Review Article

LITERATURE REVIEW ON HISTORY AND PHARMACOTHERAPY OF PARKINSON`S DISEASE

ABSTRACT

Introduction:

Parkinson's disease (PD) is a slowly progressive neurodegenerative disease characterized by: Pill rolling tremors, Akathisia(inability to sit still), Rigidity, Kinesis(akinesia, dyskinesia), Instable(stooped) posture, no arm swinging in rhythm with legs, Sialorrhea Oculogyric crisiseyes are held fixed for a variable length of time), Nervous depression, Involuntary tremors, Seborrhoea and Masked facial expression.

Parkinson's disease is a chronic, progressive, neurodegenerative disorder with an estimated prevalence of 31 to 328 per 100,000 people worldwide. It is estimated that more than 1 percent of the population over age 65 are afflicted with Parkinson's disease; incidence and prevalence increase with age. There are numerous unanswered questions regarding the diagnosis and management of Parkinson 's disease. Surgical treatment for Parkinson's disease is generally considered for patients who respond to medications but have intolerable side effects. Surgical options include ablative procedures, deep brain stimulation, and tissue transplantation. This review focused on History and management of Parkinson's disease. The purpose of this literature review is to gain an understanding of the existing research relevant to history and pharmacotherapy of Parkinson's disease.

Conclusion:

Pharmacological treatment of PD should be tailored to the individual patient. Drug therapy is not obligatory in early PD; many patients can be managed for a time with exercise and lifestyle interventions. For patients with mild symptoms, MAO-B inhibitors, amantadine, or (in younger patients) anticholinergics are reasonable choices

Keywords: Parkinson's disease, Akathisia, Rigidity, deep brain stimulation, tissue transplantation.

INTRODUCTION

Parkinson's disease (PD) is a slowly progressive neurodegenerative disease characterized by: Pill rolling tremors, Akathisia(inability to sit still), Rigidity, Kinesis(akinesia, dyskinesia), Instable(stooped) posture, no arm swinging in rhythm with legs, Sialorrhea Oculogyric crisiseyes are held fixed for a variable length of time), Nervous depression, Involuntary tremors, Seborrhoea and Masked facial expression. The term parkinsonism applies for a disease state having such common characteristics, while Parkinson's disease (paralysis agitans) is restricted to the primary or idiopathic parkinsonism.[1] Primary parkinsonism arises due to degeneration of pigmented brain stem nuclei, including the dopaminergic substantianigra pars compacta, with the presence of lewy bodies in the remaining nerve cells. Secondary or symptomatic parkinsonism results from a variety of causes that includes infections, toxins, drugs, vascular lesions, tumors and trauma. Among these, neuroleptic drugs are considered to the commonest cause of secondary parkinsonism today.[2]

Aims & Objectives:

The purpose of this literature review is to gain an understanding of the existing research relevant to history and pharmacotherapy of Parkinson's disease.

Parkinson's Disease History

Parkinson's disease is a condition that has been known about and treated since ancient times. Parkinson's disease existed in the ancient Indian medical system of Ayurveda and was called Kampavata. In Western medical literature, physician Galen described it as "shaking palsy" in AD 175. However, it was not recognized and its symptoms were not documented until 1817 that a detailed medical essay on the shaking palsy was published by the British physician James Parkinson.

The term Parkinson's disease being coined by, a French neurologist by the name of Jean Martin Charcot. Charcot was the first to truly recognise the importance of Parkinson's work and named the disease after him to venerate Parkinson's studies**.**

The underlying biochemical changes in the brain, neurotransmitter dopamine and its role on PD were identified by the Swedish scientist Arid Carlsson, in the 1950's**.**

James Parkinson, with characteristic succinctness and clarity, wrote his essay on "shaking palsy" (paralysis agitans), based on his shrewd observations on six patients. His description of the disorder was "involuntary tremulous motion, with lessened muscular power, in pars not in action and even

when supported, with a propensity to bend the trunk forward, and to pass from a walking to a running pace, the senses and intellects being uninjured". Parkinson emphasized the significance of presenting tremor and the potential prognostic importance of categories and staging by writing: "it seldom happens that the agitation extends beyond the arms with in the first two years; which period therefore, if we were disposed to divide the disease into stages, might be said to comprise the first stage." Subsequent clinical studies have amplified and somewhat modified this description, with emphasis on the muscular stiffness, immobile face and mumbling speech of the sufferer**.** [3]

Jean-Martin Charcot. He identified the cardinal features of Parkinson's disease and specifically separated bradykinesia from rigidity**.**

Charcot collected handwriting samples in his patients' charts and used them as part of his diagnostic criteria, thereby separating the large and sloppy script of patients with action tremor from the micrographia of Parkinson's disease

Gowers offered one of the most memorable similes regarding parkinsonian tremor: the movement of the fingers at the metacarpal-phalangeal joints is similar to that by which Orientals beat their small drums**.** Charcot recognized the distinctive dysautonomia of Parkinson's disease, noting how patients experienced a sense of hyperthermia even in the drafty, cold wards of the French hospitals.

