REVIEW

New Treatments for Levodopa-Induced Motor Complications

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ABSTRACT: Levodopa (L-dopa)-induced motor complications, including motor fluctuations and dyskinesia, affect almost all patients with Parkinson's disease (PD) at some point during the disease course, with relevant implications in global health status. Various dopaminergic and nondopaminergic pharmacological approaches as well as more invasive strategies including devices and functional surgery are available to manage such complications. In spite of undisputable improvements during the last decades, many patients remain significantly disabled, and a fully satisfying management of L-dopa–induced motor complications is still an important unmet need of PD therapy. This article reviews the recent trial results published from 2013 to April 2015 about pharmacological and nonpharmacological interventions to treat motor complications. Randomized controlled trials conducted in patients suffering from already established complications showed that new levodopa (L-dopa) formulations such as intrajejunal L-dopa–carbidopa infusion and bilayered extended-release L-dopa–carbidopa (IPX066) can improve motor fluctuations. Positive results were also obtained with a new monoamine oxidase B (MAO-B) inhibitor (safinamide) and a catechol-O-methyltransferase COMT inhibitor (opicapone). Pilot data suggest that new formulations of dopamine agonists (inhaled apomorphine) are also of potential interest. The development of novel nondopaminergic adenosine A2A antagonists (istradefylline, preladenant, and tozadenant) to treat motor fluctuations showed conflicting results in phase 2 and phase 3 trials. For dyskinesia, trials with new amantadine extended-release formulations confirmed the interest of the glutamatergic *N*-methyl-D-aspartate (NMDA) antagonist approach. Positive pilot antidyskinetic effects were also recently reported using serotonin agents such as eltoprazine and glutamate mGluR5 modulators such as mavoglurant. However, the translation to clinical practice of such innovative concepts remains challenging, because subsequent phase 2 trials conducted to confirm the antidyskynetic effects of mavoglurant failed, leading to the interruption of the development of this compound for this indication.

Key Words: Parkinson's disease; motor fluctuations; dyskinesias; wearing-off; levodopa; pharmacotherapy

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Background

Levodopa remains the "gold standard" treatment for Parkinson's disease (PD) motor symptoms since its introduction in the 1960s.[1] As documented in the placebo-controlled L-dopa study in early PD, although L-dopa clearly improves parkinsonism with a dose-related response, a 600-mg daily dose also may induce wearing-off (30% of patients) and dyskinesia (17% patients) after only 40 weeks of treatment.[2,3] Motor complications remains a major unmet need for the management of PD.

Effective treatments to manage motor complications have been developed during the last decades. Overall, the

rationale supporting the use for such interventions has been to find ways to prolong the duration of striatal dopamine receptors stimulation for longer than what is achieved by the short plasma elimination half-life of standard oral L-dopa. Such approaches included the use of oral, transdermal, and subcutaneous dopamine agonists, MAO-B or COMT inhibitors, and intrajejunal infusion of L-dopa. Nondopaminergic approaches also have been proposed, including nondopaminergic medications (amantadine) or functional surgery. The level of evidence supporting such strategies has been summarized in a recent systematic evidence-based medicine (EBM) review by the Movement Disorders Society EBM taskforce.[4] Briefly, adjusting L-dopa daily dose size or frequency, adding an MAOB-inhibitor (rasagiline), a COMT inhibitor (entacapone, tolcapone), or a dopamine agonist (pramipexole, ropinirole, rotigotine, pergolide, and apomorphine), were all considered as "efficacious" pharmacological interventions to reduce OFF duration. Bilateral subthalamic nucleus (STN) and globus pallidus pars interna (GPi) stimulation or unilateral pallidotomy also were considered to be "clinically useful" to treat motor fluctuations.[4] Similarly, amantadine, bilateral STN or GPi stimulation, and unilateral pallidotomy were classified as "efficacious" interventions to manage L-dopa–induced dyskinesias.[4] Dopamine agonists (pramipexole, cabergoline, and ropinirole) were found to be efficacious to delay the occurrence of motor complications when used before L-dopa. However, the long-term results of the open extensions of those trials questioned the clinical relevance of delaying the onset of dyskinesia, because this "protective" effect is lost once L-dopa has been initiated.[5-8]

Within the last few years, new trials have expanded the body of evidence supporting the management of L-dopa–related motor complications and led to regulatory approval of new L-dopa formulations (continuous intrajejunal infusion of L-dopa–carbidopa intestinal gel and extended-release L-dopa+carbidopa IPX066 tables) and of an MAO-B inhibitor (safinamide).

