Management of Parkinson's disease: Current and future pharmacotherapy

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\begin{abstract}
Parkinson's disease (PD) is chronic progressive neurodegenerative disorder characterized by profound loss of dopaminergic neurons in the nigrostriatal pathway. It is recognized by the cardinal clinical features of bradykinesia, rigidity, tremor and postural instability. Current therapeutic options are primarily dopamine replacement strategies that only provide symptomatic improvement without affecting progressive neuronal loss. These treatments often fail to provide sustained clinical benefit and most patients develop motor fluctuations and dyskinesias as the disease progresses. Additionally, non-motor symptoms such as autonomic disturbances, sensory alterations, olfactory dysfunction, mood disorders, sleep disturbances and cognitive impairment cause considerable functional disability in these patients and these features often fail to respond to standard dopaminergic treatments. This mini review outlines the current pharmacotherapeutic options for PD and highlights the emerging experimental therapies in various phases of clinical development.
\end{abstract}

\section{Introduction}

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and affects more than 5 million cases worldwide and nearly 1 million patients in US alone (Olanow et al., 2009). Although higher prevalence rates have been reported for Caucasians in Europe and North America, intermediate rates for Asians in China and Japan, and the lowest rates for Blacks in Africa, more recent studies have indicated similar prevalence rates in China and the US (Marras and Tanner, 2004). The disease usually begins in the fifth or sixth decade and the frequency increases with advancing age. Smaller proportions of patients belonging to younger age groups (less than 40 years) have also been recognized and they...
have been classified as having early onset PD. With the global phenomenon of population ageing affecting all regions and countries at various levels of development, the number of PD cases is likely to grow significantly. As per the estimates of Dorsey et al. (2007) the prevalence of PD in world’s most populous nations will at least double by 2030. The annual economic impact of PD in the United States has been estimated to exceed $14.4 billion. In 2010, patients with PD incurred medical expenses worth approximately $14 billion and the indirect costs were conservatively estimated to be $6.3 billion. This economic burden is expected to grow substantially given the estimated doubling of affected populations over the next few decades (Kowal et al., 2013).

The hallmark features of pathology of PD include progressive loss of dopaminergic neurons in substantia niagra pars compacta, significantly reduced levels of dopamine in the striatum and the presence of cytoplasmic proteinaceous inclusions known as Lewy bodies (Savitt et al., 2006). Degeneration of dopamine containing neurons leads to an imbalance between the striato-pallidal and pallido-thalamic output pathways, which is responsible for the major motor symptoms of the disease (Albin et al., 1989). Parkinson’s disease is believed to result from a complex interaction between environmental factors and genetic predisposition in individuals. PD is often familial in younger patients with early onset disease while majority of the remaining cases are considered to be sporadic. The causes of neuronal loss in PD have remained a subject of intensive research. It is believed that mitochondrial dysfunction, oxidative injury, altered protein handling, and inflammatory changes in the brain of these patients lead to cellular dysfunction and death through apoptosis or autophagy (Dorsey et al., 2007).

1.1. Clinical features of Parkinson’s disease

The signs and symptoms of PD can be divided into motor and non-motor categories based on their ability to affect movements of the body. Among them the motor symptoms have been the hallmark of the disease and include four cardinal features viz. bradykinesia, muscular rigidity, resting tremor and an impairment of postural balance leading to disturbances of gait and falling. Initially the symptoms are mild and may be confined to one side of the body. However, over the course of disease the symptoms become increasingly impairing and involve the other side as well. The disease generally involves a chronic slowly progressive course, being extremely variable in individual patients. Additional motor features seen in these patients include freezing of gait, dysphagia, speech disturbances and masked facies. The non-motor features generally precede the motor symptoms and include autonomic disturbances including orthostatic hypotension, sensory alterations, loss of smell, mood disorders esp. depression, sleep disturbances, cognitive impairment and dementia (Goetz, 2002; WHO, 2014).

