The Parkinson’s Landscape

Where Do I Even Begin…?

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Why This Document?

I was diagnosed with Idiopathic Parkinson's disease in November of 2024, likely from Agent Orange exposure in Vietnam. Being newly immersed in all things Parkinson's, I put this overview document together to try and orient and educate myself on what is an undeniably expansive and complex new universe for me (*or anyone newly diagnosed*). However, I should note that this is more a technical survey of the overall Parkinson's space rather than an attempt to provide advice in the face of a new diagnosis, which I'm in no way qualified to provide.

Concerning the information I've put together here, the document is the end product of several months of intensive study with the aid of six AI programs: Open AI ChatGPT 4o, DeepSeek-R1, Google Scholar, Google Gemini 2.0 Flash, Perplexity, and Consensus Pro. Everything in this overview has been cross-referenced through all six AI models to ensure accuracy and resolve inconsistencies. In each case, the AIs have been explicitly instructed to avoid a positive bias. The need for this became obvious almost immediately, and I suspect there is an unintended but inherent tendency of today's AIs to present a positive bias when asked for outcome summaries of pre-clinical studies and clinical trials. That bias was most pronounced when running all the supplements by asking for outcomes and proposed/potential benefits.

This document will continue to evolve as I learn more about the journey ahead. If you end up reading it, please feel free to contact me with any comments, criticism, errata, resources, or ideas you might come up with.
I hope you find this document helpful no matter what your association with Parkinson's may be…

My First Lessons…

The first lessons learned were I have to be proactive every step of the way on this journey, to be informed, and to manage what's under my control while trusting my healthcare team for what I can't. One message I had driven home by a couple of amazing and well-known rock climbers with Parkinson's is the need to remain actively engaged in every aspect of your life – especially when it comes to exercise. And now, being confronted with a "it is what it is…" circumstance, fully embracing their advice seems like the only viable option.

Caveat/Disclaimer

I am not a healthcare professional but a software engineer with some background in microbiology, genetics, and healthcare software. This document is **a personal work in its entirety,** written so I wouldn't be as utterly clueless as the day I was first diagnosed. Nothing herein should be taken as gospel truth but rather just used to ground yourself in the space, which is how I'm using it. **Always consult with your healthcare providers** before acting on anything you read in this document. I definitely do so before barging ahead with any new random thought or wild idea about how I should proceed going forward.

Also, and not to be a complete downer, keep that positive spin in mind when hearing of some discovery, promising trial, or just-announced wonder therapeutic – not everything pans out as hoped, and those that do can spend years in the pipeline before coming available for our use. I'm personally staying quite optimistic but maintaining a healthy dose of realism. Still, even with that said, I am very excited about all the new tools just now arriving in the hands of the legion of folks researching neurodegenerative diseases.

Sharing

This is an open-source document intended to be freely available for any purpose to anyone with an interest in Parkinson's disease. The document is date versioned on the cover page so you can check back at any time for new versions, and it permanently resides at this link address:

https://drive.google.com/file/d/1xQryCJXc8h0rHdVB_rHwnVatrnORjEa6/view?usp=drive_link

Contents

What Causes Parkinson's Disease?

The exact cause is still unknown, but research suggests it results from a complex interplay of environmental, genetic, and cellular factors that lead to a progressive degeneration of dopamine-producing neurons in the brain.

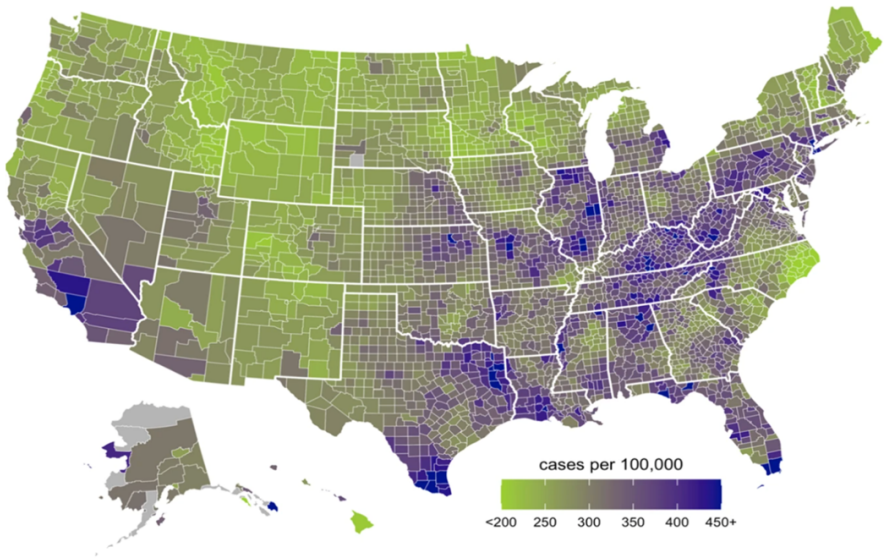
Known Factors Involved

- Mitochondrial Dysfunction – Energy Deficiency & Oxidative Stress
- Alpha-Synuclein Aggregation – Toxic Protein Clumps
- Dopamine Neuron Loss – Neurodegeneration in the Substantia Nigra
- Neuroinflammation – Overactive Immune Response in the Brain
- Gut-Brain Axis Dysfunction – Possible Origin in the Gut
- Environmental Toxins & Exposure Risks – Head Trauma, Infections, Heavy Metals, Agent Orange
- Genetic – Hereditary and Risk Genes

Parkinson's Disease Incidence

General Population

Parkinson's disease affects approximately 0.3% of the general population in industrialized countries. The incidence rate ranges between 8 to 18 per 100,000 person-years. Notably, the prevalence of Parkinson's disease increases with age, reaching about 1% in individuals over 60 and up to 4% in those over 80.



Onset Age

Age at Onset	Percentage of Cases	Notes
Under 40	2%	Rare occurrence; ~2% of are diagnosed before age 40
Under 50	4% to 10%	4% to 10% of cases are diagnosed before age 50
60 and above	Majority of cases	Most cases diagnosed at 60 years or older
80 and above	Highest prevalence of cases	Higher prevalence observed in this age group

Parkinson's Disease Symptoms

Parkinson's disease exhibits a range of motor and non-motor symptoms, which can vary greatly from individual to individual in both severity and progression.

Motor Symptoms

Motor symptoms are the hallmark features of Parkinson's disease and typically become apparent as the condition progresses. These symptoms primarily affect movement and coordination, leading to difficulties in daily activities. The most recognizable motor signs include resting tremors, bradykinesia (*slowness of movement*), rigidity, and postural instability, which contribute to an increased risk of falls. As the disease advances, individuals may experience difficulties with fine motor tasks, walking, and maintaining balance, often resulting in a characteristic shuffling gait. These impairments can significantly impact independence and quality of life, necessitating medical interventions and rehabilitative strategies.

Tremor

Is a slow shaking that usually starts asymmetrically in a hand, foot, or leg and then progresses to both sides of the body. They are most noticeable at rest (*resting tremor*). Intentional tremors occur with conscious body movements. Care needs to be taken to ensure Parkinson's tremors are distinguished and diagnosed properly, as Essential Tremors or other movement disorders can also exhibit tremors.

Rigidity

Is a persistent stiffness and resistance to movement in the muscles, affecting both voluntary and passive motion. It can occur in any part of the body, often starting on one side before becoming more widespread. This stiffness may lead to discomfort, reduced flexibility, and difficulty with everyday tasks like dressing or writing. A common sign is "cogwheel rigidity," where movement feels jerky or ratcheted when a limb is manipulated.

Bradykinesia

Is a slowing of movement that affects the ability to initiate and execute voluntary actions. It is a core symptom of the disease and contributes to difficulties with everyday tasks such as buttoning clothes, writing, or walking. Movements become smaller, slower, and less automatic over time, often leading to a shuffling gait and reduced facial expressions, known as hypomimia. Bradykinesia can also cause freezing episodes, where a person temporarily feels stuck and unable to move. Unlike simple fatigue or muscle weakness, this slowness is due to impaired signaling in the brain, making even routine motions progressively more challenging.

Postural Instability

s a loss of balance and impaired posture control, increasing the risk of falls. It arises due to difficulty in automatically adjusting body position in response to changes in movement or the environment. People with postural instability may struggle to maintain an upright stance, experience difficulty turning, or have a tendency to fall backward (*retropulsion*). Reflexes that normally help stabilize the body become less effective, making recovery from a slight push or stumble more difficult.

Gait Issues

Involve changes in walking patterns that make movement slower, unsteady, and less fluid. Affected individuals often develop a shuffling gait, taking short, hesitant steps with reduced arm swing. Difficulty starting or stopping movement is common, along with freezing episodes, where the feet seem stuck to the ground despite efforts to move. Turning can become challenging, requiring multiple small steps to change direction. Over time, gait disturbances contribute to instability and an increased risk of falls.

Non-Motor Symptoms

Non-motor symptoms can significantly impact quality of life, often contributing to disability more than movement-related issues. Because they are less visible and vary widely among individuals, they are frequently underdiagnosed or misattributed to aging or other conditions.

Cognitive and Psychiatric Symptoms

These symptoms affect thinking, mood, and behavior.

- Cognitive impairment
- Depression
- Anxiety
- Apathy
- Hallucinations
- Delusions
- Impulse control disorders

Sleep-Related

Parkinson's can cause a variety of sleep disturbances that affect both nighttime rest and daytime alertness.

- Insomnia (*both primary, falling asleep, and secondary, staying asleep*)
- REM sleep behavior disorder (*RBD*)
- Excessive daytime sleepiness
- Fatigue
- Restless Legs Syndrome (*RLS*)

Autonomic Dysfunction

The autonomic nervous system, which controls involuntary body functions, is often affected in Parkinson's.

- Orthostatic hypotension (*low blood pressure upon standing*)
- Constipation
- Seborrheic dermatitis
- Urinary dysfunction
- Sexual dysfunction
- Sweating abnormalities
- Weight changes
- Gastrointestinal issues

Sensory and Perceptual Symptoms

These symptoms affect how individuals perceive and process sensory information.

- Hyposmia (*reduced or loss of sense of smell*)
- Pain
- Vision problems
- Sensory disturbances (*e.g., tingling, burning sensations*)
- Internal tremor

Prodromal Non-Motor Symptoms

Prodromal non-motor symptoms are early signs of Parkinson's disease that can emerge years or even decades before the more characteristic motor impairments, such as tremors, become noticeable. Because they are not directly linked to obvious movement, they are easily overlooked, possibly delaying an early diagnosis.

Well-Established *(Known)* Non-Motor Prodromal Symptoms

These non-motor prodromal symptoms have the strongest supporting data as early indicators of Parkinson's disease, with large studies consistently linking them to a higher risk of developing the condition.

- REM Sleep Behavior Disorder (*RBD*) | 10–15 years
- Olfactory Dysfunction (*Hyposmia*, *Loss of Smell*) | 10 years
- Cognitive Changes (*Mild Cognitive Impairment, MCI*) | 5 years
- Autonomic Dysfunction (*Orthostatic Hypotension, Constipation, Urinary Dysfunction*) | 5–20 years
- Depression and Anxiety | 5–10 years

Suspected (*Emerging*) Non-Motor Prodromal Symptoms

These suspected or emerging symptoms have been observed in some patients and show potential as early indicators of Parkinson's disease, but further research is needed to validate their significance.

- Difficulty with Decision-Making | 5–7 years
- Apathy & Motivation Loss | 5–10 years
- Personality Changes (*Social Withdrawal [No more than usual!]*) | 5–10 years
- Seborrheic Dermatitis (*Oily Skin, Dandruff*) | 5–10 years
- Visual Changes (*Double Vision, Contrast, Motion Detection*) | 5 years
- Voice Changes (*Hypophonia*) | 1–5 years
- Gastrointestinal Issues Beyond Constipation (*SIBO, Gastroparesis*) | 5-10 years
- Excessive Daytime Sleepiness (*EDS*) | 5–10 years
- Obstructive Sleep Apnea | 5-10 years
- Restless Leg Syndrome | 5-10 years
- Dysphagia (*Swallowing Issues*) | 0–5 years
- Erectile Dysfunction | 5–10 years
- Pain (*Especially Shoulder, Neck, or Limb Pain*) | 5–10 years
- Micrographia (*Small Handwrit*ing) | 1–5 years
- Falls or Poor Balance | 1–5 years

Parkinson's Disease Subtypes

Parkinson's disease is a heterogeneous disorder with multiple subtypes that vary in their clinical presentation, progression rates, underlying pathologies, treatment responses, and genetic influences. While traditionally characterized by its hallmark motor symptoms—tremors, rigidity, bradykinesia, and postural instability—it is now recognized as a syndrome with significant diversity in how symptoms develop and progress in different individuals. Some patients experience an early predominance of tremors with relatively slow disease progression, while others may have more aggressive forms marked by rapid motor decline, cognitive impairment, or prominent non-motor symptoms such as mood disturbances, autonomic dysfunction, and sleep disorders. This variability complicates diagnosis and treatment, requiring a more personalized approach to disease management.

