2026 Volume: 02 Issue: 02 www.ijrpa.com ISSN 2456-9995 Review Article

International Journal Research Publication Analysis

Page: 01-27

PARKINSON'S DISEASE: A COMPREHENSIVE REVIEW

[*1]Dr. M.Gowthami, [2]Padakanti Naga Harshitha, [3]M.Sushma , [4]L. Sadvika

[1]Assistant professor, department of pharmacy practice, Maisammaguda, Dhulapally, Secunderabad, 500100.

[2]Pharm-D 4th year malla reddy college of pharmacy, Maisammaguda, Dhulapally, Secundrabad, 500100.

[3]Pharm-D 4th year malla reddy college of pharmacy, Maisammaguda, Dhulapally, Secundrabad, 500100.

[4]Pharm-D 4th year malla reddy college of pharmacy, Maisammaguda, Dhulapally, Secundrabad, 500100.

Article Received: 16 January 2026
Article Revised: 04 February 2026
Published on: 24 February 2026

***Corresponding Author: Dr. M.Gowthami**
Assistant professor, department of pharmacy practice, Maisammaguda, Dhulapally, Secunderabad, 500100.

DOI: https://doi-doi.org/101555/ijrpa.3532

ABSTRACT

A recognizable clinical syndrome, Parkinson's disease can have a variety of causes and clinical manifestations. The rapidly increasing global prevalence of Parkinson's disease, a neurodegenerative illness with an infectious cause, is similar to many of the traits usually seen during a pandemic. In most groups, 3–5% of 90 genetic risk variants together account for 16–36% of the heritable risk of non-monogenic Parkinson's disease, while genetic causes linked to known Parkinson's disease genes account for monogenic Parkinson's disease. Other causal associations that at least double the risk of Parkinson's disease include constipation, not smoking, and having a relative with Parkinson's disease or tremor. Clinical criteria are used to make the diagnosis; ancillary testing is only used for patients who present atypically. Bradykinesia accompanied by rigidity, rest tremor, or both is the current definition of Parkinson's disease. The clinical presentation, however, is complex and comprises a wide range of non-motor symptoms. Guidance for prognostic counselling comes from knowledge of the various disease types. There may be a prodromal phase that lasts for a long time before Parkinson's disease becomes clinically evident. Recognizing prodromal parkinsonism will likely have consequences once disease-modifying treatments become available, but at the moment, prodromal symptoms have no clinical implications beyond symptom suppression.

Each person has different treatment goals, which highlights the importance of individualized management. When a person develops Parkinson's disease-related disability, there is no justification for delaying symptomatic treatment. The drug most frequently used as first-line treatment is levodopa. A multidisciplinary team approach is necessary for optimal management, which should begin with diagnosis and include an expanding range of nonpharmacological interventions. There is currently no treatment that can stop or slow the progression of Parkinson's disease, but given new knowledge about the genetic causes and mechanisms of neuronal death, a number of promising approaches are being investigated for potential disease-modifying effects. We will demonstrate how to optimize individualized management of Parkinson's disease using the viewpoint of those who have the condition as a "red thread" throughout this seminar. [1,2]

INTRODUCTION:

The best management requires a multidisciplinary team approach that starts with diagnosis and incorporates a growing number of nonpharmacological interventions. Although there is currently no cure for Parkinson's disease, several promising strategies are being developed in light of new research on the genetic causes and mechanisms of neuronal death. Being looked into for possible effects on disease modification. Throughout this seminar, we will use the perspective of individuals who have Parkinson's disease as a "red thread" to illustrate how to best manage the condition on an individual basis. [3]The impact of Parkinson's disease on society is significant. This disease is widespread in terms of the number of individuals afflicted; roughly 6.1 million people had been impacted globally in 2016. The incidence and prevalence of this disease have increased significantly over the last 20 years for unknown reasons (panel 1). 1–3. Parkinson's disease has a huge personal impact. Degenerative diseases are unique in that they can last for decades. For those who are impacted, the usual presentation consists of a gradual progression with increasing disability. The effects of Parkinson's disease on caregivers are also significant, with the majority reporting excessive stress. 4. Parkinson's disease represents an increasing socioeconomic burden on society. 5. Numerous findings imply that Parkinson's disease may not be a singular phenomenon. First, parkinsonism is a clinical syndrome that can appear to be caused by a variety of different factors.6. Certain causes, like the fewer than ten known genes that, when mutated, can unquestionably cause parkinsonism, are known. Secondly, the disease often presents with highly variable symptoms and progression patterns, even when a specific cause is identified. For instance, despite having the same toxic cause for their parkinsonian symptoms, such as

exposure to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an analogue of heroin, the presentation can differ significantly between people. [4] 7. Third, each person with Parkinson's disease has very different needs, goals, and desires. For a worker used to lifting heavy objects, a noticeable resting tremor might be barely perceptible, but a similar level of tremor intensity could be incapacitating for a calligrapher. As a result, each person's Parkinson's disease is different. An extreme claim, taking into account all three points, would be that there are more than 6 million distinct forms of Parkinson's disease worldwide. There are consequences for clinical practice when this significant heterogeneity in causes, presentation, and individual preferences is acknowledged. Because of this heterogeneity, Parkinson's disease is a prime candidate for precision medicine, wherein the different treatments—pharmacotherapy, neurosurgery, and rehabilitation—should be customized to meet the needs and priorities of each individual, eventually taking into account their genetic makeup or other unique biological characteristics. [5] But this significant advancement in tailored precision medicine shouldn't be overhyped: Parkinson's disease patients also have similar pathophysiological pathways, like neuroinflammation or mitochondrial dysfunction, so many people who appear to be different will likely benefit from some treatments. Furthermore, there won't be any special treatments for every Parkinson's disease patient; however, certain groups of people will most likely react well to particular kinds of care. Making these clusters as fine-grained as possible will be the difficult part. [6]

EPIDEMIOLOGY:

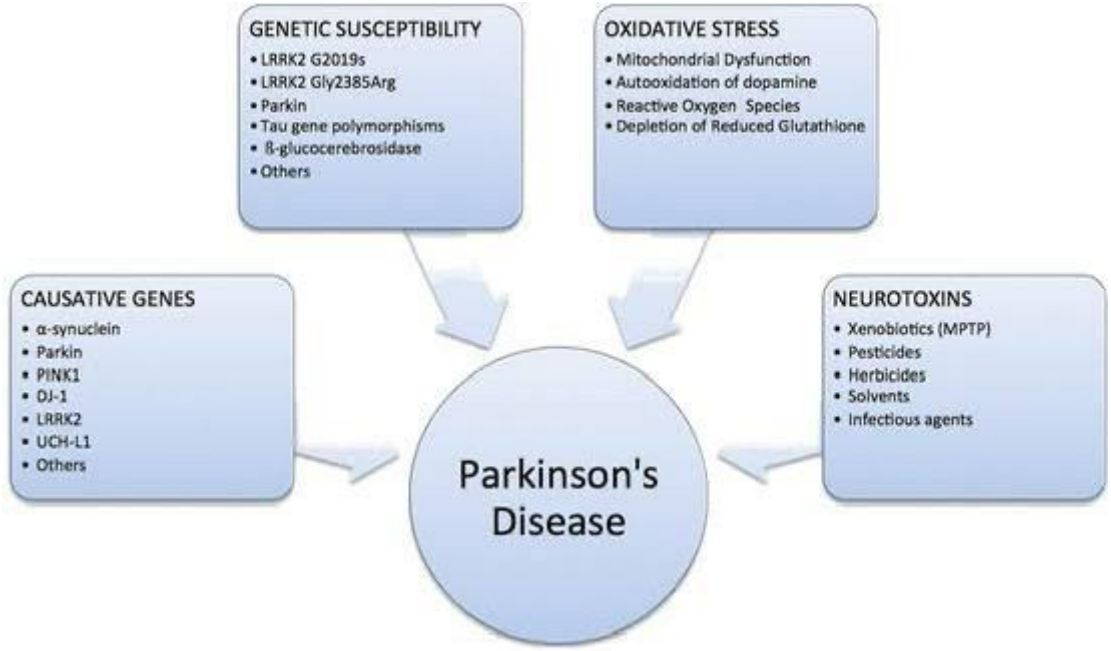
The incidence and prevalence of Parkinson's disease rise steadily with age, making it an age-related condition. But the false belief that Parkinson's disease should be disregarded if it solely impacts elderly individuals. Approximately 25% of those impacted experience symptoms before the age of 65, and 5–10% do so before the age of 50. The phrase "young-onset Parkinson's disease" was coined to describe those who have the condition and whose onset occurred before the age of forty (or possibly before fifty). There are no notable epidemiological differences in the disease's prevalence across the globe, with the exception of China's disproportionately high rate of new cases and Europe's high-income nations. Over the previous 20 years, the number of Parkinson's disease-related deaths and disabilities worldwide has more than doubled. Women may have a few advantages over men despite the fact that Parkinson's disease affects both sexes: her age at onset is higher and her incidence is lower, especially for those between the ages of 50 and 59. Men have the highest number of

years spent living with a disability. They typically weigh less, though, which results in relative overdosing. Additionally, depression and urinary complaints are more common in women. On the other hand, men are more likely to experience cognitive decline. Women with Parkinson's disease exhibit different health behaviours, including less frequent and delayed access to specialists and medical professionals. This conduct may lead to undertreatment, which could include fewer neurosurgical procedures. Crucially, women are underrepresented in trials for Parkinson's disease. [7]