2. Current pharmacotherapy for Parkinson’s disease

The treatment options for patients with PD include non-pharmacological measures, pharmacotherapy and surgical therapy. The present review will focus on pharmacological treatments available for these patients.

The discovery of dopaminergic deficit in patients with PD led to pharmacologic attempts to restore dopaminergic activity using levodopa (L-DOPA, L-3,4-dihydroyphenylalanine) and dopamine receptor agonists. These agents benefit many of the motor features of the disorder. An alternative and complementary approach has been to restore the balance between cholinergic and dopaminergic inputs on the basal ganglia by employing anticholinergic drugs. Levodopa, a precursor of dopamine, remains the single most effective agent in the treatment of Parkinson’s disease. The drug is usually administered with carbidopa, a peripheral decarboxylase inhibitor which blocks peripheral conversion of levodopa to dopamine thus allowing dose reduction and also minimizing its peripheral adverse effects. Principal adverse effects of levodopa therapy are nausea, motor complications including ‘wearing off’ phenomenon, dyskinesias and on–off effects, confusion, hallucinations, orthostatic hypotension and sleep disturbances (Schapira, 2005). Dopamine receptor agonists most commonly employed in PD patients include ropinirole, pramipexole and rotigotine. These drugs have theoretical advantages over levodopa in terms of not requiring enzymatic activation, having longer duration of actions and causing fewer adverse effects since they offer receptor selectivity unlike levodopa (Alonso Cánovas et al., 2014). These drugs are useful as the initial choice for dopaminergic therapy as they delay the need for levodopa therapy and are associated with lower incidence of motor fluctuations and dyskinesias. They are also useful as an add-on therapy to levodopa in patients who develop motor complications and allow for a reduction in levodopa doses. Adverse effect profile of dopamine receptor agonists includes hallucinations, confusion, nausea, postural hypotension, somnolence and an increased incidence of impulse control disorders including pathological gambling, shopping, eating and hypersexuality (Constantinescu, 2008). Apomorphine, another dopamine agonist is primarily used as a rescue therapy for the temporary relief of off-periods of akinnesia in patients with fluctuating response to dopaminergic therapy. Selective monoamine oxidase B (MAO-B) like selegiline and rasagiline retard the breakdown of dopamine in the striatum, thereby benefitting the PD patients. Efficacy of these agents is modest and they can be used as monotherapy in early PD (Teo and Ho, 2013). Additionally these agents can be used as adjucnts to reduce the ‘off time’ in patients with declining response to levodopa (Teo and Ho, 2013). Catechol-O-Methyltransferase (COMT) inhibitors block peripheral degradation of levodopa leading to its increased half life and enhanced central bioavailability. Between the two available COMT inhibitors, Tolcapone and Entacapone, the latter is preferred since it has not been associated with hepatotoxicity (Antonini et al., 2008). They are indicated as an adjunctive treatment in patients who develop response fluctuations to levodopa/carbidopa therapy. Anticholinergic agents like trihexyphenidyl and benztrapine have been historically used for the treatment of PD before the introduction of levodopa (Brocks, 1999). The principal therapeutic effect of these agents is on tremor and they are indicated only in the treatment of early PD or as an adjunct to dopamine replacement therapy. Their troublesome adverse effects like constipation, urinary retention, worsening of angle closure glaucoma and cognitive impairment considerably limit their usefulness in the elderly patients (Schapira, 2005). Amantadine is an anti-influenza agent which was serendipitously found to be useful in PD. Its efficacy is modest and it improves PD symptoms in mildly affected patients with early disease and reduces motor fluctuations in patients with advanced disease (Hubsher et al., 2012). Amantadine modulates the release of dopamine from dopamine terminals in the striatum, possesses anticholinergic properties and blocks glutamate NMDA receptors (Reis et al., 2006).