A MEDLINE database search was conducted to identify the most important publications between 2013 and April 2015, using the following strings: Parkinson, motor complications, levodopa-related motor complications, motor fluctuations, wearing-off, on-off fluctuations, off periods, off-time, dyskinesia. Clinical trials with outcomes involving dyskinesia severity or frequency and off-time were selected for further review, irrespective of their designs. This search retrieved more than 600 articles describing the clinical effects of 17 new drugs or formulations (Table 1). This article summarizes the evidence for these novel approaches, focusing for most of them on randomized controlled trials published since 2013. Surgical interventions are not discussed (see article, this issue, by Verhagen and Slavin).

Symptomatic Management of Levodopa-Induced Motor Complications

Motor Fluctuations

Novel Formulations of Levodopa

Besides disease duration and severity, L-dopa pharmacokinetics and delivery play a fundamental role in the development of motor complications.[9] Pulsatile stimulation of dopamine receptors of the striatal spiny neurons after the 90-minute cycle of the rise and fall in L-dopa concentration after an oral dose is believed to play a major role in development of motor complications.[10,11] Therefore, improving oral L-dopa pharmacokinetics or developing new modes of delivery to achieve more constant plasma levels may reduce or prevent motor oscillations and drug-induced dyskinesias.[9]

Levodopa Intestinal Infusion. Continuous intrajejunal infusion of L-dopa–carbidopa intestinal gel (Duodopa) bypasses gastric emptying problems and provides less variable plasma concentrations than oral formulations,[9] but the evidence documenting its clinical benefit was long restricted to open-label studies. Recently, a 12-week, randomized, double-blind, double-dummy, double-titration trial demonstrated a mean reduction in off-time of -4.04 ± 0.65 h in 35 patients allocated to the intestinal gel compared with -2.14 ± 0.66 h in 31 patients allocated to placebo ($P < 0.0015$).[12] Daily on-time without troublesome dyskinesia was also significantly increased. These effects were maintained for up to 12 or 24 months.[13,14] Most frequent adverse events were device- or infusion-related and occurred in up to 40% of patients.[15] Duodopa was compared with apomorphine subcutaneous continuous infusion in an open-label, observational study suggesting a robust improvement in motor symptoms, motor complications, and quality of life on both treatments.[16]

Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel is approved and marketed in the 30 countries of the European Economic Area.[17] It is also considered as an orphan drug by the European Medicines Agency. Finally, the drug received marketing authorization by the Food and Drug Administration (FDA) in January 2015 for the treatment of motor fluctuations in people with advanced PD.[17]

Levodopa-Carbidopa Pump for Subcutaneous Infusion. ND0612 is a proprietary formulation of L-dopa–carbidopa for continuous subcutaneous delivery through a custom patch pump. Results from an early phase 2 study in PD patients are only available in abstract form.[19] Compared with placebo, patients on the pump showed reductions in plasma L-dopa concentration fluctuations, with

TABLE 1. New drugs or formulations for the treatment of motor complications in the 2013-2015 period

