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A REVIEW ON PARKINSON'S DISEASE: ETIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS AND ITS VARIOUS MANAGEMENTS

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ABSTRACT:

Parkinson disease is the second most prevalent neurodegenerative illness. Parkinson disease is a chronic, progressive disease that affects 1% of people over the age of 60. The disease progresses vary in people, with those diagnosed early in life living longer than those diagnosed later in life. The clinical features typically associated with Parkinson's disease are tremor, rigidity, and bradykinesia, with postural instability frequently appearing as the disease progresses. A thorough history and physical examination should be included in the differential diagnosis of Parkinson's disease. It is a complex neurodegenerative disease with a wide range of motor and non-motor symptoms that necessitate an individualized care plan. Monoamine oxidase-B inhibitor is generally the first step in monotherapy. If motor fluctuations develop, consider adding a catechol-O-methyltransferase inhibitor to extend the duration of levodopa activity. Consider using an MAO-B inhibitor or a dopamine agonist instead. Consider adding amantadine to the treatment of levodopa-induced peak-dose dyskinesias. Although there is no known cure for Parkinson's disease, alternative drug, surgical, and behavioural therapies are available, and new treatments are being developed to help alleviate the adverse effects and symptomatology of this progressive disease.

Keywords: Parkinson disease, alpha synuclein, tremor, levodopa

INTRODUCTION:

Parkinson's disease (PD) is a common neurological condition that is more frequent as person gets older. Because Parkinson's disease mostly affects older persons, global ageing populations, particularly in economically developed nations, will increasingly need to devise methods to satisfy the health care requirements of those with the disease. (1) It was initially described in 1817 by James Parkinson in his seminal paper "An essay on the shaking palsy" and later defined by Jean-Martin Charcot, and our understanding of Parkinson disease is still growing. Following Alzheimer's disease, Parkinson disease is the second most prevalent neurodegenerative illness. (2,8) According to a meta-regression analysis, the prevalence of Parkinson's disease rises with age, and males are 1.5 times more likely than females to develop the disease. (4,5) Parkinson disease is a chronic, progressive disease that affects 1% of people over the age of 60. The disease progresses vary in people, with those diagnosed early in life living longer than those diagnosed later in life. (7) Although the existence of non - motor symptoms endorse neuronal loss in nondopaminergic areas, the loss of striatal dopaminergic neurons is related to the motor symptoms of Parkinson's disease. (1,6) Motor features such as resting tremor, cogwheel rigidity, and bradykinesia are used to make a medical assessment of Parkinson's disease. Non-motor symptoms like anosmia, constipation, depression, and REM sleep behaviour disorder can emerge years before motor impairments occurs. In advanced stages of the disease, non-motor symptoms such as autonomic dysfunction, pain, and cognitive decline may appear. (9) Treatment is primarily symptomatic, with drugs aiming to either restore dopamine levels in the striatum. However, a variety of other drugs are being used to treat specific symptoms such as depression or dementia. As we learn more about the pathogenesis of Parkinson's disease and novel therapeutic targets, the potential for the development of disease-modifying therapies grows. (2).

EPIDEMIOLOGY:

The incidence and prevalence of Parkinson's disease rises with age, with 1% of people over the age of 65 affected. (10) The onset of parkinsonian characteristics before the age of 40 is referred to as early-onset Parkinson's disease (EOPD). It accounts for 3-5 percent of all Parkinson's disease cases. It is divided into two types: 'juvenile' (occurring before the age of 21) and 'young-onset' (occurring after the age of 21). (11) In most populations, men are twice as likely as women to have Parkinson's disease. (12) According to health-care utilisation estimates, the annual incidence of Parkinson's disease ranges from 5/100,000 to more than 35/100,000 new cases. (1) From the sixth to the ninth decades of life, the incidence increases 5 to 10-fold. (13) Neurological disorders are now the leading cause of death worldwide, and Parkinson's disease is the fastest growing of these disorders (14).

ETOLOGY:

The actual cause of Parkinson disease is unknown, but it is believed to be caused by a combination of environmental and genetic predisposition. (22,23) The most important risk factor for Parkinson's disease is

age, with the average age of onset being 60 years old (15). The discovery of MPTP as a reason of nigral degeneration sparked the idea that Parkinson's disease could be affected by an environmental toxin. (16) Differences in the prevalence of variables such as cigarette smoking habits, use of post - menopausal hormones, and caffeine consumption may have an impact on the incidence. (17) Age-related biological dysfunction, such as telomere dysfunction, chromosomal aberrations, epigenetic modifications, ubiquitin-proteasome and autophagolysosomal dysfunction, is seen in other neurodegenerative disorders. (18,19)