Prescription dated 1877. In treating Parkinson's disease, Charcot used belladonna alkaloids (agents with potent anticholinergic properties) as well as rye-based products that had ergot activity, a feature of some currently available dopamine agonists. Charcot's advice was empiric and preceded the recognition of the well-known dopaminergic/cholinergic balance that is implicit to normal striatal neurochemical activity**.** [4]

It was in the 1960s that that the chemical differences in the brains of Parkinson's patients were identified. The low levels of dopamine cause the degeneration of nerve cells in part of the brain called the substantia nigra. It was this discovery that led to the first effective medicinal treatment of the disease. James Parkinson only had started Modern treatment of this disease. It was transformed by the dopaminergic neurons in the nigrostriatal pathway of the basal ganglia, and recognition of

dopamine deficiency as the major biochemical abnormality in PD. Despite tremendous therapeutic advances, PD continues to be one of the most common causes of disability among the elderly.

In the 1960s the drug Levodopa was first administered to treat the symptoms and has since become the "gold standard" in medication. Levodopa exploded the myth that the disease is untreatable, and triggered a surge of controlled investigation which continues to this day. The drug still remains central to all treatment regimens of PD, although it's reduced effectiveness with time in the light of the often-normal life expectancy of PD patients has created new problems in therapeutic management. These problems have not been discernibly diminished by other allied therapeutic approaches which have evolved during the levodopa period. The addition of other antiparkinsonian drugs has not added much to life expectancy.

Parkinson's disease (PD) is a neurodegenerative disorder characterized primarily by loss of dopamine neurons in the substantia nigra. Symptoms generally develop on one body side slowly over years but the progression may differ from one person to another due to the diversity of the disease. People with PD may experience tremor, mainly at rest (described as pill rolling tremor in hands), bradykinesia, limb rigidity, gait and balance problems. Prevalence is approximately 200 cases per 100,000 population, and the incidence is about 25 cases per 100,000 population, but these figures might show differences from one region of the world to another. [5]

Parkinson's disease (PD) is a neurodegenerative disease with the core features o tremor, bradykinesia, rigidity, and postural instability. Additional motor features include decreased facial expression (hypomimia), decreased blink rate, small handwriting (micrographia), stooped posture, shuffling gait with reduced arm swing, festination (increasingly rapid small steps), difficulty turning when walking, and difficulty turning over in bed. The constellation of some or all of these motor features is referred to as parkinsonism. [6]

Parkinsonism as a clinical entity was first described by James Parkinson in 1817 (Parkinson's disease; PD; paralysis agitans). It is a syndrome of varied etiology. Besides the idiopathic PD, arteriosclerotic and post-encephalitic forms, the syndrome is seen in hepatolenticular degeneration of Wilson's disease and can be induced by drugs like reserpine, haloperidol, triperidol, chlorpromazine and other halogenated phenothiazines. Point mutations in genes on several chromosomes have been reported in some patients**.**[7]

Wilson's disease (hepatolenticular degeneration) due to chronic copper poisoning, is a rare cause. [8]

GENDER AND PARKINSONISM

The available evidence indicates that men have a slightly higher risk of parkinsonism than women, with the exception of drug-induced parkinsonism. According to a meta-analysis, relative risk of parkinsonism for men compared to women is 1.5%. Suggested reasons for this risk included differential exposure to external risk factors, an X-linked genetic factor, and mitochondrial dysfunction. The lifetime risk of parkinsonism is greater in men than in women (4.4% vs. 3.7%). In older patients, 65 to 84 years, the male to female incidence ratio was 1.66 for parkinsonism and 2.13 for PD. Interestingly, although women have a longer life expectancy than men, women with PD have the same mortality rates as men with PD.

