EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 3
160-169
Year: 2018

EMERGING TARGETS FOR THE TREATMENT OF PARKINSON'S DISEASE- AN OVERVIEW

[1]*Dr. Jyoti Sharma, [2]Dr. Pulkit Kaushal and [3]Dr. Jyoti Kaushal

[1]Senior Resident, Department of Pharmacology, PGIMS, Rohtak, Haryana.
[2]International Training Fellow, (RCPsych MTI) Learning Disability Services, East Field Clinic, Westway, Scarborough, UK. YO113EG.
[3]Professor, Department of Pharmacology, PGIMS, Rohtak, Haryana.

***Corresponding Author: Dr. Jyoti Sharma**
Senior Resident, Department of Pharmacology, PGIMS, Rohtak, Haryana.

Article Received on 26/12/2017 **Article Revised on 16/01/2018** **Article Accepted on 06/02/2018**

ABSTRACT
Parkinson's disease is the second most common neurodegenerative disease. There is a loss of nigrostriatal neurons leading to motor deficits such as rigidity, tremors, bradykinesia. The exact cause of parkinson's disease (PD) is unknown in most of the cases. The most commonly used treatment of Parkinson disease is dopamine replacement therapy. The commonly used drugs are levodopa, COMT inhibitors, MAO inhibitors etc. Drugs like levodopa which is the mainstay of PD therapy, loses efficacy over a period of time and causes dyskinesias and behavioural problems & ultimately development of both motor and non-motor problems. Moreover, available therapies do not prevent neuron degeneration and provide only symptomatic relief. The new PD treatment should tackle the two unresolved problems, one is moving from symptom alleviating to disease modification and the second is to reduce the growing prevalence of non-motor disease symptoms such as loss of balance, autonomic dysfunction and cognitive impairment. The newer emerging therapies for the treatment of Parkinson's disease are Neuroprotective agents like Coenzyme Q10, Adenosine receptor antagonists, Neurotrophic factors, Glutamate antagonists, Antioxidants, PDE inhibitors, Monoclonal antibodies, Safinamide and Gene therapy. Several obstacles in developing therapies for Parkinson's exist, which include: a lack of a clear understanding about the biological processes leading to neuronal loss and a lack of a biomarker for determining progression and severity of the disease. Hence, despite availability of numerous effective drugs which provide short term relief; still research is going on to develop promising drugs and newer strategies to provide long term benefit by modifying the disease process.

KEYWORDS: Parkinson's disease, Neurotrophic, Neuroprotective.

INTRODUCTION
Parkinson disease is the second most common neurodegenerative disease. It was first described as "Shaking Palsy" of unknown origin by James Parkinson in 1917. It is a clinical syndrome characterized by lesions in basal ganglia, predominantly in substantia nigra. There is a loss of nigrostriatal neurons leading to motor deficits such as rigidity, tremors, bradykinesia.[1] However there is increasing evidence that olfactory dysfunction, constipation, sleep abnormalities, cardiac sympathetic denervation, depression and pain may antedate the onset of motor symptoms of PD.[2] As there is disease progression, hypophonia, drooling of saliva and impairment of postural reflexes may develop. It begins usually between ages of 40 and 70 years, but the appearance of pathological changes may appear as early as three decades before the appearance of clinical signs. The most common pathological hallmark of Parkinson's disease is presence of Lewy bodies. These are misfolded protein aggregates of α-synuclein protein that are immunoreactive inclusions made up of a number of neurofilament proteins together with proteins responsible for proteolysis which includes ubiquitin, a heat shock protein which plays an important role in targeting other proteins for breakdown.[3]

It is estimated that 6.3 million people suffer from PD worldwide. The World Health Organization gives an "estimated crude prevalence" (the total number of existent cases each year, old and new) of 160 per 100,000, and an estimated incidence (the number of new cases each year) of 16-19 per 100,000.[4,5]

The overall prevalence and incidence of Parkinson's disease in India is low. Age-specific prevalence rates for PD increase with advancing age and are as high as

247/100000 above age of 60.[6] The Parsi community in Mumbai has the world's highest incidences of PD where it affects about 328 out of every 100,000 people despite living in a country, India, which has the world's lowest incidence of PD (70 out of 100,000).[7]

The exact cause of parkinson's disease is unknown in most of the cases i.e. idiopathic parkinsonism. However, its etiology may be multifactorial; from hereditary predisposition to environmental factors such as pesticides and ageing. Several genes are implicated in the familial form of PD. So far, five genes have been identified that are SNCA, PARK2, PARK7, PINK1 and LRRK2. Several other chromosome regions and the genes GBA (glucosidase beta acid), SNCAIP (synuclein alpha interacting protein) and UCHL1 (ubiquitin carboxyl -terminal esterase L1) may also be linked to Parkinson's disease. The role of aging in the pathogenesis of PD is suggested by its usual occurrence in late middle age, and by marked increases in its prevalence at older ages.[8] The possible role of environmental factors has been addressed by a number of epidemiologic studies that have been well reviewed by others.[9] Many of these studies have shown associations between rural residence, well-water drinking, or herbicide/pesticide exposure and the risk of developing PD.[10] But the consumption of coffee, tobacco and NSAIDS has shown to reduce the risk of PD.[11] About 7% of with Parkinsonism have developed their symptoms following treatment with particular medications & this is called as drug induced parkinsonism. It is caused by the drugs which block the action of dopamine (dopamine antagonists). The major cause of drug induced parkinsonism is antipsychotic (neuroleptic) drugs. The newer generation of antipsychotic drugs i.e. atypical antipsychotics have lower incidence of causing it.Some other drugs which can lead to drug induced parkinsonism are older anti-hypertensives (reserpine, methyl DOPA), antiemetics (prochlorperazine), gastrointestinal prokinetics (metoclopramide), calcium channel blockers, some modern atypical antipsychotics & antiepileptics that impair dopamine function directly or indirectly.[12] The average annual incidence rate of drug-induced parkinsonism is 3.3 per 100,000 person-years, is higher in women, and is increased with older age. Drug induced parkinsonism is the fifth-most common type of parkinsonism overall.[13]

Limitations of current therapy & Need for new drugs

The most commonly used treatment of Parkinson disease is dopamine replacement therapy. The most common drug prescribed is levodopa. Other drugs include COMT inhibitors, dopamine receptor agonists, MAO-B inhibitors. However, over the time these medications become less efficient. Drugs like levodopa which is the mainstay of PD therapy loses efficacy and causes dyskinesias and behavioural problems in patients, hence people with PD may ultimately develop both motor and nonmotor problems which results in marked reduction in quality of life.

