Update on Parkinson's Disease and Parkinson-PLUS Disorders Behavioral and Cognitive Comorbidities

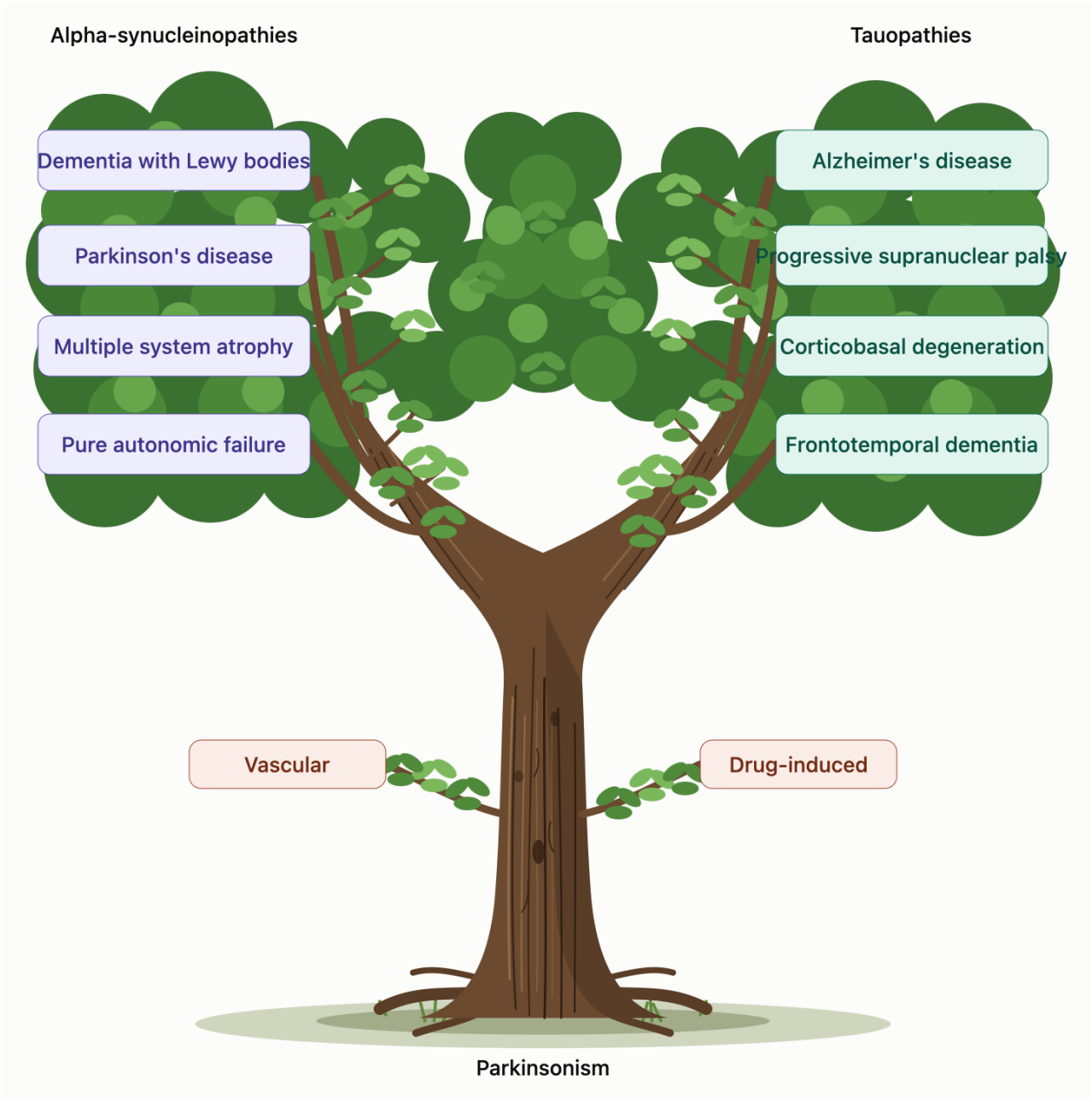
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Disclosures

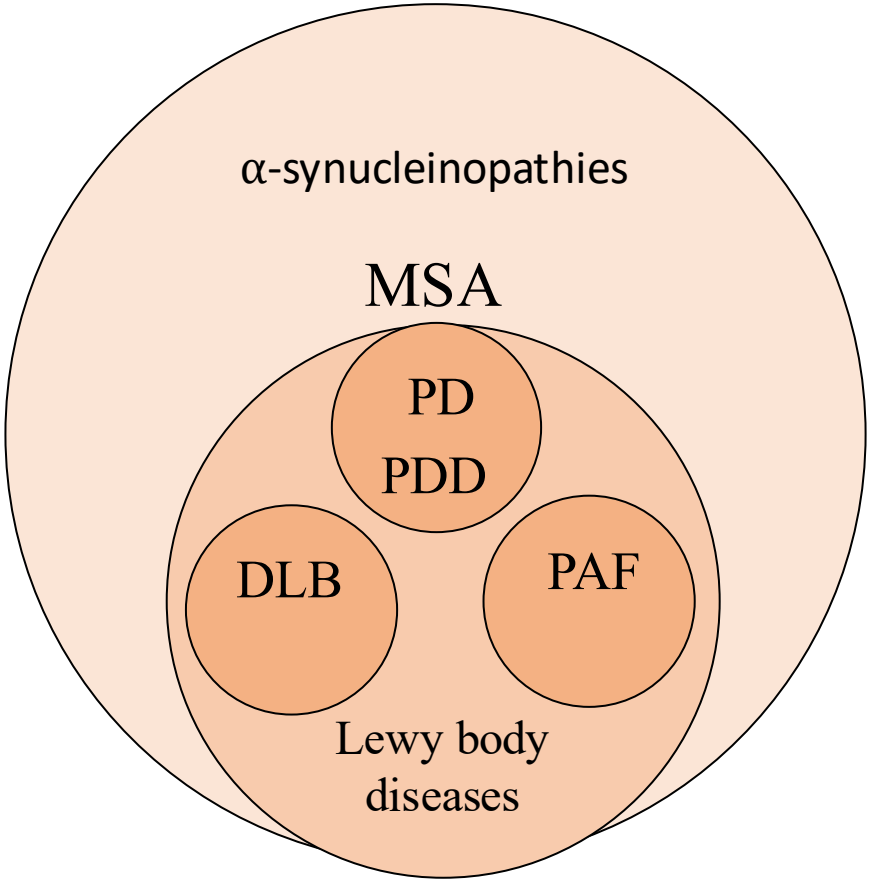
- No relevant financial relationships with commercial interests
- Dr. Pontone has consulted for AbbVie and Cognition Therapeutics
- The following talk may include unlabeled/unapproved use of medications

Parkinsonism vs Parkinson's disease

- Parkinsonism is an umbrella term that refers to brain conditions that cause slowed movements, rigidity (stiffness) and tremors. These conditions can happen for many reasons, including genetic mutations, reactions to medications, and infections
- Parkinson's disease makes up about 80% of all cases of parkinsonism, making it the most common form by far


Alpha-synucleinopathies
Tauopathies
Dementia with Lewy bodies
Parkinson's disease
Multiple system atrophy
Pure autonomic failure
Alzheimer's disease
Progressive supranuclear palsy
Corticobasal degeneration
Frontotemporal dementia
Vascular
Drug-induced
Parkinsonism

α synucleinopathies



Variable degrees of:

Autonomic dysfunction

Cognitive impairment

Motor symptoms

Shared prodromal features

DO PARKINSON'S DISEASE AND OTHER ALPHA SYN DISEASES SHARE NEUROPSYCHIATRIC FEATURES?

Neuropsychiatric symptoms and diagnosing neurodegenerative disorders

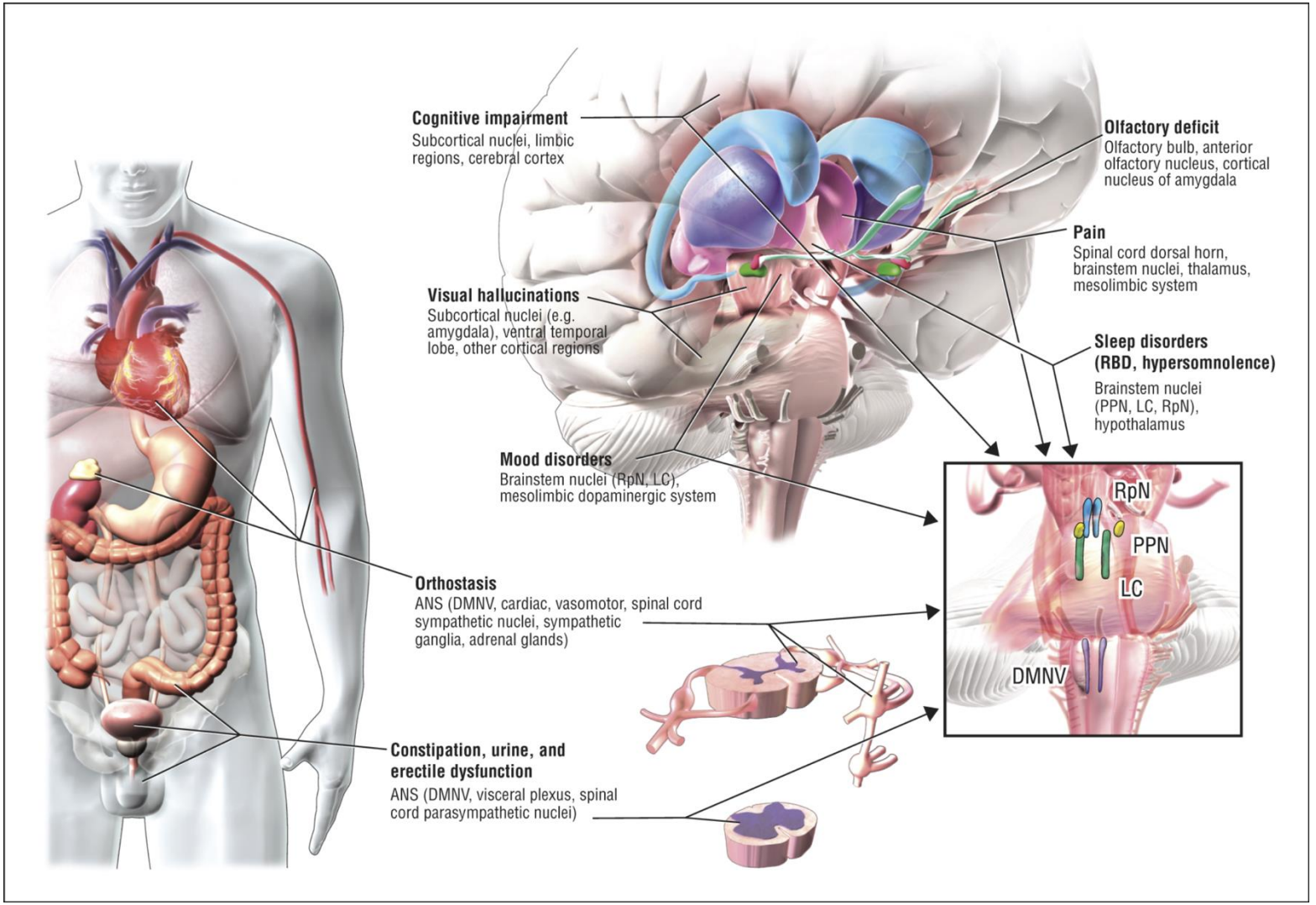
- Diagnosis of probable behavioral variant frontotemporal dementia requires the presence of NPS
- Other diagnostic criteria allow NPS to fulfill diagnostic criteria but do not specifically require the presence of NPS (e.g., AD, CBD, DLB, PSP, VCI)

