor HRQoL [20]. Gait and balance impairment is challenging to treat due to poor response to dopamine replacement [7, 20]. This unmet therapeutic need has led to exploration of nondopaminergic pathways and neural substrates as potential targets for drug development, and include the $A_{2A}R$ antagonist istradefylline; the cholinergic pathway agents varenicline, TAK-071, and rivastigmine; noradrenaline uptake inhibitors atomoxetine and methylphenidate; and high-dose vitamin D supplementation (Table 2).

Istradefylline has been primarily evaluated for motor symptoms as discussed above, but in addition, a role in gait has been suggested possibly via non-dopaminergic effects on arousal state [63], postural stability, and influence on neural networks involved in locomotor control [64]. A prospective study involving 14 patients on stable PD treatment reported significantly reduced freezing of gait questionnaire (FOG-Q) scores with istradefylline 20 mg daily for 1 month as compared to baseline [63]. This finding is in agreement with data from a multicenter, open-label study involving 31 advanced

PD patients with gait disorders treated with istradefylline 20–40 mg daily [64]. In this trial, improvements were also observed in other gait parameters including MDS-UPDRS Part II and III gait-related scores and number of overall movements measured by portable gait rhythmogram. Conversely, two other trials failed to replicate similar efficacy data on FOG [65, 66]. Apart from conflicting evidence, these studies are tempered by common limitations including small sample size, unblinded study design, lack of controls, and heterogeneity of gait-assessment methods.

Cholinergic dysfunction resulting from the degeneration of neurons in the basal forebrain and key brainstem areas is postulated to account for the cognitive and motor deficits contributing to balance and gait impairments. Originally developed as a smoking cessation therapeutic agent, varenicline acts as a partial agonist to the α4β2 nAchR and a full agonist to the α7 nAchR, with potential positive effects on balance based on earlier studies involving patients with other neurological conditions, including ataxia [67–70]. Nevertheless, varenicline failed to demonstrate significant improvements in the Berg Balance Scale scores in one placebo-controlled DBRCT [71]. Apart from the nAchR, preclinical studies have also evaluated muscarinic M1 acetylcholine receptors (mAchRs) as a potential neural target, especially in view of their putative role in the cognitive-motor aspects of gait and balance. Using rat models, administration of the M1 mAchR PAM TAK-071 was shown to be beneficial in reducing falls [72]. Currently, a Phase 2 study involving healthy controls and PD patients at risk for falls is being conducted to test the efficacy and safety of this agent in improving balance and reducing the propensity for falls (NCT04334317) [73].

Further into the role of the cholinergic pathways on gait, cholinesterase inhibitors have been investigated as a possible pharmacologic treatment for gait dysfunction and falls in PD, although conflicting data hinder establishment of firm recommendations for routine use [7]. Aiming to strengthen the available evidence, the ongoing Cholinesterase Inhibitors to Prevent Falls in Parkinson's Disease (CHIEF-PD) trial will investigate the safety and efficacy of rivastigmine patch compared to placebo in terms of reducing the incidence of falls and improving indices of motor and cognitive function among PD patients (NCT04226248) [74].

Aside from the cholinergic system, there is also emerging data implicating alterations in the adrenergic pathways in gait and balance dysfunction in PD, particularly with respect to FOG. Noradrenaline reuptake inhibitors such as atomoxetine and methylphenidate have been studied for such purposes but have so far faced limited success in clinical use due to lack of clear benefit and paucity of high-quality evidence [75, 76]. Presently, an early Phase 1 trial (TAME-PD) is being conducted to evaluate whether addition of low-dose atomoxetine or methylphenidate to conventional

Table 2 Newly approved or investigational drugs for the treatment of gait and balance symptoms in Parkinson's disease

Indication/drug	Mechanism of action	Clinical benefit	References
Istradefylline	Adenosine A_{2A} receptor antagonist	Two prospective interventional studies ($n = 45$) demonstrated improvements in indices of freezing of gait. However, two further exploratory studies ($n = 45$) failed to replicate such findings	[63–65, 229]
Varenicline	α4β2 nicotinic acetylcholine receptor (nAchR) partial agonist and α7 nAchR full agonist	DBRCT ($n = 36$ PD patients with one or more falls or near falls within 6 months prior to screening), no significant improvements in the Berg Balance Scale (43.93 ± 1.97 at baseline and 43.25 ± 1.84 at the end of the study for the drug intervention vs. 41.14 ± 2.55 at baseline and 45.13 ± 2.34 at the end of the study for the placebo arm)	[71]
TAK-071	M1 muscarinic AchR positive allosteric modulator	Phase 2 trial – ongoing.	[73]
Rivastigmine transdermal patch	Cholinesterase inhibitor	Phase 3 trial – ongoing	[74, 77]
Atomoxetine, methylphenidate	Noradrenaline uptake inhibitors	Phase 1 trial – ongoing to assess effectiveness of low-dose atomoxetine or methylphenidate + conventional PT	[78]
High-dose vitamin D supplementation	Exact mechanism unknown but possibly improves postural sway, equilibrium, and postural responses	Phase 2 DBRCT ($n = 51$, PD patients with low vitamin D) – no significant improvement in several measures of balance and gait using sensors and TUG between high dose vitamin D and placebo	[80]

AchR acetylcholine receptor, *RCT* randomized, controlled trial, *DBRCT* double-blind, randomized, controlled trial, *PD* Parkinson's disease, *PT* physiotherapy, *TUG* timed up and go

physical therapy is more beneficial for PD patients with balance or gait disorder compared to physical therapy alone (NCT04334317) [77, 78].

Vitamin D supplementation may play a role in preventing falls, with more recent evidence suggesting a U-shaped trend between vitamin D dose and fall reduction. Available data from studies in older, non-PD adults ascribe this effect to improvements in postural sway, equilibrium, and symmetry of automatic postural responses [79]. To this end, a pilot DBRCT investigated the effectiveness of high-dose (approximately 10,000 IU/day) vitamin D supplementation in improving balance parameters measured by dynamic posturography [80]. Despite an encouraging safety profile, treatment with high-dose vitamin D failed to meet the primary endpoint as well as secondary measures related to gait and leg strength. Correspondingly, post hoc analysis of data suggests a possible age-dependent efficacy of vitamin D supplementation on measures of balance.

4 Motor Fluctuations

It is estimated that the majority of PD patients eventually develop some degree of motor fluctuations after 20 years of levodopa exposure, ultimately leading to deterioration of functionality and QoL [81–83]. As previously discussed,

the underlying mechanisms for this complication are complex and may arise from patient-, disease-, and drug-related factors. Careful consideration of the individual's age and weight are important, especially when initiating treatment, as there is some evidence that early use of high levodopa doses (i.e., greater than 600 mg per day or 5–6 mg/kg/day) may be linked to a higher risk of development of motor complications [84]. Other practical approaches for motor fluctuations include administration of smaller but frequent levodopa doses, use of ER drug formulations, and combination treatment with adjunctive therapies, although the effectiveness of such strategies may be hindered by continuous disease progression and medication side effects [14]. In this context, there exists an unmet need for pharmacologic treatments to ameliorate motor fluctuations and minimize disability without precipitating troublesome LID.

4.1 Rapid-Acting Dopaminergic Therapies

While conventional oral levodopa has been in use for several decades and its effectiveness well established, the pharmacologic properties pose practical impediments in the long-term treatment of PD, specifically as patients reach the advanced stages. These limitations include the progressive diminution of the so-called long-duration response, peripheral factors related to drug absorption and food interaction, and generally short duration of action [14]. These issues often result in

delayed or no effect of an oral dose of levodopa. Thus, recent and emerging trials are now focusing on novel preparations with improved efficiency, and more rapid delivery systems of dopaminergic therapy [14, 85] (Table 3).