At present, there are no proven neuroprotective therapies, i.e. available therapies do not prevent neuron degeneration. The current therapies which are available provide only symptomatic relief. Moreover, these medications in the long run cause motor complications and behavioural problems. The ultimate aim for the treatment of PD is not just symptomatic control but ultimately to halt the disease progression.

The new PD treatment should tackle the two unresolved problems, one is moving from symptom alleviating to disease modifying therapies and the second is to reduce the growing prevalence of non-motor disease symptoms such as loss of balance, autonomic dysfunction and cognitive impairment.

Data Search Methodology: This included manual search as well as electronic search of the databases of publications and cross references. Electronic search included Pubmed, Google, etc. Electronic search of cross references yielded other relevant materials. Terminologies used for search in electronic databases included Parkinson disease, emerging targets, pipeline drugs, novel targets, newer drugs, clinical trials, recent advances etc.

Emerging Targets

Neuroprotective Therapy

Coenzyme Q10 (CoQ 10) - It has shown important role as neuroprotectant in patients of PD. It leads to production of ATP within the inner membrane of mitochondria. It is responsible for the transfer of an electron between complex I/II and complex III of respiratory electron transport chain thereby generating ATP molecules. Apart from this, it also plays an important role as a free radical scavenger, protecting the lipid membranes of mitochondria and also generates α-tocopherol from its oxidized state as α-tocopheroxyl. A phase III trial was done in which effects were observed in three groups (placebo, 1200 mg/d of CoQ10, 2400 mg/d of CoQ10) for a period of 16 months or until a disability requiring dopaminergic treatment. Coenzyme Q10 was found to be safe and well tolerated, but no evidence of clinical benefit was shown.[14]

Vitamin E Analogue- Vatiquinone (Epi-743) - It is a new drug based on vitamin E. It has also shown neuroprotective role in patients of Parkinson's disease. It also helps in improving the mitochondrial dysfunction also. It is orally bioavailable and is a part of para-benzoquinone class of drugs. It readily crosses into CNS and works by targeting NADPH quinine oxidoreductase 1 which helps in energy generation in mitochondria as well as counteracts the redox stress. Currently it is in phase II trials for the treatment of PD.[15]

Calcium Channel Antagonist- Isradipine- Isradipine is a dihydropyridine calcium channel antagonist. It was found to be neuroprotective in animal models of Parkinson's disease (PD) because of the selective vulnerability of substantia nigra pars compacta neurons that preferentially express L-type calcium channels. It had undergone a dose finding, phase 2, randomized, double-blind, parallel group trial (Safety, Tolerability and Efficacy Assessment of Dynacirc CR in Parkinson Disease [STEADY-PD]) in which subjects with early PD not requiring dopaminergic therapy (dopamine agonists or levodopa) were taken and were randomized as 1:1:1:1 to 5, 10, or 20 mg of isradipine CR or matching placebo daily. The tolerability of isradipine was found to be dose-dependent. The maximum tolerable dose of isradipine was 10mg. Dose-dependent peripheral edema and dizziness were the most common side effects reported. But no difference in efficacy between the treatment arms was found.[16] To evaluate the effect of isradipine on the progression of PD disability in untreated individuals, another placebo-controlled trialhas been designedcurrently.[17]

GM608- It is an endogenous human embryonic stage neural regulatory and signalling peptide. It is an oligopeptide with a sequence identical to one of the active sites of human Motoneuronotrophic Factor.It is currently undergoing phase 2 trial where it is being evaluated as a neuroprotective agent in Parkinson disease patients.[18]

Cannabinoids- Use of cannabinoids as a new therapeutic treatment seems to be a promising therapy for PD. The endocannabinoid system is highly expressed in the neural circuit of basal ganglia wherein it bidirectionally interacts with dopaminergic, glutamatergic and GAB Aergic signaling systems. Due to their ability to suppress excitotoxicity, glial activationand oxidative injury, cannabinoid agonists such as WIN-55,212-2 have been shown experimentally as neuroprotective agents in PD. Efficacy against bradykinesia and levodopa-induced dyskinesia in PD are the additional benefits provided by cannabinoid related compounds including CE-178253, oleoylethanolamide, nabilone and HU-210.[19]

Δ9-tetrahydrocannabinol has shown neuroprotective effects in animal and cell culture models of PD through activation of the nuclear receptor peroxisomal proliferator-activated receptor (PPAR) γ.[20]

Pioglitazone - Pioglitazone has shown neuroprotective effects in mouse models of Parkinson's disease. The proposed mechanism of action is through activation of the PPAR, induction of inducible nitric oxide synthase and nitric oxide mediated toxicity.[21,22] Pioglitazone was assessed by a phase 2, multicenter, double blind, RCT in people on a stable dose of an MAO-B inhibitor randomized to either pioglitazone or placebo for 44 weeks (NCT01280123). The primary outcome measure was change in the total UPDRS score between baseline and 44 weeks.[18] However, it was found that pioglitazone at the doses studied here is unlikely to modify progression in early Parkinson's disease.[23]

Adenosine Receptor Antagonists

Adenosine A2A receptors are expressed in basal ganglia in large numbers and many of these receptors have been observed to be co-located on dopamine receptors. Symptoms of Parkinson's disease can be improved by either activating the dopamine receptors or alternatively blocking the adenosine A2 receptors. Drugs acting on these receptors when used in combination with dopaminergic drugs (e.g. levodopa and agonists) may facilitate a reduction in the dosage of dopamine and a coincident reduction in side effects.