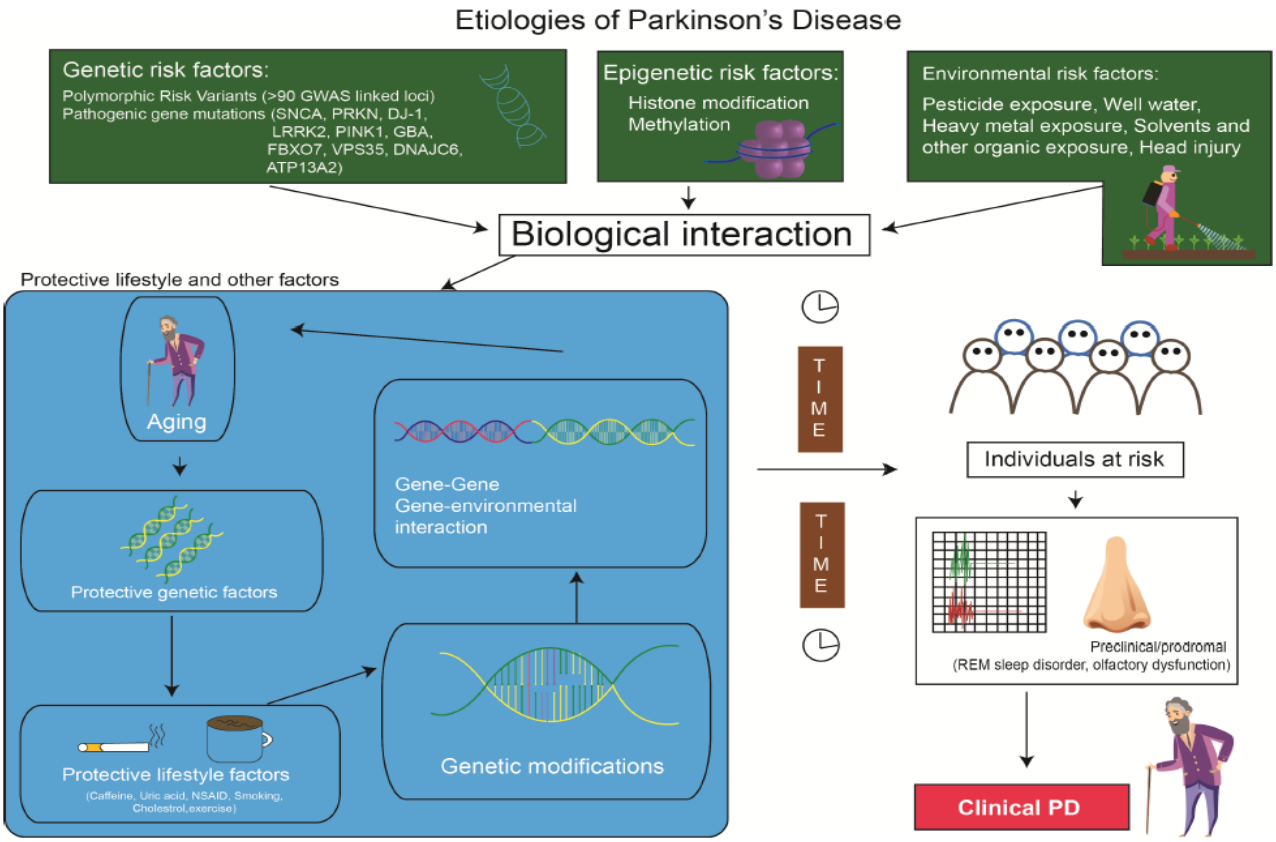

Figure 1: Etiologies of Parkinson's disease (28)

CLINICAL FEATURES:

The clinical features typically associated with Parkinson's disease are tremor, rigidity, and bradykinesia, with postural instability frequently appearing as the disease progresses. However, Parkinson's disease is associated with a wide range of non-motor symptoms, which frequently occur months or even years before the motor symptoms. The pre-motor or prodromal phase of Parkinson's disease can begin as early as 12–14 years before prognosis (24). However, only about two-thirds of Parkinson's disease patients have tremor at the time of diagnosis, and some never develop it. Tremor is most commonly found in the hands, often begins unilaterally, and has a distinctive "pill-rolling" quality. Resting tremor is usually eliminated by voluntary movement and is not present during sleep. Muscular rigidity is characterized by an increased muscular tension to passive range of motion and can be treated. (25)

