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REVIEW

Therapy for Parkinson's Disease: What is in the Pipeline?

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Abstract Despite advances in the treatment of Parkinson's disease there are still many unmet needs, including neuroprotection, treatment of motor complications, treatment of dyskinesia, treatment of psychosis, and treatment of nondopaminergic symptoms. In this review, I highlight the obstacles to develop a neuroprotective drug and some of the treatment strategies recently approved or still in clinical trials designed to meet these unmet needs.

Keywords Parkinson's disease · treatment · pipeline

Introduction

Despite advances in the treatment of Parkinson's disease (PD) there are still many unmet needs, including neuroprotection, treatment of motor complications, treatment of dyskinesia, treatment of psychosis and treatment of nondopaminergic symptoms.

In this review, I will highlight some of the treatment strategies recently approved or still in clinical trials designed to meet these unmet needs. The reader is also referred to other recent reviews of emerging therapies in PD [1–4].

Neuroprotection

A treatment able to slow down or halt the progression of PD is a major unmet need. While there have been many promising candidate agents based on laboratory studies and pathological findings, no treatment has as yet been established as neuroprotective or disease-modifying in PD. Although many drugs have been found to be "neuroprotective" in animal models [5], nearly all of them failed when tested in clinical trials. For example, a plant-derived substance PYM50028 (Cogane), which promotes expression of endogenous neural growth factors and has shown promise in vitro and in animal models [6], but failed to show improvement in a large phase II trial in early PD when compared with placebo (data on file). Other agents, such as green tea, coenzyme Q10, creatine, GPI-1485, TCH346, CEP1347, and minocycline failed to demonstrate any effect on disease progression.

Another trial examined the short-term symptomatic effects (24 weeks) and the effects of long-term treatment (120 weeks) of GM1 on disease progression [7]. The authors reported a symptomatic effect and a possible disease-modifying effect of GM1; however, the methodology and the study design did not allow any reliable conclusion to be made about the potential neuroprotective effect of the compound [7].

Several obstacles have been identified that impede the demonstration of a particular therapy as being neuroprotective. A major limitation in the development of a neuroprotective agent is the lack of understanding of cellular mechanisms of neurodegeneration in PD. A number of pathogenic factors have been implicated, including oxidative stress, mitochondrial dysfunction, inflammation, excitotoxicity, and other mechanisms leading to apoptosis [8, 9]. However, it is not known which, if any, of these factors is the primary cause of cell death, and it is possible that cell death results from a cascade of events affecting multiple pathways, and that a cocktail of agents may be required to provide a protective effect. It is also possible that cell death in PD occurs as a result of an entirely different pathogenic factor that has not yet been identified. For example, several environmental factors have been identified as risk factors, but it is not yet clear how these contribute to the pathogenesis of PD. A number of different gene mutations have been identified, but it is not well understood how these mutations lead to cell death [10].

At present, it seems likely that sporadic cases of PD are due to a complex interaction between environmental, genetic, and

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epigenetic factors. What seems clear is that there are many different causes of PD, and it is by no means certain that an agent that provides a neuroprotective effect in one form of the disease will be protective for all patients. Nonetheless, it is reasonable to consider that the different forms of the disease might share a common pathway leading to cell death.