CVT-301 is a novel inhaled levodopa formulation, a self-administered, dry inhalation powder delivered through a passive breath-actuation device, and was approved by the FDA in 2018 and in the European Union (EU) in 2021. It is now expected to be launched in Germany in mid-2022. The direct delivery to the pulmonary epithelium and alveolar capillary network allows the drug to bypass gastrointestinal absorption and first-pass metabolism with potential rapid-action [86–88]. In a Phase 3 multicenter study, adjunctive CVT-301 administered on an as-needed basis yielded a higher proportion of patients achieving an ON state (as measured by a study personnel in the clinic) compared to placebo (58% vs. 35%, $p = 0.0027$), with effects lasting up to 60 min post-dose [89] consistent with findings from exploratory efficacy assessments performed in other Phase 1 and 2 trials [90–93]. In these studies, CVT-301 exhibited a good safety and tolerability profile without any associated increase in ON-state dyskinesia. On the other hand, data regarding reductions in total daily OFF time are conflicting, which may be explained by patients' tendency to delay oral medication intake while on CVT-301, inherent limitations of diary-based assessments, or the waning robustness of drug effects over time [89, 92]. A recent meta-analysis including 4,962 patients with early-stage PD (H&Y 1–3) generated moderate and low-quality evidence supporting the efficacy of CVT-301 in terms of proportion of patients achieving an ON state and improvements in pre- and post-dose UPDRS III scores, respectively. Correspondingly, the safety analysis showed a significantly higher incidence of adverse events in CVT-301-treated patients, with results largely driven by a higher risk of occurrence of nausea, as well as respiratory symptoms including cough, discolored sputum, and throat irritation [86].

Apomorphine is a potent broad-spectrum DA that has been available for many years as an intermittent subcutaneous injection for "rescue" treatment for unpredictable OFF periods [14, 94]. However, the logistical requirement for training, repeated injections, complex device assembly, and skin-related complications including subcutaneous nodules have limited widespread use in clinical practice [94, 95]. There have been attempts to develop alternate modes of administration, but to date, all have failed primarily due to subcutaneous tissue side effects. APL-130277 is a new formulation of apomorphine that consists of a sublingual, bilayer film formulation, first registered in Canada in 2020 and FDA approved as treatment for unpredictable OFF episodes [96, 97]. A 12-week, Phase 3, DBRCT involving patients with OFF episodes despite stable anti-PD treatment evaluated sublingual apomorphine (dose range of 10–30

mg) and reported significantly greater self-rated full ON response within 30 min versus placebo, corroborated by a nominally significant full ON response using home-dosing diaries. There was also significantly greater mean change between pre- and post-dose MDS-UPDRS motor scores at week 12 (treatment difference vs. placebo: − 7.6 points, 95% confidence interval (CI) − 11.5 to − 3.7). Notably, nearly a third of patients dropped out from the trial due to treatment-related adverse events mostly related to oropharyngeal reactions [94]. However, a recent dose optimization study demonstrated additional improvements in motor scores with medication doses higher than those originally deemed to provide an ON response, without producing new safety signals [97]. Trials on long-term efficacy and safety, as well as head-to-head comparisons between the sublingual and subcutaneous preparations of apomorphine are currently underway (NCT03391882 and NCT02542696) [98, 99].

The relative clinical usefulness of these three available rapid-acting therapies, inhaled levodopa, subcutaneous apomorphine, and sublingual apomorphine, for reversal of OFF periods is as yet unknown. Several factors may determine long-term usefulness including the relative efficacy of time to onset of reversal of PD symptoms, reliability of the drug, side effects, costs, and convenience of administration. Future trials and head-to-head comparison data will hopefully provide more insight regarding the long-term effectiveness and safety of these rapid-acting drugs.

4.2 Longer-Acting Levodopa and Dopaminergic Formulations

One effective method of treating motor fluctuations is to provide CDS. The challenge with available therapies relates to the short duration of action of current dopaminergic agents. Numerous modifications of levodopa therapy have been undertaken to potentially promote CDS. These include continuous subcutaneous apomorphine infusion (CSAI); intestinal gel infusions of levodopa/carbidopa, with and without entacapone; subcutaneous infusion of levodopa such as ND0612 and ABBV-951; and novel oral levodopa preparations including IPX203, DM-1992, Accordion Pill, and DopaFuse.

Apomorphine delivered as CSAI has been available for clinical use for decades. The prospective, DBRCT Phase 3 study (TOLEDO) was recently published confirming evidence of the short- and long-term efficacy and safety of CSAI for PD patients with persistent motor fluctuations despite optimal oral and transdermal dopaminergic therapy. Thus, CSAI significantly reduced daily OFF time and increased ON time without troublesome dyskinesia (ON-WoTD) [100], with benefits persisting 52 weeks after the open-label phase [101]. This trial, along with the OPTIPUMP real-world observational cohort [102], demonstrated a favorable risk/

Table 3 Newly approved or investigational drugs for the treatment of motor fluctuations in Parkinson's disease

Indication/drug	Mechanism of action	Clinical benefit	References
CVT-301	Inhaled levodopa preparation	Systematic review and meta-analysis of five RCTs showed a significantly higher proportion of patients achieving an ON state vs. placebo (OR 2.68; 95% CI: 1.86, 3.86). Higher incidence of AEs detected in treatment arm	[86]
Sublingual apomorphine (APL-130277)		Phase 3 study ($n = 109$) showed significantly greater responder rate for self-rated full ON response within 30 min vs. placebo (35% vs. 16%; effect size: OR 2.81; 95% CI, 1.04, 7.64) Ongoing trials for long-term efficacy and safety, as well as head-to-head comparisons with subcutaneous formulation	[94, 98, 99]
Continuous apomorphine subcutaneous infusion (CSAI)	D1 and D2 receptor agonist	Phase 3 and open-label studies demonstrate good safety profile. The Phase 3 trial ($n = 107$) showed significantly reduced off time with CSAI vs. placebo (treatment difference: − 1.89 h per day, 95% CI − 3.16, − 0.62) Ongoing trials further investigating long-term efficacy and safety, as well as comparison of diurnal vs. CSAI	[100, 101, 103, 104]
Levodopa/carbidopa intestinal gel (LCIG)	Continuous intestinal delivery of levodopa/carbidopa	Earlier Phase 3 trial demonstrated reduced mean OFF time and increased ON-WoTD with LCIG compared to oral levodopa/carbidopa with treatment difference (and 95% CI) for OFF and ON-WoTD times: − 1.91 h (− 3.05, − 0.76) and +1.86 h (0.56, 3.17), respectively Several long-term registries with observation period ranging from 1 to 4 years demonstrate sustained efficacy and safety. Procedure- and device-related complications are frequent adverse events, but the longest observational cohort showed decreasing trends with long-term use	[7, 105–107]
Levodopa/entacapone /carbidopa intestinal gel (LECIG)	Continuous intestinal delivery of levodopa/carbidopa + COMT-I	Phase 1 trial ($n = 11$, treated with LCIG) showed that LECIG may allow lower doses of administered levodopa. Preliminary findings demonstrated no significant differences in treatment response scale vs. LCIG A prospective observational study is underway to evaluate long-term effectiveness and safety among patients with motor fluctuations (decrease in 4 h of mean daily h of OFF time and improvement of 4 h in mean daily h of ON time without troublesome dyskinesia)	[108, 109]
ND0612	Continuous subcutaneous levodopa/carbidopa pump	Phase 2 trials ($n = 68$) showed a reduction of approximately 2 h of OFF time per day. Mild infusion site reactions (ISRs) were frequently reported treatment-emergent adverse effects Phase 3 trial comparing ND0612 with oral levodopa – ongoing	[110–113]
ABBV-951	Subcutaneous delivery of levodopa/carbidopa phosphate prodrug	Phase 1 study ($n = 28$) demonstrated steady-state levels and degree of fluctuation similar to LCIG	[114]
IPX203	Multiparticulate capsule formulation of levodopa/carbidopa	Phase 3 ($n = 28$) trial showed a significant reduction of diary-based percentage of OFF time compared to active comparator (mean 19.3% for IPX203 vs. 33.5% for IR levodopa/carbidopa), with increased good ON time Long-term efficacy and safety data currently underway	[118, 119]
DM-1992	Gastroretentive formulation of oral levodopa/carbidopa	Phase 2 ($n = 34$) showed significantly greater reductions in percent and absolute OFF time compared to IR levodopa/carbidopa (treatment difference: -6.86% and -1.08 h, respectively)	[121]

