Review Article

Recent Drug Discovery Status against Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is a progressive irreversible chronic neurodegenerative disorder. Parkinson's is the second most common age-related neurodegenerative disease after Alzheimer's. An estimated seven to 10 million people worldwide have Parkinson's disease. In addition to this an estimated 4 percent of people with Parkinson's are diagnosed before age 50. The disease affects patients' quality of life, making social interaction more difficult and worsening their financial condition, due to the medical expenses associated with the disease. Thorough studies on the incidence of Parkinson's are important to understand the history, progression, and risk factors associated with it. Although the exact aetiology is unclear but genetic and environmental factors are found effective in predisposition of PD. The neurochemical basis of PD can be explained by dopaminergic depletion hypotheses which put forth a relationship between decreased dopamine levels causing neuronal death in substantia nigra region altering body movements. However targeting to this has paved many strategies to treat PD. A high rate of attrition combined with huge cost of new drug development has encouraged several new strategies. Modern advances in disease biology of PD have substantially assembled data from pre-clinical, clinical, in-vitro, epidemiological, toxicological, and computational sources. Thus, an implementation of systematic approaches using this on hand information can give way the next therapeutic alternative for successful management of PD. With this perspective current review aims to help healthcare experts design strategies to meet patients' needs towards better management of PD.

Keywords: Parkinson's disease, Dopamine depletion, Levodopa, Alpha-2 adrenergic receptor antagonists.

INTRODUCTION

Parkinson's disease (PD) is a long term neurodegenerative disorder which affects the motor system of body[1]. This is known after James Parkinson, who detailed in "An Essay on the shaking Palsy" in 1817[2]. The symptoms including shaking, rigidity, slow body movement and walking problem are most common in this disease[1]. Behavioural and thinking problems lead to dementia along with depression and anxiety. This motor disorder symptoms are collectively called as Parkinsonism[3,4]. Though the exact cause is unclear but genetic and environmental factors play a vital role in PD[4]. Additionally, persons who are regularly come in contact with pesticides as well as suffering from head injuries are highly prone to PD[4, 5]. The motor system degeneration in PD is associated with lack of dopamine level[6]. At the earliest it is treated with antiparkinsonian drugs like levodopa followed by dopamine agonist. At chronic stage these medications become less effective due to degeneration of hippocampal neurons resulting in involuntary writhing movements[5, 7].

After Alzheimer's disease PD is the most common neurodegenerative disorder that affects mostly seven million globally and around one million in U.S[8, 9]. According to a survey in 2015, it is observed that around 62 millions of people get affected by PD. Out of which 0.3% of disease found in industry based countries. PD is common among elderly people with the rate of 1% over 60 yrs and 4% over 80 yrs of age[9]. Males are more prone to PD than females at a ratio of 3:2[4]. The number of increased new cases per year is between 8-18 per 1, 00,000 people per year[9].

Prognosis of Parkinsonism

The prognosis of PD depends upon its onset time. At the age of 20 juvenile PD arises, around the age of 40 early onsets PD develops and after this age group it is treated as normal onset[10]. Early onset patients are less subjected to cognitive dysfunctions. However, dysfunctions of motor system are mainly detected and improved treatment option has been justified[11]. These forms of the disease are unique and as it is a neurodegenerative chronic disorder, many patients have been recognised at early stage. Out of 10,000 number of persons at the age of 65 is 50, at the age of 75 is 150 and at the age of 85 it is 400 approximately[9,12].

Postural instability, tremor, slow movement and rigidity are the four major symptoms of PD[13]. Bradykinesia is due to motor planning disturbances in documentation initiation and also difficulties seen in the whole action process. Bradykinesia leads to difficulties in every day task like bathing, dressing, moving etc[14]. Two independent motor activities can't be carried out at the same time in this case. The PD patients find difficult to ride a bicycle or climbing stair case rather than walking on a plane level. Rigidity caused due to muscle tone imbalance resulting to stiffness and resistance in limb motion[13, 15]. In PD the severity may be ratchet (cogwheel) or uniform (lead

pipe)[13, 16]. The cogwheel rigidity is the combination of both tremor and increased muscle tone[17]. The rigidity may affect the shoulder muscle, neck in early stages which is also associated with the joint pain[18]. At the later stage postural instability arises leading to balance impairment and frequent fall[19]. Loss of confidence, reduce mobility is also being associated increasing socioeconomic burden[20].

Past researches had hypothesized environmental and genetic factors for the onset of PD following several mechanisms. Pesticide exposure and some sort of head injury have been associated with PD with a modest risk. Non-smokers and non-drinkers are also linked with PD but at a minimal risk[21]. In addition to this researcher have correlated decreased urate concentration in blood serum with an increased chance of PD[22]. Many researchers revealed that onset of PD is due to a complex interaction between genetic and environmental factors[4]. Almost 15 % of individuals develop PD having relatives who has the disease and around 5-10% of the individuals develop PD due to mutation in one of several specific genes[23].