Another obstacle is the lack of a reliable animal model to test possible candidates [11]. The 6-hydroxydopamine rodent, the 1-methyl-4-phenyl-tetrahydropyridine (MPTP) mouse, and primate models of PD have been widely employed as models of degeneration of substantia nigra pars compacta dopamine neurons, and have proven to be useful in identifying dopaminergic therapies. However, these models are created by the acute administration of toxins that likely do not reflect the true etiopathogenesis of PD. Not surprisingly, they have been of limited value in predicting the results of potential neuroprotective therapies [12]. Transgenic models based on genetic causes of PD are more promising [11]. While current transgenic models do not precisely reproduce either dopaminergic or nondopaminergic pathological features of the disease, they do reflect an etiopathogenic mechanism, such as alphosynuclein accumulation, which is responsible for at least one form of PD associated with chronic and progressive neurodegeneration [13]. Prior to initiating a major drug development program, evidence of target engagement is desirable in order to ensure that the drug is gaining access to the central nervous system and interacting with the proposed target. Indeed, many pharmaceutical companies will not move forward in clinical trials until this has been clearly demonstrated. Problems are further confounded by the scales that are currently employed in clinical trials, which have a limited range and are particularly insensitive to detecting change in the early stages of the disease. These problems could be resolved by the development of a validated biomarker that could be used to confirm the diagnosis or serve as an endpoint to objectively measure disease progression and drug efficacy. Unfortunately, no such biomarker currently exists, but efforts are currently underway to try and resolve these issues [14]. The Movement Disorder Society has recently revised the Unified Parkinson's Disease Rating Scale (UPDRS) to make it more sensitive to change in early disease [15]. The Michael J. Fox Foundation has also initiated the Parkinson's Progression Markers Initiative, which is aimed at defining the natural rate of progression of both motor and non-motor features of PD at various disease stages and characterizing trait biomarkers, which indicate whether someone has the disease, and state biomarkers, which track the progression of the disease [16]. Success in these areas should greatly advance our ability to perform clinical trials of putative protective agents in PD.

Doses of study drugs chosen for clinical trials are a particular problem for potential neuroprotective agents. Benefits are often seen at very low tissue concentrations, but can follow a U-shaped curve, where protective benefits are lost with higher or lower concentrations of the drug. Thus, it is possible that a given agent may be effective only within a narrow dose range. Furthermore, with neuroprotective agents, optimal doses may not induce a short-term clinical benefit or toxic effect against which to define a dose range. It is therefore possible that negative study results with promising drugs reflect the selection of the wrong dose, rather than the futility of the therapeutic intervention.

The population of PD patients employed in a clinical trial can be critically important. Most studies have chosen to include early stage, untreated patients, as there are likely to be a greater number of remaining neurons that can be protected or rescued in comparison to patients in more advanced stages of the disease. Additionally, early-stage patients can be evaluated in an untreated state, thereby avoiding the concomitant use of potentially confounding drugs. However, there is a greater possibility of inaccurate diagnosis in early disease and a greater risk of drop out when these patients eventually need treatment. Moreover, although disease progression is generally faster in the early stages of the disease [17], the mild clinical progression, possibly due to compensatory effects, makes it difficult to detect a difference between the treatment and placebo groups [18]. Alternatively, some studies have elected to study potential neuroprotective drugs in more advanced PD patients because they are on stable therapy and less likely to drop out. However, this advantage must be mitigated by the concern that neurodegeneration may be too far advanced, and that the introduction of a neuroprotective therapy at a late stage of the disease,may preclude the potential of seeing benefit, even if the agent is effective. Intense efforts are currently underway to define a population of patients in a prodromal or premotor state of PD so that in the future it may be possible to introduce a putative neuroprotective therapy to patients at an earlier stage [14].

No drug has yet been established as a neuroprotective agent in PD. Several clinical trials of potential neuroprotective agents have shown positive results, but it could not be determined with certainty whether the benefit was due to neuroprotection as the study agent was associated with potentially confounding pharmacological or regulatory effects. Endpoints tested include time to a milestone of disease progression, change from baseline in UPDRS score, and change in a surrogate imaging biomarker of dopaminergic function. In an attempt to separate an early symptomatic from a disease-modifying effect, delayed-washout and delayed-start studies have been proposed [19]. Both are two-period studies that rely on change from baseline in UPDRS score. In the first period of each of these studies, patients are randomized to active treatment (early-start) or placebo. Benefits at this stage could be due to a symptomatic and/or a protective effect. In the second period of the delayed-washout study, the active intervention is stopped and patients in both treatment groups receive placebo. If the early-start group maintains a benefit in comparison with