Table 3 (Continued)

Indication/drug	Mechanism of action	Clinical benefit	References
Accordion Pill® (AP-CD/LD)	Combined IR and IR+CR levo-dopa/carbidopa folded into an oral capsule	Phase 2 ($n = 63$) exploratory data demonstrated that compared to oral levodopa therapy, AP-CD/LD 50/375 mg twice daily and 50/500 mg twice daily showed significant treatment differences in OFF time (-1.85 ± 2.28 and -2.32 ± 3.65 h, respectively); ON-WoTD (1.98 ± 2.39 and 2.58 ± 4.94 h, respectively); and good ON time (2.08 ± 2.16 and 2.69 ± 4.37 h, respectively) Phase 3 DBRCT – ongoing	[92, 122]
DopaFuse®	Customized dental retainer-based levodopa/carbidopa delivery system	No efficacy and safety data available at present Phase 2 trial ongoing	[123]
Ropinirole transdermal patch	D2-selective dopamine agonist	Phase 3 study (full analysis set $n = 428$), exploratory data reported noninferiority to oral tablet and significant reduced OFF time compared with placebo (treatment difference: -1.54 h, CI, -2.71, -0.36), and increased ON-WoTD and good ON time ($+0.70$ h and $+0.78$ h, respectively)	[126]
Tavapadon	D1/D5 receptor partial agonist	Phase 3 DBRCT – ongoing	[128]
Safinamide	Selective MAO-B inhibitor with blocking action on glutamate release, and voltage-gated Na$^+$ and Ca^{2+} channels	Phase 2/3 DBRCT ($n = 406$), Safinamide 50 and 100 mg significant improvements in daily ON time and mean daily OFF time, with magnitude of effect favoring the higher dose (-1.25 h and -1.72 h reduction in OFF time for 50 and 100 mg, respectively) Phase 3 DBRCT in Chinese PD patients completed – results pending	[132]
Opicapone	Third generation COMT-inhibitor	One Phase 3 DBRCT and pooled analysis of Phase 3 and open-label trials report significant reductions in OFF time and increased ON time with and without non-troublesome dyskinesia (absolute OFF reduction time of -35.1 min; CI -62.1, -8.2 for the 25 mg dose and -58.1 min; CI -84.5, -31.7 for the 50 mg dose)	[138, 140]
Istradefylline	Adenosine A$_{2A}$ receptor antagonist	Pooled analysis of Phase 2b/3 trials showed significantly reduced OFF time and increased ON-WoTD with istradefylline (least-squares mean difference of 20 and 40 mg istradefylline vs. placebo; reduced OFF time: -0.38 h; CI -0.61, -0.15 and -0.45 h; CI -0.68, -0.22 respectively)	[146]
Preladenant		Phase 2 and 3 trials showed lack of efficacy in reducing OFF time	[46, 149]
Tozadenant		Phase 3 and open-label trials prematurely terminated due to safety concerns	[144]
Zonisamide	Numerous putative mechanisms including MAO-B inhibition, voltage-gated Na+ and Ca2+ channel blockade, and modulation of levodopa-dopamine metabolism	A systematic review of Phase 2,2b/3, and 3 trials revealed a reduction in daily OFF time when added to levodopa/carbidopa $\pm$ other PD medications (zonisamide 50 mg daily decreased OFF time by -0.719 ± 0.179 h compared to -0.011 ± 0.173 h in the placebo group)	[152]
H. pylori eradication	Restoration of normal gut homeostasis and microbiota composition, as well as reduction in GI inflammation	Insufficient evidence due to conflicting data from RCTs	[158, 162]
Bumetanide	NKCC antagonist	Phase 2 study – ongoing	[165]
CVN424	GPR6 inverse agonist	Phase 2 study – ongoing	[167]

AP-CD/LD Accordion Pill, *CI* confidence interval, *DBRCT* double-blind, randomized, controlled trial, *IR* immediate release, *PD* Parkinson's disease, *CSAI* continuous subcutaneous apomorphine infusion, *LECIG* levodopa/entacapone/carbidopa intestinal gel, *mg* milligram, *ON-WoTD* ON time without troublesome dyskinesia, *MDS-UPDRS* Movement Disorders Society – Unified Parkinson's Disease Rating Scale, *RCT* randomized, controlled trial

benefit ratio with CSAI treatment, with most adverse events being mild to moderate in severity, reversible, and declining over time. Notable treatment-related adverse events consist of injection site reactions, nausea, and somnolence. Moreover, CSAI treatment was not shown to increase hyperdopaminergic behaviors [102]. A further efficacy and safety open-label trial of CSAI is ongoing (NCT02339064) [103]. In addition, a prospective phase 4 study is currently underway to assess the pharmacokinetic profile of diurnal apomorphine infusion and CSAI (NCT04887467) [104].

The last few years have paved the way for innovations in terms of enhancing levodopa's clinical utility by trying to overcome the pharmacologic limitations described earlier [85]. The levodopa/carbidopa intestinal gel (LCIG) formulation that is infused into the small intestine is one approved option [7, 14]. Recent studies have provided long-term data solidifying the existing evidence for its efficacy, safety, and real-world usefulness. Findings from the GLORIA [105] and DUOGLOBE [106] registries and the study by Fernandez et al. [107] consistently showed significant and sustained reductions in OFF time among LCIG-treated patients during an observation period ranging from 1 to 4 years. Although assessment methods were heterogeneous, the findings support long-term efficacy of LCIG in addressing motor fluctuations. In all three studies, adverse events were consistent with the known safety and tolerability profile of LCIG, with procedure- or device-related complications being the most common AEs reported [105–107]. In the longest observational study (over 4 years), the incidence of such complications showed a decreasing trend with long-term LCIG use [107].

A newer drug combination delivered similarly to LCIG is levodopa/entacapone/carbidopa intestinal gel (LECIG) infusion. With the addition of a COMT-I, this treatment is thought to reduce the peripheral metabolism of levodopa, ultimately allowing a higher concentration of levodopa to reach the brain. Additionally, this delivery system utilizes a lighter pump device versus LCIG (total weight: 227 g vs. 550 g, respectively). In a randomized, open-label, 2-day crossover trial involving 11 patients, LECIG allowed up to 20% reduction of morning, maintenance, and extra doses of LCIG without lowering systemic levodopa exposure or causing significant between-group differences in the treatment-response scale. Safety data were consistent with expected adverse events with LCIG and oral levodopa plus entacapone [108]. The ongoing Long-Term Observational Study on Effectiveness and Safety of Lecigon in Patients with Advanced Parkinson's Disease (ELEGANCE) aims to provide additional long-term data on LECIG, particularly with respect to addressing motor fluctuations (NCT05043103) [109].

ND0612 is a liquid formulation of levodopa/carbidopa that can be continuously delivered via a subcutaneous pump device [110]. Exploratory analyses from two Phase 2 trials supported the efficacy of ND0612 in reducing OFF times [97, 110]. Additionally, data from an open-label (BeyoND) study demonstrated safety with a nominally significant increase in good ON time (defined as the sum of ON-WoTD and ON time with non-troublesome dyskinesia). A treatment-emergent adverse event and common reason for discontinuation is infusion site reactions (ISRs) [111, 112]. The long-term safety data highlighted that such ISRs are frequently mild, reversible, and could be minimized with continued training. A Phase 3 trial aimed at comparing the efficacy and safety of ND0612 to oral levodopa/carbidopa is currently ongoing (NCT04006210) [113].

