Parkinson's disease: Non-motor symptoms - Diagnosis and Treatment



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Aspen course
2026

Disclosures

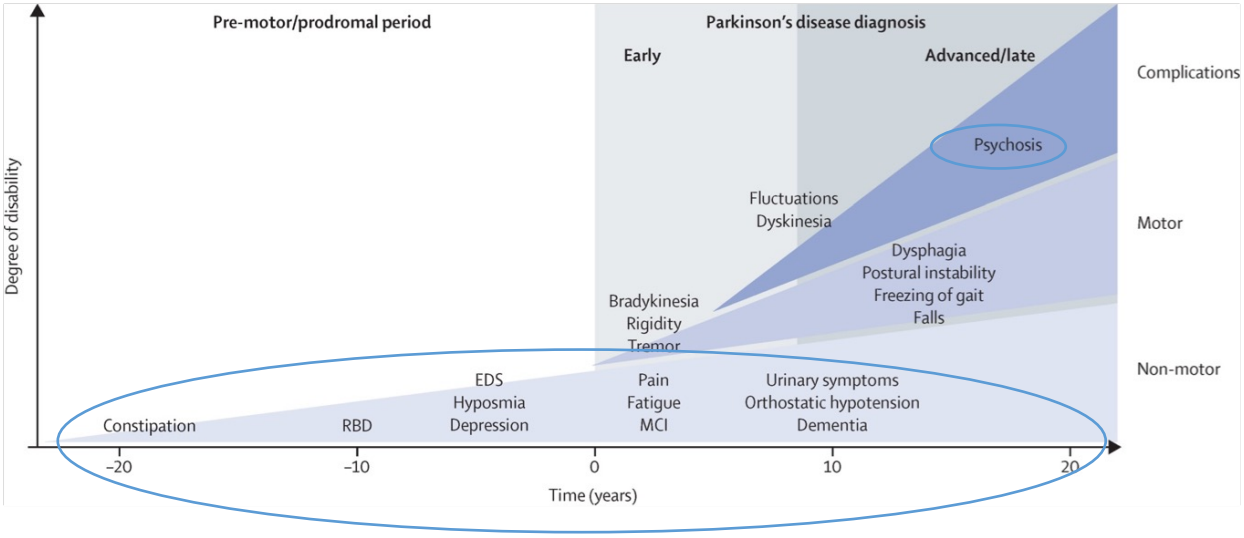
- Grants/research support: Lewy Body Dementia Association, Michael J. Fox Foundation
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- Board/leadership positions: Chair of the Lewy Body Dementia Association (LBDA) Industry Advisory Council; LBDA Board of Directors, Member at large; International Consortium for Dementia with Lewy Bodies, Executive Committee member; KeifeRx Scientific Advisory Board; Secretary of the International Parkinson and Movement Disorder Society

- Off-label medication use

Many non-motor features in PD

Neuropsychiatric	Sleep	Autonomic function	Sensory/ musculoskeletal function
• Mood • Cognition and dementia • Psychosis • Apathy • Impulse control disorders • Fatigue	• Insomnia • REM behavior disorder • Excessive daytime somnolence • Circadian disruption	• Gastrointestinal • Genitourinary • Cardiovascular • Thermo-regulatory • Dysphagia • Drooling	• Olfaction • Visual system • Pain • Musculoskeletal • Posture • Skin

Occur throughout PD course

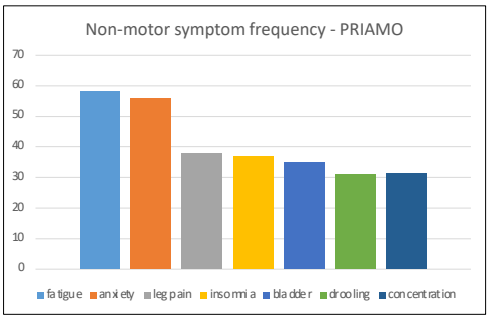


Kalia et al., 2015

Frequency & impact

- Present throughout course of PD
- Substantial impact
- Outcomes and quality of life
- Non-levodopa responsive

- PRIAMO study (n=1072)
  - 98.6% reported at least 1 non-motor symptom
  - Most frequent: fatigue (58.1%), anxiety (55.8%), leg pain (37.9%), insomnia (36.9%), bladder (35%), drooling (31%), concentration (31.4%)
  - Most frequent domains: psychiatric, sleep, GI, pain, fatigue, urinary, attention/memory



Frequency of occurrence of the eight most common non-motor symptoms.

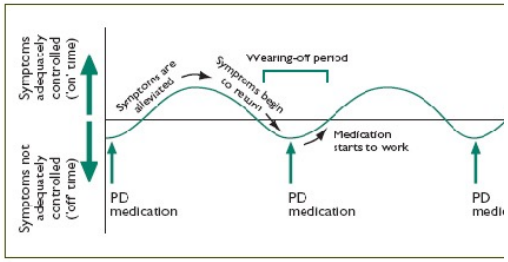
Non-Motor Symptoms	NMS-Q Mean (%)	MDS_NMS Mean (%)
Urinary problems	74%	68%
Pain	65%	65%
Fatigue	64%	65%
Sleep problems	62%	63%
Constipation	48%	48%
Cognitive impairment	46%	48%
Depression/apathy	43%	39%
Excessive drooling	35%	33%

Hely et al., 2005; Barone et al., 2009; Todorova et al., 2014; Rodriguez-Blazquez et a., 2020; Cattaneo et al., 2025

Non-motor fluctuations (off/on)

- Symptoms more common in “off”
  - Depression
  - Anxiety
  - Panic attacks
  - Also, sweats, dyspnea, restlessness, GI symptoms, pain

- Symptoms more common in “on”
  - Mania / euphoria



- Assessment tools
  - MDS-NMS
  - Neuropsychiatric Fluctuations Scale
  - Non-Motor Fluctuations Assessment (NoMoFA) questionnaire
  - Non-Motor symptoms-ON scale (NoMoS-ON)

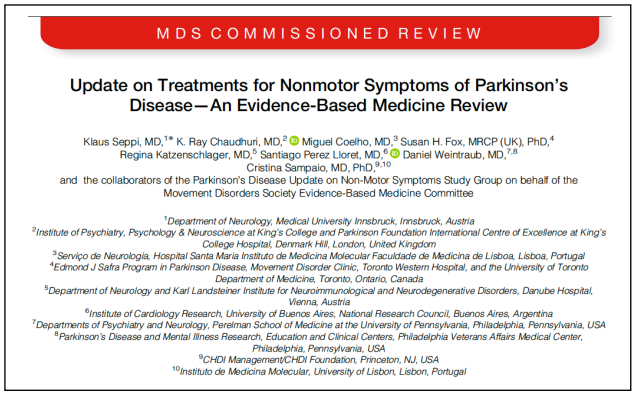
Chaudhuri et al., 2020, Schmitt et al., 2020; Kleiner et al. 2018; Donzuso et al., 2024

Non-motor symptom assessments

General
- MDS-NMS (NMSS)
- MDS-NMS-Q
- NMS-Quest
- NMS-Burden
- MDS-UPDRS
- Neuropsychiatric Fluctuations Scale
- Non-Motor Fluctuations Assessment (NoMoFA) questionnaire
- Non-Motor symptoms-ON scale (NoMoS-ON)

Rating scales for specific symptoms
- Depression
- Anxiety
- Global cognition, cognitive domains
- Psychosis
- Apathy
- Impulse control behaviors
- Fatigue
- Sleep
- Autonomic symptoms
- Pain

https://www.movementdisorders.org/MDS/MDS-Clinical-Outcome-Assessment.htm



MDS COMMISSIONED REVIEW

Update on Treatments for Nonmotor Symptoms of Parkinson's Disease—An Evidence-Based Medicine Review

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Non-motor Symptoms and Treatments in Parkinson's Disease

Jennifer G. Goldman, MD, MS[a,b,*]

KEYWORDS
• Anxiety • Apathy • Autonomic symptoms • Cognition • Dementia • Psychosis • Vision

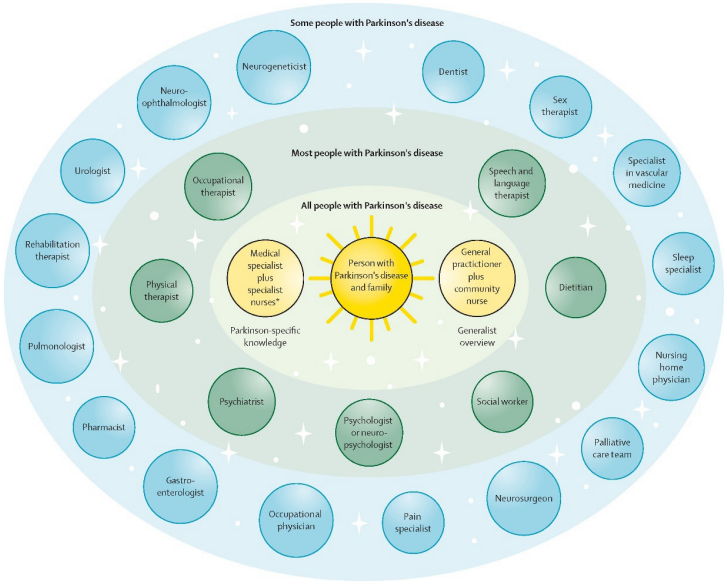
KEY POINTS
- Non-motor features in Parkinson's disease (PD) can affect cognition, mood, behavior, sleep, autonomic and sensory or musculoskeletal systems.
- These non-motor features can be present even at prodromal stages, at the time of PD diagnosis or early in the disease course, and as the disease advances.
- Fluctuations in non-motor symptoms, in some ways similar to the "off" and "on" periods associated with motor fluctuations, also can occur in PD, and these non-motor fluctuations merit careful inquiry and management.
- Timely identification of non-motor symptoms and appropriate management strategies with pharmacologic and non-pharmacological treatments are important for addressing symptoms that affect function and quality of life.