One way Parkinson's disease is categorized is based on the predominance of certain motor symptoms. The tremor-dominant subtype is often associated with a slower disease course and a relatively better prognosis, whereas the postural instability and gait difficulty (*PIGD*) subtype tends to progress more quickly and is linked to a greater risk of falls and cognitive impairment. Additionally, some patients present with an akinetic-rigid form, where movement slowness and stiffness are the most pronounced features, often leading to greater disability early in the disease. Beyond motor differences, Parkinson's can also be classified based on the dominance of non-motor symptoms, with some individuals experiencing significant psychiatric symptoms, sleep disturbances, or autonomic dysfunction as primary features.

Behavioral

Characterized by differences in personality, motivation, mood, and cognitive function, with some patients experiencing apathy, depression, or impulsivity.

Subtypes

- Dopamine Dysregulation Syndrome (*DDS*)
- Cognitive Impairment/Dementia-Prone
- Anxiety/Depressive

Metabolic

Defined by variations in brain metabolism, mitochondrial function, and oxidative stress levels, influencing disease progression and symptom severity.

Subtypes

- Hypermetabolic (*Weight Loss and High Energy Demand*)
- Hypometabolic (*Weight Gain and Insulin Resistance*)
- Gut-Brain Axis Dysfunction

Clinical

Based on observable symptoms such as tremor-dominant (*TD*) or postural instability and gait difficulty (*PIGD*), affecting disease presentation and treatment response.

Subtypes

- Tremor-Dominant (*TD*)
- Akinetic-Rigid (*AR*) / Postural Instability & Gait Difficulty (*PIGD*) Subtype
- Young-Onset Parkinson's Disease (*YOPD*) – Onset Before 50
- Late-Onset Parkinson's Disease (*LOPD*) – Onset After 70
- Parkinson's Disease with Dementia (*PDD*)

- Parkinson's Plus Syndromes (*Atypical Parkinsonism*)

Pathological

Categorized by differences in brain pathology, including Lewy body distribution and α-synuclein aggregation, which influence cognitive and motor deterioration.

Subtypes

- Lewy Body Parkinson's Disease (*LB-PD*)
- Tau-Associated Parkinsonism

Progression-Based

Classified by the rate of disease progression, with some experiencing rapid decline in mobility and cognition while others maintain a slower trajectory.

Subtypes

- Benign (*Slow Progression [nothing benign about it]*)
- Rapidly Progressing

Non-Motor Dominant

Characterized by severe non-motor symptoms like autonomic dysfunction, sleep disturbances, and hallucinations, often overshadowing motor impairment.

Subtypes

- Cognitive-Affective
- Autonomic Dysfunction
- Sleep Disorder-Dominant

Genetic

Defined by mutations in genes like LRRK2, GBA, or PARK, influencing the onset, progression, and response to treatment in familial and sporadic cases.

Subtypes

- LRRK2-Associated Parkinson's Disease
- GBA-Associated Parkinson's Disease
- PARKIN and PINK1-Associated Parkinson's Disease

Summary

Given the diverse nature of Parkinson's disease, treatment approaches must be tailored to the specific subtype and individual patient needs. Some patients respond well to levodopa and dopamine agonists, while others experience early motor fluctuations or medication-resistant symptoms, necessitating alternative interventions such as deep brain stimulation (*DBS*) or non-dopaminergic therapies. Recognizing Parkinson's disease as a spectrum rather than a single disease is crucial for advancing research, improving diagnostic precision, and developing targeted therapies that address the full range of clinical presentations. Future advancements in biomarker discovery, neuroimaging, and genetics may further refine our understanding of Parkinson's subtypes, paving the way for more effective, personalized treatment strategies.

Therapeutic Target Categories

Overview

Currently approved Parkinson's medications, along with clinical studies/trials, target a wide variety of therapeutic categories, each addressing the biological mechanism underlying some aspect of Parkinson's disease symptoms or progression. The sheer number of categories speaks to the breadth and complexity of Parkinson's disease as a heterogeneous disorder of multiple subtypes.

Disease-Modifying Therapies (*Targeting Disease Pathology*)

Cell Therapy

Uses stem cells or neural progenitor cells to generate new dopamine-producing neurons in the brain. These therapies aim to restore the neurons lost due to Parkinson's, potentially reversing motor symptoms

Gene Therapy

Involves delivering genetic material into brain cells to either boost dopamine production, protect neurons or correct faulty genes associated with Parkinson's

Anti-a-Synuclein

Targets and clears misfolded α-synuclein protein, which forms harmful aggregates called Lewy bodies—a hallmark of Parkinson's pathology

LRRK2

Mutations in the LRRK2 gene are a common genetic cause of Parkinson's. Inhibiting LRRK2 kinase activity can reduce neuronal damage and slow disease progression

GBA-Targeted

The GBA gene mutation is linked to defective lysosomal function, leading to protein accumulation and increased Parkinson's risk; these therapies aim to enhance the function of glucocerebrosidase (*GCase*), the enzyme affected by GBA mutations

Neurotrophic Factors

Proteins that support the survival, growth, and function of neurons, playing a crucial role in protecting and restoring dopamine-producing cells

Energy Regulation / Metabolic Modulators

Parkinson's is associated with mitochondrial dysfunctions; these therapies aim to enhance cellular energy production and improve metabolic efficiency in neurons

Helminth-Derived Molecules

These molecules, derived from parasitic worms, suppress chronic inflammation and promote immune tolerance, potentially reducing neuroinflammation associated with Parkinson's

Dopaminergic Therapies (Targeting Dopamine Deficiency

Dopamine Agonist

These drugs bind directly to dopamine receptors and stimulate them, compensating for the loss of natural dopamine due to neuronal death in Parkinson's; they don't increase dopamine levels but imitate its function

Dopaminergic

These therapies focus on restoring dopamine levels or enhancing dopamine-related signaling in the brain, they directly or indirectly aim to compensate for the dopamine deficit caused by neuronal loss

MOA-B Inhibitors

These drugs block the activity of the enzyme monoamine oxidase-B (*MAO-B*), which breaks down dopamine in the brain and, by inhibiting this enzyme, the natural and supplemented dopamine (*from drugs like levodopa*) lasts longer, improving motor function

COMT Inhibitors

These drugs inhibit the enzyme catechol-O-methyltransferase (*COMT*), which breaks down levodopa before it can enter the brain. By blocking COMT, more levodopa reaches the brain, increasing dopamine availability

Non-Dopaminergic Symptomatic Therapies

Non-Dopaminergic

Since Parkinson's affects more than just dopamine systems (*e.g., Glutamate, Acetylcholine, Serotonin Pathways*), non-dopaminergic treatments aim to address symptoms that dopaminergic drugs don't fully control, such as cognitive issues, sleep disturbances, and mood disorders

Anticholinergics

Parkinson's disease involves an imbalance between dopamine and acetylcholine due to dopamine loss; anticholinergic drugs block acetylcholine receptors, helping to restore this balance and reduce tremors and muscle stiffness

Cholinesterase Inhibitors

increases acetylcholine levels, a neurotransmitter in the brain essential for memory, learning, and attention, by inhibiting cholinesterase enzymes that break it down. By preventing acetylcholine degradation, these drugs help boost cholinergic activity, improving cognitive function.

Glutamate Modulator / Antioxidant

Overactivity of glutamate can cause excitotoxicity, leading to neuron death; antioxidants reduce oxidative stress, which damages neurons in Parkinson's

Inflammation & Metabolic Pathway Modulation

Anti-Inflammatory

Targets inflammation in the brain, which is thought to exacerbate neuronal death in Parkinson's

GLP-1R Agonist

Originally used for diabetes, GLP-1 receptor agonists have shown neuroprotective effects by reducing inflammation, improving mitochondrial function, and enhancing brain insulin signaling

Carbidopa / Levodopa (*The Therapeutic Gold Standard*)

Overview

Characteristics

- **Does NOT slow disease progression – it only treats symptoms**
- No other medication matches its ability to improve motor symptoms
- Carbidopa is a helper drug - it prevents levodopa from being broken down too soon
- Levodopa is the main active ingredient that converts into dopamine
- Unlike dopamine agonists, levodopa is converted directly into dopamine in the brain
- It took from 1910 to 1975 to arrive at FDA approval for the current standard formulation
- Relatively safe and affordable compared to newer, more expensive treatments
- Works for almost all patients where other drugs (*like dopamine agonists or MAO-B inhibitors*) are less effective alone
- Over 50+ years of clinical success

Formulations

Formulation	Brand	Onset	Duration	Best For	Downsides
Immediate Release (IR)	Sinemet®	30 min	2–4 hrs	General symptom control	Wears off quickly
Orally Disintegrating Tablet (ODT)	Generic	15–30 min	2–4 hrs	Swallowing issues, quick relief	Not sublingual, same as IR otherwise
Controlled Release (CR)	Generic	45–60 min	4–6+ hrs	Smoother, longer symptom control	Slower onset, absorption varies
Extended-Release (ER)	Rytary® or Duvodopa®	30–60 min	4–8+ hrs	Fewer doses, better wearing-off control	Expensive, delayed peak effect
Inhaled	Inbrija®	10 min	60 min	Rapid rescue from OFF episodes	Cough, lung irritation, not for daily use
Continuous Infusions (CI)	Vyalev®	30–60 min	24-Hours	Steady delivery to reduce fluctuations	Potential skin irritation at infusion site

Potential Limitations, Complications, Side Effects, And Interactions

Limitations

- **Wearing-off & Motor Fluctuations** Effectiveness decreases over time, leading to OFF episodes
- **Dyskinesia risk** Long-term use can cause involuntary movements
- **Short half-life** Requires multiple daily doses or extended-release options
- **Absorption issues** Affected by protein intake and gastric emptying problems

Complications (*Of Long-Term Use*)

- **Motor Complications**
  - **Wearing-off** Medication loses effect before the next dose
  - **Dyskinesia** Involuntary movements due to dopamine fluctuations
  - **On-Off Phenomenon** Unpredictable response where symptoms suddenly return

- **Non-Motor Issues**
  - **Neuropsychiatric Symptoms** Hallucinations, paranoia, confusion (*Especially in Elderly Patients*)
  - **Impulse Control Disorders** Compulsive behaviors (*Gambling, Shopping, Hypersexuality, Risk-Taking*) often linked to dopamine agonists but can occur with levodopa [*my personal favorite as a rock climber*]
  - **Autonomic Dysfunction** Low blood pressure (*Orthostatic Hypotension*), excessive sweating, urinary dysfunction

Common Side Effects

Category	Side Effects
Neurological	Dyskinesia, dizziness, headache, hallucinations
Gastrointestinal	Nausea, vomiting, constipation
Cardiovascular	Low blood pressure (O*rthostatic Hypotension*)
Psychiatric	Confusion, anxiety, vivid dreams, impulse control issues
Sleep-Related	Insomnia, excessive daytime sleepiness, sudden sleep attacks

Tips To Help With Side Effects

- Taking with food can reduce nausea but avoid high-protein meals, which can block absorption
- Titration (*gradual dose increases*) reduces side effects

Drug & Food Interactions

Interaction Type	Effect
Protein-Rich Foods	Reduces levodopa absorption; best taken 30–60 min before meals
Iron Supplements	Can bind to levodopa, reducing absorption
Dopamine Antagonists	Block dopamine, worsening Parkinson's symptoms
MAO-B Inhibitors	Can enhance effects but may cause hypertension if combined with high-tyramine foods
Antihypertensives	Increases risk of low blood pressure (*Hypotension*)
High dose Vitamin B6	Reduces levodopa effectiveness if taken without carbidopa

Carbidopa / Levodopa Bottom Line

- Most effective treatment for Parkinson's disease symptoms
- ✕ Motor fluctuations & dyskinesia develop with long-term use
- ✕ Can cause nausea, low BP, hallucinations, or impulse control issues
- ⚠ Watch for drug & food interactions (*Protein, Iron, Antipsychotics*)

Other FDA-Approved Drugs For Parkinson's Disease Symptoms

While Carbidopa/Levodopa is the 'gold standard' for treating Parkinson's, there are other FDA-approved drugs sometimes prescribed instead of Carbidopa/Levodopa or in combination with it. Generally, these drugs are for specific uses and sometimes specific Parkinson's subtypes.