The non-motor symptoms in PD patient are often poorly recognized and their treatment largely remains inadequate (Chaudhuri et al., 2006). An evidence based medicine (EBM) review on the treatment of PD with a focus on non-motor symptoms identified only four treatments as efficacious: pramipexole for depressive symptoms, clonazapine for psychosis, rivastigmine for dementia, and botulinum toxin for sialorrhea associated with PD (Seppi et al., 2011). Although lacking good quality evidence, treatment options for other non-motor symptoms are as follows: midodrine, fludrocortisone for orthostatic hypotension; trosropium chloride for urinary disturbances; polyethylene glycol for constipation; sildenafil for erectile dysfunction; modafinil, methylphenidate for daytime somnolence; clonazepam for rapid eye movement (REM) sleep behaviour disorder and levodopa/carbidopa for periodic limb movements of sleep (Oertel et al., 2006).
et al., 2010; Zesiewicz et al., 2010). Several of these currently used interventions lack a robust evidence base and require further research to clarify their role in the management of non-motor symptoms of PD.

3. Future treatments for PD

Accurate diagnosis of Parkinson’s disease still relies largely on clinical acumen due to lack of definitive diagnostic laboratory tests. Early PD has a heterogeneous presentation and an insidious onset which makes clinical diagnosis prone to errors. A valid diagnostic biomarker for PD will be critical in improving patient outcomes on several accounts: improving diagnostic accuracy especially in early stages, enabling use of neuroprotective strategies and better defined diagnostic subtypes for clinical research and subsequent development of personalized therapeutic approaches (Pfeiffer et al., 2012). Several potential cerebrospinal fluid (CSF) biomarkers including total tau and phosphotau proteins, beta-amyloid 1–42 levels, neurofilament (NFL) protein, α-synuclein and CSF urate levels are currently the subject of intense research (Jiménez-Jiménez et al., 2014; Magdalinou et al., 2014). Further well designed large scale, multi-centric, prospective studies with long term follow-up are needed to establish validated and objective biomarkers for PD.

Newer treatments aimed at addressing the current unmet needs of PD patients are being investigated and are at various stages of clinical development. None of the currently available therapies possess disease modifying effects and provide only symptomatic relief for the motor features of the disease. Newer therapies should provide continuous and sustained motor benefit, be devoid of disabling dyskinesias, treat significant co-morbidities and should retard or reverse the progression of PD (Shook and Jackson, 2011).

3.1. Adenosine A2A receptor antagonists

Adenosine receptor antagonists represent a novel class of drugs currently under evaluation for the treatment of PD patients. In the striatum, adenosine A2A receptors co-localize with dopamine D2 receptors (Aoyama et al., 2000). A2A and D2 receptors have opposing effects on cAMP production in cells; such that activation of A2A receptors inhibits dopamine D2 receptor signaling. Conversely adenosine A2A receptor antagonists have been shown to enhance D2 dependent signaling (Shook and Jackson, 2011). These drugs provide benefit by inhibiting the overactive striatopallidal pathway (Hauser and Schwarzschild, 2005). In preclinical models of PD, A2A receptor antagonists have demonstrated significant beneficial effects.

Several of these compounds including istradefylline, preladenant, vipadenant, ST-1535, and SYN-115 have progressed to clinical development. Among them, istradefylline, a xanthine based A2A receptor antagonist, is in the most advanced stages of development. This agent has demonstrated efficacy as the reason for non-approval. However, the phase III trials of preladenant in PD patients have been disappointing and the drug has failed to demonstrate significant efficacy over placebo. Consequently the sponsor, Merck has discontinued the further clinical development of preladenant (Tadena, 2013).

Another orally administered selective blocker of adenosine A2A receptors undergoing clinical evaluation is tozadenant (SYN115). In a phase 2b, multicenter, double-blind trial, patients receiving levodopa with at least 2.5 h of daily OFF time were randomized to receive tozadenant in doses of 60, 120, 180 or 240 mg twice daily, or matching placebo. Out of 420 patients randomized, 337 completed treatment with tozadenant over 12 weeks. A significant reduction in mean placebo corrected change from baseline in OFF time was observed in 120 mg and 180 mg twice daily dose groups of tozadenant (Hauser et al., 2014). In addition, significant improvements were noted in the mean placebo corrected scores on the Unified Parkinson’s Disease Rating Scale (UPDRS) part III in patients belonging to 120 mg and 180 mg groups of tozadenant. The most frequent adverse events in the tozadenant treated patients were dyskinesias, nausea, dizziness, constipation, worsening of PD symptoms, insomnia and falls (Biotie Presents Tozadenant, 2013). Further phase 3 trials of tozadenant are proposed to be initiated in 2015.

