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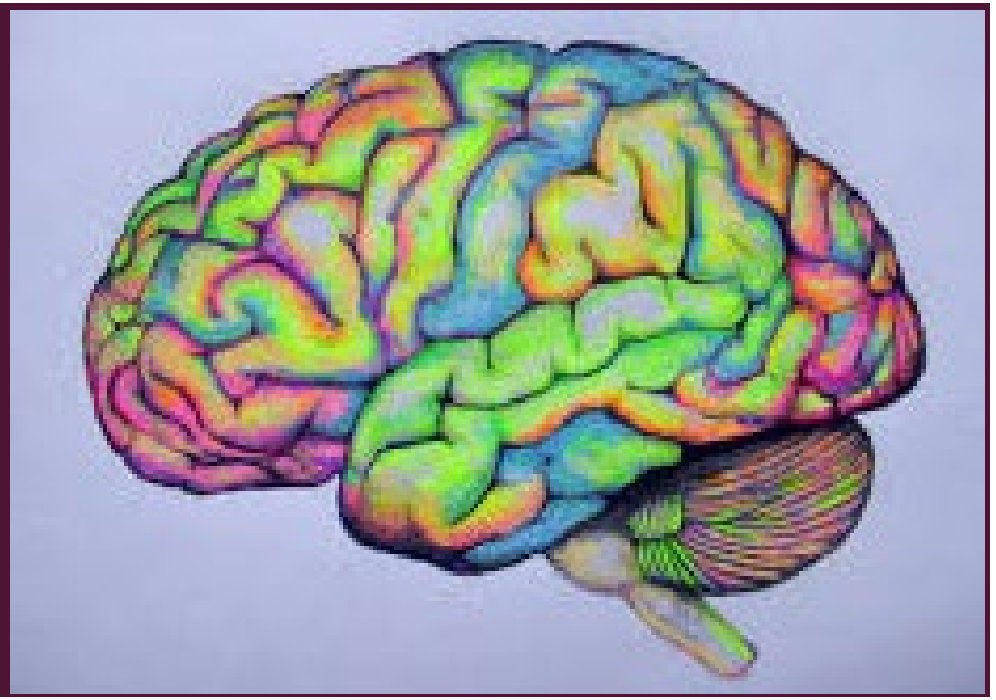
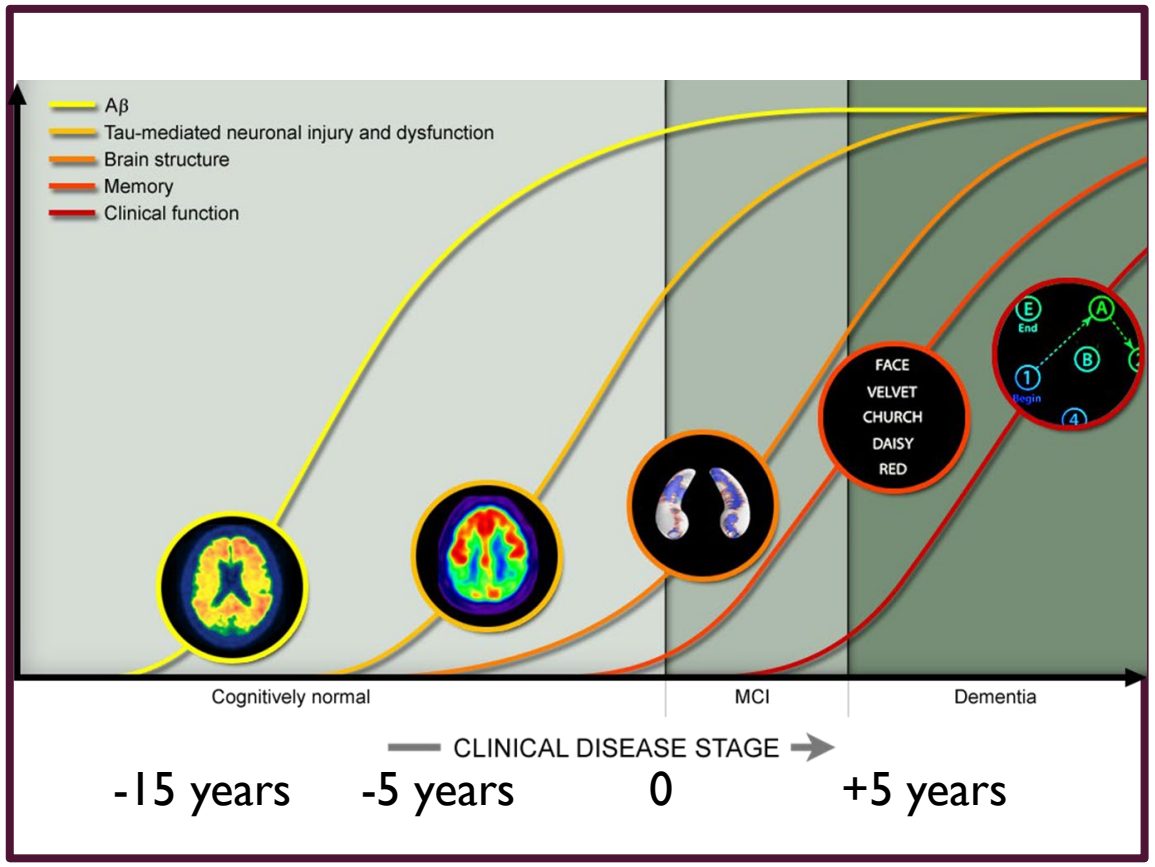
# DLB RESEARCH UPDATE 2026



