Neuroplasticity & Vitalism in Parkinson’s Disease Integrating Pharmacology with Naturopathic Neurorestorative Therapies 75-minute continuing education presentation • 50 slides Dave James, ND, BSc Evidence-informed • clinically integrative • evidence-level aware

Integrating Pharmacology with Naturopathic Neurorestorative Therapies

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Evidence-informed • clinically integrative • evidence-level aware

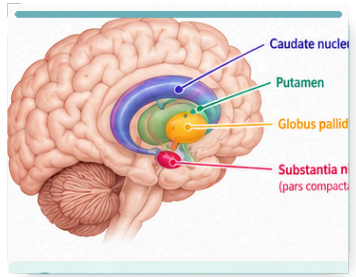
Learning objectives

Describe the neurobiology of Parkinson’s disease and the therapeutic rationale for dopaminergic pharmacology.

Explain pharmacokinetics, mechanisms, indications, adverse effects, and major interaction considerations for levodopa–carbidopa and adjunctive agents.

Differentiate symptomatic treatment from disease modification and identify common motor and non-motor treatment challenges.

Apply an evidence-informed framework to exercise, nutrition, mitochondrial support, HBOT, ketamine-assisted approaches, frequency-based therapies, and regenerative concepts.



75-minute roadmap

0–10 min | Disease biology, basal ganglia, neuroplasticity

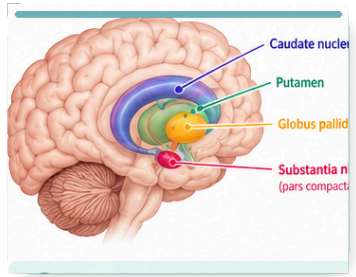
10–40 min | Pharmacology: levodopa, dopamine agonists, MAO-B, COMT, amantadine, A2A, rescue/advanced therapies

40–55 min | Naturopathic neurorestorative framework: exercise, nutrition, mitochondrial/metabolic support

55–67 min | Emerging therapies: HBOT, ketamine-assisted approaches, frequency-based interventions

67–72 min | Regenerative concepts including VSELs: evidence, uncertainty, ethics

72–75 min | Case synthesis, takeaways, CE questions



Timing is a teaching framework; adapt to audience discussion.

I. Parkinson’s biology & neuroplasticity

Clinical foundation



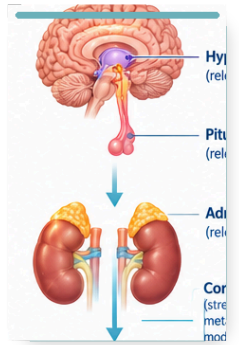
Parkinson’s disease: more than dopamine deficiency

Motor features: bradykinesia plus rest tremor, rigidity, or supportive features.

Non-motor burden may include autonomic dysfunction, sleep disorders, mood symptoms, pain, fatigue, hyposmia, and cognitive changes.

Pathobiology includes α-synuclein pathology, synaptic dysfunction, mitochondrial stress, neuroinflammation, impaired proteostasis, and circuit-level compensation.

Clinical expression reflects both neuronal loss and the brain’s ability to compensate.



MDS Fundamentals: Parkinson’s Disease (2024)

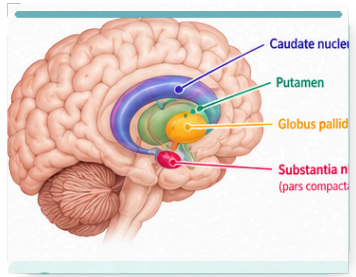
Basal ganglia circuitry: why dopamine matters

Substantia nigra pars compacta supplies dopamine to the striatum.

Dopamine facilitates movement through D1/direct-pathway signaling and reduces movement suppression through D2/indirect-pathway effects.

Loss of nigrostriatal dopamine shifts basal ganglia output toward reduced thalamocortical motor facilitation.

Levodopa and dopamine agonists restore signaling; they do not recreate the original physiologic pattern perfectly.



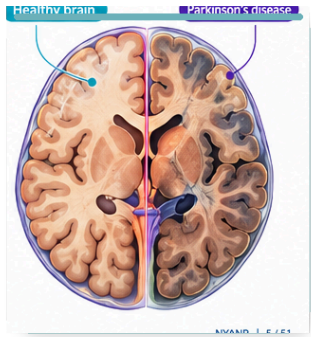
Neuroplasticity: therapeutic target vs therapeutic claim

Neuroplasticity = activity-dependent change in neural structure, function, connectivity, or network efficiency.

Exercise and rehabilitation can improve motor performance and function and may engage compensatory plasticity.