Istradefylline is an adenosine A2A receptor antagonist that has been tried in patients suffering from Parkinson's disease. The results of these studies have revealed a mild beneficial effect on wearing off and on motor fluctuations. In a phase 3 trial, istradefylline 20 mg/day reduced OFF time compared with placebo by 0.7 hours.[24] Istradefylline was also evaluated as monotherapy in early PD. In a 12-week double-blind study of 176 patients, istradefylline 40 mg/day did not provide a significant improvement in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores compared with placebo.[25] Istradefylline, has the longest half-life out of the available A2A receptor antagonists. Istradefylline easily crosses the blood-brain barrier and shows a high affinity to the human A2A receptor. It has been considered safe and well tolerated in clinical trials.[26] However**,** Istradefylline did not achieve FDA approval in the United States, but has been approved for use in Japan.

Preladenant is also an adenosine A2A receptor antagonist. Earlier studies have shown promising effects on PD related "off" periods. On the basis of a positive phase-2b dose-response, adjunctive therapy study, a phase-3 development program was initiated. No evidence supporting the efficacy of preladenant as adjunctive therapy was observed in two phase-3 trials.[27] Similarly, in another phase 3 trial,no evidence supporting the efficacy of preladenant as monotherapy was observed.[28]

Tozadenant- A phase 2b placebo-controlled, dose-finding clinical trial of tozadenant in levodopa-treated patients with Parkinson's disease who had motor fluctuations (at least 2·5 h off-time per day) was done. Eligible patients were randomly assigned to receive tozadenant 60, 120, 180, or 240 mg or matching placebo twice daily for 12 weeks. Tozadenant at 120 or 180 mg twice daily was well tolerated and was effective at reducing off-time.[29]

Vipadenant (BIIB014) and **ST-1535** are two A2A receptor compounds that remain under investigation in animal models for Parkinson's and other diseases.

Some other compounds known to block the adenosine A2A receptor and have been used in various animal and human studies are ATL-444, MSX-3, SCH-58261, 412, 348, 442,416, VER-6623, 6947, 7835, ZM-241,385.

Neurotrophic Factors/ Nerve Growth Factors

Neurotrophic factors (NTFs) are a class of molecules that influence a number of neuronal functions, including cell survival and axonal growth. One such trophic factor is glial cell-derived neurotrophic factor (GDNF), a member of the transforming growth factor beta superfamily. GDNF was first identified on the basis of its ability to support the development of embryonic dopaminergic neurons.[30]

It has since been shown to protect and restore mature dopaminergic neurons in the substantia nigra in many different lesion models. GDNF may be useful for treating PD patients after it has shown neuroprotective and neurorestorative effects in MPTP- or 6-OHDA-induced animal models of PD. Unfortunately, GDNF delivery in humans by intracerebroventricular injection or intra-striatal infusion has proven ineffective and other methods of GDNF delivery are being explored.[31] Direct injections, or infusion of GDNF using minipumps into the striatum, midbrain, or ventricles provided encouraging results in toxin-based rodent and primate models of PD Based on the preclinical results, a randomized double-blind clinical study was initiated using intracerebroventricular GDNF infusion. The results were disappointing, with no clinical improvement and adverse effects, including anorexia.[32] Thus, finding a safe and effective approach to exploit the neuroprotective effects of GDNF remains an active area of research in developing a treatment to inhibit the progression of PD.

Antiinflammatory Agents

Minocycline- Minocycline, a tetracycline derivative is a caspase inhibitor and also inhibits the inducible nitric oxide synthase which is important for apoptotic cell death. Moreover, Minocycline has been shown to block microglial activation of 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonism animal models and protect against nigrostriatal dopaminergic neurodegeneration. Efficacy and tolerability of Minocycline Vs Creatine was tested in a randomized, double-blind, Phase II clinical trial foraltering the course of early PD and it was observed that neither drug could be rejected as futile. Tolerability was 91% in the creatine group and 77% in the minocycline group.[33]

GPI-1485- An investigational new drug that belongs to a class of small molecule compounds called neuroimmunophilinligands. In preclinical experiments, it has shown to repair and regenerate damaged nerves without affecting normal, healthy nerves. GPI-1485 has been studied in PD patients in a 6-month clinical trial where the primary end point was negative but the drug was well tolerated.[34] In an animal study done by Radad et al, mice were rendered Parkinsonian with the application of rotenone and treated with minocycline. They concluded that minocycline had neuroprotective potential against the progressive loss of tyrosine hydroxylase immunoreactive neurons induced by long-term rotenone toxicity in primary dopaminergic cultures.[35]

Glutamate Antagonists

Enhanced glutamatergic activity increases the activity of dopamine D1-mediated direct pathway, which could lead to the generation of dyskinesias. Also, glutamate receptors are responsible for synaptic plasticity. In Parkinsonism and dyskinesias, abnormal synaptic plasticity may contribute to the mechanism of symptom generation. Hence, reducing excessive glutamate activity may reduce either PD motor symptoms or reduce dyskinesias.

The NMDA receptor antagonist, amantadine, is a well-established therapy for dyskinesias but patients may experience side-effects like hallucinations, livedo reticularis, and edema, thereby limiting its use.

Mavoglurant is a selective metabotropic glutamate receptor 5 antagonist. It has shown a significant antidyskinetic effect in 2 small phase II randomized clinical trials.[36] Also, findings from a larger dose-finding study of 197 patients with PD and dyskinesias provided further evidence of anti-dyskinetic benefit without worsening of parkinsonism.[37] However, it also has the potential to induce side-effects due to actions on glutamate receptors outside the basal ganglia, for example, ataxia, hallucinations, and confusion were observed. In other two phase 2 clinical trials which were designed to evaluate efficacy and safety of immediate-release (study 1) and modified-release (study 2) mavoglurant formulations in PD l-dopa-induced dyskinesia. Primary outcome was antidyskinetic efficacy, as measured by change from baseline to week 12 in modified Abnormal Involuntary Movement Scale total score. Both studies failed to meet the primary objective of demonstrating improvement of dyskinesia with mavoglurant treatment.[38] Another mGlu5 NAM, **Dipraglurant** (ADX48261), has similarly been under investigation as a putative antidyskinetic agent.

