Parkinson's Disease Comprehensive Care

Kiel Woodward, MD
Assistant Professor of Neurology, Movement Disorders
University of Nebraska Medical Center – 5/01/2024

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Financial Disclosures

None

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Objectives

Recognize importance of mental health in Parkinson's Disease

Define depression, anxiety, and apathy in PD

Identify diagnostic criteria for PD-MCI, PDD, and DLB

Describe the incidence and prevalence of mood and cognitive disorders in PD

Discuss potential treatment options for mood and cognitive changes in PD

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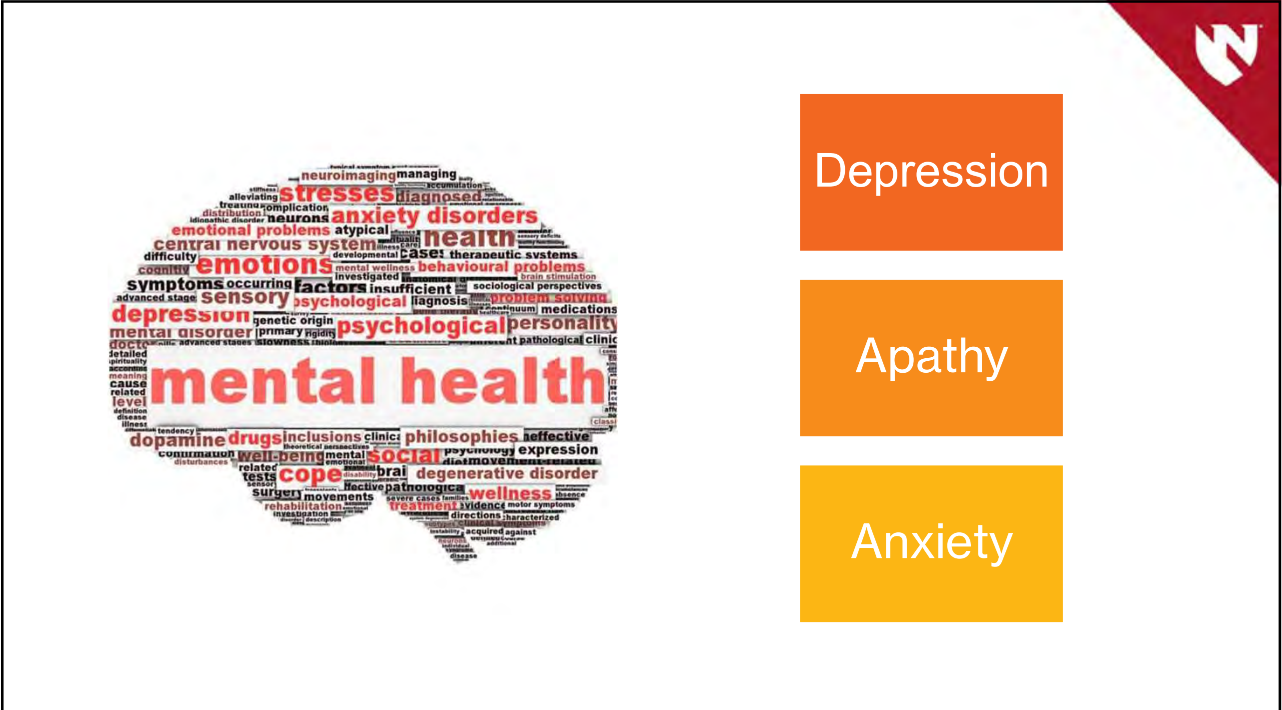

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Why is mental health important?

Mental health greatly affects quality of life

- It affects how we think, feel, and act
- It can exacerbate other Parkinsonian symptoms
- Depression and anxiety can affect overall health and quality of life at least as much the motor symptoms of PD

Depression can be deadly – increases risk of suicide

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Why is mental health important?

Mental health disorders are very common in PD

- Depression: 30% PD vs. 15% normal
- Apathy: 40% PD vs. 2% normal
- Anxiety: 40% PD vs. 33% normal

Despite being common, they are underrecognized and undertreated

Aarsland D, et al. Depression in Parkinson disease--epidemiology, mechanisms and management. Nat Rev Neurol. 2011 Dec 26;8(1):35-47.
den Brok MG, et al. Apathy in Parkinson's disease: A systematic review and meta-analysis. Mov Disord. 2015 May;30(6):759-69.

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Why are mental health issues so common in PD?

