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PARKINSON'S DISEASE AND TREATMENT-A REVIEW ARTICLE

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ABSTRACT

Parkinson disease is a neurodegenerative disease characterized by tremors, postural in stability, bradykinesia and rigidity. The pathology involved is loss of dopaminergic neurons of substantia nigra in mid brain region. Lewy bodies observed in place of degenerated neurons. This disease is treated by anticholinergic agents, dopamine precursors and agonists, catechol o-methyltransferase inhibitors and mono amino oxidase -B inhibitors. Advanced treatment strategies help the patient to get rid of the symptoms. Advanced treatment techniques used are deep brain stimulation, gene therapy, neuroprotective and neuronal transplantation.

KEYWORDS: Parkinson disease, remors postural, treatment techniques.

Parkinson disease: A chronic progressive neurologic disease caused by decreased production of dopamine in substantia nigra that is characterized by rigidity, tremor at rest, slowing of voluntary movements, postural imbalance and muscle weakness. Parkinson disease was first described by Dr. James parkinson as shaking palsy.

Etiology

1. **Genetic Factors**: Genes that link to Parkinson disease such as α-synuclein and parkin are being under study. α-synuclein is a synaptic protein where the mutations occur in gene coding of α-synuclein.
2. **Environmental factors**

MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) MPTP itself is not toxic, and as a lipophilic compound can cross the blood–brain barrier. Once inside the brain, MPTP is metabolized into the toxic cation 1-methyl-4-phenylpyridinium (MPP+) by the enzyme MAO-B of glial cells. MPP+ kills primarily dopamine-producing neurons in a part of the brain called the pars compacta of the substantia nigra.

3. Drugs that cause Parkinsonism

Parkinsonism is also caused by use of some drugs such as Phenothiazines, Butyrophenones, Reserpine.

Clinical Manifestaions

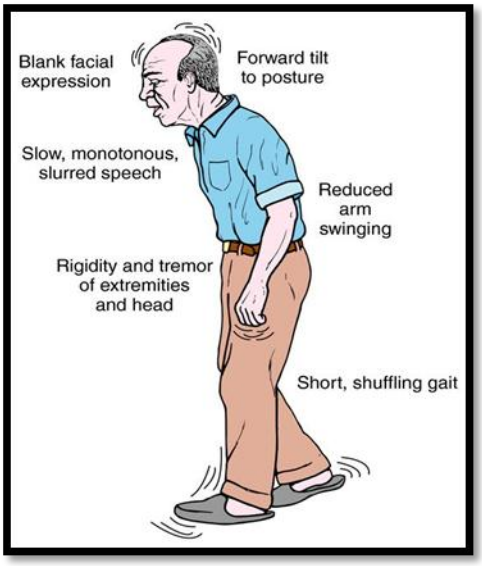
Primary Motor Symptoms

1. **Resting Tremor:** The tremor consists of a shaking or oscillating movement, and usually appears when a person's muscles are relaxed, or at rest, hence called "resting tremor." When the thumb and forefinger are involved, it is known as the pill-rolling tremor.

Bradykinesia: "slow movement" Reduction of spontaneous movement, which can give the appearance of abnormal stillness and a decrease in facial expressivity.

Rigidity: Rigidity causes stiffness and inflexibility of the limbs, neck and trunk. Muscles normally stretch when they move, and then relax when they are at rest. In Parkinson's rigidity, the muscle tone of an affected limb is always stiff and does not relax, sometimes contributing to a decreased range of motion. Rigidity can be uncomfortable or even painful.

Postural Instability: A tendency to be unstable when standing upright. A person with postural instability has lost some of the reflexes needed for maintaining an upright posture and may topple backwards if jostled even slightly.



Secondary Motor Symptoms

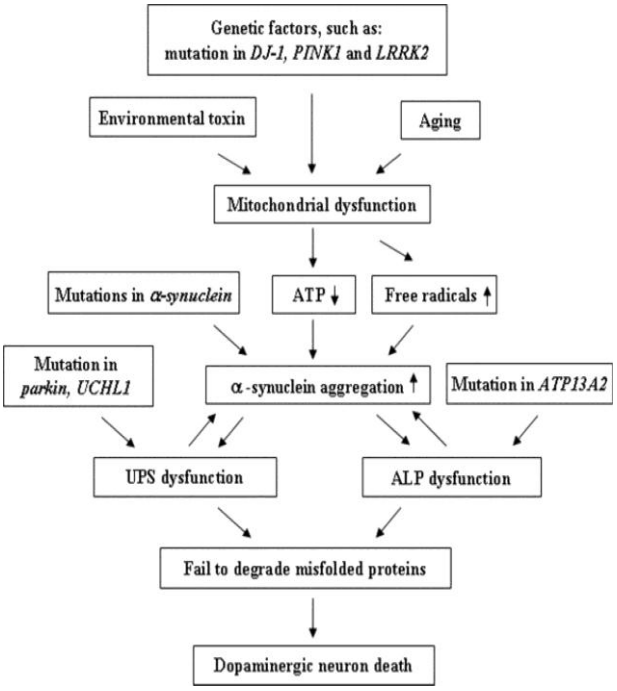
1. **Freezing:** People who experience freezing will normally hesitate before stepping forward. They feel as if their feet are glued to the floor.
2. **Micrographic:** shrinkage in handwriting.
3. **Mask-like Expression:** decreased unconscious facial movements
4. **Unwanted Accelerations:** movements that are too quick
5. Stooped posture, a tendency to lean forward
6. Dystonia
7. Impaired fine motor dexterity and motor coordination
8. Impaired gross motor coordination
9. Poverty of movement (decreased arm swing)
10. Akathisia
11. Speech problems, such as softness of voice or slurred speech caused by lack of muscle control
12. Difficulty swallowing
13. Sexual dysfunction
14. Cramping
15. Drooling and excess saliva resulting from reduced swallowing movements

