# The Parkinson's Disease Educational Course for Industry Professionals

**Honolulu, Hawaii, USA** | October 4, 2025

International Parkinson and Movement Disorder Society

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# Parkinson's Disease Trials in the Pipeline: Cognitive & Psychiatric

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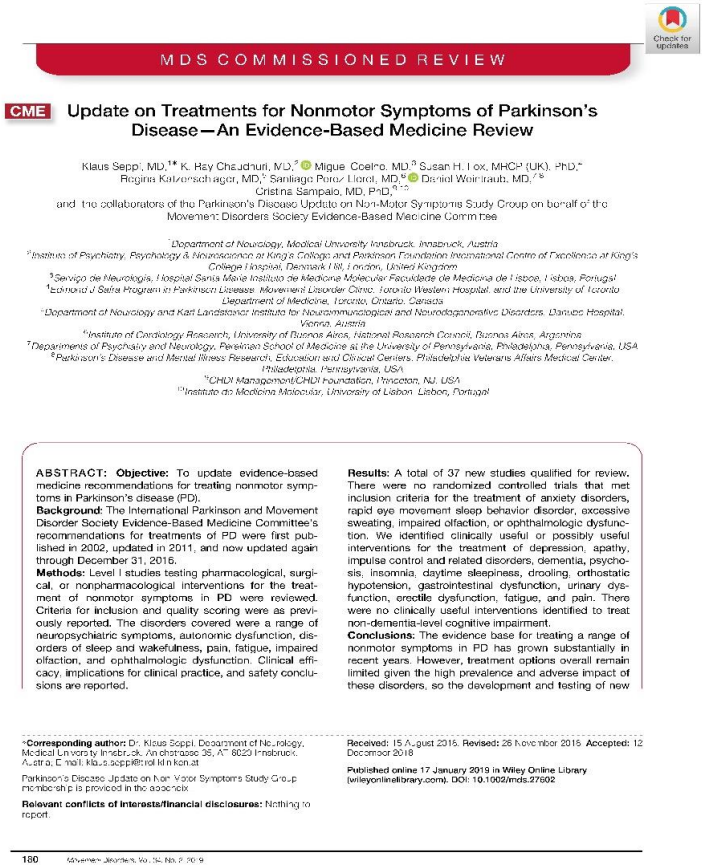
# Introduction & Background

# Background Sources



MDS COMMISSIONED REVIEW

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

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ABSTRACT: **Objective:** To update evidence-based medicine recommendations for treating nonmotor symptoms in Parkinson's disease (PD).
**Background:** The International Parkinson and Movement Disorder Society Evidence-Based Medicine Committee's recommendations for treatments of PD were first published in 2002, updated in 2011, and now updated again through December 31, 2016.
**Methods:** Level I studies testing pharmacological, surgical, or nonpharmacological interventions for the treatment of nonmotor symptoms in PD were reviewed. Criteria for inclusion and quality scoring were as previously reported. The disorders covered were a range of neuropsychiatric symptoms, autonomic dysfunction, disorders of sleep and wakefulness, pain, fatigue, impaired olfaction, and ophthalmologic dysfunction. Clinical efficacy, implications for clinical practice, and safety conclusions are reported.
**Results:** A total of 37 new studies qualified for review. There were no randomized controlled trials that met inclusion criteria for the treatment of anxiety disorders, rapid eye movement sleep behavior disorder, excessive sweating, impaired olfaction, or ophthalmologic dysfunction. We identified clinically useful or possibly useful interventions for the treatment of depression, apathy, impulse control and related disorders, dementia, psychosis, insomnia, daytime sleepiness, drooling, orthostatic hypotension, gastrointestinal dysfunction, urinary dysfunction, erectile dysfunction, fatigue, and pain. There were no clinically useful interventions identified to treat non-dementia-level cognitive impairment.
**Conclusions:** The evidence base for treating a range of nonmotor symptoms in PD has grown substantially in recent years. However, treatment options overall remain limited given the high prevalence and adverse impact of these disorders, so the development and testing of new

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Parkinson's Disease Update on Non-Motor Symptoms Study Group membership is provided in the appendix

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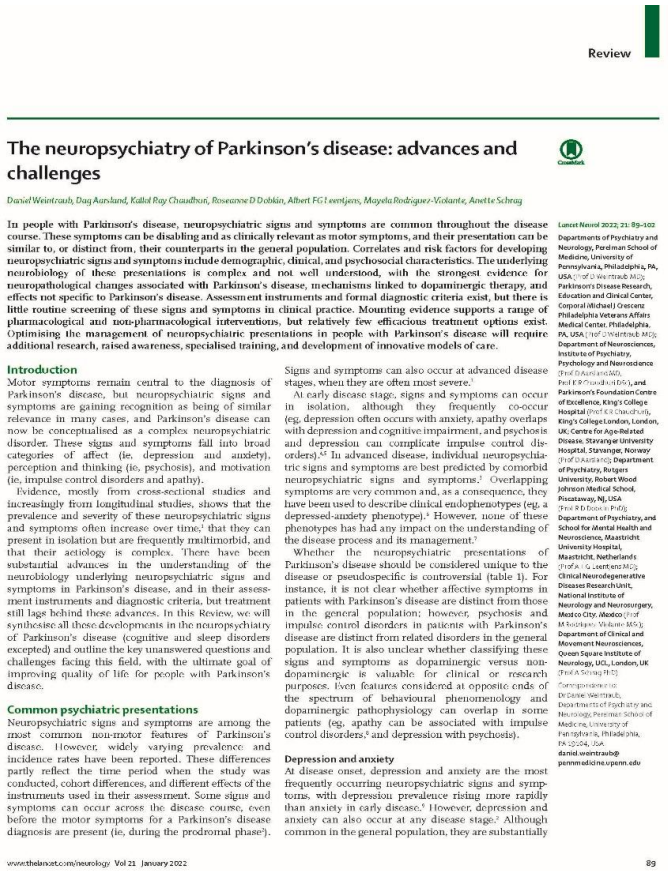

Review

The neuropsychiatry of Parkinson's disease: advances and challenges

Daniel Weintraub, Dag Aarsland, Kallol Ray Chaudhuri, Roseanne D Dobkin, Albert FG Leentjens, Mayela Rodriguez-Violante, Anette Schrag

**In people with Parkinson's disease, neuropsychiatric signs and symptoms are common throughout the disease course. These symptoms can be disabling and as clinically relevant as motor symptoms, and their presentation can be similar to, or distinct from, their counterparts in the general population. Correlates and risk factors for developing neuropsychiatric signs and symptoms include demographic, clinical, and psychosocial characteristics. The underlying neurobiology of these presentations is complex and not well understood, with the strongest evidence for neuropathological changes associated with Parkinson's disease, mechanisms linked to dopaminergic therapy, and effects not specific to Parkinson's disease. Assessment instruments and formal diagnostic criteria exist, but there is little routine screening of these signs and symptoms in clinical practice. Mounting evidence supports a range of pharmacological and non-pharmacological interventions, but relatively few efficacious treatment options exist. Optimising the management of neuropsychiatric presentations in people with Parkinson's disease will require additional research, raised awareness, specialised training, and development of innovative models of care.**

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## Introduction

Motor symptoms remain central to the diagnosis of Parkinson's disease, but neuropsychiatric signs and symptoms are gaining recognition as being of similar relevance in many cases, and Parkinson's disease can now be conceptualised as a complex neuropsychiatric disorder. These signs and symptoms fall into broad categories of affect (ie, depression and anxiety), perception and thinking (ie, psychosis), and motivation (ie, impulse control disorders and apathy).

Evidence, mostly from cross-sectional studies and increasingly from longitudinal studies, shows that the prevalence and severity of these neuropsychiatric signs and symptoms often increase over time,[1] that they can present in isolation but are frequently multimorbid, and that their aetiology is complex. There have been substantial advances in the understanding of the neurobiology underlying neuropsychiatric signs and symptoms in Parkinson's disease, and in their assessment instruments and diagnostic criteria, but treatment still lags behind these advances. In this Review, we will synthesise all these developments in the neuropsychiatry of Parkinson's disease (excluding sleep disorders except) and outline the key unanswered questions and challenges facing this field, with the ultimate goal of improving quality of life for people with Parkinson's disease.