Alpha 2 Antagonists

Alpha2 antagonists in PD have not focused on their antiparkinsonian potential, but rather on their potential to reduce dyskinesias. Within the striatum, are α2 adrenergic receptors act to modulate GABA and dopamine release.α2 antagonists have been shown to reduce Levodopa induced dyskinesia. Currently, the selective $\alpha_{2A/2C}$ receptor antagonist fipamezole is being studied for Levodopa induced dyskinesia. In a phase II study conducted in the USA and India, fipamezole failed to show a statistically significant reduction in dyskinesias.[39]

Phosphodiesterase Inhibitor

AVE8112 is a PDE4 inhibitor has shown promising procognitive activity in preclinical models. It was thought to improve cognitive aspects of Parkinson's disease. Its phase 1 clinical study was expected tocomplete in June 2015. However, this study was terminated because it failed to meet the primary endpoint.

Free Radical Scavenger (Antioxidant)

AZD3241-Myeloperoxidase [MPO] is a reactive oxygen species generating enzyme and is expressed by microglia. The novel compound AZD3241 is a selective and irreversible inhibitor of myeloperoxidase. The hypothesized mechanism of action of AZD3241 involves reduction of oxidative stress leading to reduction of sustained neuroinflammation. In a phase 2a randomized placebo controlled multicentre positron emission tomography study to examine the effect of 8 weeks treatment with AZD3241 on microglia in patients with Parkinson's disease, Parkinson patients received either AZD3241 600 mg orally twice a day or placebo for 8 weeks. The binding of (11) C-PBR28 to the microglia marker 18 kDa translocator protein, was examined using positron emission tomography at baseline, 4 weeks and 8 weeks. The outcome measure was the total distribution volume, estimated with the invasive Logan graphical analysis. In the AD3241 treatment group (n = 18) the total distribution volume of (11)C-PBR28 binding to translocator protein was significantly reduced compared to baseline both at 4 and 8 weeks. AZD3241 was safe and well tolerated.[40]

Potassium Channel Blocker

Dalfampiridine is a potassium channel blocker. It is mainly used as a research tool in characterizing the subtypes of the potassium channels. It has been currently appoved for use in multiple sclerosis for improvement in walking as 10 mg tablet. In Parkinson's disease (PD), Gait dysfunction and postural instability represent a major therapeutic challenge. There is an emerging evidence that multiple neurotransmitter deficits may contribute to mobility impairment in PD. Dalfampiridine is a potent neurotransmitter modulator. The proposed mechanisms that may facilitate its favorable effect on gait in Parkinson's disease include 1) neurotransmitter release (dopamine, glutamate, acetylcholine and noradrenaline) 2) modulation of neuronal network oscillations and 3) increased cortical excitation.[41]

In a randomized double blind trial, subjects with Parkinson's disease were randomly assigned to two groups, one group received Dalfampridine first for 4 weeks, followed by 2 weeks break and then 4 weeks placebo while the second group first received placebo and then Dalfampridine. The primary outcomes were change in the stride length and velocity, measured by movement analysis system. Secondary outcome measures included: United Parkinson Disease Rating Scale (UPDRS part III) and Freezing of Gait Questionnaire (FOGQ). Improvement in the motor UPDRS and FOGQ after 4 weeks was seen.[42] It was also evaluated in Parkinson disease related gait dysfunction. D-ER was well tolerated in PD patients, however it did not show significant benefit for gait impairment.[43] The most frequent side effects observed were dizziness, nausea and balance problems.[42]

Miscellaneous

R-Phenserine- It is a (-)-physostigmine analogue. It has multiple mechanisms of action; viz Acetylcholinesterase inhibitors, Alpha-synuclein inhibitor, Amyloid beta-protein precursor inhibitor, Tau protein inhibitor. Cholinesterase inhibitors can clinically slow cognitive decline in the later stages of PD etiology similar to their widespread use in Alzheimer's disease (AD).[44] Currently its Phase-II trial is ongoing for early Alzheimer's and Parkinson's disease in USA.[45]

Safinamide- It is an α-aminoamide derivative with a combined dopaminergic and non-dopaminergic mode of action. It is a unique molecule with novel mechanisms of action. The non-dopaminergic actions include monoamine oxidase-B (MAO-B) inhibition, sodium channel blockade and calcium channel modulation, thus inhibiting the excessive glutamate release. The sodium channel inhibition is concentration- and state-dependent, and does not influence physiological activity, avoiding depressant effects on the central nervous system (CNS). It does not affect L-type calcium channels, so no effects on blood pressure and heart rate. In phase III clinical trials with safinamide, as add-on therapy to a dopamine agonist (DA) and to levodopa (LD) in early and advanced stage PD, respectively, demonstrated an improvement of the motor symptoms.[46] Safinamide, at a 100 mg/day dose, improves fluctuations and control motor symptoms and motor complications in the short term and helps in maintaining the benefits in the long term (up to 2 years). On long-term, treatment with safinamide has shown to improve dyskinesia. Safinamide reduces daily 'off' time and early morning akinesia, improving quality of life and functionality and significantly improves in the long-term motor functions as evaluated by UPDRS III score. It is well tolerated with a favourable side-effect profile and is easy to use: once-daily dose. Overall, preclinical and clinical data with safinamide support the view that it may serve as a valuable choice for add-on therapy to DAs and LD in the early and the mid-to-late stage disease, respectively.[47] The US Food Drug Administration (FDA) has approved safinamide tablets as adjunctive treatment for patients with Parkinson's disease who experience "off" episodes while taking levodopa/carbidopa in March 2017.

Novel MAO-B Inhibitors- HT3951- is a reversible inhibitor of monoamine oxidase B (MAO-B). MAO-B is an outer mitochondrial membrane flavoenzyme involved in catabolism of neurotransmitters and exogenous amines. It is currently in phase 1 clinical study. **HT1067-**

The HT-1067 clinical program was terminated in Phase 1 studies because of unacceptable safety concerns.

