Advances in Drug Development for Parkinson’s Disease: Present Status

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Key Words
Parkinson’s disease · Motor disorder · Clinical trials · Phase I · Phase II · Phase III

Abstract
The major hallmark of Parkinson’s disease (PD) is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to the characteristic motor symptoms of resting tremors, bradykinesia and rigidity. Research in the field of PD therapy has been partly successful in terms of developing symptomatic treatments, but it also experienced several failures with regard to developing disease-modifying therapies. According to the definition of the Committee to Identify Neuroprotective Agents for Parkinson’s, neuroprotection would be any intervention that favorably influences the disease process or underlying pathogenesis to produce enduring benefits for patients. A development of effective neuroprotective therapies resulting in clinically meaningful results is hampered by several factors in all research stages. Novel solutions might be offered by an evaluation of new targets throughout clinical studies, therapies emerging from drug repositioning approaches, multitarget approaches and network pharmacology. Several promising randomized controlled trials are in progress, and the increased collaboration between pharmaceutical companies and basic and clinical researchers has the potential to bring us closer to developing an optimum pharmaceutical approach for the treatment of PD. The aim of the present review is to give an overview of the neuroprotective agents and their targets currently investigated for the treatment of PD in phase I–III clinical trials.

Introduction
Parkinson’s disease (PD) is the second most common movement disorder among neurodegenerative diseases [1], first described by James Parkinson in an essay entitled ‘An essay on the shaking palsy’ in 1817 [2]. Later, the famous French neurologist Jean-Martin Charcot further described the syndrome in the late 1800s. In fact, age is the most important risk factor for PD: worldwide, approximately 1–2% of the population older than 65 years suffer from this slowly progressive degenerative disease [3]. The majority of PD cases are idiopathic (90–95%) with no specific known cause, and the remaining ones are familial forms (5–10%). The genes that are thought to be involved in familial PD are...
α-synuclein, parkin, DJ-1, PINK-1, LRRK2, UCH-L1, ATP13A2 and HTRA2 [4, 5]. Clinically, PD is characterized by motor abnormalities including bradykinesia (especially having difficulties in initiating movement), tremor (pill-rolling movement of the forearm) and muscular rigidity with secondary manifestations such as defective posture, gait impairment, mask-like face and sialorrhea [6]. Nonmotor symptoms are depression, constipation, pain, genitourinary problems, sleep disorders, emotional changes, speech changes, dementia, cognitive problems, muscle cramps, dystonia, fatigue and loss of energy [7].

The main pathological hallmark of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta, which leads to the depletion of dopamine in the striatum and accumulation of α-synuclein protein in the brain in the form of Lewy bodies. The role of these Lewy bodies in pathogenesis remains unknown, but it was discovered that misfolded α-synuclein is a major component of the radiating filaments in PD [1]. Various other pathogenic mechanisms that are implicated in dopaminergic cell death in PD are oxidative stress, excitotoxicity, mitochondrial dysfunction, neuroinflammation, alterations in gene regulation, protein aggregation and heavy metal poisoning. These mechanisms share overlapping and redundant features and cause injury to the neurons.

Although levodopa still remains the standard drug for symptomatic treatment in reducing the motor symptoms of PD, its long-term use is associated with the development of potentially disabling motor complications including response oscillations as well as levodopa-induced dyskinesias (LID), affecting approximately 30–35% of patients after just 2 years of exposure to levodopa. In order to avoid the complications arising with levodopa, many new neuroprotective agents are under investigation, using different novel mechanisms of actions [11].
The purpose of this review is to provide details of the current status of drug development for PD. We focus on the drugs that have entered clinical phases, mainly phases II and III, but we include a brief overview of the drugs in phase I trials.

**Methods**

The screening of papers was conducted online by searching various databases such as Medline (PubMed) and the Cochrane database until June 2013. PubMed was searched using the following key words:

- Parkinson’s disease and clinical trials for the years 2009–2013
- Motor symptoms and clinical trials for the years 2009–2013
- The chemical names of every compound mentioned in any article on new drugs for PD since 2009

ClinicalTrials.gov was searched using the key words:

- Parkinson’s disease
- Motor disorder
- Parkinson’s disease phase I, phase II, phase III

Clinical trials included all trials using the key words randomized, placebo-controlled, double-blind and parallel-group design.