ETIOLOGY:

A higher risk of Parkinson's disease (PD) is linked to a number of environmental risk factors, such as pesticide exposure, rural living, well water consumption, and herbicide exposure. The longer the exposure, the higher the risk appears to be. On the other hand, smoking and caffeine consumption are linked to a decreased risk of Parkinson's disease (PD), though the exact biological causes of this association are unclear. It is impossible to evaluate environmental factors that may have had an impact decades ago or that have accumulated over time, possibly in combination with genetic features. Aetiological research is further limited by the brain's inaccessibility. We make the assumption that there is a continuum of causes, risk factors, and protective factors that counteract each other, each with varying effect sizes and occurring in distinct constellations. [8].

It is important to note that variables influencing the course of Parkinson's disease can only be evaluated in extensive longitudinal studies; they are not always the same as those raising the risk of getting the condition. Despite making up a small percentage of all Parkinson's disease, monogenic forms are significant for a number of reasons: In certain situations, determining a monogenic cause can provide a conclusive diagnosis of a specific form of Parkinson's disease in life. Genetics of Parkinson's disease may affect family counselling. Genetics has advanced our knowledge of the pathophysiology of Parkinson's disease. monogenic Parkinson's disease may respond to certain gene-targeted treatments, the first of which is undergoing clinical trials (this is a tangible example of personalized precision medicine for people with Parkinson's disease). An international initiative is creating genetic cohorts that are ready for clinical trials in order to get ready for trials of these gene-targeted treatments for Parkinson's disease . In clinical settings, attention should be paid to genes that are unquestionable associated with Parkinson's disease. The best indicator of a genetic form of this disease is a young age at onset, especially if the patient is under 40. [9]



Flow chart 1

GENETIC FACTORS:

About 10% of PD cases have genetic causes, which are more prevalent in patients whose onset occurred earlier in life. While PRKN, DJ1, and PINK1 are linked to recessive inheritance, mutations in genes such as SNCA and LRRK2 are linked to dominant inheritance. The most frequent genetic cause of autosomal-dominant Parkinson's disease is mutations in the LRRK2 gene. The most common mutation is G2019S, which accounts for approximately 2% of sporadic cases and up to 5% of familial cases in Caucasian populations. Ashkenazi Jewish and North African Berber Arab groups have significantly higher frequencies of this mutation. Levodopa usually works well for these symptoms, which are very similar to those of idiopathic Parkinson's disease. Autosomal dominant inheritance has incomplete penetrance that varies with age. In clinical practice, routine genetic testing is not advised. [10]

The oxidation hypothesis states that dopaminergic cell damage in Parkinson's disease is a result of excessive free radical production during dopamine metabolism. Hydrogen peroxide is produced when dopamine is catabolized by monoamine oxidase (MAO). Under typical circumstances, hydrogen peroxide is quickly neutralized by glutathione. Iron levels in the substantia nigra rise and reduced glutathione levels fall in Parkinson's disease. Through Fenton chemistry, this combination encourages hydrogen peroxide to be converted to extremely reactive hydroxyl radicals. These free radicals cause lipid peroxidation, harm proteins and cell membranes, and eventually cause neuronal death. This model is supported

by the increased dopamine turnover, decreased antioxidant defences, elevated iron, and lipid peroxidation markers found in PD brains. [10]

Associated conditions:

MELANOMA-

Research has shown that people with Parkinson's disease have a higher risk of developing melanoma. Parkinson patients are approximately four times more likely to have preexisting melanoma, according to one study, while another study found that the risk is seven times higher. [11]

TYPE 2 DM -

People with type 2 diabetes are more likely to develop Parkinson's disease (PD), and the risk is higher for younger patients and those who have diabetic complications.[11]

RISK FACTORS:

The field of Parkinson's disease (PD) genetics has undergone a revolution in the past 20 years. A better understanding of the molecular pathways involved in disease pathogenesis has resulted from significant progress in identifying numerous loci that confer a risk for Parkinson's disease. Despite this achievement, it is anticipated that genetics will account for a comparatively small fraction of the phenotypic variability. It follows that it is still necessary to identify common heritable components of disease. Finding therapeutic targets requires analysing the genetic makeup of Parkinson's disease (PD). Despite the significant advancements that have improved our understanding of the disease mechanism, the path to PD disease-modifying medications is a long one. In this review, We provide a summary of the known genetic risk factors for Parkinson's disease (PD), emphasizing the larger networks that have been linked after thorough pathway analysis rather than specific variants. We describe the difficulties in converting risk loci into Patho -Biologically meaningful information and highlight the necessity of incorporating big data by pointing to recent studies that have found success using a broad-scale screening method. [12]

COMPLICATIONS:

Numerous issues with the progression of the illness and its management can be linked to Parkinson's disease (PD). But it's unclear how frequently these happen overall. population of PD patients. Goal to evaluate the clinical correlates of treatment complications and disease prevalence in a community-based sample of 124 PD patients. Findings The mean

disease duration was 6 (SD 4.3) years, and the average current age was 72 (SD 10.9). In this population, falls accompanied by postural instability and other axial features were among the most frequent side effects of worsening illness (64%). [13]

About 30% and 20% of the total sample were impacted by motor fluctuations and dyskinesias, respectively. About one fifth of patients experienced mental health changes like dementia, depression, and hallucinations. The vast majority of patients experienced symptoms of autonomic nervous system dysfunction, but these symptoms were not linked to increased disease severity, duration, or overall disability. In conclusion Unlike clinical-based samples, axial features like postural instability with falls were the most common PD complications in this community-based sample. When allocating health care resources and treating PD patients' symptoms in the community, these factors ought to be given more consideration. The classic symptoms of Parkinson's disease (PD) include rigidity, tremor, postural instability, and bradykinesia. On the other hand, several other issues like Particularly as the disease progresses, symptoms such as dementia, depression, hallucinations, and treatment-induced motor fluctuations and dyskinesias may manifest. Although these PD complications are widely acknowledged, it is unclear how common they are among all PD patients. Due to variations in treatment approaches and the ascertainment bias present in these samples, the outcomes of clinic-based research can differ greatly. We examined the rate of complications and their clinical correlates in a community-based sample of PD patients in order to look into the rate of complications in the entire population of PD patients.[13]

Rate of complication: Axial features like impaired gait, postural instability with falls, and trouble turning in bed or getting out of bed were the most prevalent disease complications. About two-thirds of all patients have both speech impairment and a chair. Less frequently, about 30% and 20% of subjects experienced motor fluctuations and dyskinesias, respectively, and 20% of subjects experienced mental state changes like depression, dementia, and hallucinations. While postural faintness was less common, autonomic nervous system symptoms like constipation, loss of normal erections, and urinary dysfunction were also commonly reported. 17 percent of people with urinary dysfunction had incontinence, 27 percent had frequency, 21 percent had urgency, and 4 percent had urine retention. [13]

■ Disease symptoms and patient characteristics: Four patients were diagnosed with possible Parkinson's disease, and 124 patients were diagnosed with probable Parkinson's disease.

Their average: The average age at onset was 66 (SD 14.3) years, and the age was 72 (SD 10.9) years. There were 61 (47.7%) female patients and 67 (52.3%) male patients. The illness lasted an average of 6.0 (SD 4.6) years. The mean score on the motor portion of the UPDRS was 22.7 (SD 11.1) at the time of the patients' visit, and the mean Hoehn and Yahr score was 2.6 (SD 0.7). The average PDQ-39 score was 30.0 (SD 19.3), and the average Schwab and England disability score was 81.2 (SD 15.9).

Complication rate

Axial characteristics like postural instability and gait impairment were the most prevalent disease complications with falls, trouble getting out of a chair or turning in bed, and speech impairment, which affect roughly two-thirds of all patients. Less frequently, about 30% and 20% of subjects experienced motor fluctuations and dyskinesias, respectively, and 20% of subjects experienced mental state changes like depression, dementia, and hallucinations. While postural faintness was less common, autonomic nervous system symptoms like constipation, loss of normal erections, and urinary dysfunction were also commonly reported. 17 percent of people with urinary dysfunction had incontinence, 27 percent had frequency, 21 percent had urgency, and 4 percent had urine retention.

