Neuropsychiatric manifestations in Parkinson's and Dementia with Lewy Bodies

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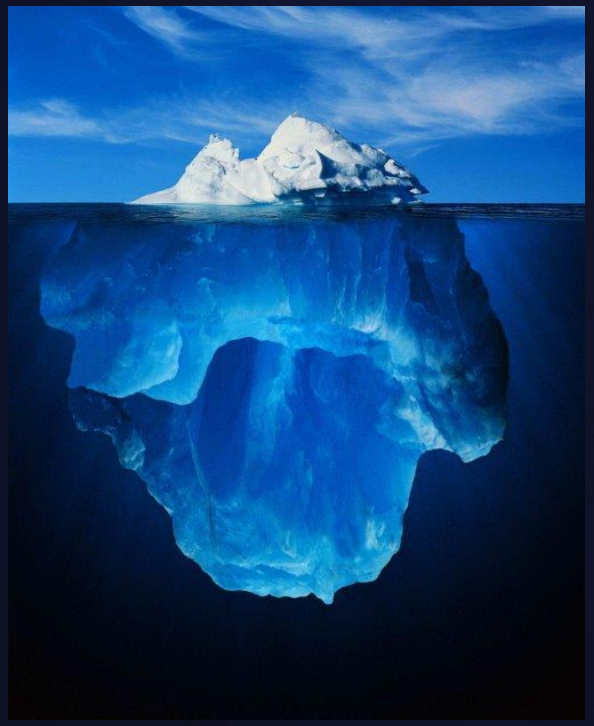
For Gral 2025

Disclosures

- In the last 2 years, Dr. Shill has received research support from Intra-cellular Therapeutics, Parkinson Study Group/UCB, Parkinson's Foundation, NINDS, MJFF, Jazz Pharmaceuticals and Barrow Neurological Foundation.
- Dr. Shill has served as a consultant for Boston Scientific, Mitsubishi Tanabe, KeifeRx, Fasikl, Abbvie, Praxis and Sage/Biogen.

Topics

- Mood disorders
- Impulse control disorders
- Psychosis
- Dementia
- Apathy



Mood disorders

- Depression
  - Global PD survey (Mov Disord, 2002)
    - Face to face interviews in 1020 patients in 6 countries
    - 50% screened positive on Beck Depression Inventory
  - 34% in movement disorder clinic (Weintraub, 2003)
    - 65% not on treatment
  - Associated with worse QOL (Schrag, 2000)

How to diagnosis

TABLE 2. *DSM-IV-TR criteria for major and minor depression*

Depressive episode	Criteria
Major depressive episode	A. Persistence and general pervasiveness of 5 or more of 9 potential symptoms during the same 2-week period that represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure that is present most of the day, nearly every day, as indicated by either subjectivc report or observation made by others. 1) Depressed mood 2) Markedly diminished interest or pleasure in all, or almost all, activities 3) Loss or gain in weight or appetite 4) Insomnia or hypersomnia 5) Psychomotor agitation or retardation 6) Fatigue or loss of energy 7) Feelings of worthlessness or excessive or inappropriate guilt 8) Diminished ability to think or concentrate, or indecisiveness 9) Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide B. Symptoms do not meet criteria for a DSM mixed episode (presence of phenomena of both a manic and a depressed episode). C. Symptoms cause clinically significant distress or functional impairment. D. Symptoms are not due to the direct physiological effects of a substance or a general medical condition. E. Symptoms are not better accounted for by bereavement.
Minor depressive episode	Requires only 2 of the 9 symptoms above, but one must be either depression/sadness or loss of interest/pleasure.

- 2 weeks
- INTERFERES WITH FUNCTION

*DSM-V nearly identical

REVIEW

Accuracy of Screening Instruments for Detection of Neuropsychiatric Syndromes in Parkinson's Disease

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- Validated scales: GDS (15, 20, and 30 items), HADS-D, HAMD-17, IDS-C, MADRS, UK National Institute for Health and Clinical Excellence (NICE) screening questions, PHQ-9, WHO-Five Well-being Index (WHO-5), and Zung's Self-rating Depression Scale (SDS)

(Mov Disorder 2015)

A few words about suicidality……..