**Phase I Trials**

Phase I trials are the first stage of testing drugs in human subjects. Normally, a small group of 20–100 healthy volunteers is recruited. This phase is designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of a drug. As it takes several years for a compound to come into the market from phase I clinical trials and the probability of success is quite low, it is meaningless to give detailed descriptions of individual compounds. Table 1 provides a brief overview of drugs for PD that are in phase I trials.

**Phase II Trials**

Once the dose or range of doses has been determined in phase I trials, the next aim is to evaluate whether the drug has any biological activity or not. Phase II trials are performed on larger groups (100–300 individuals) and are designed to assess how well the drug works as well as to continue phase I safety assessments in a larger group of volunteers and patients. Genetic testing is common, particularly if there is evidence of variations in metabolic rate (table 2).

**GM1 Ganglioside (Sygen)**

GM1 (monosialotetrahexosylganglioside), the ‘prototypical’ ganglioside, is a member of the ganglio-series of gangliosides which contain one sialic acid residue. GM1 ganglioside is normally found in the brain and is a normal part of the outer covering or membrane of nerve cells. GM1 has important physiological effects such as impacting neuronal plasticity, repair mechanisms and the release of neurotrophins in the brain. In addition, GM1 has antieiclitotoxic properties. Various studies on nonhuman primates have shown that treatment with GM1 ganglioside increased striatal dopamine levels and alleviated the parkinsonian symptoms [12, 13].

A phase II trial was designed to examine the extent to which GM1 ganglioside can improve symptoms, delay disease progression and perhaps partly restore damaged brain cells in PD patients. In addition to studying clinical measures of motor and cognitive functioning, the investigators used PET scanning to image the brain and the dopamine nerve endings in a subgroup of patients. Patients with mild-to-moderate idiopathic PD were divided into two groups. One group received GM1 for 24 weeks and the other group placebo. The study has been completed, and GM1 showed a potential role in decreasing motor symptoms and slowed the progression of disease in the PD patients [14].

**ADX48621 (Dipraglurant)**

Dipraglurant is a novel, small, orally administered molecule which inhibits the metabotropic glutamate receptor 5 (mGluR5) and has the potential to be used in combination with levodopa or dopamine agonists for the treatment of PD. After the successful completion of two phase I studies of ADX48621 in 36 healthy subjects, in which it was shown that the drug was safe and well tolerated [15], Addex Pharma S.A. started a phase II study to evaluate the safety and tolerability of ADX48621 in PD patients. This was the first study of ADX48621 in male and female PD patients with LID. It was a 4-week double-blind placebo-controlled trial with a dose titration from 50 mg once daily up to 100 mg 3 times daily at the start of week 4. Safety and tolerability were assessed by adverse event inquiry, heart rate and blood pressure measurements and 12-lead ECG as well as hematology and biochemistry testing. Efficacy assessments included the Abnormal Involuntary Movement Scale (AIMS), the Unified Parkinson’s Disease Rating Scale (UPDRS), patient PD symptom diaries, the Hospital Anxiety and Depression Scale (HADS) and the Patient and Clinician Global Impression of Change in PD and dyskinesia (PGIC and CGIC). The study has been completed. ADX48621 was well tolerated and effective and significantly advanced the treatment of PD [16].
Table 1. Drugs in phase I clinical trials for the treatment of PD