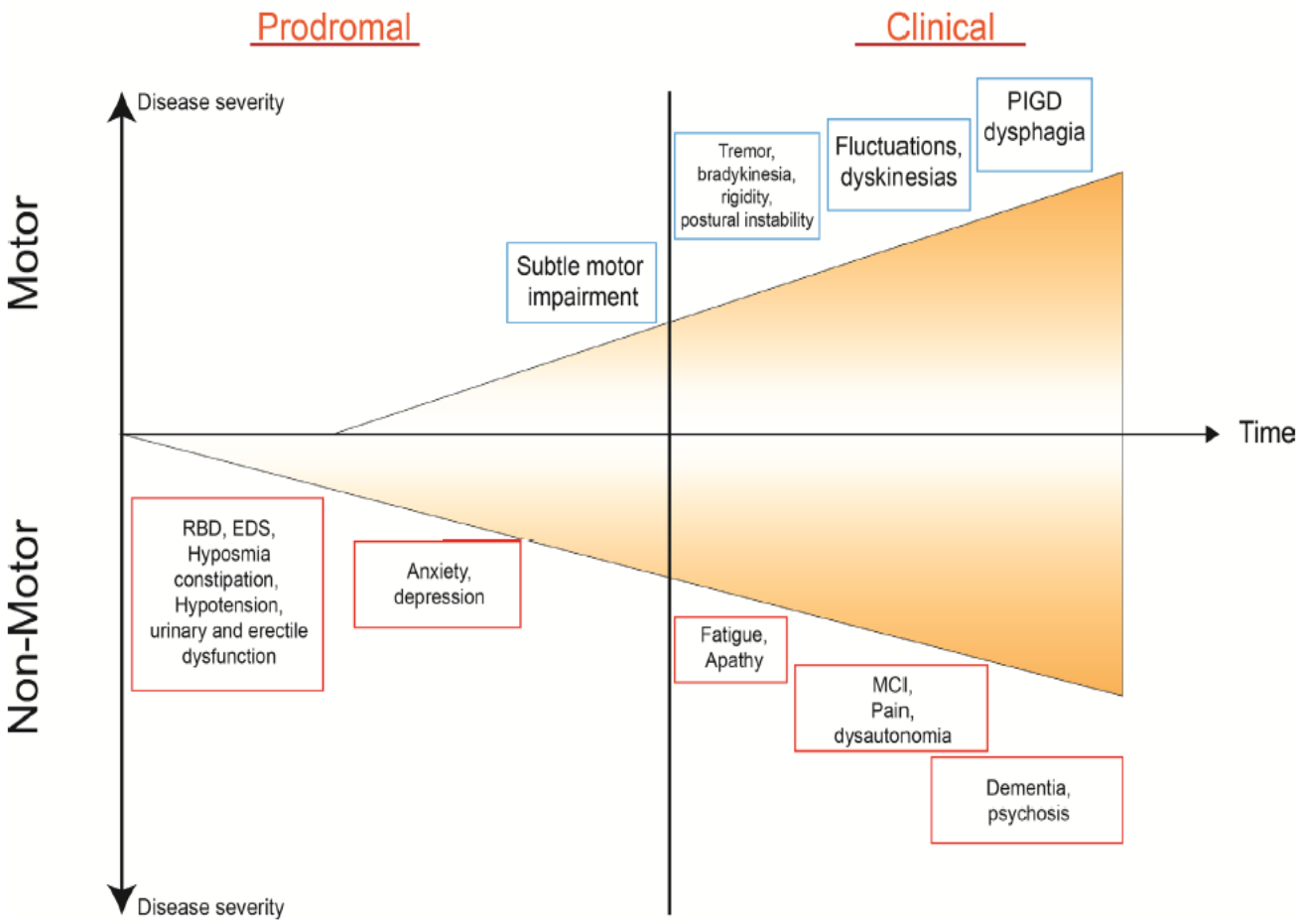

Figure 2: Clinical Phases of Parkinson's disease (28)

➢ Motor Symptoms:

- Bradykinesia
  - Occurs in 80% to 90% of patients, Slowness of movement, Decreased amplitude of movement
- Rigidity
  - Occurs in 80% to 90% of patients, Resistance to passive movement in both flexor and extensor muscles with limb relaxed, often accompanied by "cogwheel" phenomenon
- Tremor at rest
  - Common initial symptom (70% to 90% of patients), Often resolves with action or during sleep, primarily distal, involving hands, may also involve jaw, tongue, lips, chin, or legs.

➢ Non-Motor Symptoms:

- Autonomic dysfunction:
  - Constipation
  - Orthostatic hypotension
  - Sexual dysfunction
  - Sweating
  - Urinary retention
- 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)
- Psychosis (e.g., hallucinations, delusions)

- Sensory Symptoms
  - Olfactory dysfunction (hyposmia)
  - Paraesthesia
  - Pain
- Sleep Disturbance
  - Daytime somnolence
  - Insomnia
  - Rapid eye movement disorder
  - Restless legs syndrome
  - Sleep apnea (3,20,21,26,31)

DIAGNOSIS:

A thorough history and physical examination should be included in the differential diagnosis of Parkinson's disease. Despite the advances in clinical and radiographic testing, idiopathic Parkinson's disease is still diagnosed clinically. The presence of the following fundamental signs is required for a diagnosis: distal resting tremor of 3 to 6 Hz, rigidity, bradykinesia, and asymmetrical onset. Other well-known Parkinson's disease symptoms include late-onset postural instability, reduced olfaction, and micrographia (27).