Foslevodopa/foscarbidopa (ABBV-951) is another subcutaneously administered levodopa therapy in the early stages of development. This formulation utilizes phosphate prodrugs of levodopa/carbidopa with potential advantages of better aqueous solubility and sustained steady-state plasma levels [114]. To date, a Phase 1 tolerability and pharmacokinetic study showed that a 72-h dose-proportional, continuous subcutaneous infusion of foslevodopa/foscarbidopa achieved a steady-state levodopa exposure rapidly with a degree of fluctuation comparable to LCIG. Akin to other subcutaneous interventions described earlier, the main side effect was skin reaction at the injection/infusion site [115].

There are also increasing efforts to modify the physicochemical and pharmacokinetic properties of orally administered levodopa/carbidopa to overcome the challenges with bioavailability, absorption, and short half-life [14, 85]. IPX066 is a mixed immediate and ER formulation of levodopa/carbidopa that was approved for PD in 2015 [116]. IPX203 is another novel levodopa/carbidopa multiparticulate capsule formulation designed to produce both rapid and sustained therapeutic plasma drug levels, thereby allowing less frequent dosing and a longer duration of action. Pharmacodynamic and pharmacokinetic data from a randomized, open-label, crossover study demonstrated benefit of IPX203 over immediate-release (IR) and IPX066 in reducing OFF times and increasing good ON times, as assessed by a blinded clinician rater [117]. These findings were further confirmed in an open-label, rater-blinded, crossover trial of IPX203 in patients with advanced PD using IR levodopa/carbidopa as the active comparator [118]. Despite less frequent dosing (mean frequency: 2.0 vs. 3.1 for IPX203 and IR levodopa/carbidopa, respectively), patients given IPX203 had a significantly lower percentage of diary-based OFF time during waking h, translating to a 2.3-h and 1.9-h advantage of IPX203 in reducing mean OFF time and increasing mean good ON time, respectively. Dyskinesia and other dopaminergic side effects were more frequently reported in IPX203 during dose conversion, but not during dose stabilization [118]. An open-label extension phase of this study is currently being undertaken to investigate the long-term safety

and clinical utility of varying doses of IPX203 in motor fluctuations (NCT03877510) [119].

DM-1992 (DepoMed) is another investigational drug formulation made up of a gastric retentive ER core and an outer IR levodopa/carbidopa layer, all constituted as an oral tablet. Its gastric retentive property is made possible by a technology that allows the drug to swell in the stomach upon contact with gastric juices followed by slow dissolution and release of the drug to the small intestine. These properties prolong drug delivery and improve constancy of blood concentrations [120]. A Phase 2, randomized, open-label, crossover study showed that DM-1992 achieved steadier plasma L-dopa concentrations compared to IR levodopa/carbidopa, as well as greater reductions in percent and absolute OFF time without statistically significant differences in ON with troublesome dyskinesia and ON-WoTD. Despite higher percentages of reported AEs, no consistent pattern was detected for DM-1992 relative to conventional levodopa [121]. Another novel oral drug delivery platform is the Accordion Pill® (AP-CD/LD), which consists of IR, plus both IR and controlled-release levodopa/carbidopa, all imbedded into layered polymer sheets that are folded into a capsule formulation, allowing maximal gastrointestinal absorption and reduced variability in plasma levodopa concentrations with twice daily dosing [85, 92]. Its efficacy in addressing motor fluctuations was explored in a Phase 2, two-way randomized, open-label, crossover study, which showed significant improvements in daily OFF time, ON-WoTD, and good ON time in cohorts of patients administered with two varying doses of AP-CD/LD. There was no increase in troublesome dyskinesia nor new safety signals associated with the treatment [85, 92]. The results of this study guided the design of the ongoing Phase 3 DBRCT comparing the efficacy and safety of AP-CD/LD to conventional levodopa among patients with advanced PD (NCT02605434) [92, 122].

A further innovation is DopaFuse, a drug delivery system comprised of a reusable, customized dental retainer, its case, and a small, single-use drug container that continuously releases levodopa/carbidopa into the posterior aspect of the mouth. An ongoing Phase 2 open-label trial is expected to generate additional evidence regarding the pharmacokinetic, efficacy, and safety profile of this investigational drug delivery platform (NCT04778176) [123].

Recent and emerging discoveries in formulations and delivery systems of levodopa/carbidopa offer innovative ways of potentially overcoming the pharmacologic limitations of available levodopa therapies, which may be useful in the context of treating motor fluctuations. While potentially effective, future work on subcutaneous formulations should focus on factors leading to, as well as strategies to minimize, infusion-related adverse events. Additionally, larger controlled studies are warranted to further establish the clinical effectiveness and safety of newer oral formulations of levodopa. Logistical and economical evaluations will also need to be include since for many regions, these advanced therapies may be financially challenging to initiate.

4.3 Adjunctive Therapies for Motor Fluctuations; New Formulations of Dopamine Agonists and Agents that Extend the Duration of Action of Levodopa

Adjunct therapies to extend the duration of action of levodopa, or to add in to improve motor benefit, are a large area of research. Currently used agents include COMT-Is, MAOB-Is, and DAs. However, despite the availability, this remains a large unmet need due to limited efficacy and side effects. Many targets are being refined or in development and include novel DAs tavapadon and a ropinirole patch; newer enzyme inhibitors such as safinamide and opicapone; $A_{2A}R$ antagonists istradefylline, preladenant, and tozadenant; and the anti-seizure drug zonisamide (Table 3).

For many years, oral DAs have played a substantial role as add-on PD treatment, particularly in managing motor complications, by improving OFF times without further increasing levodopa levels and its innate drug-related risks [14]. However, as already described, side effects often limit their use in clinical settings, particularly the issue of ICDs [124]. Such effects may be determined by the specific dopamine receptor affinity of the DA agent [14], or possibly the duration of action, with longer-acting DAs conceivably reducing the risk of ICDs, although this is not as yet proven [125]. One novel development in this drug class is a patch formulation to potentially provide a longer duration of action in the delivery of ropinirole, a non-ergot, postsynaptic D2 receptor-selective DA. A Phase 3 study of the ropinirole patch (dose range of 8–64 mg/day) reported significantly improved UPDRS Part III motor scores versus placebo, and noninferiority compared to oral ER ropinirole tablet. ICDs were not reported in the study, and there were no differences in dyskinesia or sleep issues between the groups. Exploratory efficacy analyses revealed significantly reduced OFF time, ON-WoTD, and good ON time relative to placebo [126]. A 52-week open-label study demonstrated long-term safety and did assess ICDs, with no increased incidence reported. The most notable adverse event was application site skin reactions [127]. Another DA being investigated for motor fluctuations is the earlier discussed selective D1/D5 partial agonist tavapadon. In view of its promising results in the Phase 2 trial involving patients with early PD [29], a Phase 3, DBRCT is currently being conducted across 125 study locations to investigate its efficacy, safety, and tolerability as an adjunctive therapy for motor fluctuations (NCT04542499) [128].

