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Review Article

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ADVANCEMENTS IN DRUG THERAPY FOR PARKINSON'S DISEASE: A COMPREHENSIVE REVIEW

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative condition that causes both motor and non-motor dysfunctions due to the aggregation of misfolded α-synuclein and the death of dopaminergic neurons in the substantia nigra. The neuropharmacological basis of Parkinson's disease (PD) is brought out in this review, which focuses on important neurotransmitter changes including dopamine, acetylcholine, glutamate, and GABA that contribute to the illness's intricate pathogenesis. The functions of several diagnostic modalities in early and differential diagnosis are reviewed, including genetic testing, neurophysiological evaluations, neuroimaging, and biomarker-based techniques. Levodopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors, anticholinergics, and amantadine are examples of current pharmacological treatments that relieve symptoms but do not stop the disease's progression. Neuroprotective medication repurposing, stem-cell-based interventions, gene therapy, and α-

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synuclein-targeted immunotherapies are examples of emerging therapeutic approaches with considerable prospects for future disease-modifying treatments. This review offers a comprehensive overview of the pathophysiology of Parkinson's disease (PD), neurotransmitter involvement, advances in diagnosis, and changing therapy methods.

KEYWORDS

Parkinson’s disease, Neuropharmacology, Dopamine, Neurotransmitters

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INTRODUCTION

Neuropharmacology is a huge field of research that involves many parts of the nervous system from single cell manipulation to vast sections of the brain, spinal cord, and peripheral nerves. Neuropharmacology has two primary subfields: molecular and behavioral. The study of how drugs impact human behavior (neuropsychopharmacology), particularly the effects of drug addiction and dependency on the brain, is the main focus of behavioral neuropharmacology. In order to create new medications that will cure neurological conditions like pain, neurodegenerative illnesses, and psychological disorders, molecular neuropharmacology studies neurons, their neurochemical interactions, and receptors on neurons [1]. Major neurological conditions like Alzheimer's, Parkinson's, Multiple Sclerosis, epilepsy, stroke, and depression are all affected by neuropharmacology. In this essay, we discuss Parkinson's with a variety of origins and clinical manifestations, Parkinson's disease is a recognizable clinical condition [2]. The animals experience a typical parkinsonian syndrome, characterized by loss of dopaminergic cells in the substantia nigra and abnormalities in the spontaneous activity and sensory responses of neurons in the basal ganglia [3, 4]. Parkinson's disease, which affects about 1% of persons over 60, is the second most common movement disorder after essential tremor. Parkinson's disease is thought to be exacerbated by the combination of genetic and environmental variables, even though the precise cause is yet unknown [5].

MATERIALS AND METHODS

The methodology for this review involved a systematic search and analysis of scientific literature published between 2000 and 2025 to capture both foundational knowledge and the most recent advances in the pharmacological management of Parkinson’s disease. Databases including PubMed, Scopus, Google Scholar, and ScienceDirect were searched using keywords such as Parkinson’s disease, neuropharmacology, dopamine, neurotransmitters, levodopa, MAO-B inhibitors, COMT inhibitors, dopamine agonists, and emerging therapies. Peer-reviewed research articles, randomized controlled trials, review papers, and clinical guidelines within the specified time frame were included, while non-scientific reports, outdated pre-2000 studies, and articles with insufficient pharmacological relevance were excluded. Data were extracted on neurotransmitter alterations, diagnostic developments, established drug therapies, and novel investigational approaches. The collected information was synthesized into thematic sections to compare mechanisms, therapeutic efficacy, adverse effects, and limitations of current and emerging treatments. All referenced materials were compiled and managed systematically in accordance with standard academic citation practices.