SIGNS AND SYMPTOMS:

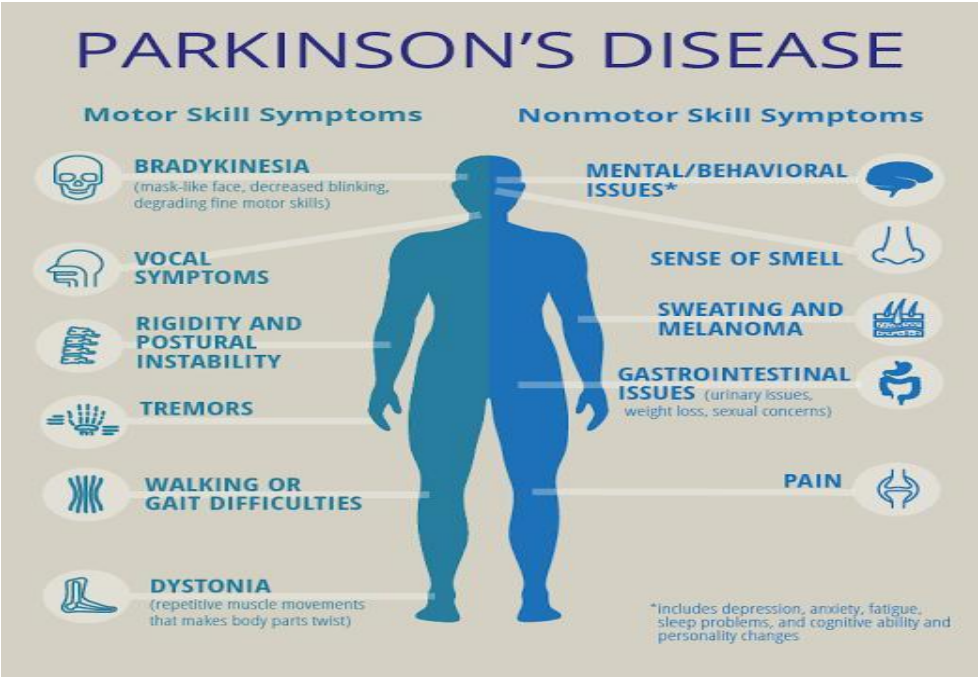


Fig 1.

Autonomic dysfunction:

The sympathetic and parasympathetic subsystems of the autonomic nervous system are part of the central and peripheral systems, respectively. with an enteric division, as well as efferent visceromotor and afferent viscero - sensory axons and neurons that connect in ganglia, both preganglionic and postganglionic. While unmyelinated postganglionic sympathetic axons are noradrenergic (apart from nicotinic innervation of the adrenal gland and sweat glands) (the adrenal gland is regarded as a sympathetic ganglion, secreting adrenaline into the blood to reinforce sympathetic action), and parasympathetic axons muscarinic (cholinergic), preganglionic myelinated (para)sympathetic neurons are nicotinic (cholinergic). The plexus of Auerbach and Meissner, which houses cholinergic and opioidergic ganglionic cells, is home to the enteric division. These cells control intestinal mucus secretion and peristaltic transport. They are both sympathetically and parasympathetically innervated, and they are both sensitive to intestinal filling. The endocrine system and projections to the brainstem (solitary tract nucleus) and spinal cord nuclei, which act on preganglionic autonomic neurons, are two ways that the cortex, hippocampus, entorhinal cortex, thalamus, basal ganglia, cerebellum, and reticular formation influence the hypothalamus's function of the peripheral autonomic system. Clinical symptoms that are specific to each of these components may appear when they fail.[14]
The central and peripheral autonomic nervous systems may be impacted by Parkinson's disease (PD) even before the illness is diagnosed. Gastrointestinal, cardiovascular, urogenital, sudomotor, and thermoregulatory dysfunctions are among the various types of resulting dysautonomia that impair patients' ability to carry out daily tasks. [14]

Digestive disorders:

While lower gastrointestinal disorders, which result from a malfunction of the enteric nervous system with loss of peristaltic transport, manifest as constipation, upper gastrointestinal disorders include swallowing disorders, drooling, and delayed gastric emptying. Oral or pharyngeal issues may be the cause of dysphagia, whether or not it is accompanied by excessive saliva and drooling. They may result from pharyngeal/ esophageal impaired motility, which is most likely brought on by Lewy body pathology in the esophageal myenteric Auerbach plexus, as well as oral mechanical motor PD-related issues. Due to synuclein inclusions in the gastric submucosal Meissner plexus, PD patients experience impaired gastric emptying, which is accompanied by nausea, abdominal pain, and bloating. This condition results in "delayed-on" or "no-on" because it inhibits levodopa's normal

intestinal absorption. Constipation (less than one bowel movement per day) and, to a lesser degree, paralytic ileus, a neurogenic intestinal pseudo-obstruction accompanied by pain, nausea, and/or bloating in the abdomen Over 50% of PD patients experience vomiting, which is the most common gastrointestinal issue in PD and is caused by impaired transport and/or disturbed anorectal evacuation. Constipation-related overflow or a disrupted anorectal reservoir can cause fecal incontinence. Megacolon, volvulus, and bowel occlusion may occasionally be observed, usually later in the course of the illness. Additionally, it has been proposed that midlife obesity and Parkinson's disease are related, though this theory is still debatable. Pressure waves, which are triggered by intestinal filling, are brought on by parasympathetic vagal (upper intestine) and pelvic (lower intestine) stimulation of the Meissner's submucous and Auerbach's myenteric plexus (dopamine inhibits, serotonin facilitates). The noradrenergic sympathetic hypogastric nerve in the lower intestine inhibits these pressure waves. The vagal nerve, sacral nuclei, enteric nervous system, and central parasympathetic structures (Barrington's defecation centre) all exhibit Lewy bodies and synuclein deposits in Parkinson's disease (PD), which occur many years before motor parkinsonism [2,25,31–37]. The risk of developing Parkinson's disease (PD) was found to be significantly higher in men who had fewer than one bowel movement per day than in those who had one or more. Dietary fibres, osmotic laxatives like polyethylene glycol (PEG) (17 g/day) or lactulose (10–40 g/day), and psyllium preparations combined with physical activity and enough hydration are the basic treatments for constipation in Parkinson's disease. Such as cholinomimetics as pyridostigmine bromide), 5-HT-4 receptor agonists (cisapride or mosapride), peripheral dopamine antagonists (domperidone to accelerate gastric emptying), and the prostaglandin misoprostol are also said to be effective in treating constipation, while dopamine-mimetic medications may be beneficial for lower intestinal and anorectal function. [15]

Heart problems:

Regarding the cardiovascular system, individuals with Parkinson's disease may experience neurogenic decreased cardiac output and impaired heart rate variability. failure of baroreflex and hypotension in ortho-statics. Synucleinopathic sympathetic and, to a lesser degree, parasympathetic denervation of this system is thought to be the cause of these symptoms. Whereas parasympathetic activation lowers cardiac output, sympathetic outflow increases it. Patients with idiopathic Parkinson's disease typically experience postsynaptic sympathetic cardiac denervation, which manifests as vasodilatation, decreased heart contraction force,

impaired heart rate variability, and orthostatic hypotension. However, multiple system atrophy is not a common symptom of this condition. Reduced TH immunoreactivity and decreased uptake of radioactive fluorodopa in the myocardial sympathetic nerves, but not in the dorsal vagal nucleus or sympathetic ganglia, confirm this denervation. Diagnostic procedures to evaluate preserved cardiac sympathetic denervation Administration of tyramine, isoproterenol, or yohimbine (with decreased dihydroxy-phenyl glycol resp. noradrenaline plasma response) and the acetylcholinesterase inhibitor edrophonium (inducing normal bradycardia and epinephrine responses) are examples of parasympathetic cholinergic and adrenomedullary hormonal components of the autonomic nervous system. Additionally, heart rate and blood pressure readings taken beat-to-beat could be useful in assessing baroreflexes. Signs of noradrenergic renal denervation may also be found in patients with this failure. Orthostatic hypotension with failing neurocirculatory baroreflexes may then be the consequence of both sympathetic and parasympathetic denervation, as in several patients later also cardiac vagal acetyl cholinergic denervation. Techniques for diagnosing preserved cardiac sympathetic denervation. Examples of parasympathetic cholinergic and adrenomedullary hormonal components of the autonomic nervous system include the administration of tyramine, isoproterenol, or yohimbine (which results in a decreased dihydroxy-phenyl glycol resp. noradrenaline plasma response) and the acetylcholinesterase inhibitor edrophonium (which causes normal bradycardia and epinephrine responses). Additionally, evaluating baroreflexes may benefit from beat-to-beat blood pressure and heart rate measurements. Patients with this failure may also exhibit noradrenergic renal denervation. Both sympathetic and parasympathetic denervation may then result in orthostatic hypotension with failing neurocirculatory baroreflexes, as in some patients later cardiac vagal acetyl cholinergic denervation.[16] dysfunction of the urogenital system Bladder dysfunction affects more than 50% of PD patients, and it is correlated with the disease's severity. Between the types of voiding and storage.