Reactionary

- Limited activities
- Reduced independence
- Chronically progressive disease without a cure

Intrinsic to Parkinson's Disease

- Loss of brain cells producing dopamine, serotonin, and norepinephrine
- These chemicals are responsible for regulating mood, energy, motivation, appetite, and sleep

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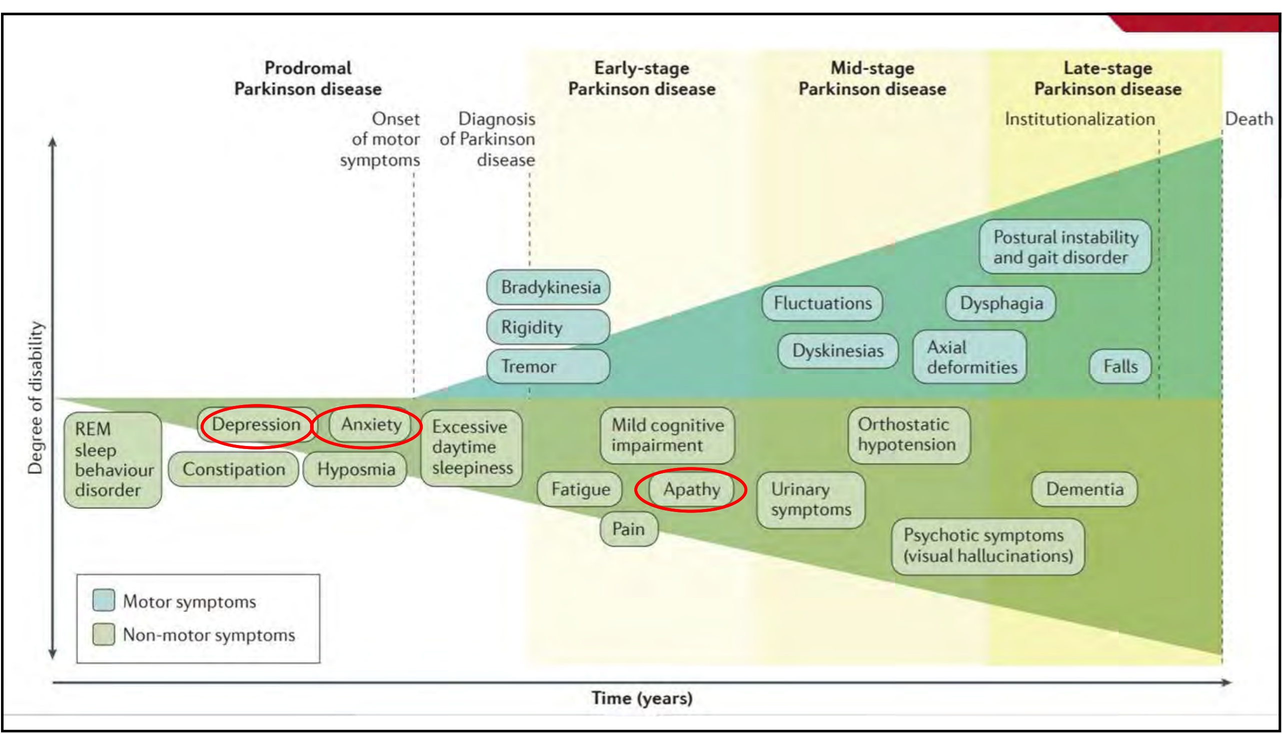

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What is Depression?

Major Depressive Disorder (MDD)
DSM-V criteria (Diagnostic and Statistical Manual of Mental Disorders):

- 2 weeks of at least 5 of the following:
  - Depressed mood**
  - Loss of interest in activities/pleasure (anhedonia)**
  - Fatigue/low energy
  - Changes in weight (gain or loss)
  - Sleep changes (insomnia or excessive sleep)
  - Motor slowness or agitation
  - Feelings of worthlessness/guilt
  - Decreased concentration
  - Thoughts of death/suicide
- Symptoms must cause significant distress or impairment

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Risk Factors for Depression in PD

Female gender
Young onset of motor symptoms (<40 years old)
Severe cognitive impairment
Other medical problems (e.g., heart disease, arthritis, diabetes)
Family history of depression

Baquero, M, Martín, N. Depressive symptoms in neurodegenerative diseases. World J Clin Cases. 2015;3(8):682–693

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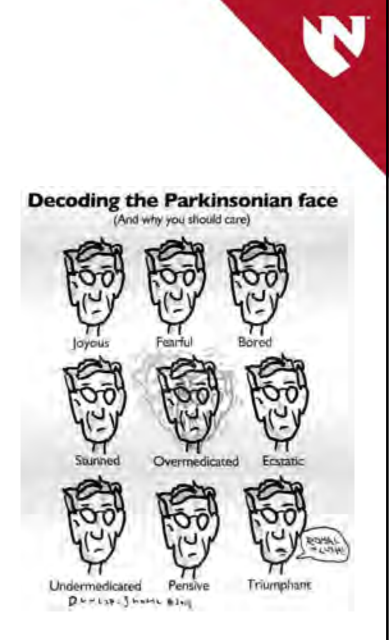
Difficulties in diagnosing depression in PD

- Many symptoms of depression overlap with symptoms of PD
- Reduced facial expression in PD makes it more difficult to express emotion
- Depression in PD often involves frequent, shorter changes in mood versus a constant state of sadness daily
- Many people with Parkinson's do not recognize they have a mood problem or are unable to explain symptoms