## Common psychiatric presentations

Neuropsychiatric signs and symptoms are among the most common non-motor features of Parkinson's disease. However, widely varying prevalence and incidence rates have been reported. These differences partly reflect the time period when the study was conducted, cohort differences, and different effects of the instruments used in their assessment. Some signs and symptoms can occur across the disease course, even before the motor symptoms for a Parkinson's disease diagnosis are present (ie, during the prodromal phase[2]). Signs and symptoms can also occur at advanced disease stages, when they are often most severe.[3]

At early disease stage, signs and symptoms can occur in isolation, although they frequently co-occur (eg, depression often occurs with anxiety, apathy overlaps with depression and cognitive impairment, and psychosis and depression can complicate impulse control disorders).[4,5] In advanced disease, individual neuropsychiatric signs and symptoms are best predicted by comorbid neuropsychiatric signs and symptoms.[3] Overlapping symptoms are very common and, as a consequence, they have been used to describe clinical endophenotypes (eg, a depressed-anxiety phenotype).[6] However, none of these phenotypes has had any impact on the understanding of the disease process and its management.[7]

Whether the neuropsychiatric presentations of Parkinson's disease should be considered unique to the disease or pseudospecific is controversial (table 1). For instance, it is not clear whether affective symptoms in patients with Parkinson's disease are distinct from those in the general population; however, psychosis and impulse control disorders in patients with Parkinson's disease are distinct from related disorders in the general population. It is also unclear whether classifying these signs and symptoms as dopaminergic versus non-dopaminergic is valuable for clinical or research purposes. Even features considered at opposite ends of the spectrum of behavioural phenomenology and dopaminergic pathophysiology can overlap in some patients (eg, apathy can be associated with impulse control disorders,[8] and depression with psychosis).

## Depression and anxiety

At disease onset, depression and anxiety are the most frequently occurring neuropsychiatric signs and symptoms, with depression prevalence rising more rapidly than anxiety in early disease.[9] However, depression and anxiety can also occur at any disease stage.[9] Although common in the general population, they are substantially



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STATE OF THE ART REVIEW

Management of psychiatric and cognitive complications in Parkinson's disease

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Check for updates

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Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

**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.

## Introduction

The occurrence of neuropsychiatric symptoms (NPSs) in Parkinson's disease (PD), and non-motor symptoms more broadly,[1] has only recently gained recognition as being almost as common, and as disabling, as motor symptoms. However, it is clear that NPSs in PD are associated with poor long term outcomes and significant caregiver burden, and require special expertise for optimal management.[2] While PD is diagnosed based on the presence of motor signs and symptoms, the high prevalence of NPSs suggests that it could be considered as a prototypic neuropsychiatric disorder.[3] Common, clinically important NPSs include depression, anxiety, psychosis, impulse control disorders (ICDs), apathy, and cognitive impairment (both mild cognitive impairment (MCI) and dementia). Several factors explain the high cumulative prevalence of many NPSs in PD, including demographic characteristics, psychological and psychosocial factors, diffuse and multiple neurodegenerative disease pathologies, other neurobiological factors, and even PD treatments themselves.

Psychopharmacology (ie, psychiatric medications) remains the mainstay for many NPSs, with clinicians relying on both clinical experience and recommendations from specialists in the field, including the revised (2019) International Parkinson and Movement Disorder Society (IPMDS) Evidence-Based Medicine (EBM) Committee's review of treatments for non-motor symptoms[3] and the National Institute for Health and Care Excellence (NICE) guideline for the management of PD.[4] However, the evidence base for pharmacological treatment of many NPSs is limited and decisions about medication need to consider both potential benefit and adverse effects on parkinsonism and other PD related symptoms. In addition, some PD patients prefer and benefit from psychotherapy or combination approaches. The increased implementation and dissemination of evidence based psychotherapies has the potential to fill critical gaps in psychosocial care for people with PD.[5,6]

Therapeutic neuromodulation or stimulation strategies (eg, deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and electroconvulsive therapy (ECT)) are increasingly being studied and used clinically. There is growing interest in other non-pharmacological interventions for NPSs in PD, particularly for mood and cognition.[7] These interventions (eg, physical exercise, yoga, mindfulness and meditation, and cognitive training) are often complementary and adjunctive to pharmacological and psychosocial approaches. They may be appealing owing to their potentially lower risk profile, non-invasiveness, accessibility,



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# PD: The Ideal Neuropsychiatric Model

- DSM-5 encapsulated
  - Cognitive impairment, depression, anxiety, psychosis, impulse control disorders (ICDs)
    apathy, sleep & wakefulness disorders
- Neural substrate relevant to psychiatry
  - Brain regions (basal ganglia, prefrontal cortex)
  - Neurotransmitters (dopamine, norepinephrine, serotonin, acetylcholine)
  - Neural pathways (cortico-striatal-thalamic circuitry)
- Prodromal psychiatric symptoms provide biological plausibility
  - Depression, anxiety, isolated rapid eye movement sleep behavior disorder (iRBD)
- PD treatments used in psychiatry
  - Selegiline patch, deep brain stimulation (DBS)
- Inducibility / reversibility of some symptoms (psychosis, ICDs) facilitates research

# MDS Research Criteria for Prodromal Parkinson's Disease

**TABLE 1.** LRs of risk and prodromal markers

| | $LR^+$ | LR |
|---|---|---|
| Risk markers | | |
| Male sex | 1.2 (male) | 0.8 (female) |
| Regular pesticide exposure | 1.5 | n/a |
| Occupational solvent exposure | 1.5 | n/a |
| Nonuse of caffeine | 1.35 | 0.88 |
| Smoking | | |
| Current | n/a | 0.45 |
| Never | 1.25 | n/a |
| Former | n/a | 0.8 |
| Sibling had PD with age onset <50 | 7.5 | n/a |
| or | | |
| Any other first-degree relative with PD | 2.5 | n/a |
| or | | |
| Known gene mutation | see Supporting Table II | n/a |
| SN hyperechogenicity | 4.7 | 0.45 |
| Prodromal markers | | |
| PSG-proven RBD | 130 | 0.62 |
| or | | |
| Positive RBD screen questionnaire with >80% specificity | 2.3 | 0.76 |
| Dopaminergic PET/SPECT clearly abnormal (e.g., <65% normal, 2 SDs below mean) | 40 | 0.65 |
| Possible subthreshold parkinsonism (UPDRS >3 excluding action tremor) | 10 | 0.70 |
| or | | |
| Abnormal quantitative motor testing | 3.5 | 0.60 |
| Olfactory loss | 4.0 | 0.43 |
| Constipation | 2.2 | 0.80 |
| Excessive daytime somnolence | 2.2 | 0.88 |
| Symptomatic hypotension | 2.1 | 0.87 |
| Severe erectile dysfunction | 2.0 | 0.90 |
| Urinary dysfunction | 1.9 | 0.90 |
| Depression (± anxiety) | 1.8 | 0.85 |

n/a, not applicable.