MAOB-Is are a class of medications that increase synaptic dopamine concentrations by blocking enzymatic

degradation of dopamine in the synaptic cleft [14], and thus extend the duration of action of levodopa. Safinamide is a newer approved drug for PD motor fluctuations, which not only acts as a selective and irreversible MAOB-I, but also blocks voltage-dependent sodium and calcium channels and reduces glutamate release [129]. Previous studies have reported efficacy and safety of safinamide in reducing daily OFF time and improving ON-WoTD, with the extension phase of one trial showing sustained benefits at 2 years [129–131]. A recent Phase 2/3 DBRCT of safinamide at 50 and 100 mg doses showed statistically significant improvements in daily ON-WoTD and mean daily OFF time [132], in agreement with findings from the earlier trials. Such benefits were maintained for up to 52 weeks of treatment, with long-term safety data being no different from those reported in previously published trials [133]. A Phase 3 DBRCT of safinamide as add-on therapy to levodopa/carbidopa among Chinese PD patients has been recently completed and results are currently anticipated (NCT03881371) [134]. Comparison of efficacy and tolerability with other clinically available MAOB-Is, selegiline and rasagiline, is unknown.

Another drug class for treating wearing-off is COMT-Is, which mainly act by blocking the peripheral metabolism of levodopa, thereby increasing its delivery and availability in the brain. Entacapone is most commonly used but has several limitations including relatively modest reductions in OFF time possibly due to a peripheral action only; need for frequent dosing with concomitant intake with levodopa; and side effects such as diarrhea and urine discoloration [34, 135]. Tolcapone is rarely used due to hepatotoxicity concerns, despite being a more lipophilic agent and having a more efficacious central COMT-I action than entacapone. Safety issues also precluded the continued use of another COMT-I, nebicapone [34]. The unmet need for a safer, highly efficacious adjunct treatment drove the development of the earlier discussed agent, opicapone (BIA 9-1067) [34]. Several trials have been undertaken to determine the short- and long-term effectiveness and tolerability of opicapone in addressing motor fluctuations. The pooled analysis of the pivotal placebo-controlled BIPARK-1 [135] and BIPARK-2 [136] trials and open-label extensions [137] demonstrated the safety of switching from entacapone to opicapone. The results also consistently showed significant reductions in mean daily OFF times as well as increases in ON-WoTD for opicapone 25 and 50 mg capsules once daily, with the magnitude of effect sizes being greater with the higher drug dose and maintained for over at least 1 year of therapy [138]. Although dyskinesias were the most frequently reported treatment-related AE, these were mostly deemed as non-troublesome and further mirrored by lack of significant differences in PD diary-based ON time with troublesome dyskinesia relative to placebo [138, 139]. The overall short- and long-term efficacy were likewise demonstrated in open-label and DBRCTs of opicapone tablet among Japanese PD patients with motor fluctuations [140, 141]. However, data regarding differences in dose-dependent efficacy between the 25 and 50 mg doses are conflicting. Contrary to findings of the pooled studies, the Japanese trials showed no dose-dependent differences in efficacy, which are hypothesized to be due to several factors including pharmacokinetic differences between the capsule and tablet formulations, body weight, and plasma exposure differences between the studied populations, and the possible yet undetermined role of COMT Val158Met polymorphism in drug metabolism. Although no direct assessments of motor fluctuations were performed, a phase 4, real-world study of opicapone 50 mg confirmed the safety data reported in earlier trials and demonstrated improvements in clinician- and patient-rated assessments of global PD condition, as well as rating scale-based evaluations of motor function, nonmotor symptoms, and QoL [142].

Preclinical and clinical studies have also generated insight regarding the role of adenosine $A_{2A}R$ in PD. These receptors co-localize with and override the D2 receptor-mediated inhibition of the indirect pathway, thus contributing to motor impairments in PD [143]. Adenosine $A_{2A}R$ antagonists restore the influence of D2 receptors on the indirect striatopallidal outflow tract, thereby improving motor function without inducing LID. To date, only three agents have entered clinical development with variable success [144]. Istradefylline is a xanthine derivative, selective adenosine $A_{2A}R$ antagonist (as discussed above) that has been widely used in Japan since 2013 and was recently approved by the FDA in August 2019 for adjunct therapy [145]. Post hoc and meta-analyses of Phase 2 and 3 clinical trials of istradefylline consistently showed a significant reduction in daily OFF time that appears to translate to an increase in good ON time with doses ranging between 20 and 40 mg per day [143, 146] (Table 3). The most frequent adverse event detected in the pooled analysis was mild to moderate dyskinesia, particularly in those with pre-existing dyskinesia at baseline [146]. Of interest, there was little to no increase in AEs attributable to concurrent levodopa or other dopaminergic therapies, further reflecting istradefylline's lack of off-target effect [146]. These findings are consistent with trends observed in preliminary results of a long-term study of istradefylline in patients with moderate to advanced PD (NCT02610231) [147]. Data from the open-label phases of other randomized trials are currently anticipated (NCT00199368) [148]. Preladenant is a selective $A_{2A}R$ antagonist that initially showed promising results in reducing mean daily OFF times in an earlier Phase 2 trial [45]. However, although found to be a generally well-tolerated drug, further clinical development of preladenant was halted due to lack of efficacy evidence from more recent Phase 2 and

3 studies [46, 149]. Similar to the two agents, tozadenant (SYN115) is an oral selective $A_{2A}R$ antagonist, which was shown to be effective in reducing daily OFF time and increasing good ON time at doses of 120 mg and 180 mg twice daily in a Phase 2b trial [150]. Preliminary data from the Phase 3 trial of tozadenant showed consistent results, but this trial and another long-term safety study were prematurely terminated due to a finding of increased frequency of serious AEs including sepsis and agranulocytosis in the treatment group [144].

An anecdotal report of zonisamide improving PD symptoms in a patient who concomitantly had a seizure [151] has led to trials investigating its role as an add-on treatment for PD. Although still unclear, it is postulated that zonisamide exerts not only dopaminergic and non-dopaminergic but also neuroprotective effects in PD [152]. A recent review of Phase 2, 2b/3, and 3 trials provided supportive evidence that zonisamide, in conjunction with levodopa with or without other antiparkinsonian drugs, reduces total daily OFF time without significantly increasing dyskinesia in patients with advanced PD. These benefits were more consistently seen with doses ranging from 50 to 100 mg daily. Zonisamide was also reported to be safe and well tolerated without any notable increase in the incidence of hallucinations or dyskinesia [152–155]. Conversely, a Phase 3 trial showed a higher incidence of somnolence and constipation at a dose of 50 mg compared to 25 mg and placebo [154]. Presently, zonisamide is approved as a treatment for motor fluctuations in Japan since 2009 and is considered an efficacious and clinically useful drug for this motor complication based on the most recent MDS evidence-based medicine review [7].

To date, several newer drugs targeting dopamine receptors, as well as MAO-B and COMT enzymes, have shown promising results in treating motor fluctuations. Targeting the adenosine receptor is also a potentially effective strategy, although the current evidence only supports istradefylline based on its favorable efficacy and safety profile. Comparative studies of these newer drugs against currently available agents have, to date, not been reported but would be important to determine relative efficacy in reducing OFF time, as well as the potential risk of inducing dyskinesia.

4.4 Other Novel Targets

Although the exact mechanisms whereby GI impairment contributes to motor symptoms remain unknown, suggestions include alterations in gut microbiota composition and small intestinal bacterial overgrowth (SIBO). Gastrointestinal inflammation that may interfere with levodopa absorption plus neuroinflammatory responses through the gut-brain axis have also been posited to contribute to worse PD function and motor fluctuations [156].

Helicobacter pylori (HP) infection has been implicated as a contributory factor to PD motor symptoms [157]. A recent randomized, placebo-controlled trial by Tan et al. [158], however, failed to demonstrate clinically meaningful improvements in motor scores in those receiving HP eradication triple therapy and in the subgroup of patients with motor fluctuations, which contrasts to positive findings reported in earlier trials [157, 159–162] and a more recent prospective cohort study [163]. Such discrepancies may be partly due to differences in study design and methods of assessment [158]. Given the conflicting evidence, the role of HP eradication in improving motor symptoms and fluctuations remains controversial and warrants further investigation through larger randomized trials.