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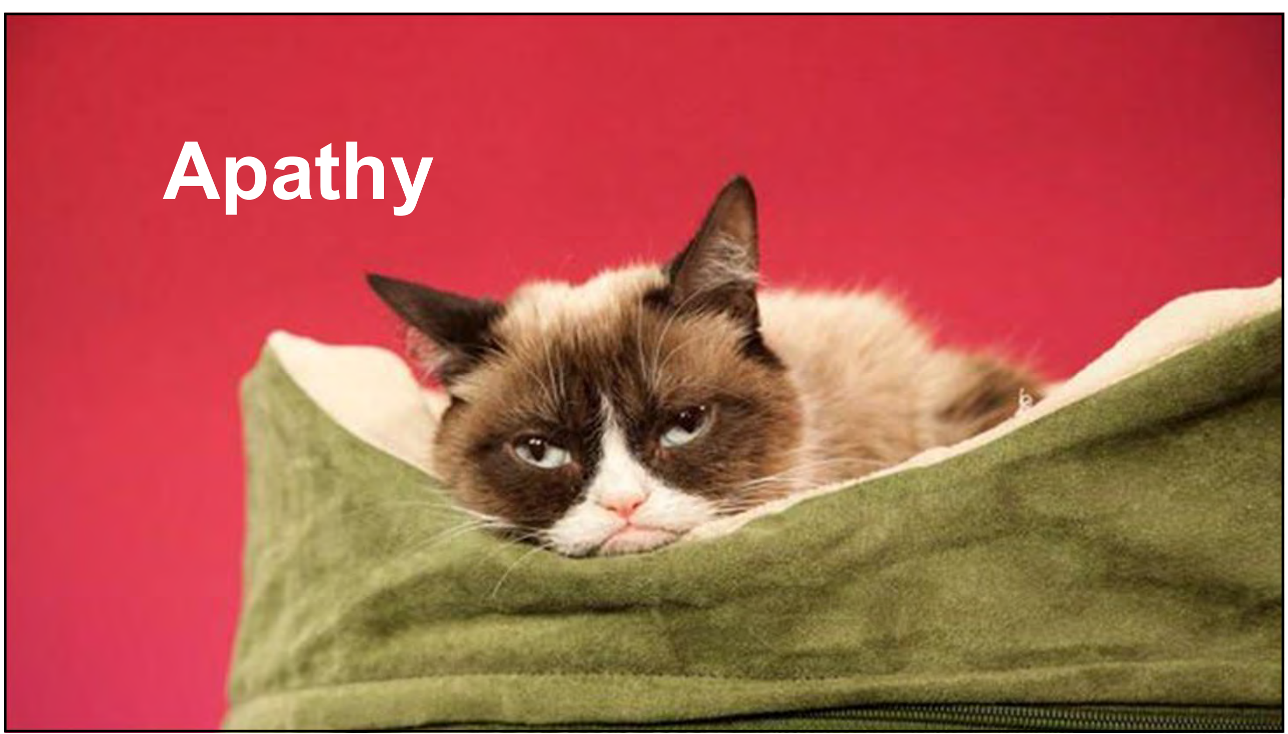

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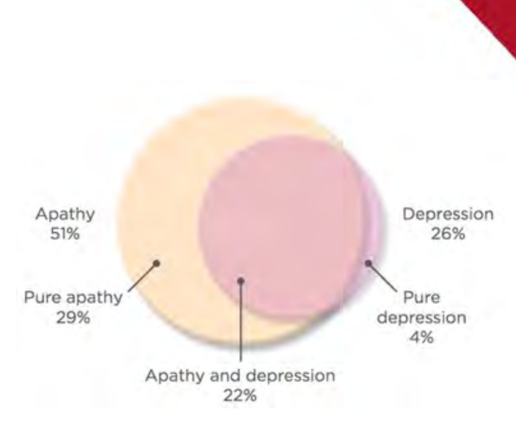
What is Apathy?

A lack of motivation, failure to initiate goal-directed behavior

Examples of apathetic behavior

- Difficulty initiating activities
- Needing prompting or reminding
- Low activity levels
- Lack of effort/reduced productivity
- Not completing tasks that were started
- Not concerned about issues that used to be important

Often seen with depression, but commonly can present as pure apathy



Kirsch-Darrow L, et al. J Int Neuropsychol Soc. 2011 Nov;17(6):1058-66.

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Depression vs. Apathy

Depression – Mood disorder

- Sadness
- Worthlessness
- Guilt
- Hopelessness
- Helplessness
- Pessimism
- Suicidal ideation

Apathy – Motivation disorder

- Decreased initiative
- Less interest in starting new activities
- Less interest in the world
- Emotional indifference
- Decreased emotional reactivity

Overlap

- Anhedonia (inability to feel pleasure)
- Less interest in usual activities
- Increased slowness

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Why is Apathy Harmful?