3.2. Safinamide

Safinamide is an α-aminoamide that has both dopaminergic and nondopaminergic mechanisms of action in PD patients. It is a highly selective and reversible inhibitor of MAO-B as well as a blocker of sodium and N-type calcium channels. While the former action reduces dopamine breakdown the latter action results in inhibition of glutamate release. Safinamide has been shown to reduce levodopa induced dyskinesias in preclinical models as well as in human studies (Onofri et al., 2008).

A recently published Phase III, multicenter, double-blind, placebo-controlled study evaluated the efficacy and safety of safinamide as an add-on therapy to levodopa in PD patients with dyskinesias. Study participants were randomized to receive safinamide in daily doses of 50 mg, 100 mg or matching placebo for 24 weeks. The primary outcome measure of the study was total ‘on’ time with no or non-troublesome dyskinesia. At the end of study week 24, mean increase in total on time with no or non-troublesome dyskinesia was 1.36 h for safinamide doses of 100 mg/day, 1.37 h for safinamide 50 mg/day, and 0.97 h for placebo treated patients. Significant improvements were
also demonstrated for off time, UPDRS Part III, and CGI-C in safinamide treatment groups versus placebo. There were no significant differences for treatment emergent adverse events or adverse events leading to treatment discontinuation (Borgohain et al., 2014). Results of two randomized, double-blind, placebo controlled Phase III studies of safinamide, Safinamide treatment as add-on to Levodopa in idiopathic Parkinson’s disease with motor fluctuations (SETTLE) and Safinamide add-on to dopamine agonist for early idiopathic Parkinson’s disease with motor fluctuations (MOTION) were presented at the 65th Annual Meeting of the American Academy of Neurology in 2013 (Safinamide Phase III MOTION and SETTLE study, 2013). The SETTLE study was performed in PD patients with mid to late stage idiopathic disease who were receiving stable doses of levodopa and other PD drugs. Treatment with safinamide significantly improved ON time without troublesome dyskinesias as compared to placebo by $0.96 \pm 0.21$ h ($P < 0.01$) in the intention to treat population. In contrast, MOTION study was performed in early PD patients receiving stable doses of a single dopamine agonist. Safinamide treated patients had significantly improved motor function as assessed by UPDRS III total scores. The drug was well tolerated and the most frequent adverse events reported by the study patients were nausea, dizziness, somnolence, headache and back pain. There were no significant differences in the incidence of these adverse effects among study groups.

The sponsors, Newron and partner Zambon have filed the marketing authorization application for safinamide with the