Clinical improvement does not automatically prove neuroprotection or slowed neurodegeneration.

Use precise language: symptom improvement, functional adaptation, biomarker change, and disease modification are different endpoints.



Parkinson's Foundation / ACSM exercise recommendations, 2026

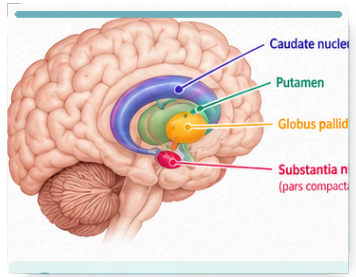
The central pharmacologic problem

Motor benefit depends on restoring dopaminergic signaling to a damaged circuit.

Early disease retains greater endogenous buffering capacity; later disease produces greater dependence on pulsatile medication delivery.

Short plasma half-life of oral levodopa contributes to fluctuations as disease advances.

Treatment strategy therefore evolves from symptomatic control toward management of OFF time, dyskinesia, non-motor symptoms, and delivery consistency.



FDA labeling; MDS evidence-based reviews

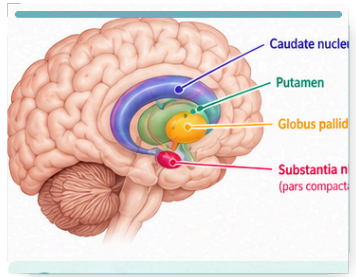
Clinical phenotype guides pharmacology

Bradykinesia/rigidity often respond robustly to dopaminergic therapy.

Tremor can respond to dopaminergic therapy but may require additional strategies.

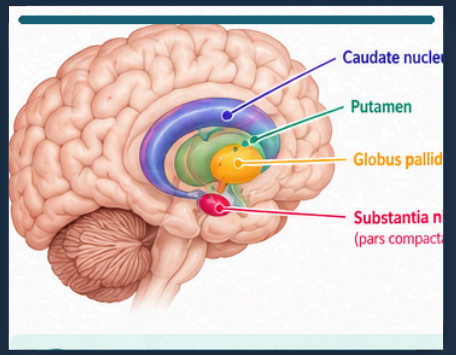
Gait freezing, postural instability, dysautonomia, cognitive impairment, sleep disorders, and pain may be less dopamine-responsive.

Always ask: what symptom are we treating, what mechanism is plausible, and what is the treatment burden?



II. Pharmacology: levodopa–carbidopa

Core 30-minute pharmacology block



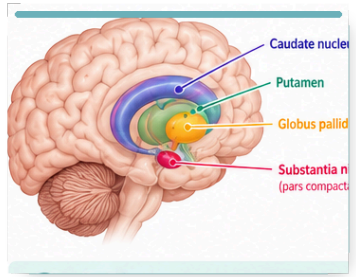
Levodopa: mechanism of action

Levodopa is the metabolic precursor of dopamine and crosses the blood–brain barrier via large neutral amino-acid transport systems.

Within the CNS, aromatic L-amino acid decarboxylase converts levodopa to dopamine.

Dopamine then stimulates striatal dopamine receptors and improves motor circuit output.

Levodopa remains the most effective medication for core motor symptoms of Parkinson’s disease.



AAN guideline; FDA Sinemet labeling

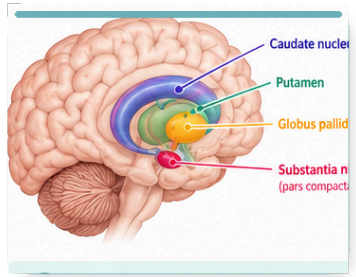
Why add carbidopa?

Carbidopa inhibits peripheral aromatic L-amino acid decarboxylase.

It does not meaningfully cross the blood–brain barrier.

Result: less peripheral conversion of levodopa to dopamine, more levodopa available for CNS delivery, and less peripheral nausea/vomiting.

Central adverse effects—especially dyskinesia and hallucinations—are not eliminated by carbidopa.



FDA Sinemet label

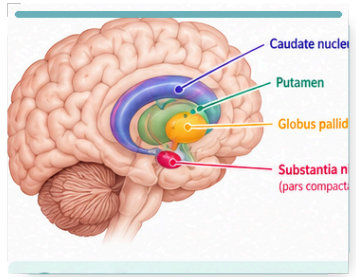
Levodopa pharmacokinetics: clinically relevant points

Oral immediate-release levodopa produces relatively rapid plasma concentration changes.

Peripheral metabolism and variable gastrointestinal absorption influence exposure.

Large neutral amino acids from protein can compete with levodopa for intestinal and blood–brain barrier transport.