Reduced daily functioning and activity
Increased caregiver stress/distress
Poor treatment compliance
Worse rehabilitation outcome

Higher Morbidity and Mortality

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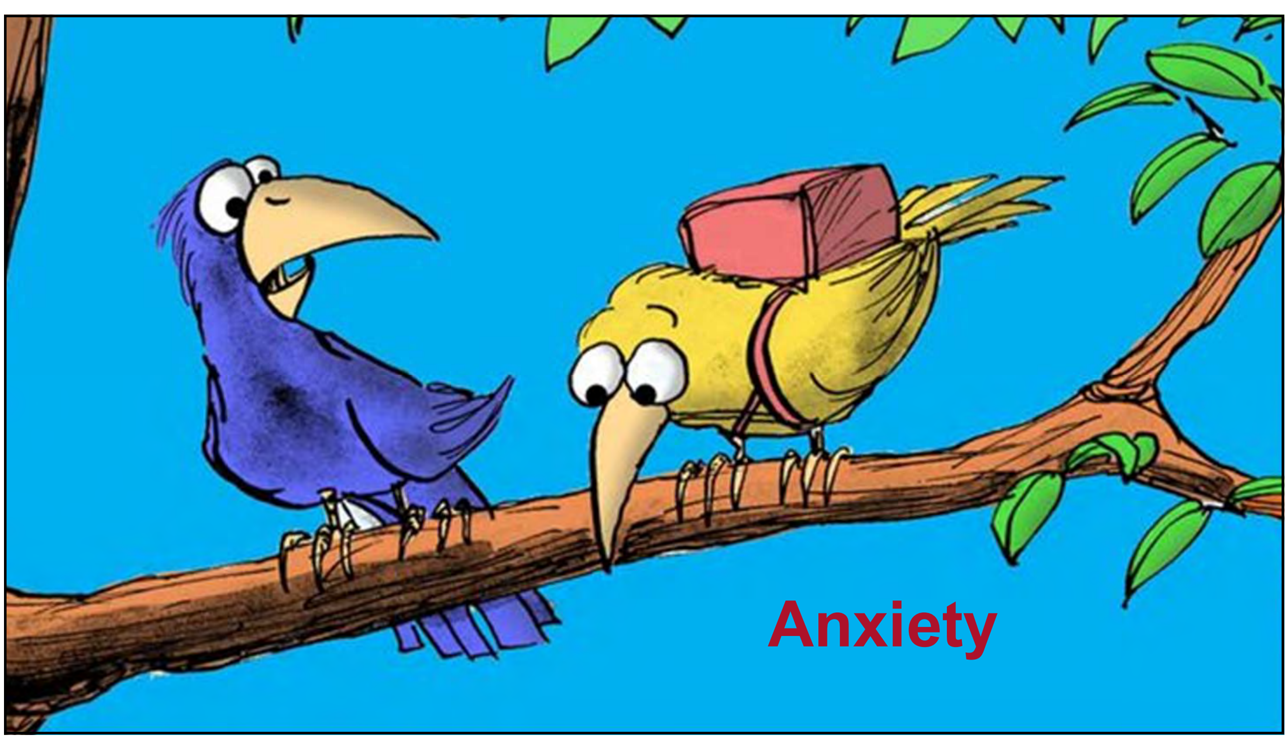

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What is an Anxiety Disorder?

Common manifestations:

- Excessive worry
- Avoidance
- Seeking reassurance
- Easily upset
- Insomnia
- Eating disorders
- Physical complaints: palpitations, hyperventilation, excessive sweating, fatigue, abdominal pain/GI changes, headaches, tremors
- Panic attacks

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What is an Anxiety Disorder?

The 3 most common types of anxiety in PD are

- Generalized anxiety disorder
- Social anxiety
- Panic attacks

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How does anxiety cause problems?

Exacerbates motor symptoms of PD

Impaired concentration and memory

Interferes with sleep

Decreased medication compliance

Friction with friends and family

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Suicide

Approximately 30% of PD patients have had thoughts about suicide

Danish study found that people diagnosed with PD were 2.2x more likely to commit suicide than the general population

If your patient endorses suicidal thoughts, encourage them to:

- Use their social support network – find a support group, stay socially engaged
- Seek professional help: primary care provider, psychiatrist, psychologist, neurologist, social worker
- Prioritize self-care
- Use emergency support services. Call 911 there is immediate need

Erlangsen A, et al. Association Between Neurological Disorders and Death by Suicide in Denmark. *JAMA.* 2020;323(5):444–454.
Lee T, et al. Increased suicide risk and clinical correlates of suicide among patients with Parkinson's disease. *Parkinsonism Relat Disord.* 2016 Nov;32:102-107.

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Suicide Resources

National Suicide Prevention Lifeline
1-800-273-8255
The Lifeline provides 24-hour-a-day, free and confidential support for people in distress, prevention and crisis resources for you or your loved ones and best practices for professionals
https://suicidepreventionlifeline.org/

The Substance Abuse and Mental Health Services Administration National Helpline
800-662-HELP (4357)
Confidential, free, 24-hour-a-day, 365-day-a-year, information service, in English and Spanish, for individuals and family members facing mental and/or substance use disorders
https://www.samhsa.gov/

Crisis Text Line
Text HOME to 741741
Crisis Text Line provides free, 24/7 mental health support via text message
https://www.crisistextline.org/

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How can we treat mental health?