Bumetanide, the clinically available Na^+-K^+-Cl^- cotransporter (NKCC) antagonist, is under investigation for PD. The mechanism of action may relate to targeting a subpopulation of cholinergic/GABAergic interneurons present in many basal ganglia and inter-related structures, and reversing effects of dopamine depletion on increased cellular chloride levels [164]. The ongoing Phase 2 CUREPARK study (NCT03899324) [165] is designed to investigate the efficacy and safety of bumetanide in PD patients including assessment of OFF and ON states as outcome measures.

Another novel compound in its early stages of development is CVN424, which mainly acts as an inverse agonist to GPR6, a highly constitutive orphan G-protein coupled receptor selectively expressed in D2-type medium spiny neurons in the striatum. It has been hypothesized that antagonism of this receptor provides a compensatory inhibition to the hyperactivity of the indirect pathway resulting from dopamine depletion. Preclinical studies using rat models have shown that CVN424 restores the normal basal ganglia circuitry and improves motor behavior in vivo [166]. A Phase 2 trial involving 135 PD patients with motor fluctuations is currently underway to evaluate the compound's safety and efficacy (NCT04191577) [167]. These novel, non-dopaminergic agents may widen the available options for the treatment of motor fluctuations. Theoretically, use of non-dopamine targets potentially reverse motor symptoms without inducing dyskinesia; however, more data are needed before these could advance into clinical development and large-scale use.

5 Levodopa-Induced Dyskinesia

As earlier discussed, LID is a common motor complication linked to factors associated with advancing disease and the consequent need for higher cumulative levodopa daily doses [17, 19]. Most employed strategies consist of modifying the ongoing PD treatments by reducing dose and timing

intervals of levodopa; and reducing adjunct DAs, MAOB-Is, and/or COMT-Is [19]. However, the negative consequence is worsening OFF symptoms. Thus, finding agents that selectively reduce LID without worsening PD motor symptoms is the key. To date, amantadine, a non-selective *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist, is the most widely use agent; however, its neuropsychiatric side-effect profile can limit routine use [168, 169]. Longer-acting preparations of amantadine have thus been developed. Several more selective glutamatergic agents such as mavoglurant, topiramate, naftazone, and foliglurax have not shown clinical benefit in recent studies. Other drugs with similar glutamatergic activity are also under investigation, including AV-101 and dipraglurant. Other novel targets in development include targeting serotonin with 5-hydroxytryptophan (5-HTP), JM-10, befiradol, eltoprazine, and piclozotan. Finally, the dopamine antagonist mesopetan and the sigma-1 receptor agonist pridopidine are currently being investigated for use in LID (Table 4).

5.1 Glutamatergic Agents

Abnormal overactive glutamate transmission is a key feature in the development of LID, and agents targeting glutamate remain a focus of investigation [170]. The non-selective NMDA receptor antagonist, amantadine, remains the only available oral medication for the treatment of LID. Two new longer-acting versions of amantadine have been approved by the FDA: amantadine ER and amantadine HCl tablets (the latter combining both IR and ER forms). The potential benefit of a longer duration of action has been suggested to reduce higher nocturnal levels of drug that may trigger hallucinations. Two Phase 3 clinical trials have previously established the efficacy of amantadine ER in not only increasing the total ON-WoTD, but also in reducing total OFF time [171, 172], and findings were made more evident in the pooled analysis (Table) [173]. Most reported side effects were related to visual hallucinations, nausea, and dry mouth, consistent with those observed for amantadine HCl tablets [174]. The relative benefit of the longer-acting versions of amantadine in clinical practice and risk of hallucinations are yet to be determined.

AV-101 (L-4-chlorokynurenine) is a prodrug that is converted to 7-Cl-kynurenic acid (7-Cl-KYNA), an NMDA receptor glycine-site antagonist. Originally investigated for treatment-resistant depression, initial results from Phase 1 and 2 trials demonstrated the drug's favorable safety profile [175, 176]. Moreover, a recent Phase 1 trial performed in healthy volunteers confirmed the NMDAR target engagement in higher doses of 1440 mg [177]. A Phase 2 DBRCT with crossover design is currently planning to investigate the therapeutic potential of AV-101 for LID. A total of 20 PD patients will be randomized to either 1440 mg AV-101 or placebo over a 14-week period (NCT04147949) [178].

Dipraglurant (ADX48621) is a metabotropic glutamate receptor 5 (mGluR5)-negative allosteric modulator that reduced LID in animal models [179–184]. A Phase 2a DBRCT confirmed the safety and tolerability of this drug in 76 PD individuals, with decrease in dyskinesia versus placebo as an exploratory outcome, as assessed using modified Abnormal Involuntary Movement Scale (mAIMS) scores during the first 2 weeks, although this difference did not remain statistically significant by day 28 [185]. The most commonly reported side effects included nausea, fatigue, dizziness, and dyskinesia. A Phase 2b/3 trial is ongoing to assess change in Unified Dyskinesia Rating Scale (UDysRS) scores from baseline to week 12 in 140 participants randomized to dipraglurant 50 mg, 100 mg tablet, or placebo (NCT04857359) [186].

Similarly, mavoglurant (AFQ056) is a selective mGluR5 inhibitor that has been evaluated as a potential therapy to reduce LID in patients with PD [187]. Although several clinical trials have been performed, the efficacy of this drug remains unclear due to contradictory findings in four DBRCTs. Mavoglurant doses (range 25–200 mg) and assessment methods for LID varied across these studies [188–190]. The most common side effects in all trials included dizziness, dyskinesia, and fatigue. A recent meta-analysis including all relevant clinical studies evaluating this drug did not support a meaningful drug efficacy [191]. Based on these results, the benefits of mavoglurant remain inconclusive, although unlikely to provide any meaningful dyskinesia control. To our knowledge, there are no ongoing or planned clinical trials of mavoglurant for LID.

Topiramate is an approved anti-seizure medication with glutamatergic activity targeting AMPA subtype glutamate receptors. Preclinical studies demonstrated that topiramate acted synergistically with amantadine, which suggested its potential in treating LID. In one DBRCT involving 21 patients, no significant differences in UDysRS scores were seen between the active (5-week titration of topiramate to a final dose of 150 mg/daily) and placebo groups [192]. There were no significant side effects, although decrease in appetite was more frequently observed in the topiramate group. Whereas a small benefit over placebo was suggested by the authors, the lack of a major impact or significant change in UDysRS halted further investigations of this drug in LID. Thus, to date, this drug does not seem promising for the treatment of LID.

Naftazone is commonly used for the treatment of varicose veins. It has previously showed the potential to improve LID in animal models of PD possibly by reducing glutamate release [193, 194]. Nevertheless, in a small randomized, controlled trial with 16 patients, naftazone did not result in better control of dyskinesia when compared to placebo during acute levodopa challenges, nor were there differences found in AIMS scores (Table 4) [195]. The drug was generally well

tolerated with minimal adverse events. Although this was a small study, it is unlikely that future trials will re-evaluate the role of naftazone in LID.

Other glutamatergic drugs have also been considered promising for the management of PD. Among them, foligrulax is a mGluR4 agonist that has been shown to be beneficial in the treatment of LID in animal models [196, 197]. On the other hand, a recent Phase 2 trial enrolling 157 individuals with PD did not demonstrate any improvement in OFF time or UDysRS scores by the end of 28 days with foliglurax 10 mg or 30 mg compared to placebo (NCT03162874) (Table 4) [198–200]. Given the negative results, the manufacturer has decided to terminate this development program.