<table>
<thead>
<tr>
<th>No.</th>
<th>Drug name/Clinical Trial.gov registration No.</th>
<th>Sponsor/investigator</th>
<th>Mechanism of action</th>
<th>Route of administration</th>
<th>Comments/status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AZD3241/NCT0145780</td>
<td>AstraZeneca</td>
<td>Myeloperoxidase inhibition</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>2</td>
<td>SCH 420814/NCT01323855</td>
<td>Schering-Plough</td>
<td>Adenosine A&lt;sub&gt;2A&lt;/sub&gt; receptor antagonists</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>3</td>
<td>BIA 9-1067/NCT01533116</td>
<td>Bial-Portela &amp; Ca. S.A.</td>
<td>Catechol-O-methyl transferase inhibitor</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>4</td>
<td>ND0611/NCT01103011</td>
<td>NeuroDerm Ltd.</td>
<td>Decreases the metabolism of L-dopa</td>
<td>Transdermal patch</td>
<td>Completed</td>
</tr>
<tr>
<td>5</td>
<td>PYM50028/NCT00875316</td>
<td>Phytopharm</td>
<td>Blocks chloride ion secretion</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>6</td>
<td>Pramipexole/NCT00666653</td>
<td>Oregon Health and Science University</td>
<td>Dopamine agonist</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>7</td>
<td>Carbidopa/NCT01229332</td>
<td>NeuroDerm Ltd.</td>
<td>Inhibitor of dopa decarboxylase</td>
<td>Subcutaneous</td>
<td>Completed</td>
</tr>
<tr>
<td>8</td>
<td>TCH346/NCT00407212</td>
<td>Novartis</td>
<td>Inhibits dopa decarboxylase</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>9</td>
<td>CD-LD ER,CD-LD IR/NCT00239564</td>
<td>Impax Laboratories Inc.</td>
<td>Stimulation of dopamine receptors and aromatic L-amino-acid decarboxylase</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>10</td>
<td>Nicotine/NCT00957918</td>
<td>Neuraltus Pharmaceuticals Inc.</td>
<td>Nicotinic acetylcholine receptor agonist</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>11</td>
<td>Fipamezole ODT/NCT01149811</td>
<td>Valeant Pharmaceuticals International Inc.</td>
<td>Selective α&lt;sub&gt;2&lt;/sub&gt;-adrenergic receptor antagonist</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>12</td>
<td>Liatermin (r-metHuGDNF)/NCT00115427</td>
<td>Amgen</td>
<td>Acts on receptor tyrosine kinase</td>
<td>Intraputaminal infusion</td>
<td>Completed</td>
</tr>
<tr>
<td>13</td>
<td>PD01A/NCT01568099</td>
<td>Affiris AG</td>
<td>Against α-synuclein</td>
<td>Subcutaneous</td>
<td>Study in progress</td>
</tr>
<tr>
<td>14</td>
<td>Intransal glutathione – (in) GSH/NCT01398748</td>
<td>Bastyr University</td>
<td>Antioxidant</td>
<td>Intranasal</td>
<td>Study in progress but not recruiting</td>
</tr>
<tr>
<td>15</td>
<td>[18F]MPPF/NCT01461083</td>
<td>Institute for Neurodegenerative Disorders</td>
<td>Inhibition of 5-HT</td>
<td>Intravenous bolus injection</td>
<td>Recruiting participants</td>
</tr>
<tr>
<td>16</td>
<td>CJH1 (CLR4001)/NCT01684475</td>
<td>Alexandria Marine and General Hospital</td>
<td>Adjunct to extend L-dopa efficacy</td>
<td>Oral</td>
<td>Recruiting participants</td>
</tr>
<tr>
<td>17</td>
<td>[18F]MK-9470/NCT01462708</td>
<td>Institute for Neurodegenerative Disorders</td>
<td>Cannabinoids reduce L-dopa-induced dyskinesia</td>
<td>NA</td>
<td>Completed</td>
</tr>
<tr>
<td>18</td>
<td>Docosahexaenoic acid/NCT01563913</td>
<td>Department of Veterans Affairs</td>
<td>Antioxidant</td>
<td>Oral</td>
<td>Recruiting participants</td>
</tr>
<tr>
<td>19</td>
<td>N-acetylcysteine/NCT01427517</td>
<td>University of Minnesota – Clinical and Translational Science Institute</td>
<td>Antioxidant</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>20</td>
<td>Dalfampridine/NCT01491022</td>
<td>University of Miami</td>
<td>Potassium (K&lt;sup&gt;+&lt;/sup&gt;) channel blocking</td>
<td>Oral</td>
<td>Recruiting participants</td>
</tr>
<tr>
<td>21</td>
<td>ND0612/NCT01486628</td>
<td>NeuroDerm Ltd.</td>
<td>Stimulation of dopamine receptors</td>
<td>Subcutaneous</td>
<td>Study in progress</td>
</tr>
<tr>
<td>22</td>
<td>L-Dopa and carbidopa solution for subcutaneous administration/NCT01725802</td>
<td>NeuroDerm Ltd.</td>
<td>Stimulation of dopamine receptors and aromatic L-amino-acid decarboxylase</td>
<td>Subcutaneous</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>23</td>
<td>SCH 900800/NCT01500707</td>
<td>Merck</td>
<td>Adenosine A&lt;sub&gt;2A&lt;/sub&gt; receptor antagonists</td>
<td>Oral</td>
<td>Not yet open for participant recruitment</td>
</tr>
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Table 2. Drugs in phase II clinical trials for the treatment of PD

