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Review Article

Overview of Parkinson Disease

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ABSTRACT

About 1 percent of Americans over 60 suffer from Parkinson disease, a degenerative neurologic condition. Bradykinesia, stiffness, tremor, and postural instability are the hallmarks of Parkinson's disease. Early diagnosis of the disease is challenging since it can be confused with several neurologic disorders. Patients suspected of having Parkinson disease should be sent to doctors with greater experience in diagnosing the condition, and those who identify it infrequently should periodically reassess the diagnosis' accuracy. When a patient starts to develop functional impairment, treatment should be initiated as it is beneficial in lowering disability and motor impairment. Although dopamine agonists and monoamine oxidase-B inhibitors are both effective and less prone to cause dyskinesias, the most effective treatment is the combination of carbidopa and levodopa. Adjunctive therapy with a dopamine agonist, monoamine oxidase-B inhibitor, or catechol O-methyltransferase inhibitor will improve motor symptoms and functional status in individuals receiving carbidopa/levodopa who have motor problems, but it will also exacerbate dyskinesias. Patients who have poorly controlled symptoms despite receiving the best medical treatment can benefit from deep brain stimulation. Speech, physical, and occupational therapy all help patients function better. Parkinson disease sufferers frequently experience melancholy, dementia, sleep issues, and fatigue. Treatment may improve these illnesses even if they are linked to a much lower quality of life.

INTRODUCTION

It is a brain disorder. When approximately 80 percent neuron are damaged then it shows symptoms of PD. It affects 1 in 100 people over the age of 60. Dr. James Parkinson initially referred to Parkinson's disease (PD) as a "shaking palsy" in 1817. It is a neurodegenerative condition that progresses over time and has both motor and nonmotor symptoms. The disease's progressive degenerative effects on muscular control and mobility have a major clinical impact on patients, families, and carers. The loss of striatal

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dopaminergic neurones is the cause of Parkinson's disease (PD) motor symptoms, while nonmotor symptoms also suggest neuronal loss in nondopaminergic areas. The motor characteristics of Parkinson's disease (PD), such as bradykinesia, muscle rigidity, and resting tremor, are collectively referred to as parkinsonism. Parkinson's disease (PD) is the most common cause of parkinsonism, although there are several other causes as well, including conditions that resemble PD.(1) The pathological features of Parkinson's disease (PD) include the buildup of misfolded α-synuclein, which is present in intracytoplasmic aggregates called Lewy bodies, and the loss of dopaminergic neurones in the pars compacta of the substantia nigra. The therapies that are now on the market effectively manage motor symptoms but do not stop the disease's progression. The goal of this article is to give general neurologists a thorough, all-encompassing, and useful study of Parkinson's disease.(2)

What is Parkinson Disease :

Parkinson's disease is a brain degenerative condition. It affects the areas of the brain linked to regular gait and equilibrium.

Symptoms of Parkinson's disease vary from person to person. The most common symptoms include:

Tremor

Slowness of movement

Rigid muscles/stiff limbs

Unsteady walk and balance and coordination problems

Muscle twisting, spasms or cramps (dystonia). The patient may experience a painful cramp in your foot or curled and clenched toes & Dystonia may occur in the other body parts of the patient.

Stooped posture.

Other symptoms include:

Decreased facial expressions

Speech/vocal changes

Handwriting changes:

Depression and anxiety.

Chewing and swallowing problems, drooling.

Urinary problems.

Mental "thinking" difficulties/memory problems.

Hallucinations/delusions.

Constipation.

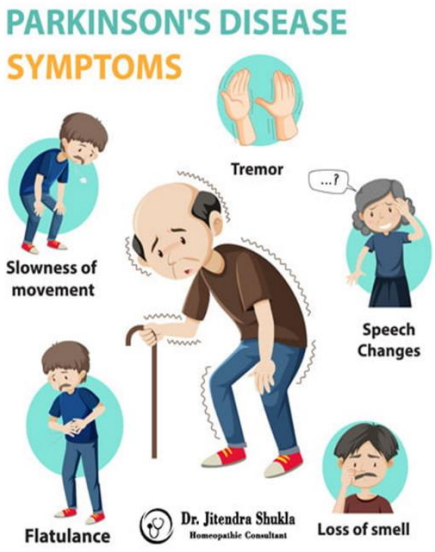
Skin problems, such as dandruff.

Loss of smell.