Advanced disease can convert pharmacokinetic variability into clinically meaningful ON/OFF fluctuations.



FDA labeling; clinical pharmacology literature

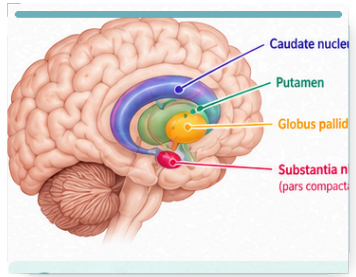
Food, protein, and levodopa timing

Protein redistribution may help selected patients whose motor response is clearly meal-related.

Do not automatically prescribe restrictive protein diets; nutritional adequacy and patient preference matter.

Separate medication timing from protein-rich meals when a reproducible interaction is present.

Monitor weight, sarcopenia risk, constipation, and overall protein adequacy—especially in older adults.



Clinical practice principle; individualized care

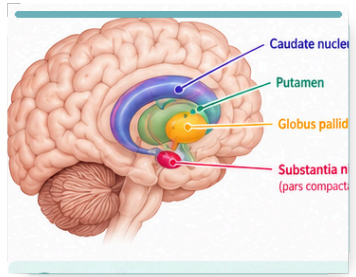
Levodopa formulations

Immediate-release carbidopa/levodopa: flexible titration and rapid onset.

Extended-release formulations: longer duration per dose for selected patients; pharmacokinetics differ by product.

Enteral levodopa delivery: continuous intestinal administration can reduce OFF fluctuations in appropriate advanced disease.

Inhaled levodopa and other rescue formulations address episodic OFF states in selected patients.



FDA-approved product labeling

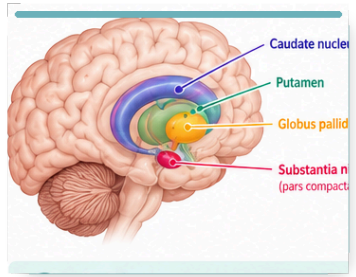
Levodopa adverse effects: recognize the pattern

Early/peripheral: nausea, appetite changes, dizziness, orthostatic symptoms.

Central: hallucinations, confusion, somnolence, and dyskinesia.

Chronic motor complications: wearing OFF, delayed ON, dose failure, unpredictable OFF, and peak-dose dyskinesia.

Sudden withdrawal or abrupt reduction can cause severe rebound motor deterioration and, rarely, a neuroleptic malignant syndrome-like emergency.



FDA Sinemet labeling

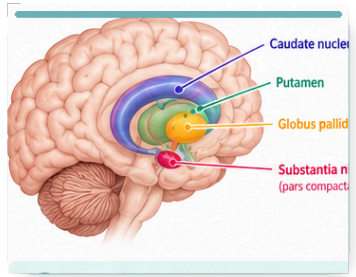
Levodopa-induced dyskinesia

Often choreiform or flowing involuntary movement occurring during ON periods.

Risk increases with disease duration, cumulative dopaminergic exposure, and individual susceptibility.

Peak-dose dyskinesia suggests excessive dopaminergic stimulation at the dose peak.

Management options include dose/formulation adjustment, adjunctive therapy, amantadine, and advanced device-aided/surgical approaches.



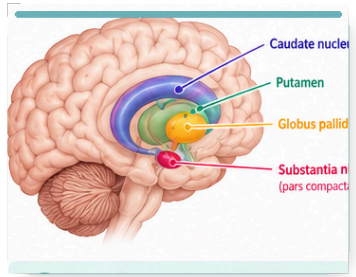
Wearing OFF: pharmacology meets disease progression

Predictable return of motor symptoms before the next scheduled dose.

Strategies: shorten dose interval, adjust formulation, or add a medication that prolongs levodopa effect.

COMT inhibitors extend levodopa exposure; MAO-B inhibitors reduce dopamine breakdown.

Dopamine agonists can provide longer receptor stimulation but have a different adverse-effect profile.



MDS EBM review; FDA labels

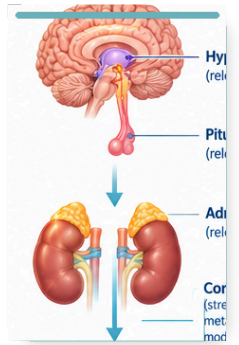
Orthostatic hypotension & autonomic burden

PD itself can impair autonomic cardiovascular regulation.

Dopaminergic drugs can worsen orthostatic symptoms in susceptible patients.

Assess symptoms, seated/standing BP, hydration, contributing medications, and fall risk.