# ALZHEIMER'S IS:



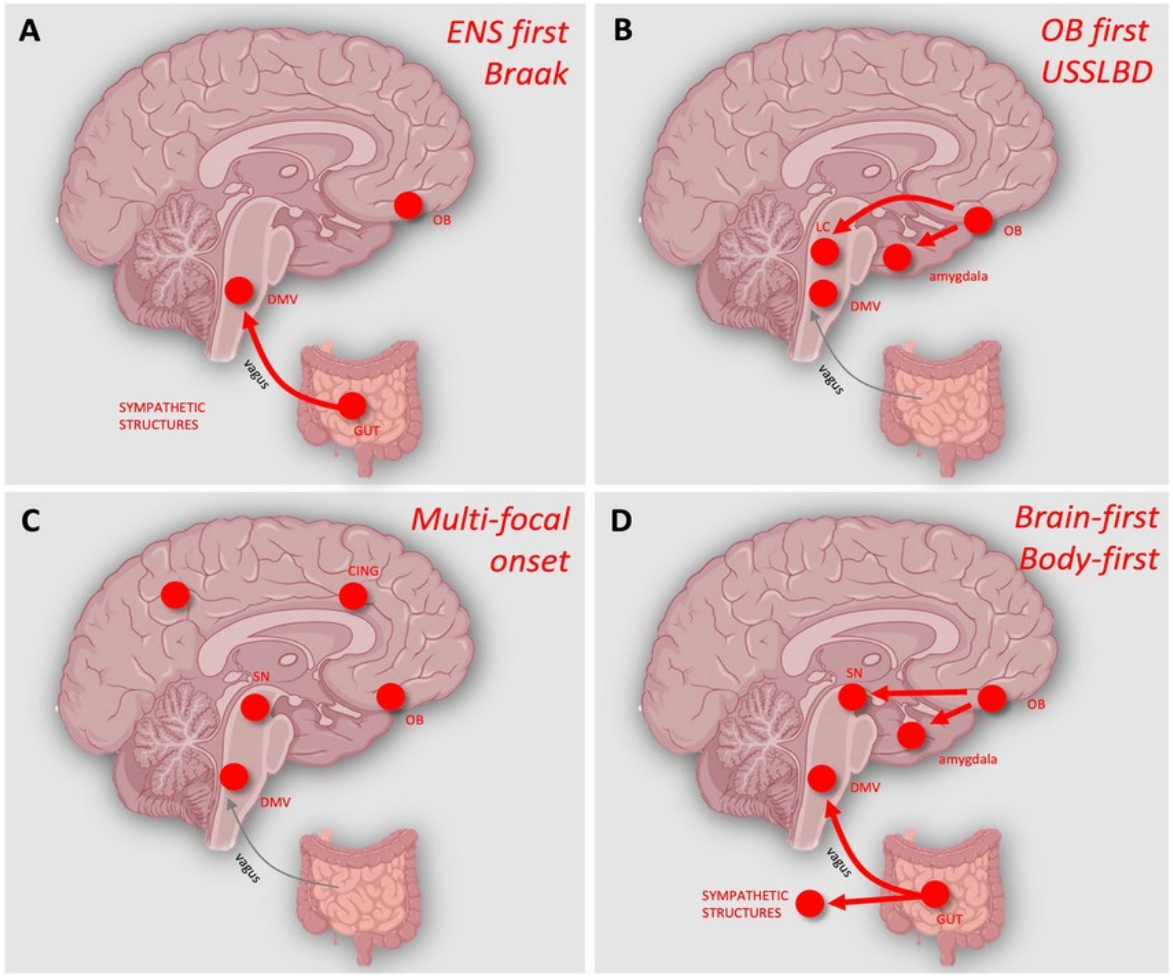

- A specific disease that can cause dementia
- A neurodegenerative disease that causes loss of neurons over time. Always progressive but speed of progression is very variable
- Associated with abnormally high levels of two neuronal proteins, beta-amyloid and tau
- Frequently has a transitional state of MCI
- When MCI is accompanied by Alzheimer's biomarkers: MCI-due-to-AD
- Now understood to start up to 20 years before someone gets clinical symptoms
- Not everyone with Alzheimer's disease has dementia

# LEWY BODY DISEASE IS:

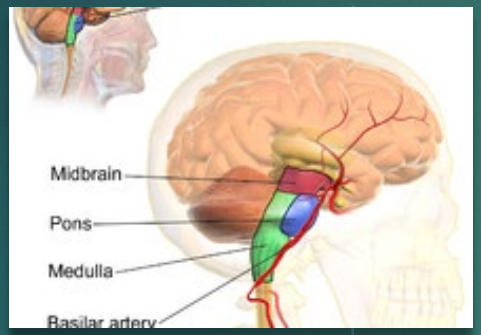
- A specific disease that can cause dementia
- A neurodegenerative disease that causes loss of neurons over time. Always progressive but speed of progression is very variable
- Associated with abnormally high levels of a neuronal protein, alpha-synuclein
- Frequently has a transitional state of MCI
- When MCI is accompanied by an LBD biomarker: MCI-due-to-LBD
- Now understood to start up to 20 years before someone gets clinical symptoms **BUT some symptoms from an early stage are likely**
- Not everyone with LBD has dementia

# DIFFERENT PATTERNS OF DISEASE ONSET AND PROGRESSION

- Different from Alzheimer's disease which has only 1 route of progression
- Can start from intestinal neurons and move up the vagus nerve into the brainstem
- Can start in the olfactory cortex and move downward into the midbrain and brainstem
- Can start in the limbic system (amygdala) and move both upward (toward cortex) and downward (toward brainstem) at the same time
- May start in multiple of the above locations and "converge"
- Makes staging much more difficult than in Alzheimer's



