Neuropsychiatry of
Diffuse Lewy Body Dementia
&
Parkinson's Disease Dementia

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Disclosures…

I have no financial or commercial interests to disclose.

Medications discussed will likely include off-label uses.

Limited data & approval → deference to expert consensus.

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Why discuss this topic?

DLB 2nd most common dementia after Alzheimer's.

Parkinson's very often leads to MCI & Dementia.

Difficult to consolidate findings into diagnosis.

Easy to misdiagnose / miss diagnosis.

Disease-specific treatment considerations.

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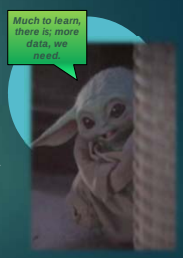
Inherent challenges in treatment

- Complex, multi-system presentation & symptoms.
  - Cognitive, Psychiatric, Autonomic, Motor, etc.
- Patient-to-patient variability of presentation.
  - No "one size fits all" strategies.
- Symptoms vary throughout course of disease.
  - Need to be adaptive to changes.
- Limited data → limited treatments, pending research.
  - Recommendations often per expert consensus.
- Treatments may worsen other features.
  - *(delicate balancing act)*



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What I intend to cover

Definitions & Terminology, e.g. Lewy Body Disease & "dementia".

Briefly discuss underlying pathophysiology of Lewy Body Disease.

Distinguish Parkinson Dementia (PDD) & Diffuse Lewy Body Dementia (DLB).

Review key identifiable features that make PDD & DLB stand out.

Discuss review treatments for cognitive & psychiatric symptoms.

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Clinical Case

68M brought in by wife for cognitive decline gradually progressive for the last year; some days significantly better than others. Symptoms include misplacing items, forgetting to take his pills, trouble balancing the check book, and increasing trouble navigating in the car. He'd previously been active in his wood shop, but has a hard time designing & completing projects. No psychiatric history, but in the last 1-2 months, he has become apathetic, withdrawn, and less facially expressive, leading PCP to start him on Escitalopram for suspected depression. They recently stopped sharing a bed due to him kicking in his sleep. He admits he sometimes sees a vivid figure of a cat as he wakes, and though they do not own any pets, he is not overly distressed by this. No physical symptoms aside from a slower gait. PMFSH & medications otherwise unremarkable.

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Major Neuro-Cognitive Disorder

"dementia"

- Disease state → impairs cognition → impairs function.
  - ***Subjective*** cognitive decline from previous baseline.
  - ***Objective*** multi-domain cognitive impairment.
  - ***Instrumental*** *dysfunction* due to impairments.
  - No equally viable contributors or differentials.
- Dementia is a severity point on a given disease continuum.
  - e.g., Alzheimer *Disease* = Pre-Clinical → Mild Impairment → Dementia.
    - Dementia stages = mild → moderate → severe → end stage.

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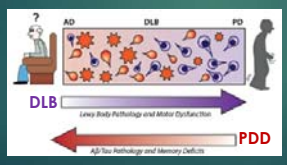
"Lewy Body Diseases"

- *Diffuse* Lewy Body Disease (**DLB**) & Parkinson's Disease Dementia (**PDD**).
  - *Common denominator* = ***Lewy Bodies***
- **1 Year Rule** of onset in DLB, *locus → symptom*.



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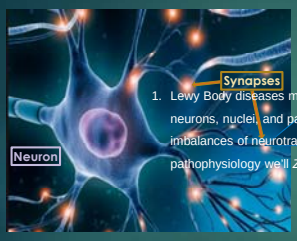
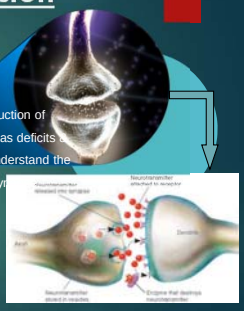
Neurotransmission



1. Lewy Body diseases manifest via destruction of neurons, nuclei, and pathways, as well as deficits & imbalances of neurotransmitters. To understand the pathophysiology we'll *Zoom* in on the sy



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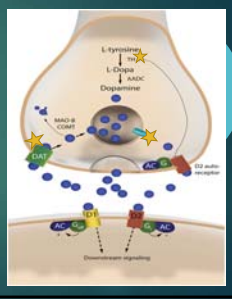
Alpha-Synuclein Function

- Hypothetical roles in **Dopamine (DA) neurotransmission**
  - Synthesis increased by disinhibiting tyrosine hydroxylase (TH).
  - Packaging: facilitation of pre-synaptic vesicles via VMAT.
  - Transport: modulates **DA T**ransporter ergo synaptic [DA].