Criteria of the UK Parkinson's Disease Society Brain Bank for diagnosing Parkinson disease (28)
• **Bradykinesia and at least one of the following**: - Rigidity - Resting tremor (4–6 Hz) – Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction • Exclusion of other causes of parkinsonism • **At least three of the following supportive (prospective) features:** - Unilateral onset - Persistent asymmetry primarily affecting the side of onset - Resting tremor (hand, leg or jaw; low frequency [4–5 Hz], asymmetric, disappears with action) - Excellent response to levodopa (70%–100%) - Progressive disorder - Severe levodopa-induced chorea (dyskinesias) - Levodopa response for five years or more - Clinical course of 10 years or more.

Table 1: Criteria of the UK Parkinson's Disease Society Brain Bank for diagnosing Parkinson disease (28)

RISK FACTORS:

Non-Modifiable Risk Factors

- Age (mean age 65 year)
- Sex (Male: Female = 1.5:1.0)
- Genetics (10% of cases)
- LRRK2 mutation (most common)
- Glucocerebrosidase gene mutation (22)

Modifiable Risk Factors

- Industrial exposure
- Heavy metals (manganese, lead, copper)
- Pesticides (rotenone, paraquat)
- Obstructive sleep apnea (23)

PATHOPHYSIOLOGY:

Parkinson disease is a neurodegenerative disorder that affects both motor and cognitive brain pathways. It is distinguished by two major pathologic processes:

(a) premature selective loss of dopaminergic neurons

(b) the build-up of Lewy bodies, which are composed of α -synuclein and become dysfunctional and accumulate in various systems of Parkinson disease patients. It is uncertain which process happens first (29).

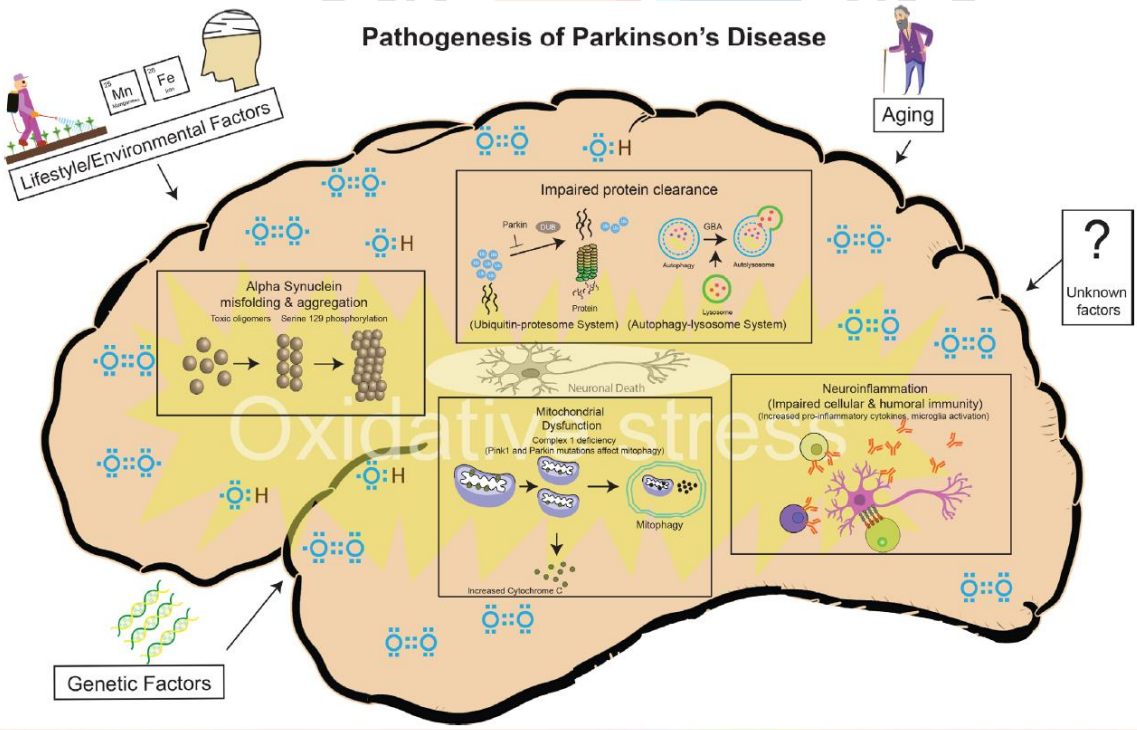

Figure 3: Pathogenesis of Parkinson's disease (28)