5.2 Serotoninergic Drugs

Serotoninergic drugs have been evaluated as a potential therapy for levodopa-induced motor complications based on preclinical studies suggesting benefit, possibly via presynaptic 5HT receptor stimulation that reduces ectopic dopamine release. However, prior experience with agents such as sarizotan did not satisfactorily improve LID, and potentially worsened PD motor scores. A recent Phase 2a trial investigated the benefits of 5-HTP, an immediate precursor of serotonin [201]. Studies in animal models demonstrated reduced dyskinesia with acute and chronic administration of the drug without necessarily worsening motor symptoms or reducing the therapeutic benefits of levodopa [202]. In a single-center, DBRCT with crossover design, 12 PD patients were randomized to either 50 mg of 5-HTP daily or placebo for 4 weeks [201]. At the end of treatment, UDysRS scores were significantly reduced in the 5-HTP group (baseline mean UDysRS: 22.9 ± 8.6; UDysRS scores at the end of the study: 17.6 ± 5.6 vs. 19.7 ± 8.8 for 5-HTP and placebo, respectively). The same trend was seen on the UPDRS part IV (subjective percentage of the day with dyskinesia) scores, with a mean score of 8.7 ± 3.1 at baseline, followed by a score of 6.6 ± 2.6 with 5-HTP and 7.2 ± 2.5 with placebo at the end of 4 weeks. No differences in motor score (MDS UPDRS part III) were reported. Although this was a small study, the positive results are promising and require confirmation in larger multicenter trials.

Another study currently recruiting patients aims to explore the benefit of JM-10, which consists of buspirone (5-HT1A agonist) plus zolmitriptan (5-HT1B/5-HT1D agonist) (NCT04377945) [203]. Based on animal models and small clinical studies, buspirone has been previously considered as a potential candidate to treat LID in PD [204–207]. Moreover, a recent Phase 2 crossover trial with JM-10 has met the endpoint for safety and efficacy in 30 patients (NCT02439203) [208]. In the ongoing

Study in Parkinson's Disease in Patients With Moderate to Severe Dyskinesia (ASTORIA), 81 participants will be randomized in a 1:1:1 ratio to either 4 mg buspirone/0.8 mg zolmitriptan, 8 mg buspirone/0.8 mg zolmitriptan followed by placebo, or placebo alone using a double-dummy design (NCT03956979) [209]. The primary outcome of this trial will include UDysRS changes over the study period and pharmacokinetic data. The Study in Parkinson's Disease Patients with Dyskinesia with Combinations of JM-010 and Its Individual Components (SHINE) is an ongoing Phase 2 multicenter study. In this two-part DBCRT, at least 188 participants in 30 sites in the USA will be randomized to fixed doses of JM-010 or placebo to assess the efficacy, safety, and tolerability of this drug over 12 weeks [203].

Another serotoninergic agent in the pipeline is befiradol (NLX-112). Preclinical studies reported a significant benefit of this highly selective 5-HT1A receptor agonist in reducing LID in 6-hydroxydopamine (OHDA)-lesioned rodents and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-macaques [210–212]. A Phase 2 trial is ongoing to investigate the safety and tolerability of befiradol (NLX-112) in 24 patients with LID (Table 4) [213, 214]. In this ongoing 8-week DBRCT, secondary endpoints include reductions in troublesome dyskinesia by measuring UDysRS, and global improvement measured by clinical global impression scale (CGI-C). An additional endpoint is the inclusion of wearable devices to objectively quantify dyskinesia (NCT05148884) [214].

Eltoprazine is a selective serotoninergic agonist at both 5-HT1A and 5-HT1B receptors. In view of positive findings on dyskinesia in animal models, eltoprazine has been subsequently studied in human subjects [215]. In a single-dose, dose-finding study, 5 mg doses significantly improved LID in 22 subjects [216]. Frequently reported side effects included fatigue, nausea, and dizziness. A Phase 2 clinical trial evaluating eltoprazine in 60 patients with LID has been listed on clinicaltrial.gov since 2016, although its status remains "unknown." Although it is unclear if the study will proceed, in 2019 the manufacturer's website states that the company has received a notice of allowance from the European Patent Office (EPO) regarding the use of eltoprazine or eltoprazine in combination with a number medications, including CBD, for the treatment of PD and LID [217].

Piclozotan, a 5-HT1A receptor agonist, has also shown potential anti-dyskinetic effects in animal models [218]. A Phase 2 trial with 27 patients comparing piclozotan versus placebo has been completed in 2021, although full results are still pending (NCT00623363) [219].

In summary, serotoninergic agents have been a promising target in preclinical studies for reducing LID. Although most drugs are currently recruiting patients for

Table 4 Newly approved or investigational drugs for the treatment of dyskinesias in Parkinson's disease

Indication/drug	Mechanism of action	Clinical benefit	References
Extended-release amantadine	Non-competitive antagonist of the NMDA receptor	Two Phase 2 trials ($n = 203$) demonstrated significant difference in ON time without dyskinesias (treatment difference of 2.9 h to placebo in a recent pooled analyses)	[171–174]
AV-101 (L-4-chlorokynurenine)	NMDA receptor antagonist	Phase 2 trial – ongoing	[178]
Dipraglurant (ADX48621)	mGluR5-negative allosteric modulator	Phase 2A DBRCT ($n = 76$) demonstrated safety and tolerability over 28 days. Decrease in mAIMS scores by day 1 (20%) and 14 (32%) but not 28 Phase 2b/3 trial ($n = 140$) – ongoing	[185, 186]
Mavoglurant (AFQ056)	Selective mGluR5 inhibitor	Conflicting results in 4 Phase 2 trials; and a meta-analysis suggested unlikely to have benefit in LID	[188–191]
Topiramate	AMPA receptor antagonist	Phase 2 ($n = 21$) no significant differences in UDysRS over 8 weeks ($- 4 \pm 11.34$ for the topiramate group and $- 1.67 \pm 10.27$ for the placebo group)	[192]
Naftazone	Glutamate release inhibitor	Phase 2 ($n = 16$), no significant improvement in LID during acute levodopa challenge; AIMS scores between naftazone-treated and placebo groups (4.4 ± 3.4 vs. 6.7 ± 4.4, respectively)	[195]
Foliglurax	mGluR4 agonist	Phase 2 trial ($n=157$) no significant improvement with doses of 10 or 30 mg of foliglurax over 28 days (UDysRS treatment difference 0.02, CI $- 4.02$, 4.06 for foliglurax 10 mg twice daily and $- 0.59$, CI $- 4.65$, 3.46 for foliglurax 30 mg twice daily)	[198–200]
5-Hydroxytryptophan (5-HTP)	Immediate precursor of serotonin	Phase 2a ($n = 12$) over 4 weeks significant reduction of UDysRS (22.9 ± 8.6 at baseline compared to 17.6 ± 5.6 at the end of the study)	[201]
JM-10 (buspirone and zolmitriptan)	5-HT1A agonist (buspirone) and 5-HT1B/5-HT1D agonist (zolmitriptan)	Phase 2 crossover trial ($n = 30$) demonstrated safety Two phase-2 trials – ongoing	[203, 208, 209]
Befiradol (NLX-112)	Selective 5-HT1A receptor agonist	Phase 2 trial – ongoing	[213, 214]
Eltoprazine	Selective agonist at 5-HT1A and 5-HT1B receptors	Phase 2 RCT ($n = 22$) demonstrated significant dyskinesia reduction in CDRS ($- 1.02 \pm 1.49$) and RDRS ($- 0.15 \pm 0.23$)	[216]
Piclozotan	5-HT1A receptor agonist	Phase 3 DBRCT ($n = 27$), results pending	[219]
Mesopetan (IRL790)	Dopamine D3 antagonist	Phase 2B DBRCT ($n = 140$) comparing 3 doses of mesdopetam with placebo for 84 days – ongoing	[223]
Pridopidine	sigma-1 receptor (σ1R) agonist	Phase 2 trial has now been listed as terminated	[226]
AQW051	Selective partial acetylcholine receptor agonist (a7-nAChR)	Phase 2 RCT ($n = 71$), no significant improvement in mAIMS scores with AQW051 10 or 50 mg/day vs. placebo (least-squares mean change -3.22 for 10 mg, $- 1.92$ for 50 mg and $- 3.14$ for placebo)	[228]