- Medications
- Psychotherapy
- Exercise
- Social Support

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Medications for Depression

Very few controlled trials of medications for depression in PD

First line therapies:

- SSRIs: citalopram, paroxetine, sertraline, others

Second line therapies

- SNRIs: venlafaxine, duloxetine
- TCAs: amitriptyline, nortriptyline
- MAOIs/COMTs: selegiline, rasagiline, entacapone
- **Antipsychotics: quetiapine, clozapine
- Others: mirtazapine, trazodone, bupropion

Bomasang-Layno E, Fadlon I, Murray AN, Himelhoch S. Antidepressive treatments for Parkinson's disease: a systematic review and meta-analysis. Parkinsonism Relat Disord. 2015;21(8):833.

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Medications for Anxiety

No controlled trials specifically for anxiety in PD

First line therapies

- SSRIs & SNRIs

Second line therapies

- TCAs
- Others: buspirone, gabapentin, pregabalin
- Antipsychotics: quetiapine, clozapine
- Benzodiazepines: clonazepam, lorazepam, diazepam

Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. MovDisord 2019;34(5):765.

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Medications for Apathy

Currently no approved treatments specifically for apathy

First line

- Optimizing Parkinson's medication regimen
  - Carbidopa/levodopa
  - Ropinirole, pramipexole, rotigotine

Second line

- Cholinesterase inhibitors: donepezil, rivastigmine
- SNRIs
- Stimulants: Methylphenidate

Mele B, et al. Diagnosis, treatment and management of apathy in Parkinson's disease: a scoping review. BMJ Open. 2020 Sep 9;10(9)

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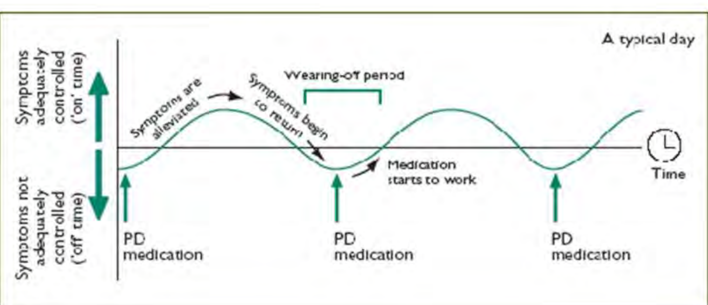
Special Considerations for PD

As PD progresses, fluctuations in symptoms can occur with changing levels of medications

Not only motor symptoms! Mental health can fluctuate, as well

Adjustment of PD medications may be required for optimal treatment



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Other Medical Interventions

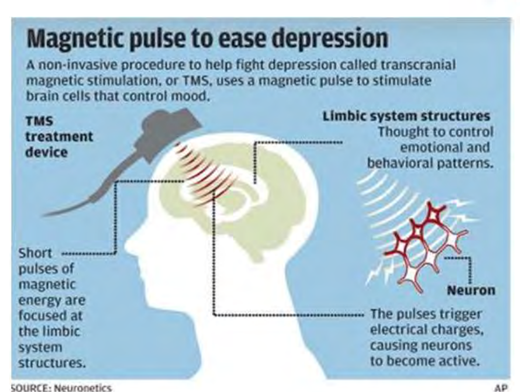
Deep brain stimulation (DBS)

Electroconvulsive therapy (ECT)

- Longstanding therapy for severe, intractable depression. No trials specifically for PD
- Safe and effective – may cause temporary confusion/delirium
- Incompatible with DBS

Transcranial magnetic stimulation (TMS)

- Recently FDA-approved for depression
- Under investigation for effects on mood and motor symptoms in PD



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Psychotherapy

Cognitive behavioral therapy (CBT)

- A therapy technique aimed at changing negative thinking and behavior patterns. Helps establishing coping techniques and thinking positively
- The most studied intervention for depression and anxiety in PD. Shown to be at least as effective than use of medication alone

Resource to find a local therapist: psychologytoday.com

Dobkin RD, et al. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, con-trolled trial. Am J Psychiatry. 2011;168(10):1066-1074

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Exercise

Exercise improves physical and psychiatric symptoms of Parkinson's Disease

Examples:

- Walking
- Stretching
- Yoga
- Tai-Chi
- Lifting weights
- Whatever gets you moving!

Wu PL, Lee M, Huang TT. Effectiveness of physical activity on patients with depression and Parkinson's disease: a systematic review. PLoS One. 2017;12(7)

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Support Groups

Helpful for both PD patients and caregivers!