Treat the patient—not just the blood pressure number—and coordinate with neurology/primary care.



FDA labeling; clinical practice

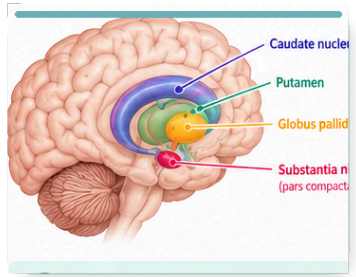
Hallucinations, psychosis, and medication review

Visual hallucinations become more common with disease progression and cognitive vulnerability.

Review medication burden before adding another drug.

Anticholinergics, dopamine agonists, amantadine, and other CNS-active agents can contribute to confusion/hallucinations.

Psychosis management requires attention to PD motor needs and should be coordinated with the treating neurologist.



MDS / Parkinson's Foundation educational materials

III. Adjunctive Parkinson’s pharmacology

Mechanisms, uses, and trade-offs



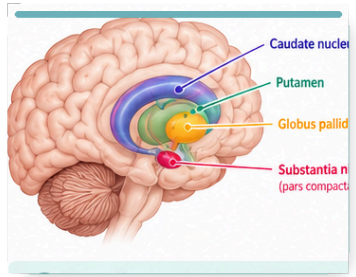
Dopamine agonists: receptor stimulation without conversion

Pramipexole and ropinirole are non-ergot dopamine agonists; rotigotine provides transdermal delivery.

They directly stimulate dopamine receptors and have longer receptor-level effects than individual levodopa doses.

Useful in selected patients for motor symptoms and as adjuncts for OFF time.

Trade-offs: somnolence, edema, orthostasis, hallucinations, and impulse-control disorders.



FDA / AAN / MDS materials

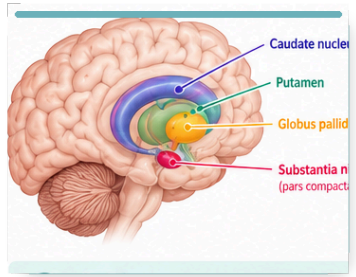
Impulse-control disorders: ask directly

Pathologic gambling, compulsive shopping, hypersexuality, and compulsive eating can occur with dopaminergic therapy.

Patients may not volunteer these symptoms because of embarrassment or lack of recognition.

Risk assessment should include dopamine agonist exposure, personal/family history, and behavioral changes.

Management commonly involves reducing/discontinuing the offending dopaminergic agent under clinical supervision.



FDA dopamine agonist labeling / movement-disorder education

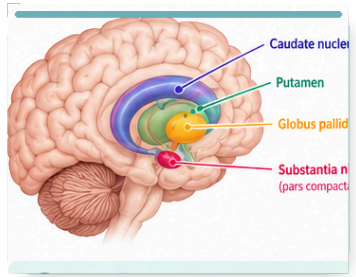
MAO-B inhibitors

Selegiline, rasagiline, and safinamide inhibit dopamine metabolism through MAO-B pathways.

Used as monotherapy in selected patients or adjunctively to levodopa in patients with motor fluctuations.

Benefits are generally modest compared with levodopa but can reduce OFF time in appropriate patients.

Medication reconciliation is essential because serotonergic and sympathomimetic interactions may matter.



MDS EBM review; FDA labeling

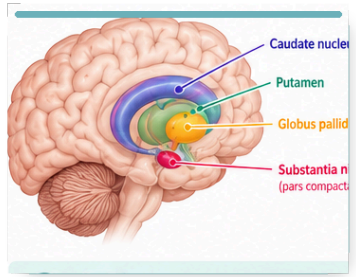
COMT inhibitors

Entacapone, opicapone, and tolcapone inhibit catechol-O-methyltransferase, increasing levodopa availability and prolonging its effect.

Typically used with levodopa/carbidopa for wearing-OFF phenomena.

Adverse effects can include dyskinesia, diarrhea, orthostatic symptoms, and urine discoloration.

Tolcapone has important hepatotoxicity considerations and requires liver monitoring.



FDA clinical reviews / product labels

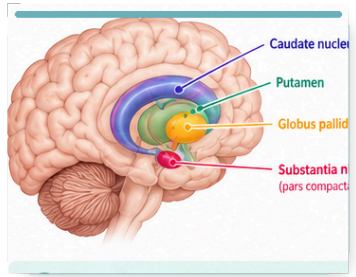
Amantadine

NMDA receptor antagonism is one proposed mechanism; additional dopaminergic effects may contribute.

Immediate-release amantadine has symptomatic utility; extended-release formulations have specific indications for dyskinesia and/or OFF episodes.