mAIMS The Abnormal Involuntary Movement Scale, *RCT* randomized controlled trial, *DBRCT* double-blind, randomized, controlled trial, *LID* levodopa-induced dyskinesias, *PD* Parkinson's disease, CI confidence interval, *CDRS* Common Clinical Dyskinesia Rating Scale, *RDRS* The Rush Dyskinesia Rating Scale, *UDysR* The Unified Dyskinesia Rating Scale, *MDS-UPDRS* Movement Disorders Society – Unified Parkinson's Disease Rating Scale
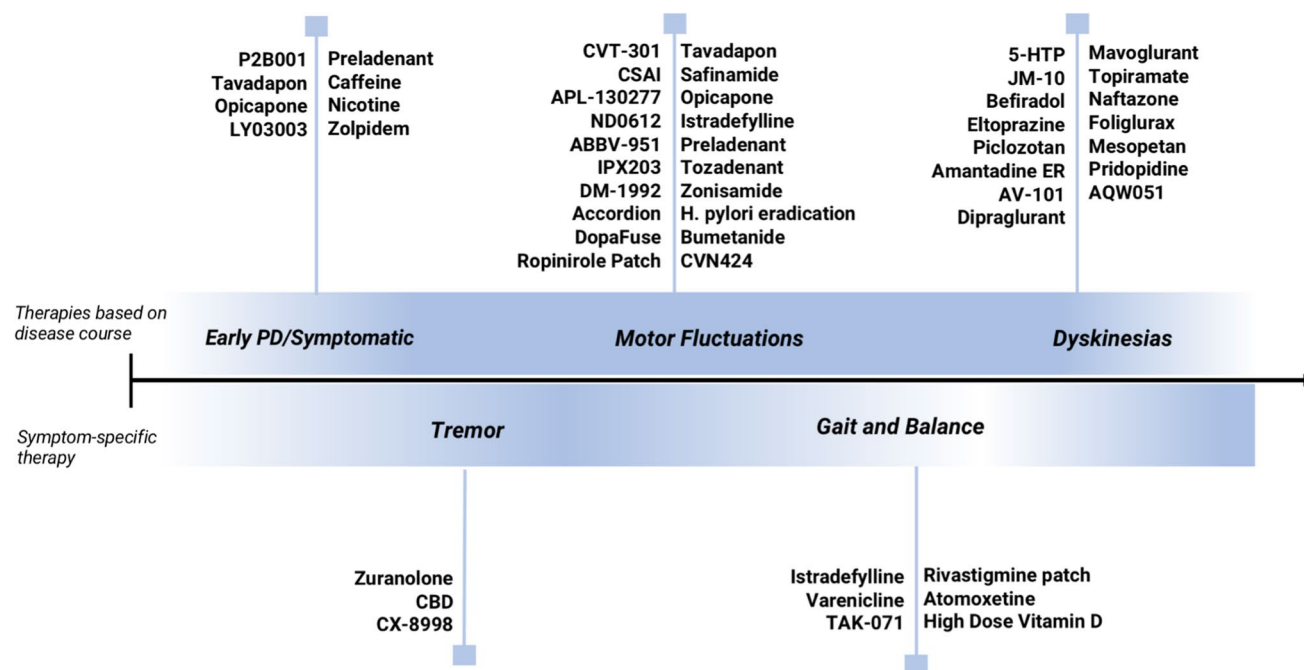
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Fig. 1 Simplified schematic view of investigational and newly approved treatments for motor symptoms in Parkinson's disease. *PD* Parkinson's disease, *CSAI* continuous subcutaneous apomorphine injection, *5-HTP* 5-hydroxytryptophan, *ER* extended release

Phase 2 trials, some therapies are likely to meet the primary safety and tolerability endpoint, and advance into larger Phase 3 trials. Critical issues to be determined will be effect of the serotoninergic drug on antiparkinsonian action of levodopa and effect on PD motor symptoms.

5.3 Dopamine Antagonist Therapies

Selective dopamine receptor antagonists are also in the pipeline for the treatment of LID. Mesopetan (IRL790) is a novel and specific dopamine D3 antagonist, which has been shown to have anti-dyskinetic effects in preclinical models, importantly without any worsening of PD motor scores [220]. Subsequent Phase 1 trials have established the safety and tolerability of this drug, with a suggestion of overall improvement in dyskinesia as measured by UDysRS by the end of 4 weeks [221, 222]. A Phase 2 trial is currently recruiting 140 individuals with PD to a DBRCT evaluating three doses of mesopetan twice daily versus placebo for 84 days (NCT04435431) [223].

5.4 Other Targets

Pridopidine (TV-7820, ACR16) was initially developed for the treatment of Huntington's Disease. It is considered to bind to the sigma-1 receptor (σ1R), although serotoninergic and adrenergic actions have also been postulated.

The benefits of pridopidine in LID was demonstrated in 6-OHDA-lesioned rats and MPTP-lesioned macaques [224, 225]. An ongoing Phase 2 trial was terminated due to the COVID-19 pandemic and future plans to resume studies are largely unknown (NCT03922711) [226].

AQW051 is a selective partial α7 nAChR agonist that has also been linked to improvement in LID in animal models of PD [227]. In a Phase 2 DBRCT, 71 patients were randomized to receive AQW051 10 mg, 50 mg, or placebo for 28 days at a ratio of 1:1:1 [228]. No significant between-group differences were found in mAIMS scores for either drug doses (Table 4). The medication was generally safe with few reports of dyskinesia, nausea, falls, and fatigue. Considering these negative results, it is unlikely that additional clinical trials will be performed examining the benefit of AQW051 for the management of LID.

6 Conclusions

Despite the effectiveness of levodopa for the treatment of motor symptoms, there remain many gaps and needs in the management of individuals with PD. Early disease therapies need to provide a therapeutic benefit as satisfactory as levodopa, but without side effects. One of the key aspects when evaluating such new approaches will be how well they compare to the overall clinical benefit of levodopa; plus, the long-term risks of motor fluctuations once levodopa is

added in. Non-dopaminergic therapies as monotherapy still do not seem to be able to provide a meaningful symptomatic benefit as demonstrated by preladenant, caffeine, and nicotine. Therefore, striatal dopamine D2 receptor stimulation appears to be a requirement for any symptomatic motor benefit. Additionally, several options for alternative formulations of levodopa to allow faster and more sustained brain delivery appear promising (Fig. 1). An essential condition will involve delivering the equivalent (or better) levodopa to the brain as an oral dose for similar good 'ON" responses, although with a more reliable and potentially longer effect. Such therapies, if successful, will be very useful in the clinical management of PD.

Adjunct treatments for motor fluctuations continue to focus on extending the duration of action of levodopa by adding in DA, MAOB-I, and/or COMT-I. Overall, data from multiple DBRCTs generally show an average of 1 h per day improved ON time, which may not always equate to a clinically meaningful change for PD patients. Such strategies tend to be helpful in the earlier stages of the disease, however become significantly less useful over time. Comparative studies remain important to determine the relative clinical usefulness of these strategies, especially with respect to levodopa therapy. Novel agents for dyskinesia focusing on non-dopaminergic targets, principally glutamate and serotonin receptors, have promising preclinical evidence, although clinical benefit is yet to be proven by larger controlled trials. Although the field has significantly shifted to prioritize strategies for early PD and neuroprotective agents, intensive research remains active in the search for effective treatments of motor fluctuations, dyskinesia, and balance and gait impairments. Recent Phase 1 and 2 clinical trials targeting multiple neurotransmitters are promising, and may lead to significant advances in the development of new symptomatic therapies to control motor features in PD.

Declarations

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