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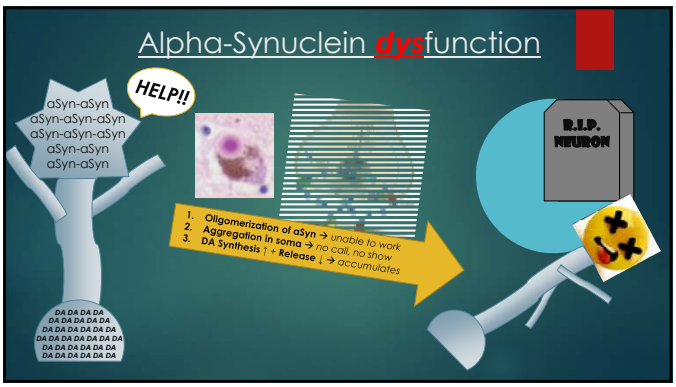
Alpha-Synuclein dysfunction



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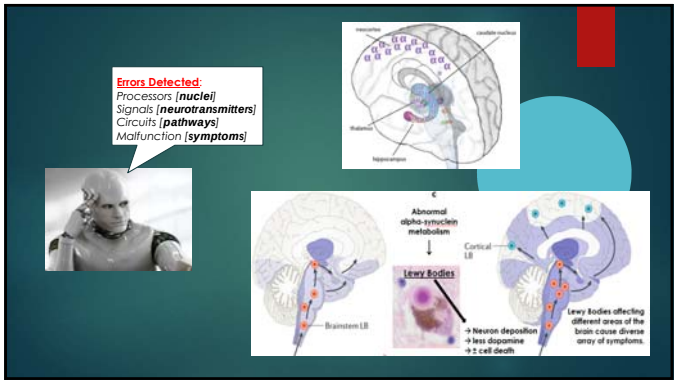

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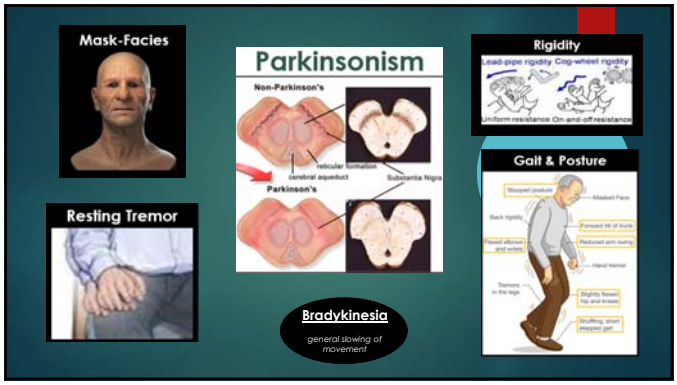

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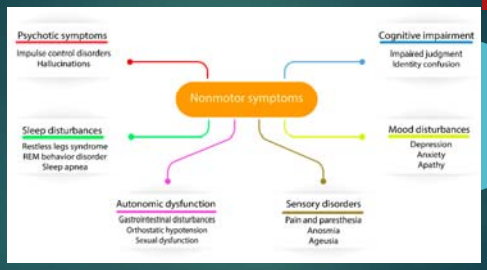
Non-Motor Symptoms



We'll focus on cognition, mood, psychosis, and sleep.

Sorry, Parkinsonian, Autonomic, and Sensory disorders.

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Parkinson's Disease Criteria

MDS (*short version*)

- Parkinsonism + (Supportive Criteria x2) – (Exclusion Criteria & Red Flags)
- **Parkinsonism**, e.g. bradykinesia + resting tremor or rigidity
- **Supportive** Criteria
  - Dopamine Therapy -- ↓ Parkinsonism
  - Levodopa-induced dyskinesia
  - Resting Tremor of any limb
  - Olfactory loss or Cardiac SNS denervation
- **Absolute Exclusion** Criteria & **Red Flags** absent.
  - *Lots of 'em, and beyond scope of lecture.*

Parkinson's Disease *Dementia* = **Parkinson's Diagnosis → Dementia later.**

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Diffuse Lewy Body Dementia

Supportive

- Antipsychotic Sensitivity
- Autonomic Dysfunction
- Postural instability & falls
- Episodes of unresponsiveness
- Excessive daytime sleepiness
- Anosmia or Hyposmia
- Anxiety, apathy, depression
- Non-visual hallucinations, Delusions

Core Criteria

Impaired Cognition ± Fluctuation
Attention, Spatial, Executive

Visual Hallucinations
Vivid / Recurrent / Hypnopompic

REM Sleep-Behavior Disorder
e.g. acting out dreams

Parkinsonism
Bradykinesia+
Rigidity / Gait / Hypomimia / Tremor

Biomarkers

Indicative

- **SPECT** or **PET**: reduced dopamine transporter uptake in basal ganglia.
- **^{123}Iodine-MIBG** Scintigraphy: ↓ low uptake.
- **Polysomnography**: REM w/o atonia.