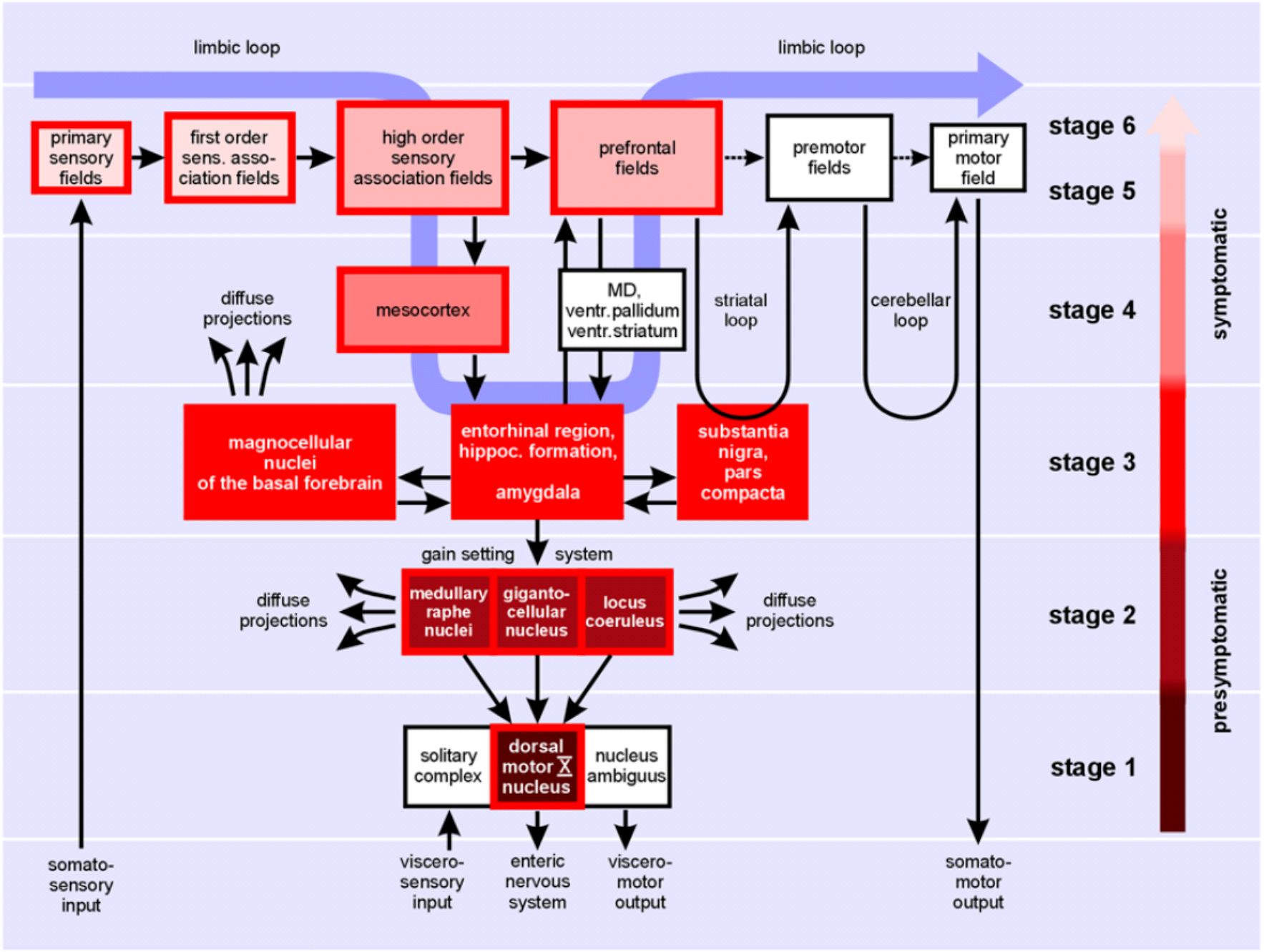
Non-motor symptoms of Parkinson's disease

- Up to 1/3 of idiopathic PD has no tremor
- Neuropsychiatric: apathy, anxiety, depression, psychosis, impulse control disorders – ubiquitous
- Cognitive impairment, up to 40% have MCI at diagnosis and 80% demented within 20 years of motor symptom onset
- Olfactory loss, up to 90%
- Dysautonomia, up to 70%
- Sleep disturbances, >30%

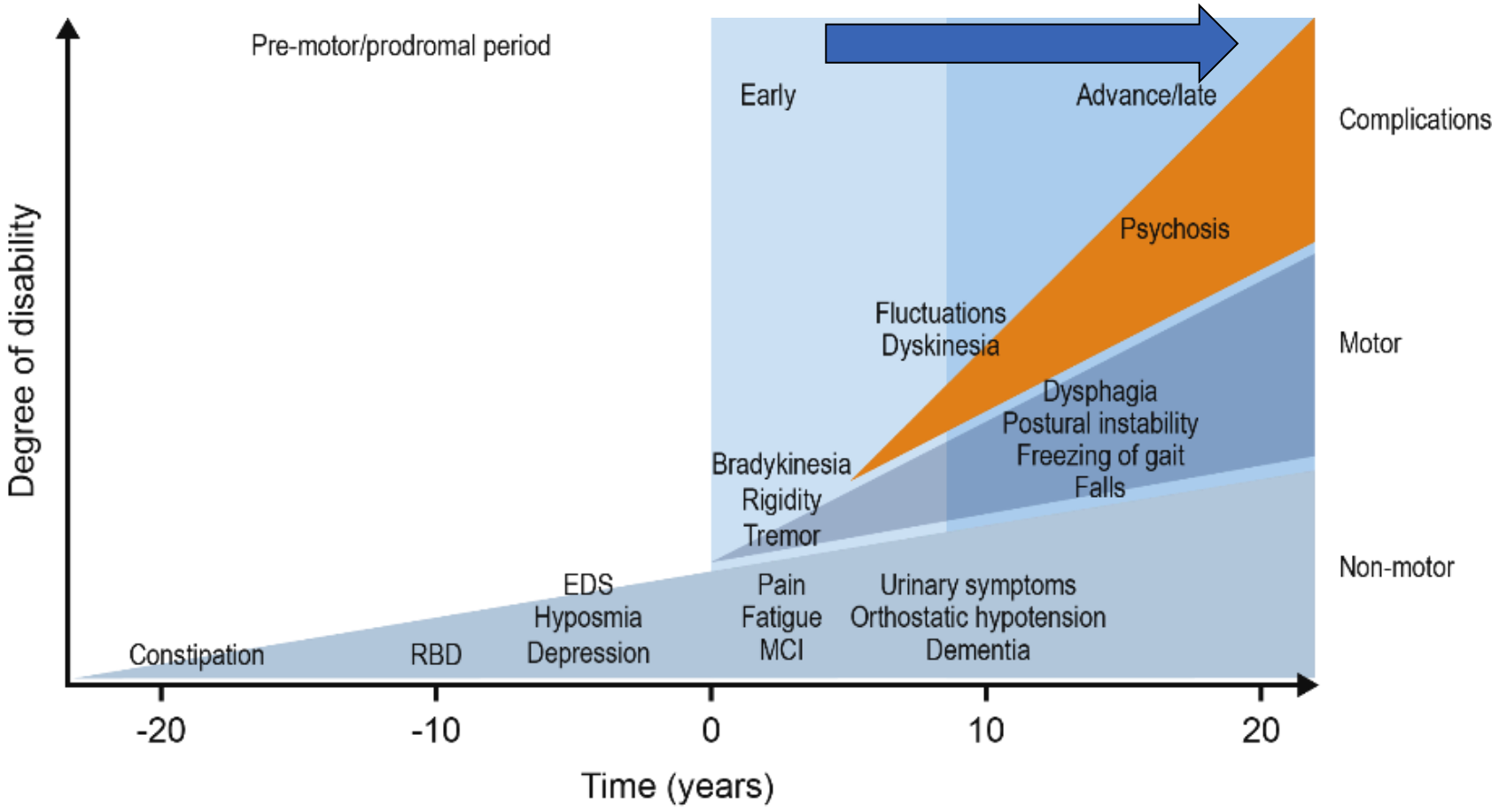
Gonera et al 1997, Tolosa et al 2009, Yarnell et al 2014

Extranigral Aspects of Parkinson's disease (Arch. Neurol 2009, Lim et al)



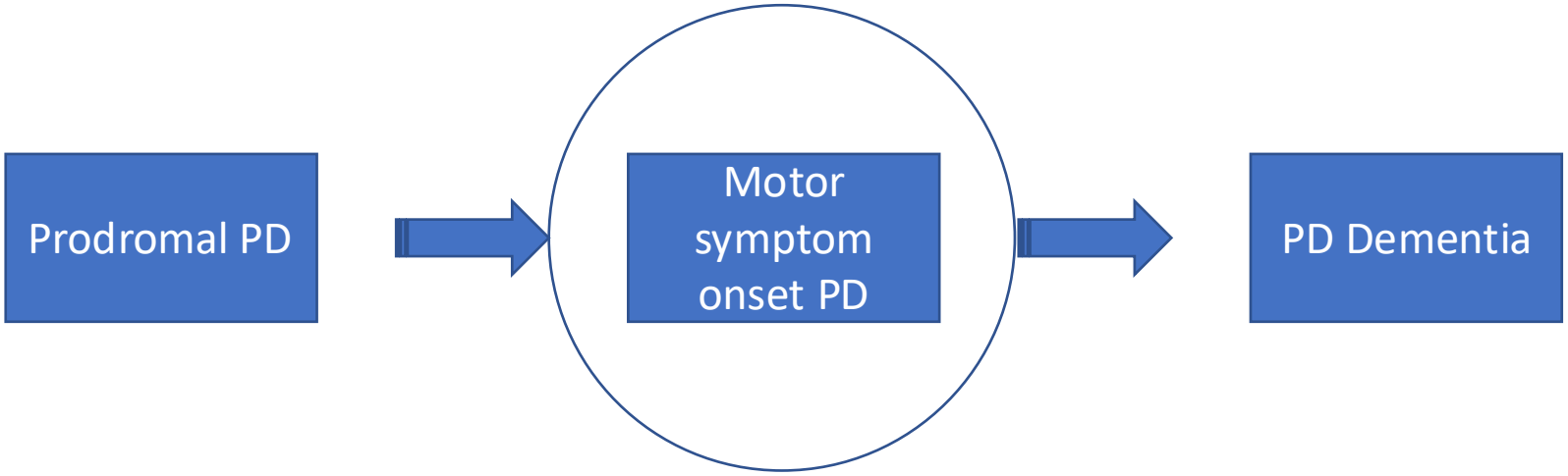

limbic loop
limbic loop
primary sensory fields
first order sens. asso-ciation fields
high order sensory association fields
prefrontal fields
premotor fields
primary motor field
stage 6
stage 5
stage 4
stage 3
stage 2
stage 1
symptomatic
presymptomatic
mesocortex
MD, ventr. pallidum ventr. striatum
striatal loop
cerebellar loop
diffuse projections
magnocellular nuclei of the basal forebrain
entorhinal region, hippoc. formation, amygdala
substantia nigra, pars compacta
gain setting system
diffuse projections
medullary raphe nuclei
gigantocellular nucleus
locus coeruleus
diffuse projections
solitary complex
dorsal motor X nucleus
nucleus ambiguus
somato-sensory input
viscero-sensory input
enteric nervous system
viscero-motor output
somato-motor output

Parkinson's as a complex neuropsychiatric condition



Kalia and Lang et al.

New Landscape of Parkinson's Disease

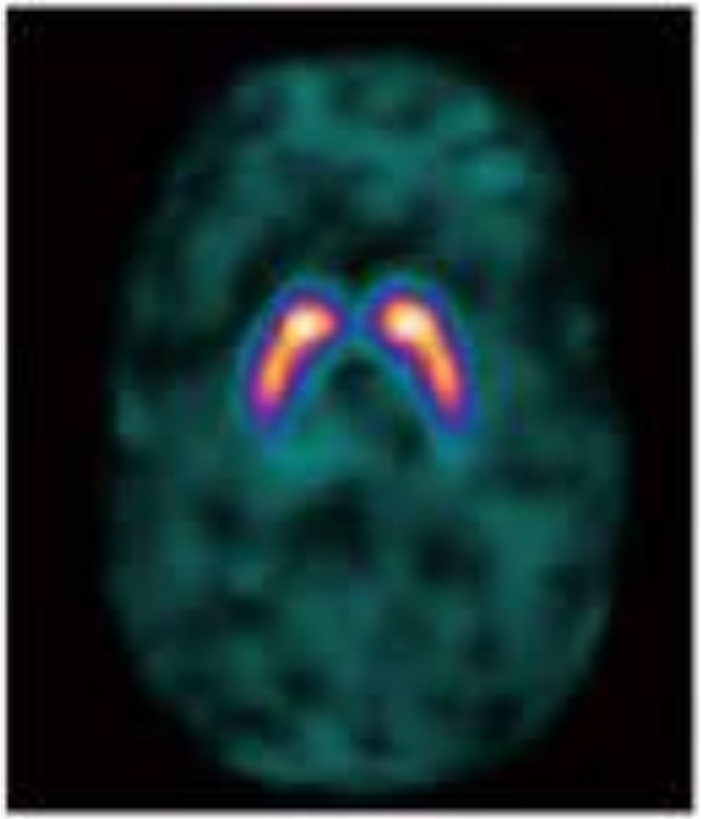


PD diagnosed by motor symptoms

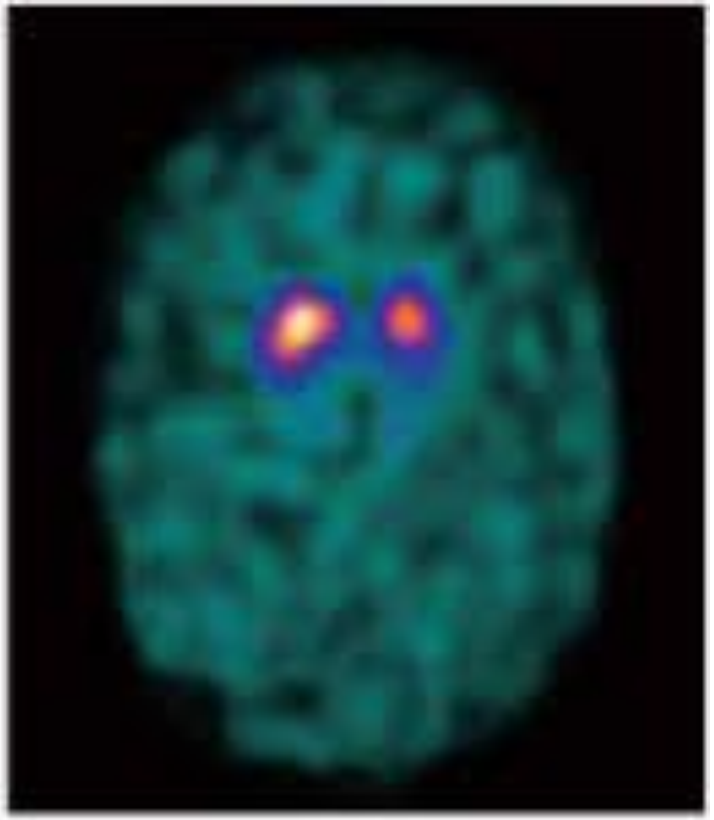
A New “early”: Prodromal Parkinson’s

- Prodromal or pre-motor symptoms occur before the movement syndrome of Parkinson’s starts
- 98% of people with Parkinson’s experience 7 or more prodromal symptoms 10 or more years before diagnosis
- The non-specific nature and lack of biomarkers for most prodromal symptoms makes early detection challenging