Non-Dopaminergic

Istradefylline (*Nourianz*)

- **Application** Reduces off-time
- **Patient Profile** Mid-to-late stage where C/L's effects are fluctuating
- **Usage With C/L** Only in combination
- **Parkinson's Subtype** Postural Instability and Gait Difficulty (*PIGD)*
- **Interactions** CYP3A4 (*a critical liver enzyme*) inhibitors/inducers, may increase dyskinesia with C/L
- **Potential Side effects** Dyskinesia, Insomnia, Hallucinations

Amantadine (*Gocovri, Osmolex ER*)

- **Application** Reduces dyskinesia and mild Parkinson's symptoms
- **Patient Profile** Experiencing significant motor complications
- **Note** It's prescribed less frequently and usually reserved for specific cases
- **Usage With C/L** Only in combination
- **Parkinson's Subtype** All subtypes (*For Dyskinesia Control*)
- **Interactions** Anticholinergic drugs may cause CNS toxicity with dopamine agonists
- **Potential Side effects** Hallucinations, Dizziness, Leg Swelling, Mottled Skin

Dopamine Agonists

Rotigotine (*Neupro*)

- **Application** Mimics dopamine
- **Patient Profile** Early-stage (*sometimes before starting C/L*) or as an adjunct to C/L in advanced stages
- **Usage With C/L** Alone or in combination
- **Parkinson's Subtype** All subtypes (*Early or Adjunct Therapy*)
- **Interactions** Dopamine antagonists, CNS depressants, and alcohol
- **Potential Side Effects** Dizziness, Drowsiness, Impulse Control Disorders

Pramipexole (*Mirapex, Mirapex ER*)

- **Application** Mimics dopamine
- **Patient Profile** Mainly for younger (< *60*) patients
- **Note** May be limited in older patients due to side effects
- **Usage With C/L** Alone or in combination
- **Parkinson's Subtype** All subtypes (*Early or Adjunct Therapy*)
- **Interactions** Dopamine antagonists, CNS depressants, may enhance sedation.
- **Potential Side effects** Nausea, Dizziness, Sleep Attacks, Impulse Control Disorders

Ropinirole (*Requip, Requip XL*)

- **Application** Mimics dopamine
- **Patient Profile** Early-stage (*sometimes before starting C/L*) or as an adjunct to C/L in advanced stages
- **Note** Comes in immediate and extended release formulations
- **Usage With C/L** Alone or in combination
- **Parkinson's Subtype** All subtypes (*Early or Adjunct Therapy*)
- **Interactions** Dopamine antagonists, CNS depressants, may enhance sedation.
- **Potential Side effects** Nausea, Dizziness, Sleep Disturbances, Impulse Control Disorders

Co-beneldopa (*Madopar, Prolopa*)

- **Application** Mimics dopamine
- **Patient Profile** Younger or non-frail older adults
- **Note** Benserazide is not available in the U.S
- **Usage With C/L** Alone
- **Parkinson's Subtype** Motor-related subtypes (*Tremor-dominant, Akinetic-rigid, Postural instability/gait difficulty*)
- **Interactions** MAO inhibitors (*non-selective*) contraindicated due to hypertensive risk
- **Potential Side effects** Dyskinesias, Dystonia, Hallucinations, Insomnia, Nausea, Dizziness, Falls, Confusion

Apomorphine (*Apokyn, Kynmobi*)

- **Application** Rescue therapy for sudden off-times
- **Patient Profile** Only For Rescues
- **Note** Only comes in injectable and subcutaneous infusion formulations
- **Note** Typically reserved for patients with significant motor fluctuations unresponsive to oral medications
- **Usage With C/L** Only in combination
- **Parkinson's Subtype** Postural Instability and Gait Difficulty (*PIGD)*
- **Interactions** Dopamine antagonists; Avoid serotonin antagonists (*e.g., ondansetron*) due to severe hypotension
- **Potential Side effects** Nausea, Dizziness, Falls, Confusion

MOA-B Inhibitors

Rasagiline (*Azilect*)

- **Application** Prevents dopamine breakdown, prolonging its action
- **Patient Profile** Early-stage Parkinson's or as an adjunct to C/L in advanced stages
- **Usage With C/L** Only in combination
- **Parkinson's Subtype** All subtypes (*Early Monotherapy or Adjunct Therapy*)
- **Interactions** SSRIs, SNRIs, MAO inhibitors, tyramine-rich foods (*Hypertensive Crisis Risk*)
- **Potential Side effects** Nausea, Dizziness, Insomnia, Serotonin Syndrome Risk

Safinamide (*Xadago*)

- **Application** Prevents dopamine breakdown, prolonging its action
- **Patient Profile** Add-on therapy to C/L in mid to late-stage to manage motor fluctuations
- **Note** Its prescription frequency is less common compared to other MAO-B inhibitors
- **Usage With C/L** Only in combination
- **Parkinson's Subtype** All subtypes (*Motor Fluctuations*)
- **Interactions** SSRIs, SNRIs, opioids, and dextromethorphan due to serotonin syndrome risk
- **Potential Side effects** Nausea, Dizziness, Falls, Confusion

Selegiline (*Idepryl, Zelapar*)

- **Application** Prevents dopamine breakdown, prolonging its action
- **Patient Profile** Early-stage as monotherapy to delay the need for C/L; Mid-stage alongside C/L to extend its effectiveness
- **Note** Its use has declined with the availability of newer MAO-B inhibitors
- **Usage With C/L** Alone or in combination
- **Parkinson's Subtype** All subtypes (*Early Monotherapy or Adjunct Therapy*)
- **Interactions** SSRIs, SNRIs, MAO inhibitors, tyramine-rich foods (*Hypertensive Crisis Risk*)
- **Potential Side effects** Nausea, Dizziness, Insomnia, Dry Mouth

Anticholinergics

Trihexyphenidyl (*Artane, Pacitane*)

- **Application** Reduces tremors
- **Patient Profile** Mainly younger patients
- **Note** Due to potential cognitive side effects, its use is limited, especially in older adults
- **Usage With C/L** Alone or in combination
- **Parkinson's Subtype** Tremor-Dominant (*For Tremor Control*)
- **Interactions** Other anticholinergic drugs, CNS depressants
- **Potential Side effects** Dry Mouth, Confusion, Memory Problems, Blurred Vision

Benztropine (*Cogentin*)

- **Application** Reduces tremors
- **Patient Profile** Mainly younger patients and drug-induced Parkinsonism
- **Note** Due to potential cognitive side effects, its use is limited, especially in older adults
- **Usage With C/L** Alone or in combination
- **Parkinson's Subtype** Tremor-Dominant (*For Tremor Control*)
- **Interactions** Other anticholinergics, CNS depressants, may worsen cognitive dysfunction
- **Potential Side effects** Dry Mouth, Confusion, Memory Problems, Blurred Vision

Cholinesterase Inhibitors

Rivastigmine (*Exelon*)

- **Application** Slows cognitive impairment
- **Patient Profile** Mild-to-moderate dementia; Elderly patients experiencing cognitive decline
- **Note** Available in a transdermal patch to reduce side effects like nausea and is preferred in frail patients
- **Usage With C/L** Alone or in combination
- **Parkinson's Subtype** Parkinson's Disease Dementia (*PDD*)
- **Interactions** Risk of bradycardia with Beta-Blockers (*e.g., Metoprolol*), Calcium Channel Blockers, or Digoxin
- **Potential Side effects** Nausea, Diarrhea, Weight Loss, Loss of Appetite, Dizziness, Headaches, Bradycardia

COMT Inhibitors

Opicapone (*Ongentys*)

- **Application** Prolongs C/L effects by preventing dopamine breakdown; Reduces off-time
- **Patient Profile** Mid-to-late stage when already on C/L but experiencing fluctuations
- **Note** Its once-daily dosing offers convenience but less commonly prescribed than entacapone
- **Usage With C/L** Only in combination
- **Parkinson's Subtype** Postural Instability and Gait Difficulty (*PIGD)*
- **Interactions** MAO inhibitors; Enhances C/L effects, may increase dyskinesia
- **Potential Side effects** Diarrhea, Nausea, Dizziness, Urine Discoloration

Entacapone (*Comtan [also in Stalevo combined C/L]*)

- **Application** Prolongs C/L effects by preventing dopamine breakdown; Reduces off-time
- **Patient Profile** Mid-to-late stage when already on C/L but experiencing fluctuations
- **Note** It's often used due to its effectiveness and availability
- **Usage With C/L** Only in combination
- **Parkinson's Subtype** Postural Instability and Gait Difficulty (*PIGD)*
- **Interactions** MAO inhibitors and Warfarin; Enhances C/L effects, may increase dyskinesia
- **Potential Side effects** Diarrhea, Nausea, Dizziness, Dark Urine

Tolcapone (*Tasmar*)

- **Application** Prolongs C/L effects by preventing dopamine breakdown
- **Patient Profile** Mid-to-late stage when already on C/L but experiencing fluctuations
- **Note** More potent, but with liver toxicity risks
- **Note** Its use is limited and typically considered only when other treatments are inadequate
- **Note** Regular liver function monitoring is required during therapy
- **Note** Not a first-line treatment; usually added when standard C/L therapy is insufficient
- **Usage With C/L** Only in combination
- **Parkinson's Subtype** Postural Instability and Gait Difficulty (*PIGD)* Reduces off-time
- **Interactions** MAO inhibitors and Warfarin; Enhances C/L effects, may increase dyskinesia
- **Potential Side effects** Diarrhea, Liver Toxicity, Nausea

Stalevo (*C/L with Entacapone*)

- **Application** Prolongs C/L effects by preventing dopamine breakdown; Reduces off-time
- **Patient Profile** Patients who experience motor fluctuations and wearing-off of C/L
- **Note** It's often used due to its effectiveness and availability
- **Note** Not for patients with severe liver disease due to entacapone metabolism
- **Note** Not for those with history of neuroleptic malignant syndrome (*NMS*) or rhabdomyolysis
- **Note** Requires careful dose adjustments to prevent excessive dyskinesia
- **Note** Requires monitoring for increased dyskinesia, as entacapone prolongs C/L's effects
- **Usage With C/L** It is a combination of C/L and Entacapone
- **Parkinson's Subtype** Postural Instability and Gait Difficulty (*PIGD)*
- **Interactions** MAO-A Inhibitors (*e.g., Phenelzine, Tranylcypromine*): Avoid due to risk of hypertensive crisis
- **Potential Side effects** Dyskinesia, Nausea, Diarrhea, Orange-Colored Urine, Hypotension

Treatments And Devices

Parkinson's disease therapeutics aren't limited to drugs. There are other forms of treatments and some devices which are purported to have therapeutic benefits.

Neuromodulation | Non-Invasive

Neuromodulation refers to the process of altering or regulating nerve activity through the delivery of electrical, chemical, or other stimuli to targeted areas of the nervous system. It is used to enhance or inhibit neural signaling to treat various neurological, psychiatric, and pain-related conditions.

Non-invasive Neuromodulation uses helmet-like or focused-energy devices and does not require surgical implants. It is usually used in early stages and in less severe cases.

Transcranial Direct Current Stimulation (*tDCS*)

- Applies a low-intensity, constant direct current (*DC*) to the scalp to modulate neuronal excitability
- Used for motor rehabilitation, depression, pain management, and cognitive enhancement
- Depth of Stimulation: Superficial (*Cortical Modulation*)

Transcranial Alternating Current Stimulation (*tACS*)

- Uses alternating current (*AC*) to influence brain oscillations and synchronize neuronal activity
- Explored for cognitive function, sleep modulation, and epilepsy treatment
- Depth of Stimulation: Superficial (*Cortical Oscillation Modulation*)

Transcranial Magnetic Stimulation (*TMS*)

- Uses magnetic fields to induce electrical currents in the brain, stimulating neurons
- Used for depression, anxiety, and motor disorders like Parkinson's disease
- Depth of Stimulation: Moderate (*Cortical Regions*)

Repetitive Transcranial Magnetic Stimulation (*rTMS*)

- Delivers repetitive magnetic pulses to specific brain regions to modulate neural circuits
- Approved for depression, OCD, and being studied for Parkinson's disease
- Depth of Stimulation: Moderate to Deep (*Varies With Intensity*)

Deep Transcranial Magnetic Stimulation (*dTMS*)

- Deeper-penetrating magnetic fields to reach subcortical brain structures
- Targets deeper brain areas; used for depression, OCD, and neuropsychiatric disorders
- Depth of Stimulation: Deep (*Reaches Subcortical Structures*)

Neuromodulation | Invasive

Invasive neuromodulation does require brain surgery to embed electrical implants. Typically used in cases where medication is no longer effective, symptoms are severe, and/or non-invasive therapies no longer work.