Supportive

- ***CT/MRI***: *preservation of medial temporal lobes.*
- ***SPECT*** *or* ***PET****: reduced dopamine transporter uptake in general.*
- ***EEG****: findings I honestly don't understand.*

Probable = Core x2 or Core x1 + Supportive

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Diagnosis: ***probable*** **Diffuse Lewy Body Dementia**

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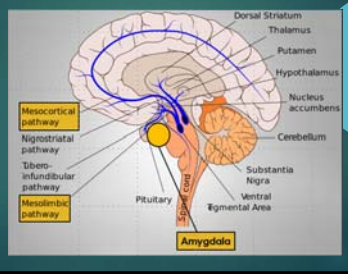
Cognitive-Psychiatric Symptoms

*Degeneration of nuclei → **neurotransmitter deficiencies**.*

Some implicated neural structures & pathways:



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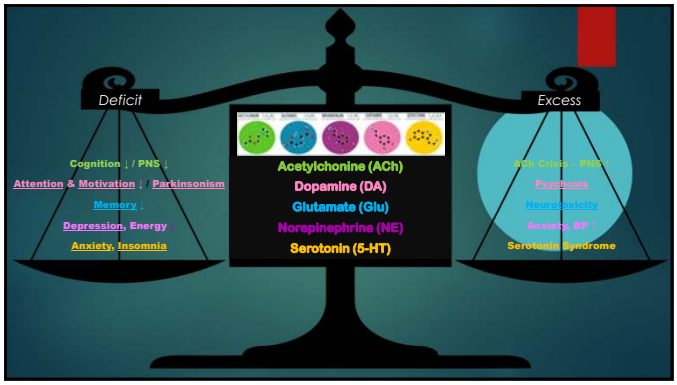

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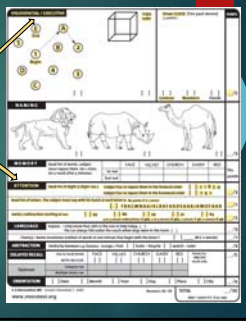
Cognitive Deficits in DLB & PDD

- Attention, Executive, Visuo-perceptual function tend to decline early in DLB.
  - *MoCA might show errors on these tasks*
- *Memory loss often not as prominent early LBD/PDD disease course as in Alzheimer's Disease.*



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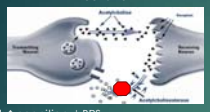
Cholinesterase Inhibitors

Mechanism



Goal: ↑ cognition, ↓ BPSx.

Side Effects: **GI** (N/V/D), **PNS** (↓HR), **Sleep** ↓

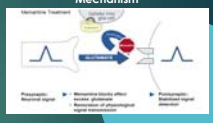
Donepezil start 5 mg PO once daily.
- *10 mg in 4 weeks if tolerated.*

Rivastigmine 4.6 mg TD once daily.
- *↑↑ monthly as tolerated.*

Galantamine: if above not tolerated.

Memantine

Mechanism



Goal: ↓ excitotoxicity, preserve cognition/function.

Side Effects: confusion, dizziness, headache.

Dose (IR): start 5 mg, +5 mg/wk → target 20 mg.

Dose (ER): start 7 mg daily, +7 mg/wk → max 28 mg.

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Anxiety

Pathophysiology: nuclei/pathways, NTs, Amygdala

Presentation: restless, sleepless, worried, phobic.

Course: often worse during "off periods"

Treatment

SRIs, e.g. Es/Citalopram, Sertraline

SNRIs, e.g. Venlafaxine (*limited data*)

Mirtazapine: NE, 5-HT, H1 neurotransmission ↑

Buspirone: $5HT_{1a}$ agonist ± D_2 antagonism?

Benzos usually not recommended

Depression

Pathophysiology: DA & NE ↓ ± Reactive

Course: often mirrors motor symptoms
Related to *DA deficiency & Tx?*

Diagnosis: *easy to misinterpret symptoms*

Hypomimia → "*emotionally withdrawn*"

Apathy → "*avolitional / anhedonic*".