# Subtypes of DLB by location of a-synuclein




## Brainstem

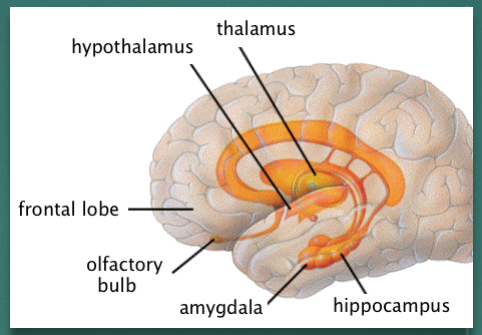
Movement control

Blood pressure control

Sleep/wake cycle control

Paralysis during dream sleep

Alertness/arousal



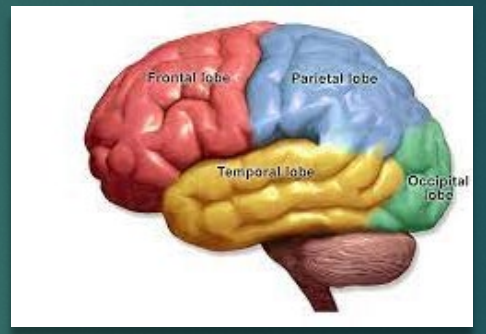

## Limbic

Emotional control

Mood control

Sense of smell

Reality testing




## Cortical

Visual and spatial processing

Judgement, reasoning

Multitasking, attention regulation

Memory

Language

# NEW DIAGNOSTICS

## THE AGE OF BIOLOGICAL DIAGNOSIS IS HERE

# DERMAL NERVE FIBER BIOPSY FOR DETECTION OF ALPHA-SYNUCLEIN

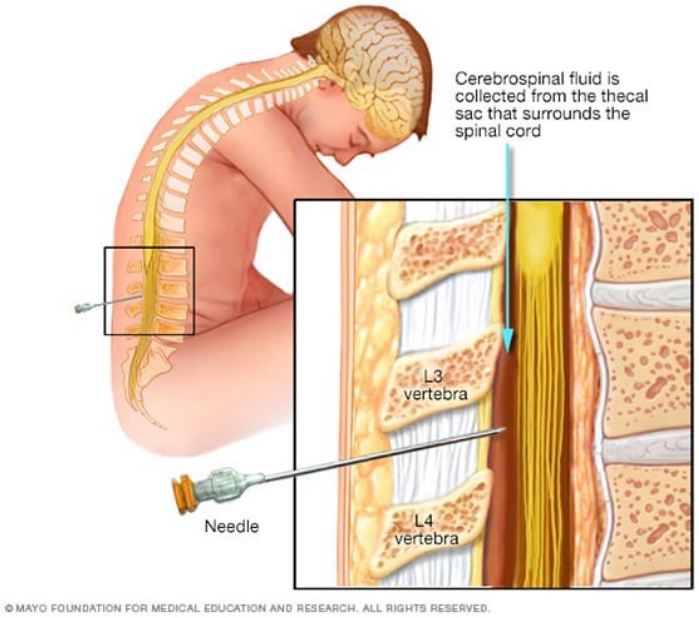
- Detect and visualize abnormal α-synuclein in cutaneous nerve fibers via multiplex immunofluorescent imaging
- Phosphorylated α-synuclein has only been detected in individuals with a diagnosis of synucleinopathy and is not present in hundreds of healthy and non-synucleinopathy disease control patients
- The Syn-One Test has demonstrated 91% sensitivity and specificity
- In research work, can distinguish PD/LBD from MSA

- Skin punch biopsy procedure from 3 sites
- Kits can be ordered from CND Life Sciences and they will provide training on how to get the samples
- Covered by Medicare and most commercial insurances

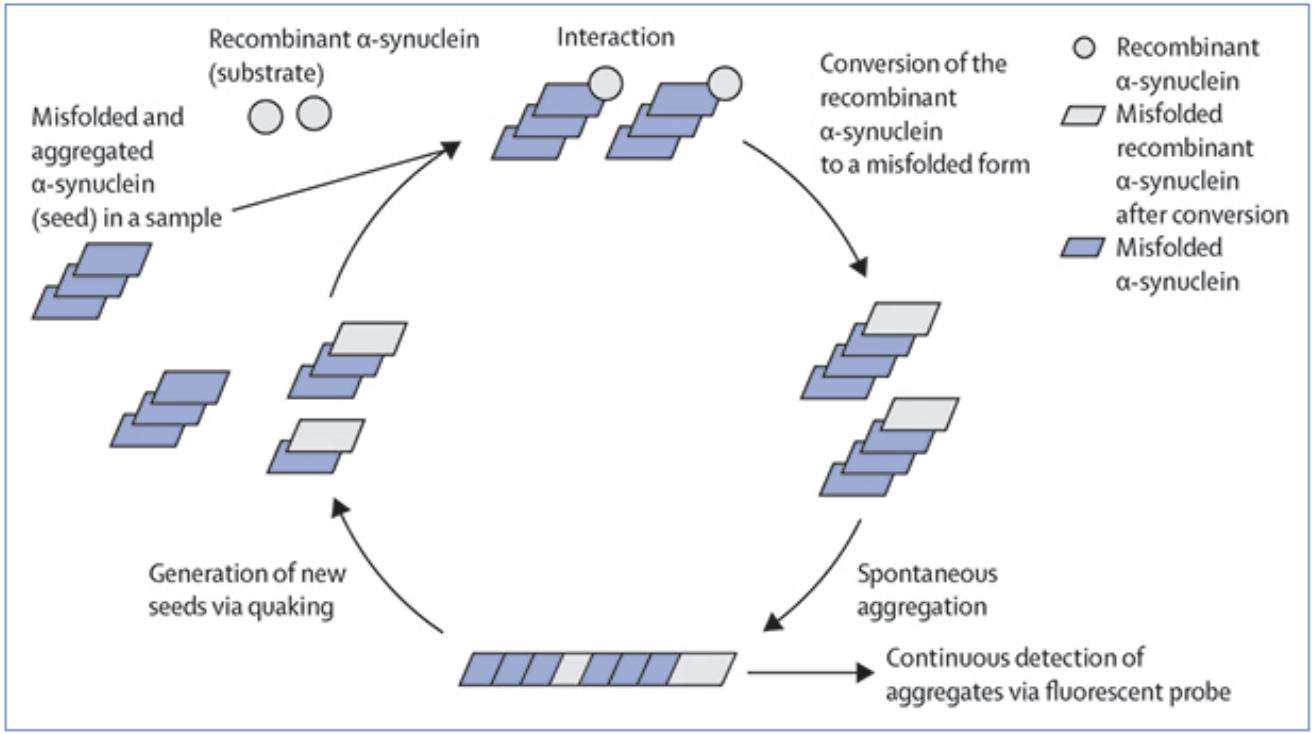
Gibbons CH, Levine T, Adler C, et al. Skin biopsy detection of phosphorylated alpha-synuclein in patients with synucleinopathies. JAMA. Published online March 20, 2024. doi:10.1001/jama.2024.0792