<table>
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<tr>
<th>No.</th>
<th>Drug name/ClinicalTrial.gov registration</th>
<th>Sponsor/investigator</th>
<th>Mechanism of action</th>
<th>Route of administration</th>
<th>Comments/status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GM1 ganglioside/NCT00037830</td>
<td>Thomas Jefferson University</td>
<td>Antiexcitotoxic property</td>
<td>Subcutaneous</td>
<td>Completed, has results</td>
</tr>
<tr>
<td>2</td>
<td>ADX48621/NCT01336088</td>
<td>Addex Pharma S.A.</td>
<td>Antagonist of mGluR5</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>3</td>
<td>MitoQ/NCT00329056</td>
<td>Antipodean Pharmaceuticals Inc.</td>
<td>Antioxidant</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>4</td>
<td>AFQ056/NCT01092065</td>
<td>Novartis</td>
<td>Antagonist of mGluR5</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>5</td>
<td>BIIB014/NCT00442780</td>
<td>Biogen Idec</td>
<td>Adenosine A2A receptor antagonists</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>6</td>
<td>SR57667B/NCT00220272</td>
<td>Sanofi</td>
<td>Acetylcholinesterase inhibition and impairment of β-amyloid formation</td>
<td>NA</td>
<td>Completed</td>
</tr>
</tbody>
</table>

Harikrishna Reddy/Misra/Medhi
MitoQ
MitoQ is an orally active antioxidant that has the ability to target mitochondrial dysfunction. It was tested in a randomized double-blind trial in which 120 participants with untreated early onset of PD had been enrolled. The participants were randomized to receive one of three treatments: 40 mg of MitoQ tablets, 80 mg of MitoQ tablets or placebo. They were assessed after 1, 2, 3, 6, 9 and 12 months of treatment, and again 28 days after the last dose. The effectiveness of the trial drug was measured by the UPDRS. The safety of the trial drug was monitored via regular participant examinations, blood tests, ECG and collecting information on adverse events. This phase II trial has been completed, and it showed that MitoQ was effective and well tolerated in early-onset PD patients; the drug is currently prepared for phase III studies [17].

AFQ056 (Mavoglurant)
Mavoglurant exerts its effect as an antagonist of mGluR5. A preclinical study conducted on 6 Macaca fascicularis 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys had shown that the administration of AFQ056 1 h prior to the administration of levodopa significantly reduced the dyskinesias and increased the antiparkinsonian effect [18].

The following phase II double-blind placebo-controlled randomized multicenter study was designed to determine whether AFQ056 is safe and effective or whether it can increase the therapeutic window of levodopa in patients whose control of their PD symptoms was limited by the development of dyskinesia induced by use of levodopa. The primary outcome measures changed from baseline to the last-observation-carried-forward endpoint at week 5 [19]. The study has been completed, and AFQ056
showed a clinically relevant and significant antidyskinetic effect without changing the antiparkinsonian effects of dopaminergic therapy.

**BIIB014**

BIIB014 is a novel nondopaminergic drug that selectively antagonizes the adenosine A2A receptor. A phase II study was designed to explore the safety of BIIB014 and how well BIIB014 was tolerated when given at different doses to patients with early-stage PD. A total of 38 patients of both sexes were recruited for this study and randomly distributed in a double-blind fashion to receive either BIIB014 or placebo. The study has been completed, indicating good tolerance and showing dose-dependent, clinically relevant results in these patients [20].

**SR57667B (Paliroden)**

SR57667B acts by inhibiting acetylcholinesterase and by impairment of β-amylloid formation in PD patients. A multicenter randomized parallel-group double-blind phase II study was designed to assess the effect of SR57667B at the dose of 4 mg/day on the progression of parkinsonian symptoms in patients with early PD. The primary outcome measure was the time until the progression of the disability warranted the initiation of levodopa or dopamine agonist treatment, and the secondary outcome measures included assessments of symptoms, activities of daily living and global clinical status. The study has been completed, and SR57667B was shown to cause a significant decline in PD symptoms [21].