**NMS first included:**

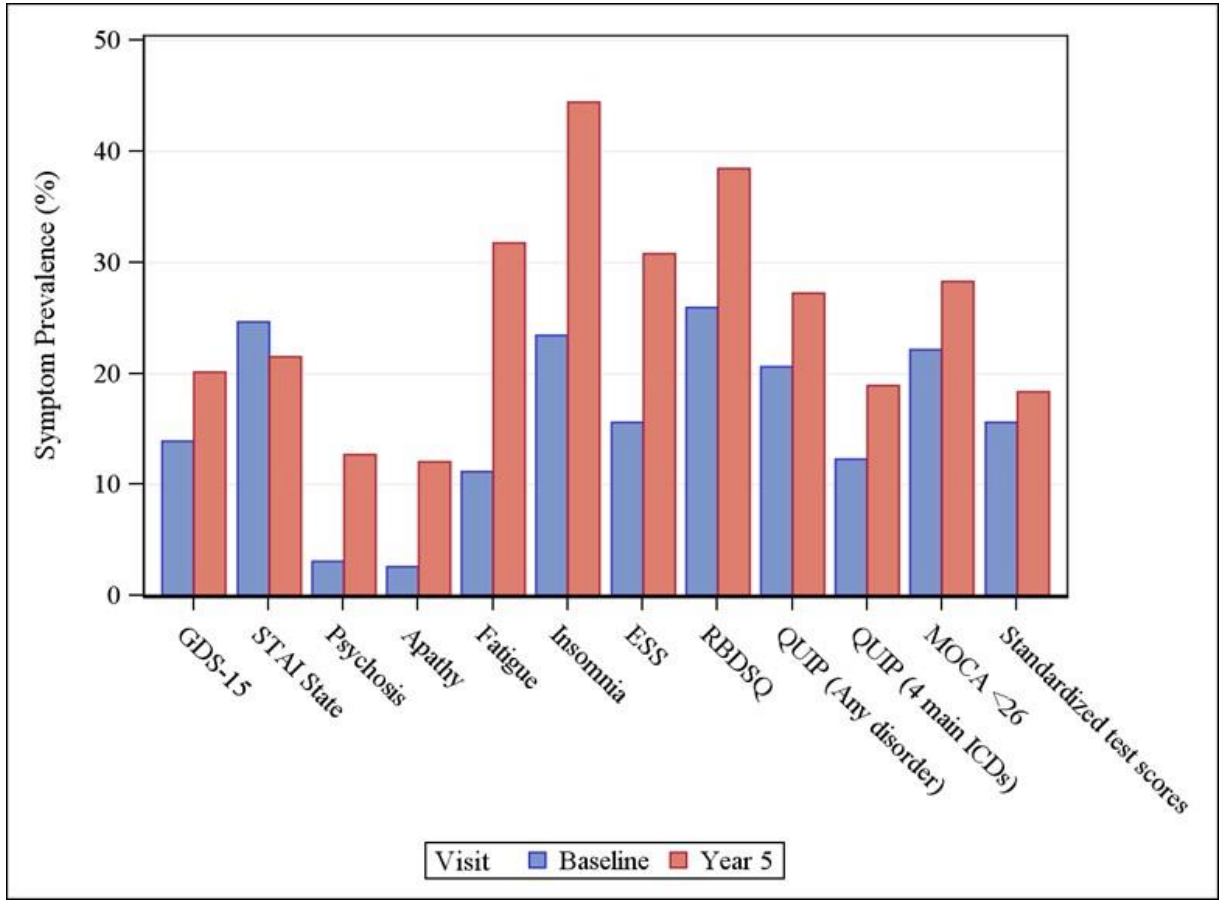
- RBD
- Olfactory loss
- Constipation
- Sleepiness
- Depression

**NMS now included:**

- Cognition

Berg et al. *Movement Disorders* 2015;30:1600-1609.
Heinzel et al. *Movement Disorders* 2019;34:1464-1470.

# Neuropsychiatric Symptoms (NPS) in PD: Common From the Start…

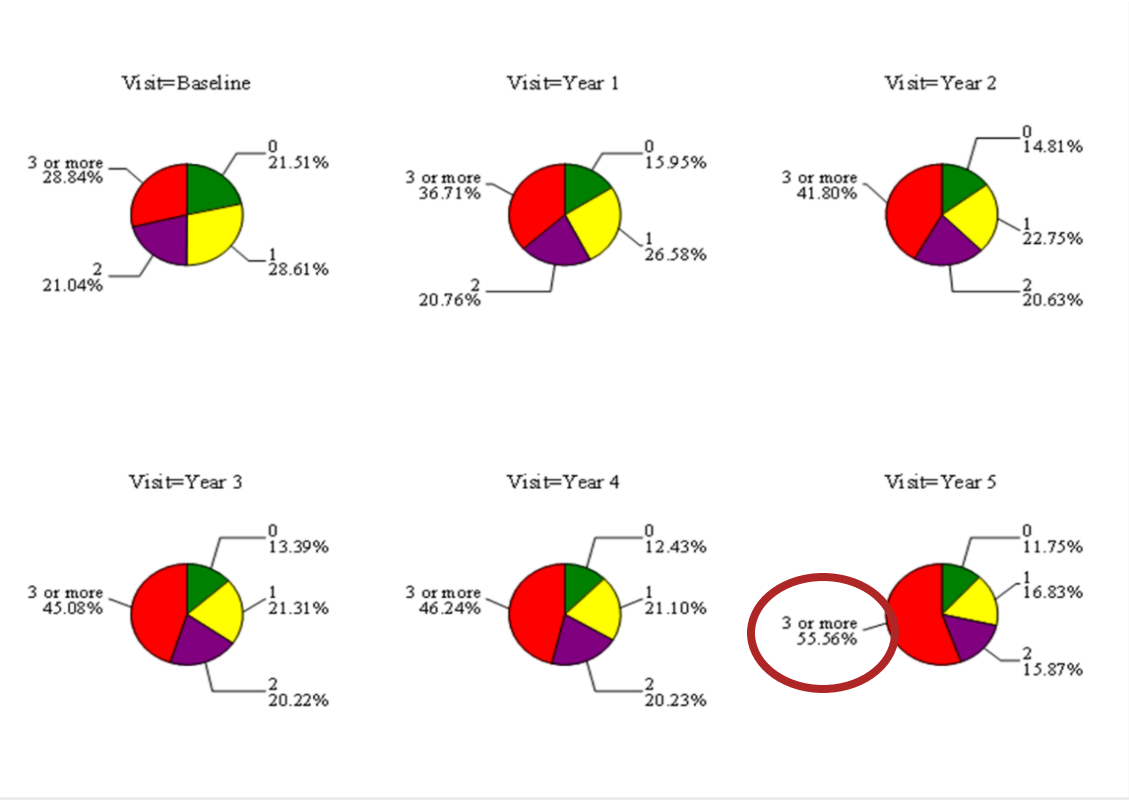



- Depression
- Anxiety
- Fatigue
- Sleep & wakefulness
- Cognitive

Data from the Michael J. Fox Foundation-funded Parkinson's Progression Markers Initiative (PPMI) study

Weintraub et al. *Ann Clin Transl Neurol*. 2020;7:449-61.

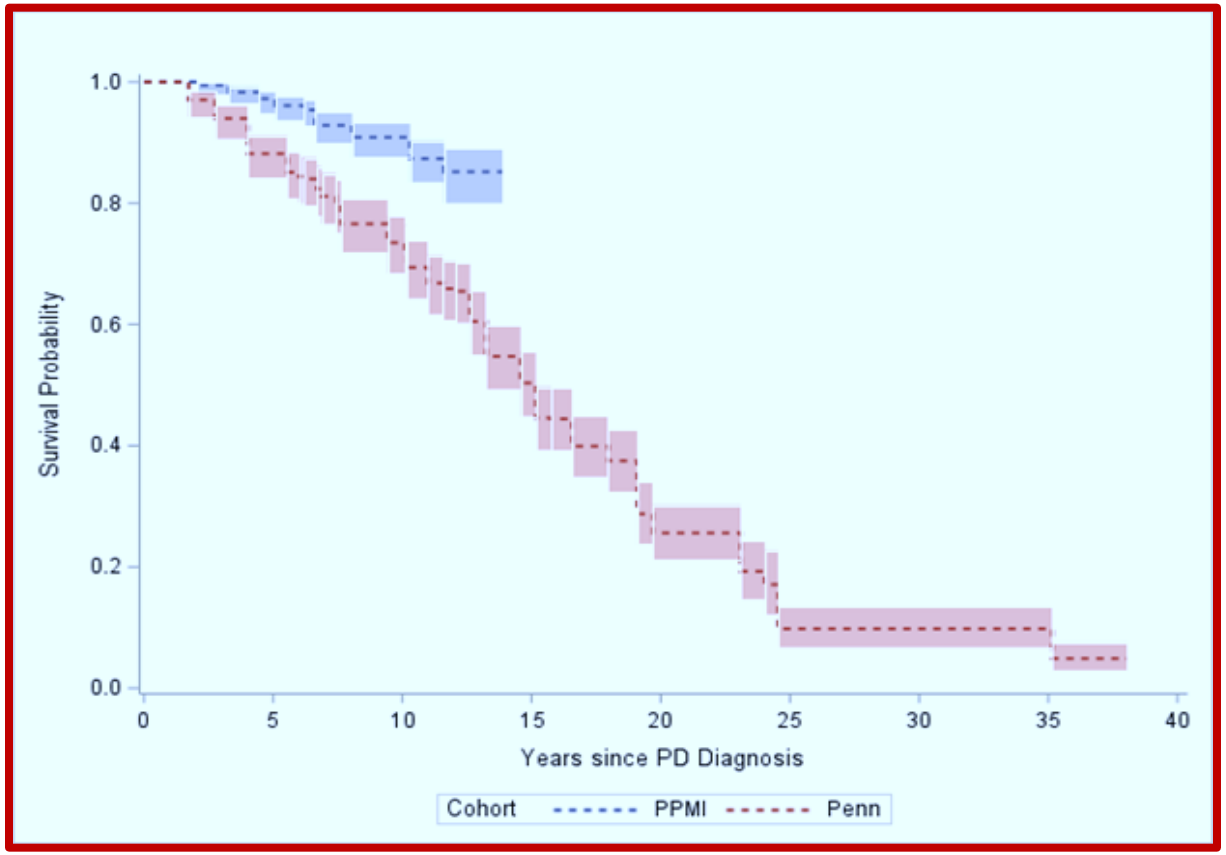
# ...And Highly Comorbid




- By disease year 5 over 50% of patients screen positive for ≥3 NPS

Weintraub et al. *Ann Clin Transl Neurol*. 2020;7:449-61.