Classification of Parkinsonism

Primary Parkinson's disease	Other Degenerative Disorders
Sporadic	Corticobasal degeneration (CBD)
Familial	Dementia with Lewy bodies (DLB)
Secondary parkinsonism	Multiple-system atrophy (MSA)
Drug-induced parkinsonism (DIP)	Progressive supranuclear palsy (PSP)
Toxin-induced parkinsonism	Spinocerebellar ataxias (SCA)
Infectious	
Creutzfeld-Jakob disease (CJD)	Hallervorden-Spatz disease Huntington's disease (HD)
Metabolic	Neuroacanthocytosis
Structural Wilson's disease	
Tumor	X-linked dystonia-parkinsonism (Lubag)
Subdural hematoma	
Vascular	

Motor Features of Parkinsonism

Tremor at rest

Rigidity

Bradykinesia

Loss of postural reflexes

Hypomimia (masked faces)

Speech disturbance (hypokinetic dysarthria)

Hypophonia

Dysphagia

Sialorrhea

Respiratory difficulties

Loss of associated movement

Shuffling, short-step gait

Festination

Freezing

Micrographia

Difficulty turning in bed

Slowness in activities of daily living

Stooped posture,

kyphosis, and scoliosis,

Dystonia, myoclonus, orofacial dyskinesia

Neuro-ophthalmologic findings

Impaired visual contrast sensitivity

Visuospatial impairment

Impaired upward gaze, convergence, and smooth pursuit

Impaired vestibuloocular reflex

Hypometric saccades

Decreased blink rate

Spontaneous and reflex blepharospasm (glabellar or Myerson’s sign)

Lid apraxia (opening or closure)

Motor findings related to dopaminergic therapy

Levodopa-induced dyskinesia (chorea, dystonia, myoclonus, tic)

Cardinal signs. [4]

Pathophysiology

The basal ganglia consist of the corpus striatum (the caudate nucleus and the putamen), globus pallidus, and substantia nigra. They modulate the extrapyramidal (EP) control of motor activity. The substantia nigra pars compacta (SNpc, which is rich in dopaminergic neuronal cell bodies), projects to the corpus striatum where dopamine is released. The latter, in turn, projects back via the globus pallidus and substantia nigra pars reticulata (SNpr) to the thalamus and finally to the cerebral, motor cortex, and regulates their involvement in voluntary movement. The nigro-striatal neurons make efferent connections with the striatum where they make contact with two types of striatal neurons: (i) those bearing excitatory D1 receptors and (ii) those bearing inhibitory D2 receptors. The neurons which bear D1 receptors relay impulses via a direct excitatory pathway (medial globus pallidus → thalamus) to the cerebral motor cortex and uses GABA, the inhibitory NT. The final outcome is enhanced stimulation by the latter of the spinal motor neurons. On the other hand, the neurons which bear D2 receptors relay impulses via an indirect inhibitory pathway (lateral globus pallidus → subthalalmic nucleus → medial globus pallidus and SNpr → thalamus) to the same cerebral motor cortical neurons; the indirect pathway has two GABAergic links and one glutamatergic link. It finally decreases stimulation by them of the same spinal motor neurons. In health, the direct pathway (excitatory) predominates as the dopamine released in the neostriatum enhances the activity of the concerned neurons**.** [7]

The most consistent lesion in PD is degeneration of neurones in the substantia nigra pars compacta (SN-PC) and the nigrostriatal (dopaminergic) tract. This results in deficiency of dopamine (DA) in the striatum which controls muscle tone and coordinates movements. An imbalance between dopaminergic (inhibitory) and cholinergic (excitatory) system in the striatum occurs giving rise to the motor defect. Though the cholinergic system is not primarily affected, its suppression (by anticholinergics) tends to restore balance. The cause of selective degeneration of nigrostriatal neurones is not precisely known, but appears to be multifactorial. Oxidation of DA by MAO-B and aldehyde dehydrogenase generates hydroxyl free radicals (• OH) in the presence of ferrous iron (basal ganglia are rich in iron). Normally these free radicals are quenched by glutathione and other protective mechanisms. Age-related and/or otherwise acquired defect in protective mechanism allows

the free radicals to damage lipid membranes and DNA resulting in neuronal degeneration. Genetic predisposition may contribute to the high vulnerability of substantia nigra neurones. Ageing induces defects in mitochondrial electron transport chain. Environmental toxins and/or genetic factors may accentuate these defects in specific areas. A synthetic toxin N-methyl-4-phenyl tetrahydropyridine (MPTP), which occurred as a contaminant of some illicit drugs, produces nigrostriatal degeneration and manifestations similar to PD by impairing energy metabolism in dopaminergic neurones. It has been proposed that MPTP-like chemicals may be present in the environment, small quantities of which accelerate age related or otherwise predisposed neuronal degeneration of parkinsonism, but there is no proof. Excess of the excitatory transmitter glutamate can cause 'excitotoxic' neuronal death by inducing Ca2+ overload through NMDA receptors. Drug-induced temporary parkinsonism due to neuroleptics, metoclopramide (dopaminergic blockers) is now fairly common, while that due to reserpine (DA depleter) is historical**.**[8]