Seppi et al., 2019; Goldman 2025

Approved therapeutics for non-motor and neuropsychiatric symptoms specifically in PD

Symptom	FDA approved	Medication
Depression	✗	
Anxiety	✗	
Mild cognitive impairment	✗	
Dementia	✓	Rivastigmine (2006)
Psychosis	✓	Pimavanserin (2016)
Apathy	✗	
Impulse control disorders	✗	
Autonomic symptoms	✓	Droxidopa (2014), for symptomatic nOH, including PD
Sleep disturbances	✗	

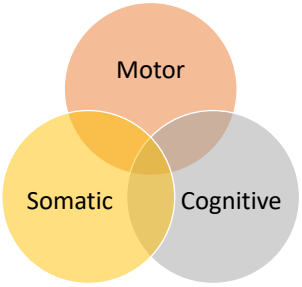
Management requires a team approach



Bloem, Okun, Klein Lancet 2021

Depression

- Frequent, prevalence ~40%
- May be subsyndromal
- Under-recognized – and under-treated
  - Low rates of screening in clinics
  - Despite AAN annual quality metrics, < 40% screened for psychiatric disorder
- Common symptoms
  - Sadness, also pessimism, irritability
  - Decreased interest (anhedonia)
  - Anxiety
  - Somatic symptoms
- Some symptoms may overlap with PD symptoms
- Suicidal risk/ideation – may be higher than previously thought
  - Meta-analysis involving more than 500K PD patients reported 22.2% and 1.25% PD to have suicidal ideation and behavior, respectively and 2 X risk of suicidal behavior than controls



Improving Parkinson's Disease Care through Systematic Screening for Depression

Connie Marras, MD, PhD;[1*] Zachary Meyer, MPH;[2] Honglang Liu, PhD;[3] Sheng Luo, PhD;[3] Sneha Mantri, MD, MS;[4] Allison Allen, MSW, LCSW;[2] Sydney Bayboyan, BA;[2] James C. Beck, PhD;[2] Amy E. Brown, MD, MS;[2] Francis Cheung, CCRP;[2] Natalia Dahodwala, MD, MS;[5] Thomas L. Davis, MD;[6] Megan Engelend, BS;[2] Conor Fearon, MD, PhD;[7] Nicole Jones, MS;[2] Kelly Mills, MD, MHS;[8] Janis M. Miyasaki, MD, MEd;[9] Anna Naito, PhD;[2] Marilyn Neault, PhD;[2] Eugene C. Nelson, DSc, MPH;[2] Ebubechukwu Onyilanya, BSc;[2] Carlos Ropa, BSc;[2] and Daniel Weintraub, MD[2,10]

Risk of Suicidal Ideation and Behavior in Individuals With Parkinson Disease
A Systematic Review and Meta-Analysis

Aaron Shengting Mai, MS; Yinxia Chao, MD, PhD; Bin Xiao, MD, PhD; Zhidong Zhou, MD, PhD; Jung Hahn Yong, MS; Ainsley Ryan Yan Bin Lee, MBBS; Eng-King Tan, MD

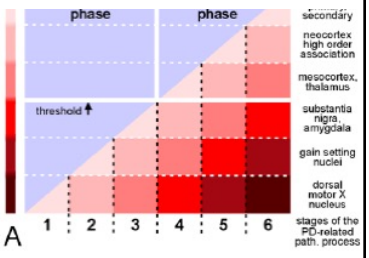
Mai et al., 2024; Marras et al., 2024

Depression

Intrinsic | Reactive | Fluctuations



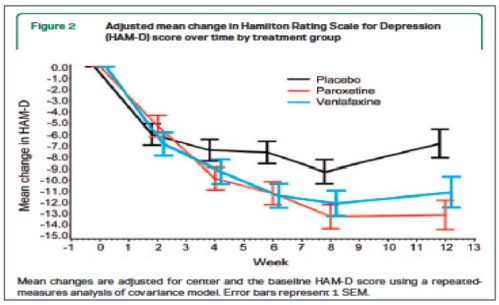
- Neuronal degeneration in mesocortical and mesolimbic DA neurons → orbitofrontal dysfunction
- Disruption in 5HT neurons in dorsal raphe → orbitofrontal-basal ganglia-thalamic circuit dysfunction
- Decreased DA transporter activity, frontal blood flow, caudate-frontal glucose metabolism in depressed PD patients vs. non-depressed PD patients
- Decreased 5HT metabolites in CSF



Bejjani et al., 1999; Braak et al., 2004; Matsui et al., 2007; Kostic et al., 2010; Vriend et al., 2013

Medications for depression

- SSRI/SNRIs – 3 studies vs. placebo
  - Nortriptyline vs. paroxetine CR vs. placebo
  - Desipramine vs. citalopram vs. placebo
  - Paroxetine vs. venlafaxine XR vs. placebo
- TCAs – likely efficacious, but side effects
- MAO-inhibitors?
- DA agonists (rotigotine - negative; pramipexole - positive)?
- 5-HTP for depression and apathy (single center, RCT, n=25)



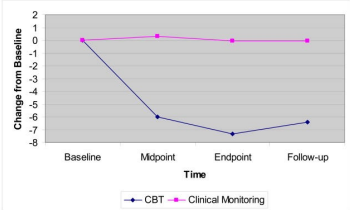
Menza et al., 2008; Devos et al., 2009; Seppi et al., 20197; Meloni et al., 2020

What about SSRI / SNRIs and MAO-B inhibitors?

Study	Design	Population	Interventions and Duration of Therapy	Outcomes
Panisset et al. (2014)[31]	Multicentre, retrospective cohort study	1504 patients with PD; mean age 67.0 years; 58.8% male	Group 1: rasagiline + antidepressant (74.5% SSRIs*; 10.0% were using > 1 antidepressant) Duration: 50.5–53.5 weeks Group 2: antidepressant only (77.0% SSRIs*; 16.6% were using > 1 antidepressant) Duration: 51.7–80.9 weeks Group 3: rasagiline	• No cases of serotonin syndrome in any group.
Richard et al. (1997)[43]	Survey of investigators from Parkinson Study Group	4568 patients with PD	Selegiline + antidepressant (including SSRIs); doses not stated	• 11 patients (0.24%) experienced symptoms possibly related to serotonin syndrome; 2 patients (0.04%) experienced symptoms judged to be serious. • See Table 3 for details about SSRI cases for which detailed information was available.
Ritter and Alexander (1997)[33]	Retrospective chart review	28 male patients with PD; mean age 68 years	Selegiline + antidepressant (7/40† SSRIs)	• One possible case of serotonin syndrome involving selegiline 10 mg/day and fluoxetine 20 mg/day.
Rihmer et al. (2000)[44]	Observational study	8 patients with PD; mean age 74.1 years, 75% male	Selegiline 5–10 mg/day + citalopram 20 mg/day Duration: 8 weeks	• No cases of serotonin syndrome. • No other adverse events.
Waters (1994)[37]	Retrospective chart review	23 patients with PD; mean age 64.6 years, 56.5% male	Selegiline 5–10 mg/day + fluoxetine 5-40 mg/day Duration: 1 month – ongoing	• No cases of serotonin syndrome. • One patient experienced worsened parkinsonian tremor, both with fluoxetine alone and with the combination of fluoxetine and selegiline.‡
Toyama and Iacono (1994)[38]	Case series	16 patients with PD	Selegiline 5–10 mg/day + SSRI (sertraline 25–100 mg/day or paroxetine 10–40 mg/day) with or without trazodone 25–150 mg/day Duration: 2–30 weeks (mean 10 weeks)	• No cases of serotonin syndrome. • No other adverse events.

Aboukarr et al., 2018

Cognitive behavioral therapy



- RCT, 10 weeks
- 80 depressed PD, HAM-D 17
- CBT group - greater reductions in depression and more treatment responders

Telephone-based cognitive behavioral therapy for depression in Parkinson disease

A randomized controlled trial

Roseanne D. Dobkin, PhD, Sarah L. Mann, PhD, Michael A. Gara, PhD, Alejandro Interian, PhD, Kailyn M. Rodriguez, BA, and Matthew Menza, MD

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Neurology® 2020;94:e1764-1773. doi:10.1212/WNL.0000000000009292

- 72 PD randomized to T-CBT + TAU or TAU only
- T-CBT weekly for 3 months, then monthly for 6 months; trained care partners to help practice habits
- T-CBT outperformed TAU on all depression, anxiety, and quality of life measures and gains persisted over 6-month follow-up ($p < 0.0001$).