Deep Brain Stimulation (*DBS*)

- **Applications** Used for Parkinson's disease, essential tremor, dystonia, OCD, epilepsy
- **Advantages** Adjustable, reversible, effective for motor symptoms in Parkinson's
- **Mechanism** Implanted electrodes deliver electrical pulses to modulate abnormal neural activity
- **Depth of Stimulations** Very deep (*Direct Stimulation Of Subcortical Structures*)
- **Target Brain Regions** Subthalamic Nucleus (*STN*), Globus Pallidus Interna (*GPi*), Thalamus (*VIM*)
- **Limitations** Requires brain surgery, risk of infection, battery replacement needed

Neuromodulation | Advanced

Advanced Closed-Loop neuromodulation is a real-time, adaptive brain stimulation approach that monitors neural activity and automatically adjusts stimulation based on a patient's brain state. It differs from open-loop neuromodulation**,** which delivers pre-programmed, continuous stimulation without real-time feedback.

Closed-Loop Advanced Neuromodulation (*Invasive Or Non-Invasive*)

- **Applications** Used for Parkinson's disease, epilepsy, psychiatric disorders (*OCD, Depression*)
- **Advantages** More precise, reduces side effects, optimizes energy use, and enhances symptom control
- **Mechanism** Implanted electrodes (*Or External Sensors in Non-Invasive Approaches*) detect brain activity
- **Closed Loop** Real-time monitoring of neural activity to adjust stimulation parameters dynamically
- **Key Components** Implanted electrodes, sensors, adaptive algorithms, and stimulation device
- **Depth of Stimulation** Very deep (*Direct Modulation of Subcortical / Cortical Structures*)
- **Target Brain Regions** Subthalamic Nucleus (*STN*), Globus Pallidus Interna (*GPi*), Thalamus (*VIM*), Motor Cortex, Hippocampus (*For Epilepsy*), and Anterior Cingulate Cortex (*For Psychiatric Applications*)
- **Limitations** Technically complex, expensive, requires extensive tuning, and not widely available yet

Neuromodulation | Focused Ultrasound (*FUS*)

Focused Ultrasound neuromodulation is an adaptive, non-invasive brain stimulation approach that uses real-time neural feedback to adjust focused ultrasound stimulation dynamically. This system allows precise and personalized modulation of brain activity without the need for surgical implants.

Magnetic Resonance-guided Focused Ultrasound (*MRIgFUS*)

- **Applications** Used for treating essential tremor, Parkinson's disease, and certain psychiatric disorders by creating precise brain lesions
- **Advantages** Precise targeting, no incisions, minimal recovery time, effective for tremor reduction
- **Mechanism** Uses MRI guidance to focus ultrasound beams on a target brain region, generating heat to ablate tissue without incisions
- **Limitations** Permanent lesioning, limited to specific conditions, requires high-end MRI and FUS

Forest Neurotech Forest 1 + Butterfly Networks iQ+

- **Applications** Explored for brain-computer interfaces, real-time brain imaging, and potential neuromodulation applications
- **Advantages** Portable, AI-enhanced imaging, potential for real-time neuromodulation and brain interface applications
- **Mechanism** Combines AI-driven ultrasound imaging with neurotechnology hardware to provide non-invasive brain monitoring and stimulation
- **Limitations** Still in development, effectiveness for clinical neuromodulation not fully validated

Exablate Neuro

- **Applications** Used for essential tremor, tremor-dominant Parkinson's disease, and clinical trials for OCD and depression
- **Advantages** Precise targeting, effective for tremor reduction, incision-free, minimal recovery time
- **Mechanism** Uses MRI to guide focused ultrasound beams for ablating specific brain regions
- **Limitations** Permanent lesioning, not reversible, limited to specific conditions, requires MRI compatibility

Vibration Therapy

Vibration therapy is a non-invasive therapeutic approach using mechanical vibrations to stimulate muscles, nerves, and brain activity. It is used for various medical and rehabilitation purposes, including improving motor function, reducing muscle stiffness, and enhancing circulation.

VILIM Ball

- **Applications** Reduces hand tremors; improves fine motor control
- **Advantages** Portable, easy to use, short therapy duration, temporary tremor relief
- **Key Components** Handheld spherical vibration device
- **Mechanism** Handheld device delivering mechanical vibrations to reduce hand tremors
- **Limitations** Temporary effects requiring repeated use

Intellinetix Therapy Gloves

- **Applications** Potentially reduces tremors and pain in hands
- **Advantages** Wearable, non-pharmacological, easy to use
- **Key Components** Wearable vibrating therapy gloves
- **Mechanism** Targeted vibration therapy to hands
- **Limitations** Temporary effects requiring repeated use

Power Plate pro7

- **Applications** Enhance mobility, circulation, and muscle activation
- **Advantages** Targets entire body, improves mobility and circulation
- **Key Components** Whole-body vibration platform
- **Mechanism** Whole-body vibration platform delivering micro-vibrations to activate muscles and circulation
- **Limitations** Bulky, expensive, and may not be suitable for all patients

VibePlate Parallel Bar

- **Applications** Aids in balance, muscle relaxation, and posture improvement
- **Advantages** Targets entire body, improves mobility and circulation
- **Key Components** Whole-body vibration machine with parallel bars
- **Mechanism** Whole-body vibration therapy platform aimed at improving balance and reducing muscle rigidity
- **Limitations** Requires dedicated space, which may not be ideal for all Parkinson's patients

LifetimeVibe Vibration

- **Applications** Improves circulation, muscle strength, and mobility for Parkinson's patient
- **Advantages** Helps with balance, blood flow, and muscle function
- **Key Components** Whole-body vibration platform
- **Mechanism** Whole-body vibration plate enhances blood circulation, strengthening muscles, and improving mobility
- **Limitations** Effects may vary and requires ongoing use for sustained benefits

Autophagy

Autophagy is the body's process of cleaning out damaged cells, recycling components, and promoting cellular repair. Several behaviors, habits, and dietary strategies can stimulate autophagy.

Fasting & Caloric Restriction

- **Intermittent Fasting (*IF*)** Fasting for 16+ hours (*e.g., 16:8 method*) can activate autophagy
- **Prolonged Fasting** 24–72 hours of fasting significantly enhances autophagy and cellular repair
- **Caloric Restriction** A long-term reduction in calorie intake (without malnutrition) is linked to increased autophagy

Ketogenic Diet

- **High-Fat, Low-Carb Diet** Mimics fasting by reducing insulin and glucose levels, stimulating autophagy
- **Ketones (*Such as Beta-Hydroxybutyrate*)** Help trigger autophagy in the brain and other organs

Exercise & Physical Activity

- **High-Intensity Interval Training (*HIIT*)** Short bursts of intense exercise trigger autophagy in muscles
- **Endurance Training** Prolonged aerobic activity (*e.g., Running, Cycling*) also induces autophagy
- **Strength Training** Resistance training contributes to cellular recycling and repair

Low-Protein or Protein Cycling

- **Reducing protein intake** Especially methionine and branched-chain amino acids can enhance autophagy
- **Periodic protein restriction** e.g., 1–2 days per week mimics fasting effects

Certain Foods & Compounds

- **Polyphenols** Found in green tea, coffee, dark chocolate, red wine, and berries
- **Resveratrol** Found in grapes, blueberries, and red wine
- **Curcumin** From Turmeric boosts autophagy and reduces inflammation
- **Sulforaphane** Found in cruciferous vegetables (*Broccoli, Brussels Sprouts, Kale*)
- **EGCG** A compound in green tea known to trigger autophagy
- **Caffeine** Coffee has been linked to autophagy activation

Heat & Cold Therapy

- **Sauna & Heat Stress** Increase heat shock proteins which enhance autophagy
- **Cold Exposure** Ice baths, cold showers, or cryotherapy may stimulate autophagy through hermetic stress

Sleep & Circadian Rhythms

- **Deep Sleep** Autophagy is most active during deep sleep
- **Melatonin** Supports autophagy and is boosted by regular sleep patterns

Certain Supplements

- **Berberine** Mimics fasting effects and activates AMPK, a key autophagy regulator
- **Spermidine** Found in fermented foods, mushrooms, and wheat germ, promotes autophagy
- **Rapamycin (*Prescription*)** Directly stimulates autophagy by inhibiting mTOR

Avoiding Autophagy Inhibitors

- **Excessive Sugar & Carbs** High insulin and glucose levels suppress autophagy
- **Constant Eating** Frequent meals reduce autophagy; spacing meals apart helps
- **Overeating Protein** Excessive animal protein, particularly rich in leucine, can inhibit autophagy

Optogenetics

Combines genetic engineering and optics to precisely control the activity of specific cells. The field of optogenetics is rapidly evolving, and while no commercial devices are currently available for clinical use in neurodegenerative diseases, future developments may lead to new therapeutic options.

Applications Used in research for Parkinson's disease, epilepsy, depression, and neuropsychiatric disorders

Advantages Unparalleled precision in neural circuit control, reversible, and cell-type specificity

Key Components Genetic modification (*Opsin Expression*), fiber-optic light delivery, and neural recording tools

Mechanism Uses light-sensitive proteins (*Opsins*) to control neurons with precise light stimulation

Invasiveness Highly invasive (*Requires Genetic Modification and Light Delivery Via Implants*)

Limitations Not yet used in humans, requires gene therapy, and involves surgical implantation of optical fibers

Sonogenetics

Sonogenetics involves genetically modifying specific cells to express ultrasound-sensitive proteins, enabling their activity to be modulated non-invasively through targeted ultrasound stimulation. Recent preclinical studies have demonstrated the potential of sonogenetics in Parkinson's disease.

Applications Studied for Parkinson's disease, epilepsy, and neuromodulation research

Advantages Precise, deep brain stimulation without implants, reversible, and spatially targeted

Key Components Genetic Modification (*Sonosensitive Ion Channels*), focused ultrasound device, and neural recording tools

Mechanism Uses genetically modified ultrasound-sensitive ion channels to control neuronal activity with focused ultrasound

Invasiveness Non-invasive

Limitations Not yet used in humans, requires gene therapy, and optimization of ultrasound parameters is needed

Diet And Nutrition

Why is Diet Important in Parkinson's Disease?