Sleep dx, e.g. hypersomnia, may be 1°.

Treatment

SRIs e.g. Sertraline reasonable 1st line

SNRIs, e.g. **Venlafaxine** & **Duloxetine**

Bupropion: **NE** & **DA** reuptake inhibitor

Dopamine Rx may improve depression

ECT & **DBS** being studied.

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Psychosis

Pathophys: complex; 5-HT, ACh, DA implicated.

Clinical: visual hallucinations, presence hallucinations, illusions, other modalities, delusions (paranoid).

Differentials: illusions, distortions of memory.

Treatment: not always needed if symptoms benign.

Our patient's hallucination did not bother him, but it probably didn't look like this →

So do we need to treat at this point?

Avoid D_2 antagonists; risk of sensitivity & mortality.

Conservative behavioral measures – limited data.

Wean Dopamine Rx gradually as follows:
Anti-Cholinergics → MAO-B inhibitors → Amantadine → dopaminergics → COMT-inhibitors → Levodopa.

Cholinesterase Inhibitors: e.g. Donepezil.

Antipsychotics w/caution if **distress** or **danger**.

Pimavanserin - $5HT_{2a>2c}$ antagonist, approved for PDD w/psychosis, not yet for DLB. $$$$

Clozapine & **Quetiapine** – $D_2/5HT_{2A}$ blockers
Dyskinesia risk low in both vs other SGAs
Effect: Clozapine > Quetiapine
Monitoring: Clozapine > Quetiapine

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Sleep Disturbances

REM Sleep Behavior Disorder
Hypersomnia, 1° vs 2°
Insomnia, 1° vs 2°
Obstructive Sleep Apnea
Parkinsonism, nocturnal
Restless Legs Syndrome
Periodic Limb Movement

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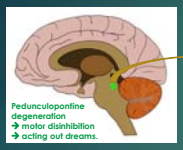
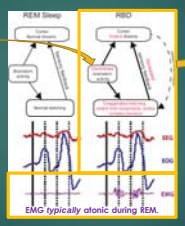
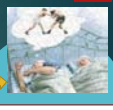
REM Sleep Behavior Disorder







Prevalence:
General Population ~1%
α-Synucleinopathies ≥ 50%
- *May be prodromal*

5-HT & NE meds may increase risk.

Diagnostic Criteria for RSBD
Repeated episodes of sleep-related vocalization and/or complex motor behaviors
These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep
Polysomnographic recording demonstrates REM sleep without atonia (RSWA)
The disturbance is not better explained by another sleep disorder, mental disorder, medication or substance abuse

Interventions: safety → reversible factors → Pharmacotherapy

Melatonin start 3 mg PO HS.
- *Effective range 6-18 mg.*

ClonaZepam start 0.25 mg PO HS.
- *Effective range 0.5-1 mg.*

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Dyssomnias, other

Hypersomnia: hygiene → evaluate / treat underlying causes:
- Primary Insomnia → Melatonin; *limited data on "Z-drugs".*
  - *Caution: Mirtazapine & Trazodone may ↑ RSBD.*
- Obstructive Sleep Apnea: CPAP if indicated.
- Nocturnal Parkinsonism: Levodopa (possible psychosis).
- Restless Legs: Ropinirole vs Pramipexole w/caution.

Hypersomnia 2.0 – still super sleepy? Trial stimulants.
- **Modafinil**: 100 mg qAM, may trial 200 mg after 1 week.
- **Methylphenidate**: start low, go slow, ER formulations.

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So…what do we do for *our* patient?

Cognitive: behavioral + pharmacologic.
- Compensatory behavioral interventions.
- Social support, e.g. delegating tasks.
- Donepezil 5 mg ± Memantine 5 mg.

Depression: assess carefully & treat if present.
- *Truly depression vs mimicking sx?*
- SSRI (Escitalopram) okay if helps.
- *Could try SNRI, e.g. Venlafaxine.*

REM Sleep Disorder: PSG for OSA/RLS/PLMS.
- Safety measures first and foremost.
- Trial **Melatonin** 3 mg HS, titrate.
- *Clonazepam, low dose, caution.*

Visual Hallucinations: do we really need to treat?
- Probably not in his particular case.
  - *Reserve for distress/danger.*

Parkinsonism: do we need to treat now? or…
- Reserve for disabling or disruptive sx?
  - *Risk of worsening psychosis.*

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Sources

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