Storage symptoms are the most prevalent type of lower urinary tract symptoms in Parkinson's disease. An overactive detrusor (increased bladder contractility) is linked to storage symptoms, which include urgency, frequency, and nocturia. Under the supervision of the pontine micturation center (which is influenced by striatal and cerebellar input), micturation is normally initiated by the frontal micturation inhibition center and activated (detrusor reflex) as soon as a sense of a full bladder reaches the sensory cortex. Bladder emptying is normally controlled voluntarily. In actuality, the detrusor contracts when the external urethral

sphincter voluntarily relaxes, inhibiting sympathetic activity and stimulating parasympathetic activity.

Detrusor-sphincter dyssynergia causes urinary urgency, and incontinence, which affects roughly 25% of PD patients, is a sign of how severe this storage dysfunction. Storage issues in Parkinson's disease (PD) are thought to be primarily caused by dopamine deficiency-induced disinhibition and hyperactivation of the micturation reflex, which starts storage symptoms. This is because striatal D-1 receptors inhibit and D-2 receptors activate the micturation reflex. Therefore, DBS-STN and dopamine-mimetics will aid in reestablishing the regular inhibition of this reflex. Alternatives include using antimuscarinic medications, such as oxybutynin chloride, tolterodine, and darifenacin (or ionic trospium or solifenacine), to inhibit postganglionic parasympathetic activity. This prevents involuntary bladder contractions by preventing acetylcholine from binding to muscarinic receptors in the detrusor muscle. Thermoregulatory and sudomotor dysfunction Disorders of thermoregulation and hyperhidrosis, which affects 30 to 50% of patients, are non-motor symptoms of Parkinson's disease. illness. In addition to frequently having diminished or absent sympathetic sudomotor skin reflexes, hyperhidrosis with drenching sweats, primarily in the face and trunk during off-periods suggests postsynaptic sympathetic (cholinergic) denervation. Actually, all autonomic nervous system-innervated skin elements exhibit marked denervation in PD patients, which is unrelated to clinically evident hyperhidrosis and/or orthostatic hypotension.

2. Issues with sleep

Dopamine may cause both sleep-onset and sleep-maintenance insomnia in patients with motor parkinsonism. nocturnal akinesia, nocturia, and/or symptoms like restless legs and/or periodic limb movements that are related to deficiencies (or "off" related). Therefore, dopamine-mimetic medication and the severity of the disease are the main factors that correlate with insomnia in PD [63]. Deep brain stimulation or medication taken at night with duodopa and/or dopamine-mimetic patches may be very beneficial in these circumstances. However, in people with Parkinson's disease (PD), excessive daytime sleepiness (EDS) and/or REM sleep behavior disorder (RBD), which is characterized by vigorous movements during REM sleep without atonia, can also cause insomnia.

3. Dysfunction of the senses:

Although PD patients have a wide range of sensory disorders, only pain, visual impairment, and hyposmia are typical. sensory aspects of this illness, which are frequently evident in the premotor stage. It has been proposed that the early onset of olfactory disturbances in PD may peak before the emergence of progressive motor symptoms, since most drug-naïve PD

patients experience these disturbances [16]. It is true that there is a higher chance of developing motor parkinsonism in hyposmics who are otherwise healthy. During the first four years of follow-up in the Honolulu-Asia Aging Study, the age-adjusted incidence of Parkinson's disease (PD) was significantly higher in the worst odour identificator quadrant (54.5/10,000) than in the upper half (8.3/10,000) [16]. In a different investigation, 10% of the hyposmic. Disorders of the nervous system: Other symptoms include apathy, panic and anxiety attacks, mood swings, mild cognitive impairment, dementia, and psychosis. extranigral issues in Parkinson's disease, both in the prodromal and motor phases. Psychosocial factors and synucleinopathic degeneration of the noradrenergic, serotonergic, and cholinergic limbic pathways (prior to nigral dopaminergic involvement) are believed to be involved in this case. Although there is considerable variation in the prevalence of depressive disorders in PD, a recent meta-analysis found that the weighted prevalence rates for major depression, minor depression, and dysthymia were 17%, 22%, and 13%, respectively [85]. Additionally, 2.5% of 433 pathologically proven PD cases at the Queen Square Brain Bank had depression as their presenting symptom [16]. Specifically, it has been discovered that anxiety-44riven depressive episodes in PD precede.

PATHOPHYSIOLOGY:

According to the pathophysiology of Parkinson's disease, abnormal α-synuclein aggregation, mitochondrial dysfunction, and lysosome dysfunction interact in a complex way. or neuroinflammation, vesicle transport, and synaptic transport problems. While many other motor and non-motor circuits are affected by the neuropathology, these disease mechanisms work together to cause accelerated neuronal death of primarily dopaminergic neurons. Bradykinesia results from a gradient of striatal dopamine depletion brought on by the loss of nigrostriatal dopamine cells, which unbalances the direct (facilitatory) and indirect (inhibitory) pathways through the basal ganglia. According to neurophysiological recordings, bradykinesia is defined as an imbalance between two oscillatory rhythms: excessive beta activity (anti-kinetic) and insufficient gamma activity (prokinetic). In particular, dopaminergic drugs or deep brain stimulation cause beta oscillations to stop, which are linked to the dopaminergic off state. According to the pathophysiology of Parkinson's disease, abnormal α-synuclein aggregation, mitochondrial dysfunction, and lysosome dysfunction interact in a complex way or neuroinflammation, vesicle transport, and synaptic transport problems. [17]

While many other motor and non-motor circuits are affected by the neuropathology, these disease mechanisms work together to cause accelerated neuronal death of primarily dopaminergic neurons. Bradykinesia results from a gradient of striatal dopamine depletion brought on by the loss of nigrostriatal dopamine cells, which unbalances the direct (facilitatory) and indirect (inhibitory) pathways through the basal ganglia. According to neurophysiological recordings, bradykinesia is defined as an imbalance between two oscillatory rhythms: excessive beta activity (anti-kinetic) and insufficient gamma activity (prokinetic). In particular, dopaminergic drugs or deep brain stimulation cause beta oscillations to stop, which are linked to the dopaminergic off state. The fact that these pathological changes are accompanied by compensatory changes in brain activity in certain areas is a relatively recent discovery. that are initially unaffected by Parkinson's disease pathology, like the recruitment of cortical regions less connected to the basal ganglia and a shift towards more anterior cortico-striatal circuits. Important pathophysiological hints have been revealed by monogenic forms of Parkinson's disease, but it is still unclear how well these discoveries apply to non-monogenic Parkinson's disease. Another warning is that a lot of research on the pathophysiology of this illness is done in lab settings using animals or cellular models. Certain pathways, like the one that forms a positive feedback loop between α-synuclein and lysosomal acid G-case and may cause a self-propagating disease, are well known or a disease-related chain reaction that starts with mitochondrial oxidant stress, oxidized dopamine buildup, and decreased lysosomal acid G-case activity and accumulation of α-synuclein. According to a 2018 study, pathological α-synuclein is formed more quickly when poly [ADP-ribose] polymerase (PARP) 1 is activated. This can be avoided by using PARP inhibitors. 67. Additionally, a specific group of peptides derived from α-synuclein drive helper and cytotoxic T-cell responses and function as potential antigenic epitopes. Similar to traditional autoimmune diseases, about 40% of patients with Parkinson's disease exhibit immune responses to α-synuclein. Furthermore, an anti-influenza medication prevented the α-synuclein aggregation that occurs with influenza virus infection. Lastly, the Parkinson's proteins linked to disease The removal of damaged mitochondria (mitophagy), which is now also connected to inflammatory processes, is facilitated by Parkin and PINK1 working together. Uncertainty surrounds the relationship between early gut disease processes and later brain neurodegeneration. One clinical clue is that constipation may occur years before motor parkinsonism manifests. This is consistent with the Braak hypothesis, the validity of which is still up for debate, which holds that Parkinson's disease develops when a foreign substance enters the central nervous system (CNS), most likely through the

gastrointestinal tract, and travels to the brain via the vagal nerve. A sophisticated study tackled this problem by using a thorough multimodal imaging technique to detect brainstem, heart, and gut dysfunction. and nigral projections in Parkinson's disease patients. Two forms of this illness were found: a brain-first type with pathology beginning in the nigrostriatal system, and a body-first type with early gut and cardiac involvement, followed by brain dysfunction, in accordance with the Braak hypothesis. There may be a genetic component to Parkinson's disease in people who exhibit a brain-first phenotype. On the other hand, a shift in gut microbiota may be the first step in the pathophysiology of Parkinson's disease in people with a body-first phenotype. According to one study, mice overexpressing SNCA only experience parkinsonism and brain damage when their gut microbiota is present; germ-free animals were shielded from neurodegeneration. Bacterial intestinal infection causes mitochondrial antigen presentation and triggers autoimmune reactions in PINK1-deficient mice. To determine whether alterations in the microbiome are a direct cause of Parkinson's disease or if they are only a reflection of secondary changes, more investigation is necessary. One key takeaway is that understanding the underlying pathophysiology may help identify new targets for diagnostic and potentially therapeutic approaches. However, it is unlikely that a single intervention will alter the course of Parkinson's disease in all of its forms due to the disease's complexity and unique manifestation in each individual. Additionally, compared to the later stages of Parkinson's disease, the pathophysiological processes during the prodromal or early symptomatic phase differ. Therefore, the type of interventions must be carefully planned adapted to the underlying disease processes. [17]