- Data not clear on risk (Review, JNNP 2018)
- Korean (1.9X), Serbian and British (5X) and Netherlands (2.9X) higher risk
- However, Myslobodsky *et al* identified a cumulative incidence of suicide **10 times lower** in PwP in the US compared with the general population (0.08%, n=122 vs 0.8%).
- Risks: depression, previous SA, maybe impulsivity (ICD), maybe DBS especially STN
- Screening: C-SSRS
  - Do you wish you were dead?
  - Do you have thoughts of killing yourself?

Recommendations


MDS COMMISSIONED REVIEW

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

Klaus Seppi, MD,[1]* K. Ray Chaudhuri, MD,[2] Miguel Coelho, MD,[3] Susan H. Fox, MRCP (UK), PhD,[4] Regina Katzenschlager, MD,[5] Santiago Perez Lloret, MD,[6] Daniel Weintraub, MD,[7,8] Cristina Sampaio, MD, PhD,[9,10] and the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the Movement Disorders Society Evidence-Based Medicine Committee

- Venlafaxine
  - clinically useful
- Paroxetine
  - possibly useful (due to conflicting data)
- Other SSRIs
  - possibly useful (due to conflicting data)
  - Citalopram >20mg avoided in those over 60 without ECG
- TCAs possibly useful
  - Avoid in cognitively impaired
  - Avoid in those at risk for overdose
- Pramipexole
  - Clinically useful

(Mov Disorders, 2019)

Non-pharmacological approaches

- rTMS (Brys, 2016; Makkos, 2016)
  - 2 high quality studies with discrepant results
  - Possibly useful
  - Short term benefits, needs to be repeated
- CBT (Dobkin, 2011)
  - Likely efficacious but insufficient evidence (1 study)
  - Possibly useful

Anxiety

- Less attention than depression
  - Includes (in order) GAD, agoraphobia, social phobia and panic
- Often undetected (Shulman, 2002)
  - 50% neurologists miss it
- Associated with more severe motor symptoms (Leentjens, 2011)
  - Off manifestation, freezing of gait
- About 40% of patients (more than double general population)
- About 65% overlap with depression (Leentjens, 2008)
  - “anxious depression”
- No good validated scales until Parkinson Anxiety Scale (Leentjens, 2014)
  - Clinician and patient rated

Parkinson Anxiety Scale

In the past four weeks, to what extent did you experience the following symptoms?

Scored 0-4, cut off 8.5

A. Persistent anxiety

A.1. Feeling anxious or nervous

A.2. Feeling tense or stressed

A.3. Being unable to relax

A.4. Excessive worrying about everyday matters

A.5. Fear of something bad, or even the worst, happening

B. Episodic anxiety

B.1. Panic or intense fear

B.2. Shortness of breath

B.3. Heart palpitations or heart beating fast (not related to physical effort or activity)

B.4. Fear of losing control

C. Avoidance behavior

C.1. Social situations (where one may be observed, or evaluated by others, such as speaking in public, or talking to unknown people)

C.2. Public settings (situations from which it may be difficult or embarrassing to escape, such as queues or lines, crowds, bridges, or public transportation)

C.3. Specific objects or situations (such as flying, heights, spiders or other animals, needles, or blood)

Anxiety Treatment

- Little data
- In the absence of data, consider:
  - SSRI
  - Address motor fluctuations
  - Benzodiazepines for as needed use
    - High caution with chronic use

Impulse Control Disorders

- 1884 patients
  - 9 patients with pathological gambling
  - 8 on pramipexole (1.5%)

Pathological gambling associated with dopamine agonist therapy in Parkinson's disease

E. Driver-Dunckley, MD; J. Samanta, MD; and M. Stacy, MD

Risk factors associated with pathologic gambling include male sex, age (25 to 29 years), comorbid psychiatric disorders, suicide, and lower socioeconomic status.[1] In addition, some authors report significant increases in both casino gambling and single-day money losses within a year after the introduction of readily available casinos.[2] The prevalence of this condition is unknown in patients with Parkinson disease (PD).[3] Some authors suggest that these symptoms may be related to high dose dopaminergic therapy, especially in subjects prone to poorly regulated, self-medicating behaviors.[4-7] We report nine patients with pathologic gambling associated with chronic high dose dopamine agonist (DA) therapy.