placebo at the end of the second period, this is consistent with the treatment having a disease-modifying effect. This design, however, has not been considered for use in PD because of the ethical and practical issues involved in withdrawing therapy from PD patients, particularly for the periods of time necessary to conduct the trial. In the second period of the randomized-start design, patients in the placebo group are placed on active intervention (delayed start), while those in the early-start group are maintained on their original treatment [20]. Thus, both groups receive the same active study intervention during the second period of the study. If there is no difference between the early- and delayed-start groups at the end of the second period, it may be hypothesized that any benefit seen at the end of the first period is due to a symptomatic effect. However, if at the end of the trial the early-start group continues to show a benefit in comparison with the delayed-start group, even though both groups are on the same treatment, there will be no evidence to suggest that UPDRS scores in the two groups are converging (i.e., the benefit is enduring): this will suggest that the treatment has slowed the rate of clinical deterioration and is consistent with the treatment having a disease-modifying effect. Such studies are complex and difficult to carry out. They require that the first period is sufficiently long for a neuroprotective effect to occur (if there is one), and the second period needs to be sufficiently long to be sure that sufficient numbers of visits can be performed to ensure that the study agent does not have a delayed symptomatic effect. However, neither period must be so long that there is undue drop out, which would severely compromise the analyses. Further, statistical analyses are complex and require the employment of multiple primary endpoints [19, 20].

The delayed-start model was employed in the ADAGIO study to determine if rasagiline had neuroprotective effects in PD [21]. Rasagiline 1 mg per day met all three prescribed primary endpoints consistent with the drug having a disease-modifying effect. However, the 2-mg dose failed to show a difference between early and delayed treatment at the end of the second period. Thus, the results of the study were inconclusive, and further studies testing these doses separately are required to determine which of these results is valid [22]. While the results of ADAGIO are not definitive, the study design does provide a method for differentiating early symptomatic and disease-modifying effects, and should facilitate the investigation of new agents. A limitation of this study is that it does not address the issue of clinical significance as it is relatively short term. Another approach is the long-term simple study, where subjects are randomized to active treatment or placebo, and then followed for a prolonged period of time (many years) in which the physician can manage the patient in any way they deem to be appropriate. This approach captures and measures factors related to the development of cumulative disability, such as falling, freezing, and dementia, in addition to standard UPDRS scores. Recently, a long-term simple study with creatinine was stopped owing to futility. A combination of the delayed-start and long-term simple studies offers assessments of mechanism and clinical significance, and provides a roadmap for the development of a neuroprotective drug. Needless to say, a pathway to regulatory approval is required if pharmaceutical sponsors are going to be willing to provide the necessary funding.

Despite these problems trials to demonstrate disease-modifying effect are ongoing.

Phosphodiesterase type 4 plays a major role in modulating the activity of virtually all cells involved in the inflammatory process. A clinical trial with AVE8112, a phosphodiesterase type 4 inhibitor, is currently in progress (clinical trials.gov).

Cannabinoids such as Δ9-tetrahydrocannabinol have been shown to be potentially neuroprotective in animal and cell culture models of PD For example Δ9-tetrahydrocannabinol has been found to be neuroprotective through activation of the nuclear receptor peroxisomal proliferator-activated receptor γ [23]. Furthermore, activation by specific agonists, rosiglitazone and pioglitazone, has also been found to be neuroprotective [23]. A futility study with pioglitazone in early PD is currently ongoing.

Symptomatic Drugs

Levodopa

There is no doubt that levodopa (LD) is the most efficacious and best tolerated antiparkinsonian compound [24]. Despite the additional administration of an aromatic amino acid decarboxylase inhibitor (carbidopa or benserazide), which markedly reduce the peripheral LD degradation, a drawback of this drug is the short half-life in plasma. Slow-release preparations of LD have given disappointing results. The use of catechol-O-methyltransferase (COMT) inhibitors improve the half-life of LD and the triple combination carbidopa (CD)–LD–entacapone (CLE) provide, at the moment, the most sustained LD plasma level [25]. Unfortunately, the triple combination also must be administered several times a day to provide a good clinical control, and it does not completely eliminate off periods in fluctuating PD patients, or prevent the development of motor fluctuations or dyskinesias [26]. Moreover, pharmacokinetic studies showed that the triple combination does not provide stable LD plasma levels [27]. A better LD preparation is needed.