Innovating Parkinson's Care: A Randomized Controlled Trial of Telemedicine Depression Treatment

Roseanne D. Dobkin, PhD,[1,2*] Sarah L. Mann, PhD,[2] Daniel Weintraub, MD,[3,4] Kailyn M. Rodriguez, BA,[2] Rachael B. Miller, LCSW,[2] Lauren St. Hill, LCSW,[2] Arlene King, PhD,[2] Michael A. Gara, PhD,[1] and Alejandro Interian, PhD[2]

- 90 PD Veterans U.S. military randomized to video-home-CBT vs. clinic-based TAU Acute – 10 weeks, longer-term – 6-month extension
- Primary outcome (Ham-D) improved significantly in video group and outperformed clinic-based TAU with effects maintained through 6 month follow up

Dobkin et al., 2011, 2020, 2021

Exercise & other

JAMA Neurology | Original Investigation

Effects of Mindfulness Yoga vs Stretching and Resistance Training Exercises on Anxiety and Depression for People With Parkinson Disease

A Randomized Clinical Trial

Jojo Y. Y. Kwok, PhD, MPH, BN, RN; Jackie C. Y. Kwan, MSocSc, PDMH, BSW, RSW; M. Auyeung, MBChB; Vincent C. T. Mok, MD, MBBS; Claire K. Y. Lau, MSc, BN, APN; K. C. Choi, BSc, PhD; Helen Y. L. Chan, PhD, BSN, RN

- RCT (n=138 PD), 8 weeks of mindfulness yoga vs. PRE
- Effective and safe, yoga > PRE ($p<0.001$) for anxiety, depression, HR QOL

Effects of Meditation and Yoga on Anxiety, Depression and Chronic Inflammation in Patients with Parkinson's Disease: A Randomized Clinical Trial

Jojo Yan Yan Kwok[a,b] Lily Man Lee Chan[a] Charis Ann Lai[a] Philip Wing Lok Ho[c,d,e] Zoe Yuen-kiu Choi[c] Man Auyeung[f] Shirley Yin Yu Pang[g] Edmond Pui Hang Choi[a] Daniel Yee Tak Fong[a] Doris Sau Fung Yu[a] Chia-chin Lin[a] Richard Walker[h,i] Samuel Yeung Shan Wong[j] Rainbow Tin Hung Ho[h,k]

- RCT (n=159 PD), 8 weeks of meditation vs yoga vs control
- Meditation and yoga > control for improving anxiety, motor, HRQOL, IL-6
- Meditation improved depression

Physical activity – variable effects in systematic review	
Aerobic training, agility exergaming, stationary cycling, resistance training	
Qigong – small RCT (Moon 2020)	
Telehealth mindfulness-based cognitive therapy (Interian et al., 2023)	
Bright light therapy (Rutten 2019; Raymackers 2019)	Positive effects in general population 2 RCTS in depressed PD – negative
Neuromodulation (rTMS to DLFPC, intermittent theta-burst stimulation (iTBS))	Shin et al., 2016 +ve, Brys et al., 2016 -ve Hou et al., 2026 +ve (iTBS)

Kwok et al., 2019, 2025; Rutten et al., 2019; Raymackers et al., 2019; Wu et al., 2017; deLima et al., 2019; Moon et al., 2020; Weintraub et al., 2023; Hou et al., 2026

JAMA Network | Open

Original Investigation | Neurology

Intermittent Theta-Burst Stimulation for Depressive Symptoms in Parkinson Disease

A Randomized Clinical Trial

Miaomiao Hou, MD; Bingjie Tian, PhD; Chen Qi, PhD; Lu Song, PhD; Bingjie Ma, PhD; Xinxin Chen, MS; Ying Wan, PhD; Na Wu, PhD; Jing Gan, MD; Zhenguo Liu, PhD; Yu Zhang, PhD



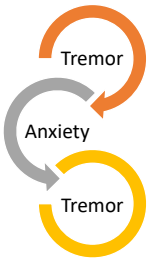
- Evaluate the antidepressant efficacy and neurofunctional effects of ultra-brief intermittent theta-burst stimulation (iTBS) for patients with PD depression compared with active HF-rTMS and sham stimulation.
- Triple-arm, randomized, sham-controlled single-center clinical trial
- PD with depression (n=54)
- 10 daily sessions over 2 weeks (week 2), then 4 weeks after (week 6)
- Primary outcome: HAMD-24
- Secondary outcomes: anxiety, motor, QoL, fNIRS
- iTBS and HF-rTMS > sham at week 2 and 6
- No serious AEs



Hou et al., 2026

Anxiety

- Common in PD and under-recognized…
- Prevalence range: 5-40%
- About 1/3rd of people with PD have several anxiety symptoms
- Increased stress, loneliness, social isolation
- Also multi-factorial – intrinsic, reactive, fluctuations, situational
- Bidirectional effects on other PD symptoms (e.g., tremor, freezing of gait)



- Depression
- Generalized anxiety disorder**
- Panic disorder
- Phobias (social, agoraphobia)**
- Obsessive-compulsive disorder
- Situational
- Non-motor fluctuations, particularly in "off" state

Leentjens et al., 2011; Dissanayaka et al., 2010, 2014; Broen et al., 2016

Management - anxiety

- Benzodiazepines with short half life - watch for sedation, falls, confusion
- SSRIs - frequently used
  - Citalopram - if depression also presented
  - EKGs
- SNRIs - may be well tolerated
  - Venlafaxine - can cause initial increase in anxiety symptoms
  - Mirtazapine - can help with sleep, weight gain; elderly
- Buspirone
  - RCT, 12 weeks, poorly tolerated, unable to assess efficacy

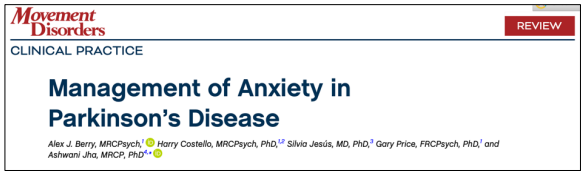
- Non-motor fluctuations
  - "Off" periods → modify dopaminergic regimen

- Non-pharmacological
  - Psychotherapy
  - Cognitive-behavioral therapy
  - Relaxation/biofeedback
  - Mindfulness
  - Yoga
  - Exercise
  - Probiotics?

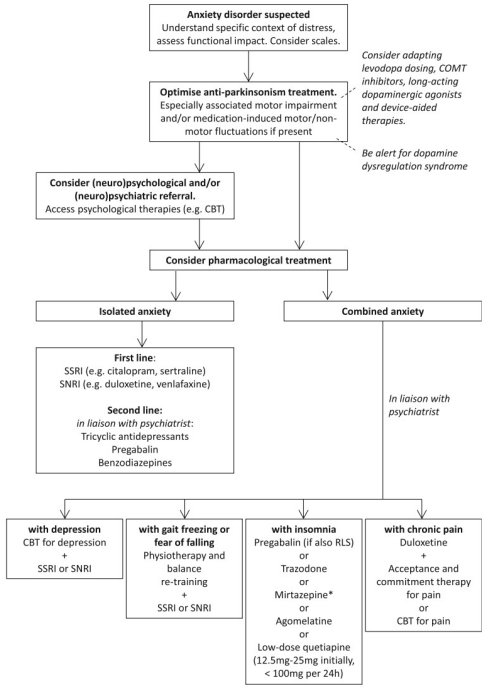
Probiotic supplementation for anxiety symptoms in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial

Joyce S. T. Lam[1], Kira N. Tosefsky[1,2], Nicholas J. Ainsworth[3,4], Dylan Meng[1], Petra Uzelman[1], Julie Zhu[1], Mihai S. Cirstea[1,5], Fabricio Pio[1], Fidel Vila-Rodriguez[6,7], Andrew K. Howard[8], B. Brett Finlay[3,9,9] & Silke Appel-Cresswell[1,9]

Prediger et al., 2012; Schneider et al., 2020; Kwok et al., 2019; Beck et al., 2020; Ghielen et al., 2017; Lam et al., 2026

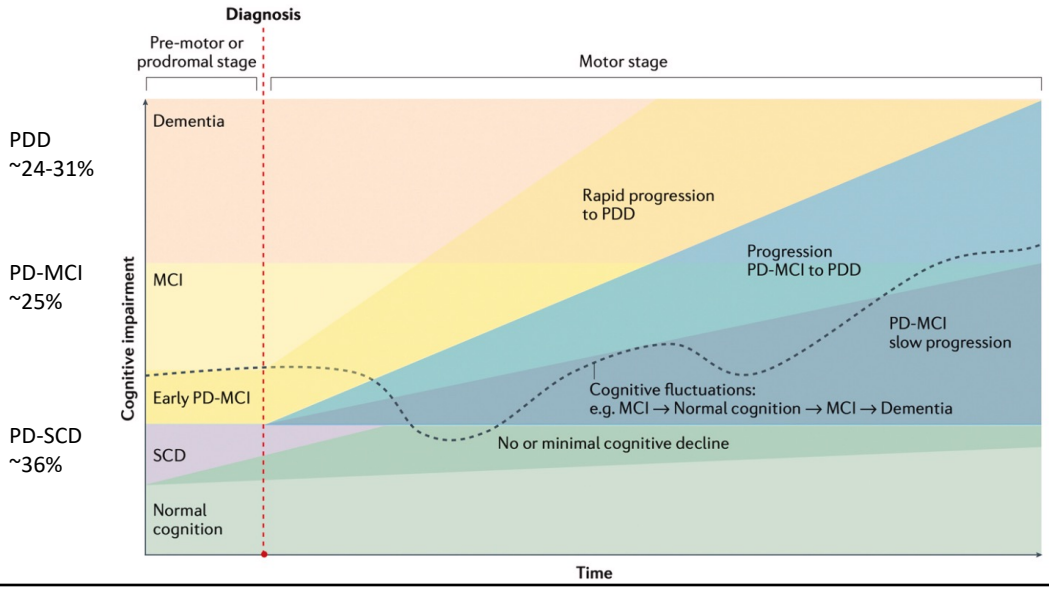


- Also includes meta-analysis of pharmacological treatments of anxiety derived from previously published systematic reviews of RCTs for depression in PD in which anxiety was a secondary outcome
- Anxiolytic medications showed a moderate overall effect compared to placebo
- Study limitations - small cohort sizes, each pharmacotherapy studied in only 1 RCT



Berry et al,. 2025

Cognitive spectrum



Aarsland et al., 2021

Cognitive decline to dementia

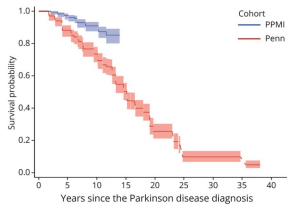
Long-Term Dementia Risk in Parkinson Disease

Julia Gallagher, BS, Caroline Gochanour, MS, Chelsea Caspell-Garcia, MS, Roseanne D. Dobkin, PhD, Dag Aarsland, MD, PhD, Roy N. Alcalay, MD, Matthew J. Barrett, MD, MSc, Lana Chahine, MD, MS, Alice S. Chen-Plotkin, MD, MSc, Christopher S. Coffey, PhD, Nabila Dahodwala, MD, MS, Jamie L. Eberling, PhD, Alberto J. Espay, MD, James B. Leverenz, MD, Irene Litvan, MD, Eugenia Mamikonyan, MS, James Morley, MD, PhD, Irene H. Richard, MD, Liana Rosenthal, MD, PhD, Andrew D. Siderowf, MD, MSCE, Tatyana Simuni, MD, Michele K. York, PhD, Allison W. Willis, MD, MSCI, Sharon X. Xie, PhD, and Daniel Weintraub, MD, for the Parkinson's Progression Markers Initiative

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- PPMI and Penn cohort
- De novo PD
- For the PPMI cohort (n=417), estimated probability of PDD at year 10 of 9% (site dx), 15% (MoCA), or 12% (MDS-UPDRS Part I cognition)
- For the Penn cohort (n=389), 47% developed PDD with median time to dementia of 15 years. Estimated probability of dementia of 27% at 10 years of disease duration, 50% at 15 years, and 74% at 20 years.