Gradual degeneration of dopaminergic neurons nigra pars compacta that endeavour to the striatum (the nigrostriatal pathway) results in dopaminergic impairment in people with Parkinson's disease. Patients tend to experience motor symptoms of Parkinson's disease only after 50 to 80 percent of dopaminergic neurons have been lost, implying the interaction of a compensatory response in the early stages of disease. D1 (excitatory type) and D2 (inhibitory type) dopamine receptors affect motor activity in the extrapyramidal

system. The basal ganglia, which includes the internal globus pallidal segment of the ventral striatum and the pars reticulata portion of the substantia nigra, are components of this system. These elements are part of larger circuits in the thalamus and cortex. (30)

Alpha-synuclein aggregation:

Because of biochemical interactions, α -synuclein is natively unfolded and takes on a tertiary structure. The protein's abnormal accumulation has been reported to be toxic to dopaminergic neurons, resulting in neurodegeneration associated with Parkinson's disease. α -synuclein conformational changes and accumulation can be influenced by oxidative stress, PD genetic abnormalities, and increased expression. Based on the experimental conditions, α -synuclein can exist in various forms/species, and the relative toxicity of its oligomeric and fibrillar species has been discussed. Some of these species can activate neuroinflammation and, more importantly, can 'seed' and spread -synuclein pathology from cell - to - cell. These findings serve as the foundation for therapeutic approaches ranging from impairing its expression to reducing oligomeric species manufacturing and cellular transmission, and some of these strategies are currently being tested in clinical trials. (53).

MANAGEMENT:

PHARMACOLOGICAL MANAGEMENT:

Parkinson's disease is a complex neurodegenerative disease with a wide range of motor and non-motor symptoms that necessitate an individualized care plan. Clinical trials that are intended to provide evidence-based data must include a well-defined population of patients and controls, as well as the most objective, reliable, and validated tools for assessing the effects of the therapeutic intervention. Although several clinical rating scales and other tools have been used to assess responses to different therapies, the UPDRS is the most commonly used as the primary outcome measure in numerous clinical trials (32).

General Approach:

- A monoamine oxidase-B (MAO-B) inhibitor is generally the first step in monotherapy.
- If motor fluctuations develop, consider adding a catechol-O-methyltransferase (COMT) inhibitor to extend the duration of levodopa activity. Consider using an MAO-B inhibitor or a dopamine agonist instead.
- Consider adding amantadine to the treatment of levodopa-induced peak-dose dyskinesias. (25)

TREATMENT FOR MOTOR SYMPTOMS:

LEVODOPA AND CARBIDOPA/LEVODOPA:

The majority of patients with Parkinson's disease need levodopa therapy within two years of appearance of symptoms. Levodopa, the most effective in treatment, it is often combined with carbidopa or benserazide, aromatic acid decarboxylase inhibitors that prevent peripheral metabolic activity and significantly reduce morning sickness (33).

MECHANISM OF ACTION

Levodopa is converted to dopamine in the central nervous system (CNS) and peripherally by l-amino acid decarboxylase (l-AAD). Carbidopa or benserazide can block l-amino acid decarboxylase in the peripheral nervous system, increasing CNS permeation of administered levodopa and reducing dopamine adverse effects (e.g., nausea, cardiac arrhythmias, postural hypotension, and vivid dreams) (25).

STARTING DOSE: 100–300mg/day

MAINTENANCE DOSE:300-1000mg/day

ADVERSE EFFECTS:

- Nausea,
- somnolence,
- dyskinesia,
- hypotension,
- hallucinations (34,35)

MONOAMINE OXIDASE INHIBITORS:

MECHANISM OF ACTION:

Selegiline inhibits dopamine breakdown and can make levodopa last up to an hour longer. It frequently allows for a one-half reduction in levodopa dose. Rasagiline also enhances the effects of levodopa and is only mildly beneficial as monotherapy (25). Monoamine Oxidase Inhibitors also inhibit neuronal dopamine reuptake and block voltage-dependent activated sodium channels and intracellular calcium entry, resulting in decreased neuronal glutamate release (36).

SELEGILINE:

Selegiline inhibits monoamine oxidase (MAO), an enzyme that catabolizes norepinephrine, serotonin, and dopamine. The inhibition of this enzyme prevents these neurotransmitters from being reabsorbed in the CNS, resulting in higher levels of biologically active monoamines at the synaptic cleft. (54)

STARTING DOSE:5-10mg/day

MAINTENANCE DOSE:5-10mg/day.