In drug-induced parkinsonism, the DA receptors in the striatum are blocked; there is no deficiency of DA. Hence, it is reversible following omission of the offending drug**.** [7]

Diagnosis and Differential Diagnosis of Parkinson's Disease

Parkinson's disease is a clinical diagnosis. A tremor predominant presentation must be distinguished from essential tremor, drug-induced tremor, physiologic tremor, and hyperthyroidism. Asymmetry of tremor and accompanying bradykinesia and rigidity on the side of tremor are suggestive of PD. Early falls and/or impaired vertical gaze with parkinsonism suggest progressive supranuclear palsy (PSP). Early and severe autonomic dysfunction with parkinsonism suggests multiple system atrophy (MSA). Dementia and hallucinations arising be ore or concurrently with parkinsonism suggest dementia with Lewy bodies (DLB). Improvement in symptoms with levodopa is also suggestive of PD, although some Parkinson plus syndromes may have an initial response to levodopa. When there is clinical ambiguity, a dopamine transporter SPEC (single photon emission computed tomography) scan can be used to look or asymmetric decreased activity in the basal ganglia. However, dopamine transporter SPEC only distinguishes a neurodegenerative parkinsonian syndrome from "not a neurodegenerative parkinsonian syndrome" (i.e., it does not distinguish between PD, multiple systemsatrophy, progressive supranuclear palsy, and corticobasal syndrome). Dopamine transporter SPEC can be use

ul in a patient in whom there is a question of PD versus essential tremor (if the latter presents asymmetrically, as it sometimes does) or PD versus drug-induced parkinsonism. [6]

Pharmacotherapy

Classification of antiparkinsonian drugs

I. Drugs affecting brain dopaminergic system

(a) Dopamine precursor: Levodopa (L-dopa)

(b) Peripheral decarboxylase inhibitors: Carbidopa, Benserazide.

(c) Dopaminergic agonists: Bromocriptine, Ropinirole, Pramipexole

(d) MAO-B inhibitor: Selegiline, Rasagiline

(e) COMT inhibitors: Entacapone, Tolcapone

(f) Glutamate (NMDA receptor) antagonist (Dopamine facilitator): Amantadine.

II. Drugs affecting brain cholinergic system

(a) Central anticholinergics: Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.

(b) Antihistaminics: Orphenadrine, Promethazine. [8]

Levodopa

Levodopa (also called L-dopa or l-3,4-dihydroxyphenylalanine), the metabolic precursor of DA, is the single most effective agent in the treatment of PD. The effects of levodopa result from its decarboxylation to DA. When administered orally, levodopa is absorbed rapidly from the small bowel by the transport system for aromatic amino acids.

The DA produced is responsible for the therapeutic effectiveness of the drug in PD; after release, it is either transported back into dopaminergic terminals by the presynaptic uptake mechanism or metabolized by the actions of MAO and COMT

In clinical practice, levodopa is almost always administered in combination with a peripherally acting inhibitor of AADC, such as carbidopa or benserazide, drugs that do not penetrate well into the CNS. If levodopa is administered alone, the drug is largely decarboxylated by enzymes in the intestinal mucosa and other peripheral sites so that relatively little unchanged drug reaches the cerebral circulation, and probably less than 1% penetrates the CNS. In addition, DA release into the circulation by peripheral conversion of levodopa produces undesirable effects, particularly nausea. Inhibition of

peripheral decarboxylase markedly increases the fraction of administered levodopa that remains unmetabolized and available to cross the bloodbrain barrier, and reduces the incidence of GI side effects and drug-induced orthostatic hypotension.

A common problem is the development of the “wearing off” phenomenon: Each dose of levodopa effectively improves mobility for a period of time, perhaps 1–2 h, but rigidity and akinesia return rapidly at the end of the dosing interval. Increasing the dose and frequency of administration can improve this situation, but this often is limited by the development of dyskinesias, excessive and abnormal involuntary movements.