# New PD Dementia Survival Curves: Glass Half-full?




Gallagher et al. *Neurology* 2024;103:e209699.

# Neuronal α-Synuclein Disease Integrated Staging System

| | | Neuronal α-synuclein biomarker (S) | Dopamine dysfunction biomarker (D) | Clinical signs and symptoms attributable to neuronal α-synuclein disease | Functional impairment attributable to neuronal α-synuclein disease |
|---|---|---|---|---|---|
| **Genetic risk** | | | | | |
| $R^L$ | (G) Genetic risk variants–low age-adjusted risk | Absent | Absent | No clinical signs or symptoms | No functional impairment |
| $R^H$ | (G) Genetic risk variants–high age-adjusted risk | Absent | Absent | No clinical signs or symptoms | No functional impairment |
| **Stage definition** | | | | | |
| 0 | Fully penetrant *SNCA* variant (G+) | S– | D– | No clinical signs or symptoms | No functional impairment |
| 1A | Characteristic pathological changes, but no evidence of clinical signs or symptoms | S+ | D– | No clinical signs or symptoms | No functional impairment |
| 1B | Characteristic pathological changes plus dopaminergic dysfunction, but no evidence of clinical signs or symptoms | S+ | D+ | No clinical signs or symptoms | No functional impairment |
| 2A | Characteristic pathological changes and subtle detectable clinical signs and symptoms, but no functional impairment | S+ | D– | Subtle clinical signs or symptoms that can be motor or non-motor: hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety | No functional impairment |
| 2B | Characteristic pathological changes plus dopaminergic dysfunction and subtle detectable clinical signs and symptoms, but no functional impairment | S+ | D+ | Subtle clinical signs or symptoms that can be motor or non-motor: hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety | No functional impairment |
| 3 | Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing slight functional impairment | S+ | D+ | Motor and non-motor signs and symptoms defined by a slight degree of functional impairment | Slight: functional impairment with minimal impact on activities of daily living |
| 4 | Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing mild functional impairment | S+ | D+ | Motor and non-motor signs and symptoms defined by a mild degree of functional impairment | Mild: functional impairment severe enough to cause some impairment in activities of faily living, but those related to personal care are intact, such as bathing, dressing, walking, using the toilet, and eating |
| 5 | Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing moderate functional impairment | S+ | D+ | Motor and non-motor signs and symptoms defined by a moderate degree of functional impairment | Moderate: functional impairment severe enough to require assistance with activities of daily living |
| 6 | Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing severe functional impairment | S+ | D+ | Motor and non-motor signs and symptoms defined by a severe degree of functional impairment | Severe: functional impairment severe enough to depend on others for activities of daily living |

- Cognition and other non-motor symptoms are part of staging system from the start
- Of equal importance to motor symptoms
- Effort ongoing to now define all proteinopathy-associated neurodegenerative diseases similar

Simuni et al. *Lancet Neurology* 2024;23:178-190.

# Cognition: Biggest Unmet Need, But a Lot Going On

# Still Hand-Me-Downs From Alzheimer's Disease

**TABLE 5.** Interventions to treat dementia and nondementia cognitive impairment in PD

| Intervention | | Efficacy | Safety | Practice implications |
|---|---|---|---|---|
| Drug class/intervention strategy | Drug/intervention | | | |
| **Dementia** | | | | |
| Acetylcholinesterase inhibitors | **Donepezil** | Insufficient evidence | Acceptable risk without specialized monitoring[a] | *Possibly useful*[b] |
| | **Rivastigmine** | Efficacious | Acceptable risk without specialized monitoring[a] | Clinically useful |
| | Galantamine | Insufficient evidence | Acceptable risk without specialized monitoring[a] | *Possibly useful*[c] |
| N-methyl-D-aspartate (NMDA) antagonists | Memantine | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| **Nondementia cognitive impairment** | | | | |
| Acetylcholinesterase inhibitors | **Rivastigmine** | *Insufficient evidence* | *Acceptable risk without specialized monitoring*[d] | *Investigational* |
| Monoamine oxidase B (MAO-B) inhibitors | **Rasagiline** | *Insufficient evidence* | *Acceptable risk without specialized monitoring* | *Investigational* |
| Nonpharmacological Interventions | **Transcranial direct-current stimulation (T-DCS)** | *Insufficient evidence* | *Insufficient evidence* | *Investigational* |
| | **Cognitive rehabilitation** | *Insufficient evidence* | *Insufficient evidence* | *Investigational* |

- Only rivastigmine FDA-approved for PD dementia (PDD)
  - Study was 20 years ago!
- No approved treatments for mild cognitive impairment (PD-MCI)
- Role for anti-amyloid immunotherapies for PD(D) or DLB

Seppi et al. *Movement Disorders* 2019;34:180-198.

# Really No Effect for Memantine in Lewy Body Dementia?

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

## Memantine improves attention and episodic memory in Parkinson's disease dementia and dementia with Lewy bodies

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**Objective:** In both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), attentional dysfunction is a core clinical feature together with disrupted episodic memory. This study evaluated the cognitive effects of memantine in DLB and PDD using automated tests of attention and episodic memory.

**Methods:** A randomised double-blind, placebo-controlled, 24-week three centre trial of memantine (20 mg/day) was conducted in which tests of attention (simple and choice reaction time) and word recognition (immediate and delayed) from the CDR System were administered prior to dosing and again at 12 and 24 weeks. Although other results from this study have been published, the data from the CDR System tests were not included and are presented here for the first time.

**Results:** Data were available for 51 patients (21 DLB and 30 PDD). In both populations, memantine produced statistically significant medium to large effect sized improvements to choice reaction time, immediate and delayed word recognition.

**Conclusions:** These are the first substantial improvements on cognitive tests of attention and episodic recognition memory identified with memantine in either DLB or PDD. 

**Key words:** memantine; dementia with Lewy bodies; Parkinson's disease dementia; attention; episodic memory; CDR System; automated cognitive tests
**History:** Received 15 December 2013; Accepted 4 March 2014; Published online in Wiley Online Library (wileyonlinelibrary.com)
**DOI:** 10.1002/gps.4109

- Treatment effect seen with computerized cognitive battery sensitive to deficits in Lewy body dementia
  - Raises questions about outcome measures, currently a topic of great focus

# Encouraging Results for Related DLB: Kinase Inhibitor

- **Neflamapimod (AscenD-LB study)**
  - p38α kinase inhibitor
  - Clinical study in DLB, not PDD
  - Partially positive
    - CDR-SB at any dose
    - Neuropsychological test battery (focus on executive abilities / attention) at higher dose
  - Good tolerability
- New study in DLB planned

Jiang et al. *Nature Communications* 2022;13:5308.

**Table 2 | Efficacy outcome measures in the clinical study**

| Outcome measure | All Neflamapimod (NFMD; includes 40 mg BID and 40 mg TID participants) vs. All Placebo | | | | | | |
|---|---|---|---|---|---|---|---|
| | Number of participants | | Mean baseline values | | Change from baseline | | |
| | NFMD | Placebo | NFMD | Placebo | Drug-Placebo Difference On-Study (95% CI) | *p*-value | Cohen's d Effect Size for Improvement - *d* |
| NTB* Composite | 39 | 37 | 0.04 | 0.05 | 0.04 (−0.11, 0.19) | >0.2 | 0.10 |
| Attention Composite | 39 | 36 | 0.04 | −0.02 | 0.14 (−0.06, 0.35) | 0.17 | 0.18 |
| Clinical Dementia Rating Sum of Boxes (CDR-SB) | 41 | 42 | 4.9 | 5.1 | −0.45 (−0.83, −0.06) | 0.023 | 0.31 |
| International Shopping List Test (ISLT) | 42 | 42 | 14.3 | 13.6 | −0.17 (−1.61, 0.87) | >0.2 | −0.02 |
| Timed Up and Go (TUG) | 39 | 38 | 12.7 | 13.5 | −1.4 (−2.7, −0.1) | 0.044 | 0.22 |

*NTB: Neuropsychological Test Battery evaluating attention, executive function, and visual learning.
The NTB was the primary outcome measure. NTB and Attention composites reported as z-scores.
Note: Difference (95% confidence interval, CI) shown is from MMRM (mixed model for repeated measures) analysis. Improvement is reflected as increases in NTB, Attention Composite and the ISLT; and as decreases in CDR-SB and TUG test. Positive *d* indicates improvement relative to placebo, and negative *d* indicates worsening relative to placebo.