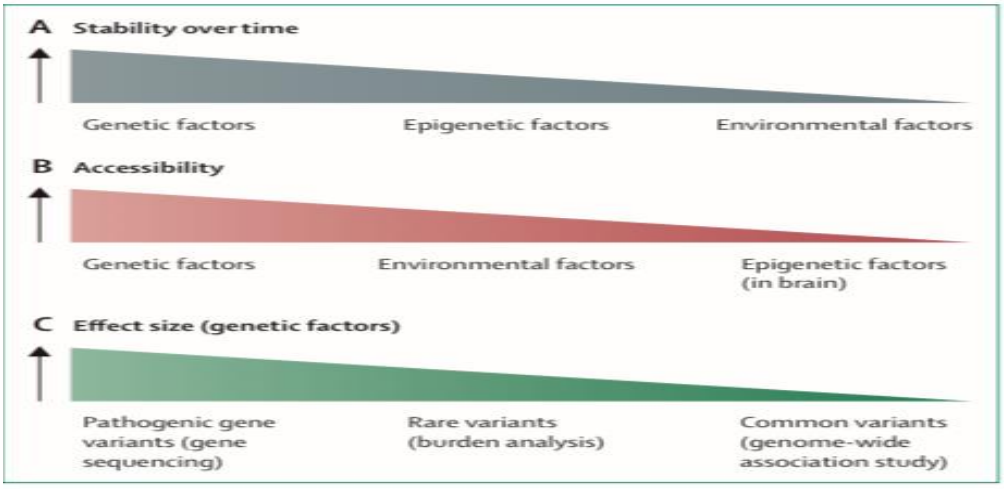
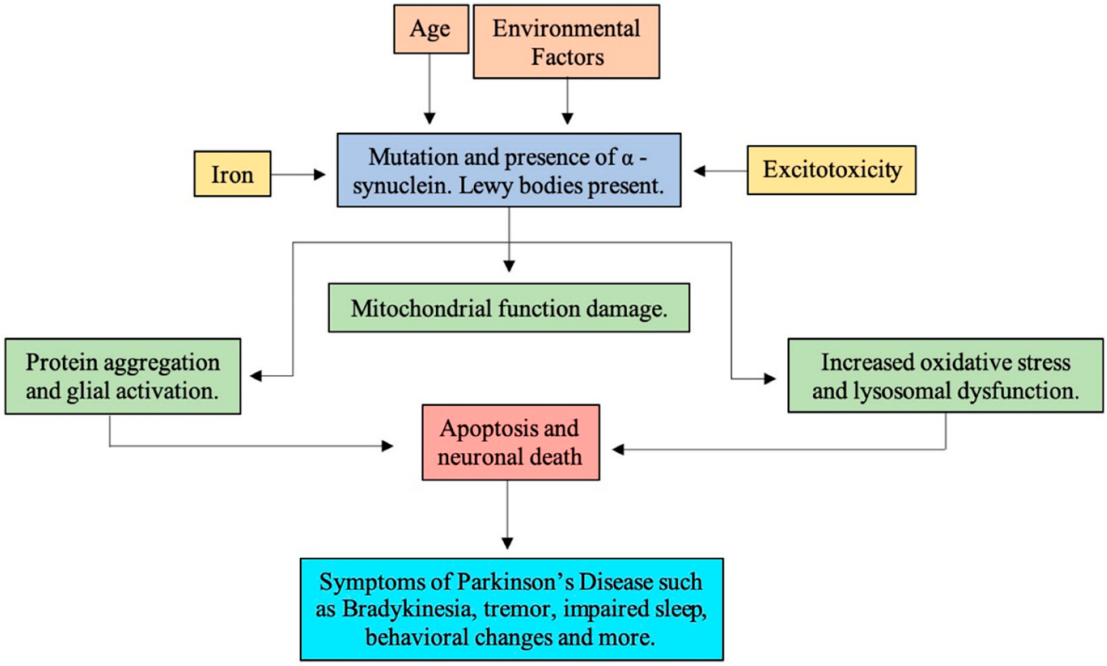


Figure 4: **The limitations of studying the causes of Parkinson's disease and modifying factors**



Flow chart 2.

DIAGNOSIS:

Parkinson's disease is diagnosed based on the presence of the core symptoms, which include tremor when the limb is at rest or rigidity, or resistance to passive movement of the joints, and slowness and paucity of movement (bradykinesia and akinesia).10, 11. Although they are frequently included in the definition, postural abnormalities typically appear later in the They have little clinical utility in the early stages of the disease because they are nonspecific and follow the course of the disorder. Tremor, a weak and unsteady limb, a stiff and sore limb, and a gait abnormality are the four typical manifestations of Parkinson's disease. The hallmark of Parkinson's disease is a resting tremor in one hand, usually, that goes away with voluntary movement. It often comes out in a hand as the person is walking. Parkinson's disease is almost always accompanied by rest tremor. However, non-classic findings like tremor when the person is holding their arms out or moving their hands voluntarily could make the diagnosis more difficult or the lack of a shudder. The condition that is most frequently mistaken for early Parkinson's disease is essential tremor. Due to their tremulous hands, patients with essential tremor often report having trouble drinking from a cup. Essential tremor typically results in symmetrical hand tremor, frequently accompanied by tremor in the head and voice. In the event that Parkinson's When the disease affects the cranial muscles, it usually manifests as a tremor in the tongue, jaw, and chin rather than the head. The two conditions can be distinguished by handwriting: Parkinson's disease

handwriting is small and irregular, while essential tremor handwriting is large and tremulous. Essential tremor is not linked to bradykinesia or rigidity. A mild hemiparesis may be suggested by early Parkinson's disease symptoms such as decreased arm swing, dragging of the foot, and slowed gait on the affected side (see the video clip in the Supplementary Appendix). Patients may experience trouble leaving rolling over in bed, getting out of deep chairs, and cars. However, in the early stages of the disease, freezing, falls, and a shuffling gait are uncommon. In Parkinson's disease, the distance between the feet is normal or even narrow; a wide gait points to other conditions. In general practice, the second most frequent misdiagnosis of Parkinson's disease was shuffled gait disorders with other causes. After a thorough history and physical examination, Parkinson's disease is diagnosed. The diagnosis is not supported by imaging studies or laboratory testing. Some patients, especially those with noticeable abnormalities in their gait, may benefit from magnetic resonance imaging of the brain or other tests to rule out other conditions, but are rarely required in a normal situation. The density of dopamine nerve terminals can be measured using ligands that bind the dopamine transporter and show up on single-photon emission computed tomography; these ligands are available in Europe and are currently being tested in the US. When clinical findings are unclear or subtle, dopamine-transporter imaging may offer helpful diagnostic information for treatment. Although the patient's reaction to a levodopa trial has been proposed as a diagnostic test for Parkinson's disease, its usefulness is debatable, especially if the severity of the symptoms does not warrant long-term levodopa therapy. [18]