A retrospective database review of all patients with PD seen at the Muhammad Ali Parkinson Research Center (MAPRC) from May 1, 1999, to April 30, 2000, was performed for pathologic gambling. Specific data collected included subject age, sex, race, duration of disease, Hoehn and Yahr stage (H&Y), Unified Parkinson's Disease Rating Scale (UPDRS) score at change in DA treatment and at the discovery of the gambling problem, duration of DA therapy, DA dose at time of onset of gambling, levodopa

Impulse control disorders (ICD)

- DOMINION study
  - 3090 subjects with IPD
  - Survey administered pseudo-randomly
  - Mean age 63.8
  - ICD in 13.6%
  - 17.1% in Dopamine Agonists vs 6.9% in non-DA (levodopa)
    - Pramipexole 17.7%, ropinirole 15.5% (NS)
  - Types of ICD:
    - Buying 7.2%, gambling 6.4%, binge-eating 5.6%, hypersexuality 4.4% in DA treated

(Presented at AAN 2008, Weintraub et al; then 2010 Archives Neurology)

Screening for ICD

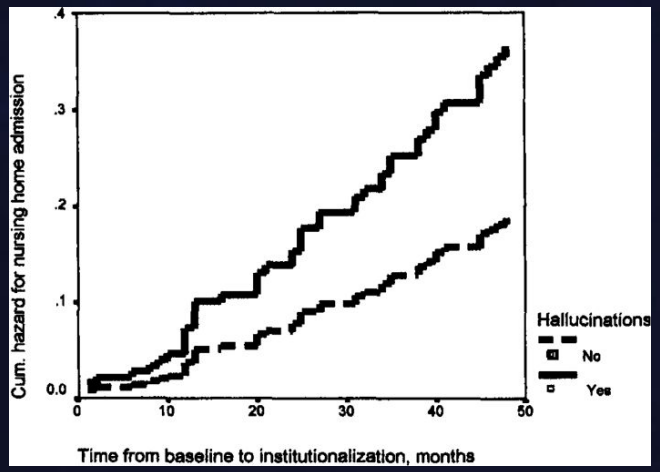
- QUIP-RS (Weintraub, 2012)
  - Gambling
  - Sex
  - Buying
  - Eating
  - Hobbies
  - Simple tasks (punding)
  - Medication overuse
- Quantifies:
  - How often
  - Excessive urge/desire
  - Difficulty controlling or can’t cut back
  - Hiding, lying, hoarding, stealing and debt to continue activity

Treating ICD

- Education and awareness prior to starting medication
- Reduce or stop dopamine agonist
- Deep brain stimulation (Kim, 2018)
- Naltrexone not effective (Papay, 2014)
- Cognitive Behavioral Therapy (Okai, 2013)
  - Likely efficacious
  - Possibly useful

Psychosis- Hallucinations

- Hallucinations high in DLB (60-80%)
- Still high in PDD (45-65%)
- Mostly visual but can be anything
- May not be frightening
- Patient may have “insight”
- Predictor of dementia (3 times OR) and nursing home placement in PD



178 community elders in Norway

(Aarsland, 1996; Aarsland, 2001; Fenelon, 2000; Aarsland, 2003; Aarsland, 2007)

Psychosis: Hallucinations

- Visual most common
- Family/Caregivers sometimes not aware
- Early in course, patient can give detailed description of complex hallucinations
- Tend to correlate with more profound visual spatial difficulties (Mori, 2000)
- More extensive pathology (Jacobson, 2014)
- Great cholinergic deficits and may respond the therapy better (Perry, 1991)