# CEREBROSPINAL FLUID TESTING FOR ALPHA-SYNUCLEIN

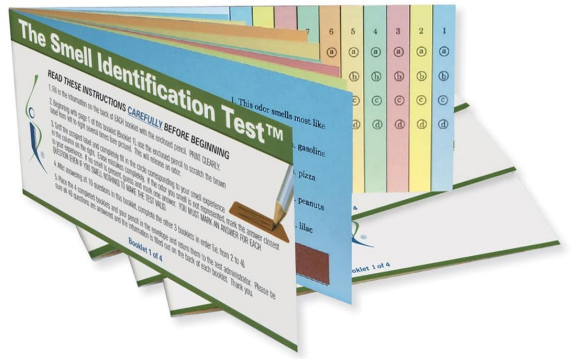
- Commercially available as the Syn-Tap Test from Amprion
- Not (yet) covered by insurance: self-pay price of $995 (patients often qualify for financial assistance)
- Now available at UNC; used primarily when patient is being tested for both Alzheimer's and DLB







# 2 STEP DIAGNOSTIC SCHEMES FOR DLB




Problem: lots of reasons that someone can have parkinsonism and/or cognitive impairment

Solution: use a cheap and easy high-sensitivity, low specificity first step

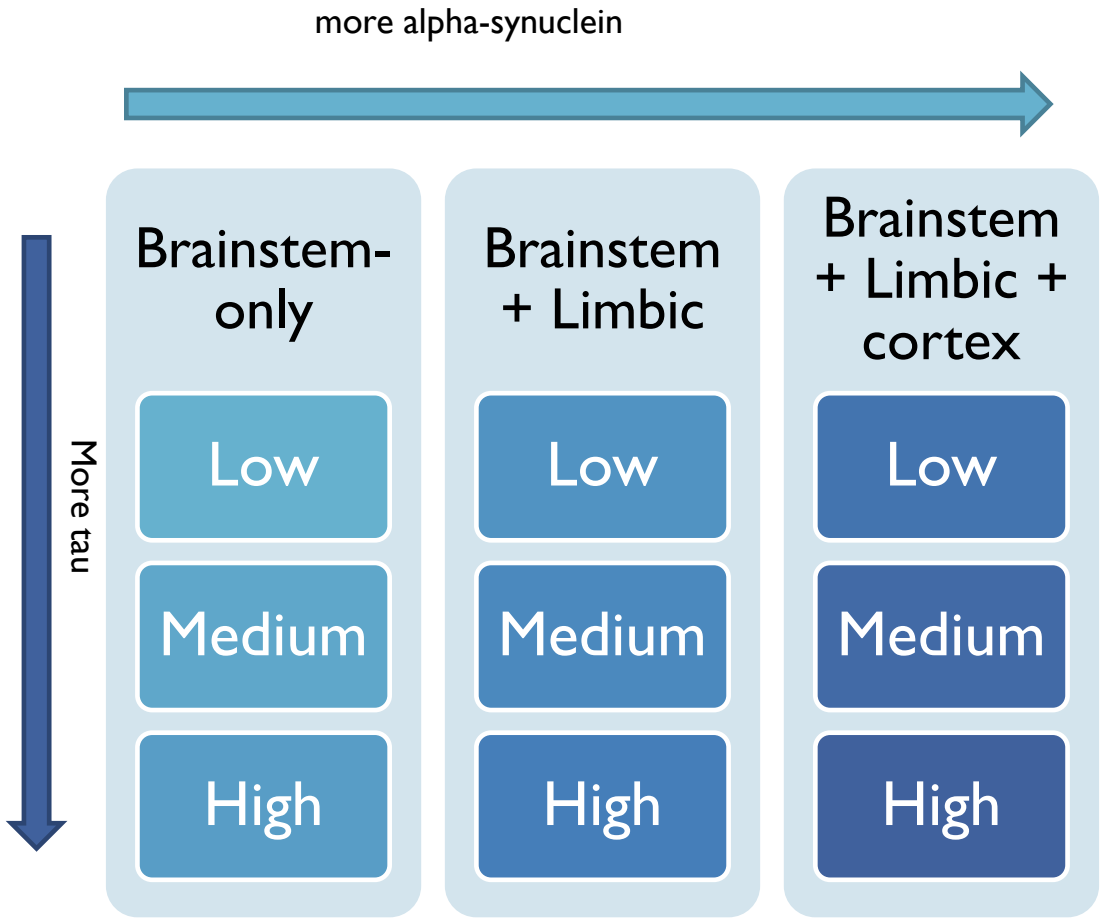
Two step UPSIT → CSF SAA

- Step 1 risk stratification using UPSIT + age + sex; Step 2 CSF α syn SAA only for those flagged high risk. Autopsy cohort N=358 with antemortem UPSIT and postmortem CSF SAA + neuropathology; external in vivo validation N=1,209 (PPMI).
- ~94% accuracy for predicting postmortem Lewy body pathology overall (95% in clinical parkinsonism; 94% in clinical AD; 93% in unimpaired).
- CSF tests reduced by ~43% overall (23% parkinsonism; 35% clinical AD; 80% unimpaired). In vivo, the model predicted CSF SAA status with ~79% accuracy (PPV ~82%, NPV ~69%) and reduced CSF testing by ~26%.
- In AD/mixed clinics, testing can triage who needs LP/SAA, limiting invasive testing while maintaining high accuracy—especially for detecting comorbid LB pathology that accelerates decline.