ADVERSE EFFECTS:

- Weight loss
- Hypotension
- Dry mouth
- Hallucinations. (34,35)

DOPAMINE AGONISTS:

MECHANISM OF ACTION:

Dopamine receptor agonists enhance dopamine receptors (G protein-coupled, two main families, D2-like (D1 and D5) and D1-like (D2, D3, and D4)), and when used early in the course of Parkinson's disease treatment, they prolong levodopa-related problems like motor variations and dyskinesias. However, evidence to support the hypothesis that early administration of dopamine agonists slows disease progression. Dopamine agonists can be used as a stand-alone treatment for motor symptoms or as an adjunctive treatment when levodopa is ineffective or when motor fluctuations are visible (37).

BROMOCRIPTINE:

Bromocriptine is a dopamine receptor stimulant with D2 dopamine receptor specificity. It specifically binds to striatal dopamine D2 receptors, enhancing motility and alleviating the bradykinetic symptoms caused by dopaminergic nigrostriatal neuron degeneration. (55,56)

STARTING DOSE:2.5-5 mg/day

MAINTENANCE DOSE:15-40 mg/day. (25)

ADVERSE EFFECTS:

- Nausea
- Headache
- Dizziness
- Pulmonary fibrosis. (34,35)

CATECHOL O-METHYL TRANSFERASE INHIBITORS:

MECHANISM OF ACTION:

COMTIs (entacapone, tolcapone, and opicapone) inhibit peripheral levodopa deterioration, and tolcapone also blocks central levodopa and dopamine deterioration. Primary function is to delay the effects of levodopa, making them useful as adjunct treatment drugs for patients experiencing levodopa-related motor fluctuations (38,39).

ENTACAPONE:

Entacapone is a selective, reversible, peripheral COMT inhibitor that modulates levodopa metabolization to 3-O-methyldopa (3-OMD) and increases LD half-life in vivo. (57)

STARTING DOSE:200-600mg/day.

MAINTENANCE DOSE:200-1600mg/day. (25)

ADVERSE EFFECTS:

- Diarrhoea
- Liver toxicity
- Orange coloured urine. (34,35)

ANTICHOLINERGICS:

MECHANISM OF ACTION:

Anticholinergics, such as trihexyphenidyl and benztropine, block acetylcholine's effects at muscarinic receptors postsynaptic to striatal inhibitory neurons. They are primarily used to treat tremor but have no impact on bradykinesia (40). They can be used alone or in combination with other antiparkinsonian medications (25).

BENZTROPINE:

Acetylcholine and histamine receptors are inhibited by benztropine. Benztropine works in the Central nervous system and smooth muscles by competing with acetylcholine at muscarinic receptors. As a result,

it diminishes central cholinergic effects by obstructing muscarinic receptors, which appears to improve Parkinson's disease symptoms. (58)

STARTING DOSE:0.5-1mg/day.

MAINTENANCE DOSE:1-6mg/day. (25)

ADVERSE EFFECTS:

- Dry mouth
- Dry eyes
- Constipation
- Hypotension
- Cognitive impairment
- Urinary retention (34,35)

AMANTADINE:

In a randomised, double-blind experiment of amantadine in patients with Parkinson's disease and dyskinesia, amantadine reduced dyskinesia by 45 percent when compared to placebo. However, the benefit lasted less than eight months, and discontinuing amantadine resulted in a 10% to 20% rebound rise in dyskinesia (41)

STARTING DOSE:100mg/day

MAINTENANCE DOSE:200-300mg/day. (25)

ADVERSE EFFECTS:

- Nausea
- Hypotension
- Hallucinations
- Confusion
- Edema (34,35)

TREATMENT FOR NON-MOTOR SYMPTOMS:

Non-motor symptoms are well recognized as an essential element of the condition known of Parkinson's disease, despite the fact that the majority of them begin with motor symptoms. (42)

Rapid Eye Movement Sleep Behaviour Disorder: Clonazepam is a first-line treatment for REM sleep behaviour disorder (RBD). Melatonin can be prescribed for patients who are unable to tolerate clonazepam (43).

CLONAZEPAM:

Clonazepam is a benzodiazepine medication. It works by acting as a GABA-A receptor stimulant. It has serotonin activity because it stimulates serotonin synthesis. (62)

DOSE:0.25-2mg at bedtime.