Common concerns: hallucinations, confusion, edema, livedo reticularis, and anticholinergic-like effects.

Renal elimination makes renal function and dose adjustment clinically important.



FDA clinical review, 2025

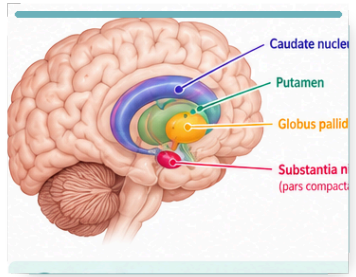
Adenosine A2A antagonism: istradefylline

Istradefylline is an adenosine A2A receptor antagonist used as adjunctive therapy with levodopa/carbidopa in adults experiencing OFF episodes.

It does not replace levodopa.

Clinical role: reduce OFF time without requiring direct dopamine receptor stimulation.

Monitor for dyskinesia, hallucinations, insomnia, and other adverse effects.



FDA clinical review

Anticholinergics: narrow modern role

Trihexyphenidyl and benztropine can reduce tremor in selected younger patients.

Anticholinergic burden can worsen cognition, constipation, urinary retention, blurred vision, and delirium.

Generally poor fit for older adults or patients with cognitive vulnerability.

Use only after explicit consideration of risk–benefit and alternatives.



FDA / movement-disorder clinical practice

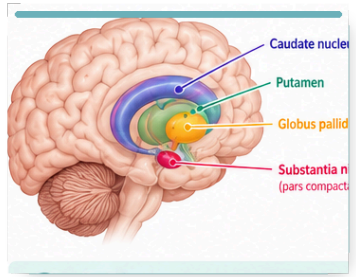
Rescue therapies for OFF episodes

Rapid-onset therapies can address episodic OFF states when oral medication is delayed or ineffective.

Apomorphine is a dopamine agonist available in rescue formulations; other rapid-onset levodopa formulations exist.

Key issues: onset speed, nausea, orthostasis, device technique, and patient/caregiver training.

Rescue therapy should complement—not replace—optimization of the baseline regimen.



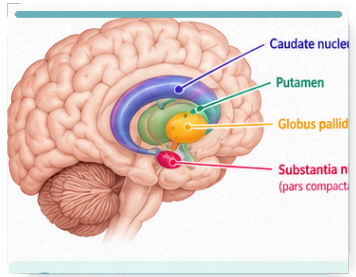
Advanced delivery: continuous dopaminergic stimulation

Concept: reduce peaks and troughs in dopaminergic exposure.

Options include intestinal levodopa delivery and continuous infusion approaches in appropriately selected advanced PD.

Benefits can include reduced OFF time; burdens include device management, procedural risks, and adverse effects.

Device-aided therapy is a movement-disorder specialist decision.



MDS / FDA clinical materials

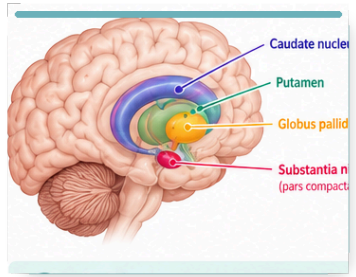
Deep brain stimulation: where pharmacology meets circuitry

DBS does not replace all medication but can reduce medication-responsive motor fluctuations and dyskinesia in selected patients.

Common targets include subthalamic nucleus and globus pallidus internus.

Best outcomes require careful candidate selection, neuropsychological assessment, and multidisciplinary programming.

DBS is symptomatic circuit modulation—not proven reversal of neurodegeneration.



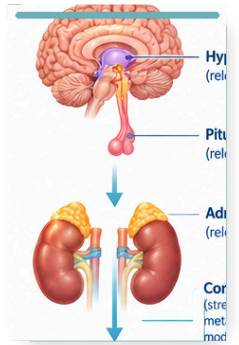
A four-layer clinical model

Layer 1 — Safety: diagnosis, medication reconciliation, falls, cognition, orthostasis, sleep, nutrition.

Layer 2 — Symptom control: optimize evidence-based pharmacotherapy with neurology.

Layer 3 — Neurorestoration: exercise, rehabilitation, nutrition, metabolic/mitochondrial support, sleep and stress management.

Layer 4 — Emerging therapies: consider only with transparent evidence grading, informed consent, and appropriate monitoring.



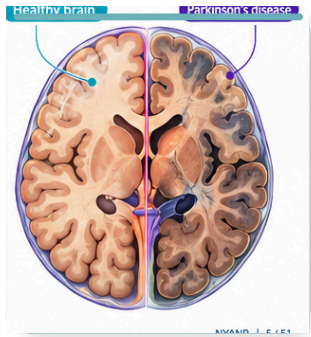
Exercise as a neuroplasticity intervention

Exercise is a core component of contemporary PD management—not merely an adjunct.