Mastenbroek SE et al. Nat Commun. 2025 Aug 5;16:7182. doi: 10.1038/s41467-025-62458-7

# "MIXED" DLB AND ALZHEIMER'S DISEASE

- Autopsy studies indicate that between a third and a half of carefully clinically diagnosed AD show some degree of LB pathology at autopsy and
- Up to 50% of Lewy Body Disease patients have at least some AD pathology
- Mixed disease patients have more severe disease and shorter survival but also depends on extent of each pathology



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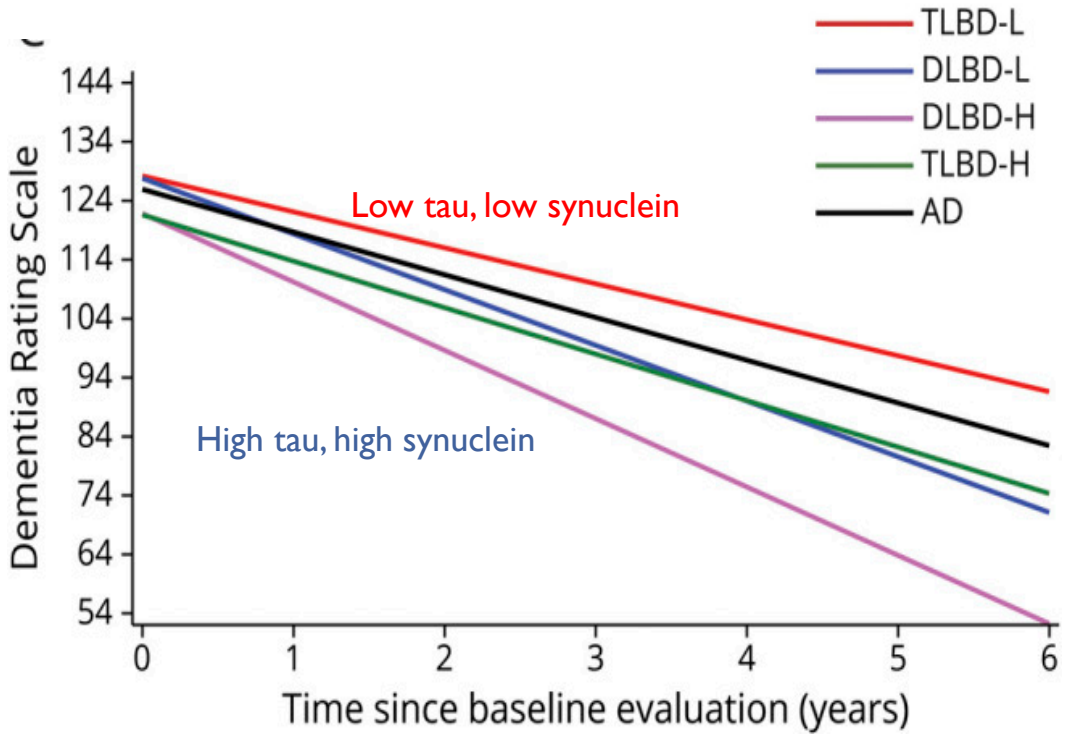



- Diagnosis of DLB was highly likely when the distribution of α-synuclein pathology was greater than tau
- Diffuse Lewy body disease had more severe pathology of each type and a shorter duration of illness than individuals with transitional Lewy body disease.
- The three pathologies (β-amyloid, tau and a-synuclein) accounted for 25% of the total variance of duration of illness,

Ferman TJ, Aoki N, Boeve BF, et al. Neurology. 2020;95(2):e155-e165. doi:10.1212/WNL.0000000000009763

Ferman TJ, Aoki N, Crook JE, et al. Alzheimers Dement. 2018;14(3):330-339 doi:10.1016/j.jalz.2017.09.014

DIAMOND
L E W Y

The U.S. Based

# DIAMOND Lewy™ Management Toolkit

**Management Overview and Symptom Management Summaries**

LBDA
LEWY BODY DEMENTIA ASSOCIATION

Used with permission from Newcastle University and Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust.

You can give a copy to your doctor!!
https://www.lbda.org/diamond-lewy/

## Lewy body dementia: Management Overview

DIAMOND
L E W Y

- Identify key problems under domain headings such as cognition; gait, balance and movement; hallucinations; fluctuations; behavior and mood; sleep, and autonomic system dysfunction.
- Establish which problems have high priority for treatment.
- Discuss benefits and risks of treatment.
- Be aware that symptom response is variable and that benefits in one might be at the cost of worsening of others
- Individual treatments may have global benefits e.g. cholinesterase inhibitors.

### COGNITIVE

**Non-pharmacological**
- cognitive stimulation, use of memory aids, increased social interaction and stimulation, and exercise.

**Pharmacological**
- **Cholinesterase inhibitors** first-line.
- **Memantine** second line.

### NEUROPSYCHIATRIC

**Psychosis**
- Non-pharmacological includes orientation, validation, reassurance, distraction.
- May respond to **cholinesterase inhibitors** especially visual hallucinations.
- Be cautious in the use of antipsychotics.
- **Quietiapine and clozapine** are least apt to worsen parkinsonism. ⚠

**Mood**
- Use of **social interventions** may enhance mood.
- SSRIs or SNRIs first line ⚠
- Avoid agents with significant anti-cholinergic side effects.
  Avoid antipsychotics for non-psychotic mood disorders

### SLEEP

**Insomnia**
- Work on **sleep hygiene.**
- **Review all medications** that could be affecting sleep.
- **Melatonin** 1 hour prior to bedtime

⚠ **Cautious consideration for other sleep aids**

**REM-sleep behavior disorder**
- Consider **non-pharmacological** as first-line and only treat if troublesome.
- **Melatonin is first line**

⚠ **Clonazepam** may help although **possible** side effects

**Motor related sleep disturbances**
- May be improved with long-acting levodopa.

**Other**
Evaluation for OSA

### AUTONOMIC

**Orthostatic hypotension**
- **non-pharmacological** management e.g. compression stockings, fluid/salt intake, stand slowly.
- pharmacological e.g. fludrocortisone, midodrine, droxidopa

✕ Reduce/remove exacerbating drugs e.g. antihypertensives.

**Constipation**
- **Hydration and fiber intake.**
- **Stool softeners or mild laxatives like polyethylene glycol**

**Gastroparesis**
- **Non-pharmacological: smaller, more frequent meals**

X **Avoid** using metoclopramide.

**Urinary dysfunction**
- **Non-pharmacological** first-line e.g. pads, sheath catheter etc.

Pharmacological: based on etiology. Consideration for referral to Urology. Agents like, Mirabegron can be considered. Botox may be considered for overactive bladder. Avoid centrally acting anticholinergics.

**Sexual dysfunction**

⚠ **Phosphodiesterase-5 inhibitors** may be considered with caution in men

**Sialorrhea**

✕ Anticholinergics should not generally be used
- **Botulinum toxin injections** to salivary glands is an effective treatment

### MOTOR

- Preferred pharmacological treatment of parkinsonism in LBD is **levodopa monotherapy.**
- Use **minimal dose** needed for benefit.