Novel COMT Inhibitor- Opicapone- Opicapone is a novel third generation long acting catechol-O-methyltransferase (COMT) inhibitorthat markedly increases systemic and central Levodopa bioavailability.[48] It is approved as an adjunctive treatment to levodopa (L-Dopa)/dopa-decarboxylase inhibitor (DDCI) therapy in adults with Parkinson's disease (PD) and end-of-dose motor fluctuations who cannot be stabilized on those combinations.[49] Its proprieties make it adequate for a once-a-day oral dose regimen. It has proved to reduce the off-time and to increase the on-time without troublesome dyskinesias in PD patients with motor fluctuations. The reported adverse events suggest an overall safe and well-tolerated profile. The most common adverse events were dyskinesia, and there were no issues of concern for hepatotoxicity, severe diarrhoea or chromaturia.[50]

Monoclonal Antibody- PRX002

PRX002 is a monoclonal antibody that targets unhealthy or pathogenic forms of alpha-synuclein protein. In its pathogenic form, this soluble protein will aggregate and clump into deposits in the brain. It interferes with neuronal functioning including dopamine production. A first-in-human, randomized, double-blind, placebo-controlled, phase 1 study assessed the impact of PRX002 administered to 40 healthy participants in 5 ascending-dose cohorts (n = 8/cohort) in which participants were randomly assigned to receive a single intravenous infusion of study drug (0.3, 1, 3, 10, or 30 mg/kg; n = 6/cohort) or placebo (n = 2/cohort). PRX002 demonstrated favorable safety, tolerability, and pharmacokinetic profiles at all doses tested, with no immunogenicity. No serious adverse events, discontinuations as a result of adverse events, or dose-limiting toxicities were reported.[51]

Gene Therapy

Currently, four divergent gene therapy approaches have been developed to treat the major symptoms of Parkinson's disease. Most gene therapy approaches directly target the terminals of degenerating nigrostriatal neurons for gene delievery.

AAV/AADC This approach uses adeno-associated viral vector serotype 2 (AAV2) to deliver aromatic amino acid decarboxylase (AADC) in the putamen. AADC is an enzyme that converts levodopa to dopamine in the neurons. Hence, by making this conversion more efficient, optimal therapeutic benefit with lower levodopa doses can be achieved thereby avoiding the treatment-related side effects. This procedure has been through a successful phase 1 trialand is currently in phase 2.[52]

AAV2/GAD (adeno-associated viral vector serotype 2/glutamic acid decarboxylase) This approach uses AAV2 to deliver glutamic acid decarboxylase (GAD) to the subthalamic nucleus.[53] GAD catalyzes the synthesis of gamma-aminobutyric acid, the major inhibitory neurotransmitter in the CNS, potentially providing lost inhibitory control in the basal ganglion motor system, thus restoring appropriate transynaptic balance. The underlying idea is that by delivering this enzyme willincrease inhibitory tone. A single controlled phase II trial with AAV/GAD was initiated involving a total of 45 patients. Two efficacy parameters (both clinical impressions rating scale) showed statistical significance while 21 other efficacy endpoints showed no difference between the groups leading to discontinuation of AAV/GAD program.[54]

Lenti-AADC/TH/GTP-CH1- The third approach [55], which is in phase 1 trials, involves a tricistronic vector encoding tyrosine hydroxylase (TH), AADC and GTP cyclohydrolase hydroxylase—the last one of which is an enzyme necessary for tetrahydrobiopterin synthesis, an essential cofactor for AADC. An uncontrolled, open label, dose escalation study was conducted in 15 PD patients. Three ascending doses were tested, involving a 5-fold dose range. The safety profile was favourable as most ADRs were mild.[56]

AAV/NRTN-Lastly, AAV2-mediated delivery of neurturin, a functional analog of glial cell derived neurotrophic factor (GDNF) aims to provide neuroprotective benefits in addition to symptomatic improvement. Neurturin provides robust neuroprotection and upregulation of dopamine function in a variety of rodent[57] and has completed a successful phase 1 clinical trial.[58] Also, two phase 2 trials have been conducted to date. The efficacy data for both the trials were mixed and disappointing as neither met the primary end points within the prescribed time frame.[56]

Vaccine

Vaccines work by helping our immune systems recognise and get rid of foreign invaders. In the brain cells that are lost in Parkinson's there is a build-up of a protein called 'alpha synuclein'. Clumps of this protein called 'Lewy bodies' appear in affected brain cells and then spread throughout the brain. Vaccines for Parkinson's work by prompting the body to recognise alpha-synuclein as a foreign invader, this should trigger an immune response to clear some of the protein.

PD01A vaccine was evaluated in a Phase 1 trial and it demonstrated good safety and tolerability, as well as the ability to induce an immune response and achieve functional stabilization. The vaccine aims to modify the disease rather than just ameliorate the severe motor symptoms of the disease. Patients were given PD01A vaccine subcutaneously in four vaccinations, either in doses of 15 micrograms or 75 micrograms. Their progress was also evaluated against a control group of patients receiving standard symptomatic medication. The study found that fifty percent of the patients who had

been administered the vaccine developed antibodies specifically responding to the presence of alpha-synuclein. Not only did these antibodies exist in the brain, they were also found in serum samples of the cerebrospinal fluid of vaccinated patients.[59] Another vaccine PD03A is currently in Phase 1 clinical trial.[60] PD03A is a synthetically produced aSyn-mimicking peptide — or protein component — that targets the aSyn protein. The 52-week Phase 1 trial evaluated the immune response, safety and tolerability of AFFITOPE PD03A in patients with early Parkinson's disease. triggered a solid immune response against the alpha-Synuclein (aSyn) protein associated with the disease, according to a Phase 1 clinical trial.[61]

Table 1: Summary.