Current Parkinson's Foundation/ACSM recommendations emphasize aerobic activity, strengthening, flexibility, and balance/agility/multitasking.

Exercise may improve motor and non-motor outcomes and may engage activity-dependent neuroplasticity.

Exercise benefit should not be described as proof of disease reversal.



Parkinson's Foundation / ACSM, 2026 ÑciteÖturn0search1Öturn0search3Ô

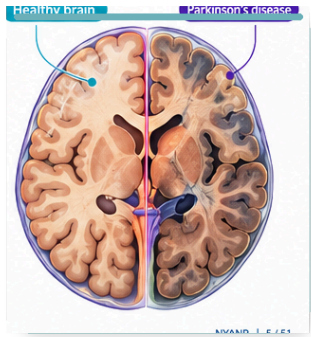
Exercise prescription: four domains

Aerobic: individualized moderate-to-vigorous activity with progression based on safety and capacity.

Strength: progressive resistance emphasizing major muscle groups and functional power.

Balance/agility/multitasking: challenge postural control, gait adaptability, and dual-tasking.

Flexibility: regular mobility work to preserve range of motion and reduce musculoskeletal limitations.



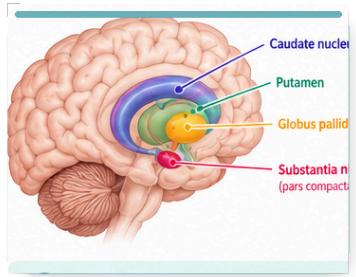
Nutrition: target adequacy first

Screen for weight loss, sarcopenia, constipation, dysphagia, dehydration, and micronutrient inadequacy.

Favor an overall dietary pattern rich in vegetables, fiber, adequate protein, and minimally processed foods when tolerated.

Coordinate protein timing with levodopa only when a clinically meaningful interaction is observed.

Supplementation should be indication-driven rather than a substitute for adequate diet or evidence-based therapy.



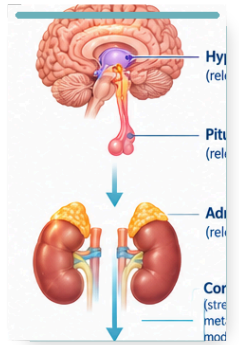
Mitochondrial resilience: biologic rationale

Mitochondrial dysfunction, oxidative stress, impaired bioenergetics, and altered quality-control pathways are implicated in PD biology.

Potential targets include exercise-induced mitochondrial adaptation, metabolic health, sleep, and selected nutrients.

Biologic plausibility is not equivalent to demonstrated disease modification.

Use biomarkers and outcomes that matter clinically rather than surrogate enthusiasm alone.



Common nutraceutical questions

CoQ10: biologically plausible but high-quality clinical evidence has not established disease modification.

Creatine: large clinical trials have not demonstrated a clear disease-modifying benefit.

Omega-3 fatty acids, vitamin D, B vitamins, polyphenols, and other compounds require indication-specific assessment.

Ask: dose, formulation, interaction, renal/hepatic considerations, evidence quality, and meaningful endpoint?



V. Emerging & investigational therapies

Evidence level matters



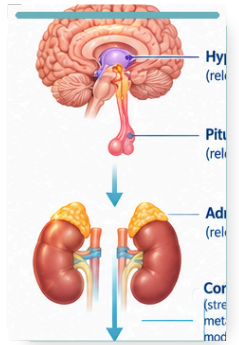
Frequency-based / bioelectromagnetic approaches

Proposed mechanisms include effects on neural oscillations, sensory processing, autonomic regulation, or cellular signaling.

Evidence varies substantially by modality, device, protocol, and endpoint.

Do not treat a frequency-based intervention as a single homogeneous therapy class.

Clinical claims should be limited to outcomes actually studied, with transparent discussion of sham/control limitations.



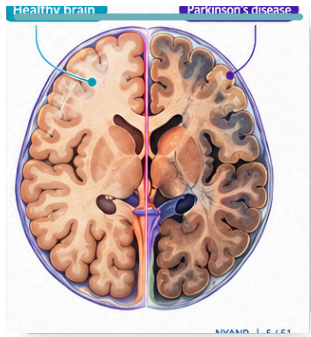
HBOT: biologic rationale

Hyperbaric oxygen increases dissolved oxygen delivery and can influence oxidative signaling, inflammation, angiogenesis, and cellular responses.

