Review Article

# Treatment and Management of Parkinson's Disease with the Use of Hetercyclic Moeities and Natural Compounds

**Fariya Nimrana*, Shaikh Gazi and Humeera Rafeeq**

Deccan School of Pharmacy, Hyderabad - 01, Telangana State, India.

**ABSTRACT**

Parkinson's disease (PD) is a neurodegenerative brain disorder that progress slowly in most people. It was medically described by JAMES PARKINSON in 1817. In his 1817 "an essay on the shaking palsy", James Parkinson first described the clinical syndrome that was later to bear his name.[1] He Identified six cases, Charcot later in the 19th century gave credit to Parkinson by referring to the disease as "maladie de Parkinson" or Parkinson's disease (PD).[2] 11 April, the birthday of James Parkinson, has been designated as World Parkinson's Day.[3] A red tulip was chosen by international organizations as the symbol of the disease in 2005.

Dopaminergic medications are currently being used as a treatment to improve many of the symptoms that characterize Parkinson's disease. Clinical manifestation of this complex disease includes motor impairments involving resting tremor, bradykinesia, postural instability, gait difficulty and rigidity. Non-motor symptoms include depression, lack of motivation, passivity, and dementia are common. The cause of the disease is not yet known.

PD is a slowly progressive parkinsonian syndrome that begins insidiously and usually affects one side of the body before spreading to involve the other side. Pathology shows loss of neuromelanin-containing monoamine neurons, particularly dopamine (DA) neurons in the substantia nigra pars compacta. However, there has been an abundance of research trying to identify potential origins. This literature review will highlight some of the main positions that researchers have on the treatment and causes of Parkinson's disease. Among the causes are environmental toxins, genetic factors, and oxidative stress.[4]

**Keywords:** Neurodegenerative, chronic, bradykinesia, gait, tremor, substantia nigra, dopamine.

## OBJECTIVE

- ✓ To Distinguish Parkinson's disease (PD) from other parkinsonian syndromes.
- ✓ To Develop a patient-specific pharmacotherapeutic plan for the selection, initiation, titration, and monitoring of therapy.
- ✓ Adjusting the therapeutic regimens to minimize motor fluctuations.
- ✓ To Design a plan for the management of drug-related adverse events encountered with PD treatments.
- ✓ Constructing a plan for the management of common complications of PD, including psychosis, dementia, and depression.
- ✓ To evaluate the role of nonstandard pharmacologic and no pharmacologic therapies in PD.[5]

## INTRODUCTION

Parkinson's disease is a common neurological condition afflicting about 1 percent of men and women over the age of seventy. Parkinson's disease (PD) is a neurodegenerative brain disorder that progresses slowly in most people medically described by JAMES PARKINSON in 1817. Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disorder with an estimated prevalence of 31 to 328 per 100,000 people worldwide.[6]

A small region in the brain, called the substantianigra, begins to deteriorate. The neurons of the substantianigra use the brain chemical dopamine. With the loss of dopamine, tremors begin and movement slows. Despite current drug therapies, it remains a progressive and incurable condition. Many patients with this neurological condition may also suffer from age related cognitive decline or have some of the symptoms of Alzheimer's disease. Parkinson's disease is both hereditary and due to environmental factors. Normally, there are brain cells

(neurons) in the human brain that produce dopamine. These neurons concentrate in a particular area of the brain, called the substantianigra.[2] Dopamine is a chemical that relays messages between the substantianigra and other parts of the brain to control movements of the human body. Dopamine helps humans to have smooth, coordinated muscle movements. When approximately 60 to 80% of the dopamine-producing cells are damaged, and do not produce enough dopamine, the motor symptoms of Parkinson's disease appear. This process of impairment of brain cells is called neurodegeneration. Galen named Parkinson's disease as 'Shaking palsy' in AD-175.[1]

In a new study, researchers in the laboratory of Steven Finkbeiner, MD, PhD, at the Gladstone Institutes used a different protein, Nrf2, to restore levels of the disease-causing proteins to a normal, healthy range, thereby preventing cell death. At their root, these disorders are triggered by misbehaving proteins in the brain. The proteins misfold and accumulate in neurons, inflicting damage and eventually killing the cells.