Delusions

- Delusions less common but still more common than in AD
- Paranoia
  - Infidelity
- Phantom boarder
- Capgras

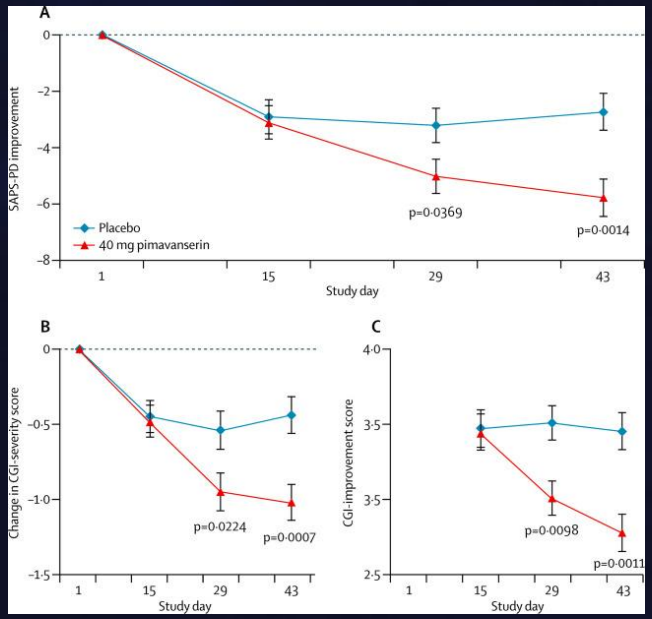
Treatment psychosis

- Tend not to treat non-interfering hallucinations
- Drop anticholinergics, amantadine, dopamine agonists
- Avoid use potent neuroleptics and most atypicals
- Avoid valproic acid (Cochrane Review, 2009)
- Gingerly use quetiapine (Seroquel)
- Clozapine should be considered (AAN parameter, 2005)
- Benzodiazepines often too sedating
- Pimavanserin (Nuplazid)

QTC:
5-8 ms pimavanserin
6-15 ms quetiapine
10 ms clozapine
(Washington, 2012)

Pimavanserin

- Pivotal study: 6 week study of 199 PD patients
- Positive symptoms (SAPS-PD)
  - Improved at 29 days
- May be better in more cognitively impaired
  - MMSE 21-25 vs > 25 (Espay, 2018)
- May be used in PD dementia (Tariot, 2021; Weintraub, 2024)
  - 15% had PDD; 7.1% had DLB
  - All dementia
    - 61% responded
    - 13% vs 28% relapse
  - PDD (n=49)
    - HR 0.052 for relapse (p<0.001)



(Cummings et al
in Lancet Neurology, 2014)

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Dementia in PD

- Terms used:
  - Diffuse Lewy Body disease
  - Lewy body variant of Alzheimer's disease
  - Lewy body dementia
  - Parkinson's dementia (PDD)
  - Dementia with Lewy Bodies (DLB)
  - Lewy Body syndrome (PDD or DLB)

Diagnostic Criteria for Dementia

Dementia

- Interferes with ability to function at work or at usual activities (due to cognition)
- A decline from a previous level of functioning
- Not delirium or psychiatric disorder
- Diagnosed by history, examination
- Involves at least 2 cognitive domains:
  - Memory
  - Reasoning and judgment
  - Visuospatial
  - Language
  - Personality, behavior, comportment

McKhann GM, et al, *Alzheimer's Dement*. 2011;7:263-69.