TID) to placebo. Importantly, in the current study the measured plasma drug concentrations, available after the statistical analyses were completed, were 50% higher in 40 mg TID recipients, compared to 40 mg BID (median steady-state concentration of 6.8 ng/mL in 40 mg BID vs 10.2 ng/mL in 40 mg TID). In these additional analyses (Suppl. Table 3, Suppl. Figs. 3 and 4) for both the NTB Composite and the Attention Composite, the z-score in 40 mg TID participants improved from baseline and was different over the course of the study from placebo (NTB Composite drug-placebo difference = 0.18 95% CI:0.00–0.35, $d = 0.47$; Attention Composite drug-placebo difference = 0.28, 95% CI 0.04–0.52, $d = 0.41$). Improvement relative to placebo was also seen with 40 mg TID in the CDR-SB (drug-placebo difference = −0.56, 95% CI:−0.96, −0.16, $d = 0.35$) and the TUG Test (drug-placebo difference =

# Another Recent Positive DLB Study

- **CT1812 (Cognition Therapeutics)**
  - Sigma-2 receptor antagonist
  - Involved in regulation of key cellular processes, which are disrupted by toxic interaction with Aβ or α-synuclein oligomers, oxidative stress and other disease drivers. Ensuing damage to synapses can progress to a loss of synaptic function
- Trial ongoing in Alzheimer's disease

SHIMMER Phase 2 study enrolled 130 patients with DLB who were randomized to receive one of two oral doses of CT1812 or placebo daily for six months. Results indicate the study met its primary endpoint of safety and tolerability, with data showing that DLB patients treated with CT1812 for six months experienced **improvement in behavioral, functional, cognitive and movement measures compared to placebo**. Importantly, there was an 82% slowing in the total neuropsychiatric inventory (NPI) with particularly strong reduction in anxiety, hallucinations, and delusions in the CT1812 treated arms. Participants treated with CT1812 experienced a slowing of decline across all three cognitive measures compared to placebo, including fluctuations in attention which declined by 91%.

# Positive Effect in LBD Cognition for Cholinergic System

- **TAK-071 (Takeda)**
  - M1R PAM (muscarinic 1 receptor positive allosteric modulator)
  - PD with cognitive impairment or DLB + at risk for falls

**MAIN OUTCOMES AND MEASURES** The primary end point was change from baseline in gait variability (stride time variability [STV]) during a 2-minute walk test with or without cognitive load. The secondary efficacy end point was change from baseline in a cognitive composite score consisting of tests of attention, executive function, and memory.

**RESULTS** Among the 54 participants included in the analysis, 45 (83%) were male, mean (SD) age was 69.7 (6.9) years, and median Montreal Cognitive Assessment score was 24 (range, 17-26). After 6 weeks of treatment, the primary outcome was negative: the change from baseline in STV did not differ between participants receiving TAK-071 or placebo, with cognitive load (geometric mean ratio, 1.15; 95% CI, 0.94-1.41; *P* = .16) or without cognitive load (geometric mean ratio, 1.02; 95% CI, 0.88-1.18; *P* = .78). TAK-071 improved the secondary efficacy outcome (cognitive composite score) vs placebo. The least squares mean difference of the change from baseline was 0.22 (95% CI, 0.05-0.38; *P* = .01).

Shanbhag et al. *Jama Neurology* 2025;82;(2):152-159.

# Glutamate NMDA Receptor Focus Has Not Worked Yet

- **Sage (SAGE-718) and Aptinyx (NYX-458)**
  - N-methyl-D-aspartate (NMDAR) modulators

April 17, 2024

Sage Therapeutics Announces Topline Results from Phase 2 PRECEDENT Study of Dalzanemdor (SAGE-718) in the Treatment of Mild Cognitive Impairment in Parkinson's Disease

- In the Phase 2 PRECEDENT Study, dalzanemdor (SAGE-718) **did not show statistically significant differences versus placebo** on the primary endpoint in patients with mild cognitive impairment in Parkinson's disease

# Interest in Adrenergic System

- **CST-103 (clenbuterol)**
  - Beta-2 adrenoreceptor agonist, ability to activate norepinephrine in the brain

**Brief Summary**

This is a Phase II, randomized, placebo-controlled, double-blind, crossover study on the CNS and pharmacodynamic effects of clenbuterol (CST-103) co-administered with nadolol (CST-107) in 4 subject populations with Neurodegenerative Disorders.

**Detailed Description**

Approximately 40 subjects with Parkinson's Disease (PD) with REM Sleep Behavior Disorder (RBD) and Depressive Symptoms, Mild Cognitive Impairment (MCI) with Depressive Symptoms, Dementia with Lewy Bodies (DLB) with Cognitive Fluctuations, and Parkinson's Disease Dementia (PDD) with Cognitive Fluctuations were to be enrolled in a 2 period, 2-way crossover design following study eligibility confirmation during the screening period. The number of subjects enrolled in each cohort could change as emerging data are reviewed from this and other studies.

https://clinicaltrials.gov/study/NCT04739423?cond=%22Rem%20Sleep%20Behavior%20Disorder%22&intr=%22Sympathomimetics%22&viewType=Table&rank=1

# Anti-synuclein Immunotherapy Being Tested

- "Prevent Cognitive Decline in GBA-associated Parkinson's Disease (PreCoDe)"
  - Proof-of-concept prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial to investigate the efficacy of IV monoclonal anti-α-synuclein antibody prasinezumab to slow or prevent cognitive decline in people with PD carrying severe mutation in the GBA (glucocerebrosidase) gene
  - Duration of the treatment will be 104 weeks with monthly infusions.
  - Target enrollment = 120 participants (60 participants per treatment arm)

https://clinicaltrials.gov/study/NCT07055087?term=AREA%5BPhase%5D(PHASE2)&rank=4

# Ambroxol Effect for PD Cognition Unclear

- Ambroxol is a chaperone for β-glucocerebrosidase, which increases the levels of β-glucocerebrosidase
- 52-week, phase 2, double-blind, placebo-controlled, RCT of two ambroxol doses (525 or 1050 mg/day)
- Participants had mild-moderate PD dementia
- Primary efficacy outcomes were ADAS-Cog-13 CGIC
- **Primary and secondary outcomes were negative**
- Study issues: Recruitment over 8 years, single site, small sample size (N=55)

- Study in DLB should be completed soon

Silveira et al. *Jama Neurology* 2025;82;(8):797-807.