Figure 1 Time From PD Diagnosis to Site Investigator Dementia Diagnosis in PPMI and Penn Cohorts



Prevalence and Characteristics of Dementia in Parkinson Disease

An 8-Year Prospective Study

Dag Aarsland, MD, PhD; Kjeld Andersen, MD, PhD; Jan P. Larsen, MD, PhD; Anette Lolk, MD, PhD; Per Kragh-Sørensen, MD, DMSc

Dementia and survival in Parkinson disease

A 12-year population study

T.C. Buter, MD
A. van den Hout, PhD
F.E. Matthews, PhD
J.P. Larsen, MD, PhD
C. Brayne, MD
D. Aarsland, MD, PhD

ABSTRACT

Background: The risk for dementia in Parkinson disease (PD) is high, with important clinical consequences for patients with PD. However, the absolute risk of dementia and how it affects survival in PD are not known. Such questions are important for patients, their families, and service providers but require long-term studies.

Methods: This study is a prospective longitudinal cohort study with patients from a prevalence study of PD in Norway. Patients were reassessed 4, 8, 9, 10, 11, and 12 years after prevalence

The Sydney Multicenter Study of Parkinson's Disease: The Inevitability of Dementia at 20 years

Mariese A. Hely, MBBS,[1*] Wayne G.J. Reid, PhD,[1] Michael A. Adena, PhD, ASTAT,[2] Glenda M. Halliday, PhD,[3] and John G.L. Morris, MD[1]

Aarsland et al., 2003; Buter et al., 2008; Hely et al., 2008; Gallagher et al., 2024

PD cognitive impairment

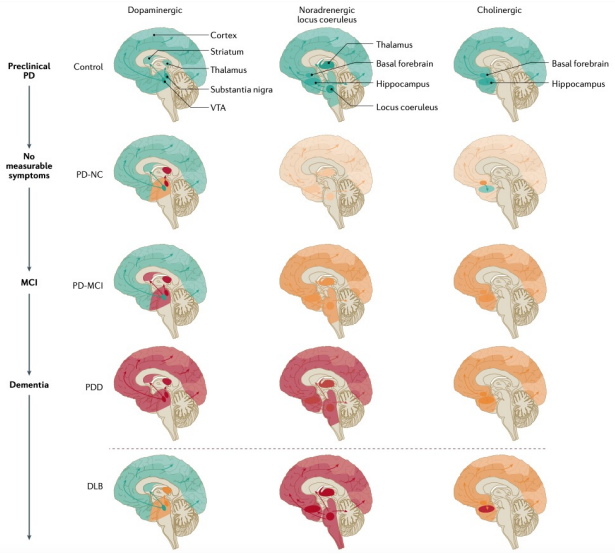
- Slowed thinking
- Decreased attention and concentration
- Trouble with multi-tasking, organizing, or planning
- Difficulty switching tasks
- Decreased initiation of activities
- Short-term memory problems
- Difficulty finding the “right words”
- Impaired sense of direction or spatial maps

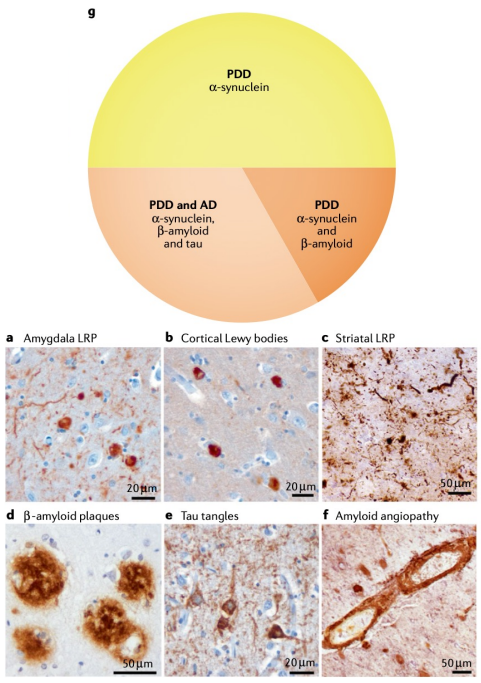
COGNITIVE

C – Capture clinical history and baseline status	**O –** Obtain collateral information from patient and informant	**G –** Gather objective metrics with baseline and serial exams
N – Note cognitive changes and any other features	**I –** Identify functional and psychosocial impacts	**T –** Treat reversible causes and initiate pharmacological, non-pharmacological, psychosocial, and other strategies
I – Involve multidisciplinary teams and care partners	**V –** Validate patient and care partner concerns and voice their needs	**E –** Educate patients, families, and healthcare providers

Goldman 2026

Cognitive impairment





Aarsland et al., 2021

Management - cognitive issues

- Objective assessments (baseline, serial)
- Exclude other causes, especially if acute (infections, mood, etc)
- Review medications (both PD and non-PD)
- Consider medications for dementia
- Non-pharmacological strategies
- Assess safety at home, driving, etc
- Discuss work, if appropriate
- Address adjustments and psychosocial impact for patient and caregiver

Managing cognitive impairment in Parkinson's disease: an update of the literature

Jennifer G. Goldman[a,b], Priya Jagota[c] and Elie Matar[d,e]

Goldman et al., 2025

Treatment – PD cognitive impairment

- Dementia (PDD)
  - Rivastigmine – FDA approved for PDD, 12 mg/day (↑ global cognition, CGIC, Emre et al., 2006)
  - Donepezil - 5-10 mg/day (↑ CGIC, Dubois et al., 2012)
  - Galantamine – 16 mg/day (small study)
  - Note, side effects of ChEI
  - Memantine – 20 mg/day, mixed results in PDD/DLB studies
  - SYN120 (5-HT6/5-HTT2 antagonist) - negative
- PD-MCI
  - Negative results for rivastigmine, rasagiline, atomoxetine
  - +/- cognitive training, non-pharmacological

Aarsland et al., 2021; Emre et al., 2004; Dubois et al., 2012; Aarsland et al., 2009; Emre et al., 2010
Mamikonyan et al., 2015; Weintraub et al., 2016; Hinson et al., 2017; Ortega et al., 2020; Fernandez et al., 2023

Recent publications



Ambroxol as a Treatment for Parkinson Disease Dementia
A Randomized Clinical Trial

Carolina R. A. Silveira, PhD; Kristy K. L. Coleman, MSc; Kathy Borron, BA; Rommel G. Tirona, PhD; Charles A. Rupar, PhD; Guangyong Zou, PhD; Robert A. Hegele, MD; Cheryl Wellington, PhD; Sophie Stukas, PhD; Elizabeth C. Finger, MD; Robert Bartha, PhD; Sarah A. Morrow, MD, MSc; Jennie L. Wells, MD, MSc; Michael J. Borrie, MB, ChB; Don Mahuran, PhD; Penny A. MacDonald, MD, PhD; Mary E. Jenkins, MD; Mandar S. Jog, MD; George Dresser, MD, PhD; Susan Fox, MD, PhD; Richard Camicioli, MD; Brian Feagan, MD; Daniel A. Mendonça, MD; Michael Mayich, MD; Manas D. Sharma, MD; Sachin K. Pandey, MD; Stephen H. Pasternak, MD, PhD

- 52-week, phase 2, DB-PC RCT, single center
- Mild-mod PDD
- Ambroxol low dose (525 mg per day), high dose (1050 mg per day), or placebo
- Main Outcomes: Safety and tolerability
- Primary efficacy outcomes: ADAS-Cog13, CGIC
- Results: 55 randomized
- Adverse events – GI symptoms ambroxol > placebo
- Target engagement –
- Concentrations measured in plasma and CSF
- Mean (SD) β-glucocerebrosidase levels were higher at week 26 in ambroxol > placebo
- No change on cognitive measures

An Acetylcholine M_1 Receptor–Positive Allosteric Modulator (TAK-071) in Parkinson Disease With Cognitive Impairment
A Phase 2 Randomized Clinical Trial

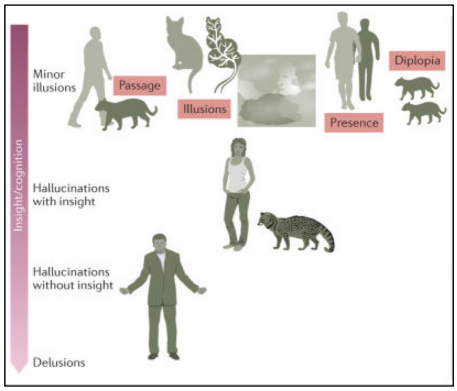
Niraj M. Shanbhag, MD, PhD; Jaya L. Padmanabhan, MD; Zheng Zhang, PhD; Brian T. Harel, PhD, JD; Hongxia Jia, MD, PhD; Tairmae Kangarloo, PhD; Wei Yin, PhD; Ariel V. Dowling, PhD; Antonio Laurenza, MD; Polyna Khudyakov, PhD; Kevin Galinsky, PhD; Robert D. Latzman, PhD; Tanya Simuni, MD; Daniel Weintraub, MD; Fay B. Horak, PhD; Cindy Lustig, PhD; Paul Maruff, PhD; Arthur A. Simen, MD, PhD

