



Anxiety and behavioral disturbances in Parkinson's Disease

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Disclosures

- No relevant financial relationships with commercial interests.
- Consultant for Acadia Pharmaceuticals Inc

Pharmacological and Nonpharmacological Treatments of Anxiety in Parkinson's Disease



Objectives:

1. Become familiar with the presentation of anxiety and behavioral disturbances in Parkinson's disease (PD)
2. Discuss how the physical/biological aspects of PD may be associated with anxiety and behavioral disturbances
3. Review the best evidence treatments for anxiety and behavioral disturbances in PD



I. Overview of anxiety in Parkinson's disease

II. Potential mechanisms or 'phenocopies' of anxiety in Parkinson's disease

III. Best evidence treatment of anxiety in Parkinson's

IV. Impulse control and other behavioral disorders in Parkinson's

Anxiety in Parkinson's disease



Prevalence of anxiety and anxiety disorders in PD

- Up to 55% have clinically significant anxiety symptoms
- 31% have an anxiety disorder
- 42% rank anxiety as a top 3 unmet need in PD
- Anxiety (and depression) greater negative impact on QoL than motor symptoms

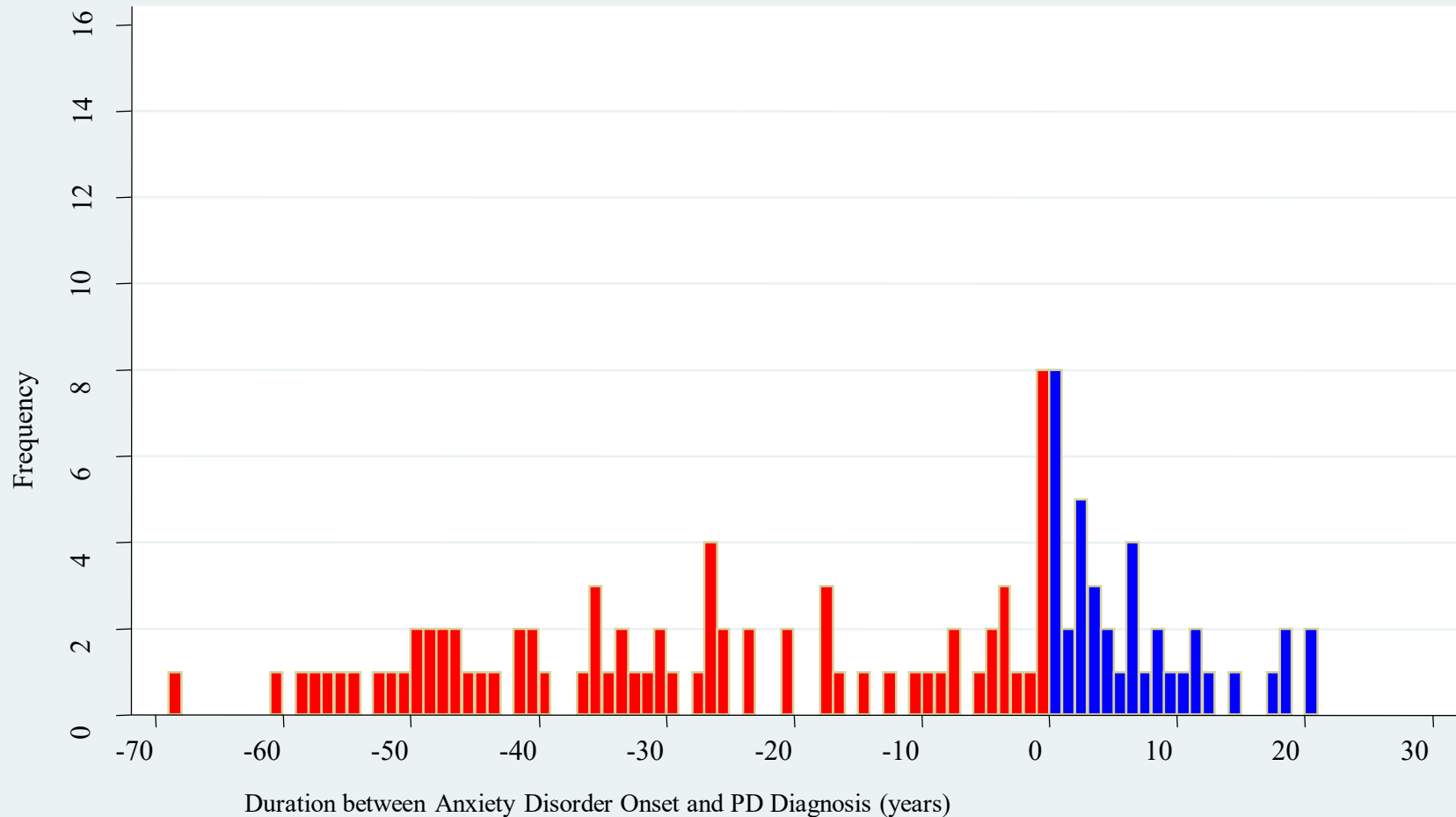
Anxiety disorders in PD

Most common anxiety disorders in PD:

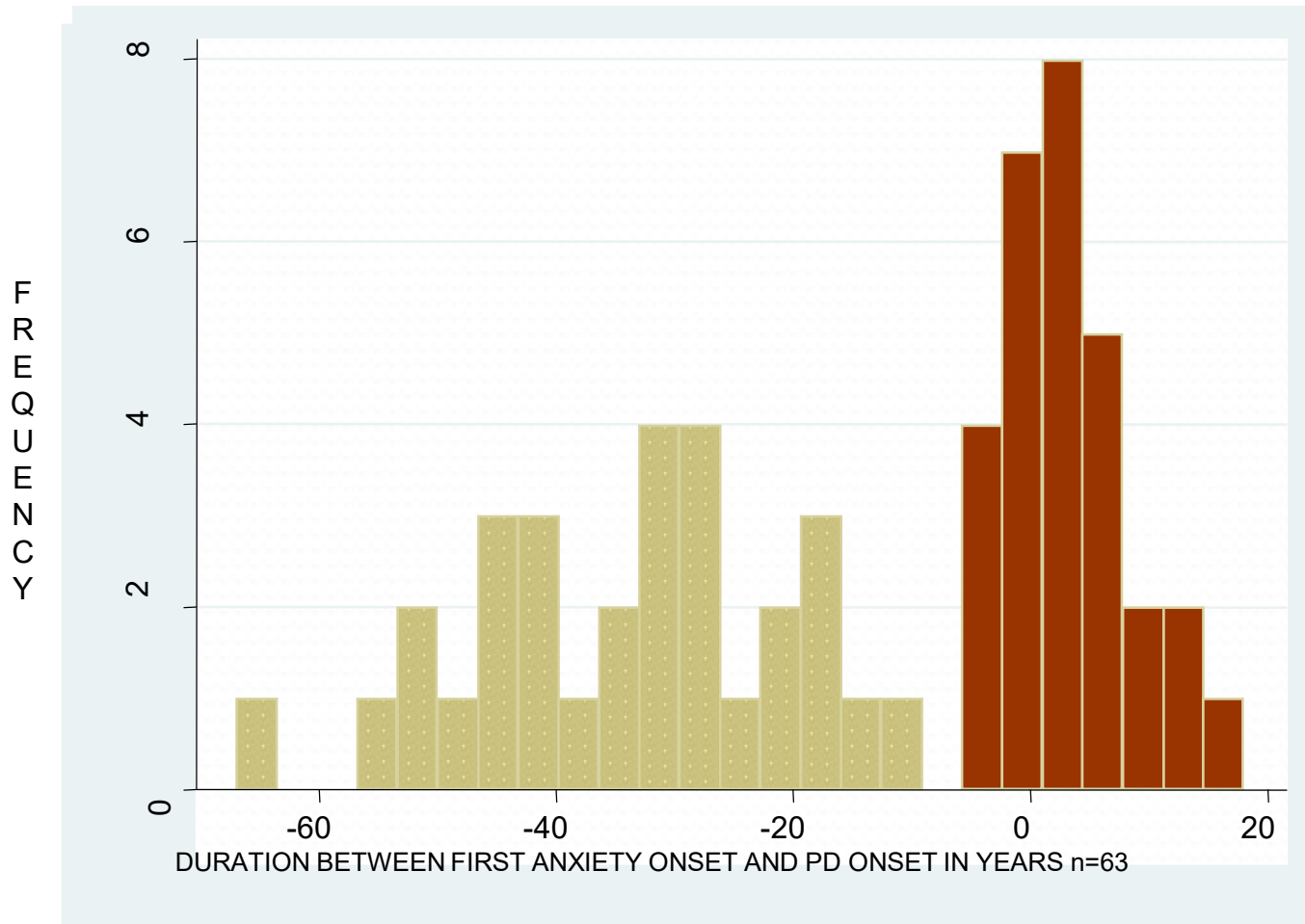
- Generalized anxiety disorder 14.1%
- Social Phobia 13.8%
- *Anxiety disorder NOS* 13.3%