Drug and formulation	New studies in the period 2013-2015	Main results	Safety	Development/ marketing status
New formulations of levodopa				
Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel	1 R, DB, DD trial vs levodopa IR[12]	Reduced daily OFF-time, increased "good" ON-time	Related to the device or infusion	Commercialized in USA and Europe
IPX066	1 R, DB, DD vs levodopa IR[20] 1 R, DB, CO, DD trial vs entacapone[21]	Reduced daily OFF-time, increased "good" ON-time	Same as L-dopa IR	Commercialized in USA
XP21279	1 R, DB, DD, CO vs levodopa IR[25]	No effects on OFF-time, reduced percentage deviation from the mean L-dopa concentration	Same as L-dopa IR	In Phase II
Melevodopa	1 OL, CS, vs levodopa IR[26]	Shorter onset of motor benefit after an oral dose	Same as L-dopa IR	In Phase II
New COMT or MAO-B inhibitors				
Opicapone	2 R, DB vs placebo or entacapone[32,33]	Increased L-dopa exposure, reduced off-time	Dyskinesia, insomnia, dizziness, nausea	In Phase III
Safinamide	1 R, DB vs placebo[38]	Increased "good" ON-time	Dyskinesia, worsening of PD, cataract, back pain, depression, headache, and hypertension	Commercialized in Europe. NDA submitted to FDA
New formulation of apomorphine				
Inhaled apomorphine	3 R, DB, vs placebo[42-44]	Greater motor improvements after a single dose	Somnolence, yawning, flushing, dysgeusia, dizziness, orthostatic hypotension	In Phase III
New formulation of amantadine				
Extended-release amantadine	1 R, DB vs placebo[56]	Reduced dyskinesia frequency/severity	Constipation, hallucinations, dizziness, dry mouth	In Phase III
New A2A antagonists				
Istradefylline	1 R, DB vs placebo[47]	Reduced OFF-time	Dyskinesia	Marketed in Japan and USA
Tozadenant	1 R, DB vs placebo[64]	Reduced daily OFF-time	Dyskinesia, nausea, dizziness	In Phase III
Caffeine	1 Exploratory cohort study[63]	Less frequent dyskinesia in consumers of 12 oz/d	—	Worldwide available in supermarket
New glutamatergic antagonists				
Mavoglurant	1 R, DB vs placebo[57] 1 R, DB vs placebo[58]	Reduced dyskinesia frequency/severity, NS reduction in OFF-time	Dizziness, hallucination, fatigue, nasopharyngitis, diarrhea, insomnia	In Phase III
New serotoninergic drugs				
Eltoprazine	1 R, DB vs placebo[62]	Reduction of dyskinesia frequency/severity	Nausea, dizziness	In Phase III
Other drugs				
Tetrabenazine	1 OL, UC[65]	Reduced dyskinesia frequency/severity	—	Available worldwide for hyperkinetic disorders
Simvastatin	1 n-of-1 trial[66]	No effects on dyskinesia	—	Available worldwide for hypercholesterolemia
Topiramate	1 R, DB, CO vs placebo[67]	No effects on dyskinesia	Dry mouth, cognitive, breathing problems	Available worldwide for epilepsy

DB, double-blind; DD, double-dummy; CO, crossover; CS, cross-sectional; IR, immediate-release; NS, nonsignificant; OL, open-label; R, randomized; UC, uncontrolled.
"Good" ON-time = ON-time without troublesome dyskinesias.
STN-DBS, Subthalamic nuclei deep brain stimulation.

complete abolition of the low trough levels. Similarly, reductions in OFF-time were greater with the pump compared with placebo.

Extended-Release Levodopa. ***IPX066.*** IPX066 (brand name Rytary®) is a novel extended-release L-dopa + carbidopa capsule containing combined

immediate- and sustained-release pellets, dissolving at different rates along their gastrointestinal passage.[9] Hauser and colleagues (ADVANCE-PD study)[20] studied IPX066 in a randomized, double-blind, placebo-controlled, double-dummy 13-week study in 393 fluctuating PD patients. IPX066 reduced daily OFF-time by -1.17 h (95% confidence interval [CI], -1.69 to -0.66; $P < 0.0001$) compared with immediate-release formulation. In a second double-blind, double-dummy, cross-over study (ASCEND-PD study), IPX066 proved to be superior to L-dopa + carbidopa + entacapone in terms of OFF-time reduction.[21] IPX066 received marketing authorization by the FDA in January 2015.[22] How easy it will be in practice to switch from standard L-dopa–carbidopa to IPX066 in terms of number of daily doses and dose equivalence remains to be established.[23]

XP 21279. XP21279 is an L-dopa prodrug actively absorbed by high-capacity nutrient transporters expressed throughout the gastrointestinal tract and then rapidly converted to L-dopa by carboxylesterases.[24] The capability for colonic absorption of XP21279 extends the duration of therapeutic plasma concentrations of L-dopa. XP21279 was studied in a pilot randomized, double-blind, double-dummy, cross-over study involving 35 fluctuating PD patients on L-dopa + carbidopa.[25] No difference was found in the mean reduction in OFF-time achieved by both treatments, but among 11 patients who completed pharmacokinetic sampling on each optimized treatment, the percentage deviation from the mean L-dopa concentration was lower on XP21279-carbidopa, suggesting more stable plasmatic concentrations.

