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

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BROADLAWNS GERIATRICS

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Disclosures…

I have no financial or commercial interests to disclose.

Medications discussed will likely include off-label uses.

This is at least in part due to limitations of available data, and reference to expert consensus in treatment.

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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 recognize and easy to misdiagnose.

Treatment nuances i.e. unique considerations.

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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 No psychiatric history, but in the last 1-2 months, he has become apathetic, withdrawn, and less facially expressive, leading PCP to start him on Escitalopram for suspected depression.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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Clinical Case

Exam

- Const: alert, interactive, comfortable, no distress, healthy habitus, well-groomed.
- Neuro: no tremors noted, subtle cogwheel rigidity, gait slow but no "shuffling".
- Psych: mood "nervous", affect flat, thought process linear, content normal.

Labs unremarkable.

Brain CT: mild atrophy sparing hippocampi; no s/o NPH or vascular disease.

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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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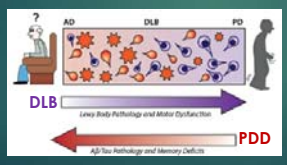
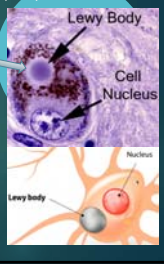
"Lewy Body Diseases"

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





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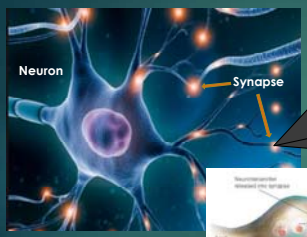
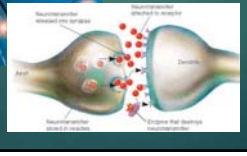
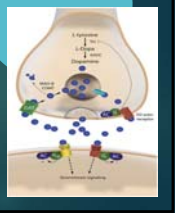
Neurotransmission







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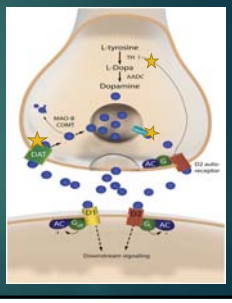
Alpha-Synuclein Function

- 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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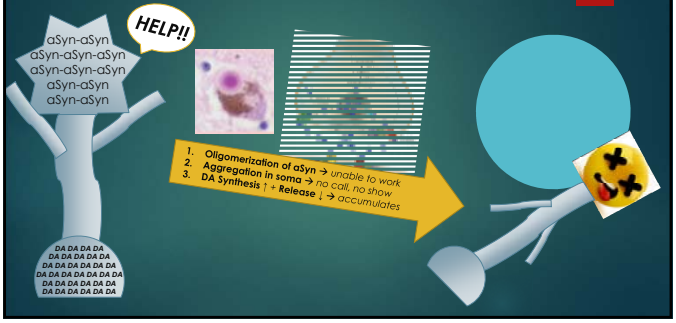
Alpha-Synuclein *dys*function



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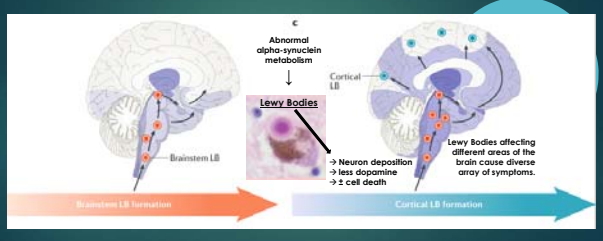
So then what happens...?