A third have two or more anxiety disorders

Anxiety disorders can occur at any stage of PD



First Anxiety Disorder Onset Relative to PD Onset



Bimodal distribution of anxiety disorder onset compared to PD onset

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; $p=0.004$)



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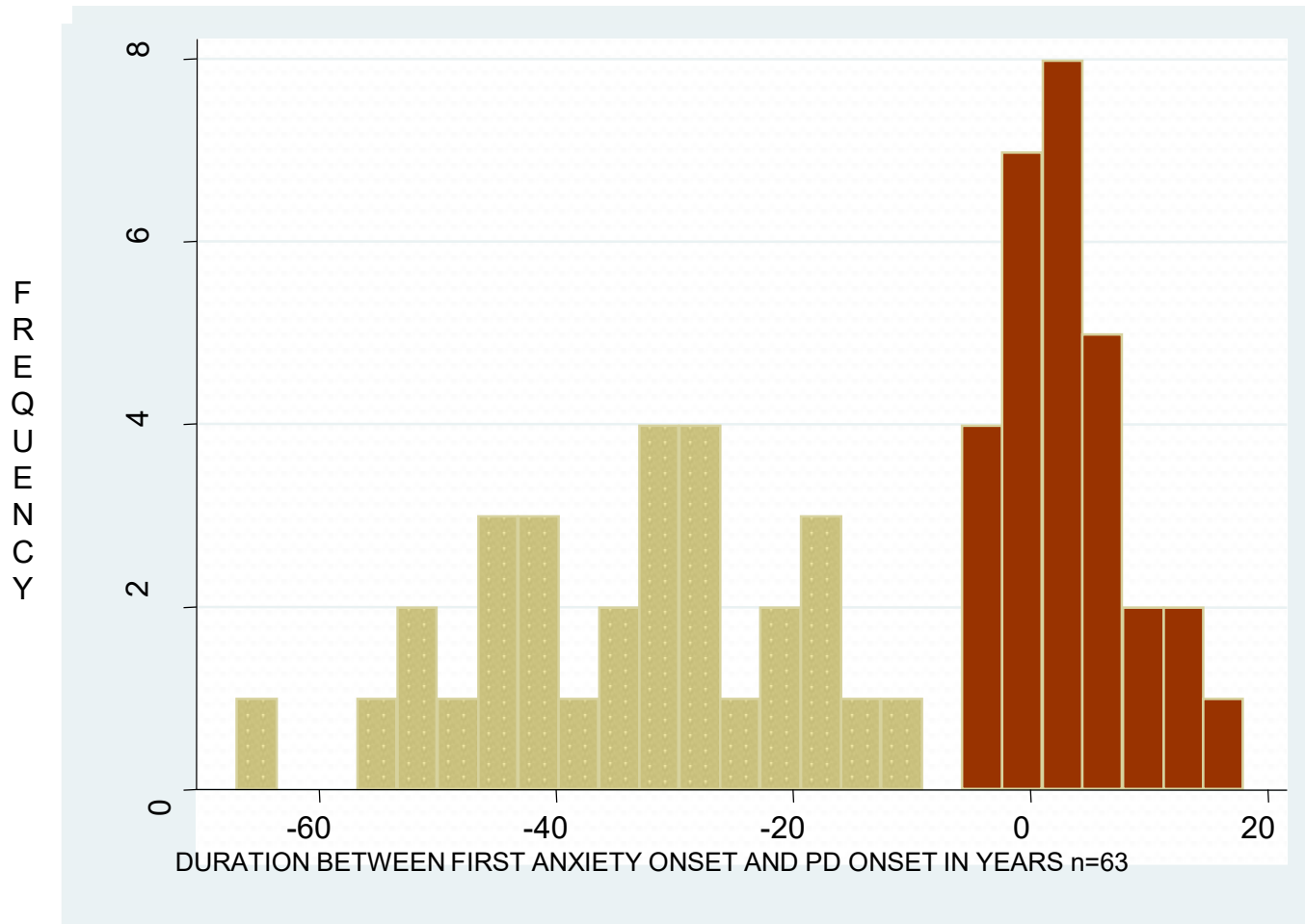
Autonomic dysfunction and anxiety in PD