**Monitor for potential neuropsychiatric side effects, if present:**

X **Withdraw in order, one at a time:** anticholinergic drugs, amantadine, selegiline, dopamine agonists and catechol-O-methyltransferase inhibitors.

- Remember that LBD patients may exhibit exaggerated responses to medications.
- Severe antipsychotic sensitivity can occur in up to 50% of patients therefore use antipsychotic agents with caution.
- Review the need for drugs which can affect brain function and/or cause sedation and falls (see Beers List).
- Minimize anticholinergic burden as this may worsen cognition and behavior, and counteract cholinesterase inhibitors.

# DLB Medication Management

**Greater optimism**

**Modest optimism**

**Caution**

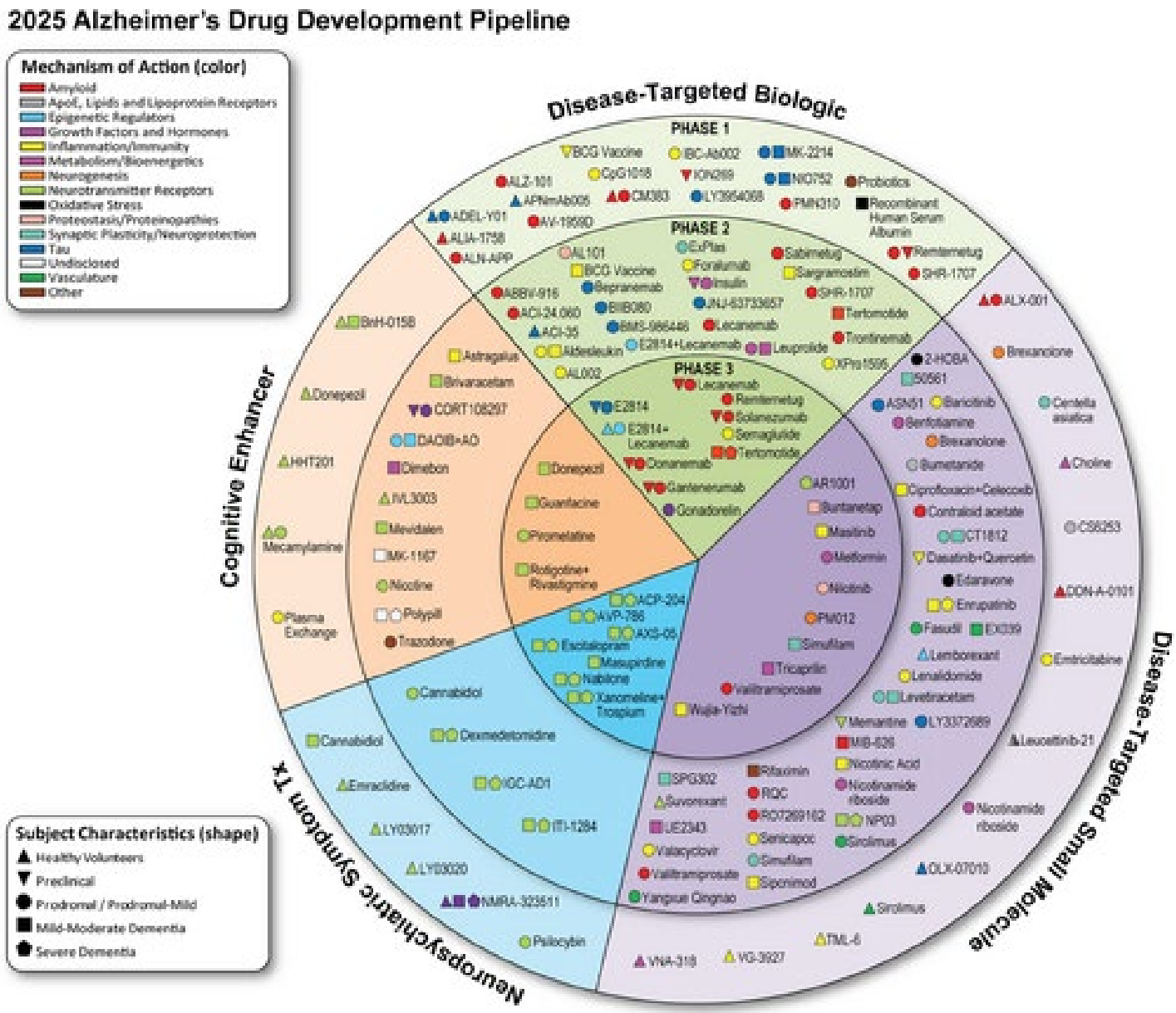
**Greater caution**

| Feature | AChEI | Memantine | Atypical Neuroleptics | SSRIs/SNRIs | Dopamin-ergics | Sleep Meds | Stimulants |
|---|---|---|---|---|---|---|---|
| ***Cognitive impairment*** | Often improves | Sometimes improves | Usually neutral but can worsen | Usually neutral | Usually neutral | Clonazepam – usually neutral but can worsen | Sometimes improves |
| ***Neuro-psychiatric features*** | Often improves VH and delusions and apathy | Sometimes improves | Often improves VH/delusions if dosed appropriately and tolerated | Usually improves depression Sometimes improves VH and delusions | Often worsens VH and delusions | Melatonin – sometimes improves VH | Sometimes improves VH |
| ***Parkinsonism*** | Rarely worsens | Usually neutral | Rarely worsens | Usually neutral | Usually improves, but effects modest | Usually neutral | Usually neutral |
| ***Sleep – daytime alertness*** | Often improves | Usually neutral | Often worsens hypersomnia | Usually neutral | Sometimes worsens | Can improve alertness by improving sleep continuity | Often improves |
| ***Sleep - RBD*** | Usually neutral | Sometimes improves | Sometimes improves | Sometimes worsens | Sometimes improves | Melatonin and clonazepam – usually improve RBD | Usually neutral |
| ***Autonomic dysfunction*** | Sometimes improves OH and constipation | Usually neutral | Often worsens OH and ED | Sometimes worsens OH and ED | Often worsens OH | Usually neutral | Can improve OH (but can worsen supine hypertension) |

# THE CLINICAL TRIALS LANDSCAPE FOR DLB

# AD DRUG DEVELOPMENT 2025

- In 2025, there are 182 trials and 138 novel drugs. Both more trials and more drugs than the 2024 pipeline.
- The pipeline is diverse, with agents that address 15 basic disease processes.
- Biomarkers play an important role in current trials to determine trial eligibility and as outcomes of trials.
- The total development time for a potential Alzheimer's disease therapy to progress from nonclinical studies to FDA review is 11-13 years.