DaTscan – dopamine transporter SPECT scan

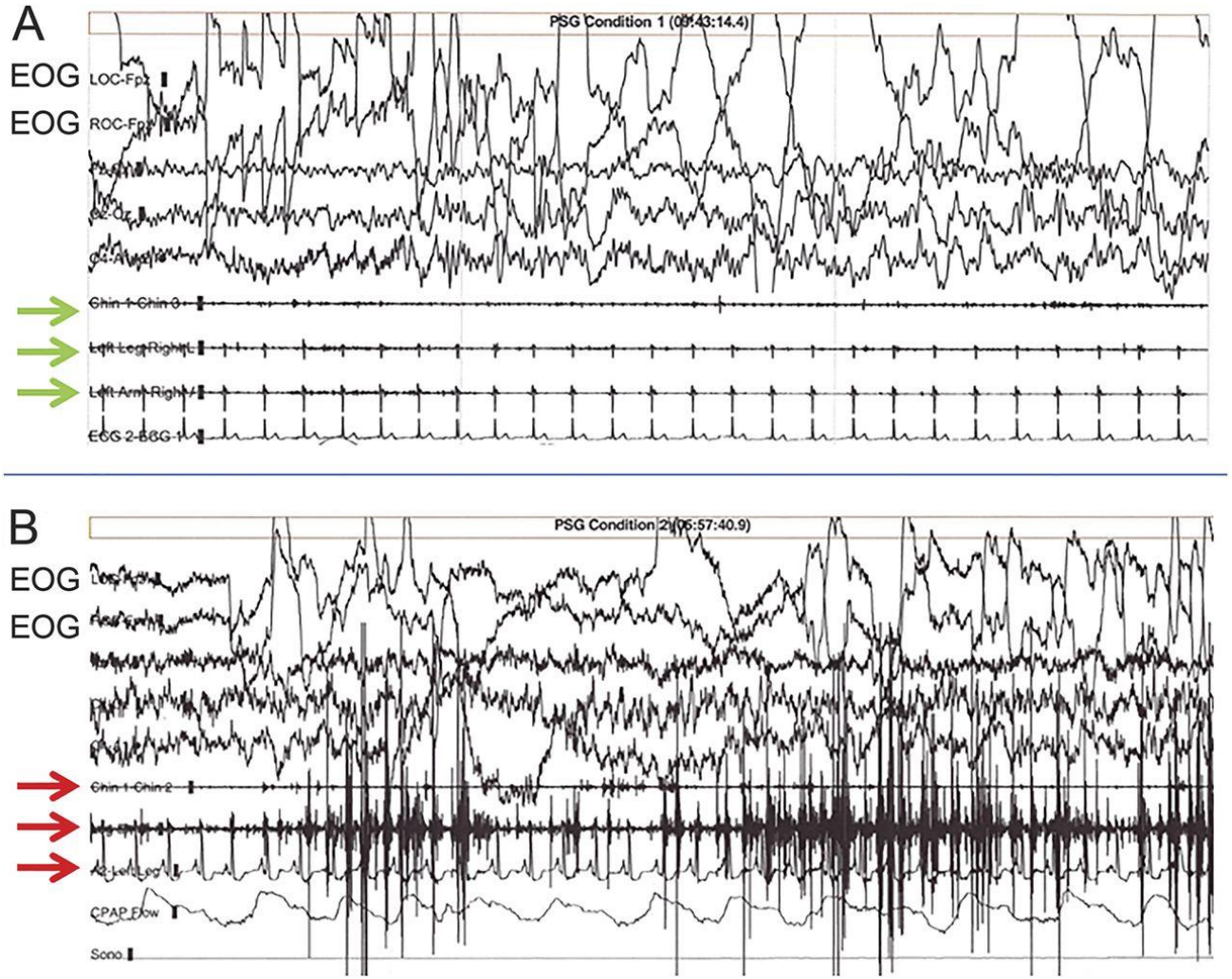


(a) Healthy Control



(b) Parkinson's Disease

Figure 3 Polysomnographic (PSG) recordings

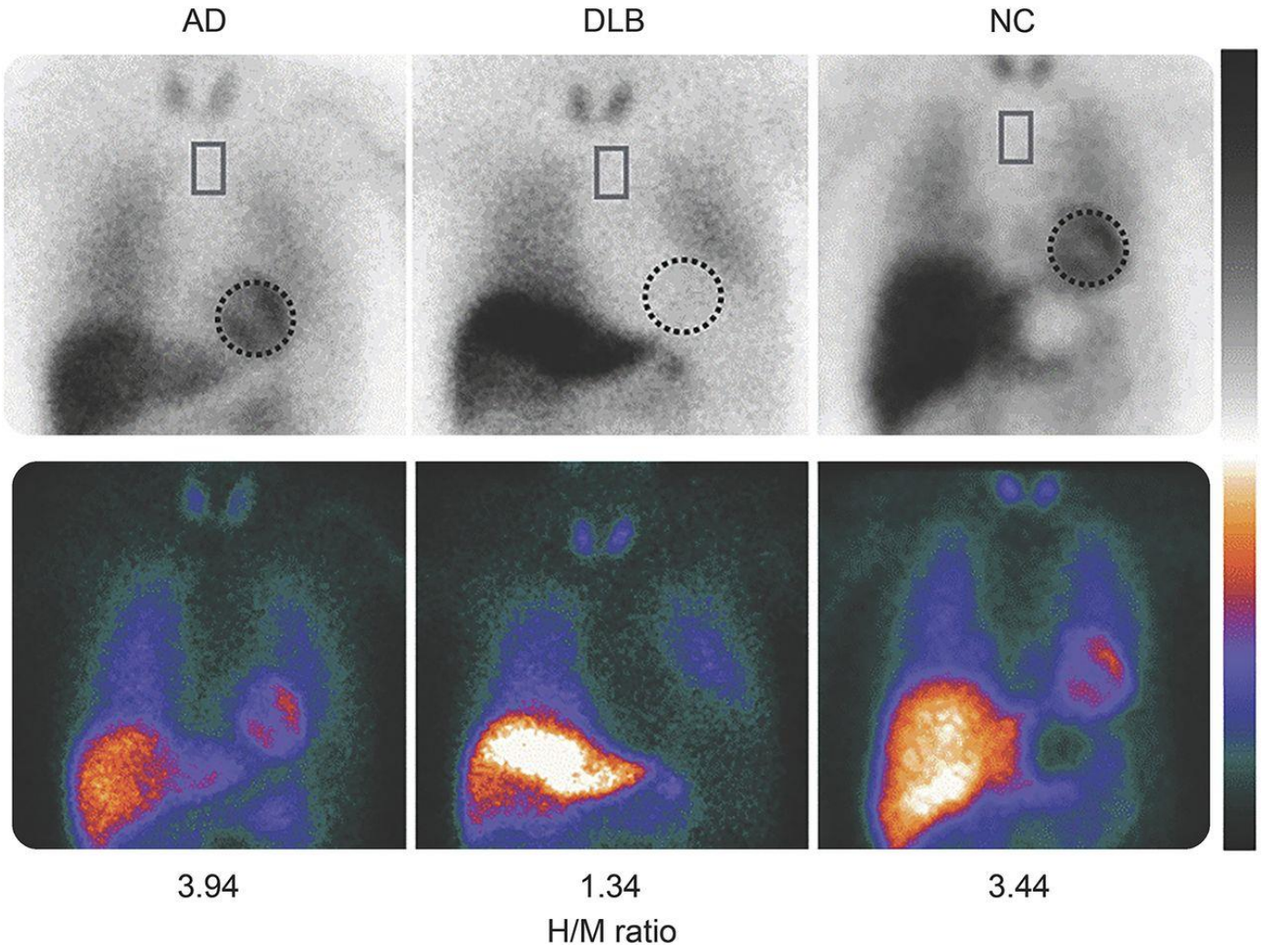


Ian G. McKeith et al. Neurology 2017;89:88-100

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Figure 2 123Iodine-metaiodobenzylguanidine myocardial imaging in patients with Alzheimer disease (AD), dementia with Lewy bodies (DLB), and age-matched normal controls (NC)



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Mild Behavioral Impairment – prodromal feature?

- Changes in behavior or personality that manifest at late age (e.g., >50)
- Persist for > 6 months
- Unrelated to another psychiatric disorder or medical condition, or medication
- five domains: (i) decreased motivation, (ii) affective dysregulation, (iii) impulse control/impulsivity, (iv) social inadequacy, and (v) abnormal perception of thought content/psychotic symptoms

Meta-analysis of anxiety and depression as risk factors for PD

- 11 Case-control studies OR 1.90 (95% CI 1.62-2.22)
- 2 Cohort studies OR 1.79 (95% CI 1.72-1.86)
- Combined OR 1.86 (95% CI 1.64-2.11)

Noyce AJ et al. Ann Neurol 2012;72:893-901

Neuropsychiatric Symptom Burden Across Neurodegenerative Disorders

Table 2. Percentage of Participants in Each Cohort (AD, ALS, FTD, PD, and CVD) Showing Symptoms (Mild, Moderate, or Severe) Evaluated on the NPI-Q.

NPI-Q Symptom	AD ($n = 126$)	ALS ($n = 40$)	FTD ($n = 53$)	PD ($n = 140$)	CVD ($n = 161$)	*P* value*
Delusions	8.7%	2.5%	13.5%	2.9%	7.3%	.06
Hallucinations	4.3%	2.5%	3.8%	9.5%	2.0%	.06
Aggression	28.2%	22.5%	40.4%	17.4%	24.5%	.02
Depression	32.5%	37.5%	37.3%	37.7%	25.8%	.2
Anxiety	25.6%	17.5%	46.2%	21.7%	15.9%	<.001
Euphoria	5.1%	5.0%	15.4%	2.9%	3.3%	.02
Apathy	38.3%	27.5%	56.9%	23.2%	23.2%	<.001
Disinhibition	23.0%	7.5%	43.1%	12.3%	14.6%	<.001
Irritability	37.9%	22.5%	59.6%	27.5%	38.0%	<.001
Motor	12.8%	12.8%	30.8%	5.0%	8.6%	<.001
Night-time behaviours	22.8%	26.3%	53.8%	52.9%	33.6%	<.001
Appetite	28.0%	41.0%	55.8%	27.5%	22.5%	<.001

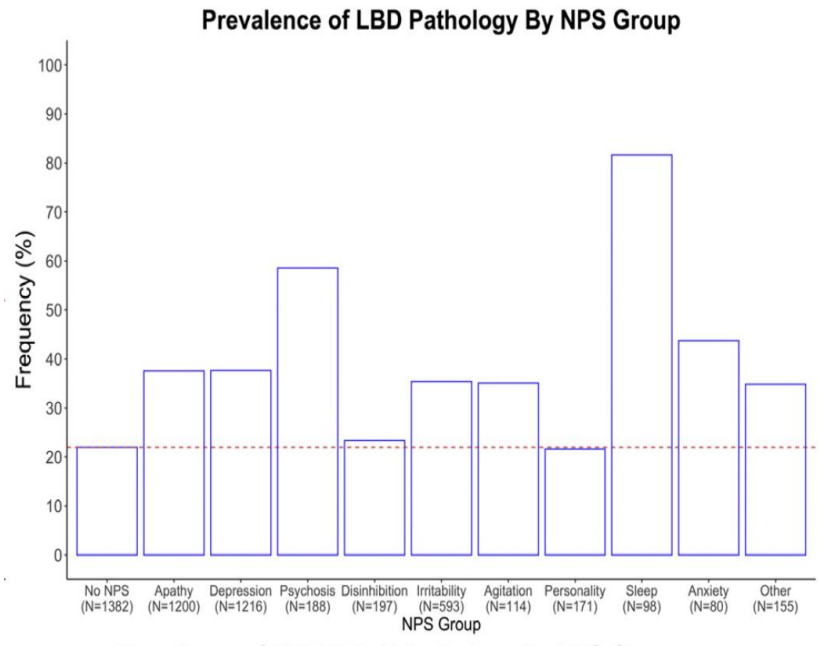
**P* values derived from chi-squared tests.