Liquid Levodopa Formulations. Melevodopa (L-dopa methylester) is a pro-drug with high solubility, thus reaching the small intestine shortly after oral administration, where it is absorbed in a more regular and rapid way than usual L-dopa/carbidopa oral formulation.[26] Patients with PD exhibit an increased prevalence of small intestinal bacterial overgrowth (SIBO), which has been associated with the severity of motor fluctuations. In an exploratory trial, PD patients with SIBO were challenged with 250 mg L-dopa and 314 mg L-dopa methylester before and after SIBO eradication.[27] At baseline, the onset of motor benefit was significantly shorter after melevodopa versus standard L-dopa (time to ON, 28.8 ± 11.5 vs 55.5 ± 40.2 min). No practical conclusions can be driven yet outside the context of the acute challenge and in PD patients with gastrointestinal infections.

Levodopa Inhaled Formulation. CVT-301 (Acorda Therapeutics) is a self-administered, inhaled formulation of L-dopa in development for treatment of OFF episodes in PD. A phase 2 trial has been recently completed, and results showing rapid motor improvement in PD OFF states with the formulation versus placebo have been published in abstract format.[28] Further trials are on their way (NCT02240030, NCT02242487, NCT02352363).

Catechol-O-Methyltransferase (COMT) Inhibitors

The co-administration of L-dopa–carbidopa with COMT inhibitors leads to increased delivery of L-dopa to the brain and reduces the levels of 3-O-methyl-levodopa, which competes with L-dopa at the blood–brain barrier transporter.[29] Entacapone is the reference drug, reducing by approximately 40 minutes time spent OFF (when compared with placebo) in fluctuating PD patients.[30] The moderate efficacy of entacapone and liver toxicity of tolcapone justify the development of novel COMT inhibitors with enhanced efficacy and safety.

Opicapone. Opicapone is a third-generation COMT inhibitor improving L-dopa bioavailability and OFF-time.[31] Opicapone (5, 15, and 30 mg once daily) was recently studied in a randomized, double-blind, placebo-controlled study in 35 patients with fluctuating PD.[32] Levodopa exposure (AUC0–6) increased by 24.7%, 53.9%, and 65.6% after opicapone 5, 15, and 30 mg versus placebo. An exploratory analysis showed a concomitant dose-dependent reduction in OFF time: -4.16% ($P < 0.05$), -29.55% ($P > 0.05$), and -32.71% ($P < 0.05$) for 5, 15, and 30 mg, respectively. The results of a larger 14-week double-blind (BIPARK-I) phase III trial were recently presented. Six hundred patients with fluctuating PD were randomized to opicapone 5 mg (n = 122), 25 mg (n = 119), 50 mg (n = 116), entacapone (n = 122), or placebo (n = 121). At endpoint, mean changes from baseline in OFF-time were: -91.3 minutes for opicapone 5 mg, -85.9 minutes for opicapone 25 mg, -116.8 minutes for opicapone 50 mg, -96.3 minutes for entacapone, and -56.0 minutes for placebo. Opicapone 50 mg significantly reduced OFF-time and increased ON-time without increasing troublesome dyskinesia and was not inferior to entacapone. The most common adverse events with opicapone were dyskinesia, insomnia, and dizziness.[33]

MAO-B Inhibitors

The MAO-B inhibitors increase the availability of dopamine in the spiny neurons synaptical clefs by inhibiting its degradation.[34] Rasagiline has demonstrated its ability to reduce by 1 hour time spent OFF when adjunct to L-dopa in patients with fluctuating PD.[35] For selegiline, the level of evidence is, however, less robust.

Safinamide. Safinamide (brand name Xadago) is a reversible MAO-B inhibitor, which also blocks sodium (Na1) voltage-sensitive channels and modulates