Diet plays a crucial role in managing symptoms, optimizing medication effectiveness, and supporting overall health**.** Since Parkinson's affects movement, digestion, and metabolism, dietary choices can impact motor symptoms, energy levels, gut health, and even cognitive function**.**

Dietary Considerations

Protein and Levodopa Absorption

- **Why it matters**
  - C/L competes with dietary protein for absorption in the gut and transport to the brain
- **Recommendations**
  - Take C/L on an empty stomach (*30-60 minutes before meals*) for better absorption
  - Consider spreading out protein intake or consuming more protein in the evening

Fiber and Gut Health

- **Why it matters**
  - Parkinson's can cause constipation due to slower digestion and reduced gut motility
- **Recommendation**
  - Increase fiber intake (*Whole Grains, Fruits, Vegetables, Legu*mes)
  - Stay hydrated with plenty of water
  - Consider probiotics and fermented foods (*Yogurt, Kefir, Sauerkraut*) for gut health

Antioxidants and Brain Health

- **Why it matters**
  - Oxidative stress from free radicals contributes to neurodegeneration
- **Recommendations**
  - Eat a diet rich in antioxidants (*Berries, Leafy Greens, Nuts, Seeds, Dark Chocolate*)
  - Follow a Mediterranean diet (*High in Healthy Fats, Vegetables, and Fish*)
  - Coffee and Green tea (*Without dairy or sugar*) and only if they don't worsen tremors

Healthy Fats for Brain Function and Neuroinflammation

- **Why it matters**
  - Omega-3 fatty acids support cognitive function and reduce inflammation
- **Recommendations**
  - Include fatty fish (*Salmon, Mackerel, Sardines*), Flaxseeds, Walnuts, and Olive Oil

Hydration and Blood Pressure

- **Why it matters**
  - Parkinson's patients are prone to low blood pressure (*Orthostatic Hypotension*), which can cause dizziness and falls

- **Recommendations**
  - Drink plenty of water and electrolyte-rich fluids (*e.g., Coconut Water*)
  - Increase salt intake if advised by a doctor

Bone Health and Vitamin D

- **Why it matters**
  - Parkinson's patients are at higher risk of osteoporosis and fractures
- **Recommendations**
  - Ensure adequate calcium and vitamin D intake (*Dairy, Leafy Greens, Fortified Foods, Sunlight Exposure*)

Specific Diets

Autophagy-Promoting Diets | Intermittent Fasting & Ketogenic

- **Why It Matters**
  - These diets stimulate autophagy, a natural process that removes damaged proteins and cellular debris, which may help protect dopaminergic neurons
- **Recommendations**
  - **Intermittent Fasting (*IF*)** Aim for 12-16+ hours of fasting to enhance dopamine function and mitochondrial health
  - **Ketogenic Diet** Focus on high-fat, low-carb intake to increase ketone production, which may reduce oxidative stress and provide an alternative energy source for neurons
- **Caution**
  - Keto diets restrict carbohydrates, which may reduce fiber intake and worsen constipation
  - Fasting may lead to low blood sugar or dizziness, especially in those prone to Orthostatic Hypotension

Mediterranean, DASH, and MIND Diets

- **Why It Matters**
  - These diets are rich in antioxidants, healthy fats, and anti-inflammatory foods, all of which support dopamine neurons and cognitive health
- **Recommendations**
  - **Mediterranean Diet** Prioritize olive oil, fish, whole grains, nuts, and leafy greens
  - **DASH Diet** Focuses on blood pressure regulation, helping prevent Orthostatic Hypotension
  - **MIND Diet (*Mediterranean + DASH*)** Specifically designed for brain health, slowing cognitive decline
- **Caution**
  - The DASH diet may include high protein intake, which could interfere with C/L absorption if not timed properly
  - Portion control is key, as excess fat intake (*even from healthy sources*) can contribute to weight gain, which may affect mobility

Foods to Avoid in Parkinson's Disease

- ✕ **Processed Foods And Trans Fats** Can promote inflammation
- ✕ **Sugary Foods** Can cause energy crashes and worsen fatigue
- ✕ **Excessive Alcohol** May interfere with medications and worsen balance issues
- ✕ **Certain Dairy Products** Some studies suggest high dairy intake may be linked to increased risk

Summary

A balanced, nutrient-rich diet can support overall health, medication effectiveness, and symptom management in Parkinson's disease. While no specific diet is a cure for Parkinson's disease, personalized nutrition strategies can improve quality of life.

Parkinson's Supplements

There are a lot of positive pre-clinical studies for supplements **but very few human trials** supporting their use, and most were either small or poorly organized. The AIs I used generated this list of potential candidates for Parkinson's Disease, provided their rationale, and then I researched each one. **Hospital pharmacy groups won't recommend supplements** due to that lack of clinical evidence but stated they don't object to people experimenting with them so long as they're not breaking the bank.

Those with a ✓ have shown some positive impact in pre-clinical studies (*of varying quality and in someone's opinion*) conducted on study models ranging from individual neurons up to nematodes, fruit flies, Zebrafish, and mice. Those with an × have not shown any or enough impact to date to recommend them. The jury's out for those with a ?. Those with a 〰 mark either have mixed results, contradicting studies, or I simply couldn't find enough data to decide one way or the other.

Autophagy Enhancing

- ✓ **Resveratrol** Known to activate autophagy via the SIRT1 gene (*Considering*)
- ✓ **Spermidine** Well-studied for autophagy enhancement (*Considering*)
- ? **Trehalose** With high doses of 5–10g inhibits α-synuclein aggregation and enhances autophagy
- ✓ **Nicotinamide Riboside (*NR*) / NMN** Boosts NAD+ levels (*Considering*)
- **Fisetin** Flavonoid with senolytic and autophagy-inducing properties, reduce neuroinflammation
- 〰 **Berberine** Also activates AMPK, which promotes autophagy

Antioxidants & Redox Support

- ✓ **N-acetylcysteine (*NAC*)** Precursor to glutathione, helps redox balance & oxidative stress (*Considering*)
- 〰 **Sulforaphane** Potent NFE2L2 gene activator protects dopamine neurons
- **Carnosine** Chelator & antioxidant helps with protein misfolding
- **Sesamin** Enhances antioxidant response via Nrf2 activation
- × **Liposomal Glutathione / Reduced Glutathione** Crucial redox homeostasis
- ? **a-Lipoic Acid** A potent antioxidant, supports mitochondrial function
- ✓ **MitoQ / Ubiquinol** MitoQ is more effective in models (*Taking*)
- 〰 **Methylene blue** Has redox-cycling properties and can enhance mitochondrial function
- **Inositol hexaphosphate (*IP6*)** Antioxidant & neuroprotective potential (*Considering*)
- 〰 **Astaxanthin / BHB (*Esters*)** Astaxanthin is a mitochondrial antioxidant; BHB neuroprotective effects
- 〰 **Tocotrienols (*Advanced Vitamin E Form*)** Protects against lipid peroxidation in neurons (*Considering*)
- **Hesperidin** Has antioxidant & anti-inflammatory properties
- **Epigallocatechin Gallate (*Green Tea Extract*)** Neuroprotective, antioxidant, and anti-aggregation
- 〰 **Curcumin** Induces NFE2L2 and helps mitigate oxidative stress (*Taking*)

Gut-Brain Axis & Microbiome Support

- **Pre/Probiotics | VSL-3** Well-known probiotic blend
- ✓ **L. plantarum PS128 | Galactooligosaccharide** (*Considering*)
- **Human-identical Milk Oligosaccharides** Supports gut microbiota & neuroprotection
- 〰 **Tributyrin** A Butyrate precursor, beneficial for gut-brain axis & neuroprotection
- **D-Ribose** Supports gut microbiota and mitochondrial energy metabolism

Mitochondrial & Energy / Metabolism Support

- **Pantethine (*B5*)** Supports Coenzyme A synthesis
- ✓ **Methylcobalamin (*B12*)** Necessary for mitochondrial & nerve function (*Taking*)
- 〰 **Thiamine (*TTFD / B1*)** Important for mitochondrial metabolism

Phosphatidylcholine Supports membrane integrity & mitochondrial function
? **CPD-Citicoline** Neuroprotective, enhances mitochondrial function
Uridine Monophosphate Supports phospholipid synthesis & brain function
Pyrroloquinoline Quinone (*PQQ*) Supports mitochondrial biogenesis (*Considering*)
Shilajit (*Fulvic Acid Complex*) Enhances mitochondrial function, inhibits α-synuclein aggregation
Acetyl-L-Carnitine (*ALCAR*) Involved in fatty acid oxidation and energy production
Creatine Helps with energy metabolism (*Considering*)
? **EPA & DHA (*Omega-3s / Fish Oil*)** Anti-inflammatory & neuroprotective (*Considering*)

Neurotransmitter Modulators & Calming Amino Acids

GABA May help with Parkinson's-related anxiety or dysautonomia
? **L-Theanine** Modulates glutamate and dopamine and reduces excitotoxicity (*Taking*)
? **Magnesium L-Threonate** Crosses blood-brain barrier and may support cognition
S-Adenosylmethionine (*SAMe*) Supports methylation and neurotransmitter metabolism
Phosphatidylserine (*PS*) Supports dopamine receptor function in the brain (*Taking*)
Taurine Modulates GABA and dopamine systems
? **Glycine** When used with Levodopa modulates NMDA receptors & glycine transporter
Lithium Orotate Neuroprotective, but generally contraindicated for Parkinson's disease

Neurotrophic, Cognitive, & Vascular Enhancers

Gingko Biloba Improves cerebral circulation & antioxidant effects
? **Gou-Teng** Anti-inflammatory & neuroprotective effects
Ashwagandha Adaptogen, a stress modulator, may have neuroprotective properties (*Taking*)
? **Bacopa Monnieri** Supports cognitive function, potential emotional benefits
? **Rhodiola rosea** Reduces dopamine breakdown, adaptogenic support
? **Lion's Mane Mushrooms** Promotes NGF (*Considering*)
? **Turkey Tail Mane Mushrooms** Support immunity (*Considering*)
? **Reishi Mushrooms** Targets mitochondrial function (*Considering*)

Concluding Thoughts

Again, the whole supplements business is quite overwhelming. The ones I marked as (*Taking*) are supplements I was already taking long before my diagnosis. As far as adding any of these into that mix, I'm not entirely sure yet as I hadn't gotten very deep into all this at the time of this writing. So, in that regard, I am likely in the same boat as you.

Warning/Caveat

Not all supplements are benign; many have undesirable interactions with particular prescription medicines. Before taking any supplements, you should understand which are contraindicated based on your prescriptions. Also, note that you may still be able to take some supplements despite interactions by offsetting the time you take them.

Therapeutic Clinical Trials

Phase I-III clinical trials of Parkinson's disease therapeutics as of 2024. Those with a have shown promise in their respective trials and either moved to the next trial phase or are applying for FSA approval. Those with an ✕ have not shown any or enough positive results to move forward. Those with a ? are either still trialing or had mixed results. Those with are still in a running trial and have yet to report results. This document section will be updated periodically as existing trials are completed and new ones begin.

Targeting Symptoms

Except for BRT-DA01, which is dual targeting, these clinical trials target Parkinson's disease symptoms.

Cell Therapy

- **BRT-DA01 (*Bemdaneprocel*)** Stem cell-derived dopamine neuron therapy aimed at restoring lost dopaminergic function in Parkinson's disease

Gene Therapy

- **NLX-P101 (*AAV-GAD*)** Adeno-associated viral vector to deliver glutamic acid decarboxylase (*GAD*) to the subthalamic nucleus, modulating motor symptoms
- **OXB-102 (*AXO-Lenti-PD*)** Lentiviral-based gene therapy designed to enhance dopamine production by delivering key enzymes involved in dopamine synthesis

Anti-α-Synuclein Therapies

- ✕ **UB-312 (*Vaccine*)** An investigational vaccine that targets misfolded α-synuclein, aiming to slow disease progression by reducing toxic protein accumulation

Dopamine Agonists

- **CVL-751 (*Tavapadon*)** D1/D5 dopamine receptor agonist designed to provide sustained motor symptom relief with fewer side effects than traditional dopamine agonists
- **SPN-830 (*Onapgo*)** Continuous subcutaneous apomorphine infusion therapy for reducing motor fluctuations in Parkinson's patients experiencing "OFF" episodes

Dopaminergic Therapies

- **IPX203 (*Crexont*)** Long-acting carbidopa-levodopa formulation designed for extended and stable symptom relief with fewer daily doses
- **ABBV-951 (*Vyalev*)** Subcutaneous infusion of carbidopa-levodopa prodrug (*Foslevodopa/Foscarbidopa*) for continuous dopaminergic stimulation
- **UCB-0022 (*Glovadalen*)** Novel dopamine-releasing agent with a unique mechanism aimed at enhancing motor symptom management

Non-Dopaminergic Therapies

- **CVN424 (*Solengepras*)** A selective GPR6 inverse agonist that modulates basal ganglia function to improve motor control without affecting dopamine receptors

Anti-Inflammatory Therapies

- **OLT-1177 (*Dapansutrile*)** Small-molecule NLRP3 inflammasome inhibitor designed to reduce neuroinflammation and slow Parkinson's progression

Glutamate Modulators

- **IRL790 (*Mesdopetam*)** Dopamine D3 receptor antagonist that reduces levodopa-induced dyskinesia and enhances movement control
- **IRL752 (*Pirepemat*)** Cortical enhancer that targets frontal cortex circuits to improve cognitive function and postural stability

Serotonin Modulators

- **NLX-112 (*Befiradol*)** High-affinity 5-HT1A receptor agonist aimed at reducing dyskinesia and motor fluctuations

Neurotropic Factors

- **GDNF** Promotes dopamine neuron survival, with potential disease-modifying effects
- **HER-096** Brain-penetrating CDNF fusion protein designed to protect and restore dopaminergic neurons

Multiple Categories (*Combination Therapy*)

- **P2B001 (*Pramipexole + Rasagiline*)** Combination therapy of a dopamine agonist (*Pramipexole*) and an MAO-B inhibitor (*Rasagiline*) for enhanced symptom control

Targeting Disease Progression

These clinical trials target the progression or reversal of Parkinson's disease.