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RESULTS

Parkinson's pathophysiology

Multiple motor and nonmotor brain circuits are affected by Parkinson's disease, a neurodegenerative illness. It is typified by two main pathologic processes: (a) early selective loss of dopamine neurons; and (b) the build-up of Lewy bodies, which are made of misfolded ?-synuclein and accumulate in several systems of Parkinson disease patients. Which process starts initially is unknown. According to pathologic research, neurons gradually deteriorate over many years, with each afflicted region matching a particular Parkinson disease symptom. Pathologic investigation reveals 30–70% cell loss in the substantia nigra when motor symptoms appear. The primary objective of treatment is to regulate the malfunctioning circuit and replace dopamine using dopaminergic drugs. Dopamine deficiencies outside of the basal ganglia or in the serotonergic and noradrenergic systems are linked to mood problems, impulse control issues, and cognitive difficulties. Pathologies beyond the brain, such as those affecting the spinal cord and peripheral autonomic nerve system, have been linked to autonomic dysfunction [6].

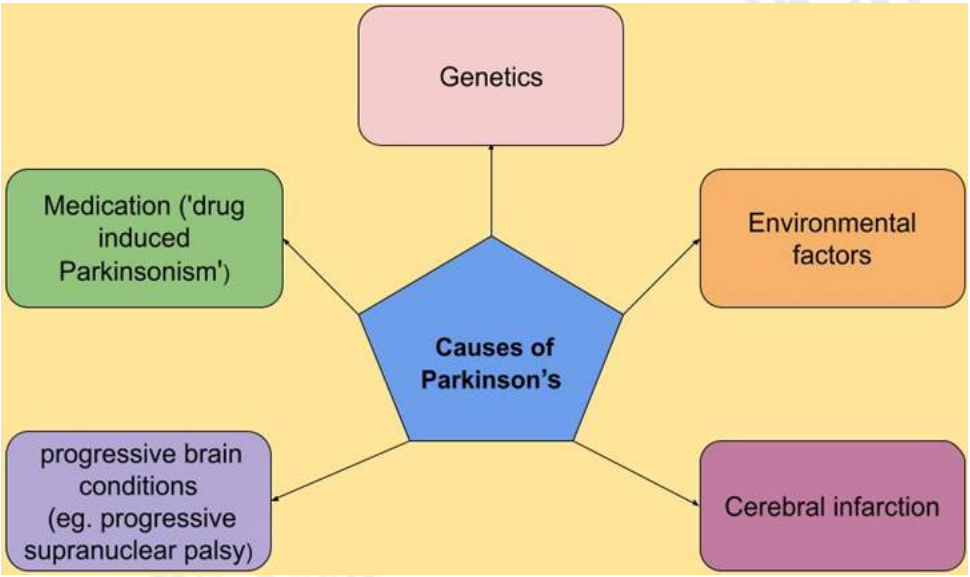


Figure:- Causes of Parkinson`s

Neurotransmitters involved in parkinsons

1. Dopamin

Neurotransmission alternations play a crucial role in the development of Parkinson disease,

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which is regulated by several neurotransmitters. In the midbrain region, PD is caused by extensive damage to dopamine-producing neurons, and the hallmark of PD pathogenesis is the aggregation of ?-synuclein protein. This dopamine deficiency causes changes in the basal ganglia circuit as well as changes in the levels of many neurotransmitters [8].

2. Acetylcholin (ach)

One of the primary cell types in the striatum is the cholinergic interneuron (ChI), which releases ACh. Because of their vast and dense arborizations, ChIs significantly affect striatal activity even though they only make up 1% to 2% of total striatal neurons. Parkinson's disease-related motor dysfunction has been associated with changes in the activity of medium spiny neurons, which may be brought on by a change in the ratio of dopamine to ACh as well as a loss of dopaminergic input[9]. Many basal ganglia-related movement disorders, including dystonia, Parkinson's disease, and Tourette's syndrome, are linked to deficiencies in ChI function [10].

3. Glutamate

An essential neurotransmitter in the basal ganglia, glutamate is linked to the development of motor symptoms in Parkinson's disease. Furthermore, the development of non-motor symptoms in Parkinson's disease is linked to an imbalance in glutamate neurotransmission in the basal ganglion and other brain regions [11].

4. GABA

Patients with Parkinson's disease have a severely disrupted GABA system. The GABA pathway is crucial for controlling the inhibitory tone, which keeps the cerebral cortex from being overstimulated. Reduced GABAergic neurotransmission is associated with dopaminergic neuron degeneration in Parkinson's disease. Reduced GABA activity increases oxidative stress and mitochondrial malfunction, all of which are closely linked to the neuropathology of Parkinson's disease [11].