stimulated release of glutamate.[36] This original combined mechanism of action may offer a unique opportunity to improve OFF episodes without worsening dyskinesia. Safinamide reduces L-dopa–induced dyskinesias in animal models.[37] Safinamide (50 mg/d and 100 mg/d) was assessed in 445 patients with fluctuating PD in a 24-week double-blind, placebo-controlled, parallel-group trial.[38] Safinamide increased the total ON time with no or nontroublesome dyskinesia by 1.36 ± 2.62 hours at the 100 mg/d dose ($P < 0.01$), 1.37 ± 2.745 h ($P < 0.02$) at 50 mg/d, versus 0.97 ± 2.375 h for placebo. Such results suggest that safinamide could improve motor symptoms and parkinsonism without worsening dyskinesia. Further long-term safinamide use in these patients was evaluated over an additional 18 months under double-blind conditions.[39] This 2-year follow-up study did not show any significant worsening of dyskinesia on safinamide versus placebo (primary outcome), whereas moderate to severely dyskinetic patients at baseline (36%) showed a decrease at the 100 mg/d dose compared with placebo ($P = 0.0317$; post-hoc analysis). Improvements in motor function, activities of daily living, depressive symptoms, clinical status, and quality of life at 6 months remained significant at 24 months.

Safinamide was recently licensed by European Medicines Agency (EMA) for the treatment of PD as add-on therapy to a stable dose of L-dopa alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.

Dopamine Agonists

Apomorphine. Apomorphine is the oldest and among the most potent dopaminergic agonists.[40] Subcutaneous use by intermittent bolus injection or continuous infusion by minipump or syringe driver are marketed to reduce OFF episodes in PD, based on a limited number of short-term or uncontrolled data. Apomorphine subcutaneaous continuous infusions have also been shown reduce dyskinesia,[41] but this has not been studied under conditions of a controlled clinical trial yet. A double-blind, placebo-controlled, randomized trial assessing the efficacy of apomorphine infusions to reduce OFF-time in patients with motor fluctuations has recently been launched and is ongoing (TOLEDO trial, ClinicalTrials.gov Identifier: NCT0200612).

Alternative administration routes of apomorphine are also being explored.

Inhaled apomorphine. A dry powder apomorphine formulation (VR040) has been recently developed, taking advantage of the drug's relatively high bioavailability via pulmonary inhalation, with rapid transfer from a much larger surface area to the bloodstream. Safety, tolerability, and pharmacokinetics of this formulation were assessed in a double-blind, placebo-controlled, randomized trial of three escalating single doses of inhaled apomorphine (0.2, 0.5 and 0.8 mg fine particle dose) involving 24 patients.[42] Inhaled apomorphine did not significantly increase the proportion of patients switching from "OFF" to "ON" or decrease the time from "OFF" to "ON" post-treatment. No serious adverse events were seen, and treatment was well tolerated. Efficacy and safety of this formulation was further explored in 47 patients with fluctuating PD in a double-blind study testing ascending doses (1.5, 2.3, 3.0, and 4.0 mg) until efficacy was achieved in patients in a practically defined "OFF" state.[43] The mean Unified Parkinson' Disease Rating Scale (UPDRS) Part 3 improvement at the highest dose (ie, the primary outcome) was significantly greater versus placebo (treatment difference, 11.6; 95% CI, 2.3-20.9; $P < 0.02$). Rapid absorption (2-7 min) translated into rapid (mean, 10 min) reversal from the OFF-state. Adverse events were somnolence, yawning, flushing, dysgeusia, dizziness, and orthostatic hypotension. Similar results were observed in another trial with the same characteristics.[44]

Sublingual Apomorphine. A formulation of apomorphine for sublingual administration has been recently developed (APL-130277, Cynapsus). Results from a phase 2, open-label, single-arm study showing rapid, clinically meaningful improvement in Movement Disorders Society (MDS)-UPDRS Part III scores for PD patients in the "OFF" state have been recently presented as an abstract.[45] A phase 3 trial is currently recruiting patients (NCT02469090).

Adenosine A_{2A} Receptor Antagonists

Adenosine A_{2A} receptors are localized in the brain, mainly within the caudate and putamen nuclei of the basal ganglia.[46] Their activation leads to stimulation of the "indirect" basal ganglia pathway. Conversely, administration of A_{2A} receptor antagonists leads to inhibition of this pathway, which was translated into reduced hypomotility in several animal models of parkinsonism.