IPX066 (Rytary; Impax Laboratories, Hayward, CA, USA) is an investigational extended-release (ER) CD–LD (1:4 ratio) formulation that is designed to provide rapid attainment and maintenance of therapeutic LD plasma concentrations for a prolonged duration, often allowing dosing intervals of approximately 6 h, regardless of disease stage studied [28, 29]. In PD

patients, the LD bioavailability of IPX066 is approximately 70 % relative to immediate-release (IR) CD–LD, and IPX066 demonstrated a rapid onset of effect with benefits on motor symptoms lasting approximately 6 h after a single dose [28, 29].

In a phase III randomized, double-blind, placebo-controlled, 30-week study of 381 LD-naïve patients, IPX066 provided significant clinical benefits at the three dosages tested compared with placebo and was well tolerated. Of the dosages tested, IPX066 145 mg q8h appeared to provide the best overall balance between efficacy and safety [30].

IPX066 was also tested in a phase III, randomised, double-blind, double-dummy study in parkinsonian patients with motor fluctuations. In this study IPX066 was compared with standard LD-CD formulation, and 393 patients were included in the main efficacy analyses. As a percentage of waking hours, 201 patients treated double-blindly with ER LD–CD (mean 3.6 doses per day [SD 0.7]) had greater reductions in off time than did 192 patients treated double-blindly with IR LD–CD (mean 5.0 doses per day [SD 1.2]). IPX066 reduced daily off time by, on average, an extra −1.17 h (95 % confidence interval −1.69 to −0.66; $p < 0{\cdot}0001$) compared with IR LD–CD. In the maintenance period, the most common adverse events were insomnia [seven (3 %) of 201 patients allocated ER LD–CD *vs* two (1 %) of 192 patients allocated IR LD–CD], nausea [six (3 %) *vs* three (2 %)], and falls [six (3 %) *vs* four (2 %)] [31].

In a more recent phase III, randomized, double-blind, double-dummy, crossover study designed to evaluate the safety and efficacy of IPX066 versus CLE in patients on stable CLE (ASCEND-PD study), 91 patients were randomized and 84 completed the study. The median (mean±SD) daily IPX066 LD dose was 1495 mg (1723±713 mg), and the LD/entacapone dose was 600/800 mg (652±252 mg/943± 174 mg). IPX066 was associated with lower mean percent off time during waking hours (24.0 % *vs* 32.5 %; $p < 0.0001$), lower mean off time (3.8 *vs* 5.2 h; $p < 0.0001$), and higher mean on time without troublesome dyskinesia (11.4 *vs* 10.0 h; $p < 0.0001$) relative to CLE [Stocchi et al., submitted].

In comparative studies, IPX066 proved to be superior to standard LD–CD and CLE preparation. IPX066 can be administered less frequently during the day and, despite the relatively higher LD dose provided by the slow release compound, there was no increase in dyskinesia.

Another LD preparation being currently studied is XP21279, a sustained-release prodrug of LD. In a phase II pharmacokinetic study on PD patients the drug provided improved pharmacokinetic performance (highlighted by a reduction in variability of LD concentration) compared with LD–CD [32].

An inhaler formulation of LD (CVT-301) to rescue fluctuating PD patients from off episodes is currently undergoing a clinical trial. ND0611 is a preparation of LD ethyl-ester formulated for transdermal use. At the moment, a proof-of-concept pharmacokinetic study on PD patients has been designed.

LD–CD Intestinal Gel

Long-lasting and dramatic reductions in motor complications have been observed in advanced PD patients in whom treatment with a continuous infusion of LD or a dopamine agonist (apomorphine, lisuride) is associated with reduced off periods and dyskinesias [33]. For example, patients randomized to receive a continuous subcutaneous infusion of lisuride have had marked reductions in both off periods and dyskinesias in comparison to those randomized to treatment with standard oral formulations of LD [34]. We reported that continuous intra-intestinal infusion of LD induces a significant reduction in both off time and dyskinesia in comparison to intermittent doses of a standard oral formulation of the drug [35], confirming the results of other studies.