Abbreviations: NPI-Q = Neuropsychiatric Inventory Questionnaire; AD = Alzheimer's Disease/Mild Cognitive Impairment; ALS = Amyotrophic lateral sclerosis; FTD = Frontotemporal dementia; PD = Parkinson's disease; CVD = Cerebrovascular disease.

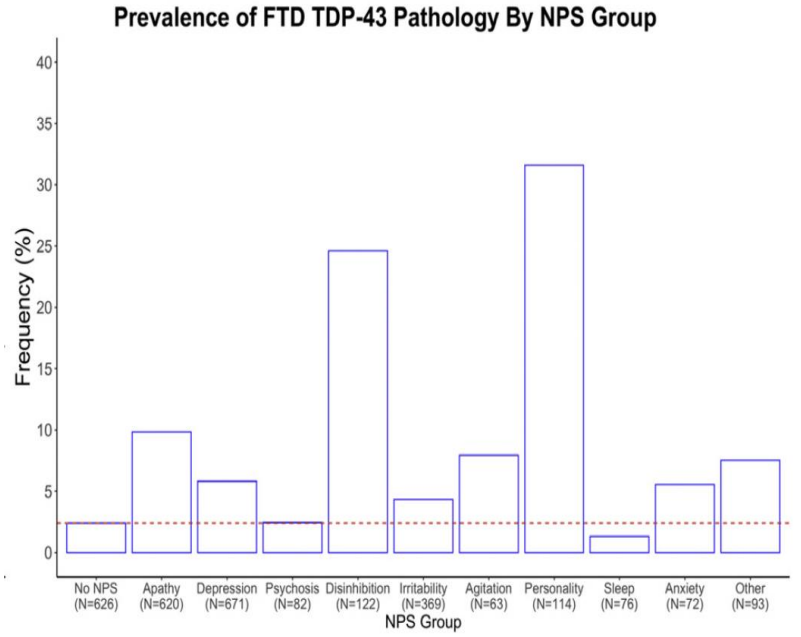
Kapustin D, Zarei S, Wang W; ONDRI investigators. Neuropsychiatric Symptom Burden across Neurodegenerative Disorders and its Association with Function. Can J Psychiatry. 2023 May;68(5):347-358. doi: 10.1177/07067437221147443. Epub 2023 Jan 13. PMID: 36637224.

Are Neuropsychiatric Symptoms Associated with Specific Neuropathological Diagnoses?

Psychosis and RBD:
Lewy Body Pathology



Disinhibition and Personality Change:
FTD with TDP-43 and Tau Pathology



Shaw JS, Leoutsakos JM, Rosenberg PB. The Relationship Between First Presenting Neuropsychiatric Symptoms in Older Adults and Autopsy-Confirmed Memory Disorders. Am J Geriatr Psychiatry. 2024 Jan 17:S1064-7481(24)00015-0. doi: 10.1016/j.jagp.2024.01.015. Epub ahead of print. PMID: 38296755.

Does mixed pathology matter?

TABLE 3 Association between neuropathological diagnoses and neuropsychiatric symptoms (n = 1027)

Symptom	Neuropathological diagnostic classification	RRR (95% CI)	*P* value
Hallucination	NP	1 (reference)	
	AD	3.53 [2.04–6.12]	**<.001**
	LBD	3.91 [1.87–8.16]	**<.001**
	AD + LBD	16.9 [7.00–40.9]	**<.001**
Agitation	NP	1 (reference)	
	AD	2.63 [1.67–4.16]	**<.001**
	LBD	0.99 [0.43–2.28]	.98
	AD + LBD	3.08 [1.25–7.61]	**.02**
Depression	NP	1 (reference)	
	AD	1.92 [1.28–2.88]	**.002**
	LBD	1.89 [1.04–3.43]	**.04**
	AD + LBD	1.99 [0.87–4.55]	.10
Delusion	NP	1 (reference)	
	AD	5.02 [2.71–9.28]	**<.001**
	LBD	2.76 [1.06–7.20]	**.04**
	AD + LBD	4.98 [1.68–14.8]	**.004**
Apathy	NP	1 (reference)	
	AD	1.90 [1.21–2.98]	**.005**
	LBD	1.38 [0.68–2.77]	.37
	AD + LBD	3.25 [1.40–7.58]	**.006**
Number of symptoms in NPI	NP	1 (reference)	
	AD	1.31 [1.20–1.42]	**<.001**
	LBD	1.15 [1.01–1.31]	**.03**
	AD + LBD	1.47 [1.27–1.71]	**<.001**

Gibson LL, Grinberg LT, Ffytche D, et al. Neuropathological correlates of neuropsychiatric symptoms in dementia. Alzheimers Dement. 2023 Apr;19(4):1372-1382. doi: 10.1002/alz.12765. Epub 2022 Sep 23. PMID: 36150075; PMCID: PMC10033459.

Anxiety in Parkinson's Disease

Anxiety is common in Parkinson's disease and can significantly impact quality of life.
It can affect both the mind and body, often alongside motor symptoms.

Mental / Emotional Symptoms



Persistent worry or panic
"What if my symptoms get worse?"



Ruminating and 'overthinking'
"I keep going over things in my mind."



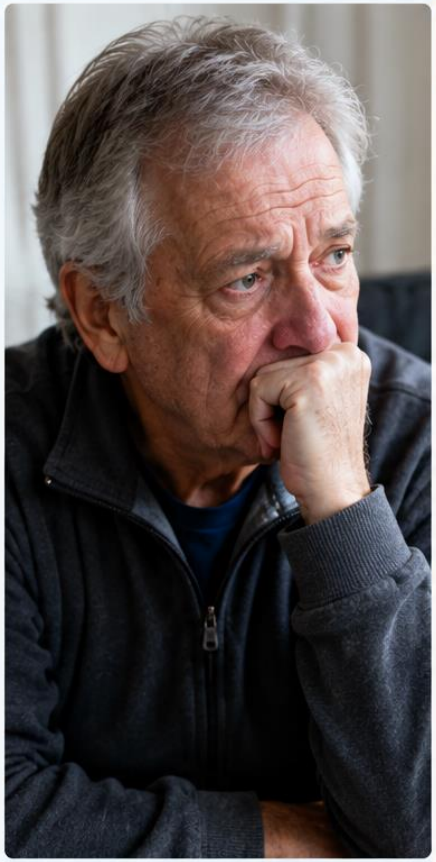
Inability to relax
"I can't seem to turn my mind off."



Feeling restless or tense
"I feel on edge all the time."



Difficulty concentrating or indecisive
"I can't focus, and it's hard to make decisions."



Physical Symptoms



Muscle tension or aches
"My muscles feel tight and sore."



Trembling
"My hands won't stop shaking."



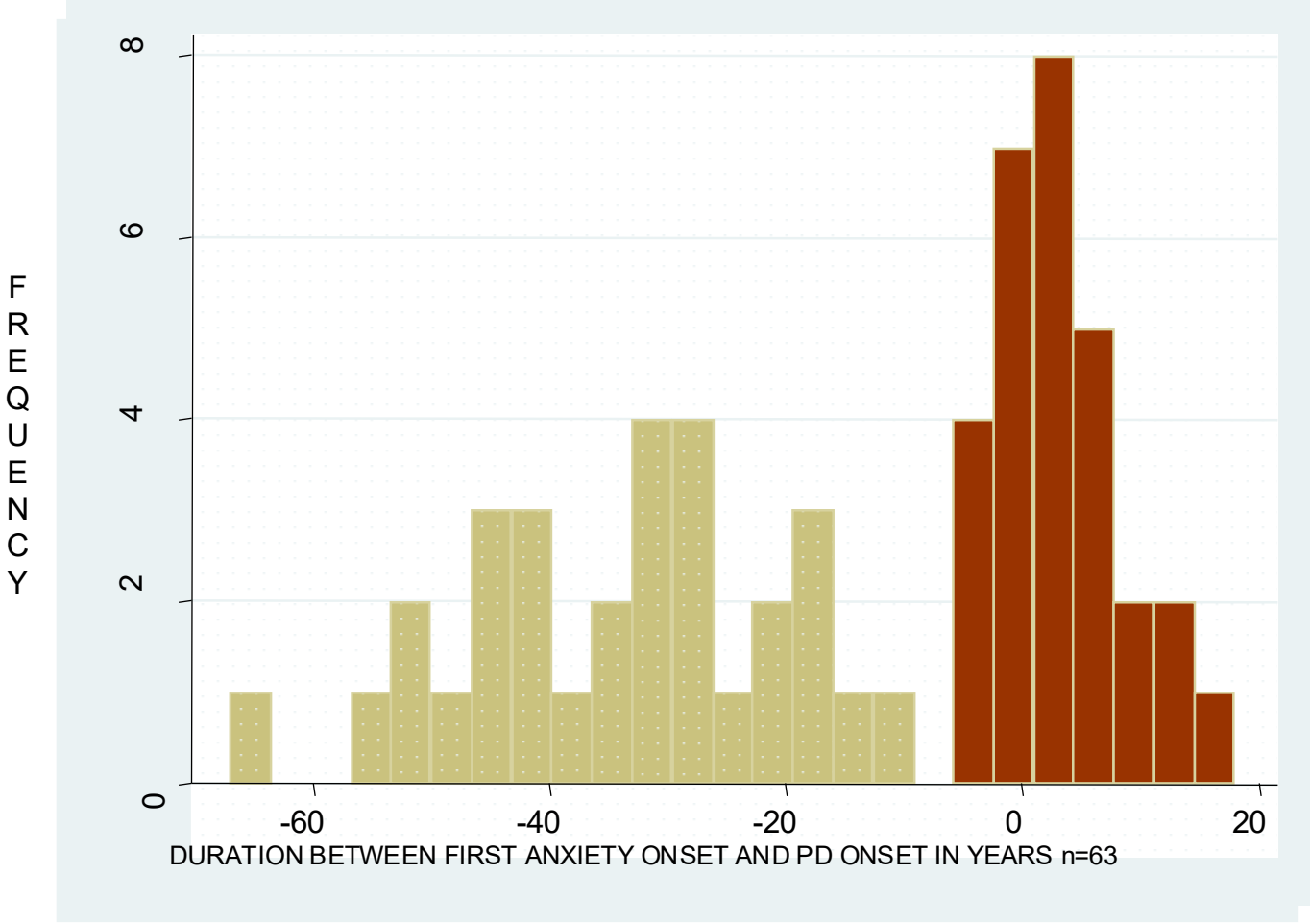
Sweating
"I'm sweating even when it's not hot."



Diarrhea or upset stomach
"I have frequent stomach upset or need to use the bathroom urgently."

Anxiety in Parkinson's disease is real, treatable, and deserves attention.