Istradefylline. The first A_{2A} antagonist developed to treat motor fluctuations in PD was istradefylline. Istradefylline was licensed in 2013 in Japan, for adjunctive treatment use in PD patients experiencing wearing-off fluctuations.[46] A "New Drug Application" was also filed in the United States, but the FDA requested additional data. Further studies are on their way (NCT01968031). A recent randomized, double-blind, placebo-controlled trial conducted in 373 patients with fluctuating PD showed a significant reduction in OFF time at 20 mg/d (-0.99 h, $P < 0.003$) and 40 mg/d (-0.96 h, $P < 0.003$) compared with placebo (-0.23 h).[47] The most common adverse event was dyskinesia. An open-label extension

suggested that efficacy was maintained over a 12-month period.[48]

Preladenant. Preladenant is the second A_{2A} antagonist that has been developed as PD therapy, and after initial positive placebo-controlled phase-2b results published in 2011,[49] two large 12-week, randomized, placebo-controlled, double-blind phase 3 trials were conducted in patients with fluctuating PD.[50] In the first trial, 778 eligible patients were randomized to preladenant 2 mg twice daily, 5 mg twice daily, 10 mg twice daily, placebo, or rasagiline 1 mg/d (active comparator). In the second trial, 476 eligible patients were randomized to preladenant 2 mg twice daily, 5 mg twice daily, or placebo. In both trials preladenant was not superior to placebo in reducing OFF time. Interestingly, rasagiline, which was used as an active comparator in the trial, also failed to demonstrate superiority over placebo. This finding questions the validity of the study, suggesting that reasons other than lack of efficacy of preladenant might account for the negative results. Nevertheless, the development of preladenant to treat OFF problems in PD has been abandoned.

Tozadenant. Tozadenant is a third A_{2A} antagonist to be developed to treat motor fluctuations in PD. A 12-week double-blind, placebo-controlled, dose-finding (60, 120, 180, or 240 mg twice daily) phase II trial involving 403 patients with fluctuating PD showed a mean daily OFF-time reduction on tozadenant 120 mg (-1.1 h, $P < 0.01$), and 180 mg (-1.2 h, $P < 0.01$). The most common adverse events in these groups were dyskinesia, nausea, and dizziness. A large phase III trial is ongoing (NCT02453386).

Delaying the Onset of Motor Complications

The early 2000s saw studies indicating that initiating PD therapy with dopamine agonists before L-dopa delays the onset of motor complications, which is a positive observation.[5,6] However, the long-term usefulness of this strategy has been subsequently challenged by the fact that motor complications inevitably emerge once L-dopa is combined with the agonist and because agonists expose the risk of troublesome adverse reactions, including daytime somnolence or impulse control disorders. Whether initial treatment for PD should consist of L-dopa or alternative options remains a matter of debate in 2015, whereas few comparative data have assessed which drug may provide the most effective long-term benefit. A recent pragmatic, open-label, long-term follow-up randomized trial, known as the PD-MED study, was designed to address such an issue.[51] Briefly, 1,620 newly diagnosed PD patients were randomly assigned between L-dopa–sparing therapy (dopamine agonists or MAO-B inhibitors) and L-dopa alone. The primary outcome was the mobility dimension on the 39-item patient-rated PD questionnaire quality-of-life scale (PDQ-39). Secondary outcomes included the incidence of motor complications. With 3-year median follow-up, PDQ-39 mobility scores averaged 1·8 points (95% CI, 0.5-3.0, $P = 0.005$) better in patients randomly assigned to L-dopa than those assigned to L-dopa–sparing therapy. Patients in the L-dopa group were more likely to develop dyskinesia than those in the L-dopa–sparing group (hazard ratio [HR] 1.52; 95% CI, 1.16-2.00; $P = 0.003$). Rates of dementia, admissions to institutions, and deaths were not significantly different. Overall, the study only identified small and clinically nonimportant differences. Moreover, lack of blindness and the unusually old age of the cohort precludes generalizing its findings.[52] A more "personalized" approach may prove to be more promising for the future. Each PD patient indeed has a specific risk profile for motor and non-motor adverse drug reaction (including motor fluctuations, dyskinesia, daytime somnolence, or impulsivity problems, among others). Predicting such susceptibilities in a given subject is difficult, if not impossible. Age, disease severity, drug dosage, sex, weight, genetics, personal and family history, personality traits, comorbidities, and co-therapies have been identified as potential risk factors influencing patients' individual response. Much remains to be explored in this field, to anticipate which patient will respond better to which drug regarding efficacy and safety. This should allow identifying the most appropriate medication to start with, so as to personalize PD management as has been successfully achieved for other disorders such as cancer or thrombosis treatments, for example.