Recently, a novel formulation of infusible LD has been developed in which the drug is embedded in a carboxymethylcellulose gel providing a concentration of LD/CD of 2.0/0.5 g in only 100 ml (Duodopa). A 100-ml cassette thus contains 2 g of LD allowing for a full day's coverage. This novel delivery system uses portable pumps that have programmable delivery rates for amounts between 10 and 200 mg of LD/h and delivery times of up to 24 h. Intrajejunal delivery is achieved through a percutaneous endoscopic gastrostomy tube in which the tip is positioned below the Treitz band in the proximal jejunum. Several studies have been conducted showing a clear improvement of motor fluctuations and dyskinesias using this LD infusional system [36, 37]. Duodopa has been available in Europe for a few years, confirming its efficacy in clinical practice. The main problems related to Duodopa treatments are severe gastrointestinal complications and peripheral neuropathy [38, 39].

A double-blind, double-dummy study of Duodopa versus standard oral treatment has just been concluded in USA. The study confirms the superiority of infusional treatment versus oral treatment in improving off time and dyskinesias in advanced PD patients.

Dopamine Agonists

The main improvement of dopamine agonists (DA) has been the introduction of slow-release preparations of oral DA and patch formulations. Attention has been paid to partial DAs. This drug class would be expected to avoid some of the side-effect limitations associated with full DAs. In blinded experiments, functional studies, and 3H-dopamine-release studies, Pardoprunox was shown to possess partial agonist properties at D2/3 receptors and agonist properties at 5-HT1A receptors *in vitro*. The 5-HT1A agonism may provide benefits in

control of dyskinesia. Unfortunately, a phase III clinical trial fail to show clear efficacy of this compound. Moreover, the tolerability of the drug was poor and therefore the program was terminated [40]. Aplindore [41] is another DA studied, but the clinical trial was terminated.

Monoamine oxidase B Inhibitors

Safinamide is a novel monoamine oxidase B (MAOB) inhibitor that also modulates dopamine reuptake and glutamate release [42]. The safety and efficacy of safinamide as an add-on to DA therapy was evaluated in a multicenter, double-blind, parallel-group study. Patients with early PD (n=270) receiving stable DA therapy were randomized to 6 months of combination therapy with safinamide (at 50–100 or 150–200 mg/day) or placebo. The primary outcome measure was the drug's effects on motor symptoms (UPDRS part III). At the end of the 6-month study, patients could enter a 12-month extension phase. Results at the end of the 6-month study showed that safinamide (50–100 mg/day) significantly improved motor symptoms, activities of daily living, quality of life, and cognition ratings compared with placebo [43]. In a long-term, double-blind extension study, safinamide proved to be safe [44].

The addition of safinamide 50 mg/day or 100 mg/day to LD in patients with PD and motor fluctuations (study 016) significantly increased on time with nontroublesome dyskinesia, decreased off time, and improved parkinsonism, indicating that safinamide improves motor symptoms and parkinsonism without worsening dyskinesia.

Moreover, there are data suggesting that safinamide may improve dyskinesia [45]. In the SETTLE study, designed to evaluate the effects of safinamide on motor fluctuations, 484/549 randomized patients completed the 24-week study. Safinamide 50–100 mg/day significantly improved on time (without worsening troublesome dyskinesia), off time, UPDRS III, Clinical Global Impression–Severity scale, clinical global impression-change (CGI-C) and Parkinson's Disease Questionnaire–39 following the first morning LD dose (i.e., latency to on) compared with placebo [46]. The submission of registration file to the Food and Drug Administration and European Medicines Agency is scheduled for 2014.

COMT Inhibitors

COMT inhibition increases the peripheral bioavailability of LD and reduces 3-O-methyldopa (3-OMD) formation. The administration of COMT inhibitors with LD ensures a more stable plasma LD level and, consequently, it improves motor fluctuations.

Opicapone is a third-generation nitrocatechol COMT inhibitor. In a pharmacokinetic study on monkeys, opicapone increased LD systemic exposure twofold, without changing C_{max} values, and reduced both 3-OMD exposure and C_{max} values fivefold. Opicapone behaved as a long-acting COMT inhibitor that markedly increased systemic and central LD bioavailability [47]. A phase III study with opicapone in fluctuating parkinsonian patients has just been concluded.