Sleeping disturbances

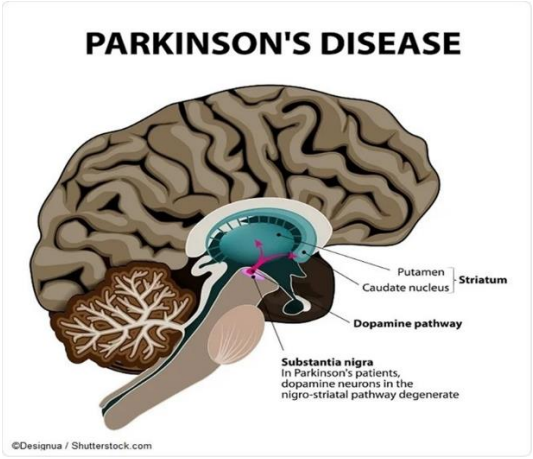
Lack of interest (apathy), fatigue, change in weight, vision changes.

Low blood pressure.(3)



Pathophysiology :

When multiple members of an Italian family living in the New Jersey region were diagnosed with Parkinson's disease (PD) in 1999, the hunt for the underlying genetic cause of this illness gathered steam. Another breakthrough was found through research on families affected by this rare autosomal dominant form of the disease. The main cause seems to be the buildup of alpha-synuclein in the brain's substantia nigra, which causes degeneration and eventual dopamine loss in the basal ganglia that regulate movement and muscle tone. Alpha-synuclein protein accumulation could be caused by an unidentified environmental contaminant or as a result of a hereditary predisposition, as the PARK-1 mutation found in the New Jersey Contursi kindred. Following reports that the earliest degenerative change in Parkinson's disease (PD) appears in the myenteric plexus on the gastrointestinal tract, it then progresses to involve the dorsal motor nucleus of the vagus nerve, the sleep centres in the pons, and finally the midbrain, there has been some recent interest in determining an infectious aetiology that triggers this alpha-synuclein accumulation. This intriguing explanation also explains why REM sleep disorder and gastrointestinal motility problems are common in PD patients, even though these conditions can exist for years before the motor symptoms of the disease. The main symptom of Parkinson's disease is the progressive death of brain cells in the substantia nigra. This region is in charge of dopamine synthesis. A chemical messenger called dopamine coordinates activity by sending information between two parts of the brain. To control muscle activation, for instance, it links the corpus striatum with the substantia nigra. The nerve cells in the striatum "fire" uncontrollably if there is a dopamine shortage in this area. As a result, the person loses the ability to control or guide their motions. The early signs of Parkinson's disease result from this. Other parts of the brain and neurological system also degrade as the disease worsens, leading to a more severe movement disability. It is unclear what specifically is causing the cell loss. Environmental and genetic factors are potential reasons. (4)



Etiology :

Both hereditary and environmental factors contribute to Parkinson's disease (PD), which is a complex illness. With a median age of onset of 60 years, age is the largest risk factor for Parkinson's disease . The disease's incidence increases with age, reaching 93.1 cases per 100,000 person-years in the 70–79 age range . Cross-cultural differences also exist; in comparison to African, Asian, and Arabic nations, a higher prevalence has been documented in Europe, North America, and South America.(5,6,7)

Diagnosis :

The clinical diagnosis of Parkinson disease is based on the presence of the cardinal features—bradykinesia, stiffness, tremor, and postural instability—as well as a persistent response to levodopa medication and a steady progression of symptoms.4. Nonetheless, other neurological disorders share some of these characteristics. Nonparkinsonian tremors like essential tremor and disorders with parkinsonian symptoms like vascular parkinsonism, progressive supranuclear palsy, and drug-induced parkinsonism are among the conditions that are frequently mistaken as Parkinson disease.

Table 1 :- Characteristics of Conditions Commonly Misdiagnosed as Parkinson Disease :