- thermoregulation, hypotension, hyperventilation, and trembling
- N=32 per group, PD>control, not related to age, did not correlate with motor sx
- Autonomic symptom scale score + correlation with HAM-A and D
- Postural BP change and beat to beat variation was associated with HAM-A in PD

Anticipatory anxiety and cognitive impairment in PD

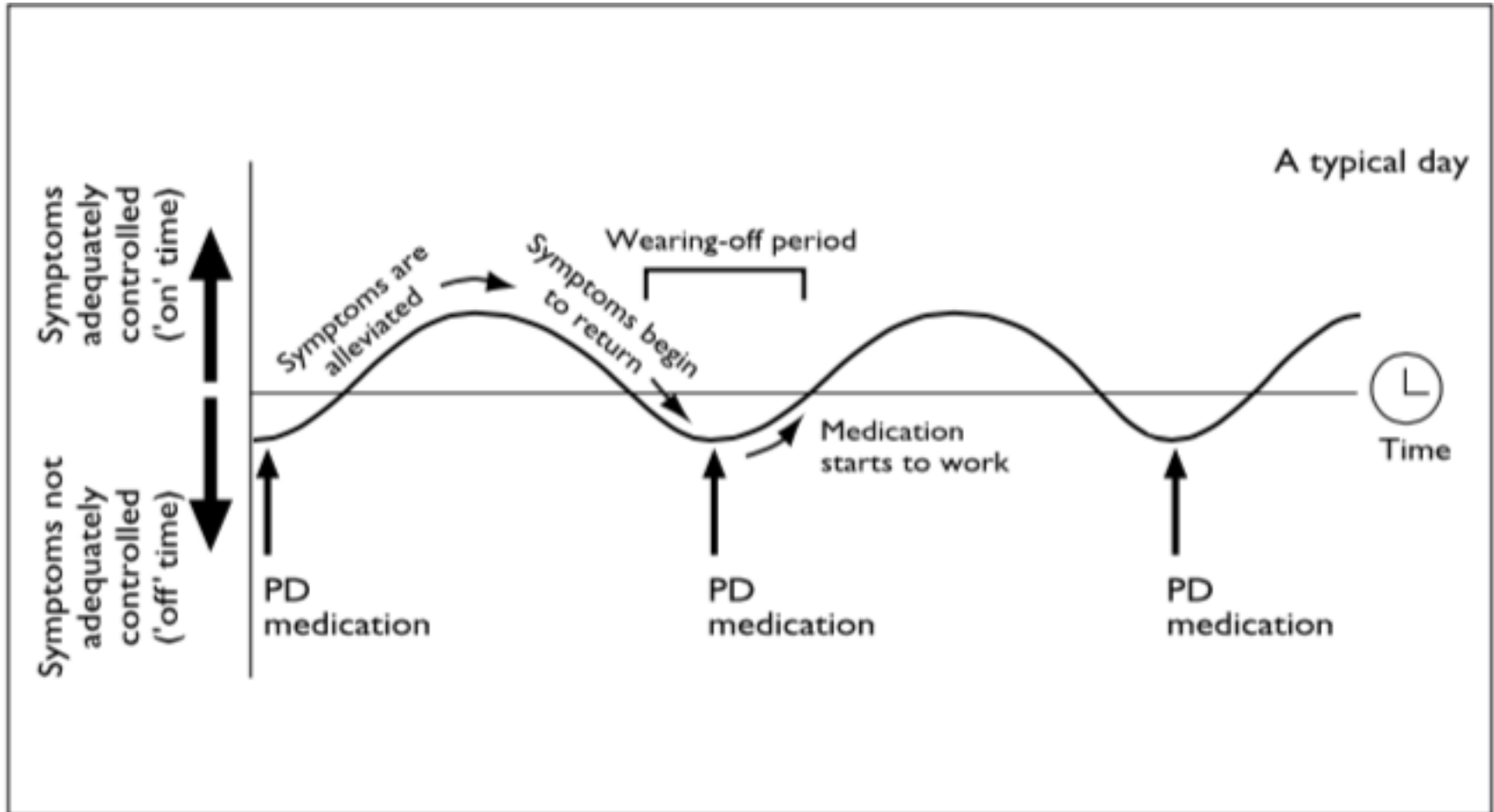
- Distressed in advance of and often avoids events in the future
- Dissanayaka et al 2017, PD MCI 3x more likely to have anxiety than non-anxious