Parkinson's Disease Diagnostic Tests

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1. **Genetic examination**
   detects mutations in alpha-synuclein, PINK1 (PTEN-Induced Putative Kinase 1), DJ1 (Protein Deglycase DJ-1), and LRRK2 (Leucine-Rich Repeat Kinase 2). mostly helpful in cases with a young onset or a family history.

2. **Tests for drug challenges**
   Dopaminergic responsiveness is assessed with an apomorphine or levodopa challenge. Parkinson's disease is supported by positive responses; negative outcomes are unimportant.

3. **Neurophysiology in clinical settings**
   comprises sphincter-electromyography, transcranial magnetic stimulation, long latency reflexes, Bereitschaft-potential investigations, and startle reactions. poor diagnostic specificity but useful for atypical parkinsonism.

4. **Testing autonomic function**
   uses urodynamic studies, head-up tilt, and cardiovascular reflex tests. Multisystem atrophy is suggested by early severe abnormalities.

5. **Olfactory evaluation**

   Approximately 90% of people with Parkinson's disease experience hyposmia. aids in distinguishing Parkinson's disease from atypical syndromes and vascular parkinsonism.

6. **MRI (Magnetic Resonance Imaging)**

   Identifies structural alterations in corticobasal degeneration, progressive supranuclear palsy, and multisystem atrophy.

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7. DAT-SPECT / FP-CIT SPECT (DAT- Dopamine Transporter, SPECT – Single Photon Emission Computed Tomography, FP-CIT – N-?-Fluoropropyl-2?-Carbomethoxy-3?-(4-Iodophenyl) Tropane)

Demonstrates an uneven decrease in striatal DAT binding. distinguishes psychogenic parkinsonism and essential tremor from Parkinson's disease.

8. MIBG-SPECT (Meta-Iodobenzylguanidine, Single Photon Emission Computed Tomography)

Demonstrates Parkinson's disease-related cardiac sympathetic denervation. aids in distinguishing progressive supranuclear palsy from multisystem atrophy.

9. PET (18F-dopa, FDG) (PET – Positron Emission Tomography)

Demonstrates typical striatal alterations; expensive.

10. Midbrain sonography

More than 90% of patients have substantia nigra hyperechogenicity [12].

Managing Parkinson's disease (PD)

Restoring dopaminergic function in the dopamine-depleted striatum is the main goal of treatment for Parkinson's disease (PD). Despite the lack of a disease-modifying treatment, a number of pharmaceuticals significantly reduce symptoms.

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1. Levodopa and DOPA Decarboxylase Inhibitors

Since levodopa passes through the blood-brain barrier and is transformed into dopamine in the central nervous system, it continues to be the best treatment for motor symptoms. Usually, it is started at modest doses and subsequently increased. Dyskinesia and on-off fluctuations are among the motor problems brought on by prolonged use. It is used in conjunction with carbidopa or benserazide, which block peripheral levodopa metabolism, to lessen peripheral adverse effects. Duodopa, a continuous intestinal gel infusion, lowers fluctuations and produces constant plasma levels. [13, 14]

2. Agonist Of Dopamine

Particularly in younger patients, dopamine agonists can postpone the need for levodopa by directly stimulating dopamine receptors. Rotigotine, apomorphine, ropinirole, and pramipexole are common agents. Although they lessen levodopa-induced motor problems, they are closely linked to impulse control disorders (ICD) such excessive shopping, hypersexuality, and gambling. Dopamine agonist withdrawal syndrome may result from abrupt cessation [15,16].

3. MAO-B Inhibitors

MAO-B medications slightly alleviate motor symptoms and lessen dopamine breakdown. Among the medications are safinamide, rasagiline, and selegiline. They are frequently used as supplementary therapy or to postpone starting levodopa in the early stages of the disease. Neuropsychiatric symptoms, nausea, and sleeplessness are among the adverse effects [15, 17].