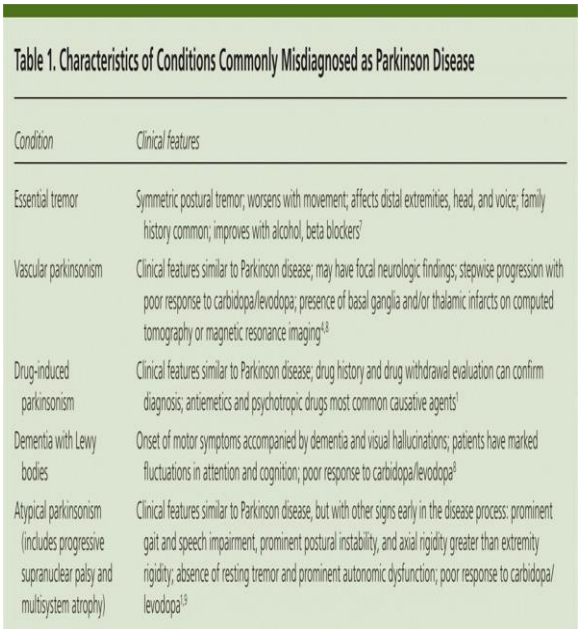


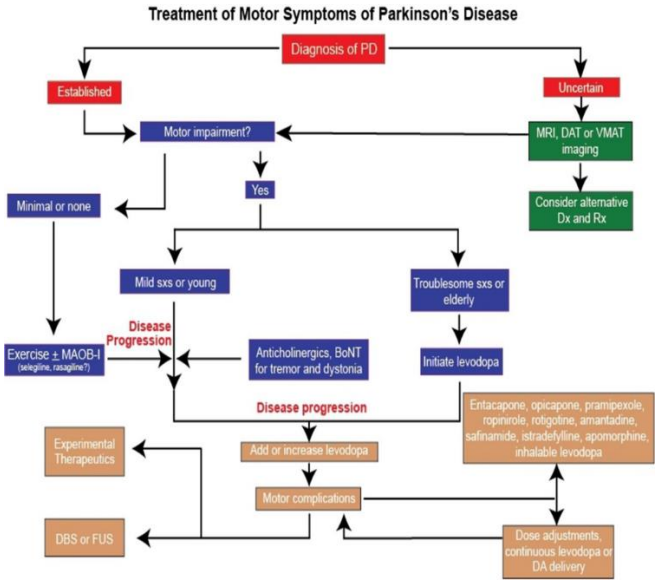
Table 1. Characteristics of Conditions Commonly Misdiagnosed as Parkinson Disease

Condition	Clinical features
Essential tremor	Symmetric postural tremor; worsens with movement; affects distal extremities, head, and voice; family history common; improves with alcohol, beta blockers[7]
Vascular parkinsonism	Clinical features similar to Parkinson disease; may have focal neurologic findings; stepwise progression with poor response to carbidopa/levodopa; presence of basal ganglia and/or thalamic infarcts on computed tomography or magnetic resonance imaging[1,3]
Drug-induced parkinsonism	Clinical features similar to Parkinson disease; drug history and drug withdrawal evaluation can confirm diagnosis; antiemetics and psychotropic drugs most common causative agents[1]
Dementia with Lewy bodies	Onset of motor symptoms accompanied by dementia and visual hallucinations; patients have marked fluctuations in attention and cognition; poor response to carbidopa/levodopa[3]
Atypical parkinsonism (includes progressive supranuclear palsy and multisystem atrophy)	Clinical features similar to Parkinson disease, but with other signs early in the disease process: prominent gait and speech impairment, prominent postural instability, and axial rigidity greater than extremity rigidity; absence of resting tremor and prominent autonomic dysfunction; poor response to carbidopa/levodopa[1-3]

Parkinson disease is challenging to diagnose, and mistakes are frequently made, especially in the early stages. A doctor who does not often identify Parkinson disease should think about sending a patient who is suspected of having it to a doctor with greater experience in order to confirm the diagnosis. Although the Parkinson's UK Brain Bank criteria increase diagnostic accuracy in patients with advanced illness, no clinical decision guidelines have been shown to be helpful in diagnosing early disease. Physicians who treat patients with Parkinson disease should frequently revisit the diagnosis due to the inherent uncertainty of the diagnosis in the early stages of the disease and the growing diagnostic accuracy with the course of the disease. (8,9,10)

Treatment :

A customised therapy approach is necessary for Parkinson's disease (PD), a complicated neurodegenerative disease with a wide range of motor and non-motor symptoms. A well-defined patient and control population must be included in clinical trials intended to produce evidence-based data, and the most impartial, trustworthy, and validated instruments should be used to evaluate the therapeutic intervention's benefits. The UPDRS is most commonly utilised as the primary outcome measure in various clinical studies, despite the fact that a number of clinical rating scales and other tools have been used to evaluate response to various medication.



