Parkinson's disease – current treatment

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Purpose of Review
The purpose is to review the results and impact of recent studies for current and future treatment of both motor and non-motor symptoms in Parkinson's disease (PD).

Recent Findings
New formulations of levodopa further optimize motor fluctuations, allowing for more on-time and less dyskinesia. On demand apomorphine continues to showcase itself as an effective and tolerable tool for treating motor off-periods. Though there are no clear treatment guidelines for PD-related constipation and sleep related disorders, several new agents for these non-motor symptoms show promising preliminary data. Expiratory muscle strength training may represent a useful and cost-effective strategy to alleviate oropharyngeal dysphagia associated with PD. There is evidence to suggest that the use of shorter pulse width and directional deep brain stimulation leads can results in a greater therapeutic window.

Summary
Though no interventions currently exist to significantly modify the disease progression of PD, new studies continue to give insight into optimal symptomatic management. Clinicians should be familiar with expanding the repertoire of tools available to treat the diverse range of symptoms and challenges associated with PD.

Keywords
dopamine agonists, levodopa, motor fluctuations, non-motor symptoms, Parkinson's disease, randomized controlled trials

INTRODUCTION

Parkinson's disease (PD) is a progressive neurological condition characterized by degeneration of dopaminergic neurons in the setting of neuronal cytoplasmic α-synuclein inclusions. PD is the second most common neurodegenerative disease, and the prevalence, morbidity, and mortality is expected to increase in the future with increasing life-expectancy [1,2]. Classically, PD presents with a variety of motor symptoms including tremor, bradykinesia, rigidity, and postural instability. There are also numerous associated non-motor symptoms such as constipation, autonomic dysfunction, sleep disorders, pain, cognitive impairment and neuropsychiatric symptoms [3]. Though the basic pathophysiology of PD has been known for decades, and the discovery of levodopa has enabled effective treatment of motor symptoms that result from dopaminergic deficits, there are currently no interventions known to significantly slow disease progression. In this review, we will cover recent advances in pharmacologic treatments for both motor and non-motor symptoms, as well as non-pharmacologic strategies including deep brain stimulation and rehabilitative strategies that have been tested for PD.

CURRENT PHARMACOLOGIC APPROACHES TO TREATING PARKINSON'S DISEASE

Initial pharmacological treatment for PD motor symptoms primarily focus on enhancing the activation of central dopamine receptors. Levodopa, dopamine agonists, and monoamine oxidase-B (MAO-B) inhibitors are all effective first-line agents [4]. The side effect profiles of these dopaminergic medications overlap, and the choice of which medication to start is largely dependent on discussion of risks and benefits with individual patients. Nevertheless, all dopaminergic medications face challenges with duration of efficacy, motor fluctuations, off-periods

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Curr Opin Neurol 2023, 36:302–308

DOI:10.1097/WCO.0000000000001166

KEY POINTS

- New trials on parenteral formulations of levodopa continue to support its potential use in treating motor symptoms while minimizing motor fluctuations
- Sublingual and inhaled apomorphine have good tolerability and show promise as an effective tool for on-demand treatment of motor off-periods
- Expiratory muscle strength training represents an effective treatment option for PD-related dysphagia
- The use of shorter pulse width and directional deep brain stimulation (DBS) leads can result in greater therapeutic windows allowing greater tolerability during DBS programming

during supra-therapeutic dopamine levels, and dyskinesia during supra-therapeutic levels (Fig. 1).

Among oral medications, levodopa is the most efficacious at improving PD motor symptoms and is generally tolerable, but levodopa does come with higher risk of dyskinesia, especially at higher doses [5]. Dopamine agonists are associated with higher risk of impulse-control disorders, somnolence, and hallucinations compared to other medication classes [6]. Selective MAO-B inhibitors, such as selegiline or rasagiline, may be similar in effectiveness with dopamine agonists but may be better tolerated than dopamine agonists, with dyskinesia and hallucinations as the most commonly reported side effects [7]. Adjunct medications such as catechol-O-methyltransferase (COMT) inhibitors, MAO-B inhibitors, and the adenosine receptor antagonist istradefylline [8] can be used to extend the effects of dopaminergic medications if the patient experiences wearing off symptoms. In addition to adjustment of dopaminergic medication dosing, adjuncts such as amantadine [9] and clozapine [10] can be used to specifically address dyskinesia. Finally, anticholinergics may be an option for young patients with tremor-predominant PD. A summary of the pharmacological classes of medications for both motor and the non-motor PD symptoms are listed in Table 1.