Treatment of Levodopa-Induced Dyskinesias

New Formulations of Amantadine

Dyskinesias are consistently associated with abnormal indices of glutamate transmission in the basal ganglia in animal models, leading to the concept that blocking glutamate transmission should be beneficial.[53] Amantadine, a glutamate NMDA antagonist, is the sole drug with robust evidence supporting its antidyskinetic effect.[54,55] Three doses (260 mg, 340 mg, 420 mg) of ADS-5102, a once-daily extended-release capsule formulation of amantadine, have been recently tested in an 8-week randomized, double-blind, placebo-controlled, parallel-group study in 83 PD patients with troublesome dyskinesia.[56] The 340-mg dose reduced by 27% the Unified Dyskinesia Rating Scale (UDysRS) score versus placebo ($P < 0.005$) and increased ON time without troublesome dyskinesia. Most common adverse events were constipation, hallucinations, dizziness, and dry mouth. The rate of study withdrawal increased with dose, and it was

40% in the 340-mg group compared with 9% in the placebo group.

Other Glutamatergic "Antagonists"

As mentioned earlier, glutamatergic transmission blockade should be beneficial for dyskinesias, with amantadine, an ionotropic NMDA blocker, being an effective antidyskinetic drug.[53] Metabotropic glutamate receptors are also present in striatal spiny neurons, being the mGlu5 receptor of particular importance. Studies in animal PD models have shown mGlu5 receptor overexpression in association with dyskinesias. Therefore, the mGlu5 receptor is a promising therapeutic target, because it modulates glutamatergic transmission compared with the direct effects achieved through the inhibition of the ionotropic glutamate receptors.

Mavoglurant (AFQ056). Mavoglurant, a selective metabotropic mGlu5 receptor allosteric modulator, showed significant antidyskinetic effects in two early phase 2 randomized, double-blind, placebo-controlled, parallel-group trials.[53] These positive results led to the conduction of a 12-week randomized, double-blind, placebo-controlled, dose-finding (20, 50, 100, 150, or 200 mg daily) phase 2b study in 180 dyskinetic PD patients.[57] The 200-mg dose was superior to placebo on the modified Abnormal Involuntary Movements Scale (-2.8; 95% CI, -5.2, -0.4; $P = 0.007$), but dropout rate was high, with common adverse reactions including hallucinations and insomnia. In a further randomized, double-blind, placebo-controlled trial, mavoglurant was tested in 14 patients (7 in each group) in whom L-dopa dose were increased by up to 300 mg/d (mean, 160 mg/d).[58] Results showed a nonsignificant reduction in daily OFF-time without appreciable changes in clinician-based dyskinesia rating scales, and the development program of mavoglurant has been abandoned.

Serotoninergic Drugs

There is a dense serotonergic innervation of the basal ganglia from the raphe nuclei, which are lost in PD because of the neurodegenerative progress.[59] In a recent historic cohort study, exposure to selective serotonin reuptake inhibitors delayed the onset and reduced the severity of dyskinesia in a sample of PD patients, suggesting the importance of serotoninergic neurotransmission for this condition,[60] supporting experimental evidence that maladaptive plasticity with increased serotonergic basal ganglia signaling occurs in response to L-dopa therapy and parallels the emergence of motor complications.,

Eltoprazine. Eltoprazine is a selective partial agonist at the 5-HT1A and 5-HT1B receptors with antidyskinetic acitivity in animal models.[61] It was tested in 22 dyskinetic PD patients in a pilot double-blind, randomized, placebo-controlled, dose-finding trial involving a suprathreshold L-dopa acute challenge.[62] Eltoprazine 5 mg significantly reduced the area under the curves of the "Clinical Dyskinesia Rating Scale" (-1.02 ± 1.49, $P < 0.004$) and of the "Rush Dyskinesia Rating Scale" (-0.15 ± 0.23, $P < 0.003$), with no change in UPDRS III motor score. Further trials are needed to confirm such findings.

Caffeine

Caffeine is an unspecific adenosine receptor antagonist, which might reduce dyskinesia by blocking the A_{2A} receptor.[46] Results from a recent secondary analysis of the CALM-PD (Comparison of the Agonist Pramipexole with Levodopa on Motor Complications of PD) study, and its extension, showed that self-reported caffeine consumption higher than 12 oz/d was associated with less frequent dyskinesia as compared with consumers of less than 4 oz/day.[63]

Conclusions: Where Do We Stand?