First Anxiety Disorder Onset Relative to Parkinson's Onset



Bimodal distribution of anxiety disorder onset compared to PD onset

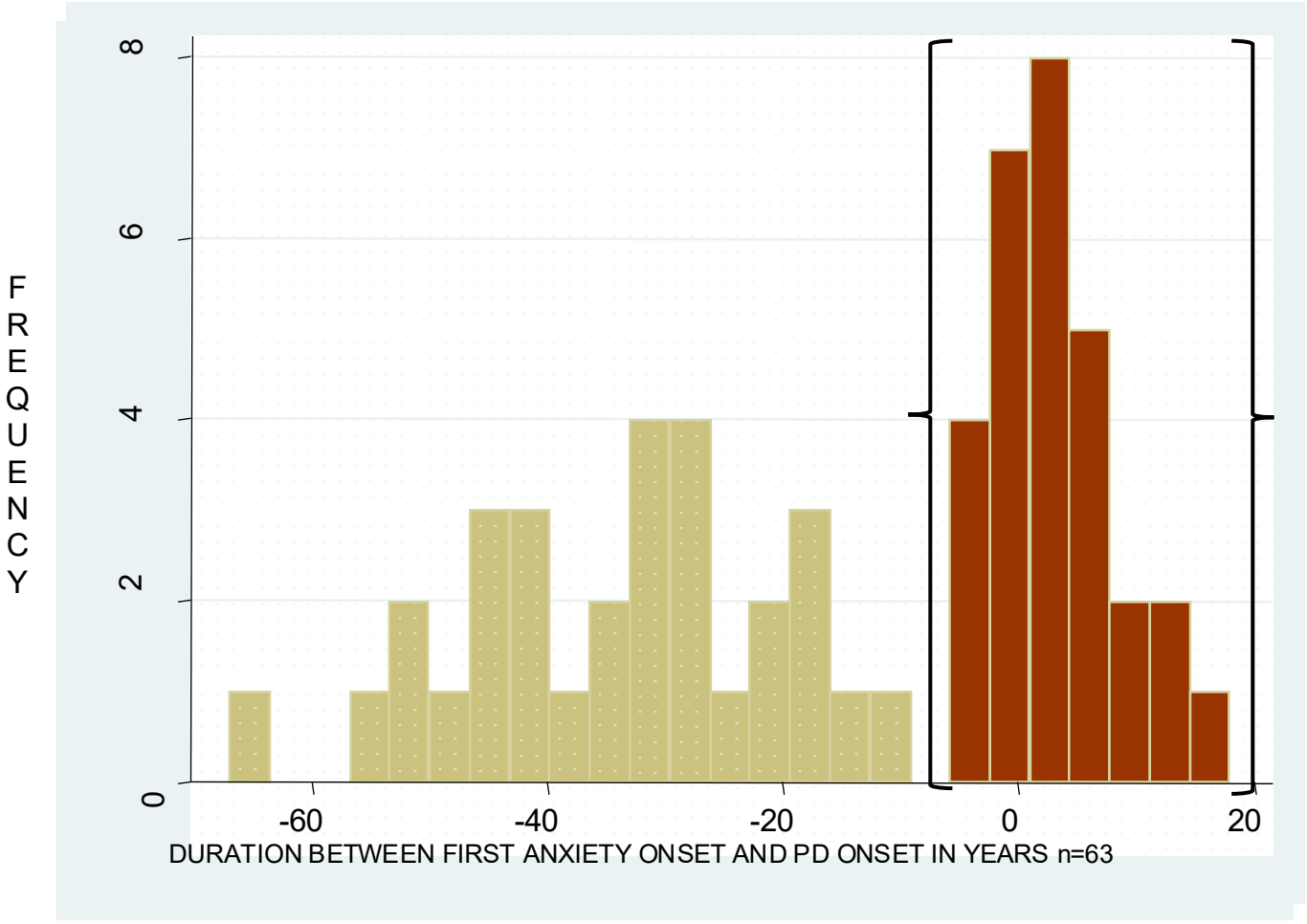
Pontone et al 2009

Anxiety as a ‘premotor’ symptom of Parkinson’s disease

- Anxiety **disorders** are associated with later development of PD: OR 2.2 (95% CI 1.4-3.4; p=0.0003) up to 20 years before PD onset
- **Symptoms** of phobic anxiety are associated with increased risk of PD: RR 1.5 (95% CI 1.0-2.1; p=0.01)
- Anxious **personality** was associated with increased risk of PD: HR 1.63 (95% CI 1.16-2.27; p=0.004)

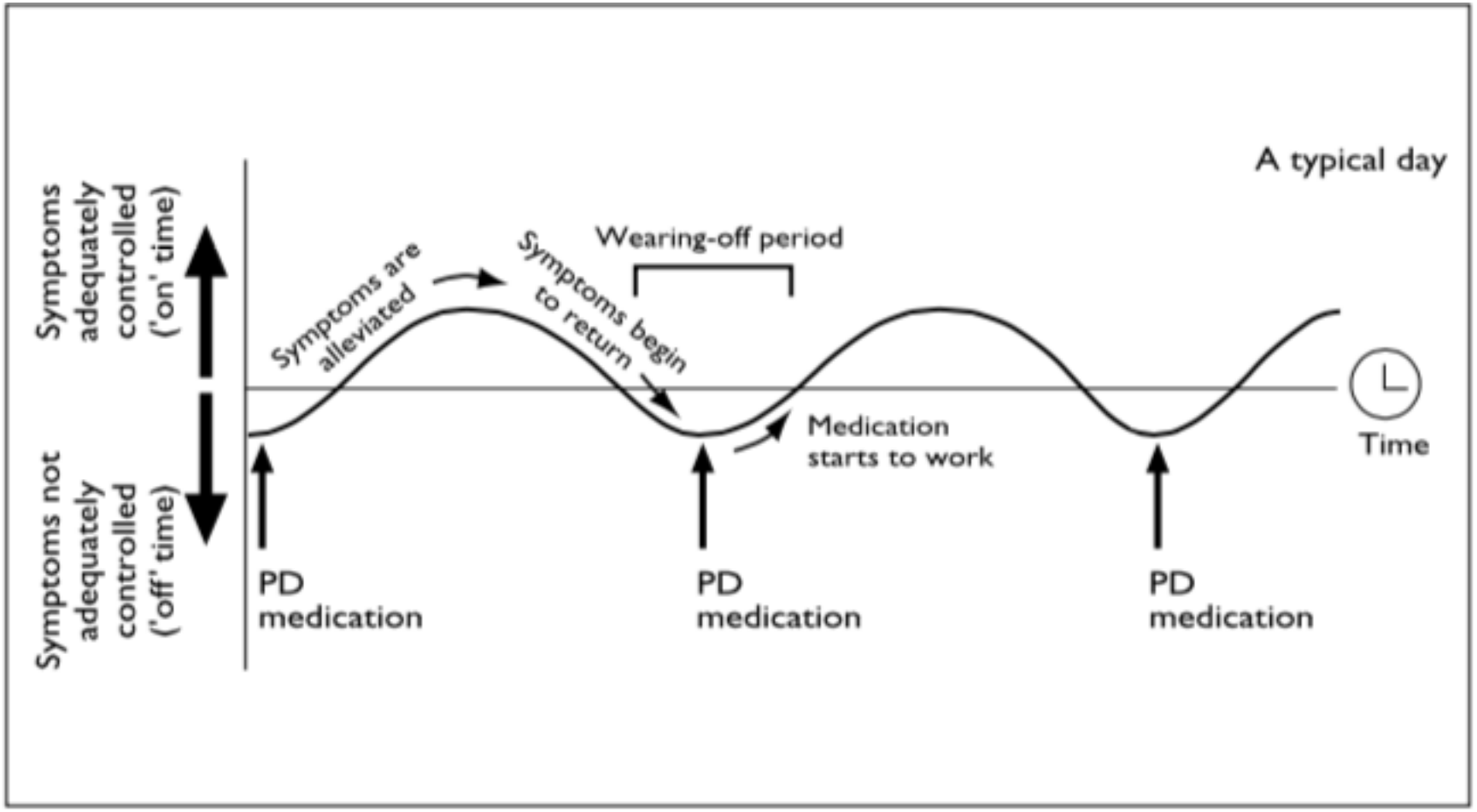
Shiba et al 2000, Weisskopf et al 2003, Bower et al 2010

First Anxiety Disorder Onset Relative to PD Onset – "fluctuation associated anxiety"



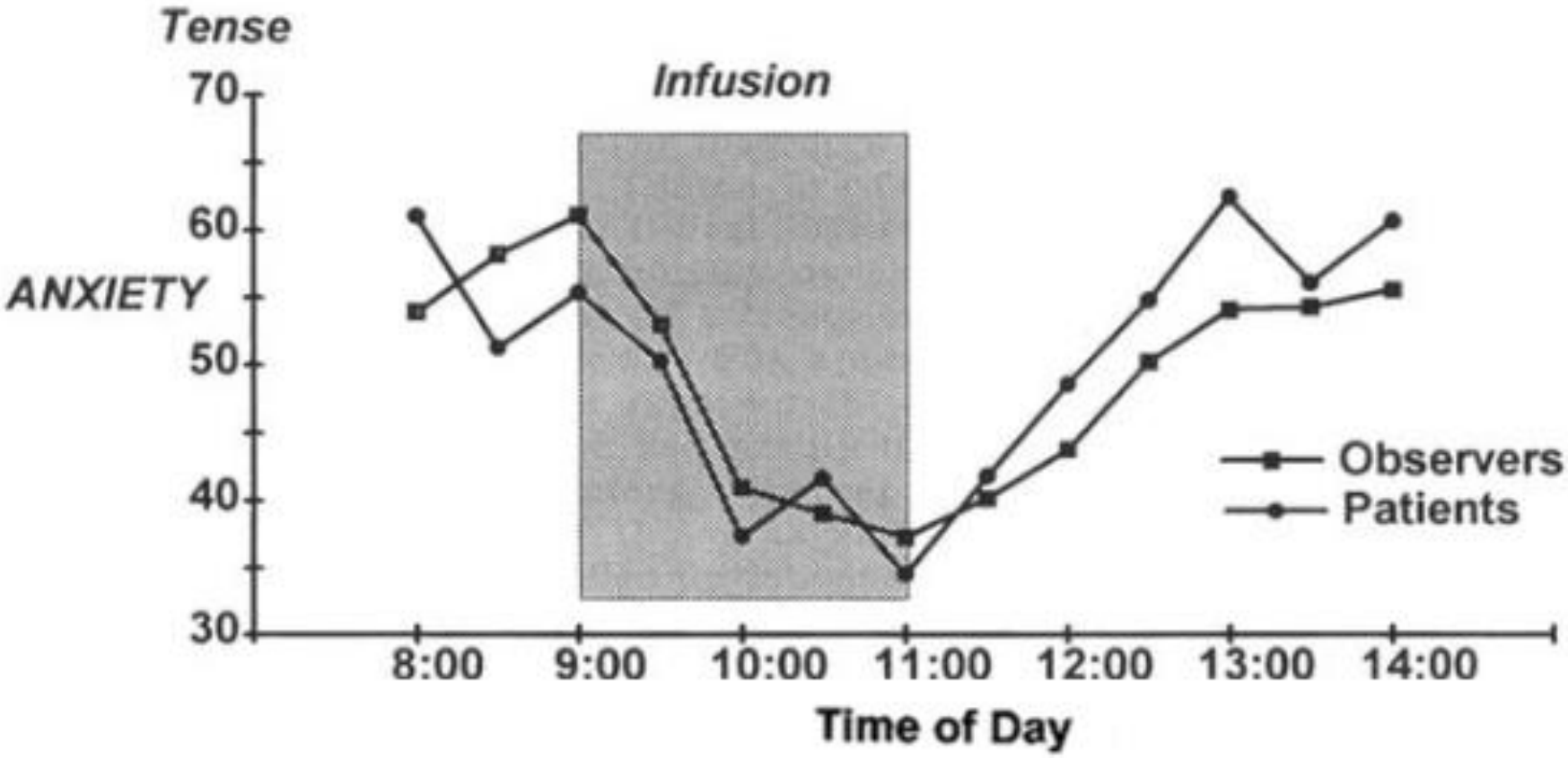
Bimodal distribution of anxiety disorder onset compared to PD onset

Dopaminergic medication on-off fluctuations in PD



Stacey M. and Hauser R. 2007

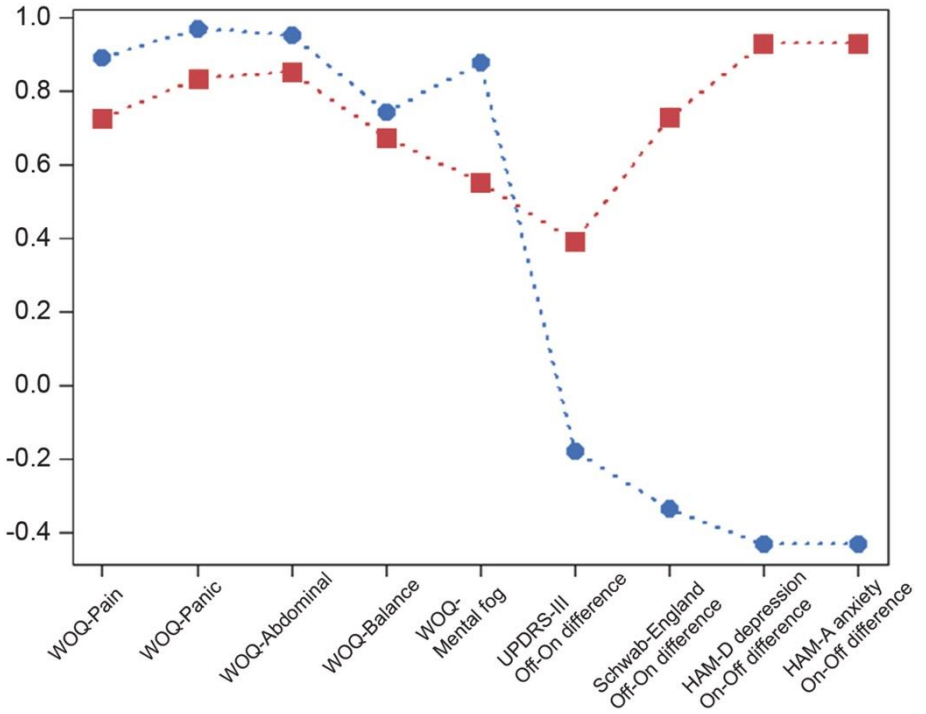
Anxiety fluctuation with levodopa infusion



Maricle RA et al 1995

”Anxious fluctuators”

- 200 PD assessed in on- and off-dopamine medication state
- 31% 3-fold worsening of anxiety in off-state
- Depression, motor function, and ADL functioning also worsened
- Family hx of anxiety and male sex increased odds of anxious fluctuations



Pontone GM, Perepezko KM, Hinkle JT, Gallo JJ, Grill S, Leoutsakos JM, Mills KA, Weiss HD, Mari Z. 'Anxious fluctuators' a subgroup of Parkinson's disease with high anxiety and problematic on-off fluctuations. Parkinsonism Relat Disord. 2022 Dec;105:62-68.