Recently, two new formulations of levodopa intended to address wearing off have been approved. RYTARY carbidopa-levodopa extended-release capsules contain both immediate- and extended-release beads that provide reduced off time in patients with motor fluctuations. DUOPA carbidopa-levodopa intestinal gel is administered through a gastrostomy tube into the jejunum using a pump and can have a dramatic effect on reducing “off ” time. [10]

Administration of levodopa with nonspecific inhibitors of MAO accentuates the actions of levodopa and may precipitate life-threatening hypertensive crisis and hyperpyrexia; nonspecific MAO inhibitors always should be discontinued at least 14 days before levodopa is administered (note that this prohibition does not include the MAO-B subtype-specific inhibitors selegiline and rasagiline). Abrupt withdrawal of levodopa or other dopaminergic medications may precipitate the neuroleptic malignant syndrome of confusion, rigidity, and hyperthermia, a potentially lethal adverse effect. [9]

Dopamine Receptor Agonists

The DA receptor agonists in clinical use have durations of action substantially longer than that of levodopa; they are often used in the management of dose-related fluctuations in motor state and may be helpful in preventing motor complications (Parkinson Study Group, 2000). DA receptor agonists are proposed to have the potential to modify the course of PD by reducing endogenous release of DA as well as the need for exogenous levodopa, thereby reducing free-radical formation. Two orally administered DA receptor agonists are commonly used for treatment of PD: ropinirole and pramipexole. Both are well absorbed orally and have similar therapeutic actions. There is also a transdermal formulation of the DA agonist rotigotine available. Ropinirole and pramipexole have selective activity at D2 class sites (specifically at the D2 and D3 receptor). Rotigotine acts at D2 sites.

Pramipexole, ropinirole, and rotigotine may produce hallucinosis or confusion, similar to that observed with levodopa, and may cause nausea and orthostatic hypotension. They should be initiated at low dose and titrated slowly to minimize these effects. The DA agonists, as well as levodopa itself, are also associated with fatigue and somnolenceand also has activity at D1 class sites. Like levodopa, these DA agonists can relieve the clinical symptoms of PD.

Apomorphine.

Apomorphine is a dopaminergic agonist that can be administered by subcutaneous injection. It has high affinity for D4 receptors; moderate affinity for D2, D3, D5, and adrenergic α1D, α2B, and α2C receptors; and low affinity for D1 receptors. Apomorphine is FDA-approved as a “rescue therapy” for the acute intermittent treatment of “off ” episodes in patients with a fluctuating response to dopaminergic therapy. Apomorphine has the same side effects as the oral DA agonists. Apomorphine is highly emetogenic and requires pre- and posttreatment antiemetic therapy. Oral trimethobenzamide, at a dose of 300 mg, three times daily, should be started 3 days prior to the initial dose of apomorphine and continued at least during the first 2 months of therapy.

Profound hypotension and loss of consciousness have occurred when apomorphine was administered with ondansetron; hence, the concomitant use of apomorphine with antiemetic drugs of the 5HT3 antagonist class is contraindicated. Other potentially serious side effects of apomorphine include QT prolongation, injection site reactions, and the development of a pattern of abuse characterized by increasingly frequent dosing leading to hallucinations, dyskinesia, and abnormal behaviour. Because of these potential adverse effects, use of apomorphine is appropriate only when other measures, such as oral DA agonists or COMT inhibitors, have failed to control the off episodes. Apomorphine therapy should be initiated with a 2-mg test dose in a setting where the patient can be monitored carefully. If tolerated, it can be titrated slowly up to a maximum dosage of 6 mg. For effective control of symptoms, patients may require three or more injections daily.

Catechol-O-Methyltransferase Inhibitors

COMT inhibitors block the peripheral conversion of levodopa to 3-O-methyl DOPA, increasing both the plasma t 1/2 of levodopa and the fraction of each dose that reaches the CNS. The COMT inhibitors tolcapone and entacapone reduce significantly the “wearing off ” symptoms in patients

treated with levodopa/carbidopa (Parkinson Study Group, 1997). The two drugs differ in their pharmacokinetic properties and adverse effects: Tolcapone has a relatively long duration of action and appears to act by inhibition of both central and peripheral COMT. Entacapone has a short duration of action (2 h) and principally inhibits peripheral COMT. Common adverse effects of both agents include nausea, orthostatic hypotension, vivid dreams, confusion, and hallucinations. An important adverse effect associated with tolcapone is hepatotoxicity. At least three fatal cases of fulminant hepatic failure in patients taking tolcapone have been observed, leading to addition of a black-box warning to the label. Tolcapone should be used only in patients who have not responded to other therapies and with appropriate monitoring for hepatic injury. Entacapone has not been associated with hepatotoxicity. Entacapone also is available in fixed-dose combinations with levodopa/carbidopa.