First Anxiety Disorder Onset Relative to PD Onset

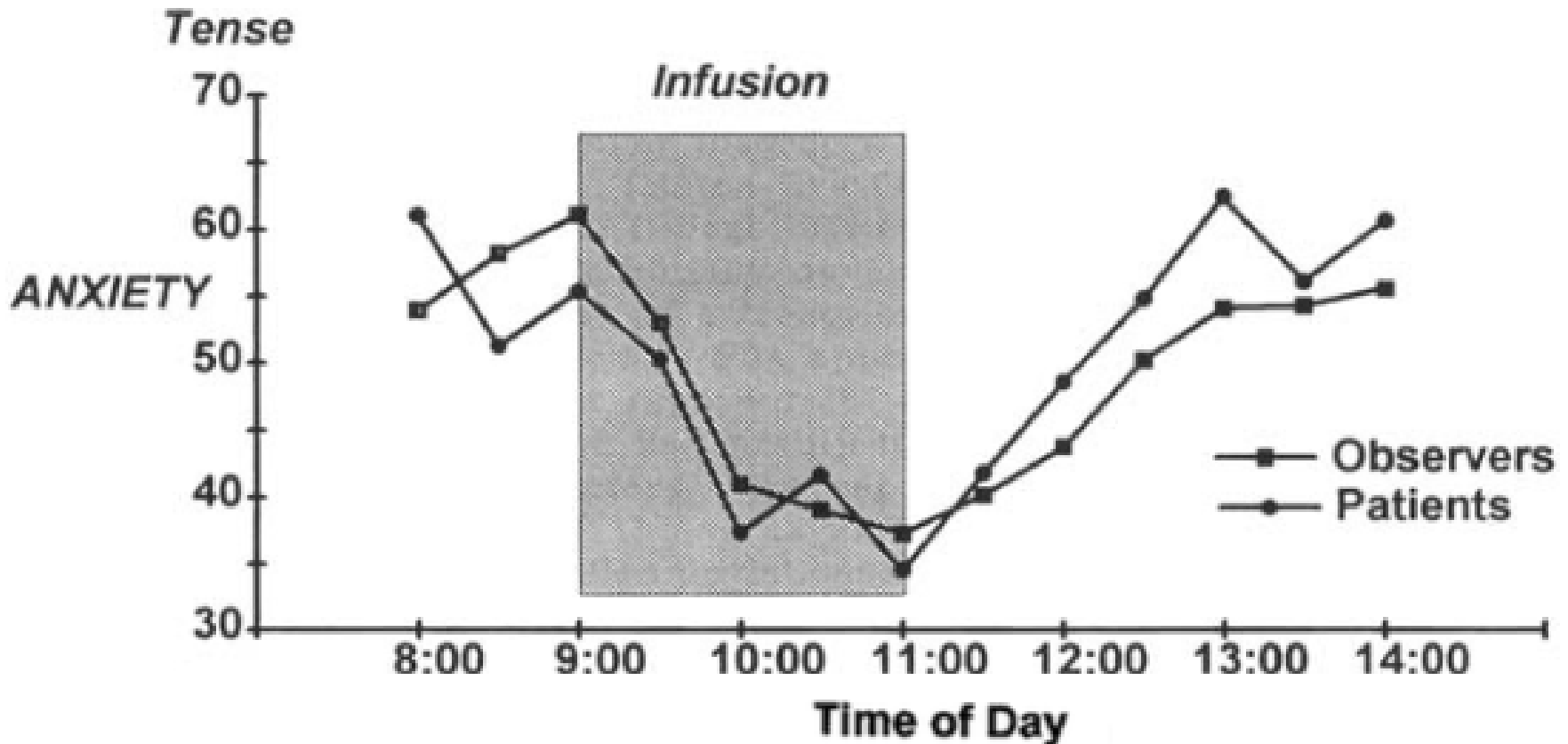


Bimodal distribution of anxiety disorder onset compared to PD onset

Dopaminergic medication on-off fluctuations in PD



Anxiety fluctuation with levodopa infusion



Fear of falling

- Fear of falling (FOF) assessed in 22 studies in PD
- 51.5% of 1012 patients across studies experience FOF
- FOF experienced, more frequent freezing, turning hesitation, slower gait speed, greater postural impairment