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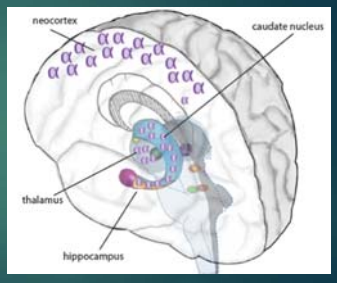
Errors Detected:
*Processors [**nuclei**]*
*Signals [**neurotransmitters**]*
*Circuits [**pathways**]*
→ Malfunction



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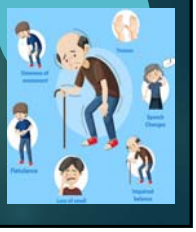
Parkinson's Disease Criteria
MDS (*short version*)

- Parkinsonism + (Supportive Criteria x2) – (Exclusion Criteria & Red Flags)
- **Parkinsonism**, i.e. bradykinesia + resting tremor or rigidity
- **Supportive** Criteria
  - Dopaminergic therapy beneficial
  - 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, delusions
Non-visual hallucinations

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 + Biomarker*
***Possible** = Core x1 or Biomarker x1*

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What do we do for our patient?

Inherent challenges in treatment include:

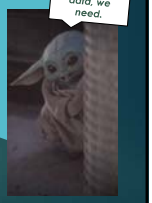
Symptoms complex & multiple system.

Treatments may worsen other features.

Symptoms vary patient-to-patient.

Symptoms vary in disease course.

Many recommendations = expert consensus.



We'll focus on cognition, mood, psychosis, and sleep.
Parkinsonism & dysautonomia out of scope for this lecture.

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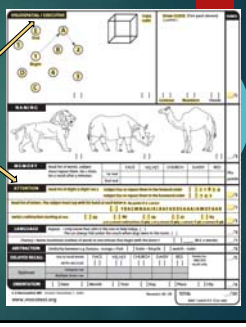
Cognitive Deficits in DLB & PDD

- 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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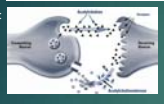
Cognitive Impairment

Cholinesterase Inhibitors

Mechanism:



Benefit: ↑ cognition, ↓ fluctuation, ↓ psych symptoms.

Contraindications: bradycardia & <3 conduction dx.

Side Effects: GI (N/V/D), PNS (bradycardia), Sleep issues.

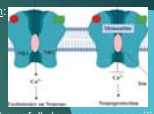
Donepezil: 5 mg PO → 10 mg if tolerates x4 weeks; if not.

Rivastigmine: 4.6 mg TD, titrate q4 weeks as tolerated.

Galantamine – if Donepezil & Rivastigmine not tolerated.

NMDA-r antagonist, Memantine

Mechanism:



Benefit(?): *hopefully* to preserve cognition & function.

Caution in cardiac, hepatic, renal, seizure disorders.

Side Effects: confusion, dizziness, headache.

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

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

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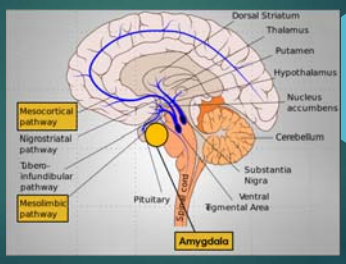
Neuropsychiatric symptoms

Degeneration of nuclei → neurotransmitter deficiency.
Implicated structures & neural pathways:



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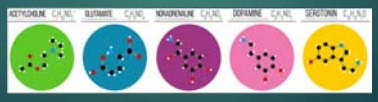
Deficiency…	Neurotransmitter	*Excess!!!*
	Acetylcholine	
Inattention & Motivation low, Parkinsonism	Dopamine	Psychosis
Fatigue, Memory ↓	Glutamate	Neurotoxicity, Anxiety, Sleep Disturbances
Depression, Energy ↓	Norepinephrine	Anxiety, Hyperactivity, BP ↑
Anxiety, Insomnia	Serotonin	5-HT Syndrome



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Anxiety

- Pathophysiology:
  - Mesolimbic/cortical degeneration
  - Amygdala dysfunction
  - Degeneration of NE/5-HT synthesizing nuclei
- **Presentation**: inability to relax, worrying, insomnia, phobias.
- Course: often worse during "off periods"
- Treatment
  - **SSRIs**, e.g. Citalopram, Escitalopram, Sertraline
  - **SNRIs**, e.g. Venlafaxine (*limited data*)
  - Mirtazapine
  - Buspirone
  - Benzos usually not recommended

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Depression

Pathophysiology
- Pathological DA & NE deficiency.
- Reaction to diagnosis & disability.