Selective MAO-B Inhibitors Two isoenzymes of MAO oxidize catecholamines: MAO-A and MAO-B. MAO-B is the predominant form in the striatum and is responsible for most of the oxidative metabolism of DA in the brain. Selective MAO-B inhibitors are used for the treatment of PD: selegiline and rasagiline. These agents selectively and irreversibly inactivate MAO-B. Both agents exert modest beneficial effects on the symptoms of PD. The basis of this efficacy is, presumably, inhibition of breakdown of DA in the striatum. Selective MAO-B inhibitors do not substantially inhibit the peripheral metabolism of catecholamines and can be taken safely with levodopa. These agents also do not exhibit the “cheese effect,” the potentially lethal potentiation of catecholamine action observed when patients on nonspecific MAO inhibitors ingest indirectly acting sympathomimetic amines such as the tyramine found in certain cheeses and wine. Selegiline is generally well tolerated in younger patients for symptomatic treatment of early or mild PD.

In patients with more advanced PD or underlying cognitive impairment, selegiline may accentuate the adverse motor and cognitive effects of levodopa therapy. Metabolites of selegiline include amphetamine and methamphetamine, which may cause anxiety, insomnia, and other adverse symptoms. Selegiline is available in an orally disintegrating tablet as well as a transdermal patch. Both of these delivery routes are intended to reduce hepatic first-pass metabolism and limit the formation of the amphetamine metabolites. Unlike selegiline, rasagiline does not give rise to

undesirable amphetamine metabolites. Rasagiline monotherapy is effective in early PD. Adjunctive therapy with rasagiline significantly reduces levodopa-related wearing off symptoms in advanced PD. Although selective MAO-B inhibitors are generally well tolerated, drug interactions can be troublesome. Similar to the nonspecific MAO inhibitors, selegiline can lead to the development of stupor, rigidity, agitation, and hyperthermia when administered with the analgesic meperidine. Although the mechanics of this interaction are uncertain, selegiline or rasagiline should not be given in combination with meperidine. Tramadol, methadone, propoxyphene dextromethorphan, St. John's wort, and cyclobenzaprine are also contraindicated with MAO-B inhibitors. Although development of the serotonin syndrome has been reported with coadministration of MAO-B inhibitors and antidepressants (tricyclic or serotonin reuptake inhibitors), this appears to be rare, and many patients are treated with this combination without difficulty. If concurrent treatment with MAO-B inhibitors and antidepressants is undertaken, close monitoring and use of low doses of the antidepressant are advisable. [9]

In cell-culture systems, selegiline's neuroprotective effect is mediated by new protein synthesis. Selegiline induces transcriptional events that result in increased synthesis of antioxidant and antiapoptotic proteins. Evidence indicates that one of selegiline's metabolites, desmethylselegiline, is the active agent for neuroprotection. It is possible that selegiline's amphetamine metabolites may interfere with its neuroprotective actions. [11]

Muscarinic Receptor Antagonists

Anticholinergic agents can be used for patients who have disability due to tremor that is not adequately controlled with dopaminergic medication, but these are not first-line drugs, because of their limited efficacy and the possibility of neuropsychiatric side effects. [11]

Antimuscarinic drugs currently used in the treatment of PD include trihexyphenidyl and benztropine mesylate, as well as the antihistaminic diphenhydramine hydrochloride, which also interacts at central muscarinic receptors. The biological basis for the therapeutic actions of muscarinic antagonists is not completely understood. They may act within the neostriatum through the receptors that normally mediate the response to intrinsic cholinergic innervation of this structure, which arises primarily from

cholinergic striatal interneurons. These drugs have relatively modest antiparkinsonian activity and are used only in the treatment of early PD or as an adjunct to dopamimetic therapy. Adverse effects result from their anticholinergic properties. Most troublesome are, sedation memory difficulty, confusion, and hallucinations. All anticholinergic drugs must be used with caution in patients with narrow-angle glaucoma and in general anticholinergics are not well tolerated in the elderly. [9]

Amantadine

The FDA approved amantadine extended-release (ER) capsules for the treatment of dyskinesia in Parkinson disease patients receiving levodopa-based therapy, with or without concomitant dopaminergic medications. It is commonly introduced at a dose of 100 mg per day and slowly increased to an initial maintenance dose of 100 mg 2 or 3 times daily. The most concerning potential side effects of amantadine are confusion and hallucinations. Common side effects include nausea, headache, dizziness, and insomnia. Less frequently reported side effects include anxiety and irritability, ataxia, livedo reticularis, peripheral edema, and orthostatic hypotension. [10]