Many trials have enriched our knowledge of managing motor complications in PD within the last few years. Although different drugs and mechanisms of action have been tested, the candidates providing the most consistent and promising results for a rapid translation into clinical practice remain largely restricted to dopaminergic medications (new L-dopa formulations, new COMT or MAO-B inhibitors). This is to say that the dopamine hypothesis is still the most robust concept on which to base our management of motor problems in PD, whereas more innovative approaches using nondopaminergic targets still struggle to generate new therapeutic solutions in the short-term.

After several years without new licensed medicines for the treatment of motor fluctuations in PD, IPX066 received marketing authorization by the FDA, and this may help patients facing such problems. The long-term impact of using IPX066 early in place of standard L-dopa formulations, to delay or avoid the onset of motor complications, remains unknown. Safinamide was also recently approved by the EMA for the treatment of PD. Whether the potential low dyskinetic profile of safinamide will provide an advantage over older MAO-B inhibitors remains to be confirmed. Similarly, the advantages of opicapone over other COMT-inhibitors remain to be assessed. Long-awaited level 1 evidence supporting the benefit of intra-jejunal L-dopa infusion in managing severe motor fluctuations confirmed previous open-label data and reinforced the notion that it provides a greater reduction in time spent OFF as compared with optimized oral therapies,

at the price of much higher costs and frequent device-related tolerability issues. Similar results are lacking for apomorphine infusion.

A strong preclinical rationale exists for the development of non-dopamine interventions to treat motor fluctuations, based on more than two decades of experimental efforts. Such non-dopaminergic drugs might not necessarily provide a stronger effect in reducing OFF problems than the already available dopaminergic drugs, but they could induce fewer dopaminergic adverse reactions (edema, dyskinesia, somnolence, impulse control disorders), which would be of great practical benefit. Unfortunately, at the moment, the available results with different adenosine A_{2A} antagonists remain inconsistent, preventing predicting their future practical potential. For dyskinesia, the results obtained with new extended-release capsule formulations confirm the already known anti-dyskinetic effect of standard amantadine, whereas other glutamatergic approaches with mGluR5 antagonists proved to be disappointing.

The newly licensed and marketed drugs for the treatment of PD will offer new options for the management of advanced PD. Although intrajejunal L-dopa infusion was already marketed in the European Union, the extension of the license to the United States will increase the number of patients being treated. The complexity of its implementation and the frequency of device-related adverse events will oblige treating centers to offer an intervention that is demanding and, like functional surgery, requires the expertise of multidisciplinary teams.

The marketing of IPX066 will make available a new L-dopa formulation, and clinical practice will show how physicians will place this new formulation when compared with the already available immediate- and controlled-release formulations, keeping in mind the complexity of switching to a novel regimen in terms of timing and dosing.

The marketing of safinamide and the expected licensing of opicapone will add new oral pharmacological options for the management of motor fluctuations. When compared with entacapone, opicapone presents as potential advantages a once-daily intake and a possible greater potency. It could then theoretically become an interesting alternative to tolcapone, as long as greater efficacy and hepatic safety are confirmed in large populations. Surgical options, discussed elsewhere in this issue, also need to be integrated with pharmacological therapies, and to arrive at individualized, patient-centered recommendations for clinical practice.

Future Research Directions

An obvious need exists to further clarify and demonstrate the benefit–risk ratio of new drugs using innovative nondopaminergic mechanisms, such as A_{2A} antagonism for fluctuations or serotonin mechanisms for dyskinesia, for example. Comparing and positioning these future new treatments among the already available therapies will then become mandatory, and demonstrating the real add-value of new COMT and MAO-B inhibitors and new formulations of amantadine will soon become urgent. Many "strategic" studies remain to be conducted, to better understand which interventions, in which order, and at which stage of the disease should be preferred. Randomized trials comparing the respective advantages and disadvantages of different devices (L-dopa intestinal infusion, apomorphine subcutaneous infusion, functional surgery) are missing. Further studies are also crucial to understand better when and to whom such interventions should be proposed. Finally, long-term studies, testing the impact on the emergence of motor complications of the early use (as first-line therapies) of compounds such as, for example, IPX066 or amantadine are justified. ■

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