# Role for GLP-1 Agonists?

**Safety, tolerability, and efficacy of NLY01 in early untreated Parkinson's disease: a randomised, double-blind, placebo-controlled trial**

Andrew McGarry, Shane Rosanbalm, Mika Leinonen, C Warren Olanow, Dennis To, Adam Bell, Daniel Lee, Jamie Chang, Jordan Dubow, Rohit Dhall, Daniel Burdick, Sotirios Parashos, Jeanne Feuerstein, Joseph Quinn, Rajesh Pahwa, Mitra Afshari, Aldolfo Ramirez-Zamora, Kelvin Chou, Arjun Tarakad, Cornelia Luca, Kevin Klos, Yvette Bordelon, Marie-Helene St Hiliare, David Shprecher, Seulki Lee, Ted M Dawson, Viktor Roschke, Karl Kieburtz

**Exenatide once a week versus placebo as a potential disease-modifying treatment for people with Parkinson's disease in the UK: a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial**

Nirosen Vijiaratnam, Christine Girges, Grace Auld, Rachel McCormish, Alexa King, Simon S Skene, Steve Hibbert, Alan Wong, Sabina Melander, Rachel Gibson, Helen Matthews, John Dickson, Camille Carroll, Abigail Patrick, Jemma Inches, Monty Silverdale, Bethan Blackledge, Jessica Whiston, Michele Hu, Jessica Welch, Gordon Duncan, Katie Power, Sarah Gallen, Jacqueline Kerr, K Ray Chaudhuri, Lucia Batzu, Silvia Rota, Edwin Jabbari, Huw Morris, Patricia Limousin, Nigel Greig, Yazhou Li, Vincenzo Libri, Sonia Gandhi, Dilan Athauda, Kashfia Chowdhury, Tom Foltynie

The NEW ENGLAND JOURNAL of MEDICINE

- Now being tested in s orders (AUD, OUD)
- Large Alzheimer's dis emaglutide to be completed soon

ORIGINAL ARTICLE

**Trial of Lixisenatide in Early Parkinson's Disease**

W.G. Meissner, P. Remy, C. Giordana, D. Maltête, P. Derkinderen, J.-L. Houéto, M. Anheim, I. Benatru, T. Boraud, C. Brefel-Courbon, N. Carrière, H. Catala, O. Colin, J.-C. Corvol, P. Damier, E. Dellapina, D. Devos, S. Drapier, M. Fabbri, V. Ferrier, A. Foubert-Samier, S. Frismand-Kryloff, A. Georget, C. Germain, S. Grimaldi, C. Hardy, L. Hopes, P. Krystkowiak, B. Laurens, R. Lefaucheur, L.-L. Mariani, A. Marques, C. Marse, F. Ory-Magne, V. Rigalleau, H. Salhi, A. Saubion, S.R.W. Stott, C. Thalamas, C. Thiriez, M. Tir, R.K. Wyse, A. Benard, and O. Rascol, for the LIXIPARK Study Group*

# Depression: Options Exist

# Published Research

| Intervention | | | | |
|---|---|---|---|---|
| Drug class/ intervention strategy | Drug/intervention | Efficacy | Safety | Practice implications |
| Dopamine Agonists | Pramipexole | Efficacious | Acceptable risk without specialized monitoring | Clinically useful |
| | Pergolide | Insufficient evidence | Acceptable risk with specialized monitoring | Not useful |
| | **Rotigotine** | *Unlikely efficacious* | *Acceptable risk without specialized monitoring* | *Investigational* |
| Monoamine oxidase B (MAO-B) inhibitors | **Rasagiline** | *Insufficient evidence* | *Acceptable risk without specialized monitoring* | *Investigational* |
| | Selegeline | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| | Moclobemide | Insufficient evidence | Acceptable risk with specialized monitoring[a] | Investigational |
| Tricyclic antidepressants | Nortriptyline | Likely efficacious | Acceptable risk without specialized monitoring[b] | Possibly useful |
| | Desipramine | Likely efficacious | Acceptable risk without specialized monitoring[b] | Possibly useful |
| | Amitriptyline | Insufficient evidence | Acceptable risk without specialized monitoring[b] | *Possibly useful*[c] |
| Selective serotonin reuptake inhibitors/selective serotonin norepinephrine reuptake inhibitors | Citalopram | Insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[d] |
| | Sertraline | Insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[d] |
| | **Paroxetine** | insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[d] |
| | Fluoxetine | Insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[c] |
| | **Venlafaxine** | *Efficacious* | *Acceptable risk without specialized monitoring*[e] | *Clinically useful* |
| Other antidepressants | Atomoxetine | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| | Nefazodone | Insufficient evidence | Unacceptable risk | Not useful |
| Alternative therapies | 'Ω-3 fatty acids | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| Nonpharmacological interventions | **rTMS** | *Insufficient evidence* | *Acceptable risk without specialized monitoring*[f] | *Possibly useful (short term)* |
| | **CBT** | *Likely efficacious* | *Insufficient evidence*[g] | *Possibly useful* |

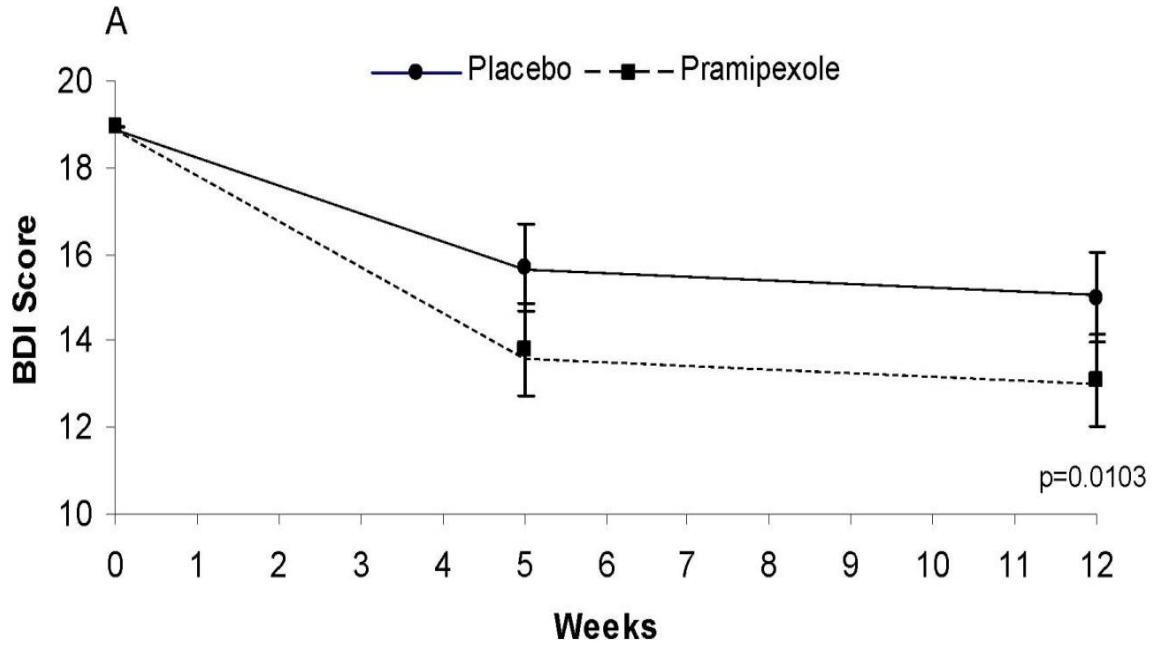
- For depression, evidence for efficacy for compounds targeting serotonin, norepinephrine and dopamine

*"No randomized controlled trials that met inclusion criteria for the treatment of anxiety disorders."*

Seppi et al. *Movement Disorders* 2019;34:180-198.

# Does Enhancing Dopamine Work for PD Depression?

- Dopamine agonists
  - 1 positive **pramipexole** study
  - 1 negative **rotigotine** study
- MAO-B inhibitor
  - 1 negative **rasagiline** study




Barone et al. *Lancet Neurol* 2010;9:573-580; Chung et al. *Expert Opin Pharmacother* 2016;17:1453-1461; Barone et al. *Eur J Neurol* 2015;22:1184-1191.

# Psychedelics and Related Compounds

- Psilocybin feasibility study for PD depression
  - 12 participants received psilocybin (one 10 mg followed by one 25 mg dose) with psychotherapy
  - No SAEs, no medical interventions required to manage effects of psilocybin, and no exacerbation of psychosis.
  - 10 participants experienced TEAE (e.g., anxiety, nausea, and increased BP)
  - No worsening of motor symptoms
  - Non-motor symptoms, motor function, and some cognitive domains improved with treatment
- Ongoing studies for ketamine for PD depression

Bradley et al. *Neuropsychopharmacology* 2025;50:1200–1209.

# Psychosis: Confusing Story

# Published Research

| Drug | Efficacy | Safety[a] | Practice implications |
|---|---|---|---|
| Clozapine | Efficacious | Acceptable risk with specialized monitoring | Clinically useful |
| **Olanzapine** | *Not efficacious* | Unacceptable risk | *Not useful* |
| Quetiapine | Insufficient evidence | Acceptable risk without specialized monitoring | *Possibly useful*[b] |
| **Pimavanserin** | *Efficacious* | *Acceptable risk without specialized monitoring*[c] | *Clinically useful* |

- Pimavanserin available only in US
- Clozapine rarely prescribed (<2%)
- Quetiapine still most frequently prescribed AP (80+% of AP use?)
- Up to 1/3 receive high potency APs (typicals + atypicals)

Seppi et al. *Movement Disorders* 2019;34:180-198.
et al. *Archives of Neurology* 2011;68:899-904.