- TAK-071, a muscarinic acetylcholine M1 positive allosteric modulator for PD with increased fall risk and cognitive impairment.
- Phase 2, DB-PC randomized controlled crossover trial
- PD with at least 1 fall in prior 12 months, MoCA 11-26, and no acetylcholinesterase inhibitors.
- TAK-071 or placebo for 6 weeks, washout, 6 weeks of crossover treatment (n=55)
- Primary end point: change from baseline in gait variability during walk test +/- cognitive load
- Secondary end point: change from baseline in a cognitive composite score (Attn, EF, memory)
- Primary outcome was negative; improvement in 2ndary

Silveira et al., 2025; Shanbhag et al., 2025

Psychosis

- Illusions
- Hallucinations
- Delusions



- Affects > 50% on chronic PD meds
- Visual hallucinations, most common type
- Multiple reasons why psychosis occurs
- Risk factors – older age, longer PD duration, cognitive impairment, sleep disturbances

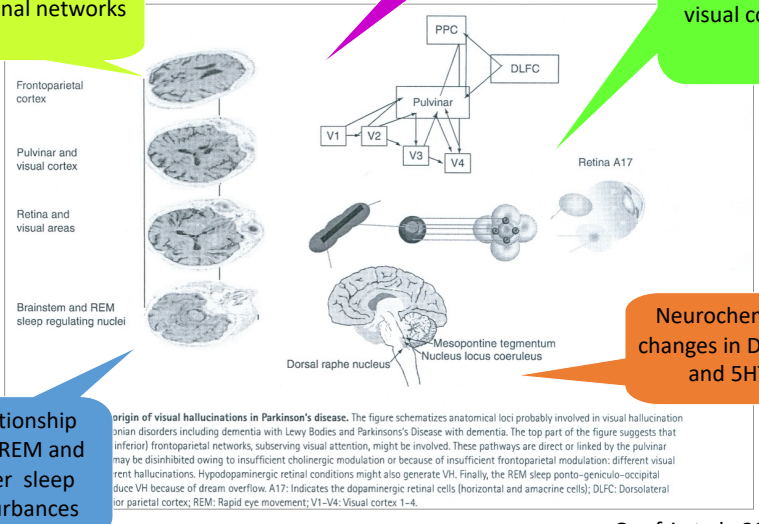
Ravina et al., Mov Dis 2007; ffytche et al., Nat Rev Neurol 2017

Psychosis

Medication effects

Alterations in attentional networks

Visual system involvement from retina to visual cortex



Neurochemical changes in DA, NE, and 5HT

Relationship with REM and other sleep disturbances

origin of visual hallucinations in Parkinson's disease. The figure schematizes anatomical loci probably involved in visual hallucination onian disorders including dementia with Lewy Bodies and Parkinsons's Disease with dementia. The top part of the figure suggests that inferior) frontoparietal networks, subserving visual attention, might be involved. These pathways are direct or linked by the pulvinar may be disinhibited owing to insufficient cholinergic modulation or because of insufficient frontoparietal modulation: different visual rent hallucinations. Hypodopaminergic retinal conditions might also generate VH. Finally, the REM sleep ponto-geniculo-occipital duce VH because of dream overflow. A17: Indicates the dopaminergic retinal cells (horizontal and amacrine cells); DLFC: Dorsolateral ior parietal cortex; REM: Rapid eye movement; V1–V4: Visual cortex 1–4.

Onofrj et al., 2007

Psychosis management - especially if acute

Table 2: Evaluation of Acute PD Psychosis

Differential Diagnosis

P -	Parkinson's disease medications
SY -	Systemic illness
C -	Centrally acting medication
H -	Hepatic, renal, or other metabolic dysfunction
O -	Overdose of medications or intoxication
S -	Sensory deprivation (hearing, visual impairment)
I -	Infection (urinary tract infection, pneumonia)
S -	Structural lesions (stroke, subdural hematoma, intracranial hemorrhage, trauma)

Vaughan and Goldman 2012, 2020

Management - psychosis

- Treat underlying medical illness, if needed
- Discontinue medications that may exacerbate hallucinations
- Reduce or discontinue PD meds
- Antipsychotics
- **AVOID** dopamine blocking meds!
- Cholinesterase inhibitors

Anticholinergics
Amantadine
Selegiline, rasagiline
Dopamine agonists
COMT inhibitors
Levodopa

- Non-pharmacological/coping strategies
  - Visual aids, night lights, redirection, art therapy, etc

Olanow et al., 2001; Diederich et al., 2003; Goldman et al., 2011; Frucht 2002; Diederich et al., 2003

Antipsychotics

- Quetiapine
  - 3 DB-PC trials without change in psychosis or motor function
  - Low doses (12.5 – 150 mg/daily)
  - Insufficient data, acceptable safety, no specialized monitoring, investigational
- Clozapine
  - 3 DB-PC trials favoring clozapine > placebo
  - Low doses (6.25-100 mg/daily)
  - CBC monitoring, sedation, hypotension
  - Efficacious, acceptable safety, specialized monitoring, clinically useful
- Pimavanserin
  - 5HT-2A inverse agonist/antagonist
  - FDA approval PDP (2016), 34 mg/day
  - Studied in MMSE > 21, larger change in MMSE 21-24 (cog imp)
  - Lower risk of relapse (vs. placebo) in PDD

Seppi et al., 2019; Cummings et al., 2014; Expay et al., 2018; Weintraub et al., 2024

Apathy

- Primary loss of motivation
- Behavioral, cognitive, affective (emotional) components
- Prevalence 15-70%
- Distinct from depression but can overlap
- Opposite of ICB/ICDs (?)

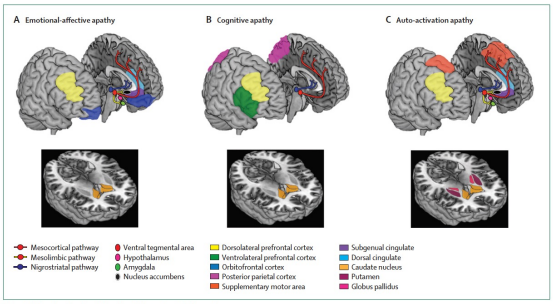
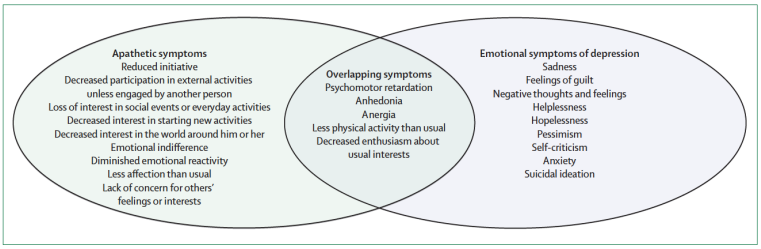


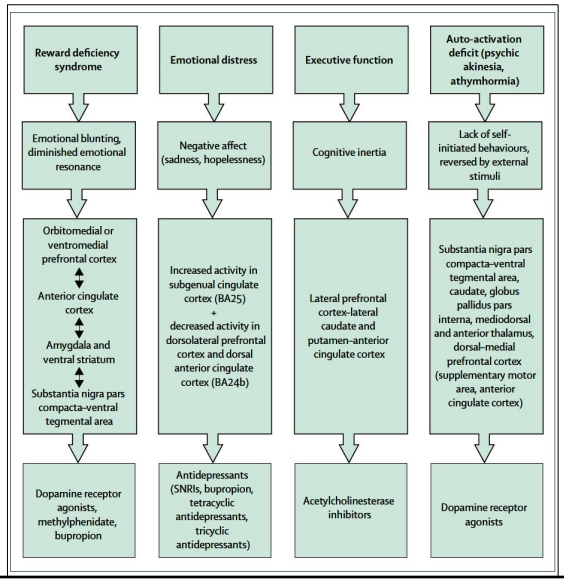
Figure 3: **Neural networks subserving different apathetic syndromes**
The upper set of images show the cortical regions and ascending nigrostriatal (blue), mesolimbic (yellow), and mesocortical (red) dopaminergic pathways associated with the emotional-affective, cognitive, and auto-activation subdomains of apathy. The lower set of images show the subcortical basal ganglia regions associated with each subdomain of apathy. Clinically relevant apathy is typically associated with bilateral dysfunction. Dorsolateral prefrontal cortex-caudate circuits are key structures implicated in any form of apathy. Orbitofrontal and subgenual cingulate dysfunction contribute to emotional-affective symptoms (A). Ventrolateral prefrontal cortex and posterior parietal dysfunction is involved in cognitive apathy (B). Supplementary motor or diffuse basal ganglia dysfunction, comprising bilateral caudate–putamen or pallidum, are reported in apathy with prominent auto-activation deficit (C).