Table 1

	Purpose	Indications
MRI	Cerebrovascular lesions (ie, lacunes, white matter hyperintensity, and perivascular spaces); normal pressure hydrocephalus; atypical parkinsonism	Presence of >2 red flags or absolute exclusion criteria
Dopaminergic neuroimaging*†	Identify degeneration of the nigrostriatal system (thus establishing parkinsonism)	Dystonic tremor *vs* Parkinson's disease; essential tremor *vs* Parkinson's disease; people with Parkinson's disease with a functional overlay; drug-induced parkinsonism *vs* (concurrent) Parkinson's disease; vascular parkinsonism; enrichment biomarker—for use in clinical trials only‡
Sympathetic cardiac [123I]-metaiodobenzylguanidine scintigraphy	Differentiate Parkinson's disease and dementia with Lewy bodies (decreased binding) from multiple system atrophy and progressive supranuclear palsy (normal binding)	Diagnostic uncertainty
Transcranial ultrasound of the substantia nigra	Presence of hyperechogenicity predicts Parkinson's disease diagnosis, normal echogenicity predicts atypical parkinsonism and poorer treatment response	Restricted use (by experienced examiner, for people with a sufficient bone window)
Genetic testing	At present, the only way to establish a definitive diagnosis of a particular type of Parkinson's disease during life	Research: identification of candidates for trials of gene-targeted treatments; clinical practice: onset at a young age (younger than 40 years), or positive family history, or both§
Copper (serum, 24 h urine), plasma ceruloplasmin, Kayser-Fleischer rings in peripheral cornea	Exclude Wilson's disease	Age at onset is younger than 50 years
Autonomic function tests	Establish autonomic dysfunction	Might aid in differentiating Parkinson's disease from multiple system atrophy, in which autonomic dysfunction appears earlier and more prominently
Polysomnography	Detection of idiopathic rapid eye movement sleep behaviour disorder	Presence suggests underlying synucleinopathy (Parkinson's disease, multiple system atrophy, Lewy body dementia)
Olfactory tests	Detect hyposmia	Provides supportive criterion to establish diagnosis of Parkinson's disease
Tremor analysis (eg, neurophysiology, accelerometers, wearables)	Classification of tremor (eg, frequency and amplitude)	Aids in differential diagnosis (eg, functional parkinsonism *vs* Parkinson's disease)

*Dopaminergic neuroimaging remains normal in conditions that mimic parkinsonism; note that dopaminergic neuroimaging does not distinguish Parkinson's disease from the various forms of atypical parkinsonism; therefore, dopaminergic neuroimaging is not recommended for routine use in daily clinical practice but can be useful for specific indications. †Individuals with suspected parkinsonism but who have normal dopamine transporter scans have been referred to as having SWEDDS (scans without evidence of extrapyramidal dopaminergic deficit); such a normal scan renders a diagnosis of Parkinson's disease highly unlikely, and most will have alternative diagnoses, such as dystonic tremor or essential tremor; the scan might later become abnormal in a small subgroup who might end up having Parkinson's disease after all. ‡Dopaminergic neuroimaging was approved by both the US Food and Drug Administration and the European Medicines Agency in 2018 as an enrichment biomarker for clinical trials, aiming to ascertain that a higher proportion of people with a presynaptic dopaminergic deficit are included in Parkinson's disease studies.[48] §Results should be considered preliminary and reporting to people with Parkinson's disease is not yet considered standard of care.

Table 2: **Ancillary diagnostic tests that can be considered in people presenting with parkinsonism**

DIFFERENTIAL DIAGNOSIS: The causes of parkinsonism are numerous and include poisons, central nervous system infections, brain structural abnormalities, metabolic illnesses, as well as additional neurological conditions. The majority of these causes are uncommon and are typically indicated by unusual findings in the examination or history. Drug-induced parkinsonism and "parkinsonism-plus" syndromes are two alternate diagnoses that clinicians frequently have to take into account in practice. It's critical to identify drug-induced parkinsonism because it can be reversed, though it might take weeks or months after the offending medication is stopped. According to a population-based study, 20% of cases of parkinsonism were caused by drugs. 4 Parkinsonism can be brought on by dopamine antagonists, such as neuroleptics, atypical neuroleptics, antiemetic medications, and calcium channel antagonists (flunarizine and cinnarizine). Although rare and through unknown mechanisms, other medications like lithium, amiodarone, and valproic acid can also cause parkinsonism. Additionally, dopamine antagonists worsen Parkinson's disease and ought to be avoided whenever possible when treating those who have it. It is discovered that about 25% of patients who were initially diagnosed with Parkinson's disease actually have parkinsonism as a component of another illness, such as one of the so-called parkinsonism-plus syndromes. 12 Characteristics that point to the presence of other disorders include early-stage falls or dementia, symmetric parkinsonism, wide-based gait, aberrant eye movements, Babinski signs, significant orthostatic hypotension, urine retention, and the emergence of significant disability within five years of the onset of symptoms. The prognosis for parkinsonism-plus syndromes is worse than that of idiopathic Parkinson's disease, and they react poorly to antiparkinsonian drugs. If the clinical characteristics point to these additional diagnoses, a neurologic consultation is necessary.[19]

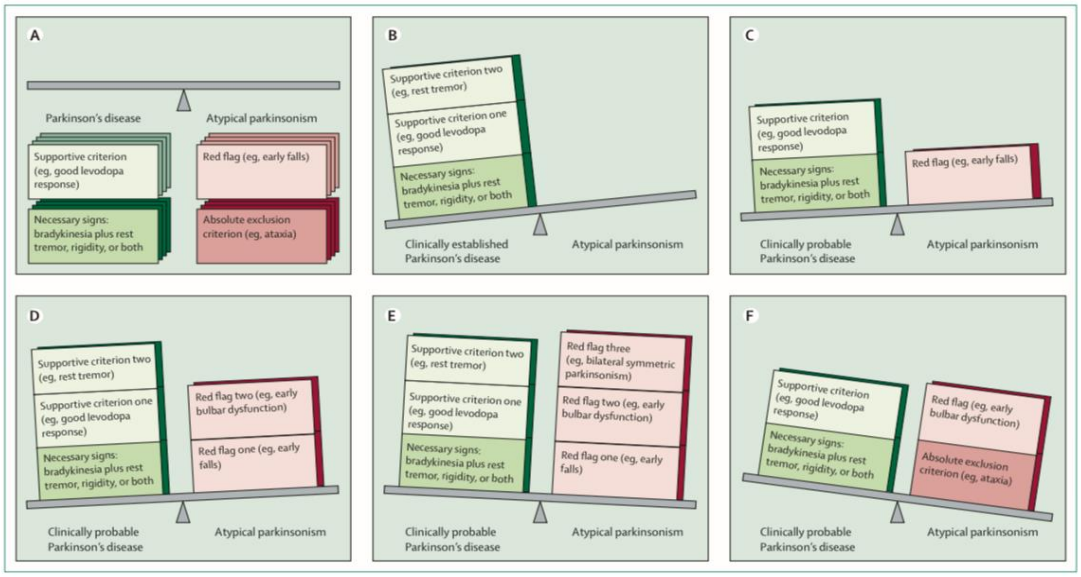


***Figure 2*: The diagnostic weighting process according to the International Parkinson and Movement Disorder Society diagnostic criteria for Parkinson's disease**
According to these criteria,[15] a diagnosis of Parkinson's disease is made on positive grounds on the basis of a combination of symptoms or signs that should be present, and exclusion of symptoms or signs that should not be present. (A) Absolute exclusion criteria refer to highly specific signs of alternative diagnoses that rule out any diagnostic rating of Parkinson's disease. Red flags refer to signs that provide a relative argument against the presence of Parkinson's disease and that are suggestive of alternative pathology, but their specificity is lower or uncertain. (B–D) The various possible scenarios to establish clinically established Parkinson's disease or clinically probable Parkinson's disease. A diagnosis of clinically established Parkinson's disease requires absence of absolute exclusion criteria, presence of at least two supportive criteria, and no red flags. A diagnosis of clinically probable Parkinson's disease requires absence of absolute exclusion criteria, whereas the presence of up to two red flags can be cancelled out by the presence of two supportive criteria. (E, F) Scenarios that suggest the presence of a form of atypical parkinsonism.