ADVERSE EFFECTS:

- Daytime sleepiness
- Dizziness
- Headache. (44)

Depression: Begin counselling; consider drug treatment with selective serotonin reuptake inhibitors or tricyclic antidepressants (because of side effect profile, use tricyclic antidepressants with caution). (45)

CITALOPRAM:

Citalopram is a selective serotonin reuptake inhibitor (SSRI) that works as an antidepressant by increasing serotonergic activity in the brain. (61)

DOSE:10-20 mg once daily

ADVERSE EFFECTS:

- Akathisia
- Anorexia
- Nausea
- Drowsiness
- Sexual dysfunction. (44)

Cognitive Impairment: Cholinergic dysfunction may contribute to the cognitive problems seen in the majority of Parkinson's disease patients over time. Rivastigmine improved actions of dementia, perception, and behavioural symptoms modestly. (46)

RIVASTIGMINE:

Rivastigmine blocks acetylcholine breakdown by inhibiting acetylcholinesterase and butyrylcholinesterase. Rivastigmine improves cholinergic depletion. (60)

DOSE: 1.5-6 mg twice daily.

ADVERSE EFFECTS:

- Gastrointestinal symptoms
- Bradycardia
- Vivid dreams. (44)

Orthostatic Hypertension: Orthostatic hypotension can be a serious problem in Parkinson's disease and should be monitored on a regular basis. Orthostatic hypotension can be a natural part of Parkinson's disease as a result of neurological impairment, but it can also be a side effect of dopaminergic drug. Midodrine was studied for the treatment of neurogenic orthostatic hypotension. (47)

MIDODRINE:

Midodrine is an alpha 1 adrenoreceptor agonist that causes arterial and venous constriction as well as an increase in blood pressure. (59)

DOSE: 2.5-10 mg thrice daily.

ADVERSE EFFECTS:

- Hypertension
- Nausea
- Weakness
- Heartburn
- Scalp tingling. (44)

Treatment Option	Summary	Pros	Cons
Drug Treatments		Limited to no invasive treatment required	May lose effectiveness over time Various side effects for each drug
Dopaminergic Medications	Dopamine agonists taken orally or through injection	• Current "gold standard for treatment" • High responsiveness (80%) in idiopathic PD • Favoured treatment for late-onset PD • May affect both motor and non-motor side effects • Most patients ultimately take dopamine agonists as the disease progresses and other treatments stop being effective	• Less favoured for early-onset PD treatment due to levodopa-related dyskinesia • Levodopa requires increasing dosage over time "on-off" fluctuations with oral medication • Irritation or problems at pump site for injection method
MAOIs, inhibitors and antagonists	Inhibit breakdown of levodopa and dopamine through oral drugs	• Do not need increased dosage over time • May help with cognitive decline in later stages of PD • Milder side effects than dopaminergic drugs • May treat L-DOPA-related dyskinesia	• Lack extensive effects on symptoms for late-stage PD • Must be supplemented with a group of drugs for some treatments, such as COMT inhibitors
Anticholinergics	Reduce acetylcholine activity at choline receptors through oral drugs	• Rapid absorption, used for tremor-predominant PD • Can be a monotherapy in early stages	• Less tolerance in elderly patients • Lack of testing in elderly patients • New testing may show cholinergic, rather than anticholinergics may improve PD symptoms • Largely replaced by dopamine agonists in current treatment regimens • Little

Treatment Option	Summary	Pros	Cons
			pharmacokinetic information
Neurotrophic Factors: GDNF	Small natural proteins, specifically glial cell line-derived neurotrophic factor (GDNF), delivered through an implantation in the brain	• Improvement of parkinsonian symptoms • Increased striatal dopamine levels • Prevention from neurotoxic damage of dopaminergic neurons in the midbrain and noradrenergic neurons in the locus coeruleus	• Difficult delivering this NTF to brain cells across the BBB • Studies show differing outcomes on the effectiveness of GDNF on symptomatic relief • Requires more research
Nanomedicine	Modification of existing drugs to improve delivery method	• Greater delivery through the blood brain barrier or circumventing it • Less drug lost in peripheral tissue, increasing effectiveness and decreasing side effects • Growing field with investigations into protective factors and imaging improvements	• Relatively new field that requires more testing before being a standard practice
Surgical Treatments		Can have high effectiveness with long-term results	Most invasive of the treatment methods Some methods and side effects are irreversible
Ablative Surgery	Incision into the global pallidus, thalamus, or subthalamic nucleus either bilaterally or unilaterally	• High-effectiveness, relieving rigidity, hypokinesia, and tremors.	• Irreversible procedure, may have permanent side effects
Deep Brain Stimulation	Implant that stimulates the basal ganglia through high frequency electrical stimulation	• Bilateral DBS is likely safer than bilateral ablative surgeries • Established treatment for advanced PD • Can improve both motor and non-motor symptoms • Equal improvement compared to L-DOPA for tremor, bradykinesia and rigidity • Closed-loop DBS is being investigated to reduce side effects and allow greater feedback • Effective at minimizing “off” episodes • Benefits can last 10+ years in some individuals	• Conventional DBS is open-loop, not allowing for feedback and patient adjustment • Less effective for reducing gait, balance, and speech symptoms • May include dysarthria, imbalance, and dyskinesia • Limited battery life