Non-motor symptoms

1. Loss of sense of smell, constipation
2. REM behavior disorder (a sleep disorder)
3. Mood disorders
4. Orthostatic hypotension (low blood pressure when standing up).

Pathophysiology

The ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (ALP) are the two most important mechanisms that normally repair or remove abnormal proteins (mutant alpha synuclein). Alterations in the function of these systems to degrade misfolded and aggregated proteins play a role in the pathogenesis of Parkinson's disease.



Diagnosis

Positron emission topography (PET) scan is used to assess activity and function of brain regions involved in movement.

CT scan: Computed tomography, uses X-rays and computers to produce images of inside the body including the brain**.**

MRI

Magnetic resonance imaging, is a test that produces very clear pictures, or images, of the human body without the use of X-rays.

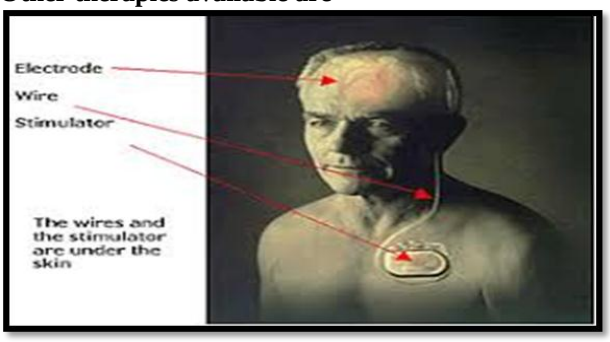
Treatment

Drug class, drug, brand name	dose	Adverse effects	Mechanism of action
Anticholinergic Agents			
Benztropine **[COGENTIN]**	1 to 2 mg orally per day	(1) **Peripheral anticholinergic effects** dry mouth, decreased sweating, urinary retention, constipation, increased intraocular tension; and nausea. (2) **CNS effects** dizziness, delirium, disorientation, anxiety, agitation, hallucinations, and impaired memory.	This class of drugs blocks the excitatory neurotransmitter cholinergic influence in the basal ganglia. These drugs are more effective for
Biperiden **[AKINETON]**	2 mg orally 3 to 4 times a day		
Procyclidine **[KEMADRIN]**	5 mg three times a day		
Trihexyphenidyl	6 to 10 mg/day in 3		