Flow chart 3

MANAGEMENT OF PARKINSONS DISEASE:

Table 2

Target	Therapy	
	Preclinical studies	Clinical studies
SNCA	Beta-2 adrenergic receptor, siRNA, non-steroidal anti-inflammatory drugs, antistreptolysin O	Thiazolidinedione (glitazones)
Misfolded α-synuclein fibrils	Anti-LAG3 antibody, small molecule inhibitors, CLR01, KYP	Active or passive immunotherapy (eg, BIIB065), nilotinib, deferiprone
Autophagy lysosomal pathway	LTI-291, AT3375	Ambroxol, glucosylceramide synthase inhibitors
Calcium ion homoeostasis	Calcium ion channel blockers	Calcium ion channel blockers (eg, isradipine)
Mitochondria dysfunction Parkin pathway	Ursocholanic acid, mitochondrial division inhibitor 1, MIRO reduction, sirolimus	11-dehydrosinularoiolide, MitoQ, exenatide, LRRK2 small molecule kinase inhibitors
Neurotrophic factors	Brain-derived neurotrophic factors, vascular endothelial growth factor	Cerebral dopamine neurotropic factor, glial cell line-derived neurotrophic factor, neurturin
Inflammation	Anti-inflammatory (eg, non-steroidal anti-inflammatory drugs)	Sargramostim, exenatide, liraglutide, lixisenatide, AZD3241
Oxidative stress	DJ-1 chaperones	Deferiprone, inosine, coenzyme Q10, caffeine, nicotine, creatine
Therapies under investigation		
Vaccines, neuroinflammatory therapies, diets and microbiome, cannabinoids, novel druggable targets, gene therapy, and next generation adaptive deep brain stimulation Emerging future therapies		

NON-PHRMACOLOGICAL TREATMENT: When diagnosing Parkinson's disease, patient education and support are essential. Patients ought to be aware that Parkinson's disease frequently has a course that lasts for decades, the rate of progression varies widely from person to person, and there are numerous methods to lessen symptoms. For those who have just received a diagnosis, support groups that include patients with more advanced illness may be frightening rather than beneficial. Though only a few short-term studies indicate that these may enhance daily living activities, gait speed, and balance, patients should still receive counselling regarding exercise, including stretching, strengthening, cardiovascular fitness, and balance training. [20]

Table 3

	Quality according to GRADE system*
Physiotherapy	
Aerobic exercise[112,113]	High
Alternative movement strategies[114]	Low
Virtual-reality enhanced gait and balance training[115,116]	Moderate
LSVT-BIG†[117]	Low
Dual task training[118]	High
Cognitive training for freezing[119]	Moderate
Combined approaches[120,121]	Moderate
For people with multiple system atrophy[122]	Low
Occupational therapy[123]	Moderate
Speech and language therapy[124]	Moderate
Nurses for people with Parkinson's disease	
Home visits[125,126]	Low
Care management[127]	High
Mindfulness and yoga[128]	Moderate
Dance[129]	Low
Bright light therapy[130,131]	Low
Palliative care[132]	Moderate
Pain management[133]	Low

GRADE=grading of recommendations, assessment, development, and evaluations. High=high confidence that the estimate of the effect from the available literature is very close to the true effect. Low=the estimate of the effect might be substantially different from the true effect. Moderate=the estimate of the effect is close to the true effect, but there might be substantial differences. *GRADE is a rating system (based on four rankings) developed to address shortcomings from previous grading systems and rates the quality and strength of a specific intervention before its recommendation for clinical practice. †LSVT-BIG is a variant of the Lee Silverman Voice Treatment in which the therapist instructs the person with Parkinson's disease to purposely make very large (big) amplitude movements.

Table 3: **Non-pharmacological interventions for people with Parkinson's disease, supported by new, graded evidence**

PHARMACOLOGICAL TREATMENT:

It is not always necessary to start medication therapy after receiving a Parkinson's disease diagnosis. When the disease is causing disability or when the patient's symptoms are bothering them enough to want treatment, drug therapy is warranted; patients' preferences are essential to this decision-making process. Levodopa, dopamine agonists, amantadine,

anticholinergic drugs, and selective monoamine oxidase B (MAO-B) inhibitors are effective first-line treatments for patients who require treatment for motor symptoms. There are no reliable comparisons of the efficacy of these drugs, with the exception of levodopa and individual dopamine agonists; however, clinical experience indicates that dopaminergic agents are more effective than amantadine, selective MAO-B inhibitors, and anticholinergic agents. Dopaminergic medications are therefore frequently the first course of treatment suggested for patients exhibiting problematic symptoms. According to the American Academy of Neurology's guidelines and the Movement Disorder Society's evidence-based review, starting treatment with levodopa or a dopamine agonist is sensible. [21]

LEVODOPA: The best antiparkinsonian medication is thought to be levodopa, a dopamine precursor. Activities of daily living and motor characteristics were compared in randomized trials between levodopa and a dopamine agonist. Levodopa caused a 40–50% improvement in Parkinson's disease symptoms. There are immediate-release and controlled-release formulations of levodopa that are combined with a peripheral decarboxylase inhibitor, like carbidopa, to lessen the decarboxylation of levodopa prior to its entry into the brain. Another preparation called carbidopa plus levodopa combined with entacapone, a catechol O-methyltransferase inhibitor, is intended to prolong the action of levodopa by blocking its O-methylation. As an initial treatment, controlled-release preparations have not been shown to be more effective than immediate-release preparations in randomized trials. Preparations of entacapone are being tested. [22]Failure to respond to levodopa can be caused by a variety of factors, such as the use of an inappropriate index of response, such as tremor, insufficient dosage, insufficient treatment duration, and drug interactions (such as concurrent use of risperidone or metoclopramide). A levodopa trial before determining that a patient is not responding to levodopa, it should be administered for three months with a gradual titration upward to at least 1000 mg daily (immediate-release form) or until the onset of dose-limiting side effects. Since less than 10% of patients with pathologically confirmed Parkinson's disease do not respond to a sufficient levodopa trial, failure raises the possibility of another illness and suggests that no medication or surgery is likely to be helpful. [23]

DOPAMINE AGONISTS: Dopamine agonists are an alternate first-line treatment for Parkinson's disease, despite being marginally less effective than levodopa. The effectiveness of the different dopamine agonists is comparable. One possible benefit of these agents is that, in contrast to Using levodopa is linked to a two or three-fold decreased risk of motor

fluctuations and dyskinesia during the first four to five years of treatment, especially for patients on dopamine-agonist monotherapy. It is unknown how long the risk of motor complications is reduced when levodopa is added to a dopamine agonist, but it is typical for levodopa to be required in addition to dopamine-agonist therapy within a few years of diagnosis to control advancing symptoms. Rarely, the ergot derivatives of the older dopamine agonists pergolide and bromocriptine can cause pericardial, pleural, and retroperitoneal fibrosis. Furthermore, an association has just been documented between the use of pergolide and cardiac valve thickening and dysfunction. According to echocardiography, patients on pergolide for an extended period of time may have restrictive valvular disease two to four times more frequently than Parkinson's disease patients not on pergolide. Agonists that are not derived from ergot, like pramipexole and ropinirole, are currently preferred in light of this concern. [24]

OTHER PHARMACOLOGICAL AGENTS: Anticholinergic medications are generally avoided for Parkinson's disease due to the negative side effects they can cause. But occasionally, they are included if tremor is extremely annoying and unresponsive to other medications, though there is insufficient proof to substantiate their specific effectiveness in treating tremor. Anticholinergic medications are generally avoided when treating patients over 70 years of age and are contraindicated for dementia patients. Although amantadine and MAO-B inhibitors have fewer side effects and require less titration to achieve therapeutic doses, their generally moderate effects make them ineffective symptomatic treatments when taken alone. [25]

SURGICAL THERAPY: When Parkinson's disease tremor is severe and not alleviated by medication, thalamotomy and thalamic stimulation—deep brain stimulation using implanted electrodes—can be effective treatments. All aspects of Parkinson's disease can be improved by pallidotomy, pallidal deep brain stimulation, and subthalamic deep brain stimulation. illness in which severe motor fluctuations and dyskinesia complicate the response to antiparkinsonian drugs. In the early stages of Parkinson's disease, surgical therapy is useless due to the lack of this indication and the associated risks and costs. [26]

NEUROPATHIC THERAPIES: There aren't any proven neuroprotective treatments available right now. Clinical trials, however, indicate that coenzyme Q1036, selective MAO-B inhibitors, and dopamine agonists may slow the progression of Parkinson's disease.

Information are required to elucidate these agents' and other potential neuroprotective therapies' neuroprotective effects. [27]

INITIATION OF LEVODOPA: It's unclear when levodopa therapy should be started. Levodopa's use should be postponed for as long as possible due to limited in vitro data that raise concerns that it may be toxic to dopamine neurons and may even hasten the course of the disease. But there isn't much proof of toxicity in vivo in animals and none in people. In a randomized study of patients with early-stage Parkinson's disease, those who received levodopa therapy for 40 weeks (with a 2-week withdrawal period) demonstrated improved motor function in comparison to those who received a placebo, indicating that levodopa was not toxic. However, neuroimaging revealed that patients receiving levodopa had fewer dopamine transporters; these findings indicate the potential for a harmful effect, but it could also be the result of pharmacologic down-regulation of the transporters. [28]

CHOICE OF INITIAL THERAPY: Whether levodopa therapy or dopamine-agonist therapy is a better option for Parkinson's disease initial treatment is up for debate. The cost-benefit ratio for fewer motor complications using Ankle oedema, hallucinations, freezing of gait, and an increase in the rate of somnolence are among the adverse events that dopamine agonists have, in addition to being less effective antiparkinsonian drugs. Quality of life metrics do not distinguish between patients receiving levodopa as their first treatment and those receiving dopamine agonists. It is reasonable to start dopaminergic therapy with either levodopa or dopamine agonists, according to guidelines from the American Academy of Neurology. Additionally, it is unclear if lowering pulsatile dopaminergic stimulation—as happens with levodopa oral preparations that release immediately—will lessen the likelihood of motor fluctuations and dyskinesia. There isn't any proof yet that levodopa preparations with controlled release reduce this danger. The effects of carbidopa, levodopa, and entacapone in combination preparations as first-line therapy are being investigated in ongoing studies. [29]

Table 4.