4. COMT Inhibitors

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COMT inhibitors are mostly utilized for end-of-dose wearing off and extend the half-life of levodopa. Examples include opicapone, tolcapone, and entacapone. Hepatotoxicity from tocapone necessitates liver surveillance [15,18].

5. Anticholinergics

Particularly in younger patients with tremor-predominant Parkinson's disease, anticholinergic medications help reduce tremor and rigidity. Procyclidine, trihexyphenidyl, and benztropine are common agents. Due to cognitive adverse effects, particularly in elderly persons, their use is restricted. [18, 19].

6. Amantadine

Amantadine, which was first developed as an antiviral medication, helps lessen levodopa-induced dyskinesia and may alleviate moderate motor symptoms. It is thought to work by antagonistic interaction with NMDA receptors. There is still little proof of overall symptomatic benefit [20,21].

7. Emerging and Experimental Therapies

The goal of such approaches is to alter the course of the disease, especially by focusing on ?-synuclein pathology. Active and passive immunotherapies with promising early-phase safety and biomarker results include PD03A, PRX002, and BIIB-054. Restoring physiological dopamine production is the goal of ProSavin gene therapy experiments. Exenatide and nilotinib are repurposed medications with neuroprotective potential that have demonstrated long-term improvements in motor scores. Clinical development is also underway for stem-cell-based restorative techniques [22, 23, 24].

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DISCUSSION

This review effectively summarizes current and emerging pharmacological approaches for Parkinson's disease (PD), emphasizing that while dopamine replacement—primarily through levodopa—remains the cornerstone of symptom management, long-term complications and lack of disease-modifying effects limit its impact. The discussion highlights the importance of non-dopaminergic neurotransmitters such as acetylcholine, glutamate, and GABA, reflecting the multifaceted neurochemical dysfunction underlying both motor and non-motor symptoms.

Advancements in diagnostic tools, including DAT-SPECT, MIBG imaging, and genetic testing, are recognized as essential for improving early and differential diagnosis. Emerging therapies—such as ?-synuclein immunotherapy, gene therapy, and repurposed neuroprotective agents like exenatide and nilotinib—offer promising avenues for slowing disease progression, although evidence remains preliminary. Overall, the review underscores that while symptomatic treatments are well-established, significant unmet needs persist. Future progress will depend on developing reliable biomarkers, targeting disease mechanisms beyond dopamine loss, and advancing therapies with true disease-modifying potential.

CONCLUSION

The study of the nervous system is included in neuropharmacology, which mostly focuses on conditions like Parkinson's disease (PD). Lewy bodies (made of alpha-synuclein) and the selective loss of dopamine neurons are the hallmarks of Parkinson's disease (PD), a neurodegenerative condition. Significant cell loss in the substantia nigra causes motor complaints. Dopamine, acetylcholine (ACh), glutamate, and GABA are important neurotransmitters involved in Parkinson's disease (PD) pathogenesis. Restoring dopaminergic activity is the main goal of treatment, which is mostly symptomatic. Levodopa, frequently in combination with DOPA Decarboxylase Inhibitors, is the most successful treatment for motor symptoms. Amantadine, MAO-B and COMT inhibitors, and dopamine agonists are other therapies. By focusing on alpha-synuclein pathology through immunotherapies, gene therapy, and stem-cell-based approaches, emerging medicines are investigating disease modification.

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ABBREVIATIONS

PD- Parkinson's Disease

GABA- Gamma-Aminobutyric Acid

MOA-B - Monoamine Oxidase-B

ACH- Acetylcholin

ChI - Cholinergic Interneuron

PINK1 -PTEN-Induced Putative Kinase 1

DJ1 -Protein Deglycase DJ-1

LRRK2 -Leucine-Rich Repeat Kinase 2

MRI -Magnetic Resonance Imaging

DAT - Dopamine Transporter

SPECT- Single Photon Emission Computed Tomography

FP-CIT – N-?-Fluoropropyl-2?-Carbomethoxy-3?-(4-Iodophenyl) Tropane

MIBG- Meta-Iodobenzylguanidine

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CONFLICT OF INTERESTS

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