These mechanisms create a biologic hypothesis for neurorehabilitation and neuronal resilience.

However, protocol heterogeneity and limited high-quality PD trials constrain conclusions about disease modification.

HBOT should be presented as an adjunctive/emerging intervention—not established neuroprotective therapy.



Recent systematic reviews/meta-analyses ṆciteÖturn1search0Öturn1search3Ô

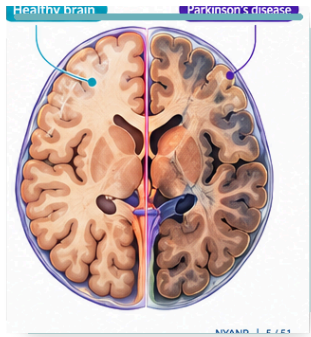
HBOT: what does the current evidence show?

Recent meta-analyses report improvements in selected motor and non-motor outcomes, including sleep and mood measures.

Studies differ in pressure, session duration, frequency, control conditions, and outcome measures.

These differences make it difficult to identify an optimal PD protocol or determine long-term disease-modifying effects.

Use standardized outcome measures and careful patient selection when evaluating HBOT clinically.



2024–2026 systematic reviews/meta-analyses
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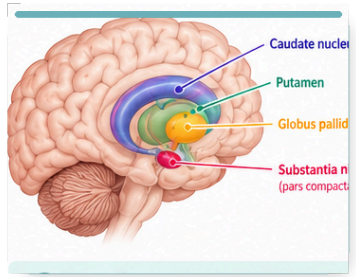
Ketamine-assisted neuroplasticity: hypothesis and limits

Ketamine is an NMDA receptor antagonist with downstream effects on glutamatergic signaling and synaptic plasticity.

Research in depression and pain provides a mechanistic basis for studying ketamine-assisted neuroplasticity.

PD-specific clinical evidence is limited relative to established dopaminergic therapies.

Potential risks include dissociation, blood-pressure changes, sedation, perceptual effects, and misuse potential; protocols require appropriate monitoring.



Evidence-level framing; PD-specific evidence remains emerging

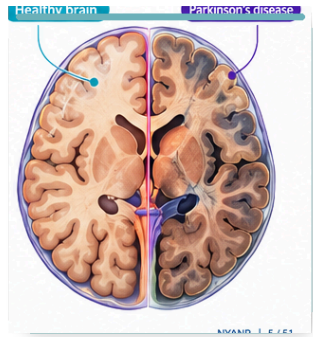
Regenerative medicine: where VSELs fit

Very small embryonic-like stem cells (VSELs) have been proposed as a pluripotent/stem-cell population with regenerative potential.

PD applications remain investigational; biologic hypotheses should not be presented as established clinical efficacy.

Stem-cell literature in PD has historically been heterogeneous, with uncertainty regarding cell identity, delivery, survival, integration, and clinical benefit.

Clinical use outside appropriate research/regulated pathways requires careful ethical, regulatory, and informed-consent considerations.



Systematic-review evidence indicates unresolved efficacy questions ṆciteÖturn1search5Ọ

Evidence hierarchy for an integrative PD practice

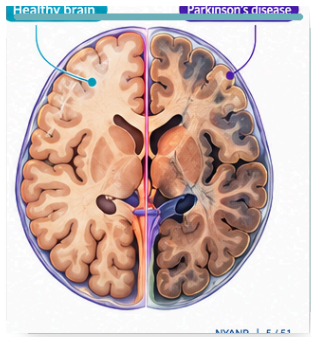
Level A: established symptomatic therapies with regulatory approval and/or strong clinical evidence.

Level B: supportive interventions with meaningful clinical evidence—exercise and rehabilitation are central examples.

Level C: promising adjunctive interventions with preliminary or heterogeneous evidence.

Level D: mechanistic hypotheses, early-stage interventions, or therapies requiring controlled clinical research.

Your language should match the evidence level.



Evidence-based medicine principle; MDS EBM methodology

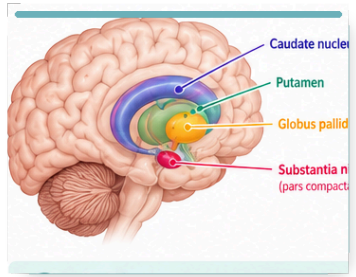
Case: early Parkinson’s disease

62-year-old with new bradykinesia, rigidity, mild rest tremor; still working and exercising.

Questions: What symptoms are most important? What is the patient's treatment goal? What risks matter most?

Discuss levodopa versus dopamine agonist/MAO-B strategies in the context of age, function, cognition, sleepiness, and patient preference.