- Often more troublesome to caregiver
- Reduced initiative/participation in activities
- Affects quality of life and relationships



Pagonabarraga et al., Lancet Neurol 2015

Management - apathy



Treatment of Apathy in Parkinson's Disease and Implications for Underlying Pathophysiology

Senan Maher [1,*], Eoghan Donlon [1], Gerard Mullane [1], Richard Walsh [1,2], Tim Lynch [1,3] and Conor Fearon [1,3]

- Rivastigine
  - DB-PC, RCT, Lille Apathy Rating scale – sig difference
- Piribedil - efficacious in those after DBS
- Rotigotine - no change on apathy scale
- SSRI/SNRIs – only 1 open label study (paroxetine, escitalopram, duloxetine)
- Memantine – 1 trial, no sig effect
- Methylphenidate – in AD study; PD FOG study with no sig change in LARS apathy score

- Exercise interventions
- Mindfulness
- Behavioral activation
- Music therapy

Pagonabarraga et al., 2015; Devos et al., 2014; Thobois et al., 2013; Hauser et al., 2016; Seppi et al., 2019; Maher et al., 2024

Impulse control behaviors and related disorders



- Range of behaviors
  - Pathological gambling, compulsive shopping, hypersexuality, binge eating
  - Punding
  - Dopamine dysregulation syndrome (DDS)
- Frequency ~2-10%
- Characteristics
  - Impulsivity - failure to resist the impulse or temptation to perform a certain behavior
  - Compulsivity - repetitive execution with a lack of self-control
  - Functional impact - negative consequences

- Risk factors
  - Psychiatric, addiction history
  - Dopamine agonists
  - Impaired decision making
  - Younger age at PD onset, motor fluctuations, male gender

- Linked to dopamine
  - Meds – D2, D3; resolves upon d/c
  - Enhanced DA release to conditioned cues and gambling task on ^{11}C-raclopride PET
  - Increased ventral striatal activity to rewards on fMRI
  - Lower striatal DAT levels on ^{123}I-FP-CIT (R caudate/putamen) in PD with ICD compared to PD without ICD

- Structural and functional abnormalities
  - Cortical thinning in fronto-striatal-limbic regions
  - Altered connectivity between striatal and associative/limbic cortical regions

Weintraub and Claassen 2017
Voon et al., 2013; Biundo et al., 2015; Carriere et al., 2015

Impulse control disorders

Management of Impulse Control and Related Disorders in Parkinson's Disease: An Expert Consensus

Ines Debove, MD,[1*] Steffen Paschen, MD,[2*] Deborah Arnstutz, MSc,[1] Francisco Cardoso, MD, PhD,[3] Jean-Christophe Corvol, MD, PhD,[4] Victor S.C. Fung, PhD, FRACP,[5] Anthony E. Lang, MD, FRCPC,[6,7] Pablo Martinez Martin, MD, PhD,[8] Maria C. Rodriguez-Oroz, MD, PhD,[9] Daniel Weintraub, MD,[10,11] Paul Krack, MD, PhD,[1] Günther Deuschl, MD, PhD,[2]
and the Members of the ICBD in PD Management Consensus Group[**]

- **<u>Education, prevention, surveillance!</u>**
- Adjustment of PD medications
  - Reduce oral DA agonist, etc
  - Monitor for dopamine withdrawal syndrome
- Psychiatric management
  - Antidepressants, atypical neuroleptics (antipsychotics)
- Cognitive behavioral therapy (likely efficacious, insufficient evidence, Seppi et al., 2019)
- DBS
- Naltrexone – opioid antagonist
  - 50 PD, 8 weeks, DB-PC
  - Primary outcome measure - CGIC and 2nd change in QUIP severity. Not efficacious in global assessment of response but sig for QUIP.
- Clonidine (n=41), 8 week, RCT DB-PC, well-tolerated, some reduction in QUIP-RS
- Research (opioid, cannibinoid, and nicotinic or other dopamine systems)

Pappay et al., 2014; Samuel et al., 2015; Debove et al., 2023; Laurencin et al., 2024

Fatigue

- Symptoms:
  - Overwhelming sense of tiredness
  - Lack of energy
  - Feeling of exhaustion
- Common and debilitating for some
- Related to, but different from, sleepiness, depression, apathy



- Peripheral (body)
  - Localized muscular fatigue
  - Inability to perform force during repeated muscle contractions
- Central (brain)
  - Difficulty initiating and sustaining physical and mental tasks
  - Independent of cognitive and physical impairments

Fatigue

- Challenging to treat and requires complex management
- Distinct from daytime sleepiness and depression
- Exclude other causes
- Few studies with good quality evidence base

- Rasagiline – efficacious, possibly useful
- Safinimide, n=39 fluctuating PD patients with fatigue, 24 week treatment, add-on → sig reduced fatigue scores (FSS, PF-S16) (Pauletti et al., 2023)

- Acupuncture, stimulants?
- Exercise, rehab therapies and strategies?

Lazcano-Ocampo et al., 2020

STATE OF THE ART REVIEW

Management of psychiatric and cognitive complications in Parkinson's disease

Daniel Weintraub,[1,2] Dag Aarsland,[3,4] Roberta Biundo,[5,6] Roseanne Dobkin,[7] Jennifer Goldman,[8,9] Simon Lewis[10]

Check for updates

[1]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
[2]Parkinson's Disease Research, Education and Clinical Center (PADRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, PA
[3]Department of Old Age Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, England
[4]Centre for Age-Related Diseases, Stavanger University Hospital, Stavanger, Norway
[5]Department of General Psychology, University of Padua, Padua, Italy
[6]Study Center for Neurodegeneration (CESNE), Department of Neuroscience, University of Padua, Padua, Italy
[7]Department of Psychiatry, Rutgers-The State University of New Jersey, Robert Wood

Abstract

Neuropsychiatric symptoms (NPSs) such as affective disorders, psychosis, behavioral changes, and cognitive impairment are common in Parkinson's disease (PD). However, NPSs remain under-recognized and under-treated, often leading to adverse outcomes. Their epidemiology, presentation, risk factors, neural substrate, and management strategies are incompletely understood. While psychological and psychosocial factors may contribute, hallmark PD neuropathophysiological changes, plus the associations between exposure to dopaminergic medications and occurrence of some symptoms, suggest a neurobiological basis for many NPSs. A range of psychotropic medications, psychotherapeutic techniques, stimulation therapies, and other non-pharmacological treatments have been studied, are used clinically, and are beneficial for managing NPSs in PD. Appropriate management of NPSs is critical for comprehensive PD care, from recognizing their presentations and timing throughout the disease course, to the incorporation of different therapeutic strategies (ie, pharmacological and non-pharmacological) that utilize a multidisciplinary approach.

Weintraub et al., BMJ 2022

Sleep symptoms

- Night-time
- Primary sleep related
  - Insomnia
  - Sleep fragmentation
  - Restless legs syndrome
  - Sleep apnea
  - REM sleep behavior disorder
- PD related
  - Recurrent motor symptoms
  - Akathisia (restlessness)
  - Cramps/rigidity/pain
  - Poor mobility
- Excessive daytime sleepiness
  - Medication effects
  - Sleep attacks
  - Nocturnal sleep disruption
  - Cognitive changes
- Circadian disruption
  - "Internal timekeeper"
  - Day-night disturbances
  - Other effects (autonomic, metabolic, etc)

REM sleep behavior disorder



- Initial description in 4 elderly men (Schneck 1986)
- Intermittent loss of REM sleep EMG atonia
- Appearance of complex motor activity associated with dream mentation
- May precede onset of parkinsonism and dementia
- Strongly associated with synucleinopathies (PD, MSA, DLB)
- Conversion rates ~6.3% per year, with 73.5% converting after 12 years
- Sleep disruption
- Risk of caregiver injury

Postuma et al., Brain 2019

Management of sleep disorders

- REM behavior disorder
  - Medications, e.g., melatonin, clonazepam
  - Bedroom environment and safety
- Night-time sleep issues (depends on reason)
  - Good sleep hygiene
  - Treat different causes, e.g., sleep apnea, restless legs
  - Night-time PD symptoms
  - Careful use of sedative-hypnotics
- Daytime sleepiness – and also fatigue
  - Decrease sedating medications
  - Caffeine?
  - Activities, exercise, stimulation, daylight, light therapy

Sodium oxybate in treatment-resistant rapid-eye-movement sleep behavior disorder

- DB, PC RCT, n=24 (PD-RBD or iRBD),
- 2 withdrew, NS difference but reduced monthly RBD episodes SXB>placebo

Efficacy of biologically-directed daylight therapy on sleep and circadian rhythm in Parkinson's disease: a randomised, double-blind, parallel-group, active-controlled, phase 2 clinical trial

- DB, PC RCT, n=60, 2 light therapies (Day Mel, Enhanced Mel), 30 min/day over 4 weeks
- Both improved measures of restorative deep sleep but NS differences

Melatonin on sleep in Parkinson's disease: A randomized double blind placebo controlled trial

Postuma et al., 2012; Neikrug et al., 2014; Seppi et al., 2019; McGrane et al., 2015; Jug 2016; Kakhaki et al., 2020; Videnovic et al., 2020, 2021; Lin et al., 2021; Sugumaran et al., 2024

Autonomic symptoms

- Cardiovascular
- Gastrointestinal
- Genitourinary
- Thermoregulatory

- Estimated frequencies ~ 14-80% (variable measures)

- Significant effect on quality of life
  - Constipation > orthostatic BP > urinary (nocturia)

Chauduri et al., 2006; Magerkurth et al., 2005

Orthostatic hypotension (OH)

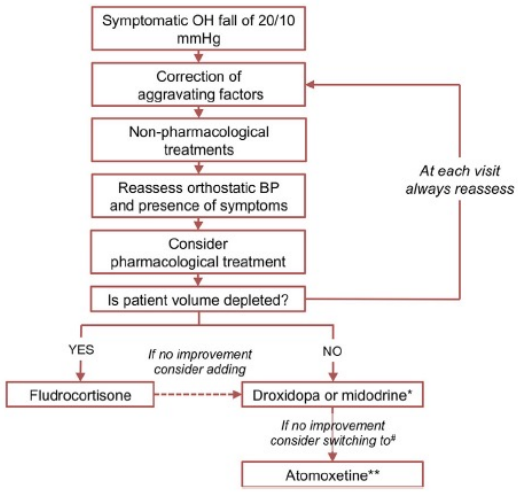


- Definition: >20mm Hg drop systolic or >10 diastolic on change to upright position
- Frequency ~30-58%
- May occur early (15% at onset) or precede motor signs

- Beware of medication and other contributors
  - PD medications
  - Anti-hypertensives
  - Dehydration

- May be associated with other symptoms like fatigue, anxiety, cognitive changes, and falls

Management - OH



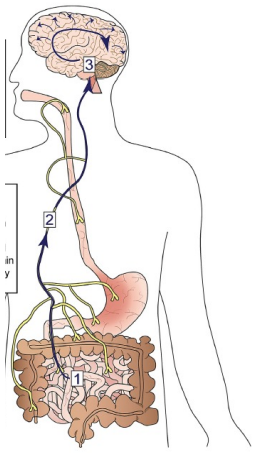
- Non-pharmacological
  - Increase fluid and salt intake
  - Compression stockings, abdominal binders
  - Elevation of HOB by 30 degrees
  - Small, frequent meals
  - Avoid triggers

- Medication
  - Reduce anti-HTN and/or DA drugs
  - Fludrocortisone (mineralcorticoid), 0.1-0.5 mg/day
  - Midodrine (peripheral alpha1 agonist), 5-10 mg TID
  - Droxidopa (prodrug NE, crosses BBB)
  - Pyridostigmine, domperidone, indomethacin, atomoxetine (?)