It is an antiviral agent used for the prophylaxis and treatment of influenza A, has antiparkinsonian activity.amantadine appears to potentiate CNS dopaminergic responses. It may release dopamine and norepinephrine from storage sites and inhibit the reuptake of dopamine and norepinephrine. It has been reported to antagonize the effects of adenosine at adenosine A2A receptors, which may inhibit D2 receptor function. It has anticholinergic properties, and blocks NMDA glutamate receptors. It is used as initial therapy of mild PD. It may offer additional benefit in patients experiencing maximal or waning effects from levodopa. It also may be helpful as an adjunct in patients on levodopa with dyskinesias. [11]

Advanced therapies for Advanced Stages.

In patients in whom conventional oral pharmacotherapy has been exhausted and cannot be optimized, three main device assisted therapies should be considered, all of them based on the concept of CDS: (1) continuous subcutaneous infusion of apomorphine; (2) intra-intestinal infusion of levodopa carbidopa gel (LCIG); and (3) deep-brain stimulation (DBS). The optimal timing for initiating these advanced therapies to improve of quality of life (QoL) and prevent complications is critical and

requires that patients and caregivers be informed early about the evolution to later stages of the disease with their complications. As the decision to initiate any of these therapies should be made by a MD specialist and a multi-disciplinary team, the role of the GN in timely referral is critical for adequate patient management. Apomorphine, a D1 and D2 dopamine receptor agonist, has rapid onset of action and is used in earlier stages as rescue injections during “off” periods. In advanced PD, it is delivered as a continuous subcutaneous infusion by means of a portable pump. It has shown effectiveness in treating MS and some NMS in advanced stages of the disease. LCIG is delivered directly to the proximal jejunum via a percutaneous gastrojejunostomy (PEG-J) tube connected to a portable infusion pump. This therapy is used to avoid erratic gastric emptying and to improve intestinal absorption. LCIG is an effective treatment for reducing motor fluctuations, improving “on” time without dyskinesia and improving health-related quality of life (HRQoL) in advanced PD. [12]

In January 2015, the FDA approved a carbidopa/levodopa enteral suspension that is infused into the jejunum by a portable pump. The efficacy of the enteral suspension to decrease off-time and increase on-time was shown in a multicentre, international study. [13]

Levodopa inhaled, a dopamine agonist, was approved in December 2018 for intermittent treatment of "off" episodes in patients who are already treated with oral carbidopa/levodopa. The inhaled dosage form bypasses the digestive system, thereby providing a quick onset of action as soon as 10 minutes[14]

Safinamide, a MAO-B inhibitor, was approved by the FDA in March 2017 as add-on treatment for patients with Parkinson disease who are currently taking levodopa/carbidopa and experiencing “off” episodes. [15], [16]

The U.S. Food and Drug Administration today approved Istradefylline tablets as an add-on treatment to levodopa/carbidopa in adult patients with Parkinson’s disease (PD) experiencing "off" episodes. An "off" episode is a time when a patient’s medications are not working well, causing an increase in PD symptoms, such as tremor and difficulty walking. [17], [18]

In April 2020, the U.S. Food and Drug Administration (FDA) approved Opicapone to use, with levodopa, to lessen the total amount of “off” time, when Parkinson’s symptoms return, each day. Opicapone boosts levodopa’s effect for better symptom control. Opicapone is a catechol-O-methyltransferase (COMT) inhibitor, which prevents levodopa breakdown so that more gets to the brain and turns into dopamine. Because opicapone works by boosting levodopa’s effect, it must be added to a medication regimen containing levodopa. (It does not work on its own.)

Potential benefits of the new drug include - Opicapone is taken once daily. (Other COMT-inhibitors must be taken several times a day or with each levodopa dose.) In clinical trials, Opicapone increased daily “on” time (when symptoms are controlled) by an average of one hour and was “non-inferior” to (no less effective than) entacapone, another COMT-inhibitor.