Cummings et al. Translational Research & Clin. Interv. 03 June 2025 doi.org/10.1002/trc2.70098

# DLB THERAPIES BEING EVALUATED IN CLINICAL TRIALS

**Neflamapimod** (CervoMed)

An oral small molecule that inhibits p38 alpha kinase, an enzyme involved in brain inflammation. By reducing inflammation, it may help form new connections between brain cells.

A Phase 2b trial (RewinD-LB) in dementia with Lewy bodies (DLB) has shown encouraging results, with a Phase 3 trial anticipated for mid-2026. It has also received Fast Track designation from the FDA.

**Zervimesine** (CT1812) (Cognition Therapeutics)

A sigma-2 receptor antagonist that is thought to displace or remove toxic oligomers of both beta-amyloid and alpha-synuclein from brain cells.

In December 2024, topline results from the Phase 2 'SHIMMER' study in DLB showed therapeutic benefits across behavioral, cognitive, and motor assessments. The company is focused on advancing the therapy into late-stage clinical trials.

**Nilotinib** (KeifeRx)

A repurposed cancer drug (originally by Novartis) that can enhance protein clearance in the brain. This is intended to mitigate neurodegeneration.

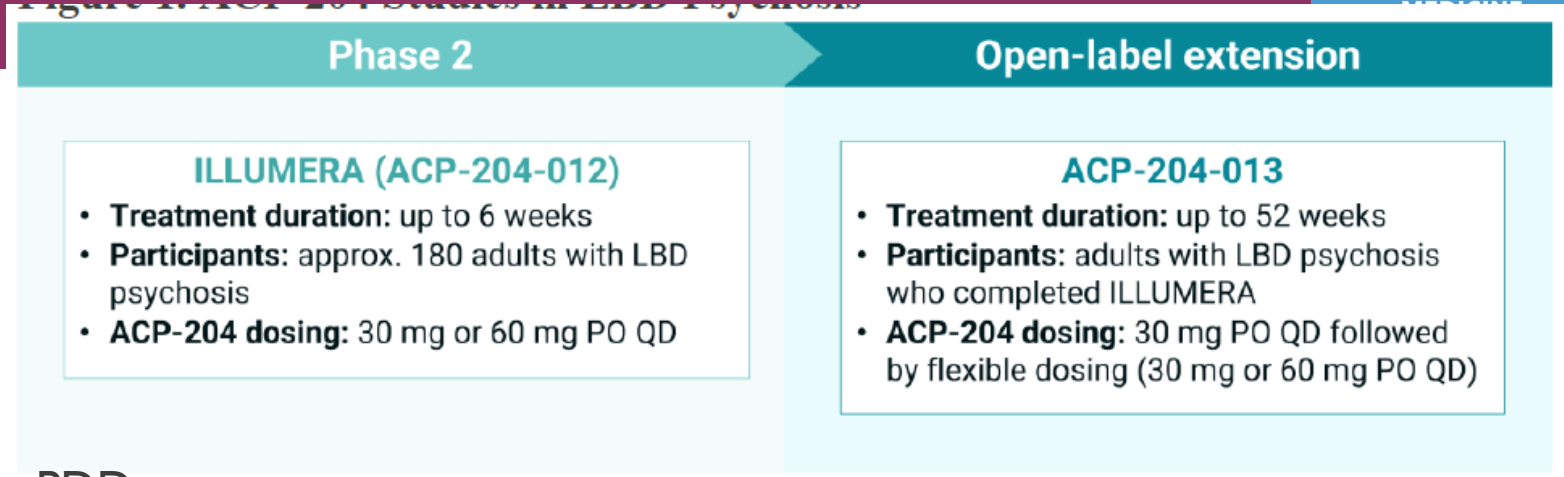
Preliminary findings from a Phase 2 trial in Parkinson's disease dementia (PDD) and DLB have suggested improvements in cognition and motor skills.

# DLB SUPPORTIVE AND REPURPOSED THERAPIES

In addition to novel drug candidates, ongoing clinical trials are exploring the benefits of existing medications and other non-pharmaceutical interventions.

**Cholinesterase Inhibitors:** Commonly used for Alzheimer's disease, recent studies confirm their effectiveness in slowing cognitive decline in people with LBD.
**Combination Therapies:** The AXON trial in Australia is testing a combination of ambroxol and the antibiotic doxycycline to evaluate its potential for disease modification in DLB.
**Transcranial Magnetic Stimulation (rTMS):** Researchers in France are exploring the use of rTMS to improve function in people with DLB.
**Targeting Hallucinations and delusions:** ACP-204 (Acadia Pharmaceuticals) Currently in Phase 2/3 clinical trials to assess efficacy and safety. ACP-204 was designed to be more potent than its predecessor pimavanserin (Nuplazid) at this receptor while having a lower risk of cardiac issues, a shorter half-life, and better central nervous system penetration.