Add exercise/rehabilitation early; monitor response using function and patient-reported outcomes.



AAN guideline: early PD treatment options ȵciteÖturn0search10Ô

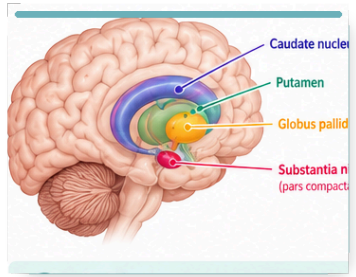
Case: wearing OFF + dyskinesia

68-year-old on carbidopa/levodopa develops predictable OFF before doses and peak-dose dyskinesia.

First define the timing pattern with a medication/motor diary.

Potential strategies: adjust levodopa dose/interval/formulation; consider COMT or MAO-B adjunct; consider amantadine for dyskinesia.

If fluctuations remain disabling, discuss advanced therapies with a movement-disorder specialist.



Case: integrative plan

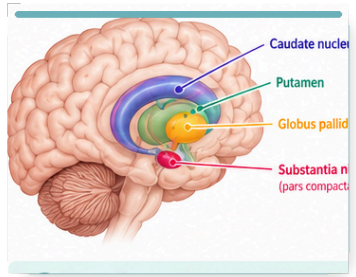
70-year-old with PD, constipation, fragmented sleep, orthostasis, deconditioning, and anxiety.

Medication review: identify contributors to orthostasis, sedation, hallucinations, and constipation.

Build a progressive exercise plan spanning aerobic, strength, balance/agility, and flexibility.

Nutrition: adequate calories/protein/fiber and hydration; coordinate levodopa timing if needed.

Emerging interventions are considered only after foundational care and with evidence/risk discussion.



Parkinson's Foundation / ACSM exercise recommendations, 2026

Clinical safety: red flags for referral

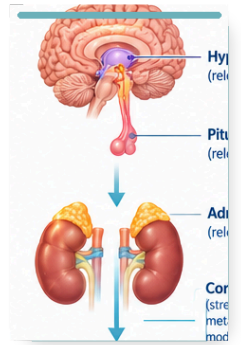
New rapid cognitive decline, recurrent falls, syncope, severe hallucinations, or marked autonomic dysfunction.

New dysphagia, aspiration concern, unexplained weight loss, or significant sleep attacks.

Severe medication fluctuations, disabling dyskinesia, or abrupt medication interruption.

Suspected atypical parkinsonism or diagnostic uncertainty.

Coordinate with movement-disorder neurology, PT/OT/SLP, nutrition, and other specialists as appropriate.



MDS educational framework

Key takeaways

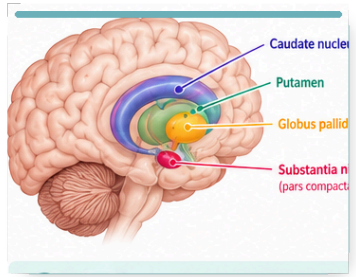
Levodopa remains the benchmark symptomatic therapy for motor Parkinson's disease.

Carbidopa improves CNS levodopa availability and reduces peripheral dopaminergic adverse effects.

Motor complications reflect both pharmacokinetics and disease progression; treatment is individualized.

Exercise and rehabilitation are foundational neuroplasticity-oriented interventions.

Emerging therapies should be matched to their actual evidence level—not their mechanistic appeal.



CE assessment & selected references

CE Q1: What is the primary therapeutic role of levodopa–carbidopa? → Symptomatic improvement through restoration of CNS dopaminergic signaling.

CE Q2: What best represents an evidence-informed integrative approach? → Conventional pharmacotherapy plus exercise/rehabilitation, nutritional and supportive strategies individualized to the patient.

CE Q3: How should emerging therapies such as HBOT, ketamine-assisted approaches, frequency-based therapies, or VSELs be approached? → Evaluate evidence, risks, patient selection, informed consent, and clinical endpoints; do not overstate efficacy.

Selected references: FDA Sinemet labeling; FDA clinical reviews for PD therapies; International Parkinson and Movement Disorder Society EBM reviews; AAN early-PD guideline; Parkinson's Foundation/ACSM exercise recommendations (2026); recent HBOT systematic reviews/meta-analyses.

Sources: FDA • MDS • AAN



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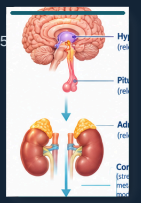
Integrating Pharmacology with Naturopathic Neurorestorative Therapies in Parkinson·s Disease

NYANP

Reference list · Slide 5



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