### Table 1

<table>
<thead>
<tr>
<th>Study (trial identifier)</th>
<th>Design</th>
<th>Intervention</th>
<th>No. of patients</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Reference</th>
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<tbody>
<tr>
<td>6002-009 (NCT00955526)</td>
<td>12 week, multicenter, double-blind, randomized, placebo-controlled study in Japanese patients</td>
<td>Istradefylline (adjunct to levodopa) in PD patients with motor complications</td>
<td>Placebo group: 126 subjects; Istradefylline 20 mg group: 123 subjects, 40 mg group: 124 subjects</td>
<td>Both doses of istradefylline significantly reduced daily OFF time compared with placebo ($P = 0.003$)</td>
<td>Istradefylline was well tolerated and most common adverse event was dyskinesia.</td>
<td>Mizuno and Kondo, 2013</td>
</tr>
<tr>
<td>6002-US-013 (NCT00199407)</td>
<td>12 week, multicenter, double-blind, randomized, placebo-controlled study in US patients</td>
<td>Istradefylline (adjunct to levodopa) in PD patients with motor complications</td>
<td>Placebo group: 115 subjects; Istradefylline 20 mg group: 116 subjects</td>
<td>At the end of 12 weeks, istradefylline treated patients had significant placebo-corrected reductions in daily OFF time from baseline 4.6% ($P = 0.03$) and 0.7 h ($P = 0.03$).</td>
<td>Dyskinesia, lightheadedness, tremor, constipation, and weight loss were commonly reported in istradefylline group.</td>
<td>Hauser et al., 2008</td>
</tr>
<tr>
<td>6002-US-018 (NCT00199420)</td>
<td>12 week, multicenter, double-blind, randomized, placebo-controlled study in US patients</td>
<td>Istradefylline (adjunct to levodopa) in PD patients with motor complications</td>
<td>Placebo group: 146 subjects; Istradefylline 10 mg group: 149 subjects, 20 mg group: 144 subjects, 40 mg group: 145 subjects</td>
<td>At the end of 12 weeks, the amount and percentage of OFF time did not differ significantly between istradefylline and placebo groups. In the 40 mg dose group, there was a modest but significant improvement from baseline in UPDRS motor scores as compared to placebo. (2.9 vs. 0.8; $P &lt; 0.05$)</td>
<td>Istradefylline was well tolerated and the most commonly reported adverse event was dyskinesia.</td>
<td>Pourcher et al., 2012</td>
</tr>
<tr>
<td>6002-US-007 (NCT00955045 Phase II/III)</td>
<td>52 week, multicenter, open label study with flexible dosing scheme in US/Canada patients</td>
<td>Istradefylline (adjunct to levodopa/carbidopa) in PD patients with motor complications</td>
<td>Study included 496 patients who had already participated in one of three 12-week, double-blind, placebo-controlled studies. Group I: 315 subjects, Group II: 181 subjects.</td>
<td>Group I patients: Improvements in daily awake OFF time seen with 12 week istradefylline therapy were sustained over the 52 week trial period. Group II patients: demonstrated improvement from baseline in the total hours of daily awake OFF time at each visit ($-0.53$ to $-1.19$ h) consistent with earlier studies.</td>
<td>Treatment emergent adverse events were reported in 86% of subjects, most common being dyskinesia/aggravated dyskinesia, dizziness and nausea (24%, 17% and 14% respectively). Occasional AEs were seen in 10% patients, they were treatment related in only 8 patients. Most frequent was aggravated PD.</td>
<td>Factor et al., 2010</td>
</tr>
</tbody>
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European Medicines Agency (EMA). The marketing application for US is expected to be filed soon (Newron and Zambon file, 2013).

3.3. Newer formulations of levodopa

3.3.1. Duodopa – levodopa/carbidopa intraduodenal gel

Duodopa is a combination of 20 mg/ml Levodopa and 5 mg/ml Carbidopa applied in form of a gel into the duodenum. It is indicated for the treatment of advanced PD with severe motor fluctuations and dyskinesia where response to conventional therapy has remained unsatisfactory. Duodopa has received orphan status in US, EU, Japan and Australia (Nyholm, 2012) and is currently approved for use in Europe, Canada and Australia. Clinically, duodopa is introduced following an initial trial using a nasoduodenal catheter system. If the drug is well tolerated and demonstrates a positive response, a percutaneous endoscopic gastrostomy (PEG) is performed for delivery via a portable pump and a duodenal catheter. A large majority of studies support the clinical efficacy of Duodopa in relieving the symptoms of advanced PD and improving quality of life in comparison with conventional approaches (Antonini et al., 2008; Eggert et al., 2008; Nyholm, 2012). Additionally an improvement in the non-motor symptoms including cardiovascular, sleep/fatigue, attention, memory, pain, gastrointestinal, urological and cognitive disturbances has been demonstrated (Honig et al., 2009). Adverse events are mainly related to infusion system e.g. dislocation, obstruction and breakage of the duodenal catheter or surgical procedure including peritonitis and local inflammation.