Lewy Body Dementia

- DLB (Dementia with Lewy Bodies)
  - Dementia first
- PDD (Parkinson's disease with dementia)
  - Parkinson's first

Dementia with Lewy Bodies

- Dementia with memory impairment NOT required plus:
- Core features (at least 2):
  - Fluctuating Cognition
  - Recurrent Visual Hallucinations
  - REM Sleep Disorder
  - Spontaneous Features of Parkinsonism
- Indicative biomarkers (one or more with at least 1 core)
  - Low dopamine imaging (PET/SPECT)
  - Low Iodine-MIBG myocardium
  - PSG without REM sleep atonia
- Supportive Biomarkers
  - No medial temporal atrophy
  - Reduced occipital perfusion +/- cingulate sign
  - Posterior slow wave activity on EEG
- Supportive clinical features
  - Repeated falls and syncope
  - Transient, unexplained unconsciousness
  - Autonomic dysfunction
  - Other types of hallucinations
  - Delusions
  - Depression/Anxiety
  - Apathy

(4th DLB Consortium, Neurology 2017)

Parkinson's disease with dementia (PDD)

- Looks like DLB but they have PD first and PD is present for at least 1 year.
- Emre criteria:
  - Established PD
  - Dementia syndrome
  - Different cognitive profile than AD (we will talk about)
  - Behavioral Features:
    - Apathy
    - Depression and anxiety
    - Hallucinations and delusions
    - Daytime sleepiness

(Emre, 2007)

Mild Cognitive Impairment (MCI)

- Guidelines for PD-MCI level I and level II categories
- A. Level I (abbreviated assessment)
  - **Impairment on a scale of** global cognitive abilities **validated for use in PD or**
  - **Impairment on at least two tests, when a limited battery**
- B. Level II (comprehensive assessment)
  - Neuropsychological testing that includes **2 tests within each of the 5 cognitive domains**
  - Impairment on at least two neuropsychological tests

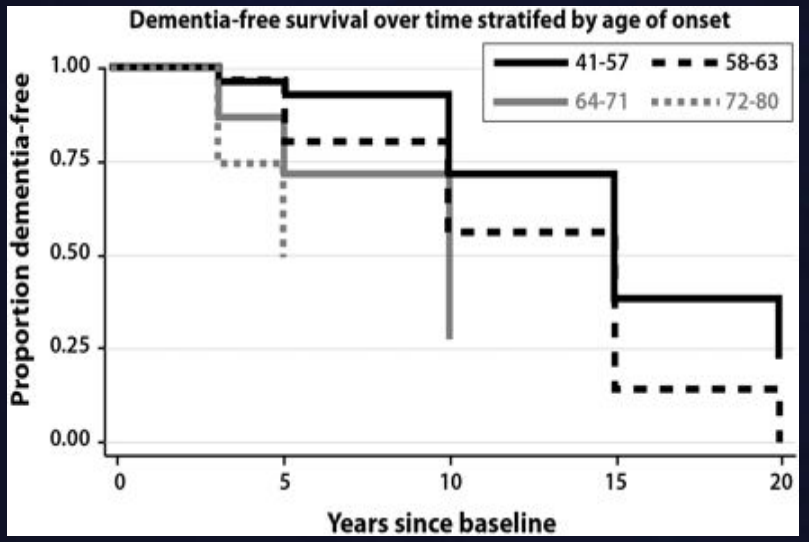
(MDS -MCI Task Force, 2012)

Cognitive impairment and dysfunction
MCI

- Global cognition
  - MoCA (Dalrymple-Alford, 2010)
    - <26 MCI
    - <21 PDD
  - PD-Cognitive Rating Scale (Pagonabarraga, 2008)
  - SCOPA-COG (Kulisevsky, 2009; Verbaan, 2007)
  - Mattis Dementia Rating Scale (Villeneuve, 2011)

Dementia Risk in PD

- 83% of 149 denovo PD at 20 years
- Risks:
  - Age onset
  - MCI at baseline
  - Akinetic rigid
  - Hallucinations
    - 3-10 OR for dementia at 5-8 years



(Sydney Multicenter Study, Reid et al, 2011)

Core features DLB: Fluctuations

- "Are there episodes where thinking seems quite clear and then becomes muddled?"
- 3 or more of the following:
  - Daytimes drowsiness and lethargy
  - Daytime sleep > 2 hours
  - Staring into space for long periods
  - Episodes of disorganized speech