# Recent Trials

- **Pimavanserin for dementia-related psychosis (HARMONY Trial)**
  - 5-HT2A inverse agonist/antagonist
  - Randomized, placebo-controlled discontinuation study for responders to open-label treatment
  - Included PDD, DLB, FTD, AD and vascular dementia
- **SEP-363856**
  - 5-HT1A and TAAR1 (trace amine-associated receptor 1) agonist
  - Small RCT with negative results on SAPS-PD
- **Cholinesterase Inhibitors to Slow Progression of Visual Hallucinations (CHEVAL study)** terminated early due to poor enrollment
  - No effect on conversion to transition time from minor visual hallucinations to psychosis or dementia during the 24-month follow-up period

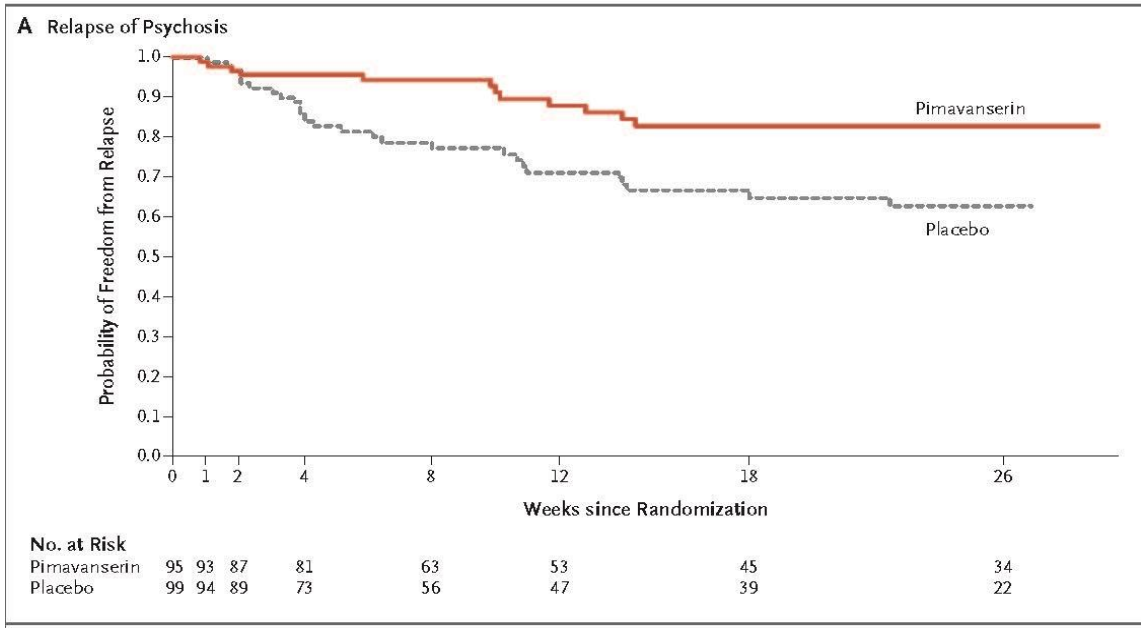
van Mierlo et al. *Brain and Behavior* 2021;11:e2257.

ORIGINAL ARTICLE

# Trial of Pimavanserin in Dementia-Related Psychosis

Pierre N. Tariot, M.D., Jeffrey L. Cummings, M.D., Sc.D., Maria E. Soto-Martin, M.D., Ph.D., Clive Ballard, M.D., Deniz Erten-Lyons, M.D., David L. Sultzer, M.D., Davangere P. Devanand, M.D., Daniel Weintraub, M.D., Bradley McEvoy, Dr.P.H., James M. Youakim, M.D., Srdjan Stankovic, M.D., M.S.P.H., and Erin P. Foff, M.D., Ph.D.

**HARMONY Study: Basket Trial**




Tariot et al. *NEJM* 2021;385:309-319.

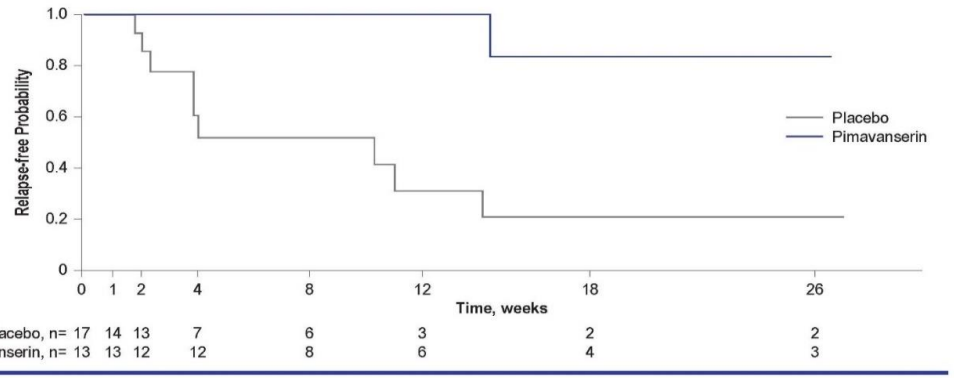
# HARMONY Study: Pimavanserin Highly Efficacious in PDD Subgroup

**Table 2. Time to Relapse in the Double-Blind Period**

| | Double-Blind Period | |
|---|---|---|
| | Placebo (N=17) | Pimavanserin 34 mg (N=13) |
| Patients with a relapse event, n (%) | 9 (52.9) | 1 (7.7) |
| Patients censored from survival analysis, n (%) | 8 (47.1) | 12 (92.3) |
| Completed week 26 without a relapse | 2 (11.8) | 3 (23.1) |
| Prematurely discontinued prior to week 26 | 3 (17.6) | 3 (23.1) |
| Ongoing at time of database cutoff | 3 (17.6) | 6 (42.6) |

Efficacy data reflect the intent-to-treat analysis set at the time of the interim analysis (N=30). Six additional patients had been randomized by the time the study was stopped, based on recommendation by the Data Safety Monitoring Board for positive efficacy. These 6 subjects were not part of the efficacy analyses.

**Figure 2. Kaplan-Meier Estimation of Time to Relapse in the Double-Blind Period**




Weintraub et al. *Parkinsonism Relat Disord* 2024;119:105951.

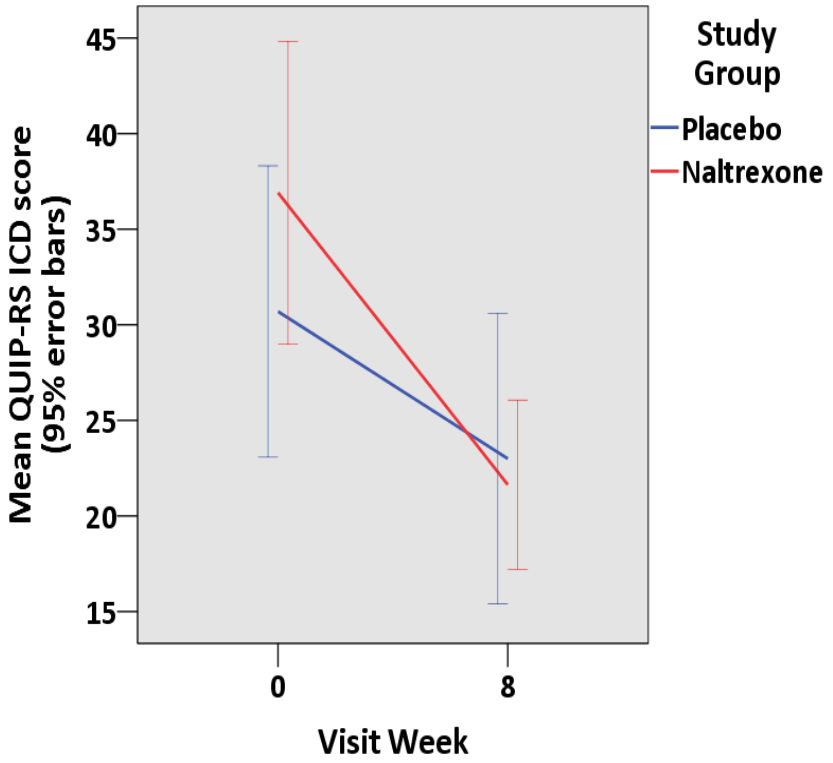
# Ongoing Trials

- **Ondansetron (TOP HAT)**
  - 5-HT3 antagonist
  - For PD hallucinations through Parkinson's UK
- **CANnabidiol for Parkinson's Disease Psychosis (CAN-PDP)**
  - Part I: multi-centre, open-label, safety, tolerability, dose-finding study (N=24)
    - 200-1,000 mg/day
  - Part II: multi-centre, double-blind, placebo controlled, 1:1, pilot RCT (N=120)
- **Pimavanserin vs. Quetiapine** randomized comparator study
  - Veterans Affairs CSP #2015 study
  - 24 VA sites, N~350