Patterns and timing of use of levodopa and existing adjunct medications have been studied in two scenarios: at time of initiation of therapy, and when motor fluctuations cannot be controlled by adjustments to levodopa therapy. An earlier pragmatic trial in the UK suggested that administration of levodopa was superior to dopamine-sparing agents such as MAO-B inhibitors and dopamine agonists at time of initiation of therapy on mobility-related quality of life measures (PDQ-39 Mobility, median follow-up time of 3 years) [5]. Another large study of 222 individuals with early PD were randomized to either early or delayed-start of carbidopa/levodopa 25/100 three times daily [11]. Bradykinesia, rigidity and tremor all responded well to levodopa, and notably, at 80 weeks, 38% of the participants assigned to the delayed-start developed motor fluctuations compared to 23% of participants in the early-start group. With respect to strategies to treat PD motor fluctuations, a recently published large randomized controlled trial (RCT) in the UK comparing dopamine agonists with dopamine reuptake inhibitors (e.g., either an MAO-B inhibitor or a COMT inhibitor) to treat PD motor fluctuations showed similar mobility-related quality of life outcomes among both groups, suggesting equivalence.

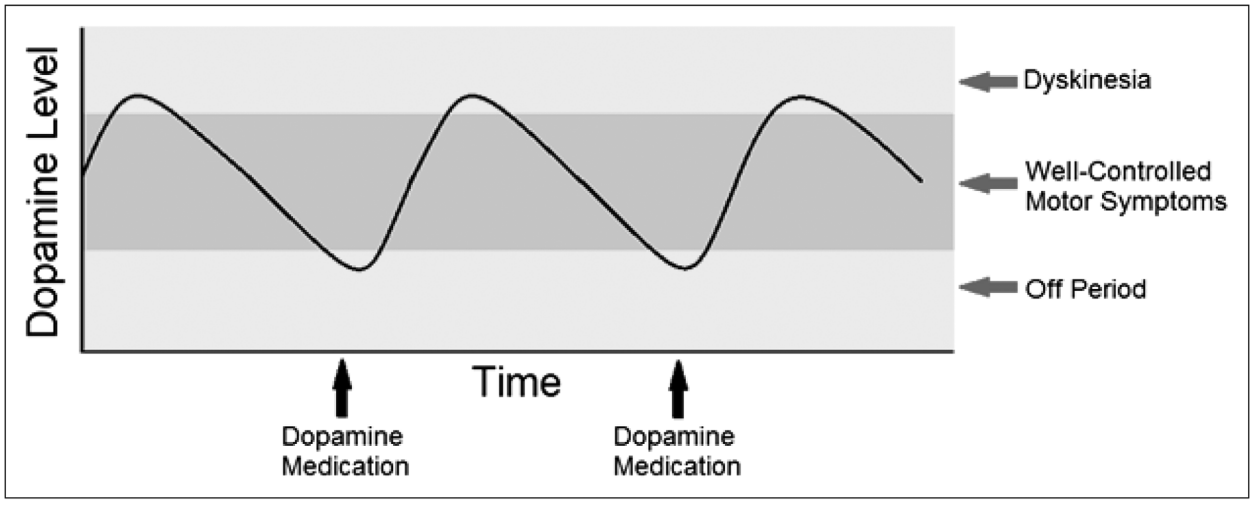

FIGURE 1. Motor fluctuations in response to medications. Black line represents level of brain dopamine concentrations over the course of a day. The area in green represents levels of dopamine associated with good control of motor symptoms, with yellow boxes above and below representing levels of dopamine associated with dyskinesia and off-periods.

Table 1. Current pharmacological classes of medications for the treatment of Parkinson's disease

Symptom	Dopaminergic	Acetylcholine	Serotonin	Norepinephrine	Other
Motor impairment	Carbidopa-Levodopa Dopamine agonists MAO-B Inhibitors COMT Inhibitors	Anticholinergics			Amantadine Istradefylline Adenosine receptor antagonists
Cognitive impairment		Cholinesterase inhibitors			
Neuropsychiatric	Limited antipsychotics (e.g., quetiapine or clozapine)	Cholinesterase inhibitors Tricyclic antidepressants	Pimavanserin SSRI	SNRI	
Sleep disorders	Subcutaneous apomorphine		Trazodone		Clonazepam Melatonin
Orthostatic hypotension		Pyridostigmine		Droxidopa	Fludrocortisone Midodrine
Constipation					Fiber Laxatives Probiotics

COMT, catechol-o-methyltransferase; MAO-B, monoamine oxidase B; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

However, within the dopamine reuptake inhibitor class, MAO-B inhibitors were associated with better mobility-related quality of life than was seen with COMT inhibitors, leading the authors to suggest that MAO-B inhibitors might be underused for the purpose of treating PD motor fluctuations [12▪].