(Ferman, 2004)

Cognitive profile-Attention

- Slower in complex attention task (Noe, 2004; Beatty, 2003)
- More variability with repeat performance (Ballard, 2002)
  - Suggests fluctuations in alertness
- 29% PDD
- 42% DLB
- “She is fine one minute and the next minute is out of it”
- “It’s like I have 2 dads”

Cognitive profile- Memory

- Presenting complaint in:
  - 67% PDD
  - 94% DLB
  - 100% AD
- Both verbal and visual memory
- Less severe than in AD in mild to moderate disease
- Advanced LBD with similar memory profile as AD
- In very early disease, recognition better than free recall

(Aarsland, 2003; Cahn-Weiner, 2002; Litvan, 1991; Paolo, 1995, Noe, 2004)

Cognitive profile-executive function

- Speech initiation reduced greater than AD
- Total verbal fluency reduced in both
- In general, more executive dysfunction in PDD/DLB than AD
- “tip of tongue”
- Apathy (more on this later)
- “He gets up and falls even when I tell him to stay seated”

Aarsland, 2003; Cahn-Weiner, 2002; Litvan, 1991; Paolo, 1995, Noe, 2004

Cognitive profile- construction and praxis

- More troubles with clock drawing in PDD/DLB
- More troubles with design copying in PDD/DLB
- DLB may be worse than PDD
- “He can’t operate the remote” “She can’t use the microwave”

(Emre, 2004, Aarsland, 2003; Cahn-Weiner, 2002; Litvan, 1991; Beatty. 2003; Starkstein, 1996)

Cognitive profile- visual spatial

- PDD/DLB worse than AD (Starkstein, 1996)
- “She can’t see even though the eye doctor says her vision is fine”

Cognitive profile- Language

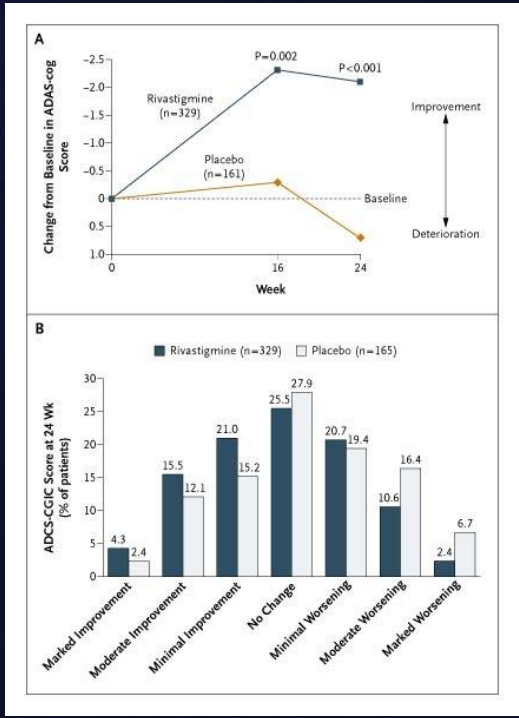
- Better with PDD/DLB than AD
- AD more impaired with naming
- AD more impaired with speech content (fewer different words)
- Verbal fluency reduced in PD (more executive dysfunction)

Cognitive profile summary

- Better long term memory and language than AD
- Worse executive dysfunction and visual spatial skills
- About the same Short Term Memory in PDD/DLB and AD

Treatment

- Cholinesterase inhibitors
  - Rivastigmine approved 2000
    - Patch better than pill
  - Donepezil likely works
    - Insufficient evidence
    - Better tolerated pill form compared with rivastigmine
- Memantine
  - Conflicting studies
  - May be helpful
    - 27% with meaningful benefit in Aarsland study
  - Acceptable risk