Palma and Kauffman 2018

Gastrointestinal symptoms

- Constipation
  - Frequent, ~70-80%
  - May occur before onset of motor symptoms
  - Due to delayed colonic transfer, low motility, and/or defecatory dysfunction
  - Peripheral and central nervous system involvement
- Nausea/vomiting
  - For some, medication related
  - Slowed motility
  - Constipation



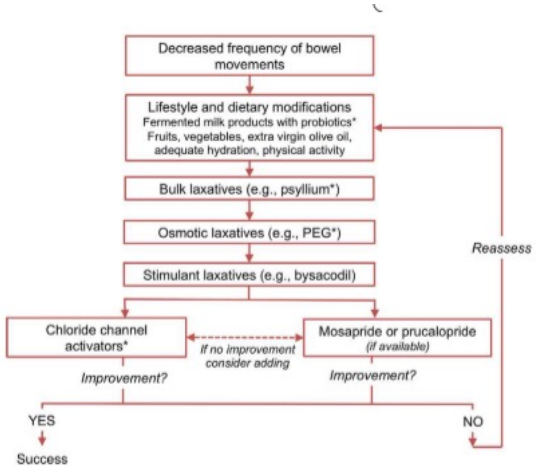
Borghammer and Van Der Berge 2019; Bindas et al., 2021

Management - GI symptoms

Consensus practice recommendations for management of gastrointestinal dysfunction in Parkinson disease

Delaram Safarpour [a,*], Natividad Stover [b], David R. Shprecher [c], Ali G. Hamedani [d], Ronald F. Pfeiffer [e], Henry P. Parkman [f], Eamonn MM. Quigley [f], Leslie J. Cloud [g], On behalf of the Other Non-motor Features Working Group of the Parkinson Study Group

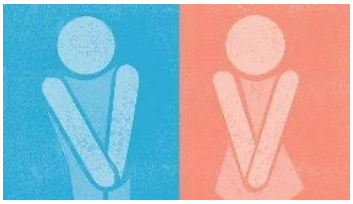
- Nausea/vomiting
  - Take PD meds with light snack, add extra carbidopa
  - Avoid DA blocking meds (metoclopramide, prochlorperazine)
  - Consider domperidone, trimethobenzamide, ondansetron
- Constipation
  - Exercise
  - Maximize dietary factors (water, fiber)
  - Medications:
    - Colace, Senna, Bisacodyl, Magnesium sulfate, lactulose
    - Miralax (Polyethylene glycol): more evidence
    - Lubiprostone (Ondo et al., 2012)
    - Probiotics (Ibrahim et al., 2020; Tan et al., 2021)
    - Enemas



Palma and Kauffman 2018; Seppi et al., 2019; Safarpour et al., 2024

Genitourinary dysfunction

- Symptoms
  - Urinary frequency, urgency, and nocturia – more common
  - Delayed or incomplete bladder emptying
  - Recurrent UTIs
- Common (up to 60%)
- May be seen in early and later PD



Bladder dysfunction

- Standard agents for neurogenic bladder dysfunction
  - Anticholinergics: oxybutynin, tolterodine, solifenacin, etc
    - Monitor for side effects (hypotension, constipation, cognition)
    - Solifenacin (Zesiewicz et al., 2015; DB-PC RCT, 8 weeks, no change primary outcome)
  - Muscarinic agonists (bethanechol)
  - B3 adrenergic agonist (mirabegron) –
    - DB-PC, RCT, n=110, 13 weeks, significant improvement in OAB symptom score and OAB-questionnaire short form (Moussa et al., 2022); DB-PC RCT with pelvic floor exercises, n=30, 10 weeks, NS difference in OAB composite score (Madan et al., 2022)
- Catheterization
- Pelvic floor physical therapy
- Behavioral therapies, bladder training
  - McDonald et al., 2020; 12 week RCT, improved patient perceptions but not urgency episodes
- Tibial nerve stimulation (?) (Smith et al., 2022; McClurg et al., 2022)
- Botulinum toxin: OnabotulinumtoxinA (FDA approved for overactive bladder)

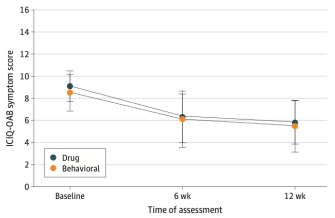
Cheng et al., 2023 – meta-analysis and systematic review

Behavioral Compared With Drug Therapy for Overactive Bladder Symptoms in Parkinson Disease
A Randomized Noninferiority Trial

Camille P. Vaughan, MD, MS; James F. Morley, MD, PhD; Jessica Lehosit, DO; Gerald McGwin, PhD; Lisa Muirhead, DNP; Anjali Khakharia, MS; Theodore M. Johnson II, MD, MPH; Marian L. Evatt, MD, MSc; Taressa Sergent, BA; Kathryn L. Burgio, PhD; Alayne D. Markland, DO, MSc

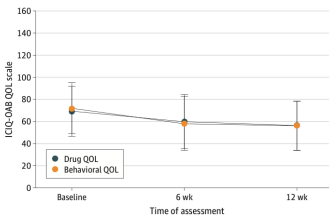
- Noninferiority of behavioral vs solifenacin drug therapy for OAB in PD
- 12-week randomized noninferiority trial, n=77
- 4 US Veterans Affairs health care systems
- PD with an International Consultation on Incontinence Questionnaire OAB module (ICIQ-OAB) symptom score of 7 or higher, MoCA $\geq$ 18
- Behavioral therapy done by NP included pelvic floor muscle training and urge suppression strategies vs solifenacin 5-10 mg daily
- Primary outcome: 12-week ICIQ-OAB score across groups within a 15% noninferiority margin
- At 12 weeks, ICIQ-OAB scores across groups indicated clinically significant improvement and were within the a priori noninferiority margin of 15%
- Drug group – greater dry mouth and falls

Figure 2. ICIQ-OAB Symptom Score Among Participants With Parkinson Disease in Drug and Behavioral Therapy Groups (With Imputation)



International Consultation on Incontinence Questionnaire overactive bladder module (ICIQ-OAB) symptom score range of 0 to 16, with higher scores indicating more frequent urinary symptoms of overactive bladder (urgency, frequency, nocturia, urgency incontinence). Test for noninferiority *P* value of .02.

Figure 3. ICIQ-OAB QOL Score Among Participants With Parkinson Disease in Drug and Behavioral Therapy Groups (With Imputation)



International Consultation on Incontinence Questionnaire overactive bladder module (ICIQ-OAB) quality of life (QOL) score of 0 to 160, with higher scores indicating worse QOL. Test for noninferiority *P* value of .02.

Vaughan et al., 2025

Sexual dysfunction

- Few studies

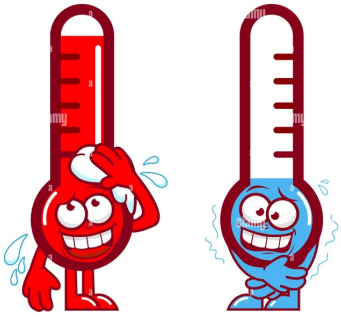
- Sildenafil - DB, cross-over study
- Hussain et al., 2001
  - n=24, 10 weeks, for erectile dysfunction in PD and MSA
  - Improvement in ED, QoL sex life domain
- Bernard et al., 2017
  - n=20, 8 weeks, for PD
  - Improvement in ED (International index)

- Neither study with significant improvement on quality of life

Hussain et al., 2001; Seppi et al., 2011; Bronner et al., 2015; Bernard et al., 2017

Thermoregulatory dysfunction

- Symptoms include:
  - Excessive sweating
  - Intolerance of hot environments
  - Flushing
- May relate to timing of PD medication response or cycle of medications
  - "Off" or "on" periods, including peak dose dyskinesia
- Hypothalamic dysfunction
- Limited treatments – adjust meds, propranolol, cool packs



Musculoskeletal issues

- Dopaminergics
- Anticholinergics
- Botulinum toxin injections to paraspinal muscles
- Orthotics
- PT/postural rehab
- DBS – PPN?
- Spinal stimulation?
- Variable results, small studies



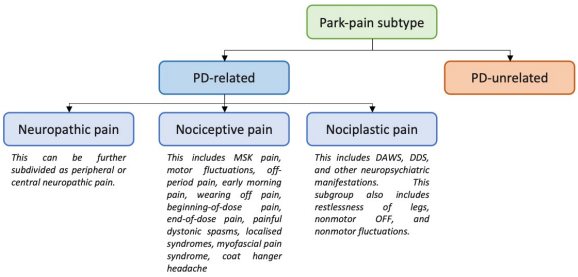
: Summary of the effect of the included interventions on the outcomes.