Information on local support groups can be found at:

- www.ParkinsonsNebraska.org

- www.Parkinson.org
- www.APDAParkinson.org
- www.MichaelJFox.org

Also, many on-line support groups

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Cognitive Changes in PD

Wide range of presentation in symptoms, severity, and progression

- Subtle, subjective complaints
- "Mild cognitive impairment" (PD-MCI)
- Parkinsons Disease Dementia (PDD)

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Cognitive Impairments in PD

- Slowness of thought process ("bradyphrenia")
- Impaired executive function
  - Decision making, problem solving, sequencing, planning, prioritizing
- Impaired recall > encoding of memories
  - Cueing can help with recall
  - Better able to learn new things compared to Alzheimer's

ABSTRACTION	Similarity between e.g. banana - orange = fruit [x] train – bicycle [x] watch - ruler							2/2
DELAYED RECALL	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [x]	Points for UNCUED recall only	1/5
Optional	Category cue	x			x		MIS: 9/15	
	Multiple choice cue		x	x				

Cummings, JL, Benson DF. Arch Neurol.1984

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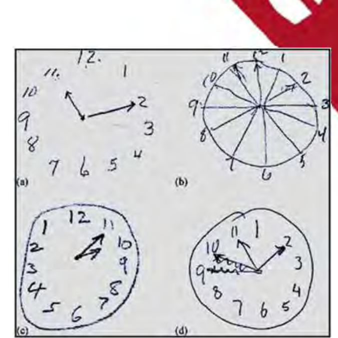
Cognitive Impairments in PD

- Impaired working memory
- Visual-spatial perception problems
  - Unsafe driving
  - Difficulty learning new routes
  - Misplacing objects, forgetting where the car is parked
- Variable performance, inattention, cognitive fluctuations



Cummings, JL, Benson DF. Arch Neurol.1984

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Mild Cognitive Impairment in PD (PD-MCI)

Diagnostic Criteria:

- Diagnosis of Parkinsons Disease
- Gradual decline in cognitive abilities noted by patient, informant, or clinician
- Cognitive deficits on cognitive testing (e.g., bedside cognitive screening test, neuropsychological testing)
- Cognitive deficits are not sufficient enough to interfere significantly with everyday function

Diagnostic Criteria for MCI in PD. Movement Disorders 2012; 27(3):349-356

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PD with Dementia (PDD)

Diagnosis of Parkinson's Disease

Evidence of dementia

- Inability to perform activities of daily living due to cognitive impairment
- Should have typical features of PD dementia (e.g., attention, subcortical, and visual-spatial deficits may predominate)
- Dementia not due to other conditions

Motor symptoms of PD must precede the symptoms of dementia by more than one year, typically many years

Emre M, et al. Movement Disorders 2007; 22:1689-1707.

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Dementia with Lewy Bodies (DLB)

Progressive dementia
- Attentional, subcortical, and visuospatial deficits may predominate

Core features
- Signs of Parkinsonism
- Early, prominent, recurrent visual hallucinations
- Fluctuating cognition

Cognitive changes present within one year of (or prior to) onset of motor symptoms of Parkinsonism

McKeith et. al. Neurology 1996;(47):1113.

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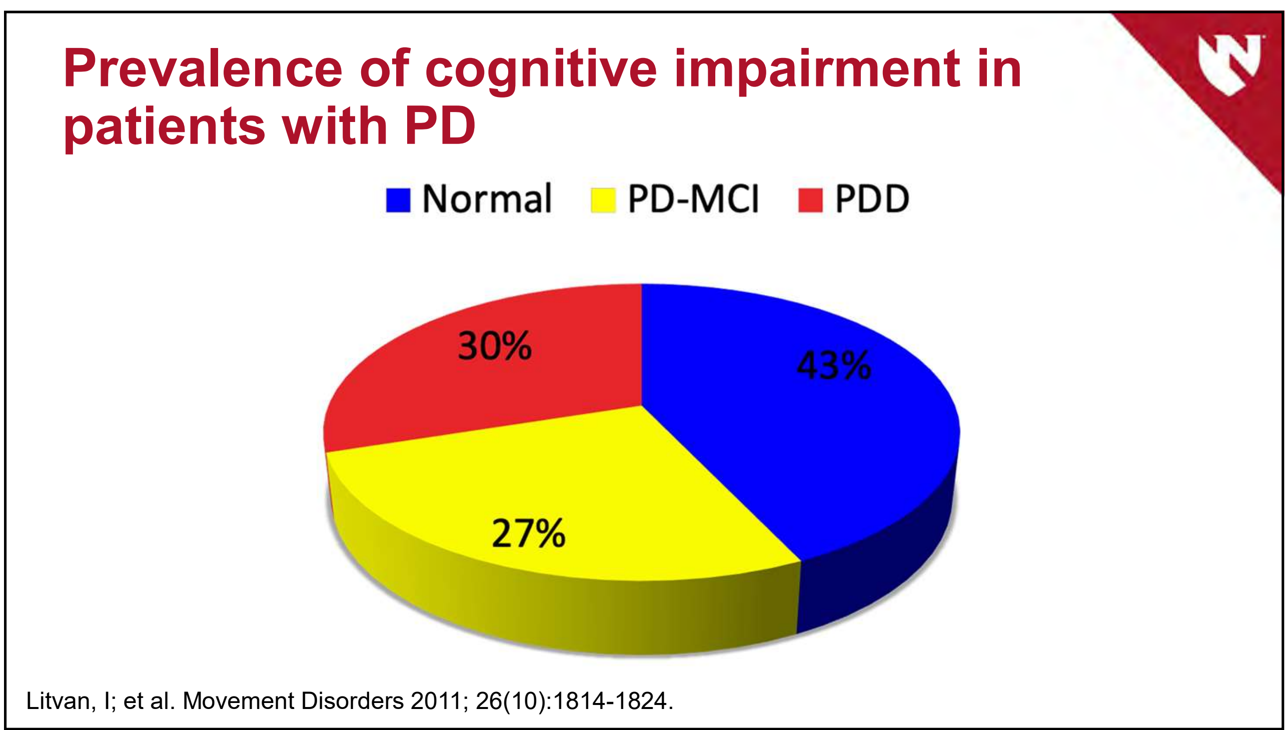
Prevalence of cognitive impairment in patients with PD