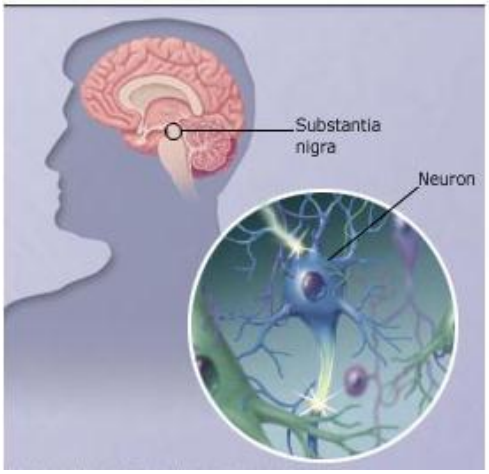


**Fig. 1: Parkinson's disease**

**Parkinson's Types**

- ✓ **Idiopathic Parkinson's disease**
- ✓ Vascular Parkinsonism
- ✓ Drug-induced Parkinsonism
- ✓ Dementia with Lewy bodies
- ✓ Inherited Parkinson's
- ✓ Juvenile Parkinson's
- ✓ Other types of atypical Parkinsonism [7]

**Primary Symptoms**

Bradykinesia, Dementia and Freezing of gait [8].

**Secondary Symptoms**

Speech**,** Swallowing**,** Drooling, Seborrheic dermatitis, Visual problems**,** Weight loss, Constipation and other gastrointestinal (GI) problems, Sexual dysfunction, Dizziness and lightheadedness, Aches, pains, and dystonia

**Diagnosis**

The abundance of guidelines for PD diagnosis is reflective of the difficulty in diagnosing this condition. One relatively straightforward list of research criteria for probable PD includes:

1. Evidence of disease progression.
2. Presence of at least two of the three cardinal features of Parkinsonism (tremor, rigidity, bradykinesia)
3. Presence of at least two of the following:
   a. Marked response to L-dopa (functional improvement or dyskinesia)
   b. Asymmetry of signs
   c. Asymmetry at onset
4. Absence of clinical features of alternative diagnosis
5. Absence of etiology known to cause similar features. Other diagnostic guidelines incorporate requirements pertaining to disease duration, and more specifics regarding tremor and response to dopaminergic agonists.

The great variation in reporting results of SPECT scan studies precludes any conclusion regarding the utility of SPECT scans in diagnosis or management of PD.[9]

**Treatment and management**

**Heterocyclic compounds**

Pharmacologic treatment of Parkinson disease can be divided into symptomatic and neuroprotective (disease modifying) therapy. At this time, there is no proven neuroprotective or disease-modifying therapy.

**L-Dopa**

(S)-2-Amino-3-(3,4-dihydroxyphenyl) propanoic acid. Usually L-dopa is combined with benserazide or carbidopa. It is used in the management of Parkinson's disease in combination with L-dopa (Levodopa) as co-beneldopa (BAN), under the brand names Madopar in the UK and in Canada, Prolopa both made by Roche. They do not cross the blood-brain barrier but inhibit the conversion of L-dopa to dopamine peripherally by blocking the enzyme aromatic acid decarboxylase that catalyses this reaction.[4]

**Dopamine Agonists**

Drugs belonging to this class act directly on dopamine receptors, mimicking the endogenous neurotransmitter. They can be classified into ergot derivates (bromocriptine, pergolide, lisuride, and cabergoline) and the nonergolines (apomorphine, pramipexole, and

ropinirole). They are commonly used as adjunctive therapy to L-dopa after motor complications have developed but may also be considered as monotherapy before starting L-dopa, particularly in younger patients.[10]

**Pergolide**

trade names Permax, Prascend

(8β)-8-[(methylthio)methyl]-6-propylergoline

Pergolide which stimulates both D1 and D2 receptors unlike bromocriptine which only stimulates D2 receptors has been demonstrated to be beneficial in Parkinson's disease.

**Ropinirole**

(INN; trade names Requip, Repreve, Ronirol, Adartrel)

Ropinirole is one of three medications approved by the FDA. ner A report of an ongoing study suggests that monotherapy with ropinirole might be more effective than monotherapy with bromocriptine.