**Pioglitazone**

Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor-γ (PPAR-γ) and, to a lesser extent, PPAR-α. A preclinical study on an MPTP mouse model of PD showed that pioglitazone reduces the dopaminergic nerve cell death in the substantia nigra pars compacta and helps in reducing parkinsonian symptoms [22].

The following multicenter double-blind placebo-controlled phase II clinical trial of two doses of oral pioglitazone (15 and 45 mg) was designed for safety, tolerability and futility studies. Subjects who have been on a stable dosage of rasagiline 1 mg/day or selegiline 10 mg/day for at least 8 weeks but no more than 8 months will be randomized to one of the two doses of oral pioglitazone or matching placebo. The study will measure disease progression by the change in total UPDRS score between the baseline visit and 44 weeks. The study is active, even though the recruitment of participants has not started yet [23].

**CEP-1347 (KT7515)**

CEP-1347 (KT7515) is an antiapoptotic drug. It enhances neuronal survival in a variety of nonclinical models and was found to be safe and well tolerated in PD [24].

A randomized double-blind placebo-controlled dose-finding phase II study was conducted in approximately 800 participants to establish its safety and to determine an efficacious dose of CEP-1347 for the treatment of PD. Safety and tolerability were assessed by the number of participants experiencing adverse events. The study was terminated as CEP-1347 did not cause any significant decline in the progression of PD [25].

**Topiramate**

Topiramate is an AMPA glutamate antagonist. A preclinical examination of topiramate in an MPTP-lesioned marmoset model of PD showed a significant decline in LID [26].

A phase II double-blind trial to evaluate the effect of topiramate on LID in PD patients was designed. The patients were randomized to receive tablets of placebo or topiramate in a double-blind crossover design using randomization tables. Following the completion of the first arm of the study and the tapering and washout phases, the patients received topiramate or placebo in a crossover design for the same treatment duration. The dose of topiramate was slowly escalated twice each week as tolerated. If a patient could not tolerate the higher dose, it was reduced to the previously tolerated dose. The study was terminated due to slow recruitment of participants [27].

**Pardoprunox (SLV-308)**

Pardoprunox is a new partial dopamine agonist being developed for PD. A multicenter randomized double-blind pramipexole-controlled parallel-group study of pardoprunox and pramipexole as adjunctive treatment to levodopa was designed.

Approximately 44 patients were randomized at a 3:1 ratio to two possible treatment groups, pardoprunox and pramipexole. The first part of the study was blinded and consisted of a minimum 1-week screening period, a 4-week switch and stabilization period and an 8-week maintenance period. The second part of the study was an open-label pardoprunox treatment with a dose adjustment period of 4 weeks followed by long-term maintenance treatment. There was a high dropout rate of participants due to adverse events (primarily nausea, somnolence and dizziness); thus, the study was terminated [28].
Phase III Trials

Phase III trials are generally designed to assess the effectiveness of a new intervention and, thereby, its value in clinical practice. They are randomized controlled multicenter trials in large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective a drug is in comparison with current ‘gold-standard’ treatment (table 3).

**EMD 1195686 (Safinamide)**

Safinamide is a monoamine oxidase B (MAO-B) inhibitor, reducing the degradation of dopamine, and a glutamate release inhibitor. It also inhibits dopamine reuptake. Additionally, safinamide blocks sodium and calcium channels. Various in vitro models showed that safinamide has neuroprotective and neurorescuing effects [29].

A total of 965 subjects were enrolled in a phase III clinical study to evaluate the long-term safety and tolerability of safinamide in PD patients. All the subjects first received 50 mg/day of safinamide, with an increase in the target dose to 100 mg/day after 14 days of a taper period until the end of the treatment. In case of any intolerance, the daily dose of 100 mg was decreased to 50 mg [30]. The study has been completed, and its results are extremely encouraging, with a significant improvement in the motor symptoms of LID. Based on its efficacy and the reduced side effect profile of safinamide, it can be used as a novel addition to the currently available therapeutic options for PD patients.

**ADS-5102 (Nurelin)**

ADS-5102 (Nurelin) is a proprietary formulation of amantadine in development for the treatment of central nervous system disorders including LID in PD patients. A phase III randomized double-blind placebo-controlled 4-arm parallel-group study was designed to evaluate the tolerability and efficacy of each of three dose levels of ADS-5102 oral capsules, an extended-release formulation of amantadine, dosed once daily for the treatment of LID in subjects with PD. The novel pharmacokinetic profile of ADS-5102 was expected to achieve higher amantadine plasma concentrations during daytime hours, when dyskinesia as well as motor and nonmotor symptoms of PD are most problematic, and low amantadine plasma concentrations overnight, which may reduce the sleep disturbances and occasional vivid dreams.