Cell Therapy

- **ANPD001** Novel stem cell-based therapy aimed at replenishing lost dopamine neurons
- **BRT-DA01 (*Bemdaneprocel*)** Stem cell-derived neuron designed to restore dopaminergic function
- **NouvNeu001** Cell therapy approach targeting the regeneration of damaged neural pathways
- **STEM-PD** Stem cell transplantation therapy for dopamine neuron replacement
- **ATHX-105 (*MultiStem*)** Multi-stem cell therapy to reduce inflammation and promote neural repair

Gene Therapy

- **AB-1005 (*AAV2-GDNF*)** AAV2 vector to deliver glial cell line-derived neurotrophic factor (*GDNF*) to promote neuronal survival
- **CERE-120 (*Neurturin*)** Gene therapy approach delivering Neurturin, a GDNF-family growth factor, to support dopamine neurons
- **GDNF-Expressing Macrophages** Genetically modified macrophages to release GDNF, enhancing neuroprotection

Anti-α-Synuclein Therapies

- **ANVS401 (*Buntanetap*)** Small molecule designed to reduce toxic α-synuclein aggregates and improve cognitive/motor function
- **TEV-56286 (*Anle138b or Emrusolmin*)** Targets α-synuclein oligomerization, aiming to slow neurodegeneration
- **BIIB-054 (*Cinpanemab*)** Monoclonal antibody therapy designed to neutralize misfolded α-synuclein
- **UCB0599 (*Zilucoplan*)** Oral small molecule that prevents α-synuclein propagation and neuronal toxicity
- **PRX002 (*Prasinezumab*)** Investigational monoclonal antibody aiming to slow progression
- **NDC-0524** Monoclonal antibody therapy targeting **nitrated alpha-synuclein (nSyn)**

GLP-1R Agonists (*Diabetes Medications with Neuroprotective Potential*)

- **NN9535 (*Semaglutide*)** Long-acting GLP-1 receptor agonist with potential neuroprotective effects
- **NN2211 (*Liraglutide*)** Diabetes drug repurposed, targeting neuroinflammation and mitochondrial function
- **ZP10 (*Lixisenatide*)** GLP-1 analog that may reduce oxidative stress and neuronal degeneration
- **AC2993 (*Exenatide*)** Well-studied GLP-1 receptor agonist showing promise in slowing progression
- **NLY01 (*Pegylated Exenatide*)** Modified Exenatide designed for longer-lasting neuroprotective effects

Anti-Inflammatory Therapies

- **VENT-02** An oral, brain penetrant that inhibits NLRP3 inflammasome, a key driver of chronic inflammation in neurodegenerative diseases
- **NSC-3908 (*Azathioprine*)** Immunosuppressant with potential neuroinflammatory reduction
- **NE3107 (*Bezisterim* | *SUNRISE-PD*)** Small-molecule inhibitor targeting inflammation and insulin resistance
- **KO706 (*Vodobatinib*)** Multi-kinase inhibitor potentially neuroprotective and anti-inflammatory
- **AMN107 (*Nilotinib*)** Tyrosine kinase inhibitor that may help clear toxic proteins like α-synuclein
- **GM-CSF (*Sargramostim*)** Growth factor that may enhance immune function and neuronal repair

LRRK2 Inhibitors (*Targeting Genetic Variants*)

- **DNL151 (*Bipolaris*)** LRRK2 kinase inhibitor aimed at reducing mutant LRRK2-related toxicity
- **DNL201 (*Nodisertib*)** Selective LRRK2 inhibitor designed to restore dopaminergic neuron function
- **BIIB122 (*Lixudebart*)** Small-molecule LRRK2 inhibitor being developed for genetic and sporadic Parkinson's

GBA-Targeted Therapies (*Targeting GBA1 Mutations*)

- **Ambroxol** Repurposed mucolytic agent that may enhance glucocerebrosidase (*GCase*) activity, reducing α-synuclein accumulation
- **GZ (*Venglustat*)** Glucosylceramide synthase inhibitor aimed at modifying lipid metabolism in GBA-associated Parkinson's disease
- **BIA 28-6156** Small molecule enhancing GCase activity to improve lysosomal function
- **OGT-918 (*Miglustat*)** Compound designed to reduce glucocerebrosidase dysfunction, potentially slowing progression
- **GT-02287** Aims to restore GCase function, which is often impaired due to GBA1 mutations or age-related stress, leading to the accumulation of misfolded alpha-synuclein

Neurotrophic Factors

- **GDNF** Neurotrophic growth factor that may restore and protect dopamine-producing neurons
- **HER-096 (*CDNF*)** Brain-penetrating neurotrophic factor designed to slow neurodegeneration
- **aFGF-1 (*Acidic Fibroblast Growth Factor 1*)** Neuroprotective growth factor being studied for its role in dopamine neuron survival

Energy Regulation / Metabolic Modulators

- **Nicotinamide Riboside** NAD+ precursor potentially mitochondrial-boosting and neuroprotective
- **EPI-589 (*Troloxamide Quinone*)** Redox-active molecule aimed at reducing oxidative stress and enhancing cellular metabolism
- **Urolithin A** Compound that promotes mitophagy, potentially improving mitochondrial function

Glutamate Modulators / Antioxidants

- **MCI-186 (*Edaravone*)** Free-radical scavenger that may protect neurons from oxidative stress

- **N-acetylcysteine (*NAC*)** Precursor to glutathione, a key antioxidant that protects dopamine neurons
- **RP54274 (*Riluzole*)** Glutamate-modulating drug known for its use in ALS, being studied for neuroprotection

Multiple Categories

- ? **Metformin** Diabetes drug being explored for its neuroprotective, anti-inflammatory, and metabolic-modulating effects
- **Statins (? *Lipophilic* / × *Hydrophilic*)** Cholesterol-lowering drugs being studied for reducing neuroinflammation

Helminth-Derived Molecules

Molecule	Source	Mechanism	Parkinson's Relevance
ES-62	*Acanthocheilonema viteae*	TLR4 inhibition, anti-inflammatory	Reduces neuroinflammation
Cystatins	*H. polygyrus*, others	Protease inhibition, IL-10 induction	Limits microglial activation
Hpb-GLP-1	*H. polygyrus*	GLP-1 receptor agonism	Neuroprotective, reduces oxidative stress
Hp-TGM	*H. polygyrus*	TGF-β mimic	Enhances anti-inflammatory pathways
Omega-1	*Schistosoma mansoni*	Treg activation	Suppresses systemic inflammation
Extracellular Vesicles	*H. polygyrus*	miRNA delivery	Modulates gut-brain axis
FhHDM-1	*Fasciola hepatica*	Lipid modulation	Reduces inflammatory damage

Parkinson's Subtype Details

Behavioral

Dopamine Dysregulation Syndrome (*DDS*)

- Characterized by compulsive overuse of dopaminergic medications, leading to behavioral addiction
- Associated with impulse control disorders (*ICDs*) such as pathological gambling, hypersexuality, compulsive shopping, and binge eating
- Patients may exhibit mood swings, irritability, and manic-like behavior
- Often occurs in individuals on high-dose C/L or dopamine agonists
- Difficult to manage, as reducing dopaminergic therapy can worsen motor symptoms
- Requires careful medication adjustments and behavioral therapy for management

Cognitive Impairment / Dementia-Prone

- Marked by early cognitive decline, particularly in executive function, memory, and visuospatial skills
- More common in older patients and those with PIGD or akinetic-rigid subtypes
- Strongly associated with alpha-synuclein pathology and Lewy body accumulation in cortical areas
- Increased risk of developing Parkinson's disease dementia (*PDD*)
- Poorer response to dopaminergic therapy, with increased sensitivity to side effects such as hallucinations and confusion
- May require cholinesterase inhibitors (*e.g., Rivastigmine*) for cognitive support

Anxiety/Depressive

- Characterized by persistent anxiety, depression, and apathy, often preceding motor symptoms
- May have fluctuating mood disturbances, with periods of panic attacks or excessive worry
- Strongly linked to dysfunction in serotonin and norepinephrine pathways, in addition to dopamine
- Increased risk of social withdrawal, sleep disturbances, and decreased quality of life
- Can negatively impact motor symptoms, as stress and anxiety worsen tremors and rigidity
- Requires a combination of antidepressants (*e.g., SSRIs*), cognitive-behavioral therapy (*CBT*), and lifestyle modifications for management

Metabolic

Hypermetabolic Subtype (*Weight Loss and High Energy Demand*)

- Characterized by unexplained weight loss despite adequate or increased caloric intake
- Associated with higher resting energy expenditure (*REE*) and increased metabolic demand
- More common in advanced ca and patients with severe motor fluctuations and dyskinesias
- May involve increased catabolism of muscle and fat stores, leading to frailty and muscle wasting
- Can result in nutritional deficiencies and worsened overall health outcomes
- Requires high-calorie, protein-rich dietary interventions and nutritional supplementation

Hypometabolic Subtype (*Weight Gain and Insulin Resistance*)

- Characterized by weight gain, insulin resistance, and altered glucose metabolism
- More common in early-stage Parkinson's disease and patients with reduced physical activity
- Increased risk of type 2 diabetes, metabolic syndrome, and cardiovascular disease
- May be linked to dopaminergic dysfunction in metabolic regulation and changes in gut microbiota
- Poorer response to dopaminergic therapy, with increased susceptibility to medication-induced metabolic side effects

- Requires dietary modifications, exercise, and potential metabolic interventions to manage weight and insulin resistance

Gut-Brain Axis Dysfunction Subtype

- Characterized by severe gastrointestinal symptoms, including constipation, bloating, and gastroparesis
- Strongly associated with gut microbiome imbalances and intestinal permeability *("leaky gut")*
- May contribute to alpha-synuclein aggregation in the gut, potentially playing a role in pathogenesis
- Often presents years in advance, making it an early prodromal biomarker for Parkinson's disease
- Increased risk of malabsorption and nutritional deficiencies, particularly B vitamins, vitamin D, and iron
- Requires probiotic therapy, dietary adjustments, and gut-targeted treatments for symptom management

Clinical

Tremor-Dominant (*TD*)

- Characterized by resting tremor as the predominant symptom
- Slower disease progression compared to other forms
- Better response to dopaminergic therapy (*e.g. C/L*)
- Less associated with cognitive impairment or non-motor symptoms
- Likely linked to distinct neurobiological pathways affecting basal ganglia circuits

Akinetic-Rigid Parkinson's Disease (*AR-PD*)

- Characterized by bradykinesia (*slowness of movement*) and rigidity as predominant symptoms
- Minimal or no resting tremor, distinguishing it from tremor-dominant
- Faster disease progression compared to tremor-dominant
- Higher risk of non-motor symptoms, including cognitive decline, depression, and autonomic dysfunction
- Poorer response to dopaminergic therapy, often requiring adjunct treatments
- More associated with greater disability and earlier functional impairment

Postural Instability and Gait Difficulty (*PIGD*)

- Marked by balance problems, frequent falls, and freezing of gait
- Faster progression compared to tremor-dominant
- Higher risk of cognitive decline and dementia
- Poor response to dopaminergic therapy, requiring alternative treatment strategies
- Strongly associated with non-dopaminergic neurodegeneration
- More likely to require assistive devices (*e.g., Walkers, Canes*) earlier in the disease course

Young-Onset Parkinson's Disease (*YOPD*) | Onset Before 50

- Symptoms begin before age 50, often in the 30s or 40s
- More likely to have a genetic component, especially PARKIN, PINK1, or LRRK2 mutations
- Slower disease progression but higher risk of motor complications, such as dyskinesias and motor fluctuations
- Less likely to develop early cognitive impairment, but more prone to psychiatric symptoms like depression and anxiety
- Good response to dopaminergic therapy, but long-term treatment increases risk of complications
- More likely to be treated with deep brain stimulation (DBS) earlier in the disease course

Late-Onset Parkinson's Disease (*LOPD*) | Onset After 70

- Symptoms begin after age 70, often presenting with bradykinesia and gait disturbances
- Faster progression with earlier onset of cognitive decline and dementia
- Increased fall risk due to postural instability and balance issues

- More pronounced autonomic dysfunction, including orthostatic hypotension, urinary dysfunction, and constipation
- Poorer tolerance to dopaminergic therapy, with increased risk of hallucinations, confusion, and delirium
- Higher care dependency due to greater functional impairment