Included Intervention	Number and type of Included Studies	Summary of the effect of the included intervention
Deep brain stimulation	N=6 Case report (n=3) Case series (n=3)	- Deep brain stimulation could improve Lateral and anterior trunk flexion, Spine pain, Trunk posture abnormalities, unified Parkinson disease rating scale, and Levodopa equivalent daily dose. - Conflict results in long-term follow-up treatment. - PD severity could be related to DBS voltage amount
Botulmin toxin	N=6 Case report (n=3) RCT (n=2) Case series (n=1)	- Botulmin toxin could improve the Unified Parkinson disease rating scale, Trunk anterior and lateral flexion, Spine pain, Trunk Dystonia Disability Scale, EMG paraspinal muscle activity, and Function independence measure. - The improvement can be sustained for 3-12 months follow-up.
Posture exercises	N=4 RCT (n=2) Case series (n=2)	- Therapeutic exercises could improve the unified Parkinson's disease rating scale part II and III, Trunk anterior and lateral flexion, Berg balance scale, Timed up and go test, Activity balance confidence scale, Fall, and Parkinson's disease questionnaire -39. - The improvement may be sustained for 1-3 months follow-up.
Lidocaine injection	N= 1 Case series (n=1)	- Lidocaine injection could improve Lateral Trunk flexion, Berg balance scale, Camptocormia questionnaire, and Ten-meter walk test. - The long-term follow-up was not measured
Oculomotor correction	N=1 Case series (n=1)	- Oculomotor correction could improve Trunk lateral flexion, Paraspinal muscle activity, and Spine pain. - The long-term follow-up was not measured
Spinal cord stimulation	N=1 Case report (n=1)	Spinal cord stimulation could improve, spine pain, UPDRS, TuG, Hospital Anxiety and Depression Scale, and EuroQol (EQ-5S) quality of life. - The long-term follow-up was not measured

Michel et al., 2015; Etoom et al., 2020

Pain

- Prevalence 40-85%
- Type and timing of pain
  - Musculoskeletal*
  - Dystonia*
  - Off period, nocturnal
  - Central
  - Not related to PD



- Risks / benefits of opioids
- Non-pharmacological: PT, exercise
- TCAs or SNRIs?
- Gabapentin, pregabalin?

TABLE 10. Interventions to treat pain in PD

Drug	Efficacy	Safety	Practice Implications
Rotigotine	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Oxycodone-naloxone prolonged release	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Possibly useful*[a]

[a]There were some significant benefits in the active arm such as the practice implications for oxycodone/naloxone prolonged release for the treatment of pain is "possibly useful" because of the established efficacy and license of oxycodone/naloxone prolonged release in adults with severe chronic pain outside PD.[112,113]

DeAndrade et al., 2023; Qamar et al., 2024; Seppi et al., 2019

Sensory systems

- Olfaction
- Vision

Table 1
Ophthalmic pathology and management in Parkinson's disease. Treatment recommendations are often not PD-specific and are taken from general ophthalmologic practice, literature review and author's experience. See text for details

Eyelid/Ocular surface
- Decreased blink rate
- Dry eye syndrome
- Blepharitis
- Meibomian gland dysfunction
- Blepharospasm

Treatment
- Preservative-free artificial tears [7]
- Tear duct occlusion [7]
- Lid hygiene [7]
- Botox for blepharospasm [14]
- Increase in dopaminergic agents

Diplopia

Monocular
- Refractive error
- Corneal pathology
- Cataract formation
- Macular disease

Binocular
- Convergence insufficiency
- Decompensated strabismus

Treatment
- Refraction
- Manage underlying pathology
- Cataract surgery
- Single vision reading glasses [7]
- Base-in prisms
- Typoscope [24]
- Proper lighting [7] [24]
- Reading stand (mitigates reading impairment from hand tremor) [7]
- Monocular occlusion [7]

Visual loss and visuospatial impairment

Retina/optic nerve
- Decreased acuity and color vision
- Reduced contrast sensitivity
- Visual field defects

Cortical
- Visual hallucinations

Treatment
- Visual rehabilitation [24]
- Occupational therapy [24]
- Dopaminergic therapy [37]
- See Figure 1 for hallucination algorithm

Savitt and Aouchiche 2018

Dermatologic features

- Seborrhea - oily, flaking or inflamed skin
- Dry skin
- Excessive sweating or too little perspiration
- Livedo (with amantadine)
- Increased melanoma risk (?)
- Irritation / skin changes due to subcutaneously delivered drugs or DBS leads

- Management depends on etiology
- Dermatology referrals
- Corticosteroid topicals, cyclines, botulinum toxin, etc.

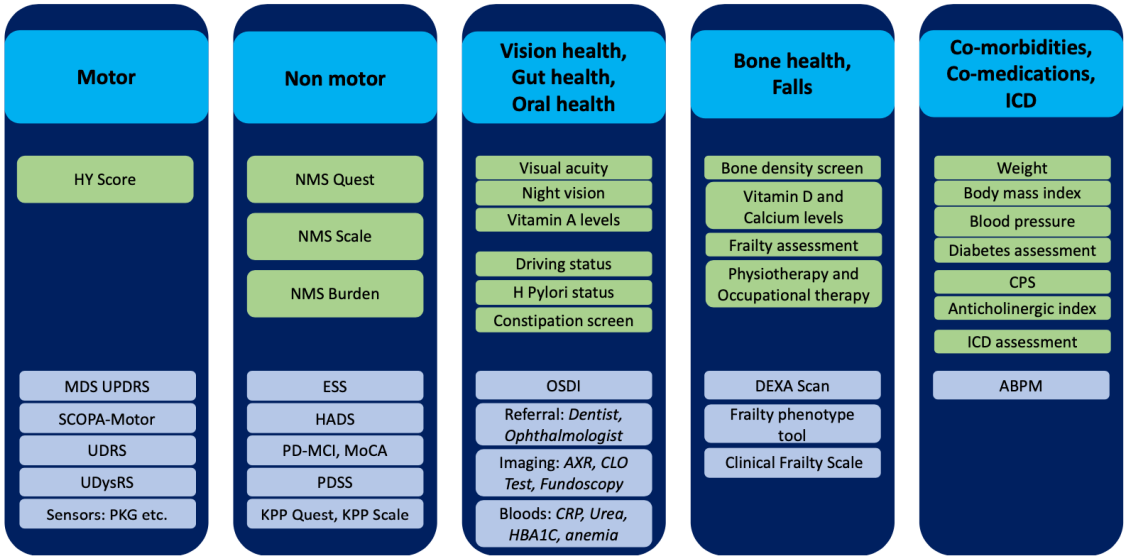




http://www.aafp.org http://www.patienthelp.org

Neimann et al., PRD 2021

The Parkinson's Vitals Dashboard



Chaudhuri et al., 2022

Healthy lifestyle habits



- Exercise
- Restorative sleep
- Positive social connections
- Minimizing risky substances
- Healthy eating
- Stress management

Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2024 Update

Kevin McFarthing[a], Sue Buff[b], Gary Rafaloff[c], Kenneth Pitzer[d], Brian Fiske[e], Anaya Navangul[f], Katelyn Beissert[f], Aleksandra Pilcicka[f], Rosie Fuest[f], Richard K. Wyse[f] and Simon R.W. Stott[f,*]

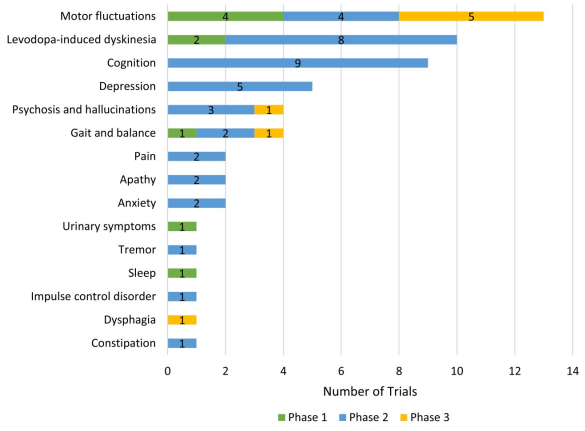


Fig. 3. Symptom-specific targets of active PD drug trials as of January 31, 2024, ClinicalTrials.gov. Some trials are targeting multiple specific symptoms and are counted several times in this figure.

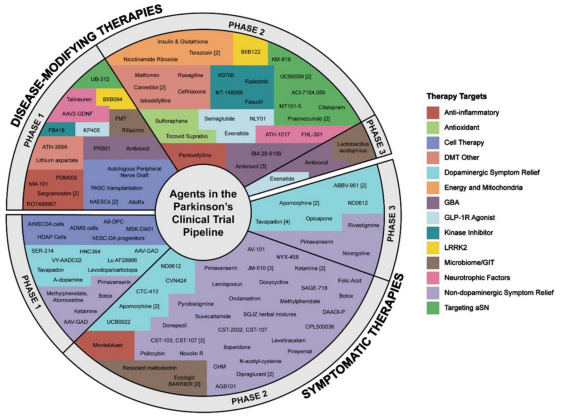


Fig. 2. A schematic of all of the agents in active clinical trials for PD, registered on ClinicalTrials.gov as of the January 31st, 2024 – 107 agents being tested in 136 trials. [#] after agent name indicates trial count, e.g., Apomorphine.[2] The pie graph is divided up according to the % of total trials, with ST Phase 1 : 14%, ST Phase 2 : 32%, ST Phase 3 : 10%, DMT Phase 1 : 16%, DMT Phase 2 : 26%, and DMT Phase 3 : 2%.

McFarthing et al., 2024


Thank you for your attention!
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