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Pharmacologic treatment of anxiety in PD

- MDS Task Force on Evidenced Based Medicine and the American Academy of Neurology – “the evidence to support or refute specific treatments for anxiety is insufficient”
- Limited evidence (secondary outcomes) from RCTs
- Optimizing motor function and addressing motor fluctuations is likely important

Buspirone for anxiety in Parkinson's disease

- N=21, randomized 4:1, 4 placebo, 17 buspirone median dose 7.5mg BID
- Mean improvement (NS) was -3.9 on HAMA and -7.1 PAS
- Tolerability was an issue with 53% AE related to motor function and 41% failed to complete study

Nabilone phase II for non-motor symptoms in PD

- Nabilone, synthetic tetrahydrocannabinol analogue
- Phase II open label responders randomized to continue nabilone or switch to placebo for 4 wks
- 77% had AEs during open label titration, but AEs were similar in double blind phase, no serious AEs
- May lower anxiety and help sleep, primary outcome MDS-UPDRS I

Non-pharmacologic treatments of anxiety in PD

- Cognitive Behavioral Therapy (CBT) for anxiety in PD
- Mindfulness based therapies
- Exercise based therapies
- Neuromodulation emerging option, e.g., rTMS, tDCS, and DBS (none in PD have anxiety as primary outcome)

Cognitive behavioral therapy for anxiety in Parkinson's disease



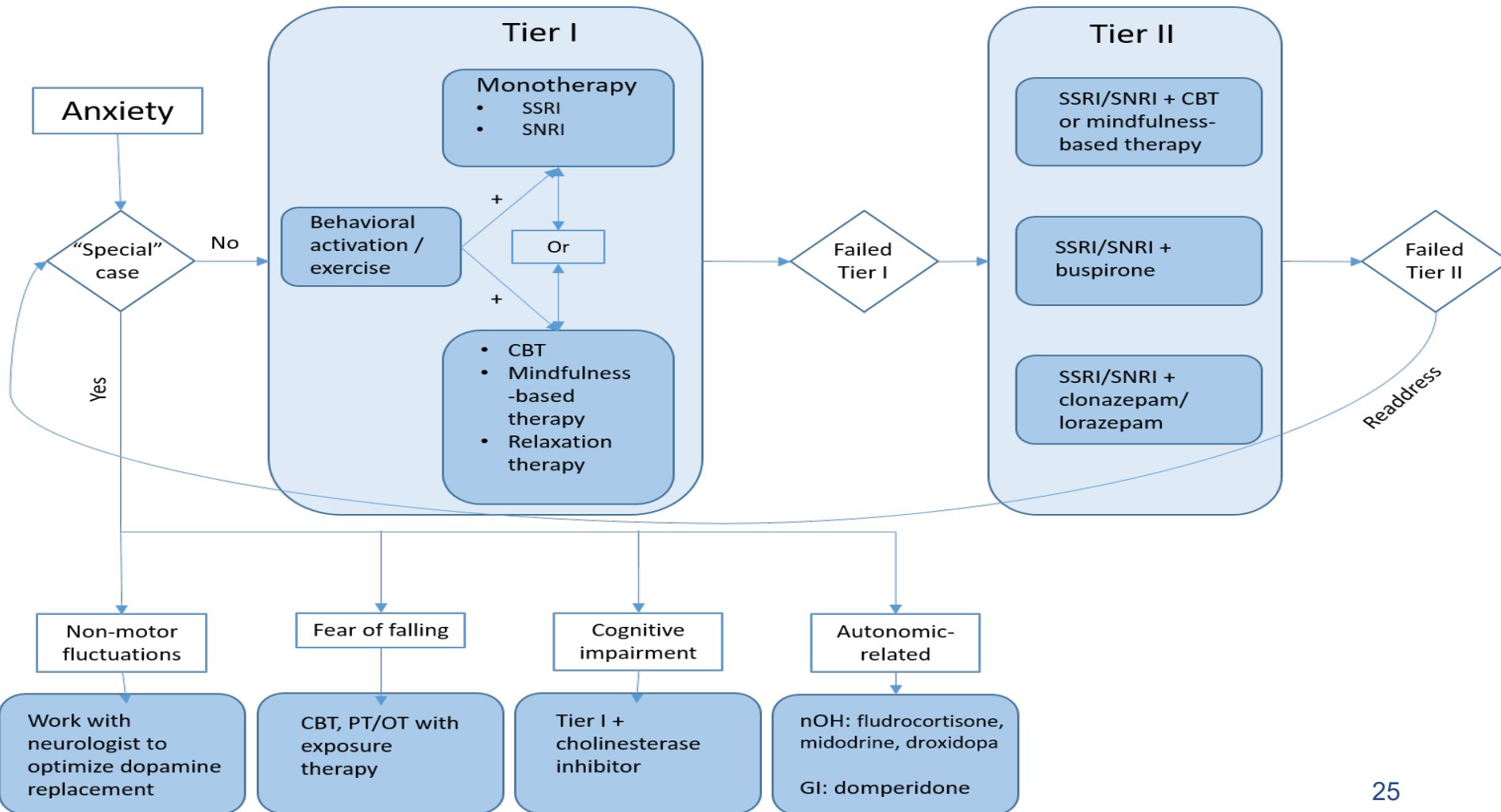
- n=48, 1:1 CBT vs clinical monitoring only, 10 weekly sessions
- Primary outcomes Hamilton Anxiety Rating Scale and Parkinson Anxiety Rating Scale
- NS changes in HAMA
- PAS CBT 9.9 vs CMO 5.2 $p=0.012$, sustained improvement at 3 and 6 months