Parkinson's Disease with Dementia (*PDD*)

- Characterized by progressive cognitive impairment, typically occurring after the onset of motor symptoms
- Deficits in memory, executive function, visuospatial skills, and attention
- Strongly associated with hallucinations, delusions, and apathy
- Poorer response to dopaminergic therapy, with increased sensitivity to medication side effects
- Often requires cholinesterase inhibitors (*e.g., Rivastigmine*) to manage cognitive symptoms
- Greater caregiver burden and increased need for long-term care

Parkinson's Plus Syndromes (*Atypical Parkinsonism*)

- A group of disorders that mimic Parkinson's disease but have distinct features and a poor response to dopaminergic therapy includes conditions such as:

  Multiple System Atrophy (*MSA*) – Severe autonomic dysfunction, early falls, and cerebellar signs
  Progressive Supranuclear Palsy (*PSP*) – Early postural instability, vertical gaze palsy, and rapid progression
  Corticobasal Degeneration (*CBD*) – Asymmetric rigidity, apraxia, and cortical sensory deficits
  Dementia with Lewy Bodies (*DLB*) – Early cognitive impairment, fluctuating attention, and visual hallucinations
  More rapid progression and shorter survival time compared to idiopathic Parkinson's disease
  Treatment is largely symptom management, as no disease-modifying therapies are available

Pathological Lewy Body Parkinson's Disease (*LB-PD*)

- The classic form of Parkinson's disease with alpha-synuclein aggregates (*Lewy bodies*) in neurons
- Accounts for most sporadic/idiopathic cases
- Associated with motor symptoms and a wide range of non-motor symptoms (*e.g., REM sleep behavior disorder, cognitive decline*)

Tau-Associated Parkinsonism

- Some cases exhibit tau protein pathology, which is also seen in progressive supranuclear palsy (*PSP*) and corticobasal degeneration (*CBD*)
- More likely to involve cognitive decline, rigidity, and postural instability
- Often mistaken for atypical Parkinsonian syndromes

Progression-Based

Benign Parkinson's Disease (*Slow Progression*)

- Milder motor symptoms
- Minimal cognitive involvement
- Longer duration before significant disability

Rapidly Progressing

- Faster decline in motor and cognitive function
- Higher risk of dementia
- More treatment-resistant symptoms

Non-Motor Dominant

While Parkinson's disease is primarily a movement disorder, many patients experience significant non-motor symptoms, leading to the classification of non-motor-dominant subtypes.

Cognitive-Affective

- Early-onset cognitive decline, depression, anxiety, and apathy
- More likely to develop Parkinson's disease dementia (*PDD*)
- Possibly linked to frontal and limbic system dysfunction

Autonomic Dysfunction

- Severe orthostatic hypotension, urinary dysfunction, and gastrointestinal issues
- Overlaps with multiple system atrophy (*MSA*)
- Non-motor symptoms precede motor dysfunction

Sleep Disorder-Dominant

- REM sleep behavior disorder (*RBD*) is an early predictor
- More likely to have cognitive impairment later
- May be associated with greater Lewy body pathology

Genetic

Genetic causes only account for 10-15% of all Parkinson's disease cases. There are monogenic (*Single Mutations*) and non-monogenic genetic forms that have been identified, each associated with distinct clinical features. These are the top four mutations by prevalence with others listed under the 'Parkinson's Disease Mutations' heading.

GBA-Associated

- Caused by mutations in the GBA gene, which is linked to Gaucher's disease
- Higher risk of cognitive decline and dementia
- Increased prevalence in Ashkenazi Jewish populations
- May have more severe non-motor symptoms, including REM sleep disorder

LRRK2-Associated

- Most common genetic cause, especially in Ashkenazi Jewish and North African Berber populations
- Typically presents with tremor, rigidity, and bradykinesia
- Often has a slower progression and may have less cognitive involvement
- Patients respond well to dopaminergic therapy

PARKIN and PINK1-Associated

- Typically associated with early-onset Parkinson's disease (*before age 40*)
- PARKIN mutations lead to slow disease progression and good response to levodopa
- PINK1 mutations are associated with mitochondrial dysfunction
- Patients often have less cognitive decline and fewer non-motor symptoms

Clinical Implications of Parkinson's Disease Subtypes

Tailored Treatment Strategies

- **Tremor-dominant** Responds well to dopaminergic therapies, while PIGD-type may require deep brain stimulation (*DBS*) or alternative treatments
- **Cognitive-affective** May need cholinesterase inhibitors (*e.g., Rivastigmine*) for cognitive symptoms
- **Autonomic dysfunction** May require non-dopaminergic medications (e.*g., Midodrine for Orthostatic Hypotension*)

Personalized Prognosis

- Tremor-dominant has a slower progression
- PIGD and cognitive-affective progress more rapidly
- Genetic forms (*LRRK2, PARKIN, GBA*) provide insight into disease course

Biomarker Development

- Identifying specific biomarkers for each subtype can improve early diagnosis and targeted therapy
- Alpha-synuclein levels in cerebrospinal fluid (*CSF*) or blood may distinguish different subtypes

Neuroprotective Strategies

- Future research may focus on subtype-specific treatments, such as LRRK2 inhibitors for LRRK2-PD or GBA-targeted therapies

Conclusion

Parkinson's disease is not a single disorder but a spectrum of syndromes with distinct clinical presentations, genetic underpinnings, and progression patterns. Identifying Parkinson's disease subtypes is crucial for improving diagnosis, personalizing treatment, and developing future therapies.

Parkinson's Disease Mutations

Autosomal Dominant Mutations

Only one mutated copy of the gene is needed to increase the risk of Parkinson's disease.

Gene	Function	Mutation Details	Associated PD Type
LRRK2 (*Leucine-Rich Repeat Kinase 2*)	Regulates cellular processes and lysosomal function	G2019S (*Most Common*), R1441C/G/H, I2020T	Late-onset, common in Ashkenazi Jewish and North African Berber populations
SNCA (*Alpha-Synuclein*)	Involved in synaptic function; forms Lewy bodies	A53T, A30P, E46K, H50Q, G51D, duplication/triplication	Early-onset, severe progression, associated with dementia
VPS35 (*Vacuolar Protein Sorting 35*)	Involved in protein recycling and autophagy	D620N	Late-onset, similar to idiopathic Parkinson's disease

Autosomal Recessive Mutations

Both copies of the gene must be mutated for the disease to manifest.

Gene	Function	Mutation Details	Associated PD Type
PARK2 (*PRKN*, *Parkin*)	Regulates mitochondrial function and protein degradation	Multiple mutations	Early-onset PD (*< 40 years*), slow progression, minimal Lewy bodies
PINK1 (*PTEN-Induced Kinase 1*)	Maintains mitochondrial quality control	Multiple mutations	Early-onset PD, slow progression, responsive to levodopa
DJ-1 (*PARK7*)	Antioxidant function, protects neurons	Multiple mutations	Early-onset PD, no Lewy bodies, slow progression
FBXO7 (*F-box protein 7*)	Regulates proteasome-mediated protein degradation	Multiple mutations	Early-onset PD, may present with pyramidal signs

Risk Factor Genes (*Associated with Sporadic / Idiopathic Parkinson's Disease*)

Mutations increase risk but do not directly cause Parkinson's disease.

Gene	Function	Mutation Details	Associated PD Type
GBA (*Glucocerebrosidase*)	Lysosomal enzyme, involved in degradation of cellular waste	N370S, L444P, T369M (*Common*)	Increases risk 5-10x, with faster progression and cognitive decline
TMEM175 (*Transmembrane Protein*)	Lysosomal potassium channel	Variants affect lysosomal function	Associated with sporadic Parkinson's disease
GCH1 (*Guanosine Triphosphate Cyclohydrolase 1*)	Regulates dopamine synthesis	Variants linked to dopa-responsive dystonia (*DRD*)	Increases risk of Parkinson's disease and dopamine synthesis deficits

Other Candidate Genes Under Investigation

Some studies suggest their involvement, but they are not confirmed as major Parkinson's disease genes yet.

- **CHCHD2** Regulates mitochondrial function
- **DNAJC13** Involved in vesicular trafficking
- **ATP13A2 (*PARK9*)** Linked to Kufor-Rakeb syndrome, a juvenile parkinsonism form
- **PLA2G6 (*PARK14*)** Associated with neurodegeneration with brain iron accumulation (*NBIA*)

Genetic Testing Considerations

- Genetic mutations are only **responsible for 10-15%** of all Parkinson's disease cases
- **LRRK2 and GBA are the most common** genetic risk factors for Parkinson's disease
- Early-onset Parkinson's disease (< *50 years old*) is more likely to have a genetic cause
- Genetic testing is recommended for those with a family history or early-onset disease

CRISPR / Cas9 Gene Editing | Applications In Parkinson's Disease

The promise of CRISPR-Cas9 gene editing in neurodegenerative diseases is immense, as it offers a potential way to correct genetic mutations**,** modulate gene expression**,** and even restore lost neuronal function**.**

Recent Studies

- Utilization of the CRISPR-Cas9 Technology to Dissect Neuroinflammatory and Neuropharmacological Mechanisms in Parkinson's disease | *Journal of Neuroimmune Pharmacology*
- CRISPR-Cas9-Based Technology and Its Relevance to Gene Editing in Parkinson's disease | *Pharmaceutics*
- Extracellular vesicle and CRISPR gene therapy: Current applications in Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease | *European Journal of Neuroscience*
- Application of CRISPR/Cas9 in the management of Alzheimer's disease and Parkinson's disease: a review | *Annals of Medicine and Surgery*
- CRISPR/Cas9 genome editing for neurodegenerative diseases | *EXCLI Journal*
- CRISPR/sgRNA-directed synergistic activation mediator (*SAM*) as a therapeutic tool for Parkinson´s disease | *Gene Therapy*
- Development of CRISPR Cas9, spin-off technologies and their application in model construction and potential therapeutic methods of Parkinson's disease | *Frontiers in Neuroscience*

AI-Driven CRISPR

AI enhances CRISPR applications in multiple ways, from improving gene-editing accuracy to discovering new gene functions and designing therapeutic interventions.

CRISPR Guide RNA (*gRNA*) Design

- CRISPR works by using a guide RNA (*gRNA*) to direct the Cas9 enzyme to a specific DNA sequence Designing an effective gRNA is critical for precision and efficiency
- AI models, such as deep learning algorithms, can predict on-target efficiency (*how well CRISPR binds to the intended DNA sequence*) and off-target effects (*Unintended Mutations*)
- Tools like DeepCRISPR, CRISPR-Net, and CHOPCHOP use AI to optimize gRNA selection

Predicting and Reducing Off-Target Effects

- One of the biggest challenges in CRISPR is the risk of unwanted genetic modifications
- AI models analyze large genomic datasets to predict where CRISPR might mistakenly cut similar DNA sequences, helping scientists design more precise gene-editing strategies
- AI-powered tools like DeepSpCas9 and CRISPR-ML predict off-target mutations, reducing risks for clinical applications

CRISPR and AI for Genetic Disease Treatment

- AI helps identify disease-associated genes, making CRISPR-based therapies more targeted
- AI-driven databases (*e.g., Human Gene Mutation Database and ClinVar*) analyze genetic variations to predict which mutations can be effectively treated with CRISPR
- CRISPR combined with machine learning-driven drug discovery can help create personalized medicine solutions

AI-Assisted Protein Engineering for Improved Cas9 Variants

- AI is being used to engineer new Cas enzymes that are smaller, more precise, and less immunogenic

- Tools like AlphaFold *(by DeepMind)* predict protein structures, aiding in designing improved versions of Cas9 and other CRISPR-associated proteins

AI and CRISPR in Synthetic Biology

- AI can help design synthetic genes and circuits that allow CRISPR to edit genomes with greater precision
- AI models analyze large biological datasets to optimize genetic pathways for agriculture, biofuels, and pharmaceuticals

AI for CRISPR Data Analysis

- CRISPR experiments generate vast amounts of sequencing data AI helps automate the analysis, improving accuracy and speed
- AI tools like DeepVariant and CRISPResso2 enhance genome sequencing and analysis of CRISPR edits

Future Prospects

- Autonomous CRISPR AI platforms: AI may eventually automate gene-editing processes for high-throughput experiments
- AI-powered CRISPR drug discovery: Machine learning can help find new CRISPR-based gene therapies faster
- CRISPR + AI for aging research: AI can help identify longevity-related genes that CRISPR might modify to slow aging

Neuroimaging in Parkinson's Disease: Techniques and Applications

Overview

Neuroimaging plays a crucial role in the diagnosis, classification, and monitoring of Parkinson's disease, providing valuable insights into the structural, functional, and biochemical changes that occur in the brain. Since **Parkinson's disease is primarily a clinical diagnosis based on symptom presentation and medical history**, imaging serves as an essential tool to support diagnosis, differentiate Parkinson's from other movement disorders, and track disease progression over time. Although no single imaging modality can definitively confirm Parkinson's disease, advances in neuroimaging have improved our ability to detect early neurodegenerative changes, assess the integrity of the dopaminergic system, and identify biomarkers that may help classify different Parkinson's disease subtypes.