Adenosine A2A Antagonists

Adenosine is an endogenous nucleoside found extracellularly in the central nervous sytem. Adenosine is also an important neuromodulator within the basal ganglia. Adenosine A2A receptors are selectively located on the cell bodies and terminals of the gamma-aminobutyric acid (GABA)ergic indirect striatal output pathway and are functionally linked to dopamine D2 receptor function [48]. Adenosine, via the A2A receptor, may contribute to the overactivity of the indirect pathway in PD by enhancing GABA release in the external globus pallidus [49]. Corticostriatal glutamatergic activity via N-methyl D-aspartate (NMDA) receptor stimulation is increased in PD and results in adenosine release and stimulation of A2A receptors—an action that may further increase activity of the indirect GABAergic pathway.

Changes in adenosine A2A receptors have been reported in PD.

Thus, adenosine A2A antagonists have become recognized as potentially useful agents in the treatment of PD, and several are in development. Preclinical studies have shown that adenosine A2A antagonists can, as monotherapy, alleviate parkinsonism in experimental animals [50, 51]. In combination with a low dose of LD, adenosine A2A antagonists can enhance antiparkinsonian actions without exacerbating dyskinesias [52].

Istradefylline, is a selective A2A antagonist that has been recently approved in Japan for the treatment of fluctuating PD. Istradefylline was not previously approved by the Food and Drug Administration, but other studies are ongoing and the drug can be reconsidered. In a very recent trial conducted in Japan [53], daily off time was significantly reduced in the istradefylline 20 mg/day (−0.99 h; $p=0.003$) and istradefylline 40 mg/day (−0.96 h; $p=0.003$) groups compared with the placebo group (−0.23 h). The most common adverse event was dyskinesia (placebo, 4.0 %; istradefylline 20 mg/day, 13.0 %; istradefylline 40 mg/day, 12.1 %) [53].

Preladenant, another A2A antagonist proved to be well tolerated and provided sustained off time reductions and on time increases in a phase II study [54]. Unfortunately, a large phase III program on early and advanced PD patients failed to show any improvement versus placebo. The results of the studies are confounded by the lack of efficacy also showed by the active comparator rasagiline. The developing program of preladenant has been terminated.

The A2A antagonist vipadenant (BIIB014) has recently been tested in a phase II trial, which demonstrated that

vipadenant was effective in reducing the waking time spent in off state in patients at the late stage of PD treated with LD. Two studies to evaluate tozadenant (SYN115) have been concluded, but the results have not yet been published.

Glutamate Antagonists

Enhanced glutamatergic activity may drive increased activity of the dopamine D1-mediated direct pathway, with resultant inhibition of the basal ganglia outputs and the generation of dyskinesias [55]. In addition, glutamate receptors are critical to synaptic plasticity. In parkinsonism and dyskinesias, abnormal synaptic plasticity similar to long-term depression and long-term potentiation seen in the hippocampus may contribute to the mechanism of symptom generation. Thus, in the striatum in PD loss of long-term depression in the indirect pathway may lead to enhanced glutamatergic signaling and overactivity of that pathway. Thus, reducing excessive glutamate activity may reduce either PD motor symptoms or reduce dyskinesias.

Preclinical studies in the 1-methyl 4-phenyltetrahydropyridine-lesioned primate have demonstrated that NMDA-selective glutamate antagonists, for example MK801 and LY235959, reduce LD-induced chorea [56–58]. In addition, the NMDA receptor antagonist, amantadine, is now a well-established therapy for dyskinesias [59]. Follow-up studies have reported maintained benefit after 1 year [60], but longer-term follow-up studies have not been reported. In addition, some PD patients may experience side-effects that include hallucinations, livedo reticularis, and edema, thus limiting use. Very recently, the results of a large trial using slow-release amantadine has been presented. In this study, amantadine showed a very significant improvement of dyskinesia (MDS meeting, Sydney 2013).

Targeting metabotropic glutamate receptors has also been investigated in PD, and has been suggested as a better option than NMDA or alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonists owing to a wider therapeutic index.

Mavoglurant (AFQ056) is a selective metabotropic glutamate receptor 5 antagonist that improved dyskinesia in PD patients in a phase II study [61]. Recently, the results of another phase II study with mavoglurant standard formulation and a phase II study with mavoglrant slow-release formulations have been released. Both formulations of mavoglurant showed no effect on dyskinesia, and the program has been terminated.