Mindfulness Yoga vs Stretching and Resistance Training for Anxiety



- n=138, 1:1 yoga vs SRTE, 8 weeks
- Primary outcome Hospital anxiety and depression scale, baseline, 8wk, 20wk
- Yoga was superior to SRTE for anxiety and depressive symptoms, T1: β , -1.79 [95% CI, -2.85 to -0.69; $P = .001$]; T2: β , -2.05 [95% CI, -3.02 to -1.08; $P < .001$])
- Equally efficacious for UPDRS part III

PD anxiety treatment algorithm





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Impulse control disorders in Parkinson's disease



Impulse control disorders (ICDs) in PD

- “An assortment of behaviors performed repetitively, excessively, and with a ***lack of self-control*** to an extent that interferes with life functioning”
- **Associated with dopamine agonist medications** and other dopamine replacement therapies

Impulse control disorders in PD

- Pathological gambling
- Compulsive buying/shopping
- Hypersexual behaviors
- Binge eating

Dopamine dysregulation syndrome

- Drug addiction-like state marked by self-medication with inappropriately high doses of dopaminergic medications
- May be more common in early onset PD and males—prevalence 3%-4%
- Co-occurs with ICDs, psychosis, panic attacks

Punding



- Repetitive, purposeless behaviors, characterized by an intense preoccupation with specific items or activities – collecting, arranging, or taking apart objects
- Hobbyism – higher level repetitive behaviors, e.g. excessive internet use, reading, art work, work on projects

Treatment of ICDs in PD


- Withdrawal or reduction of dopamine agonist (complicated by DA withdrawal syndrome 1/3 and worsening motor function)
- Amantadine and Naltrexone have been tried; insufficient evidence
- Cognitive behavioral therapy may help (Okai et al.
- Addiction model – 12-step groups, involve caregiver and family

Anxiety, depression, and agitation in dementia = 'distress'

"Doctor,
what can
you do
for Pop?"




for prompt and sustained relief from
severe mental and
**emotional
stress**



THORAZINE* SPANSULE* capsules
chlorpromazine, S.X.F. sustained release capsules, S.X.F.

30 mg. 75 mg. 150 mg. 200 mg. 300 mg.

 Smith-Kline & French Laboratories

*U.S. Reg. U.S. Pat. Off.

Nonpharmacological intervention for anxiety in dementia

- CBT and mindfulness may not be appropriate in PD dementia
- Limited evidence for interventions and screening in dementia
- Music therapy
- Activity therapy

Questions?