Emerging targets	Drugs	Mechanism of action	Phase
Neuroprotective therapy	Coenzyme Q 10	ATP generation	III
	Vatiquinone	Targets NADPH quinine oxidoreductase 1	II
	Isradipine	Calcium channel antagonist	II
	GM 608	Neural regulatory and signalling peptide	II
	Cannabinoids	PPAR- γ activation	Preclinical
	Pioglitazone	NOS & PPAR activation	II
Adenosine receptor antagonists	Istradefylline	A2A receptor antagonist	Approved in Japan
Neurotrophic factors	GDNF	Protect mature dopaminergic neurons	Preclinical
Antiinflammatory	Minocycline	caspase inhibitor	II
Glutamate antagonists	Mavoglurant	metabotropic glutamate receptor 5 antagonist	II
Antioxidant	AZD3241	Myeloperoxidase inhibitor	II
Potassium channel blocker	Dalfampiridine	K+ channel blocker	III
Miscellaneous	Safinamide	MAO-B inhibition, Na+ channel blockade & Ca+2 channel modulation	Approved in March 2017
	Monoclonal antibody-PRX002	Targets □-synuclein	Phase I completed
	Gene therapy	AAV/AADC, AAV2/GAD, Lenti-AADC/TH/GTP-CH1, AAV/NRTN	Various phases of development
	Vaccine- PD01A		Phase I completed

Drugs for Drug Induced Parkinsonism

Drug induced parkinsonism is generally treated by stoppage of the offending drugs. Patients can be switched on to atypical antipsychotics that have a lower incidence of extrapyramidal symptoms. Centrally acting anticholinergics (benztropine, trihexyphenidyl) or amantadine may be used in individuals under or over 60 years of age, respectively. However, because of number of side effects of these drugs work is being done to find more options for treatment of drug induced parkinsonism. PD01A vaccine was evaluated in a Phase 1 trial and it demonstrated good safety and tolerability, as well as the ability to induce an immune response and achieve functional stabilization. The vaccine aims to modify the disease rather than just ameliorate the severe motor symptoms of the disease. Patients were given PD01A vaccine subcutaneously in four vaccinations, either in doses of 15 micrograms or 75 micrograms. Their progress was also evaluated against a control group of patients receiving standard symptomatic medication. The study found that fifty percent of the patients who had been administered the vaccine developed antibodies specifically responding to the presence of alpha-synuclein. Not only did these antibodies exist in the brain, they were also found in serum samples of the cerebrospinal fluid of vaccinated patients.[59] Another vaccine PD03A is currently in Phase 1 clinical trial.[60] PD03A is a synthetically produced aSyn-mimicking peptide — or protein component — that targets the aSyn protein. The 52-week Phase 1 trial evaluated the immune response, safety and tolerability of AFFITOPE PD03A in patients with early Parkinson's disease triggered a solid immune response against the alpha-Synuclein (aSyn) protein associated with the disease, according to a Phase 1 clinical trial.[61] DRUGS FOR DRUG INDUCED PARKINSONISM Drug induced parkinsonism is generally treated by stoppage of the offending drugs. Patients can be switched on to atypical antipsychotics that have a lower incidence of extrapyramidal symptoms. Centrally acting anticholinergics (benztropine, trihexyphenidyl) or amantadine may be used in individuals under or over 60 years of age, respectively. However, because of number of side effects of these drugs work is being done to find more options for treatment of drug induced parkinsonism.

In an animal study done by Naeem S et al, it was shown that NSAIDS i.e. ibuprofen and celecoxib showed neuroprotective and memory enhancing effect against Chlorpromazine induced Parkinson's model.[62] In another animal study, it was shown that Nigella sativa-oil (NS) (black cumin seeds)-a traditional medicine used for the seizure treatment in eastern country-may reduce the haloperidol (HAL)-induced extrapyramidal symptoms

(EPS)-like behavior in rats. After combined treatment with HAL (1 mg/kg) & NS (0.2 ml/rat), rats displayed a significant decreased EPS-like behavior including movement disorders and oral dyskinesia as compared to controls.[63] Preclinical studies suggest a role of 5-hydroxytryptamine (serotonin)-1A and 2A/2C receptors in the modulation of dopaminergic neurotransmission in schizophrenia patients. Adjunctive treatment with antioxidants such as vitamin E, red rice bran oil, and curcumin in the early phases of schizophrenia, may prevent additional oxidative injury and thus improve and prevent further possible worsening of related neurological and behavioral deficits.[64]

In another study done by Itokawa et al, it was demonstrated that high-dose pyridoxamine add-on treatment can be effective for a subpopulation of schizophrenia patients with enhanced carbonyl stress. Moreover, reduction of greater than 20% in the assessment scale of drug-induced parkinsonism occurred. Further randomized, placebo-controlled trials with careful monitoring are required to validate the efficacy of high-dose pyridoxamine for these patients.[65]

CONCLUSION

PD is a progressive neurodegenerative disorder manifested by a broad spectrum of motor and non-motor features. The management of Parkinson's disease has improved considerably in the past two decades because of introduction of new therapies and better use of old ones. Most of the affected individuals now have a relatively good quality of life due to improvement in most of the signs and symptoms. Several obstacles in developing therapies for Parkinson's exist, which include: a lack of a clear understanding about the biological processes leading to neuronal loss in Parkinson's, inadequate translational research, and a lack of a biomarker for determining progression and severity of the disease. So, there is current need to develop good neuroprotective agents and disease modifying drugs. Recent developments have led to significant advances in Parkinson's disease treatment. Despite availability of numerous effective drugs which provide short term relief; still research is going to develop promising drugs and newer strategies which can provide long term benefit by modifying the disease process.