Moreover, the experience with movoglurant confirms that NMDA antagonism may reduce dyskinesia, but also has the potential to induce side-effects due to actions on glutamate receptors outside the basal ganglia, for example, ataxia, hallucinations, and confusion. Given these issues, the next obvious development of NMDA antagonists in PD would be to identify a subtype of NMDA receptors specifically involved in the generation of parkinsonism and dyskinesia, and develop drugs to selectively target these.

Other agents that may potentially reduce overactive glutamate neurotransmission in PD include safinamide, which acts on glutamate release showing effect on dyskinesia (see above); and zonisamide, which has demonstrated efficacy in a large phase III study in PD patients showing a significant reduction in off time from baseline [−1.3 h (50 mg daily) and −1.63 h (100 mg daily) compared with −0.2 h (placebo)] [62]. A randomized. double-blind placebo-controlled study of zonisamide in early Parkinson disease (ZONIST) is planned to start.

Alpha2 Antagonists

Alpha2 antagonists in PD have not focused on their antiparkinsonian potential, but rather on their potential to reduce dyskinesias. Within the striatum, the alpha2C adrenoceptor subtype is located on GABAergic spiny neurons [63] and appears to modulate activity of the direct striatopallidal pathway, possibly by regulation of GABA release [64]. Thus, reducing the activity of the overactive direct striatopallidal pathway via alpha2C receptor antagonism may reduce LD-induced dyskinesia (LID). The effect of fipamezole, a selective alpha2-adrenergic receptor antagonist, on dyskinesia was evaluated in a phase II study [65]. The total study population showed no statistically significant primary endpoint difference. However, because of inhomogeneity recognized between US and Indian study populations, a prespecified subgroup analysis of US patients was conducted, showing that fipamezole at 90 mg reduced dyskinesia [mean, 95 % confidence interval, LID rating improvement *vs* placebo −1.9 (0.0 to −3.8; $p=0.047$)] The study was not conclusive, but fipamezole deserve further attention.

5-Hydroxytryptamine and Dyskinesia

The recurring theme in basic scientific studies on the role of 5-hydroxytryptamine (HT) in basal ganglia function is an ability to modulate neurotransmitter release. Thus, 5-HT1A receptors in the dorsal raphe nucleus and striatum, 5-HT1B receptors on striatopallidal pathways, and 5-HT2A/2C receptors within the substantia nigra pars reticulata and internal globus pallidus have been shown to modulate dopamine, GABA, and glutamate release. From the above discussion, it is clear that there is a likely role for 5-HT-focused therapies in dyskinesia.

Clinical studies have been performed with 5-HT1A agonists such as buspirone and sarizotan, but they did not show clinical benefit on dyskinesia [66].

A selective 5-HT2A receptor inverse agonist, pimavanserin

(ACP-103) developed to treat psychosis in Parkinson's disease has been tested on dyskinesia. A double-blind, phase II trial of ACP-103 in 12 PD patients with LID and motor complications demonstrated good tolerability and reduced dyskinesia, without worsening of parkinsonian symptoms [67]. Pimavanserin has been extensively studied to treat psychosis in PD. In a double-blind, randomized, multicenter 28-day study, the tolerability and efficacy of pimavanserin was compared with placebo in 60 patients with LD or DA-induced PD psychosis (PDP). Motor function was evaluated using UPDRS parts II and III. Antipsychotic efficacy was evaluated using multiple measures from the Scale for the Assessment of Positive Symptoms (SAPS) and a UPDRS part I psychosis-relevant item. Pimavanserin did not differentiate from placebo