[ARTANE] Ethopropazine **[PARSITAN]**	to 4 divided doses	(3) **Cardiovascular effects** include hypotension and orthostatic hypotension	tremor and rigidity than for bradykinesia and less effective for postural imbalance**.**
Dopamine Precursors			
Levodopa plus carbidopa **[RYTARY, SINEMET]**	100 mg daily Levodopa should be taken with food to minimize stomach upset	(1) **GI-effects** anorexia N/V and abdominal distress. (2) **Cardiovascular effects** postural hypotension, tachycardia. (3) **Musculoskeletal effects** dystonia (4) **CNS effects** confusion, memory changes, depression, hallucinations, and psychosis. (5) **Hematological effects** hemolytic anemia, leukopenia, and agranulocytosis	Levodopa is converted to dopamine by the enzyme dopa decarboxylase, which elevates CNS levels of dopamine
DOPAMINE AGONISTS			
Bromocriptine **[PARLODEL]**	Initial: 1.25 mg twice daily with meals. Titration: Add 2.5 mg/day, with meals, to dosage regimen every 14 to 28 days	**GI effects**, anorexia/V and abdominal distress **Cardiovascular effects** postural hypotension, tachycardia. Blood pressure must be monitored, particularly for patients taking antihypertensive medication. **Pulmonary effects**: Reversible infiltrations, pleural effusions. **CNS effects** confusion, memory changes, depression, and halucinlations,	direct stimulation of postsynaptic dopamine receptors; it is most commonly used as an adjunct to levodopa therapy
pramipexol [**MIRAPEX, MIRAPEXIN]**	0.125 three times a day. Do not increase more frequently than every 5 to 7 days. (c) Maintenance treatment: 1.5 to 4.5 mg daily in three divided doses with or without levodopa.	nausea, insomnia, constipation, dizziness, somnolence, GI side effects, and visual hallucinations, orthostatic hypotension	Pramipexole fully stimulates the dopamine receptors to which it binds. Its action may be related to its capacity to function as an antioxidant and oxygen free-radical scavenger.
Ropinirole [**REQUIP]**	0.25 mg three times daily may be titrated	Nausea, dizziness, somnolence, headache, fatigue, and abnormal vision. Sleep attack, by falling asleep during activity daily living. Orthostatic hypotension.	Fully stimulates the dopamine receptors to which it binds. Its action may be related to its capacity to function as an antioxidant and oxygen free-radical scavenger
Amantadine **[SYMMETREL]**	100 mg/day, may be increased to 200 to 300 mg/day	Peripheral anticholinergic effects (b) CNS effects include seizures (c) Cardiovascular effects. CHF blood pressure M.I or arrhythmias. (d) Dermatological effects include livedo reticularis, a diffuse rose-color mottling of the skin, which is reversible on discontinuation of the drug. (e) Hematological effects. (4) Renal function impairment.	Amantadine increases dopamine levels at postsynaptic receptor sites by decreasing presynaptic reuptake and enhancing dopamine synthesis and release.
Apomorphine Hydrochloride Injection SC **(APOKYN)**	Dose should be started at 2 mg increase to maximum of 6 mg.	QT prolongation, Sleep attack, falling asleep during daily activities, Hallucination, Sulfite sensitivity	Stimulating of postsynaptic dopamine D2-type receptors within caudate and putamen in brain**.**
COMT INHIBITORS			
Tolcapone **(TASMAR)**	Starting dose of 100 to 200 mg three times daily	Liver toxicity**,** Fibrolic complications, such as retroperitoneal fibrosis, pulmonary infiltrates or effusion, or pleural thickening.	Tolcapone is a selective and reversible inhibitor of COMT.Tolcapone inhibits COMT both peripheral and centrally.
Entacapone **(COMTAN)**	200 mg with each dose of l-dopa up to eight times daily	Hepatic function impairment, Fibrotic complication. Cases of retroperitoneal fibrosis, pulmonary infiltrates pleural effusion, and pleural thickening, prostate	Entacapone is a selective and reversible inhibitor of COMT and permits

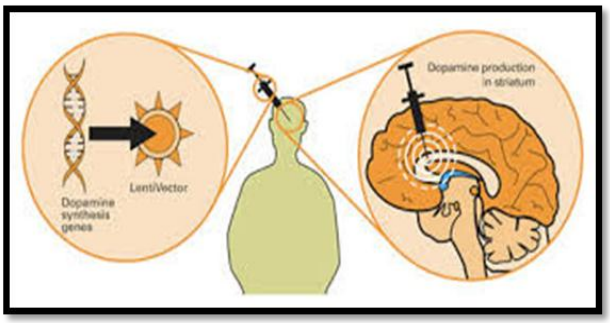
	with a maximum dose of 1600 mg daily.	cancer. Other side effects. Dyskinesia/hyperkinesia, nausea, urine discoloration (brownish orange), diarrhea, and abdominal pain	additional levodopa to reach the brain. It does not have any anti-Parkinson effect of its own.
MAO-B INHIBITORS			
Selegiline **[ELDEPRYL]**	10 mg/day	CNS effects include dizziness, confusion, headache, hallucinations, vivid dreams, dyskinesias, behavioral and mood changes, and depression. orthostatic hypotension, hypertension, arrhythmia, palpitations, sinus bradycardia, and syncope,GI effects include nausea and abdominal pain and lead to GI bleeding, weight loss, poor appetite, and dysphagia. slow urination, transient nocturia, and prostatic hypertrophy. Increased sweating, diaphoresis, and photosensitivity. Transient elevations in liver function tests.	Selegiline is a selective inhibitor of MAO-B, which prevents the breakdown of dopamine selectively in the brain at recommended doses
Rasagiline **(AZILECT)**	0.5-1mg/day		

Other therapies available are



1. Deep brain stimulation

The use of deep brain stimulation in treatment of Parkinson disease dates from 1987.at present this procedure is only used for patients whose symptoms cannot be controlled with medications or use of those medications may cause side effects.it directly effects on brain neurotransmitter system by sending high frequency electrical impulses into specific area and reduce the symptoms. There are few sites in brain that can be targeted to achieve results they are subthalamic nucleus and Globus pallidus interna. In U.S.A food and drug administration authority has approved this process to treat parkinsonism. This process carries complications related to hemorrhage and infections.



2. Gene therapy

The main use of gene therapy in parkinsonism is to generate dopaminergic neurons and then transplant these cells to patient. This is because the neuronal cells cannot be regenerated or proliferated so, replacing lost neurons is a process currently going under investigation. Embryonic dopaminergic cells are difficult to obtain, and modifications of cell only made on somatic cells not germline cells.

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