Treatment of Motor Symptoms:-

Table 3. Drugs Used to Treat Motor Symptoms in Patients with Parkinson Disease

Drug/drug class	*Examples*	*Advantages*	*Disadvantages*
Carbidopa/levodopa (Sinemet)	Immediate- and sustained-release carbidopa/levodopa	Most effective, improves disability, prolongs capacity to perform instrumental activities of daily living	Motor complications: dyskinesias, dystonia, confusion, psychosis, sedation
Dopamine agonists	Nonergot: pramipexole (Mirapex), ropinirole (Requip) Ergot: bromocriptine (Parlodel), pergolide	Can be used as monotherapy in early disease or added to levodopa for treatment of motor complications Less risk of developing motor complications in early disease	All: dopaminergic adverse effects (nausea, vomiting, orthostatic hypotension), neuropsychiatric adverse effects (hallucinations, psychosis, impulse control disorder), excessive daytime sleepiness Ergot: pulmonary fibrosis, cardiac valve fibrosis, erythromelalgia
Monoamine oxidase-B inhibitors	Selegiline (Eldepryl), rasagiline (Azilect)	Can be used as monotherapy in early disease or to treat motor complications in late disease Once-daily dosing, well tolerated	Amphetamine and methamphetamine metabolites may cause adverse effects, risk of serotonin syndrome
Catechol *O*-methyltransferase inhibitors	Entacapone (Comtan), tolcapone (Tasmar)	Used to treat motor complications; no titration, decreased off time,* mild improvement in activities of daily living and quality-of-life scores	Dopaminergic adverse effects, discoloration of urine, tolcapone associated with explosive diarrhea and fatal liver toxicity
Injectable dopamine agonist	Apomorphine (Apokyn)	Reduces off time in late disease	Requires initiation in hospital, regular subcutaneous injections
N-methyl-D-aspartate receptor inhibitor	Amantadine	Treatment of dyskinesias in late disease	Cognitive adverse effects, livedo reticularis, edema, development of tolerance, potential for withdrawal
Anticholinergics	Benztropine, trihexyphenidyl	Useful for the treatment of tremor in patients younger than 60 years without cognitive impairment	Use limited by anticholinergic adverse effects

Carbidopa- levodopa :

The best medication for Parkinson's disease is levodopa. It is a naturally occurring substance that enters the brain and transforms into dopamine. Carbidopa and levodopa are combined to help levodopa get to the brain and to avoid or reduce adverse effects including nausea. Nausea and orthostatic hypotension, or lightheadedness when standing, are possible side effects. Dyskinesia, or involuntary movements, can result from higher levodopa dosages. You might need to reduce or modify your dosage if this occurs. Over time, levodopa's benefits can diminish. It could wax and wane as well. We refer to this as wearing off. If you have advanced Parkinson's disease, it is usually better to take carbidopa-levodopa on an empty stomach. Observe the recommendations of your medical team regarding when to take it.

Dopamine agonists. :

Dopamine agonists do not convert to dopamine like levodopa does. Rather, they replicate the effects of dopamine in the brain. When it comes to treating symptoms, they are less successful than levodopa. However, they have a longer half-life and can be used in conjunction with levodopa to enhance its effectiveness.

Dopamine agonists include:
Pramipexole (Mirapex ER).
Rotigotine (Neupro), given as a patch.
Apomorphine (Apokyn), a short-acting dopamine agonist shot for quick relief.

Monoamine oxidase B (MAO B) inhibitors.

These medicines include:

Selegiline (Zelapar).

Rasagiline (Azilect).

Safinamide (Xadago).

MAO B inhibitors help block an enzyme called monoamine oxidase B (MAO B) that breaks down brain dopamine. When selegiline is given with levodopa, it may keep levodopa from wearing off. Side effects of MAO B inhibitors may include headaches, nausea, insomnia and confusion.

Catechol O-methyltransferase :

By preventing an enzyme that degrades dopamine, they prolong the effects of levodopa medication. Among them are: Comtan, or Entacapone. Ontario's Opicapone. Tasmar, or Tolcapone. Due to the possibility of severe liver damage and liver failure, this medication is rarely administered. An elevated risk of involuntary movements is one of the possible side effects of COMT inhibitors. Diarrhoea, nausea, or vomiting are other possible side effects.