3.3.2. DM-1992

DM-1992 is an investigational gastric retentive, extended-release formulation of levodopa/carbidopa being developed for patients with advanced PD suffering from motor fluctuations. In late 2012, the results of a Phase 2 study of DM-1992 were announced. This open label, randomized, crossover study enrolled 34 patients with advanced PD and motor fluctuations. Study participants received either DM-1992 twice daily or immediate-release (IR) levodopa/carbidopa as needed for 6 days. This period was followed by a 3-day patient self-assessment period. The mean baseline “off” time during waking hours was 5.4 h/day (32.5%), as compared to 4.5 h (27.2%) with DM-1992 and 5.5 h (33.5%) for the active comparator. This reduction in percent “off” time reported with DM-1992 patient self-assessment period relative to the immediate release levodopa/carbidopa was statistically significant ($P=0.047$) (Depomed Reports Top Line Data, 2012). The investigational agent well tolerated and no serious adverse events were reported. DM-1992 is currently poised to enter phase 3 clinical development.

3.3.3. IPX066

IPX066 is a newly developed oral formulation of levodopa/carbidopa that contains both an immediate-release and a sustained-release levodopa component. The formulation is designed to achieve rapid absorption and onset of clinical effect similar to immediate release levodopa/carbidopa, and to provide more sustained therapeutic levels of levodopa and longer duration of clinical benefit thus minimizing the development of dyskinesias and motor fluctuations. IPX066 has undergone clinical evaluation in three phase 3 studies: Efficacy and safety of IPX066, a New Carbidopa–Levodopa (CD–LD) Extended-Release Formulation, in levodopa-naive Early Parkinson’s Disease (APEX-PD), Comparison of IPX066, a Novel Carbidopa–Levodopa (CD–LD) Extended-Release Formulation, and CD–LD-Entacapone (CLE) in Advanced Parkinson’s Disease (ASCEND-PD) and Double-blind, Controlled Trial of IPX066, a Novel Carbidopa–Levodopa Extended-Release Formulation, in Advanced Parkinson’s Disease (ADVANCE-PD). While the first study evaluated its role in early PD, the other two studies involved investigation in advanced PD patients.

The APEX-PD study was a randomized, fixed-dose, placebo-controlled trial that evaluated the clinical safety and efficacy of IPX066 in patients with early PD. The study enrolled 381 subjects in North America and Europe, who were randomized to one of four groups for 30 weeks: IPX066 145 mg TDS; IPX066 245 mg TDS; IPX066 390 mg TDS or placebo. The primary outcome measure was mean change from baseline in UPDRS Part II and III scores at week 30. All three doses of IPX066 showed significant improvement as compared to placebo ($P<0.0001$). Secondary outcome measures, Clinician Global Impression of change and Patient Global Impression of change were also statistically improved in the three IPX066 groups compared with placebo (Pahwa et al., 2011).

ADVANCE-PD was a randomized, double blinded, double-dummy study conducted at 68 centers in North America and Europe. This study enrolled 471 PD patients who initially underwent a two stage open label period, first 3 weeks of open label immediate release carbidopa/levodopa dose optimization followed by 6 week period of dose conversion to IPX066. Subsequently, 393 patients were randomly allocated (1:1) to 13 weeks of double-blind treatment with IPX066 or IR carbidopa/levodopa plus matched placebos. Mean off time was reduced by a greater extent for patients treated with IPX066 as compared to those treated with IR carbidopa–levodopa. An additional 1.2 h reduction in the off time was observed in experimental treatment group ($P<0.0001$). Mean on time without troublesome dyskinesia was increased in the IPX066 treated patients as compared to IR carbidopa–levodopa group ($P<0.001$), but mean increases in on-time with troublesome dyskinesia did not differ significantly between study groups. Patients on IPX066 demonstrated a significant reduction in UPDRS scores and an improvement in Patient and Clinical Global Impression (PGI, CGI) scales (Hauser et al., 2013). The most common adverse effects reported by patients receiving IPX066 were insomnia, nausea, falls, dizziness and dyskinesia.