The study has recently been completed, and the results from the EASED (Extended Release Amantadine Safety and Efficacy Study in Levodopa-Induced Dyskinesia) trial were presented at the 17th International Congress of Parkinson’s Disease and Movement Disorders on June 18, 2013, in Sydney, Australia [31]. ADS-5102 caused a significant reduction in the duration and severity of troublesome dyskinesia among PD patients. The encouraging data from this trial indicate that ADS-5102 has the potential to positively impact the lives of PD patients, and Adamas Pharmaceuticals is moving forward with new drug application activities.

**IPX066**

IPX066 is a dopamine receptor stimulant. A randomized placebo-controlled fixed-dose parallel-arm study of three doses of IPX066 versus placebo was designed to examine its efficacy as compared with placebo in PD. Approximately 350 subjects aged 30 years and older were equally randomized and received one of three doses (145, 245 or 390 mg) of IPX066 or matching placebo orally.

The study duration was approximately 30 weeks for each subject. The trial was completed, with the positive results demonstrating that IPX066 produced a significant improvement in the control of motor symptoms in subjects with advanced PD with potential benefits including a decreased off time (time to reappearance of the symptoms in between doses when levodopa’s effects wear off) and a reduced levodopa dosing frequency [32].

**SCH 420814 (Preladenant)**

SCH 420814 (preladenant) is a drug developed by Schering-Plough which acts as a potent and selective antagonist of adenosine A\textsubscript{2A} receptor. Positive results were reported in a phase II clinical trial in humans with respect to its safety and efficacy [33].

A phase III 40-week active-controlled double-blind double-dummy extension study of preladenant in subjects with moderate-to-severe PD was designed to assess its safety and characterize its efficacy; data were collected for up to 52 weeks from these patients. Due to lack of efficacy and safety as compared with placebo, the study was terminated [34].

**Caffeine**

Caffeine can improve the motor deficits in PD similarly to adenosine A\textsubscript{2A} receptor antagonists such as isradefylline, which reduces off time and dyskinesia associated with standard dopamine replacement treatments.
<table>
<thead>
<tr>
<th>No.</th>
<th>Drug name/ClinicalTrial.gov registration No. and molecular structure</th>
<th>Sponsor/investigator</th>
<th>Mechanism of action</th>
<th>Route of administration</th>
<th>Comments/status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EMD 1195686 Safinamide/NCT00865579</td>
<td>EMD Serono</td>
<td>Inhibits MAO-B and glutamate release and is a dopamine reuptake blocker</td>
<td>Oral</td>
<td>Completed</td>
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<td>2</td>
<td>ADS-5102 (extended release amantadine HCl)/NCT01397422</td>
<td>Adamas Pharmaceuticals Inc.</td>
<td>Stimulation of dopamine receptors</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>3</td>
<td>IPX066/NCT00880620</td>
<td>Impax Laboratories Inc.</td>
<td>Stimulation of dopamine receptors</td>
<td>Oral</td>
<td>Completed</td>
</tr>
<tr>
<td>4</td>
<td>Preladenant and rasagiline/NCT01215227</td>
<td>Merck</td>
<td>Adenosine A2A antagonist</td>
<td>Oral</td>
<td>Terminated due to lack of efficacy vs. placebo</td>
</tr>
<tr>
<td>5</td>
<td>Caffeine/NCT01738178</td>
<td>McGill University Health Center</td>
<td>Nonselective antagonist of adenosine receptors</td>
<td>Oral</td>
<td>Not yet open for recruitment</td>
</tr>
<tr>
<td>6</td>
<td>Zonisamide/NCT01766128</td>
<td>Mazandaran University of Medical Sciences</td>
<td>Blockage of voltage-dependent sodium and T-type calcium channels</td>
<td>Oral</td>
<td>Not yet open for recruitment</td>
</tr>
<tr>
<td>7</td>
<td>E2007/NCT00360308</td>
<td>Eisai Ltd.</td>
<td>Selective noncompetitive AMPA-type glutamate receptor antagonist</td>
<td>Oral</td>
<td>Terminated due to lack of efficacy vs. placebo</td>
</tr>
<tr>
<td>8</td>
<td>Rasagiline/NCT01187888</td>
<td>Ludwig Maximilian University of Munich</td>
<td>MAO-B inhibitor</td>
<td>Oral</td>
<td>Terminated due to lack of eligible patients</td>
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</table>
Recent studies have consistently found that people who do not use caffeine are at higher risk of developing PD. This study was designed to evaluate the efficacy of caffeine 200 mg twice daily versus matching placebo for motor and nonmotor aspects of the disease. It will be performed in three stages. In the first 6-month stage, medications will be held constant to see whether caffeine produces benefits regarding motor symptoms. Then, in a 4-year extension stage, it will be established whether the effects of caffeine persist (or even increase) and whether caffeine helps reduce the doses of other PD medications and/or prevents their side effects. Finally, the trial will be finished with a 6-month stage, in which all the patients will be placed on caffeine treatment; this will allow to assess its use in later disease, but more importantly, it will assess whether early use of caffeine produces long-term changes beyond its immediate effects. This study has not yet started recruitment. It is estimated to be completed by February 2021 [35].