Pathophysiology

The main reason of PD is due to cell death in basal ganglia and inheritance of Lewy bodies in the remaining neurons[24]. The neuron loss is associated with loss of astrocytes and increased count of microglia in substantia nigra[25]. The five major pathways in brain namely motor oculomotor, associative, limbic and orbit frontal circuits which connect with other areas of brain with basal ganglia are get affected by PD. and this also leads to many symptoms like difficulties in learning, movements etc[26].

Therapeutic Management

Parkinson's disease is not curable but treatments like medication, surgery and physical treatments are found to be more effective. Drugs like levodopa (combinations of dopa decarboxylase inhibitor and COMT inhibitor), dopamine agonist and MAOB inhibitors are very useful in treating motor symptoms[27]. Three stages can differentiate: first stage- in this the individual develop some disability and require pharmacological treatment. Second stage related levodopa complication and third stage when the levodopa treatment is predominant[28]. First stage treatment is to maintain balance with symptom control and treatment side effects. MAO-B inhibitor and dopamine agonist is used initially on behalf of levodopa in order to avoid levodopa induced complications[29]. Hence the use of levodopa against dyskinesia is self-limiting[30]. The second stage focused to reduce the PD symptoms. Over use and sudden withdrawal of medications has to be reconsidered for a successful treatment against PD[31]. However, failure to oral treatment has promoted apomorphine infusion, central dopa pumps and surgery. At the third stage palliative care is followed to improve life quality[32].

Past researchers also revealed that exercise at the mid age may help to reduce the risk of PD. Additionally, antioxidants were also proposed to act against the disease but no positive effect has been proved[9]. However anti-inflammatory drugs and calcium channel blockers are found effective against this disease[4]. According to 2010 Meta-analysis non-steroidal anti-inflammatory agents (expect aspirin) help to reduce the development of PD[33].

Drug Discovery against PD

1. Levodopa

The PD results in the decrease of dopamine production in the basal ganglia. Use of dopamine is self-limiting due to its poor ability to cross blood brain barrier. The precursor of dopamine (L-DOPA) is used for better penetrability through blood brain barrier followed by conversion into dopamine. Levodopa with a little reduction to the motor symptoms is widely used more than 40 years in case of PD[34]. The potential bio-distribution of levodopa to other tissues produces several side effects like vomiting, nausea, orthostatic hypotension restricting its use[35]. However, co-administration of carbidopa and benserazide along with levodopa is preferred due to inhibition of dopa-decarboxylase resulting in no conversion of levodopa to dopamine outside the brain. Thus, it improves the levodopa availability in brain with reduced side effects[36]. Also, sudden withdrawal of levodopa to reduce complications may be dangerous as it may lead to neuroleptic malignant syndrome[37]. However controlled release of levodopa shows better result than conventional formulations. Thus, newer extended release formulations pave a better way for management of PD with little persistent complications[36].

2. COMT Inhibitors

The complimentary effect of tolcapone to L-DOPA resulted in increase of dopamine concentration due to COMT inhibition. However, this therapy was found as a self-limiting approach because of alteration to liver function whereas, entacapone is found effective without affecting the liver function[37].

3. Dopamine agonist

Several dopamine agonists were also used due to reduction of complications in PD patients. They elicit same effect as of levodopa by binding to dopamine receptors. Dopamine agonists including apomorphine, pergolide, ropinirole, bromocriptine etc are used as a first-line therapy with an aim to delay levodopa induced complications[38]. In case of older age patients, it is prone to produce more complications while in younger patient's dyskinesia is rare and negligible[39]. Thus, use of levodopa is more preferable in older patients and dopamine agonists in young patients with mild side effects like hallucination, insomnia, constipation, nausea, drowsiness. However, apomorphine treated patients should be under close supervision due to arise of side effects like confusion and hallucination[37]. Additionally, lisuride and rotigotine are the dopamine agonists administered as skin patches and are useful in initial stage[40]. Monoamine Oxidase-B (MAO-B) is an enzyme associated in breakdown of dopamine in basal ganglia. In this perspective MAO-B inhibitors were used to

increase the dopamine level in basal ganglia. However, their application against PD is restricted due to side effects and found less effective than levodopa[37].

4. Other drugs

In past number of drugs are also used in treating PD including cholinesterase inhibitors for dementia, quetiapine for psychosis whereas their applications suffer due to lack of evidence. To date a few, use of drugs like amantadine and anticholinergics are limited due to less research[41].