Possible side effects may include dyskinesia (involuntary movement), difficulty sleeping, sleepiness, abnormal dreams, dizziness, headache, low blood pressure, constipation, vomiting, dry mouth, muscle spasms or hallucinations (seeing things that aren’t there). Some possible complications, such as dyskinesia, may relate to the levodopa boost rather than a direct effect of Opicapone. [19], [20]

Conclusion:

Pharmacological treatment of PD should be tailored to the individual patient. Drug therapy is not obligatory in early PD; many patients can be managed for a time with exercise and lifestyle interventions. For patients with mild symptoms, MAO-B inhibitors, amantadine, or (in younger patients) anticholinergics are reasonable choices. In most patients, treatment with a dopaminergic drug, either levodopa or a DA agonist, is eventually required. Many practitioners prefer a DA agonist as initial therapy in younger patients in an effort to reduce the occurrence of motor complications, although the evidence supporting this practice is inconclusive. In older patients or those with substantial comorbidity, levodopa/carbidopa is generally better tolerated. [9]

Surgery: Thalamotomy, pallidotomy and deep-brain stimulation with implanted electrodes may benefit patients under 50 who suffer from severe symptoms unresponsive to drugs.[7]

Though it is the hard time for proper and reliable treatment for PD, it deals a great difficult in identifying and defining the exact nature of disease. The treatment continues to be a mystery for its complete cure by pharmacological ways. Various transplantation approaches have been tried and

injection of mid brain neurons from aborted human foetus to substantia nigra of PD patients is under clinical trials. The success rate of such transplants is variable and benefits are short lived.

Ayurveda with its medicinal plants and treatment approaches, can strengthen the therapeutic armamentarium of PD to improve clinical outcomes, if these leads are systematically further investigated by well-designed long term studies.

REFERENCES:

1. http://www.parkinsons.org/parkinsons-history.html
2. https://www.atrainceu.com/content/1-history-parkinsons disease
3. T. Pavan Pradeep andS. Venkataraman, Literature review on history and screening models for parkinsonism, International Journal of Pharmacological Screening Methods, Vol 2 / Issue 1 /2012/ 24-37
4. Rajesh Pahwa,Kelly E. Lyons HANDBOOK OF Parkinson's Disease, Early Iconography of Parkinson's Disease, fourth edition, Informa Healthcare 2007,5-19
5. https://www.movementdisorders.org/MDS/About/Movement-Disorder Overviews/Parkinsons-Disease--Parkinsonism.
6. Aaron L. Berkowitz, Clinical Neurology and Neuroanatomy A Localization-Based Approach, Diseases of the nervous system, Mc grow hill education 2017:248
7. Sathoskar RS, Bhandarkar SD, Ainapure SS. Drug therapy of parkinsonism and other degenerative disorders of CNS. *Pharmacology and Pharmacotherapeutics, Twenty fourth edition,* Elsevier. 2015: 380-392.
8. Tripathi KD. Antiparkinsonian drugs. *Essentials of Medical Pharmacology,* seventh edition, Jaypee Brothers Medical Publishers 2013: 425.
9. Laurence L. Brunton et al Goodman &Gilman's The pharmacological basis of therapeutics, Treatment of Central Nervous System Degenerative Disorders, thirteenth edition, Mc grow hill education 2018: 330-333.
10. https://emedicine.medscape.com/article/1831191-treatment

11. Bertram G. Katzung,Basic & Clinical Pharmacology, Pharmacologic Management of Parkinsonism & Other Movement Disorders, Fourteenth Edition, Mc grow hill education 2018: 501
12. ZvezdanPirtošek, Ovidiu Bajenaru, Norbert Kovács, Ivan Milanov, Maja Relja, Matej Skorvanek, "Update on the Management of Parkinson's Disease for General Neurologists", *Parkinson's Disease*, vol. 2020.
13. Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. *Lancet Neurol*. 2014 Feb. 13(2):141-9 [Medline].
14. LeWitt PA, Hauser RA, Pahwa R, Isaacson SH, Fernandez HH, Lew M, et al. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Neurology. 2019 Feb 01;18(2):145-154.
15. Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C, et al. Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients with Parkinson Disease and Motor Fluctuations: A Randomized Clinical Trial. *JAMA Neurol*. 2017 Feb 1. 74 (2):216-224.
16. Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D, et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. *Mov Disord*. 2014 Feb. 29 (2):229-37.
17. Mizuno Y, Kondo T, Japanese Istradefylline Study Group. Adenosine A2A receptor antagonist istradefylline reduces daily OFF time in Parkinson's disease. *Mov Disord*. 2013 Jul. 28 (8):1138-41.
18. https://www.fda.gov/news-events/press-announcements/fda-approves-new-add-drug-treat-episodes-adults-parkinsons-disease
19. https://www.michaeljfox.org/news/newly-approved-parkinsons-drug-aims-lessen-time
20. https://www.michaeljfox.org/news/ongentys-opicapone