ADVANCES IN PHARMACOLOGICAL INTERVENTIONS FOR MOTOR SYMPTOMS

Novel oral levodopa formulations

Since the discovery of levodopa in the 1960s, multiple formulations of carbidopa-levodopa have been developed to better manage associated dyskinesia and motor fluctuations. The goal of these novel formulations and various modes of delivery has been to more consistently maintain a steady serum level of levodopa or dopamine agonist within a therapeutic window. With regards to new oral levodopa agents, the U.S. Food and Drug Administration is scheduled to review a New Drug Application for IPX203 in mid-2023. IPX203 is a carbidopa-levodopa extended-release capsule that is composed of immediate release levodopa granules combined with extended-release polymer-coated levodopa-containing beads to facilitate levodopa absorption in contrast to Rytary-branded extended-release carbidopa-levodopa. A phase 2 study showed that IPX203 maintained a 50% peak plasma concentration for 4.6 h compared to only 1.5 h for immediate-release carbidopa-levodopa (IR CD-LD) as well as 2.3 h less off time than IR CD-LD [13]. In the RISE-PD trial, IPX203 showed significant improvement in on-time (0.53 h) and off-time (-0.48 h) for subjects taking IPX203 compared to IR CD-LD despite needing only a three times daily dosing, however the full results of the study have not yet been published in manuscript form [14▪]. These trials demonstrate that carbidopa-levodopa remains a good agent in patients with advanced PD if absorption and pharmacokinetics can be further optimized.

Parenteral formulations of levodopa

Levodopa-carbidopa intestinal gel (LCIG), continuously delivered via percutaneous endoscopic gastrojejeunostomy tube, has previously been shown to be effective in improving on time without troublesome dyskinesia in patients with advanced PD. However, there was limited data on its efficacy in patients with prominent dyskinesia [15]. Recently, the randomized, open-label phase 3 DYSCOVER trial confirmed the efficacy of LCIG in advanced PD patients with prominent dyskinesia. Subjects randomized to LCIG were found to have significant improvement in dyskinesia (UDysRS), off-time, as well as quality of life during the 12-week trial when compared to optimal medical management [16▪▪]. Subcutaneous delivery of levodopa has been developed as a less invasive method of continuous dopaminergic medication delivery. A recent small randomized, controlled phase 2 study showed subcutaneous infusion of levodopa (ND0612) to be effective in reducing fluctuations in plasma levodopa concentrations compared to oral agents, though a statistically significant difference in off time was not levodopa

soluble found between standard of care with and without NDS0612 [17]. A larger randomized controlled phase 3 study of efficacy was not yet published at the time of this review. A novel formulation, foscarbidopa/foslevodopa, created for subcutaneous administration, was found in a large randomized controlled phase 3 study to be effective in increasing on time without troublesome dyskinesia (2.72 [0.52] vs. 0.97 [0.50] h; difference 1.75 h) and reducing off time (-2.75 [0.50] vs. -0.96 [0.49] h; difference -1.79 h) [18]. Infusion site reactions including erythema and pain were common with both subcutaneous products, and both are pending with the US FDA for new drug application review.

Newer formulations of dopamine agonists

Apomorphine is a direct dopamine agonist that has similar overall efficacy as levodopa for PD motor symptoms, but requires non-oral formulation due to very limited oral bioavailability [19]. Subcutaneous apomorphine is clinically useful in reducing daily off-periods by over 50%, and unique in its rapid onset and short duration of effect. Currently, both subcutaneous and sublingual apomorphine are approved for use in the US and Europe. Though subcutaneous apomorphine infusion has been shown to be effective at reducing motor fluctuations in patients with longstanding PD [20] showing good long-term safety, it is not yet approved in the US [21]. Sublingual apomorphine film was approved by the FDA in 2020, and has been shown to have peak effect at 30 min after administration [22]. A recent trial showed that it was tolerable up to several doses, further supporting its clinical use for off-periods [23]. However, sublingual apomorphine is known to be associated with a high risk of oropharyngeal side-effects, limiting its tolerability. As such, newer formulations are being developed, with a recent phase 2 study of inhalable apomorphine (AZ-009) [24] showing favorable pharmacokinetics of AZ-009 with peak concentrations around 2 min after administration with mild side effects. AZ-009 was clinically effective at reducing Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III scores after 10 min.