Recent Advances in Drug Discovery

1. Glucagon like peptide-1 agonist

Exenatide being a pipeline drug is expected to be effective against PD. It is a glucagon-like peptide-1 (GLP-1) agonist used for the treatment of type-II diabetes. Several preclinical studies have advocated its role in inhibiting cell death, reducing oxidative stress, promoting neuronal function[42]. Recently placebo-controlled trail including elderly patients of age 62 with moderate PD in conjunction with their regular medication has showed the antiparkinsonian effect[43]. Furthermore, it needs more exploration towards its effective uses in PD.

2. A2A receptor antagonists

Adenosine 2A receptor (A2A) antagonists inhibit the release of GABA, which enhances motor function. They also modulate release of acetylcholine with release of dopamine from nigro-striatal tract[44, 45]. They may exert a neuroprotective effect by preventing excitotoxicity and ischaemic neuronal injury. In addition to this A2A receptor antagonists may also prevent drug-induced dyskinesia. The A2A receptor requires activation by other drugs to cause troublesome motor effects. Therefore, blocking the receptors may help to minimize deteriorations associated with chronic anti-PD drug treatment[45]. Additionally, istradefylline like A2A receptor antagonists were studied in phase III clinical trials for reducing off-time in PD patients using levodopa therapy[46]. However, it received a non-approvable letter in 2008 from the US Food and Drug Administration due to lack of efficacy[47].

3. Alpha-2 adrenergic receptor antagonists

Alpha-2 receptor blockade is expected to be useful in the management of dyskinesia since depletion of noradrenergic neurons is an additional component of PD pathophysiology, leading to motor and non-motor deficits[48]. The phase II trial involving the fipamezole is being tested for the treatment of levodopa-induced dyskinesia. The study revealed that, it reduces dyskinesia without worsening PD symptoms. It is currently being developed as an oromucosal formulation[49]. However, more researches are needed to establish its use against PD.

4. Glutamate receptor-5 antagonists

Receptors for glutamate are found in high concentration in the striatum. Over activity of these receptors has been linked with PD symptoms and levodopa-induced dyskinesia[45]. AFQ056 is a selective metabotropic glutamate receptor-5 antagonist may reduce glutaminergic activity. Phase II trials ended in October 2010. The phase II trial investigated its potential to reduce levodopa-induced dyskinesia in October 2010. The study revealed a significant anti-dyskinetic effect without affecting antiparkinsonian activity of levodopa[50].

Alternative Managements for PD

1. Surgery

After the introduction of levodopa, the surgery treatment has been completely declined. Few decades before, surgery techniques showed impressive results and it was used in advanced PD where the drug therapy was not up to the mark. Surgery techniques are classified into two groups: lesional and deep brain stimulation (DBS). Areas that are taken in to account include thalamus and subthalamic nucleus. On this contrary in 1980s DBS was the most common method to be used whereas, other surgical therapies also suppressed the over activity of specific sub cortical areas[51].

2. Rehabilitation

Exercise programs are always recommended to the people affected with PD [7]. Regular physical exercise proved to be beneficial in order to maintain mobility, flexibility and quality of life[52]. Techniques including slow rotational movements of trunks, diaphragmatic breathing is found effective[53]. Similarly, Lee silverman voice treatment (LSVT) is one of the most practiced treatment used for speech disorder patients in PD. In addition to this, occupational therapy (OT) also focuses to increase health and quality of life[54]. Though speech or mobility problems showed a positive result in rehabilitation but due to inadequate researches it remains underrated[52].

3. Palliative care

Palliative care has paved the way to improve the quality of life of patients associated with problems of life-threatening illness, stress and pain[55]. As it is believed that Parkinsonism is not curable, so all treatments being palliative slowly enhance life effectiveness[56]. The palliative care must be introduced earlier in the disease state as it deals with emotional conditions including depression, loss of job, fear etc[57, 58].

CONCLUSION

Parkinsonism being a neurodegenerative disorder affects the motor system of body resulting in socioeconomic insult to the patient. Ambiguity towards exact aetiology of the disease has made an alarming episode however, genetic and environmental factors are believed to play a major role in disease progression. Since reduction of dopamine level leads to development of Parkinson's disease currently marketed drugs like levodopa, COMT Inhibitors, dopamine agonists etc are studied for their efficacy against PD. Many of them have the potential against PD and some of them

are not preferred due to their complications. In this perspective, many of the newer drugs are under pipeline to address limiting factors of conventional drugs. With advances made in disease biology of PD, there is huge data available from pre-clinical, clinical, epidemiological, toxicological, in vitro and computational sources. Hence, with further systematic approaches using available information it can be expected to have a better therapeutic option for successful management of PD.

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Research Interest: His areas of research include Neuropharmacology, Neurodegenerative disorder, Neuroendocrinology etc.