Food and Drug Administration approval of IPX066 has been withheld subject to agency’s satisfactory re-inspection of one of the manufacturing facility owned by the sponsor (FDA Issues Complete Response, 2013).

3.3.4. XP21279

XP21279, a novel levodopa prodrug, is a sustained-release formulation that is actively transported by high capacity nutrient pathways located throughout the lower gastrointestinal tract. This unique mechanism addresses the pharmacokinetic limitations of IR levodopa/carbidopa which can be transported only across a short segment of the small intestine. XP21279 can be absorbed through the colon as well, allowing maintenance of therapeutic levodopa concentrations in the plasma. This is believed to result in lowering of dosing frequency while decreasing the OFF time without causing disabling dyskinesias (LeWitt et al., 2014). A recent double blind study compared treatment with IR carbidopa/levodopa and XP21279–carbidopa in PD patients with motor fluctuations. XP21279–carbidopa administered thrice daily produced a reduction in off time similar to that of carbidopa–levodopa administered four or five times daily. The novel drug combination also significantly reduced the variability in levodopa concentrations compared with immediate release formulation (LeWitt et al., 2014).

3.4. Newer treatments for levodopa induced dyskinesia

Amantadine, by virtue of its antiglutamatergic properties through non-competitive antagonism of NMDA receptors has shown efficacy in preclinical as well as clinical studies investigating its role in levodopa induced dyskinesia (LID) (Stoof et al., 1992). These findings lend support to hypothesis linking alterations of glutamatergic system to pathophysiology of LID (Calon et al., 2003). ADS-5102, an investigation extended release formulation of amantadine, is being...
investigated in patients with LIDs. A randomized, double blind, placebo controlled, phase II/III trial of ADS-5102 was carried out in 83 PD subjects aged 30–85 years. Patients were randomized to receive either 260 mg, 340 mg, or 420 mg of ADS-5102 or placebo once at night for 8 weeks. The 340 mg and 420 mg dose levels of ADS-5102 significantly reduced LID as measured by the change in Unified Dyskinesia Rating Scale (UDysRS) total score compared to placebo. While the lowest tested dose of ADS-5102 reduced UDysRS scores, it failed to achieve statistical significance at 3 weeks (P = 0.159) (Adamas Pharmaceuticals Presents, 2013). The adverse effects experienced by study participants were consistent with the known safety profile of amantadine.

Metabotropic glutamate receptors are found abundantly in basal ganglia and play a key role in regulating neuronal excitability and motor control (Conn et al., 2005). As far as treatment options for LID is concerned, metabotropic glutamate receptor 5 (mGlur5) is the one that has generated considerable interest and progressed furthest in terms of clinical development. Activation of mGlur5 potentiates NMDA receptor currents in the striatum and subthalamic nuclei. Consequently, antagonism of mGlur5 attenuates NMDA receptor overactivity and resultant overexcitability, thus proving beneficial in preclinical and clinical studies of LIDs (Gasparini et al., 2013; Johnson et al., 2009). Dipraglurant (ADX48621) is a selective antagonist of mGlur5 and is currently undergoing clinical evaluation for LID. A phase IIa, double blind, placebo controlled study of dipraglurant enrolled 76 subjects with moderate or severe PD associated LID. The subjects received 50 mg doses of active treatment from day 1 to day 14 followed by 100 mg from day 14 until day 28. Dipraglurant met the primary study objective i.e demonstration of a good safety and tolerability profile. Exploratory efficacy was the secondary objective. Patients treated with dipraglurant demonstrated statistically significant reduction in LID severity with both study doses (Addex Reports Positive, 2012). Development of another mGlur5 receptor antagonist, mavoglurant (AFQ056) was discontinued by the sponsor following its failure to demonstrate efficacy in two Phase II trials (UK Medicines Information, 2013).