**Zonisamide**

Zonisamide is a sulfonamide anticonvulsant approved for use as an adjunctive therapy in adults with partial-onset seizures and infantile spasm. The exact mechanism of action is not known. An open trial of zonisamide on 9 patients with PD showed positive results by lessening PD symptoms, especially wearing-off [36].

A phase III study was designed to investigate the neuroprotective effect of zonisamide in early PD. A total of 60 patients aged 45–85 years with early PD who have met the study criteria will be enrolled and alternately randomized into two groups, based on their visit date. Demographic data, UPDRS scores, modified Hoehn and Yahr scale scores and modified Schwab and England Activities of Daily Living scale scores will be determined and registered for each patient. The patients of group A will be treated with zonisamide 50 mg/day for 12 months, and the other group with placebo for the same time period. The mentioned scores will be registered every 2 months for both groups by blinded neurologist. Also, regular blood tests will be performed to prevent drug adverse events. This study is not yet open for participant recruitment [37].

**E2007 (Perampanel)**

E2007 (perampanel) is a first-in-class, orally administered, highly selective noncompetitive AMPA-type glutamate receptor antagonist. A study was conducted to establish the efficacy of E2007. Following the completion of the first phase III study in 301 patients, a second phase III study was conducted in 302 patients in North America. The second phase III study was a 20-week double-blind placebo-controlled trial comparing two doses (2 and 4 mg) of perampanel with placebo. Compared with placebo, the results did not show a significant difference in efficacy; thus, the study was terminated [38].

**Rasagiline**

Rasagiline is a MAO-B inhibitor used in PD. Various in vitro and in vivo models of PD showed the beneficial effect of rasagiline in the treatment of PD [39, 40]. A randomized double-blind study was designed to assess the safety and efficacy of the drug in patients aged 50–80 years. The study was terminated due to the unavailability of eligible patients [41].
Discussion

Currently available treatments for PD can effectively control the motor symptoms of the disease in the early stages, but they do not slow or halt the relentless progression of the disease. An explosion of discoveries during the past decade is now providing renewed hope of a therapy. A number of clinical studies have investigated numerous compounds with an enormous variety of mechanisms of action, and they are in different developmental stages (table 4). To make advancements in PD research, experts suggest that a wide array of individuals participate in clinical studies, ranging from subjects with PD (at all stages) to those without PD. The agents in phase I, II and III clinical trials of PD are shown in tables 1, 2, and 3, respectively. The agents that are in development have shown both affirmative and negative results. The recent failures of phase III trials after the positive phase II studies highlight the need for new guidelines in preclinical and clinical phases of drug development, such as the use of validated biomarkers and error management checklists for drug developers that can identify and control sources of error in each phase of a drug study. Another problem in the development of PD therapy is that designing selective compounds without undesirable and potentially toxic side effects is difficult, and reaching the stage of clinical testing can take many years.

As reviewed in this paper, several promising randomized controlled trials are in progress, and an increased collaboration between pharmaceutical companies and basic and clinical researchers has the potential to bring us closer to developing an optimum treatment for PD. Thus, new treatments that slow the underlying disease are desperately needed. It is too soon to predict the exact compound that will be the treatment option for PD.

References