Table 2. Initial Therapy for Symptoms in Parkinson's Disease.*

Drug Class	Example	Initial Dosage	Usual Dosage	Side Effects
First-line dopaminergic agents				
Carbidopa plus levodopa				
Immediate release (Sinemet)	25 mg carbidopa, 100 mg levodopa	1/2 tablet three times daily	1 to 2 tablets three times daily	At initiation: anorexia, nausea, vomiting, dizziness, hypotension (a 1:4 ratio of carbidopa:levodopa reduces gastrointestinal symptoms), long-term therapy: motor fluctuations, dyskinesias, confusion, hallucinations
Controlled release (Sinemet-CR)	25 mg carbidopa, 100 mg levodopa	1 tablet three times daily	—	Same as for immediate-release preparations
	50 mg carbidopa, 200 mg levodopa	1/2 tablet three times daily	1 tablet three times daily	
Carbidopa plus levodopa plus entacapone (Stalevo)	12.5 mg carbidopa, 50 mg levodopa, 200 mg entacapone	1 tablet three times daily	—	Same as with preparations above, plus diarrhea
	25 mg carbidopa, 100 mg levodopa, 200 mg entacapone		—	
	37.5 mg carbidopa, 150 mg levodopa, 200 mg entacapone		—	
Dopamine agonists				
Nonergot	Pramipexole (Mirapex)	0.125 mg three times daily	0.5–1.5 mg three times daily	Nausea, vomiting, hypotension, ankle edema, excessive daytime sleepiness, compulsive behavior, confusion, and hallucinations
	Ropinirole (ReQuip)	0.25 mg three times daily	3–8 mg three times daily	Same as for pramipexole
Ergot	Pergolide (Permax)	0.05 mg three times daily	1 mg three times daily	Same as for nonergot drugs plus retroperitoneal, pulmonary, and cardiac fibrosis
Second-line alternatives				
Anticholinergic agents	Trihexyphenidyl (Artane)	1 mg three times daily	2 mg three times daily	Impaired memory, confusion, constipation, blurred vision, urinary retention, xerostomia, and angle-closure glaucoma
	Benztropine (Cogentin)	0.5 mg twice daily	1 mg twice daily	Same as for trihexyphenidyl
Selective MAO-B inhibitors	Selegiline (Eldepryl)	5 mg daily	5 mg twice daily	Insomnia, nausea, anorexia, hallucinations, potential for interactions with SSRIs and meperidine
NMDA antagonist	Amantadine (Symmetrel)	100 mg twice daily	100 mg twice daily	Dizziness, insomnia, nervousness, livedo reticularis, hallucinations, confusion

* All antiparkinsonian drugs are started at low doses and increased slowly to reduce adverse effects. Likewise, slow withdrawal of these drugs after long-term treatment is prudent to avoid a marked worsening of parkinsonism or even the neuroleptic malignant syndrome (discussed by Keyser and Rodnitzky[20]). MAO-B denotes monoamine oxidase B, SSRI selective serotonin-reuptake inhibitor, and NMDA *N*-methyl-D-aspartate.

GUIDELINES OF PARKINSONS DISEASE:

Evidence-based recommendations for Parkinson's disease therapy have been published by the Movement Disorder Society, and the American Academy of Neurology has released clinical-practice guidelines for initial therapy in Parkinson's disease. The present review's recommendations align with these guidelines. [30]

REFERENCES:

1. **1** GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019; 18: 459–80.
2. **2** Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. J Parkinsons Dis 2018; 8: S3–8.
3. **3** Deuschl G, Beghi E, Fazekas F, et al. The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017. Lancet Public Health 2020; 5: e551–67.
4. **4** beliovich A, Gitler AD (2016) Defects in trafficking bridge Parkinson's disease pathology and genetics. Nature 539(7628):207–216
5. **5** ArticlePubMedGoogle Scholar Anheim M, Elbaz A, Lsage S, Durr A, Condroyer C, Viallet F… French Parkinson Disease Genetic Gup. (2012). Penetrance of Parkinson disease in lucocerebrosidase gene mutation carriers. Neurology, 78(6), 417–420
6. de Rijk MC, Breteler MM, Graveland GA, et al. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. Neurology 1995;45:2143-6.
7. Marras C, Tanner CM. Epidemiology of Parkinson's disease. In: Watts RL, Koller WC, eds. Movement disorders: neurologic principles & practice. 2nd ed. New York: McGraw-Hill, 2004:177-95.
8. U.S. interim projections by age, sex, race, and Hispanic origin. Washington, D.C.: U.S. Census Bureau, 2004. (Accessed August 11, 2005, at http://www.census.gov/ ipc/www/usinterimproj/.)
9. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976-1990. Neurology 1999;52:1214-20.
10. Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry 2004;75:637-9.
11. Lees AJ, Katzenschlager R, Head J, Ben Shlomo Y. Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial. Neurology 2001;57: 1687-94.
12. Fall PA, Saleh A, Fredrickson M, Olsson JE, Granerus AK. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. Mov Disord 2003;18:1312-6.
13. Healy DG, Abou-Sleiman PM, Wood NW. PINK, PANK, or PARK? A clinicians' guide to familial parkinsonism. Lancet Neurol 2004;3:652-62.

14. Payami H, Larsen K, Bernard S, Nutt J. Increased risk of Parkinson's disease in parents and siblings of patients. Ann Neurol 1994;36:659-61.
15. Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745-52.
16. Gelb DJ, Oliver G, Gilman S. Diagnostic criteria for Parkinson's disease. Arch Neurol 1999;56:33-9.
17. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-4.
18. Meara J, Bhowmick BK, Hobson P. Accuracy of diagnosis in patients with presumed Parkinson's disease. Age Ageing 1999;28:99-102.
19. Riley D, Lang AE, Blair RD, Birnbaum A, Reid B. Frozen shoulder and other shoulder disturbances in Parkinson's disease. J Neurol Neurosurg Psychiatry 1989;52:63-6.
20. Marshall V, Grosset D. Role of dopamine transporter imaging in routine clinical practice. Mov Disord 2003;18:1415-23.
21. Jennings DL, Seibyl JP, Oakes D, Eberly S, Murphy J, Marek K. (123I) beta-CIT and single-photon emission computed tomographic imaging vs clinical evaluation in Parkinsonian syndrome: unmasking an early diagnosis. Arch Neurol 2004;61:1224-9.
22. Clarke CE, Davies P. Systematic review of acute levodopa and apomorphine challenge tests in the diagnosis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 2000;69:590-4.
23. Hirsch MA, Toole T, Maitland CG, Rider RA. The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease. Arch Phys Med Rehabil 2003;84:1109-17.
24. Ellis T, de Goede CJ, Feldman RG, Wolters EC, Kwakkel G, Wagenaar RC. Efficacy of a physical therapy program in patients with Parkinson's disease: a randomized controlled trial. Arch Phys Med Rehabil 2005;86:626-32.
25. Keyser DL, Rodnitzky RL. Neuroleptic malignant syndrome in Parkinson's disease after withdrawal or alteration of dopaminergic therapy. Arch Intern Med 1991;151:794- 6.
26. Mazzulli JR, Xu YH, Sun Y, et al. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell 2011; 146: 37–52.
27. Burbulla LF, Song P, Mazzulli JR, et al. Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson's disease. Science 2017; 357: 1255–61.

28. **28.**Kam TI, Mao X, Park H, et al. Poly(ADP-ribose) drives pathologic α-synuclein neurodegeneration in Parkinson's disease. Science 2018; 362: eaat8407.
29. Sulzer D, Alcalay RN, Garretti F, et al. T cells from patients with Parkinson's disease recognize α-synuclein peptides. Nature 2017; 546: 656–61.
30. Marreiros R, Müller-Schiffmann A, Trossbach SV, et al. Disruption of cellular proteostasis by H1N1 influenza A virus causes α-synuclein aggregation. Proc Natl Acad Sci USA 2020; 117: 6741–51. Rakovic A, Ziegler J, Mårtensson CU, et al. PINK1-dependent mitophagy is driven by the UPS and can occur independently of LC3 conversion. Cell Death Differ 2019; 26: 1428–41.