Litvan, I; et al. Movement Disorders 2011; 26(10):1814-1824.

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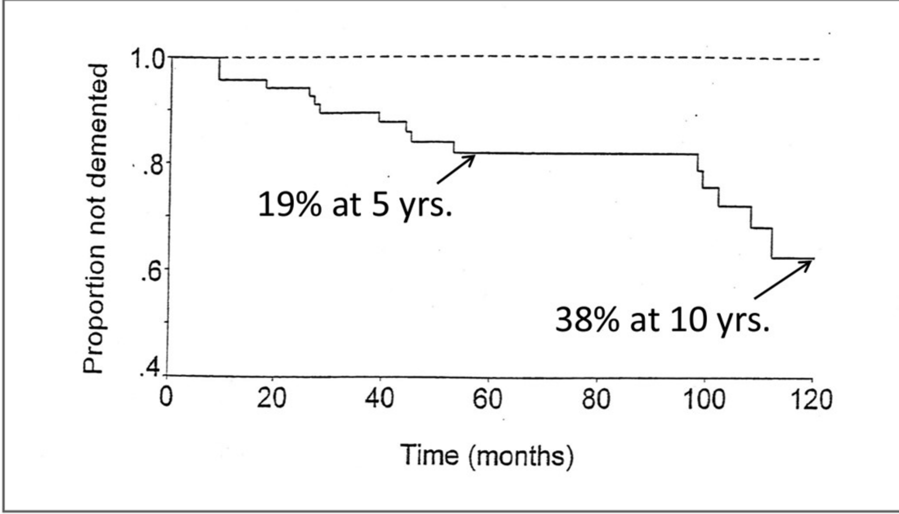
Incidence of Dementia in PD



Hughes, TA. Neurology 2000;54:1596-02.

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Risk Factors for PDD

Older age at onset of motor symptoms
Greater severity of motor symptoms
Longer duration of PD
Poor responsiveness or intolerance to dopamine
Presence of REM sleep behavioral disorder
Presence of orthostatic hypotension

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Evaluation of Cognitive Complaints

Rule out non-PD causes of cognitive problems
- Vitamin deficiencies, thyroid hormone levels, kidney or liver dysfunction
- Sleep disorders (e.g., sleep apnea, REM behavioral disorder)
- Depression, anxiety, and other mood disorders

Review medications

Cognitive testing
- Bedside examinations: MMSE, MoCA, SLUMS, others
- Consider formal neuropsychological testing

Consider brain imaging

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Medications to Avoid

Anticholinergic medications
- Diphenhydramine (Benadryl), anti-spasmodic medications (e.g. oxybutynin, cyclobenzaprine)

Opiate pain medications or related narcotics
- For example: hydrocodone, morphine, fentanyl

Sedatives and benzodiazepines during the day
- For example: clonazepam, lorazepam, primidone

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Treatment of Cognitive Impairment

Keep mentally and physically active, socially connected, eating a "heart healthy"/Mediterranean diet

Medications

- Cholinesterase inhibitors: rivastigmine* [FDA-approved], donepezil, galantamine
- Can improve memory, attention, and neuropsychiatric symptoms
- May worsen tremor in PD, can cause nausea, diarrhea, rhinorrhea, vivid dreams

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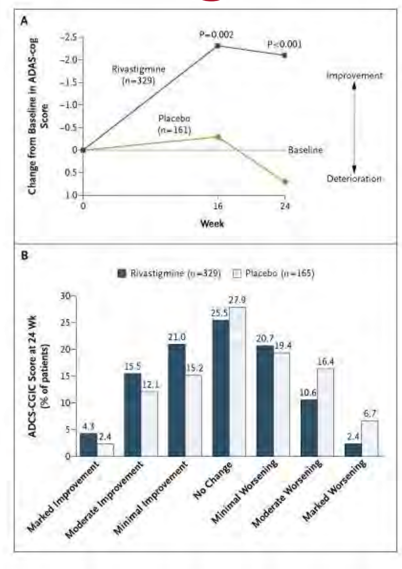
Rivastigmine for PDD



- Mild/moderate improvement in cognitive testing scores
- Mild clinically significant improvement compared to placebo
- GI side effects may be mitigated with transdermal (patch) formulation