REFERENCES

1. Olanow CW, Tatton WG. Etiology and pathogenesis of Parkinson's disease. Annu Rev Neurosci, 1999; 22: 123-44.
2. O'Sullivan SS, Williams DR, Gallagher DA, Massey LA, Silveira-Moriyama L, Lees AJ. Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study. Mov Disord, 2008: 23: 101-6.
3. Davie CA. A review of Parkinson's disease. British Medical Bulletin, 2008; 86: 109–27.
4. Gupta BM, Bala A. Parkinson's disease in India: An analysis of publications output during 2002-2011. Int J Nutr Pharmacol Neurol Dis, 2013; 3: 254-62.
5. Incidence, prevalence and cost of Parkinson's disease. [Internet] 2011. [cited Apr]. Available from: http://www.eng.ircminternational.com.
6. Gourie-Devi M. Epidemiology of neurological disorders in India: Review of background, prevalence and incidence of epilepsy, stroke, Parkinson's disease and tremors. Neurol India, 2014; 62: 588-98.
7. Tags, Chris. Who gets Parkinson's disease? [Internet], 2012. [cited 2012 July 16]. Available from: http://www.pdring.com.
8. Mayeux R, Denaro J, Hemenegildo N, Marder K, Tang MX, Cote LJ, *et al*. A population-based investigation of Parkinson's disease with and without dementia. Arch Neurol, 1992; 49: 492–7.
9. Langston JW, Koller WC, Giron LT. Etiology of Parkinson's disease. In: Olanow CW, Lieberman AN, editors. The scientific basis for the treatment of Parkinson's disease. Park Ridge, NJ: Parthenon, 1992; 33–58.
10. Tanner CM. Epidemiology of Parkinson's disease. Neurol Clin, 1992; 10: 317–29.
11. Blanchet P, Kivenko V. Drug induced parkinsonism: diagnosis and management. Journal of Parkinsonism and Restless Legs Syndrome, 2016; 6: 83-91.
12. Powers KM, Kay DM, Factor SA, Zabetian CP, Higgins DS, Samii A, *et al*. Combined effects of smoking, coffee and NSAIDS on PD risk. Mov Disord, 2008; 23: 88-95.
13. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Mielke MM, Rocca WA. Incidence and time trends of drug-induced parkinsonism: A 30-year population-based study. Mov Disord, 2017; 32: 227-34.
14. Beal MF, Oakes D, Shoulson I, Henchcliffe C, Galpern WR, Haas R, *et al*. A randomized clinical trial of high-dosage coenzyme Q10 in early Parkinson disease: no evidence of benefit. JAMA Neurol, 2014; 71: 543-52.
15. http://adisinsight.springer.com/drugs/800033222.
16. Parkinson study group. Phase II safety, tolerability, and dose escalation study of isradipine as a potential disease modifying intervention in early parkinson's disease.(STEADY-PD). Mov Disord, 2013; 28: 1823.
17. Biglan KM, Oakes D, Lang AE, Hauser RA, Hodgeman K, Greco B, *et al*. A novel design of a Phase III trial of isradipine in early Parkinson disease (STEADY-PD III). Ann Clin Transl Neurol, 2017; 4: 360–8.
18. Goetz CG, Pal G. Initial management of Parkinson's disease. BMJ, 2014; 349: 6258.
19. More SV, Choi DK. Promising cannabinoid-based therapies for Parkinson's disease: motor symptoms to neuroprotection. Mol. Neurodegener, 2015; 10: 17.

20. Carroll CB, Zeissler ML, Hanemann CO, Zajicek JP. Δ^9-tetrahydrocannabinol (Δ^9-THC) exerts a direct neuroprotective effect in a human cell culture model of Parkinson's disease. Neuropathol Appl Neurobiol, 2012; 38: 535–47.
21. Breidert T, Callebert J, Heneka MT, Landreth G, Launay JM, Hirsch EC. Protective action of the peroxisome proliferator-activated receptorgamma agonist pioglitazone in a mouse model of Parkinson's disease. J Neurochem, 2002; 82: 615-24.
22. Dehmer T, Heneka MT, Sastre M, Dichgans J, Schulz JB. Protection by pioglitazone in the MPTP model of Parkinson's disease correlates with I kappa B alpha induction and block of NF kappa B and iNOS activation. J Neurochem, 2004; 88: 494-501.
23. NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators. Pioglitazone in early Parkinson's disease: a phase 2, multicentre, double-blind, randomised trial. Lancet Neurol, 2015; 14: 795–803.
24. Hauser RA, Shulman LM, Trugman JM, Roberts JW, Mori A, Ballerini R, *et al*. Istradefylline 6002-US-013 Study Group. Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. Mov Disord, 2008; 23: 2177–85.
25. Fernandez HH, Greeley DR, Zweig RM, Wojcieszek J, Mori A, Sussman NM. 6002-US-051 Study Group. Istradefylline as monotherapy for Parkinson disease: results of the 6002-US-051 trial. Parkinsonism Relat Disord, 2010; 16: 16–20.
26. Müller T. The safety of istradefylline for the treatment of Parkinson's disease. Expert Opin Drug Saf, 2015; 14: 769-75.
27. Hauser R, Stocchi F, Rascol O, Huyck S, Ha X, Capece R, *et al*. Phase-3 Clinical Trials of Adjunctive Therapy with Preladenant, an Adenosine 2a Antagonist, in Patients with Parkinson's Disease. Neurology, 2014; 82: 7.087.
28. Stocchi F, Rascol O, Hauser RA, Huyck S, Tzontcheva A, Capece R, *et al*. Randomized trial of preladenant, given as monotherapy, in patients with early Parkinson disease. Neurology, 2017; 88: 2198-206.
29. Hauser RA, Olanow CW, Kieburtz KD, Docu-Axelerad EP, Lew M, Kozyolkin O, *et al*. Tozadenant (SYN115) in patients with Parkinson's disease who have motor fluctuations on levodopa: a phase 2b, double-blind, randomised trial. The Lancet, 2014; 13: 767-76.
30. Lin LF, Doherty DH, Lile JD, Bektesh S, Collins F. GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. Science, 1993; 260: 1130-2.
31. Peterson AL, Nutt JG. Treatment of Parkinson's disease with trophic factors. Neurotherapeutics, 2008; 5: 270-80.
32. Coune PG, Schneider BL, Aebischer P. Parkinson's Disease: Gene Therapies. Cold Spring Harb Perspect Med, 2012; 2: a009431.
33. NINDS NET-PD Investigators. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. Neurology, 2006; 66: 664-71.
34. NINDS NET-PD Investigators A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. Neurology, 2007; 68: 20-8.
35. Radad K, Moldzio R, Rausch WD. Minocycline protects dopaminergic neurons against long term rotenone toxicity. Can J Neurol Sci, 2010; 37: 81–5.
36. Berg D, Godau J, Trenkwalder C, Eggert K, Csoti I, Storch A, *et al*. AFQ056 treatment of levodopa-induced dyskinesias: results of 2 randomized controlled trials. Mov Disord, 2011; 26: 1243–50.
37. Stocchi F, Rascol O, Destee A, Hattori N, Hauser RA, Lang AE, *et al*. AFQ056 in Parkinson patients with levodopa-induced dyskinesias: 13-week, randomized, dose-finding study. Mov Disord, 2013; 28: 1838–46.
38. Trenkwalder C, Stocchi F, Poewe W, Dronamraju N, Kenney C, Shah A, *et al*. Mavoglurant in Parkinson's patients with l-Dopa-induced dyskinesias: Two randomized phase 2 studies. Mov Disord, 2016; 31: 1054-8.
39. Lewitt PA, Hauser RA, Lu M, Nicholas AP, Weiner W, Coppard N, *et al*. Randomized clinical trial of fipamezole for dyskinesia in Parkinson disease (FJORD study). Neurology, 2012; 79: 163-9.
40. Jucaite A, Svenningsson P, Rinne JO, Cselényi Z, Varnäs K, Johnström P, *et al*. Effect of the myeloperoxidase inhibitor AZD3241 on microglia: a PET study in Parkinson's disease. Brain, 2015; 138: 2687-700.
41. Luca CC, Singer C. Can 4-aminopyridine modulate dysfunctional gait networks in Parkinson's disease? Parkinsonism Relat Disord, 2013; 19: 777-82.
42. Luca C , Nadayil G, Dong C, Field-Fote E, Singer C. Dalfampridine extended release in patients with Parkinson's disease related gait dysfunction: A randomized double blind trial. Neurology, 2015; 84: 6.049.
43. Luca CC, Nadayil G, Dong C, Nahab FB, Field-Fote E, Singer C. Dalfampridine in Parkinson's disease related gait dysfunction: A randomized double blind trial. J Neurol Sci, 2017; 379: 7-11.
44. Mikkilineni S, Cantuti-Castelvetri I, Cahill CM, Balliedier A, Greig NH, Rogers JT. The Anticholinesterase Phenserine and Its Enantiomer Posiphen as 5′Untranslated-Region-Directed Translation Blockers of the Parkinson's Alpha Synuclein Expression. Parkinsons Dis., 2012; 2012: 142372.
45. http://adisinsight.springer.com/drugs/800021506.
46. Dézsi L, Vécsei L. Safinamide for the treatment of Parkinson's disease. Expert Opin Investig Drugs, 2014; 23: 729-42.
47. Kulisevsky J. Emerging Role of Safinamide in Parkinson Disease Therapy. Eur Neurol Rev, 2014; 9: 108-12.