# STARTING SOON AT UNC: A NEW TRIAL FOR DLB PSYCHOSIS




**Selected inclusion criteria**

- ≥55 and <85 years of age, with DLB or PDD

Had psychotic symptoms for ≥2 months prior to screening visit

Has the following scores at screening and baseline:

- SAPS Hallucinations or Delusions global item (H7 or D13) score ≥3 AND a score ≥3 on at least one other non-global item using the SAPS-LBDP
- CGI-S-LBDP score ≥4

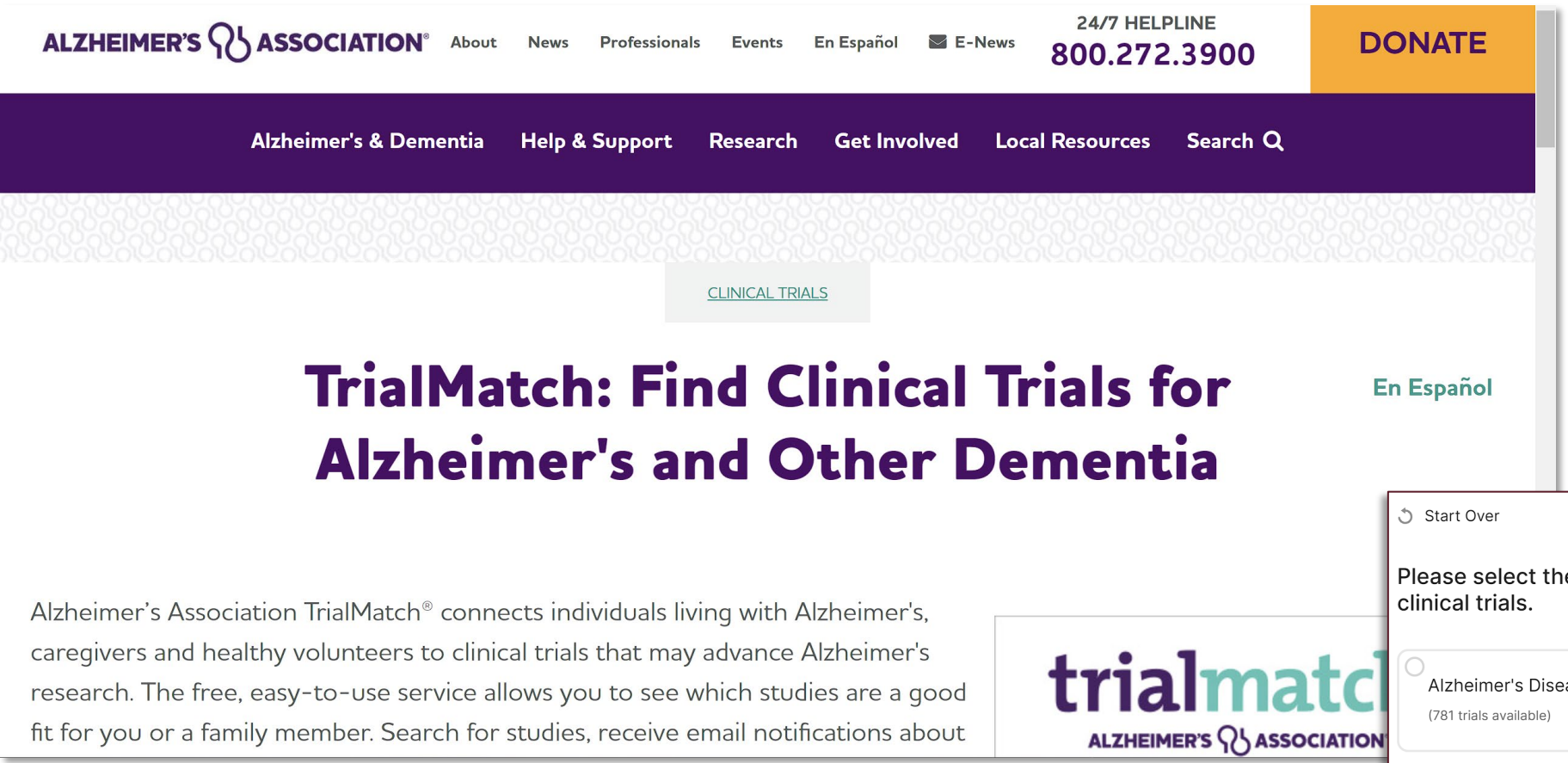
Has a prior MRI or CT scan of the brain that is consistent with the diagnosis of LBD

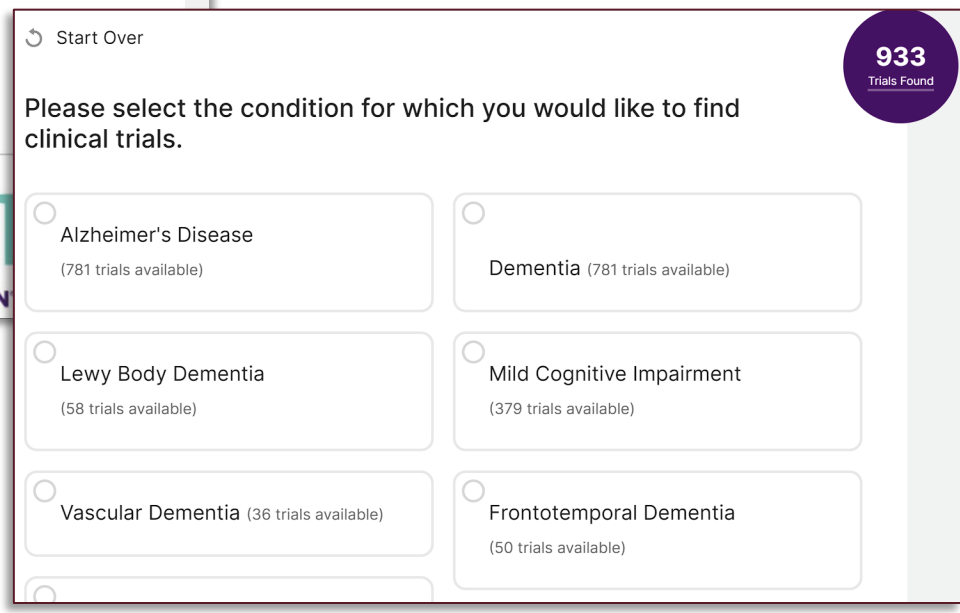
Must be on a stable dose of cholinesterase inhibitor, memantine, and/or dopaminergic medications for ≥12 weeks prior to baseline or discontinued ≥2 weeks prior to baseline

Antipsychotics must be discontinued ≥3 days prior to baseline

# TRIALMATCH.ALZ.ORG

UNC SCHOOL OF MEDICINE



# “THANKS FOR LISTENING. ANY QUESTIONS?”