Emre M, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med. 2004

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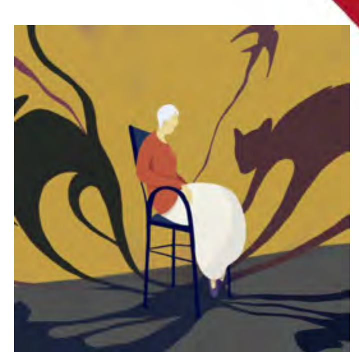
Psychosis in PD and DLB

22-38% of PD patients

80-90% of DLB patients

Visual hallucinations most common, but also auditory hallucinations and delusions

Risk factors: cognitive impairment, anti-cholinergic medications, dopaminergic agonist medications, underlying infections, surgical procedures, poor sleep



Weintraub D, Mamikonyan E. Am J Geriatr Psychiatry. 2019

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Management of Psychosis in LBD

Conservative treatments:

- Rule out infection or medical illness
- Review any new medication changes
- Improve sleep, as able
- If hospitalized: reorientation, safe mobilization, use of glasses/hearing aids if needed, adequate nutrition/hydration
- Consider adjusting dopaminergic Parkinsons medication regimen with neurologist

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Management of Psychosis in LBD

Pharmacologic treatments:

- Consider adding cholinesterase inhibitor (donepezil, rivastigmine, galantamine) or increasing the dose if already taking
- Consider low-dose of an atypical antipsychotic with low-risk of worsening Parkinsonism
- Consider trial of pimavanserin

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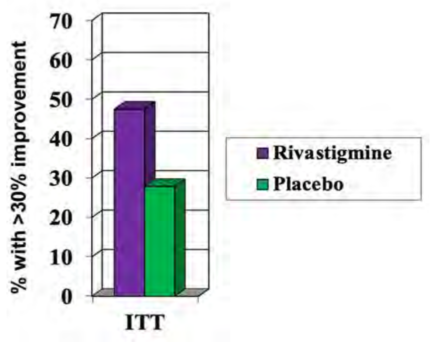
Rivastigmine for Neuropsychiatric Symptoms in PD



- Significant difference in number of patients with >30% improvement in NPI-4 score (delusions, hallucinations, apathy, depression)
- No worsening of motor symptoms

McKeith I, et al. Lancet 2000; 356:2031-6.

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Antipsychotic Medications in LBD

Antipsychotic medications block dopamine receptors and can cause medication-induced Parkinsonism

- Clozapine has higher affinity for D4 receptors than D2 receptors and has a much lower risk of causing Parkinsonism. Limited by potential severe side effects, requires frequent monitoring
- Quetiapine has higher affinity for $5\text{-}HT_{2A}$ antagonism, but still has some action on D2 receptors and many others. Has not been proven to significantly reduce psychosis in placebo-controlled trials

Associated with small but statistically significant increased risk of death and stroke in older patients with dementia

Weintraub D, Mamikonyan E. Am J Geriatr Psychiatry. 2019

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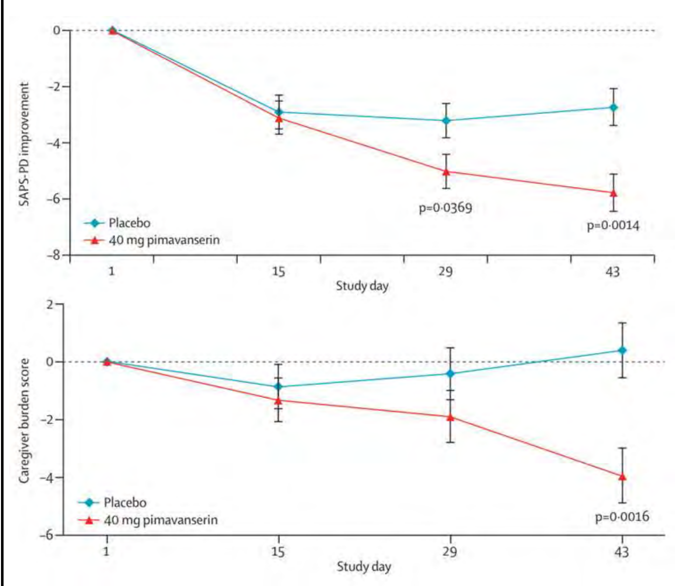
Pimavanserin for PD Psychosis



Selective $5\text{-}HT_{2A}$ receptor inverse agonist

- No action on dopaminergic, muscarinic, adrenergic, or histaminergic receptors

Significant reductions in psychosis and caregiver burden scales

<u>No worsening of PD motor symptoms</u>

FDA-approved for treatment of PD psychosis

Cummings J, et al. Lancet 2014; 383:533-40

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Take-Home Points

- Mood and cognitive disorders are very common in PD
- They can affect quality of life as much as motor symptoms
- Depression increases risk of suicide
- Mood disorders in PD are underdiagnosed: recognition of the symptoms is key!
- Cognitive decline and psychosis in PD require careful review and adjustment of medications to balance neuropsychiatric and motor symptoms
- Address mood and cognitive concerns from the patient (and family) at least annually

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