Although noradrenergic receptors have been localized within the striatum, their exact role in modulating basal ganglia transmission is still not clearly defined (Fox, 2013). Experimental studies have suggested a role of alpha 2A/2C antagonists in amelioration of levodopa induced dyskinesias (Barnum et al., 2012; Henry et al., 1999). One such agent fipamezole has been evaluated in a double-blind, randomized, placebo-controlled, dose-escalating 28-day study in PD patients with LID. The trial was conducted in US (n = 115) as well as in India (n = 64). Fipamezole in doses of 90 mg was found to be efficacious only in the US subpopulation and the investigators ascribed this discrepancy to inhomogeneity between U.S. and Indian study populations. The new drug was well tolerated and produced mild, transient blood pressure elevation (LeWitt et al., 2012).

Recent data from experimental studies indicate a complex role of serotonergic pathways in genesis of LIDs. Levodopa induced dyskinesias in MPTP lesioned primate model of PD as well as in clinical studies have been shown to respond to agents that possess 5HT1A receptor agonist activity like buspirone, clozapine and mirtazapine (Irvani and Jenner, 2011). Piclozotan is an investigational serotonin (5-HT1A) receptor agonist proposed to be useful for PD-LID. While most of currently available 5-HT1A agonists are also dopamine antagonists, piclozotan has no such activity and in fact it possesses agonistic activity at dopamine D3 receptors. Consequently it may have a unique ability to improve both LID as well as reduce OFF time in PD patients (Piclozotan (SUN N4057), n.d.). Effects of piclozotan were evaluated in rat model of advanced PD. Study animals, 6-OHDA lesioned rats, were treated with levodopa for 8–9 weeks. Based on the results of rotational behavior and forelimb hyperkinesia in fifth week, the rats were allocated to further three treatment groups that received either saline or piclozotan (in two dosing rates: 0.018 and 0.036 mg/kg/h) through continuous subcutaneous infusion using an osmotic pump (Tani et al., 2010). Piclozotan reduced levodopa-induced forelimb hyperkinesia by 55% (0.018 mg/kg/h group) and 69% (0.036 mg/kg/h group) at 1 h as compared to the control group. Piclozotan (0.036 mg/kg/h) also significantly prolonged the duration of rotational behaviour by 26% vs. the controls as well as diminished the raised striatal levodopa derived extracellular dopamine levels.

4. Conclusions

The current therapeutic options available for the management of PD suffer from several limitations. They offer only symptomatic relief and none of the available treatments are capable of slowing or stopping disease progression. After several years of treatment, complications in the form of motor fluctuations and dyskinesias are inevitable. Currently there are no approved therapies for management of these dyskinesias. Deep brain stimulation (DBS), a form of stereotactic surgery is an adjunct option for treatment of PD as well as for overcoming the limitations imposed by long term levodopa therapy. The advantages of DBS include its reversibility and allowing adjustment of stimulation parameters in response to alterations in patient’s condition. The main disadvantages are the risk of infection and prohibitive costs of procedure as well as device maintenance (Munhoz et al., 2014; Panikar and Kishore, 2003). Several investigational drugs aimed at addressing the unmet need of PD management are currently being evaluated in various stages of clinical development. Some of these treatments aim at providing sustained antiparkinsonian effect while others are targeted to improve levodopa induced dyskinesias. Drugs acting through non-dopaminergic mechanisms can be useful in non-motor manifestations of PD. In addition, gene therapies based on delivery of glatamic acid decarboxylase (GAD) (LeWitt et al., 2011), tyrosine hydroxylase (TH), aromatic amino acid decarboxylase (AADC), GTP-cyclohydroxylase-1 (GCH-1) (Muramatsu et al., 2002; Shen et al., 2000; Sun et al., 2003) and neurotrophic factor genes (Gasmii et al., 2007; Kordower et al., 2000) and stem cell therapies (Drouin-Ouellet and Barker, 2014) are a key current focus of research.

References