Structural Imaging

Structural imaging techniques provide detailed anatomical views of the brain, allowing clinicians to assess brain morphology, volume loss, and potential abnormalities associated with Parkinson's disease. While Parkinson's disease does not cause major structural brain changes in its early stages, these imaging techniques help rule out other neurological conditions, such as strokes, tumors, or atypical Parkinsonian disorders, which may present with similar symptoms.

Magnetic Resonance Imaging (*MRI*)

Used to rule out alternative causes of symptoms, such as strokes, tumors, or atypical parkinsonian syndromes (*e.g., Multiple System Atrophy, Progressive Supranuclear Palsy*).

- **High-resolution T1/T2 MRI** may reveal subtle midbrain atrophy seen in atypical parkinsonism (*e.g., Hummingbird Sign in PSP or Putaminal rim sign in MSA*)
- **Neuromelanin-sensitive MRI** can visualize degeneration of dopamine-producing neurons in the substantia nigra, offering potential as an early biomarker

Computed Tomography (*CT*)

Less commonly used for Parkinson's disease diagnosis but helps exclude structural abnormalities, such as vascular damage or tumors that could mimic Parkinsonian symptoms.

- **Standard (*Conventional*) CT** Used to rule out structural abnormalities such as strokes, tumors, or hydrocephalus that could mimic Parkinsonian symptoms
- **High-Resolution CT (*HRCT*)** Helps detect subtle brain atrophy and ventricular enlargement, particularly in atypical parkinsonian syndromes like PSP or MSA
- **CT Perfusion Imaging (*CTP*)** Assesses cerebral blood flow, which may show reduced perfusion in Parkinson's-related neurodegeneration
- **Single-Photon Emission Computed Tomography (*SPECT-CT*)**: Enhances dopamine transporter imaging **(DaTscan)** to differentiate Parkinson's disease from essential tremor and other movement disorders
- **Positron Emission Tomography-Computed Tomography (*PET-CT*)** Combines metabolic and anatomical imaging to evaluate dopamine synthesis, receptor binding, and glucose metabolism, aiding in subtype differentiation

Functional Imaging

Functional imaging examines brain activity, neurotransmitter function, and metabolic changes, offering a deeper understanding of the neurochemical alterations seen in Parkinson's disease. These techniques provide critical insights into dopaminergic neuron loss, dopamine receptor availability, and glucose metabolism, which can help

differentiate Parkinson's disease from other movement disorders. By visualizing real-time functional deficits, functional imaging plays a key role in both early diagnosis and disease monitoring.

Dopamine Transporter (*DaT*) SPECT Scan (*DaTscan*®)

- Measures dopamine transporter (*DaT*) availability in the striatum, reflecting the integrity of the dopaminergic system
- Useful for differentiating Parkinson's disease from essential tremor or drug-induced parkinsonism
- Shows asymmetric dopamine loss in Parkinson's disease, whereas atypical Parkinsonian syndromes may exhibit more widespread reductions

Positron Emission Tomography (*PET*) Scans

- Measures dopamine metabolism and receptor activity, offering a more detailed functional assessment than SPECT
- Uses radiotracers such as:
  - **[18F]-DOPA PET** Tracks dopamine synthesis and uptake in the striatum
  - **[11C]-Raclopride PET** Assesses dopamine receptor binding, which can be altered in progression
  - **[18F]-FDG PET** Measures glucose metabolism, helping distinguish Parkinson's disease from atypical Parkinsonian disorders, as MSA and PSP often show distinct metabolic patterns

Advanced Neuroimaging Techniques

Advanced neuroimaging methods go beyond traditional structural and functional imaging to assess subtle microstructural, metabolic, and biochemical changes in the brain. These techniques, such as magnetic resonance spectroscopy (*MRS*), diffusion tensor imaging (*DTI*), and machine-learning-enhanced imaging analysis, are helping researchers detect preclinical biomarkers of Parkinson's disease, refine subtype classification, and improve treatment response predictions. As these imaging approaches continue to evolve, they hold great promise for advancing personalized medicine and early intervention strategies in Parkinson's disease management.

Magnetic Resonance Spectroscopy (*MRS*)

- Measures brain metabolism, including dopamine-related neurochemical changes and mitochondrial dysfunction
- Potentially useful for identifying biochemical abnormalities before clinical symptoms emerge

Diffusion Tensor Imaging (*DTI*)

- Assesses white matter integrity, detecting microstructural changes in brain pathways affected
- Helps differentiate Parkinson's disease from atypical parkinsonian syndromes, such as MSA or PSP, which exhibit distinct white matter degeneration patterns

Artificial Intelligence (*AI*) in Imaging Analysis

- Machine learning models applied to MRI, PET, and DaTscan data can improve pattern recogniti**on** for early diagnosis and disease progression tracking

Summary

As imaging technology advances, it will continue to play a key role in early detection, subtype classification, and personalized treatment strategies for Parkinson's disease.

Biomarker Tests for Parkinson's Disease

For Parkinson's disease, the most common and promising biomarker tests focus on detecting early signs of neurodegenerative disease progression and differentiating Parkinson's from other neurodegenerative disorders. Here are the key biomarker tests used or under investigation:

Alpha-synuclein Biomarkers

Alpha-synuclein Aggregation Assay (*SAA*)

- Detects misfolded alpha-synuclein aggregates in cerebrospinal fluid (*CSF*) or saliva
- Highly specific for Parkinson's disease and related synucleinopathies (*e.g., Multiple System Atrophy*)
- Used in research and some diagnostic pipelines but not yet widely available in clinical practice

Total Alpha-synuclein Levels

Measured in CSF, though this method lacks the sensitivity and specificity of SAA

Phosphorylated Alpha-synuclein

- Found in peripheral tissues like skin or salivary glands and is used experimentally to detect Parkinson's disease pathology outside the brain

Neurofilament Light Chain (*NfL*)

- Found in CSF and blood
- Helps differentiate Parkinson's disease from other neurodegenerative diseases like Multiple System Atrophy (*MSA*) or Progressive Supranuclear Palsy (*PSP*), where NfL levels are typically higher

Dopamine Transporter (*DAT/ DaTscan*) Imaging

- Visualizes dopamine transporter levels in the brain
- A reduction indicates dopamine neuron loss, which is characteristic of Parkinson's Disease
- Often used to differentiate Parkinson's disease from essential tremor

Cerebrospinal Fluid (*CSF*) Biomarkers

- Beta-amyloid and Tau Proteins: Lower beta-amyloid and altered tau levels can sometimes help differentiate Parkinson's disease with dementia from Alzheimer's disease

Inflammatory Markers

- Elevated cytokines (*e.g., IL-6, TNF-alpha*) in blood or CSF suggest neuroinflammation, though they are not specific to Parkinson's Disease

Metabolic and Mitochondrial Biomarkers (*Emerging*)

- Measures of oxidative stress and mitochondrial dysfunction in blood or CSF are being studied as potential markers of Parkinson's disease progression

Emerging Biomarker Technologies

- Skin Biopsy for Phosphorylated Alpha-synuclein: Shows promise in identifying Parkinson's disease pathology
- Salivary Alpha-synuclein: A non-invasive method under investigation
- Genetic Testing: For mutations in LRRK2, GBA, or SNCA genes linked to familial Parkinson's Disease

Resources

Foundations

- Michael J. Fox Foundation For Parkinson's Research
- Parkinson's Foundation
- American Parkinson Disease Association (*APDA*)
- European Parkinson's Disease Association (*EPDA*)
- Cure Parkinson's
- Parkinson's UK
- Davis Phinney Foundation

News

- Parkinson's News Today
- ScienceDaily: Parkinson's News
- Nature: Parkinson's Disease
- JAMA Network
- Medical Xpress: Parkinson's Disease News
- Medical News Today: Parkinson's Disease
- News-Medical: Parkinson's Disease News

Studies

- https://www.researchgate.net/search?q=Parkinson%27s%20Disease

Research Centers

- Parkinson's Disease and Movement Disorders Center at Johns Hopkins University (*USA*)
- National Institute of Neurological Disorders and Stroke (*NINDS*) (*USA*)
- Mayo Clinic Parkinson's Disease and Movement Disorders Center (*USA*)
- Massachusetts General Hospital - Parkinson's Disease Research Center (*USA*)
- University College London (*UCL*) Queen Square Institute of Neurology (*UK*)
- Oxford Parkinson's Disease Centre (*UK*)
- Florey Institute of Neuroscience and Mental Health (*Australia*)
- Oregon Health Sciences University – Brain Institute

Agent Orange

- Veterans Administration: Public Health - Agent Orange Page
- VA Parkinson's Disease Research, Education and Clinical Centers (*PADRECC*)

Clinic Studies And Trials

I was asked to join the MITO-PD study because I fit the inclusion criteria and live nearby. The others just seemed like the least I could do, given all the work the folks in the field are trying to accomplish for us.

Studies I've enrolled in

OHSU | MITO-PD Biomarker Study | Portland, Oregon

In this study, they are trying to learn more about what causes Parkinson's disease and if they can predict how it might progress in a person. It involved a blood draw and long sMRI followed by the same after one year.

Michael J. Fox | PPMI Clinical Trial | Nationwide

Establishing a Deeply Phenotyped PD Cohort - The overall goal of PPMI is to identify markers of disease progression for use in clinical trials of therapies to reduce the progression of Parkinson's disease disability.

Michael J. Fox | PD GENEration Study | Nationwide

Mapping the Future of Parkinson's Disease - PD GENEration is a global research study that provides genetic testing and genetic counseling at no cost for people diagnosed with Parkinson's disease.

Northwestern University | SPARX3 | Numerous Research Sites (*Pending*)

Investigate the effects of moderate and high-intensity aerobic exercise on disease progression in untreated patients with Parkinson's.

Oregon Health Sciences University | Digital Markers of Mobility in Daily Life to Track Progression in Newly Diagnosed Parkinson's Disease (*Pending*)

The study aims to identify objective, real-world mobility markers that can sensitively monitor disease progression in individuals recently diagnosed with Parkinson's disease.

Clinic Trial Finder

There are a lot of Parkinson's-related clinical trials going on at any given time. Some you have to be local to an institution involved in a trial, and others you can participate in remotely.

Michael J. Fox Foundation | Trial Finder

clinicaltrials.gov

Appreciation

I feel compelled to say a very heartfelt thank you to the good folks at the VA's NW Parkinson's Disease Research, Education, and Clinical Center (*PADRECC*). They work hand-in-hand with the Oregon Health Sciences University Neurology Department and Brain Institute. I'm lucky to live somewhere with such wonderful access and resources.

I also need to give a nod and thank you to my dear friend Stephanie, who, with her unflagging research into her daughter's Prader-Willi Syndrome, is absolutely the muse and inspiration for this work.

Revision History

20240411 – Add OHSU longitudinal study, Add Co-beneldopa, Add NDC-0524 trial,

20240407 – Minor typos and incorrect icons on supplements

20240311 – Removed the duplicate aFGF-1 trial from symptom trials; Added VENT-02 to progression trials

20240310 – Added brand name Pacitane to the Anticholinergic drug Trihexyphenidyl

20250304 – Added Symptoms section; More formatting fixes

20250303 – Fixed formatting (*it's endless!*); Mixed fonts snafu; Added links to the trials I'm in; Added the SPARX3 trial; Appreciation for my muse Stephanie; Pending on the SPARX3 trial

20250302 – Fixed formatting fixes (*a lot of them*); Added brand names to other FDA-approved drugs; Added Studies to the Resources section; Added text to the Clinical Trial Finder section

20250228 – Fixed content errors; Added Neuroimaging section and Incidence sections; Updated the document link for correct versioning