Treatment Option	Summary	Pros	Cons
Transplantation and Gene Therapy	Transplantation of stem cells into the striatum, insertion of non-disease and disease modifying transgenes	• Can generate long-lasting improvement and replace diseased neurons • Can treat PD at a genetic level, correcting dopamine pathways	• Must consider ethical bounds for embryonic stem cell use • Developing fields that require more research, especially human testing
Therapy		Can address multiple symptoms at once, both motor and nonmotor Non-invasive treatment	Usually requires other forms of treatment in addition to therapy
Physical Therapy	Addresses mobility and motor-related symptoms through physical training	• Can greatly increase quality of life • Treat multiple symptoms at once • Multiple forms of PT exist, allowing for patient-specific care that adapts	• May require other treatments, especially as the disease progresses • Limited by patient involvement and motivation
Occupational Therapy	Help patients maintain work, leisure, and self-care activities for as long as possible	• Promotes independence • Allows one to engage meaningfully • Addresses social and environmental side effects and factors	• Usually requires PT with it, as well as additional treatments • Does not address PD at a physiological level • Limited by patient involvement and motivation
Speech Therapy	Improves speech through voice exercises	• Focuses on a single parameter but improves multiple voice symptoms • Improves quality of life	• Helpful for only speech disorders
Cognitive Behavioural Therapy	Management of a symptom through behavioural training methods	• Alternative for symptoms commonly treated with drugs, helping to reduce complications • Few side-effects • As effective as drugs in treating insomnia • May be done remotely	• Cannot be double-blinded testing • Manages only one symptom • Needs more testing • Dependent on patient motivation

Table 1: Pros and Cons of Various Treatment for Parkinson Disease (52)

NON-PHARMACOLOGICAL MANAGEMENT:

Nonpharmacologic interventions do not improve the cardinal symptoms of Parkinson's disease, but they do help patients maintain their overall health. Stretching, strengthening, and balance training helps to enhance gait speed, stability, and involvement in everyday routines. (48)

- DEEP BRAIN STIMULATION:

  Deep brain stimulation employing implanted pulse generators has largely replaced ablative surgical approach. The primary advantage of DBS over ablative lesioning is that the stimulation specifications can be tailored to the patient's specific needs in order to enhance the effectiveness. Thalamic DBS is most widely used to manage high amplitude tremor in patients with movement

disorders, but STN or GPi are the most common targets for DBS treatment of patients with Parkinson's disease (PD) who have disabling uncontrollable shaking and/or levodopa-related motor difficulties. (49)

- FOCUSED ULTRASOUND:
  Focused ultrasound lesioning of the thalamus (in tremor-dominant aspects of Parkinson's disease) has been proven to be helpful in some patient populations, particularly if the symptoms are noticeably asymmetric. (50)
- CELL REPLACEMENT THERAPIES:
  Prior foetus tissue-derived cell transplants in Parkinson's disease have had mixed results. Although some relocated patients improved initially, many developed 'off' dyskinesias despite excellent graft survival. (51).
- PHYSICAL THERAPY:
  It utilises physical training to treat mobility and motor-related illnesses. Can significantly improve quality of life and treat multiple symptoms simultaneously.
- OCCUPATIONAL THERAPY:
  Assist patients in continuing to engage in work, relaxation, and personality activities for as long as necessary. Encourages independence, allows meaningful participation, and addresses environmental and economic negative consequences and considerations.
- SPEECH THERAPY:
  This therapy enhances speech by using voice activities. Improves quality of life by focusing on a single variable but improving multiple voice signs.
- COGNITIVE BEHAVIOURAL THERAPY:
  Symptom management using behavioural training methods. There are very few side effects. This could be done remotely. (52).

CONCLUSION:

Parkinson's disease is one of the most prevalent neurodegenerative disorders affecting the elderly, and it is associated with higher morbidity and mortality. Awareness of disease manifestations, treatments, and the disease's progressive long-term course is required for optimal case management. Although there is no known cure for Parkinson's disease, alternative drug, surgical, and behavioural therapies are available, and new treatments are being developed to help alleviate the adverse effects and symptomatology of this progressive disease. Physical, occupational, and speech therapies are non-drug alternatives that can be used in conjunction with medications or on their own for those who prefer a more rational approach. They can assist in the treatment of specific symptoms as they emerge. There is still potential for more research into under-researched therapies for Parkinson's disease, but the future of PD treatment seems like for patient-specific care that is more efficient and has fewer side effects.

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