ADVANCES IN PHARMACOLOGICAL INTERVENTIONS FOR NON-MOTOR SYMPTOMS

PD is associated with a variety of non-motor symptoms that may benefit from pharmacological intervention. In this section, we focus on recent clinical trials for the pharmacological treatment of PD-related constipation and sleep disorders.

Constipation

Chronic constipation occurs in up to two-thirds of patients with PD, and there had previously been a handful of RCTs studying pharmacological treatment of PD-related constipation. These trials of variable size and quality studied tegaserod ($n = 15$), relamorelin (recruitment goal not met), lubiprostone ($n = 54$), macrogol ($n = 57$), and fermented milk with probiotics ($n = 120$) [25]. However, the limited available trials have not been sufficient to establish clear treatment guidelines. Two recent RCTs were carried out for the treatment of PD-related constipation. The first trial randomized 150 PD subjects to placebo vs. squalamine phosphate (ENT-01), a novel medication that disrupts polymerization of α-synuclein in the enteric nervous system [26▪]. Pathological examination of gastrointestinal tissue in patients with prodromal PD have shown elevated phosphorylated alpha-synuclein [27], which is thought to contribute to constipation. In the group receiving ENT-01, the rate of spontaneous bowel movement (SBM) improved from 0.7 per week to 3.2 per week, was significantly better than placebo (0.7 per week to 1.2 per week), and also represents a larger effect size compared to laxatives in prior studies [28,29]. A similar effect size was seen in another RCT on multistrain probiotic capsules involving 72 PD subjects with chronic constipation, the SBM rate increased significantly by 1.3 per week after a similar 4-week study period [30]. Though ENT-01 has insignificant systemic absorption [14▪], side effects included significant rates of nausea (34.4%) and diarrhea (19.4%), so dosing may ultimately need to be adjusted. In the future, it would be very helpful to have head-to-head comparisons of the various interventions for PD-related constipation.

Sleep

Up to 80% of patients with PD experience nocturnal sleep disturbance, including insomnia, restless leg syndrome, and rapid eye movement sleep behavior disorder (RBD) that can negatively impact quality of life if untreated [31]. With regards to insomnia, a number of pharmacological agents are currently available, including melatonin, doxepin, benzodiazepines, zolpidem, and antidepressants like amitriptyline and trazodone. The evidence for these insomnia medications is limited by lack of high-quality studies [32], and there have not been any RCTs comparing various insomnia medications until recently. In a recent study randomizing 93 subjects with PD to melatonin 3 mg, clonazepam 1 mg, and trazodone 50 mg were all found to similarly improve sleep quality as measured by the Pittsburgh Sleep Quality Index [33]. Though clonazepam and

melatonin are currently the two main treatments commonly used for RBD, this study found a greater reduction in RBD Screening Questionnaire for melatonin compared to clonazepam with a better side effect profile. Subcutaneous apomorphine was also studied in a randomized controlled double-blind crossover study in 46 individuals with PD and moderate to severe insomnia [34] showing marked improvement in the active treatment group compared to placebo on the Parkinson's Disease Sleep Scale. A number of other investigational drugs are being developed which show promising preliminary data [35,36], but further confirmatory studies await. Of note, a recent phase 2/3 trial of cannabidiol did not show significant benefit over placebo for treatment of RBD in PD [37].

ADVANCES IN NON-PHARMACOLOGICAL THERAPIES

Physical exercise

Although many symptoms associated with PD can be improved with pharmacological therapy, other symptoms like balance and freezing gait are difficult to treat with medications. Nonetheless, there have been several trials of non-pharmacological interventions such as structured physical therapy programs to improve gait, balance, strength, coordination, and overall functional capacity in PD patients [38]. However, recent trials have also found benefit in non-regimented exercise such as yoga [39], dance rhythms [40], and even Wii-Sports [41]. In particular, one study randomized 95 patients in a 1:1:1 ratio to either biweekly 60-min sessions of Tai-Chi, biweekly 60-min sessions of brisk walking, or no exercise [42]. In particular, this study assessed the subjects with several clinical performance scales (Berg Balance Scale, Unified Parkinson Disease Rating Scale (UPDRS) total and motor score, Timed Up and Go test) as well as functional MRI and serum metabolite testing over a 1 year period. This study found that individuals assigned to Tai Chi to have better performance in all the above outcomes, compared to the group assigned brisk walking and to no exercise.