Course
- Mirrors motor manifestations.
  - Both related to DA deficiency..?
  - Both often ultimately refractory.

Diagnostic consideration
- Clearly important to diagnose & treat
  - Significant impact on quality of life.
- Diagnose carefully due to ease of misinterpreting unrelated symptom clusters, e.g. hypomimia, *apathy*, and insomnia.

Treatment
- **SSRIs**: favorable side effects, reasonable 1st line.
  - *Paroxetine* avoided d/t anticholinergic ADEs.
- SNRIs: **Venlafaxine**, **Duloxetine**
- **Bupropion**: NE & DA reuptake inhibitor!
- Dopaminergics often improve depression.
- **ECT** & **DBS** being studied.

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Psychosis

- May not always need treatment, especially if symptoms benign in nature.
- Pharmacotherapy if distressing/endangering & conservative measures fail.
  1. *Minimize dopaminergics, e.g. levodopa, which may cause/worsen psychosis.*
  2. *Non-pharmacological interventions can be considered; limited data.*
  3. Cholinesterase Inhibitors: Donepezil, Rivastigmine, Galantamine.
  4. Antipsychotics with caution d/t risk of sensitivity & black-box warning.
     1. **Pimavanserin** novel antipsychotic, 5HT2a antagonist w/o D2 activity.
     2. **Quetiapine**
     3. **Clozapine**
     4. **Risperidone**

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Psychosis

- Pathophysiology: implications in neurotransmitter systems including 5-HT, ACh, and DA.
- Clinical: visual hallucinations, presence hallucinations, illusions, hallucinations in other modalities, delusions (often paranoid).
- Course
- Differentials
- Treatment – avoid D2 receptor antagonism → worse motor symptoms
- Clozapine most efficacious, significant monitoring burden

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Weaning Dopaminergics in Psychotic Patients

- PD/DA medications should be removed gradually as follows:
  1. Anticholinergics (Benztropine, trihexylphenidyl (sometimes used for tremors)
  2. MAO-B inhibitors
  3. Amantadine
  4. Dopaminergic
  5. COMT-inhibitors
  6. Levodopa

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Sleep Disturbances

- REM Sleep Behavior Disorder
- Hypersomnia
- Primary Insomnia
- Obstructive Sleep Apnea
- Parkinsonism, nocturnal
- Restless Legs Syndrome
- Periodic Limb Movement

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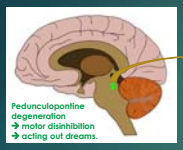
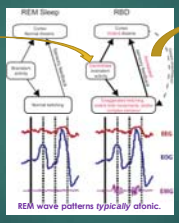
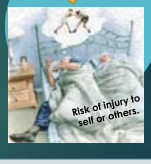
REM Sleep Behavior Disorder (RSBD)







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

SSRIs/SNRIs sometimes factors in RSBD.

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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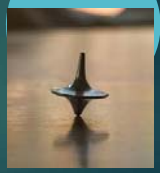
Other Dyssomnias

- **Daytime 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:



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Again, what do we do for our patient?

Cognitive: behavioral + pharmacologic
- Organize items & meds, delegate bills, etc.
- Cholinesterase Inhibitor ± Memantine

Depression: assess carefully & treat w/caution.
- *Truly depression or hypomimia from DLB?*
- PHQ/GDS → SSRI okay if helps; may consider Venlafaxine if not.

REM Sleep Disorder: PSG for OSA/RLS/PLMS.
- Safety measures first and foremost.
- Trial **Melatonin** 1st → Clonazepam.

Visual Hallucinations: do we really need to treat?
- Reserve SGAs for distress or danger.
  - *May cause/worsen Parkinsonism.*

Parkinsonism: trial dopaminergics with caution.
- Reserve for disabling or disruptive sx.
- May cause or worsen psychotic sx.

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Sources

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