Table 1 Experimental therapeutics in Parkinson's disease

	Substance	Mechanism of action	Ongoing status
Neuroprotection			
	Cogane PYM50028	Plant-derived substance that promotes expression of endogenous neural growth factors	Failed
	GM1	Neurotrophic factor	Inconclusive study
	Δ9-Tetrahydrocannabinol	Activation of the nuclear receptor PPARγ	Study ongoing
	AVE8112		Study ongoing
Levodopa			
	IPX066	ER CD–LD	Approved by FDA
	XP21279	Sustained release prodrug of LD	Phase II
	CVT-301	Inhalator formulation of LD	Phase II
	ND0611	LD ethyl-ester for transdermal use	Phase I
	Duodopa	LD/CD intestinal gel	Approved by EMA
Dopamine agonists			
	Pardoprunox	Partial agonist properties at D2/3 receptors and agonist properties at 5-HT1A receptors	Failed, program terminated
	Aplindore	Dopamine agonist	Program standby
MAO inhibitors			
	Safinamide	Inhibits dopamine reuptake MAOB and glutamate release	Finished phase III, registration file submitted
COMT inhibitors			
	Opicapone	Third-generation nitrocatechol COMT inhibitor	Phase III
Adenosine A2A antagonists	Istradefylline	Selective A2A antagonist	Approved in Japan
	Preladenant	A2A antagonist	Program terminated
	Vipadenant (BIIB014)	A2A antagonist	Finished phase II
	Tozadenant	A2A antagonist	Standby
Glutamate antagonists	Mavoglurant (AFQ056)	Selective mGluR5 antagonist	Program terminated
	Zonisamide	Glutamate release inhibitor	Planned phase III
Alpha2 antagonists			
	Fipamezole	Selective alpha2-adrenergic receptor antagonist	Standby
5-HT agonists			
	Pimavanserin	Selective 5-HT2A receptor inverse agonist	Finished phase III on psychosis, exploring dyskinesia
Gene therapy			
	AAV2–GAD	Transfer GAD in the subthalamic nucleus to modulate GABA	New studies planned
	AAV–neurturin		New studies planned

MAO=monoamine oxidase; COMT=catechol-O-methyltransferase; 5-HT=5-hydroxytryptamine; AAV=adeno-associated virus; GAD=glutamic acid decarboxylase; PPAR γ=peroxisomal proliferator-activated receptor γ; ER=extended release; CD=carbidopa; LD=levodopa; MAOB=monoamine oxidase B; mGluR5=metabotropic glutamate receptor 5; GABA=gamma aminobutyric acid; FDA=Food and Drug Administration; EMA=European Medicines Agency.

with regard to motor impairment, sedation, hypotension, or other side-effects. The principal measures of efficacy of antipsychotic response to pimavanserin, the SAPS total domain score, only showed a trend. However, the pimavanserin-treated patients showed significantly greater improvement in some, but not all, measures of psychosis, including SAPS global measures of hallucinations and delusions, persecutory delusions, and the UPDRS measure of delusions and hallucinations. Pimavanserin showed significantly greater improvement in psychosis in patients with PDP at a dose that did not impair motor function, or cause sedation or hypotension [68]. A number of other studies have been performed, but the results have only been presented in meetings. The impression is that pimavanserin may represent a novel treatment for PDP. Furthermore, these results support the hypothesis that attenuation of psychosis secondary to DA receptor stimulation in PDP may be achieved through selective 5-HT(2A) receptor antagonism.

Gene and Cell-based Therapy

Despite cell-based therapy in PD remaining a key research priority, so far controlled fetal cell transplant studies have failed to provide clear evidence for symptomatic efficacy in parkinsonian patients. Moreover, there are concerns about the development of abnormal movements and potential host-to-graft propagation of Lewy body disease in PD patients who have received embryonic nigral transplants [69]. The use of microcarriers (spheramine) to deliver dopamine in the striatum failed to demonstrate efficacy in a study on PD patients [70].

An alternative approach to restorative treatment is represented by the viral vector-based targeted delivery of therapeutic genes. This approach is covered in elsewhere in this journal [71].

Conclusion

Neuroprotection or disease-modifying therapies remain a major unmet need in the treatment of PD. Better understanding the pathogenesis of PD, more disease-relevant animal models, development of sensitive and specific biomarkers for early detection and to measure progression, and reliable instruments and trial design are determining factors for developing a disease-modifying therapy. Despite numerous failures there are still many promising drugs and other strategies in development. Although the therapeutic pipeline in PD is not as healthy as we would like, pharmacological research is active and may eventually lead to a better quality of life of patients with PD (Table 1).

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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