**Cabergoline**

(brand names Caberlin, Dostinex and Cabaser). The chemical name for cabergoline is 1-[(6-allylergolin-8β-yl)- carbonyl]-1-[3-(dimethylamino) propyl]-3-ethylurea, a long acting predominantly D2 receptor agonist is effective as adjunct therapy in advanced Parkinson's disease and also as monotherapy in de novo patients. In a trial comparing L-dopa with cabergoline monotherapy for up to one year cabergoline was slightly less effective than L-dopa.

**Apomorphine**

The use of apomorphine in Parkinson's disease was first reported by Schwab et al who noticed improvement in tremor and rigidity. It was later shown that oral apomorphine reduced "on"/ "off" effects but treatment was limited by nausea, vomiting, postural hypotension, and sedation.

**Monoamine Oxidase B Inhibitors**

Selegeline is an example of this class of drug also known as L-deprenyl, is a substituted phenethylamine. It selectively and irreversibly inhibits intracellular and extracellular monoamine oxidase B (MAO B) and therefore reduces or delays the breakdown of dopamine to dihydroxyphenylacetic acid (DOPAC) and hydrogen peroxide.

**Amantadine**

This antiviral agent has been used in Parkinson's disease for almost 30 years and several possible mechanisms of action have been advocated. It may increase dopamine synthesis, it may be a dopamine and nor adrenaline presynaptic reuptake blocker, and it also has a mild anticholinergic action.[11]

**Anticholinergics**

Current drugs available in the UK are biperiden, orphenadrine, benztropine, Procyclidine. Benzhexol: Trihexyphenidyl (Artane, Apo-Trihex, Parkin, Pacitane), also as Trihexyphenidyl and trihex. Anticholinergic drugs improve tremor and stiffness to a greater degree than akinesia and are overall mildly effective.[6]

**Catechol O-Methyl Transferase Inhibitors**

L-dopa is converted to dopamine by a reaction catalysed by the enzyme aromatic acid decarboxylase which is inhibited by carbidopa and benserazide. Significant peripheral metabolism of L-dopa is also mediated by catechol-omethyltransferase (COMT) which catalyses the O-methylation of L-dopa to 3-Omethyldopa.

**Tolcapone**

(Brand name Tasmar) chemical name: 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone inhibits COMT both peripherally and centrally whereas entacapone acts only peripherally.

**Entacapone** (INN-International Nonproprietary name) is currently the only available COMT inhibitor in the UK.[12]

**Natural Compounds**

**Metabolic Support**

Coenzyme Q10 Coenzyme Q10 is an essential co-factor in the electron transport chain and is a potent antioxidant in both mitochondria and lipid membranes. One RCT studied the effects of coenzyme Q10 100 mg three times daily or placebo for a period of three months.

**Antioxidants**

Tocopherol (Vitamin E) Tocopherol is a biologically active component of vitamin E that attenuates the effects of lipid peroxidation by trapping free radicals. A large placebo controlled trial (n=800) investigated the effect of selegiline or tocopherol on slowing functional decline in patients with early, untreated Parkinson's disease.

**Resveratrol**

Resveratrol, a polyphenolic compound naturally present in red wine and grapes, has a number of pharmacological effects including anti-inflammation, anti-apoptosis, antioxidation, antifungal, anticancer, and others. It is also able to cross the blood-brain barrier and is water soluble. [13]

**ADR**

- ✓ Orthostatic hypotension (low blood pressure)
- ✓ Bladder and bowel problems
- ✓ Cognitive changes

**Advices**

- ✓ See a specialist
- ✓ Build a health care team
- ✓ Take medications on time
- ✓ Read and learn about PD
- ✓ Exercise
- ✓ Expect the best, plan for the worst
- ✓ Build connections, expect resilience.[14]

**CONCLUSION**

PD progression is a complex that involves the inter-relationship of disease pathology, Symptoms and treatments. In looking at disease progression, it is natural to primarily focus attention on the process of improving treatment, but it is also important to focus on 'life progression' as whole. A thorough understanding of the broad spectrum of clinical manifestations of PD is essential to the proper diagnosis of the disease. Genetic mutations or variants, neuroimaging abnormalities and other tests are potential biomarkers that may improve diagnosis and allow the identification of persons at risk. Apart from this, patient counseling will help for the improvement in disease condition.

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