Anxiety treatments

- Best evidence (pharmacologic) – no randomized controlled trials for the treatment of anxiety in PD have demonstrated efficacy
- Meta-analysis including secondary outcomes from RCTs – (Berry AJ et al 2026), SSRI>TCA>SNRI>mirtazapine>atomoxetine
- Best evidence (non-pharmacologic) – cognitive behavioral therapy >> rTMS mixed evidence >> GPi and STN DBS mixed evidence (no studies of tDCS for PD anxiety)

Berry AJ, Costello H, Jesús S, Price G, Jha A. Management of Anxiety in Parkinson's Disease. Mov Disord Clin Pract. 2025 Oct;12(10):1490-1501. doi: 10.1002/mdc3.70144. Epub 2025 Jun 26. PMID: 40568748; PMCID: PMC12528972.

Pharmacologic Treatment of Anxiety in Parkinson's Disease

1. First Line Treatment

Start with non-pharmacologic and pharmacologic therapy:

Behavioral Activation (Exercise + Socialization)
- Regular physical activity
- Increased social engagement

+

SSRI
(e.g., sertraline, escitalopram, citalopram)

+

CBT or Mindfulness-Based Therapy or Relaxation Therapy
- Cognitive behavioral therapy
- Mindfulness-based therapy
- Relaxation techniques

If first line treatment fails

2. Second Line Treatment

Choose one of the following options:

Tricyclic Antidepressant
(e.g., nortriptyline, desipramine)

OR

SNRI
(e.g., venlafaxine, duloxetine)

OR

Mirtazapine
(especially if sleep or appetite issues are prominent)

If second line treatment fails

3. Combination Treatment

Add one of the following to the antidepressant:

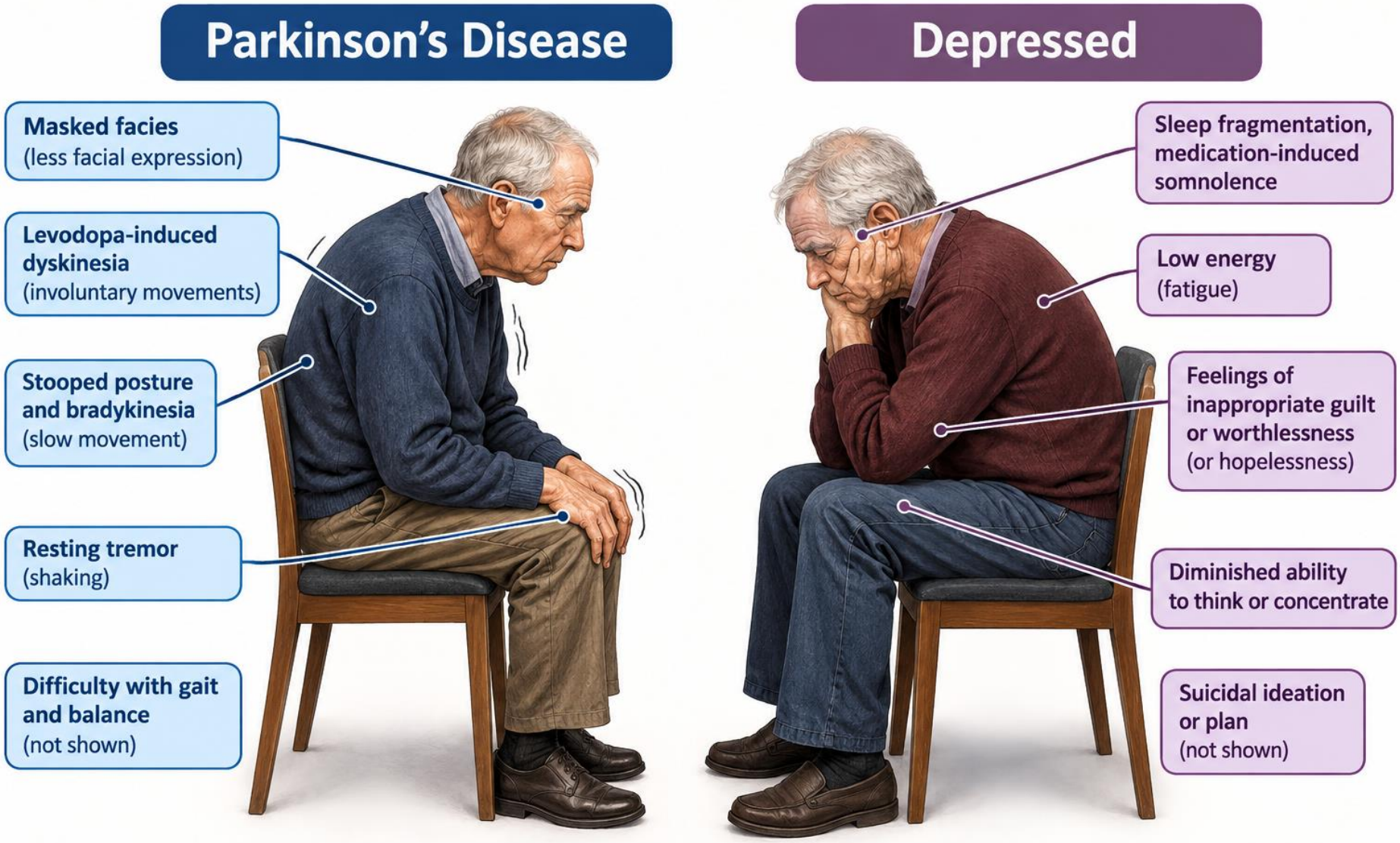
Clonazepam or Lorazepam
(benzodiazepine)

OR

Quetiapine
(at low dose)

OR

Atomoxetine
(noradrenergic agent)


Parkinson's Disease
Masked facies
(less facial expression)
Levodopa-induced dyskinesia
(involuntary movements)
Stooped posture and bradykinesia
(slow movement)
Resting tremor
(shaking)
Difficulty with gait and balance
(not shown)
Depressed
Sleep fragmentation, medication-induced somnolence
Low energy
(fatigue)
Feelings of inappropriate guilt or worthlessness
(or hopelessness)
Diminished ability to think or concentrate
Suicidal ideation or plan
(not shown)

Parkinson's Foundation

- **Parkinson's Outcomes Project**, a longitudinal look at which treatments produce the best health outcomes in PD n=12,000+
- **The impact of depression on quality of life is almost twice that of the motor impairments**

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

The longitudinal impact of depression on disability in Parkinson disease

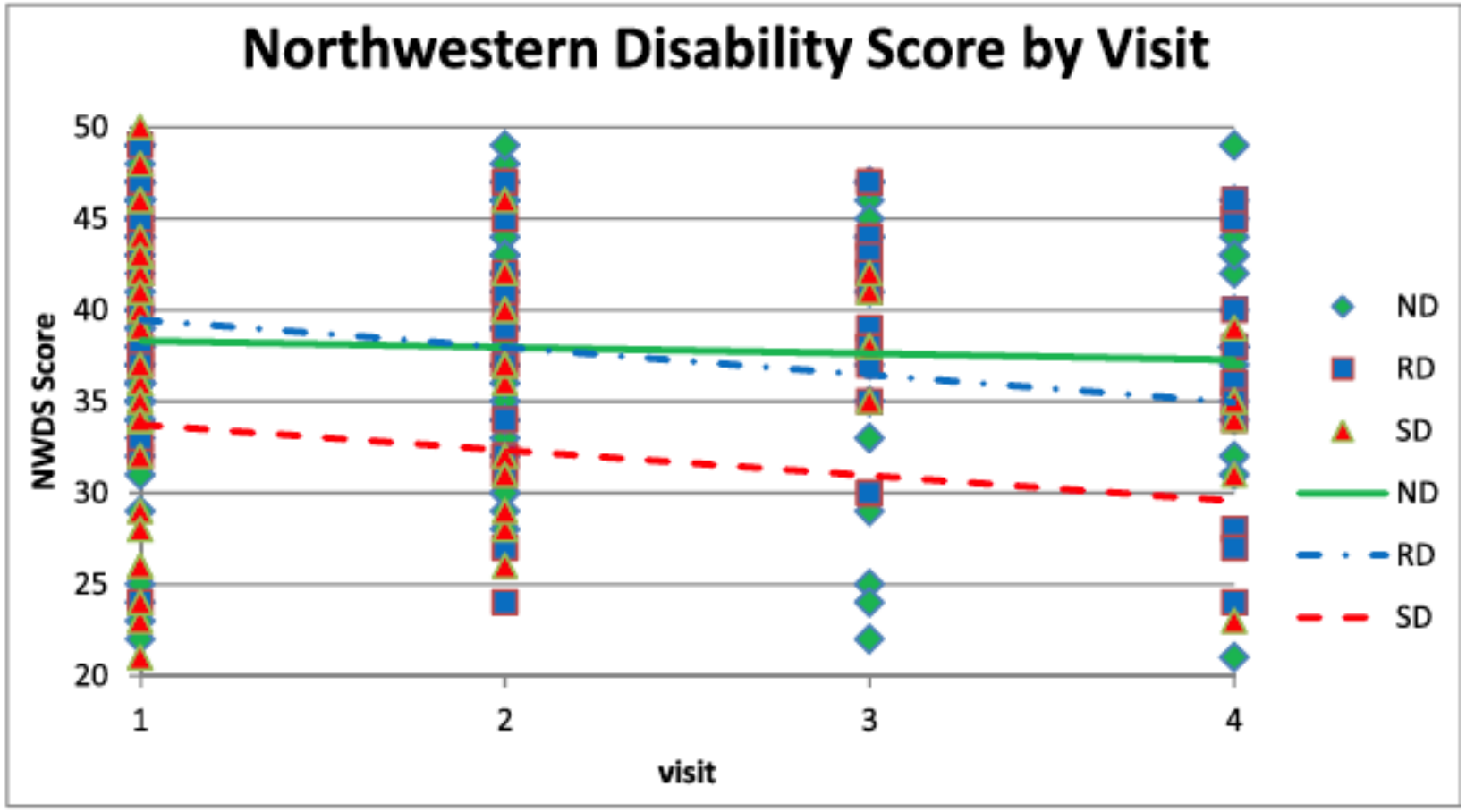
Gregory M. Pontone[1,2], Catherine C. Bakker[1,2], Shaojie Chen[3], Zoltan Mari[2,4], Laura Marsh[1,2†,‡], Peter V. Rabins[2,1], James R. Williams[1§] and Susan S Bassett[1,2]

Objective: This study examined the association between physical disability and DSM-IV-TR depression status across six years

Methods: 137 adults with idiopathic PD. A generalized linear mixed model with Northwestern Disability Scale score as dependent variable to determine the effect of baseline depression status on disability

Results: 43 depressed at baseline vs 94 without depression. Symptomatic depression predicted greater disability compared to both never depressed (p=0.0133) and remitted depression (p=0.0009) after controlling for sex, education, dopamine agonist use, and motor fluctuations.

Longitudinal impact of depression on disability in PD (Pontone et al 2016)



ND=never depressed, RD=remitted depression, SD=symptomatically depressed

Treatment Algorithm for Depression in Parkinson's Disease

Diagnosis and Initial Assessment

- Confirm diagnosis of depression (screening tools, clinical interview)
- Assess severity (mild, moderate, severe) and suicide risk
- Evaluate contributing factors (e.g., motor symptoms, medication effects, cognitive impairment, sleep disturbance, pain, social isolation)
- Review current PD medications and potential drug interactions

Step 1: First-Line Treatment

Psychotherapy

- Cognitive behavioral therapy (CBT)
- Behavioral activation
- Supportive therapy / psychoeducation

AND/OR

Antidepressant Medication

- SSRI (e.g., sertraline, escitalopram)
- SNRI (e.g., venlafaxine, duloxetine)
- Mirtazapine (may help with sleep/appetite)
- Bupropion (consider if low energy/apathy)

Start with a low dose and titrate slowly. Monitor for efficacy and tolerability, including effects on motor symptoms, sleep, and cognition.