# Impulse Control Disorders: Momentum Lost

# Published Research for ICDs: Big Unmet Need

| Intervention | | | | Practice implications |
|---|---|---|---|---|
| Drug class/intervention strategy | Drug/intervention | Efficacy | Safety | |
| N-methyl-D-aspartate (NMDA) antagonists | Amantadine[a] | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| Anti-opioids | **Naltrexone**[b] | *Insufficient evidence* | *Insufficient evidence* | *Investigational* |
| Nonpharmacological interventions | **CBT**[b] | *Likely efficacious* | *Insufficient evidence*[c] | *Possibly useful* |




Seppi et al. *Movement Disorders* 2019;34:180-198.

# Recently Completed or Ongoing Trials

- **Clonidine**
  - α-2 noradrenergic agonist
  - 75 ug bid
  - Negative study
- **Pimavanserin**
  - 34 mg qd
  - Through NS-PARK/FCRIN network, the French Clinical Research Network for Parkinson's disease and Movement Disorders
- Role for GLP-1 agonists?

# Anxiety: Another Big Unmet Need

# Buspirone for Anxiety in PD

- 5-HT1A post-receptor partial agonist
- Very small RCT (N=21) for safety and tolerability
- 15-60 mg daily
- Poor motor tolerability with buspirone (surprising)

Schneider et al. *Park Rel Disord* 2020;81:69-74.

# Apathy: Under the Radar Screen

# Apathy: Even Bigger Unmet Need

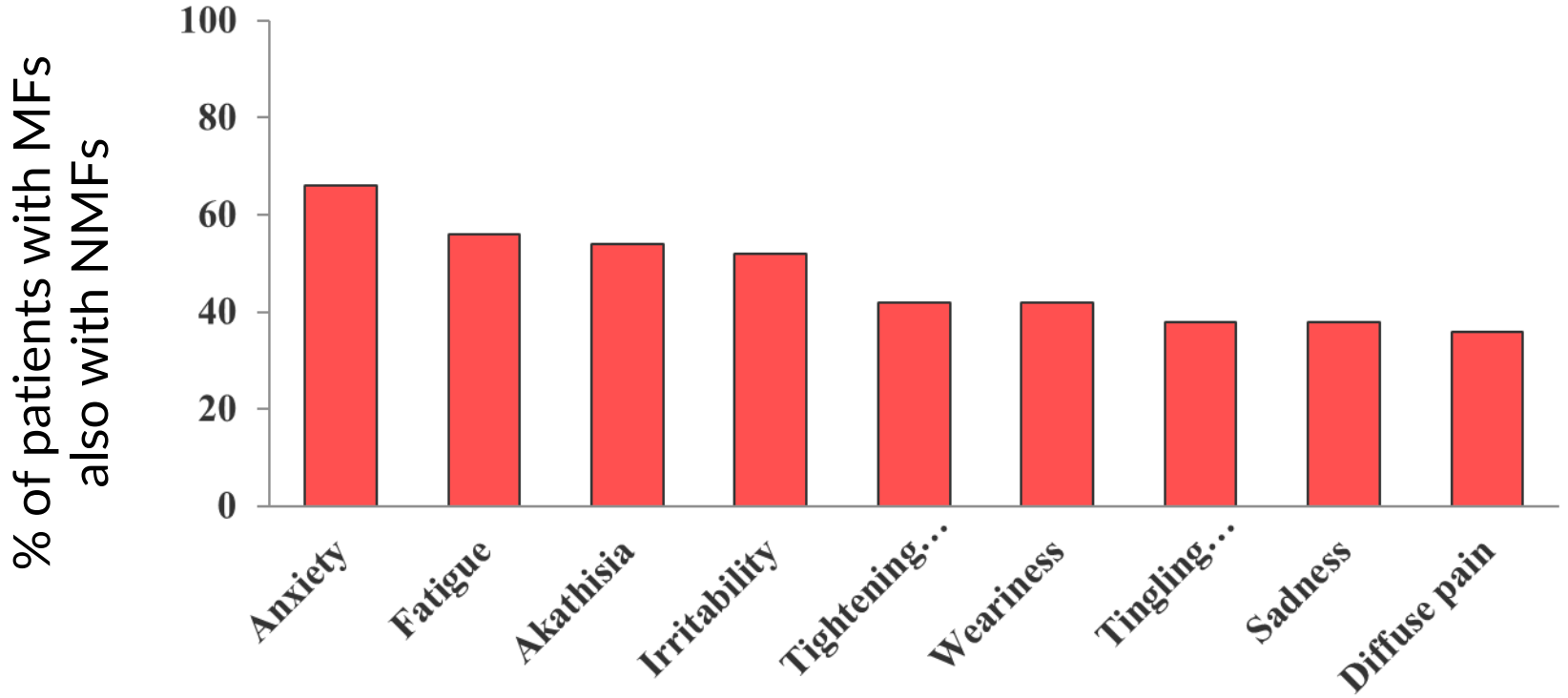
| Intervention | | | | |
|---|---|---|---|---|
| Drug class/intervention strategy | Drug/intervention | Efficacy | Safety | Practice implications |
| Dopamine agonists | **Piribedil**[a] | *Likely efficacious* | *Acceptable risk without specialized monitoring* | *Possibly useful* |
| | **Rotigotine** | *Unlikely efficacious* | *Acceptable risk without specialized monitoring* | *Investigational* |
| Acetylcholinesterase inhibitors | **Rivastigmine** | *Efficacious* | *Acceptable risk without specialized monitoring*[b] | *Possibly useful* |

- Removing dopamine agonist therapy resolves ICDs and induces apathy, and reintroduction of dopamine agonist therapy does the opposite

Seppi et al. *Movement Disorders* 2019;34:180-198.

# Global NPS or Non-Motor Fluctuations: The New Frontier

# Non-Motor Fluctuations (NMFs): Effect of Chronic, Fluctuating Dopamine Levels




Witjas et al. *Neurology* 2002;59:408-413.

# Recent Studies

- **Levodopa-Carbidopa Intestinal Gel for Non-motor Symptoms (NMS) in Advanced PD**
  - Recently reported no effect on NMSS and PDSS-2
- **Non-Invasive Brainstem Modulation Device for the Management of Non-Motor and Motor Symptoms in Parkinson's Disease (STEM-PD)**
  - ThermoNeuroModulation solid state caloric vestibular stimulation (CVS) device
  - Primary outcome is MDS-NMS
  - Negative study

Chung et al. *Parkinsons Disease*. 2022;10.1155/2022/1216975.

# Conclusions

# Clinical Management of NPS in PD

- Many treatment options, few with evidence for efficacy and tolerability in PD
  - Depression with most efficacious treatments, cognitive impairment biggest unmet need, really no evidence for anxiety and ICDs
  - Only 2 FDA-approved for PD specifically (rivastigmine, pimavanserin)
- Constant balancing of risks versus benefits
  - Motor vs. non-motor, efficacy vs. safety / tolerability
- Clinical care hampered by lack of mental health clinicians with PD expertise
  - Interest in use of virtual care and extending care (VA NTMHC)

# Clinical Research for NPS in PD

- Significant advancement in assessment instruments and diagnostic criteria
- Still borrow a lot of treatments from general population and AD
- Growing interest looking across neurodegenerative diseases/dementias
  - All dementias (HARMONY study), PDD vs. DLB dilemma unsolved still
- Interest looking at NPS/NMS broadly, as opposed to individually
- Many novel trials ongoing (particularly cognition) and non-pharmacological treatments are on the rise (e.g., psychotherapy, stimulation, cognitive training, exercise, diet)
- Clinical trials hard to conduct for NPS in PD
  - Therefore, NPS assessments need to be included in all PD clinical trials, including cognition