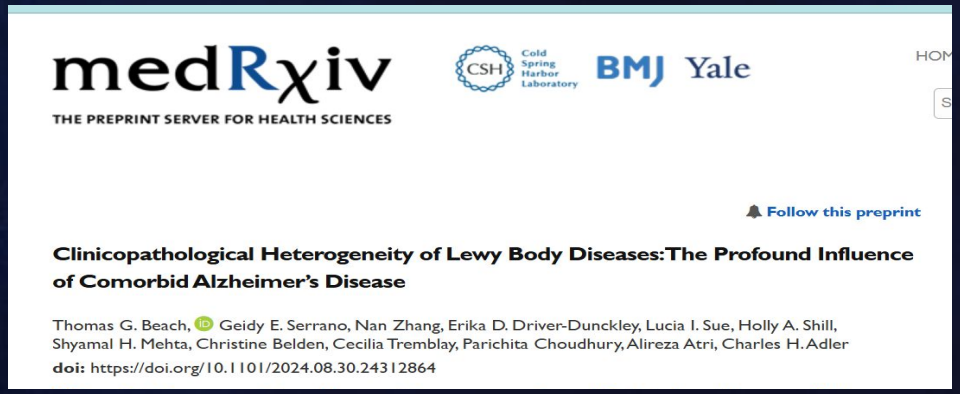


(Emre, 2004)

Apathy

- Different from depression but can be associated
- Likely due to executive dysfunction
- About 40% of patients (Meta-analysis: den Brok, 2015)
- Difficult to treat
  - Cholinesterase inhibitors may help (McKeith, 2000; Devos, 2014)
  - Dopamine agonists
    - Useful after DBS (Thobois, 2013)
      - piribedil
    - Not useful otherwise (Hauser, 2016)
      - rotigotine

The elephant in the room……



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Clinicopathological Heterogeneity of Lewy Body Diseases:The Profound Influence of Comorbid Alzheimer's Disease

Thomas G. Beach, Geidy E. Serrano, Nan Zhang, Erika D. Driver-Dunckley, Lucia I. Sue, Holly A. Shill, Shyamal H. Mehta, Christine Belden, Cecilia Tremblay, Parichita Choudhury, Alireza Atri, Charles H. Adler

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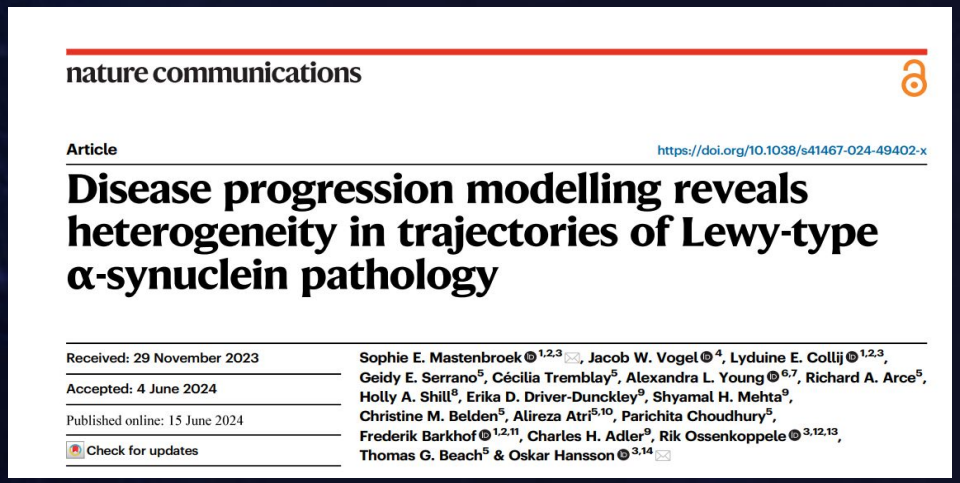

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Article

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Disease progression modelling reveals heterogeneity in trajectories of Lewy-type α-synuclein pathology

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Summary

- Depression can be recognized and should be treated
- Anxiety can be recognized; more research needs to be done in treatment
- Problematic impulse control disorders can be prevented
- Psychosis is a worrisome symptom that can be difficult to manage
- Cognitive decline in PD remains disabling and difficult to treat
- Apathy needs additional research and treatment options

THE END

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