Step 2: Inadequate Response (after 6–8 weeks at therapeutic dose)

Optimize Current Treatment

- Ensure adequate dose and adherence
- Consider switching to another first-line agent
- Address residual symptoms (e.g., sleep, anxiety)

OR

Augmentation Strategies

- Add psychotherapy (if not already)
- Consider bupropion (for apathy/low energy)
- Consider mirtazapine (for sleep/appetite)
- Consider atypical antipsychotic if psychosis present or in refractory cases
- If refractory, consider ECT (in severe cases)

Step 3: Persistent Symptoms or Severe Depression

Advanced / Refractory Strategies

- Switch to a different antidepressant class
- Consider combination therapy (e.g., SSRI + bupropion)
- Augmentation with atypical antipsychotic (e.g., quetiapine), — monitor for motor side effects
- Consider neuromodulation (e.g., ECT) in severe, refractory, or life-threatening cases

Continue Multidisciplinary Care

- Neurology (PD management)
- Psychiatry (medication management)
- Psychology (CBT/support)
- Physical/occupational therapy (function)
- Social work (resources, support)

Ongoing Monitoring

Regularly reassess mood, motor symptoms, side effects, and quality of life.

Key Considerations

Special Considerations in PD

- Overlap between depression and motor symptoms
- Higher risk of medication side effects (e.g., orthostasis, confusion, hallucinations)
- Impact on cognition and function

Medications to Use with Caution or Avoid

- Tricyclic antidepressants (anticholinergic effects)
- Paroxetine (anticholinergic side effects and potential withdrawal syndrome)
- Benzodiazepines (risk of sedation, falls, cognitive impairment)

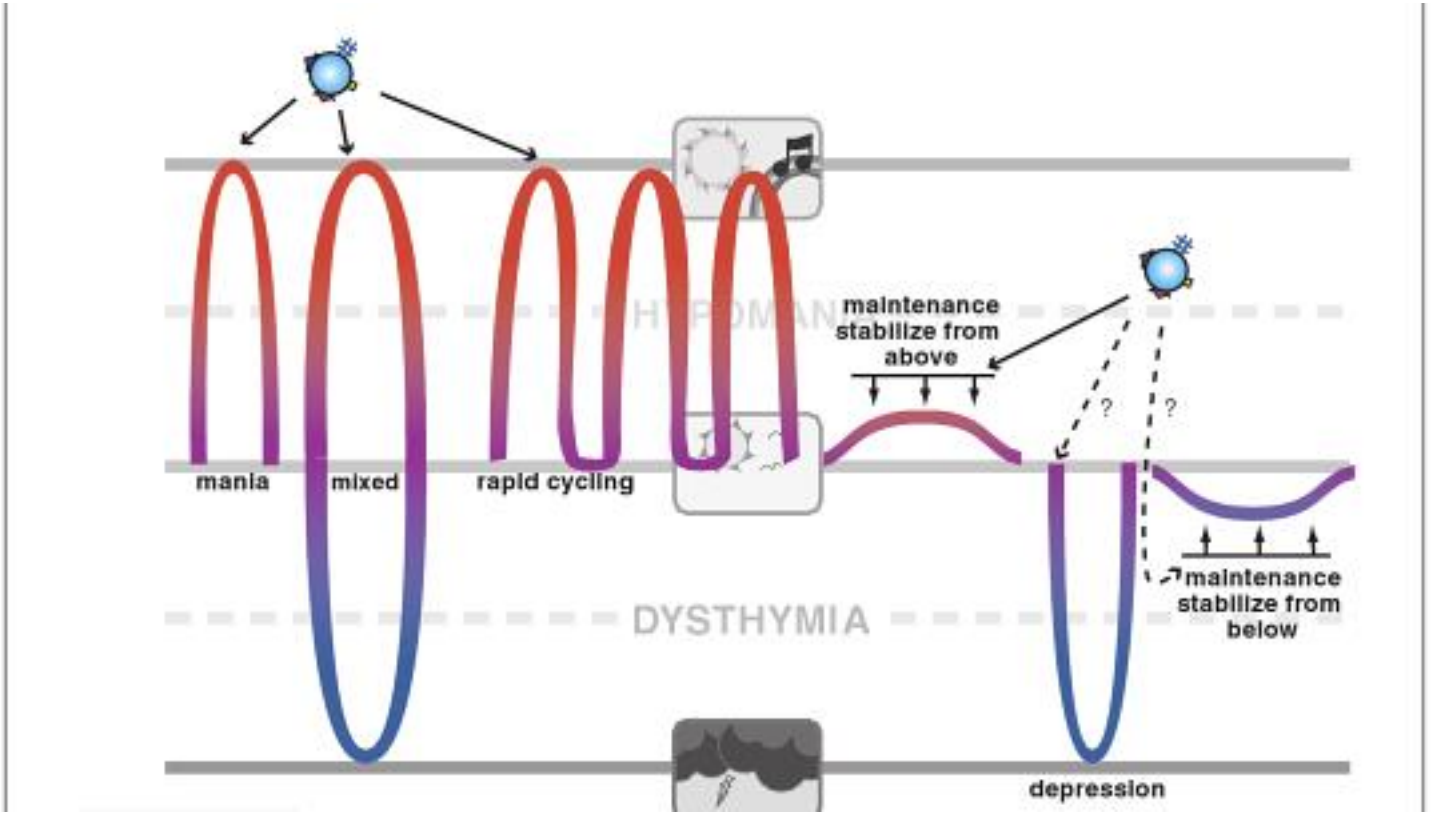
Treatment Goals

- Improve mood and anxiety
- Enhance quality of life
- Maintain motor function
- Minimize side effects
- Address comorbid symptoms (sleep, apathy, cognitive issues)

When to Seek Urgent Help

- Suicidal ideation or behavior
- Severe functional decline
- Psychosis or severe agitation

Bipolar disorder: mood cycling



Stahl SM 2004

Bipolar Affective Disorder

- Lifetime prevalence up to 4% for any BPAD, type I is up to 2%
- Lifetime risk of suicide is up to 20%
- Alternating depressive and manic episodes; depression is 3-times more common than mania
- No central neuropathology or pathophysiology has been identified and there is no generally accepted animal model
- Criteria for BPAD I, one or more manic episodes

Bostwick and Pankratz 2000

Bipolar disorder in Parkinson's disease

- Seven studies included 4 374 211 participants
- A previous diagnosis of bipolar increased the likelihood of a subsequent diagnosis of idiopathic PD (odds ratio, 3.35; 95% CI, 2.00-5.60; I^2 = 92%)
- An important confounder when evaluating risk of PD in psychiatric disorders is the usage of psychotropic medications.
- The standard treatment for bipolar includes mood stabilizers (lithium and antiepileptic drugs) and antipsychotic medications which can contribute to drug-induced parkinsonism, which may be clinically indistinguishable from PD
- Long term treatment with antiepileptic drugs for mood stabilization in patients with late onset bipolar disease was associated with an increased risk of PD, while taking lithium was not

Faustino PR, Duarte GS, Chendo I, Castro Caldas A, Reimão S, Fernandes RM, Vale J, Tinazzi M, Bhatia K, Ferreira JJ. Risk of Developing Parkinson Disease in Bipolar Disorder: A Systematic Review and Meta-analysis. JAMA Neurol. 2020 Feb 1;77(2):192-198. Huang MH, Cheng CM, Hsu JW, Bai YM, Su TP, Li CT, Tsai SJ, Chan YE, Chen MH. Risk of subsequent Parkinson's disease among patients with bipolar disorder or major depression: A nationwide longitudinal study in Taiwan. Psychiatry Clin Neurosci. 2025 Jan;79(1):29-36.

Impulse Control Disorders in Parkinson's Disease

Pathological Gambling



Pathological gambling: Compulsive, repetitive gambling despite negative consequences (e.g., financial loss, strained relationships).

Hypersexuality



Hypersexuality: Increased sexual thoughts, urges, and behaviors (e.g., multiple partners, risky sexual behavior, inappropriate advances).

Impulsive Buying



Impulsive buying: Unplanned, excessive purchases of goods or services (e.g., luxury items, electronics) despite financial harm.

Binge Eating



Binge eating: Recurrent episodes of consuming large amounts of food in a short period of time, with a sense of loss of control.

Synthesis of Results: Interventions for Impulse Control Behaviors (ICBs) in Parkinson's Disease

Intervention (comparator)	Key Outcomes	Effect Estimate (95% CI)	Participants (n)
Amantadine vs. placebo	• Adverse events *One study evaluated amantadine; did not assess other review outcomes.*	**RR 4.50** (0.25 to 81.76) *Very uncertain evidence*	**17**
Naltrexone vs. placebo	• Change in ICB severity • Adverse events (dizziness, nausea, headache, blood pressure changes)	**MD −7.37** (−14.18 to −0.56) *Low-certainty evidence* • Dizziness: **RR 4.00** (0.48 to 33.22) • Nausea: **RR 15.00** (0.90 to 248.78) • Headache: **RR 1.25** (0.38 to 4.10) • Blood pressure changes: **RR 1.67** (0.72 to 3.86)	**50** (*ICB severity*) **48** (adverse events)
Clonidine vs. placebo	ICB outcomes • Change in frequency of ICBs • Change in severity of ICBs Adverse events • Sleepiness, falls, nausea, orthostatic hypotension, restless legs syndrome, fatigue, asymptomatic bradycardia Other outcomes • Quality of life, depression, anxiety	**RR 0.89** (0.54 to 1.47) **MD −7.40** (−14.10 to −0.70) *Very uncertain evidence* **RRs 0.53–3.15** (various 95% CIs) *Very uncertain evidence* **MD −13.60** (−29.03 to 1.83) [QoL] **MD 1.20** (−3.00 to 5.40) [depression] **MD 4.10** (−2.46 to 10.66) [anxiety] *Very uncertain evidence*	**39** (all outcomes)
CBT vs. wait-list control	• Change in ICB frequency • Change in ICB severity	**RR 0.79** (0.50 to 1.26) **MD −3.80** (−7.75 to 0.15) *Low-certainty evidence*	**42** (frequency) **31** (severity)

Key Takeaways

- Evidence is limited and generally of low or very low certainty.
- No clear evidence of benefit or harm for any intervention.
- Studies were small, heterogeneous, and precluded meta-analysis.

Risk of Bias

- All 4 studies were judged to have some concerns or a high risk of bias overall.

Overall Conclusion

- The available evidence is insufficient to support firm conclusions regarding the comparative efficacy or safety of amantadine, naltrexone, clonidine, or CBT for ICBs in Parkinson's disease.

Abbreviations

RR = risk ratio
MD = mean difference
CI = confidence interval
ICB = impulse control behavior
QoL = quality of life

Note: Effect estimates are from individual studies (no meta-analysis). "Very uncertain" indicates very low certainty of evidence; "low-certainty" indicates low certainty of evidence.

Mantovani E, Martini A, Purgato M, Tamburin S. Pharmacological and non-pharmacological treatments for impulsive-compulsive behaviors in Parkinson's disease. Cochrane Database of Systematic Reviews 2025, Issue 10. Art. No.: CD015046.

Apathy in Parkinsonian Diseases

A loss of motivation, not a loss of ability — affecting > 30% of patients

A typical day

"Mr. R, 68, sits by the window most of the day. His medication is working — he can walk and dress without help — yet he no longer gardens, calls his daughter, or watches his team play."



Core features

- Reduced initiative and goal-directed activity
- Loss of interest in hobbies and social contact
- Flat emotional response; little concern or worry
- Needs prompting from family to begin tasks

Apathy ≠ depression

Apathy: indifferent, not distressed, no guilt
Depression: sadness, guilt, hopelessness

Can co-occur; clinical assessment needed

Management: optimize dopaminergic therapy • exercise • structured routines • caregiver education • rivastigmine may help

Apathy in Parkinson's disease

- meta-analysis on apathy prevalence reported a pooled prevalence value of 40%
- accounting for only those with apathy, who had been screened and excluded if they had depression and/or cognitive impairment, the prevalence was 20%
- discrepancies between caregiver and self-rated apathy screening tools
- persons with PD and apathy have limited awareness of their behavior, and therefore assess themselves as less apathetic

Original Article

EPUB

Greater Apathy Associated With Selective Serotonin Reuptake Inhibitor Use in Parkinson's Disease

Rachel N. Schade, MSc [1], Connor B. Etheridge, BA, BS[1], Lauren E. Kenney, MS[1], Adrianna M. Ratajska, MS [1], Katie Rodriguez, MS[1], Francesca V. Lopez, PhD[1], Joshua Gertler, MS[1], Alyssa Ray, BS[1], Lauren Santos, MA[1], Christopher Hess, MD[2], and Dawn Bowers, PhD[1,2]

Objective Apathy, a motivational disorder, is common in Parkinson's disease (PD) and often misdiagnosed as depression. Use of selective serotonin reuptake inhibitors (SSRIs) has been associated with increased apathy in adolescents and adults with depression. Based on observations that serotonin may downregulate dopaminergic systems, we examined the relationship between apathy and SSRI use in individuals with PD.