Anticholinergics. :

These medicines were used for many years. They aren't used as often now because of their modest benefits and risk of side effects. They may be helpful in controlling severe tremor for some people with Parkinson's disease. They include:
Benztropine.
Trihexyphenidyl.
Side effects of anticholinergics may include memory loss, urinary problems, confusion, blurred vision, dry mouth and constipation.(12,13,14)

Treatment of Non Motar Symptoms :

Despite the fact that the majority of PD patients initially exhibit motor symptoms, it is widely acknowledged that non-motor symptoms make up a significant portion of the clinical spectrum. Insomnia, RBD, olfactory dysfunction, pain, exhaustion, depression, anxiety, apathy, psychosis, cognitive impairment, dementia, impulse control dysfunction, and autonomic dysfunction (drooling, orthostatic hypotension, urinary retention/incontinence, erectile dysfunction, gastrointestinal dysfunction, excessive perspiration).106 Even more than motor issues, non-motor symptoms can have an impact on quality of life. Motor symptoms may be preceded by RBD, gastrointestinal disorders, and olfactory impairment. The existing treatments for PD's non-motor symptoms were thoroughly reviewed by the Movement Disorders Society study group. Here, we focus on how to address a few typical non-motor symptoms. Patients with PD-associated dementia may benefit somewhat with memantine (an NMDA receptor antagonist) and donepezil and rivastigmine (cholinesterase inhibitors). Atypical antipsychotics like quetiapine and clozapine, which have a lower risk of aggravating parkinsonism than other antipsychotics (dopamine receptor blockers), typically help with hallucinations, which are frequently linked to PD dementia and/or brought on by anti-PD medications. The FDA approved pimavanserin, a non-dopaminergic, selective serotonin inverse agonist with high affinity at the 5-HT2A receptor, in 2016 for the treatment of PD-related hallucinations and delusions.107 It comes in 34 mg capsules and 10 mg tablets.(15,16)

Table :- Non Motar Symptoms of Parkinson Disease (17):-

Autonomic Dysfunction[a]
• Constipation (parasympathetic nervous system cholinergic) • Orthostatic hypotension (sympathetic nervous system noradrenergic) • Sexual dysfunction (parasympathetic nervous system cholinergic) • Sweating (sympathetic nervous system cholinergic) • Urinary retention (parasympathetic nervous system cholinergic)
Neuropsychiatric Symptoms
• Anxiety • Cognitive impairment (mild) • Dementia • Depression (e.g., dysphoria, suicidal ideation, apathy) • Impulse-control disorders (e.g., preoccupations, hypersexuality, compulsive shopping, binge eating)[b] • Panic disorder • Psychosis (e.g., hallucinations, delusions)
Sensory Symptoms
• Olfactory dysfunction (hyposmia) • Paresthesias • Pain
Sleep Disturbance[c]
• Daytime somnolence • Insomnia • Rapid eye movement disorder • Restless legs syndrome • Sleep attacks • Sleep apnea
Other
• Fatigue • Sialorrhea • Weight loss
[a] Depends on components of nervous system that are affected. [b] Usually associated with use of dopamine agonists. [c] Complex etiology; linked to neurodegenerative process, motor features, and drug therapy.

Surgical Treatment :

Deep Brain Stimulation :

Patients with chronic Parkinson's disease may occasionally benefit from deep brain stimulation surgery. A tiny impulse-generating device is implanted in the chest wall and connected to the brain via a thin cable that is positioned beneath the skin. The Parkinson's disease-affected areas of the brain are stimulated by the device's small electric current release. This isn't a cure, but it might help with the symptoms.

Other surgical methods include pallidotomy (used in unilateral dyskinesia, severe 'on-off' fluctuations and drug failure), thalamic and Subthalamic surgery (for controlling tremors) etc.(18,19,20)

Side effects of deep brain stimulation may include:

Bleeding in the brain.

Injury or death of tissue.

Infection.

Skin breakage.

Muscle twitches.

Depression.

Speech or vision problems.

CONCLUSION:

Understanding the disease mechanisms sparked by genetic research will result in new neuroprotective and restorative treatments, much like the groundbreaking discoveries that recognised Parkinson's disease (PD) as a disease of dopamine deficiency led to the development of rational symptomatic therapies like levodopa and dopamine agonists. The pathophysiology of Parkinson's disease (PD) has been linked to protein misfolding, oxidative stress, abnormal phosphorylation, proteasomal and mitochondrial dysfunction, and the discovery of monogenetic forms of the disease. The challenges for the future are to conduct further study to identify the elements that are most close to the cell death process and those that are most responsive to pharmacological intervention, even though the interaction and temporal relationship among these pathologic processes are now unclears.

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