48. Stocchi F. Therapy for Parkinson's disease: What is in the Pipeline? Neurotherapeutics, 2014; 11: 24–33.
49. Scott LJ. Opicapone: A Review in Parkinson's disease. Drugs, 2016; 76: 1293-300.
50. Rodrigues FB, Ferreira JJ. Opicapone for the treatment of Parkinson's disease. Expert Opin Pharmacother, 2017; 18: 445-53.
51. Schenk DB, Koller M, Ness DK, Griffith SG, Grundman M, Zago W, *et al*. First-in-human assessment of PRX002, an anti–α-synuclein monoclonal antibody, in healthy volunteers. Mov Disord, 2017; 32: 211–8.
52. Eberling JL, Jagust WJ, Christine CW, Starr P, Larson P, Bankiewicz KS, *et al.* Results from a phase I safety trial of hAADC gene therapy for Parkinson disease. Neurology, 2008; 70: 1980–3.
53. Kaplitt MG, Feigin A, Tang C, Fitzsimons HL, Mattis P, Lawlor PA, *et al.* Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial. Lancet, 2007; 369: 2097–105.
54. LeWitt PA, Rezai AR, Leehey MA, Ojemann SG, Flaherty AW, Eskandar EN, *et al*. AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial . Lancet Neurol, 2011; 10: 309–19.
55. Palfi S. Towards gene therapy for Parkinson's disease. Lancet Neurol, 2008; 7: 375–6.
56. Bartus RT, Weinberg MS, Samulski RJ. Parkinson's disease Gene Therapy: Success by Design Meets Failure by Efficacy. Mol Ther, 2014; 22: 487–97.
57. Gasmi M, Randon EP, Herzog CD, Wilson A, Bishop KM, Hofer EK, *et al*. AAV2-mediated delivery of human neurturin to the rat nigrostriatal system: long-term efficacy and tolerability of CERE-120 for Parkinson's disease. Neurobiol Dis., 2007; 27: 67–76.
58. Marks WJ. Jr, Ostrem JL, Verhagen L, Starr PA, Larson PS, Bakay RA, *et al*. Safety and tolerability of intraputaminal delivery of CERE-120 (adeno-associated virus serotype 2-neurturin) to patients with idiopathic Parkinson's disease: an open-label, phase I trial. Lancet Neurol, 2008; 7: 400–8.
59. Successful Phase 1 Trial for Parkinson's Vaccine [Internet].2014[cited 2014 July 8]. Available from: http://www.ipwatchdog.com.
60. Study Assessing Tolerability and Safety of AFFITOPE® PD03A in Patients With Early Parkinson's Disease (AFF011) [Internet], 2015. Available from: https://clinicaltrials.gov/ct2/show/NCT02267434.
61. https://parkinsonsnewstoday.com/2017/06/15/affitope-pdo3a-vaccine-triggers-immune-response-against-protein-linked-to-parkinsons/.
62. Naeem S, Ikram R, Khan SS, Rao SS. NSAIDs ameliorate cognitive and motor impairment in a model of parkinsonism induced by chlorpromazine. Pak J Pharm Sci., 2017; 30: 801-8.
63. Malik T, Hasan S, Pervez S, Fatima T, Haleem DJ. Nigella sativa Oil Reduces Extrapyramidal Symptoms (EPS)-Like Behavior in Haloperidol-TreatedRats. Neurochem Res., 2016; 41: 3386-98.
64. Shireen E. Experimental treatment of antipsychotic-induced movement disorders. J Exp Pharmacol, 2016; 8: 1-10.
65. Itokawa M, Miyashita M, Arai M, Dan T, Takahashi K, Tokunaga T, *et al*. Pyridoxamine: A novel treatment for schizophrenia with enhanced carbonyl stress. Psychiatry Clin Neurosci., 2018; 72: 35-44.