Dysphagia

PD-related oropharyngeal dysphagia, another symptom that is common in advanced disease stages and difficult to alleviate through medications, was shown in a recent RCT to improve with expiratory muscle strength training [43]. In this study, 50 individuals with PD were randomized to training with either a handheld respiratory device or a sham device. Expiratory muscle strength training was performed 5 days per week over a 4-week period, and swallowing was then assessed periodically with flexible endoscopic evaluation of swallowing (FEES). There was significant improvement in both FEES video rating scores and pharyngeal residue quantity after the 4 weeks of respiratory training. Much of the benefits were retained 8 weeks after the training sessions with no notable side effects. Though the devices require individualized calibration, they may still contribute meaningfully to the overall PD treatment plan in a cost-effective way. Given the wide range of symptoms associated with PD, these trials demonstrate the importance of incorporating non-pharmacological interventions.

ADVANCES IN DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and the globus pallidus internus has become a standard treatment option for patients with advanced PD. A recent meta-analysis of outcome measures confirmed that STN DBS is effective long-term at improving UPDRS motor scores, dyskinesia, off-time, quality of life, and can result in medication reduction [44]. Nevertheless, there remain challenges with stimulation-related side effects, and programming can be labor-intensive for the clinician. As such, there has been continued study into ways to further optimize DBS programming and clinical outcomes. For example, one recent controlled study assessed the use of shorter pulse widths, 30 μs or 40 μs compared to the conventional 60 μs [45]. The rationale is that a shorter pulse width is less likely to excite nearby unrelated fiber tracts, but this single small study was not sufficiently powered to demonstrate superiority. However, a subsequent meta-analysis pooling data on five available studies found that short pulse width DBS does increase the therapeutic window with a higher threshold for side effects when compared to conventional DBS [46]. Similarly, there have been developments in the design of the leads with directional steering to enable customizable stimulation fields [47]. A recent large randomized cross-over study with 234 enrolled subjects with PD compared directional STN DBS with conventional STN DBS [48▪]. This study found a mean increase of 41% of the therapeutic window with directional DBS. Though there was no major difference in UPDRS-III scores, a significantly higher number of patients reported preferring directional DBS (52.8%) over conventional DBS (25.9%).

DISEASE MODIFICATION STRATEGIES

Studies have shown no consistent disease-modifying properties with the currently available

symptomatic medications [4]. A number of monoclonal antibodies targeting α-synuclein aimed at reducing aggregation and spread of alpha-synuclein were recently shown to be ineffective for slowing disease progression compared to placebo [49,50]. There are ongoing clinical trials into disease-modifying agents that work through various putative neuroprotective mechanisms, such as oral antioxidants, oral kinase inhibitors, intracerebral gene therapy, and more [51]. Potentially promising disease-modifying drugs in the pipeline include glucagon-like peptide 1 agonists such as exenatide [52], leucine rich repeat kinase 2 (LRRK2) inhibitors such as DNL151 and glucocerebrosidase enhancers such as ambroxol [53].

CONCLUSION

The results from recent clinical trials have given us insight into both new treatments for PD, as well as ways to make known treatments more effective. Numerous options are currently available for PD motor symptoms, and the addition of newer formulations of levodopa and apomorphine can further optimize clinical management when motor fluctuations become problematic. Symptoms that have traditionally challenging to ameliorate, like dysphagia, also show benefit from specifically designed non-pharmacological interventions. High-quality clinical trials related to PD-related constipation, PD-related sleep disorders, and optimal configuration of DBS are all still scarce, but there are promising future treatment options in each of these areas. Additionally, many new ideas in the pipeline are being tested for all aspects of PD treatment including disease-modifying therapy.

Acknowledgements

None.

Financial support and sponsorship

Financial disclosures and conflicts of interest. LCS receives consulting fees for clinical trial oversight from Medtronic.

Conflicts of interest

There are no conflicts of interest.

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