Methods Medications, mood/motivation scales, and clinical data were collected from a convenience sample of 400 individuals with PD. Depression and apathy were measured using the Beck Depression Inventory-II (BDI-Il) and the Apathy Scale (AS). Antidepressant medications were grouped by mechanism type.

Results Of the 400 PD patients, 26% were on SSRIs. On standard mood/motivation scales, 38% of the sample exceeded clinical cut-offs for apathy and 28% for depression. Results of hierarchical regression analyses revealed that SSRIs were the only antidepressant that were significantly associated with higher apathy scores ($\beta = .1$, $P = .02$). Less education ($\beta = -.1$, $P = .01$) worse cognition ($\beta = -.1$, $P = .01$), and greater depressive symptoms ($\beta = .5$, $P < .001$) were also significant predictors of apathy.

Conclusion These findings suggest that use of SSRIs, but not other antidepressants, is associated with greater apathy in PD. Given the interactive relationship between serotonin and dopamine, the current findings highlight the importance of considering apathy when determining which antidepressants to prescribe to individuals with PD. Similarly, switching a SSRI for an alternative antidepressant in individuals with PD who are apathetic may be a potential treatment for apathy that needs further study.

Keywords

Apathy treatments

Best evidence (pharmacologic) – rivastigmine, piribedil (following STN DBS)

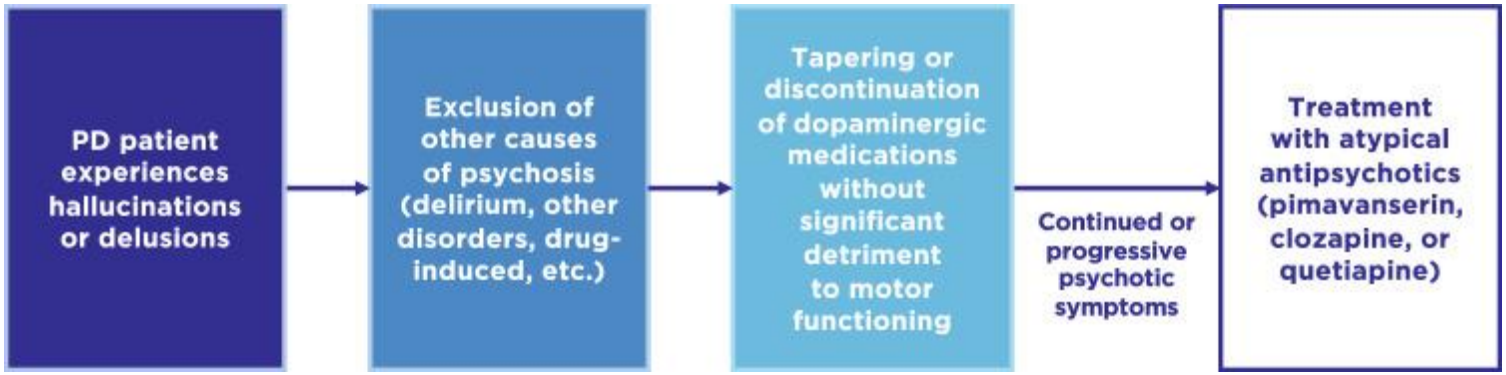
Best evidence (non-pharmacologic) – na

Psychosis in Parkinsonian Diseases

- **Hallucinations** – false sensory perceptions in the absence of external stimuli
- **Delusions** – false, fixed, idiosyncratic belief
- **Attenuated psychotic symptoms or 'minor phenomena'** – illusions, passage hallucinations, sense of presence

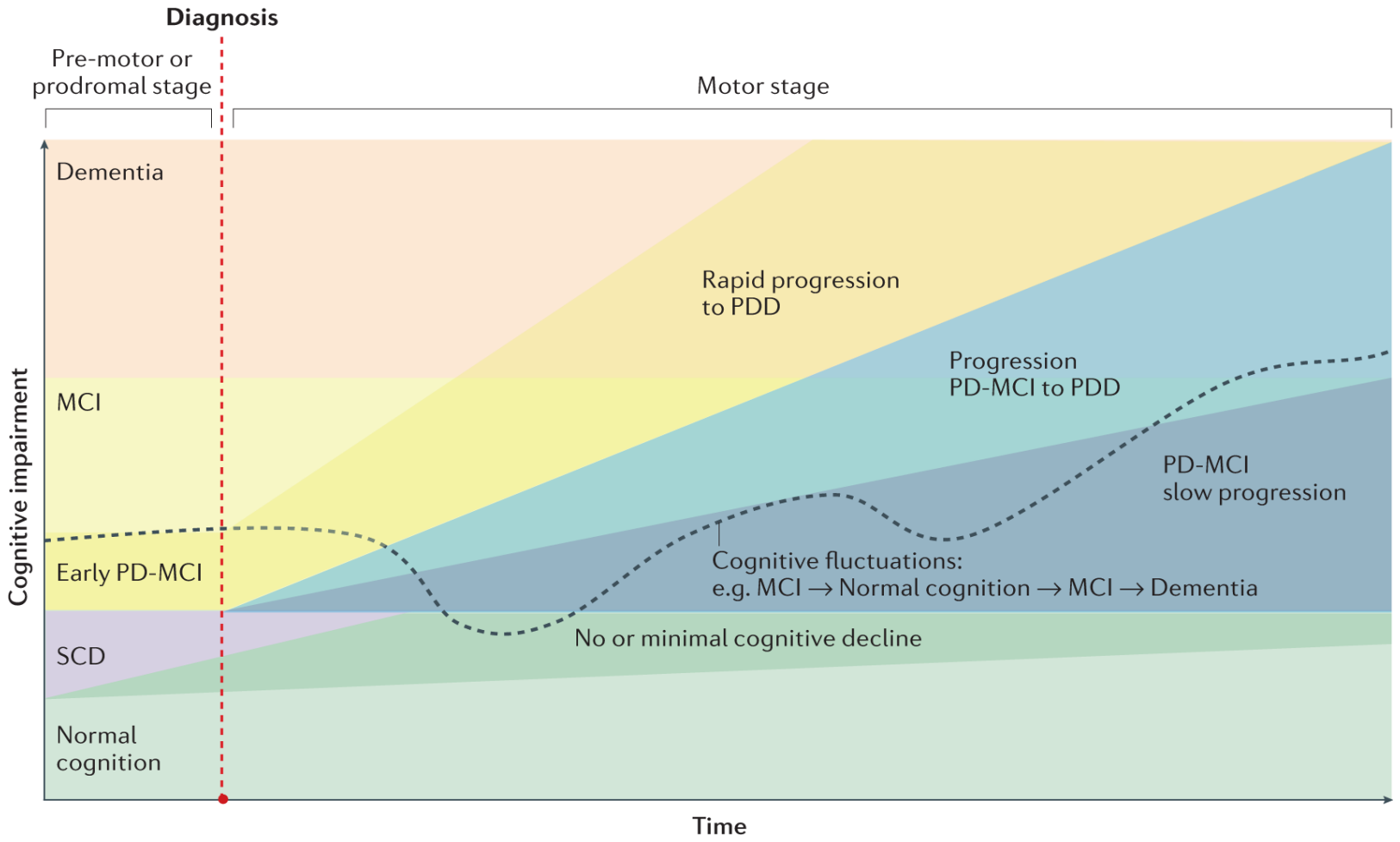


Management strategy for PD Psychosis



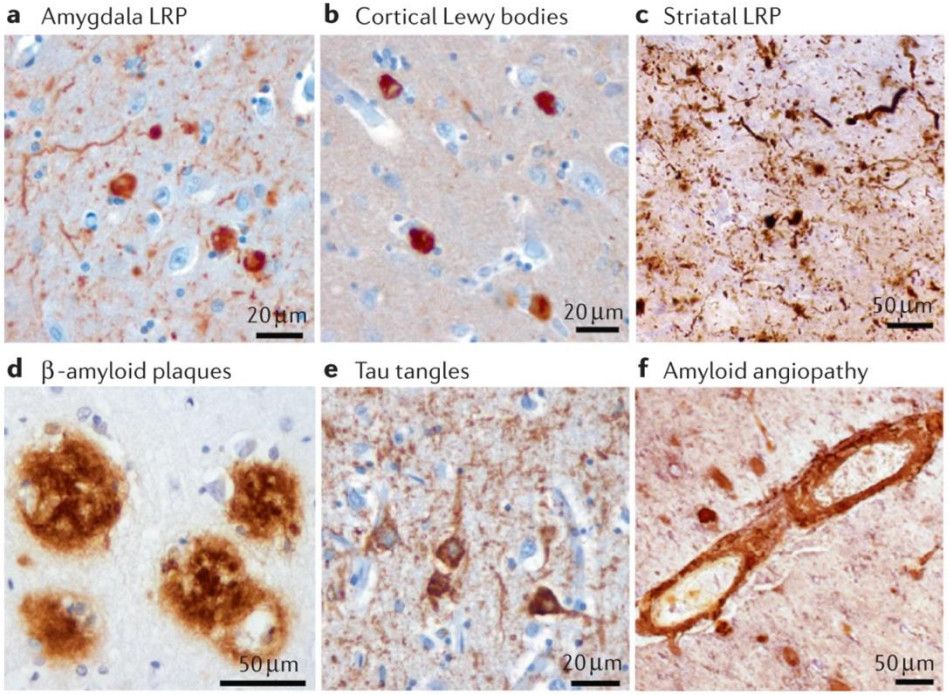
Pagan FL, Schulz PE, Torres-Yaghi Y, Pontone GM. On the Optimal Diagnosis and the Evolving Role of Pimavanserin in Parkinson's Disease Psychosis. CNS Drugs. 2024 May;38(5):333-347. doi: 10.1007/s40263-024-01084-1. Epub 2024 Apr 8.

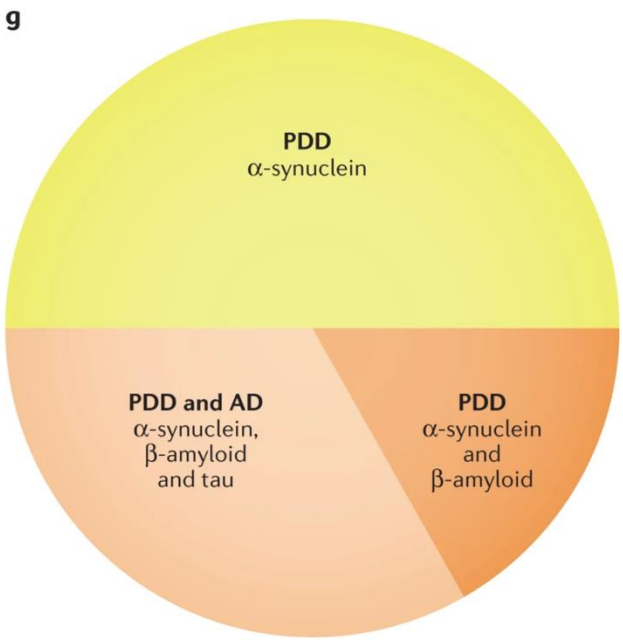
Cognitive change in Parkinson's



Aarsland, D., Batzu, L., Halliday, G.M. *et al.* Parkinson disease-associated cognitive impairment. *Nat Rev Dis Primers* **7**, 47 (2021).

The most common neuropathologies associated with Parkinson's disease dementia





Non-pharmacologic treatments for neuropsychiatric symptoms (in dementia)

- Behavioral management centered on individual patients' behavior are generally successful for reduction of NPS-effects of these interventions last for months
- Psychoeducation intended to change caregivers' behavior is effective, especially if it is provided in individual rather than group settings--improvements in NPS are sustained for months
- Music therapy and some types of sensory stimulation, are useful NPS during the session but have no longer-term effects
- Benefit of exercise is variable across studies, but generally positive

Livingston G, Johnston K, Katona C, Paton J, Lyketsos CG; Old Age Task Force of the World Federation of Biological Psychiatry. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. Am J Psychiatry. 2005 Nov;162(11):1996-2021. doi: 10.1176/appi.ajp.162.11.1996. PMID: 16263837.

Questions?

