Penn State College of Medicine
Continuing Education

Neurology for the Non-Neurologist

Friday, March 6, 2026

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Any names or ages used on the upcoming slides are fictitious and not referring to an actual patient.

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Dementia and Mild Cognitive Impairment

Part 1: Diagnosis and Treatment

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Learning Objectives

- Review diagnosis of mild cognitive impairment and dementia
- Describe when and how to use biomarkers
- Discuss approaches to prevention and treatment of dementia

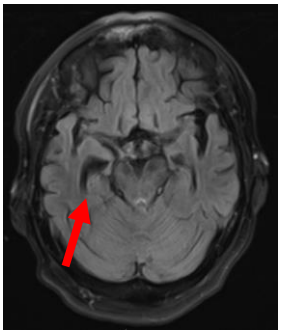
Case 1

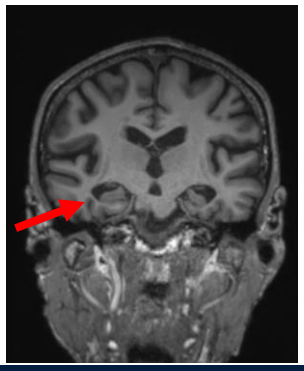
- 79 year old female with hypertension and hypothyroidism
- 2-3 years of cognitive and behavioral changes
  - Cognitive Symptoms:
    - Patient: "**anxious**" and **mild memory issues**
    - Daughter: anxiety during move into independent living, **short term memory** issues, **asking the same question,** trouble with **complex planning, misplacing items**
  - Neuropsychiatric symptoms:
    - Anxiety and depression. **No significant lifelong mood or anxiety issues**
    - **Snoring and daytime tiredness**
    - No issues with appetite, hallucinations, delusions, apathy, disinhibition
  - Functioning:
    - **Paid a credit card bill twice** because she forgot
    - **Asking more questions** related to text messages vs email messages

Case 1

- MoCA= 25/30
  - 1/5 delayed recall, no improvement with cues
  - 0/1 phonemic fluency
- Labs: CBC, CMP, TSH, B12, folate
- MRI brain w/o contrast (dementia protocol)
  - Generalized Radiology reports
    - "Volume loss proportional to age"
    - "Enlargement of the ventricles"
  - Ordering instructions
    - Be specific-- axial, sagittal, and coronal, SWI
    - "Memory-predominant syndrome, please assess for hippocampal atrophy"

Key Points:
1. Amnestic impairment
2. Be cautious of generalized radiology reports
3. Specify your image request





Case 1

- Which of the following is the best diagnosis:
  - A. Generalized anxiety disorder and Major depressive disorder
  - B. Mild Cognitive Impairment due to multiple possible etiologies
  - C. Major neurocognitive disorder, mild, due to Alzheimer's Disease
- What is the next best step in work up?
  - A. Further assessment for sleep apnea
  - B. Start treatment for depression and anxiety
  - C. Biomarkers for Alzheimer's Disease
  - D. All the above

Dementia vs Mild Cognitive Impairment

Subjective Cognitive Impairment	Mild Cognitive Impairment	Dementia (mild, mod, severe)
	Mild Behavioral Impairment	
+ Subjective symptoms	+/- Subjective symptoms	+/- Subjective symptoms
- Objective findings	+ Objective findings	+ Objective findings
- Loss of functioning	- Loss of functioning	+ Loss of functioning

+/- Neuropsychiatric Symptoms

Dementia = Major neurocognitive disorder
Objective impairment in cognition causing loss of independent functioning

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Mild Behavioral Impairment

Mild Behavioral Impairment

- 35-97% of patients with MCI have neuropsychiatric symptoms

→ increased risk of dementia

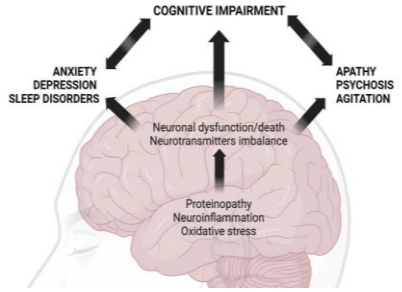
Faster decline, hospitalization, functional impairment, caregiver stress, quality of life

Depression	**Appetite**	**Disinhibition**	**Delusions**
Anxiety	**Sleep**	**Elation**	**Hallucinations**
Irritability	**Compulsions**	**Apathy**	**Aggression**

Journal of Alzheimer's Disease 56 (2017) 929–938
DOI 10.3233/JAD-160879
IOS Press

The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations

Zahinoor Ismail[a,b,*], Luis Agüera-Ortiz[c], Henry Brodaty[d], Alicja Cieslak[b], Jeffrey Cummings[e], Corinne E. Fischer[f], Serge Gauthier[g], Yonas E. Geda[h], Nathan Herrmann[i,j], Jamila Kanji[k], Krista L. Lanctôt[l], David S. Miller[b], Moyra E. Mortby[f], Chiadi U. Onyike[m], Paul B. Rosenberg[m], Eric E. Smith[b], Gwenn S. Smith[n], David L. Sultzer[o] and Constantine Lyketsos[p] for the NPS Professional Interest Area of the International Society of to Advance Alzheimer's Research and Treatment (NPS-PIA of ISTAART)



Teixeira AL, Rocha NP, Gatchel J. Behavioral or neuropsychiatric symptoms of Alzheimer's disease: from psychopathology to pharmacological management. Arq Neuropsiquiatr. 2023 Dec;81(12):1152-1162

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Instruments for Cognitive Impairment / Dementia

- **Cognitive screening instruments**
  - MoCA, RUDAS, Mini-COG, SAGE, SLUMS, MMSE
  - Non-English / Low literacy: AD-8
- **Neuropsychiatric screening instruments**
  - NPI-Q, NBI, Geriatric Depression Scale, apathy rating scales
- **Functional screening instruments**
  - Functional Assessment Questionnaire, Lawton-Brody IADLs
- **Severity Assessments**
  - Global Deterioration Scale, Alzheimer's Association Staging, CDR

Global Deterioration Scale

1	**No Cognitive Decline** — No noticeable symptoms or memory problems
2	**Very Mild Cognitive Decline** — Subtle memory lapses, generally not detected
3	**Mild Cognitive Decline** — Increased forgetfulness, slight concentration problems
4	**Moderate Cognitive Decline** — Clear-cut memory loss, difficulty with complex tasks
5	**Moderately Severe Cognitive Decline** — Assistance with daily activities often needed
6	**Severe Cognitive Decline** — Significant memory issues, personality changes
7	**Very Severe Cognitive Decline** — Loss of verbal abilities, total dependence on caregivers

SAGE: https://wexnermedical.osu.edu/brain-spine-neuro/memory-disorders/sage

AD-8: https://www.alz.org/getmedia/6e7291bf-4ac8-40ed-a148-824d4591ed7e/ad8-dementia-screening.pdf

GDS:https://geriatrictoolkit.missouri.edu/cog/Global-Deterioration-Scale.pdf

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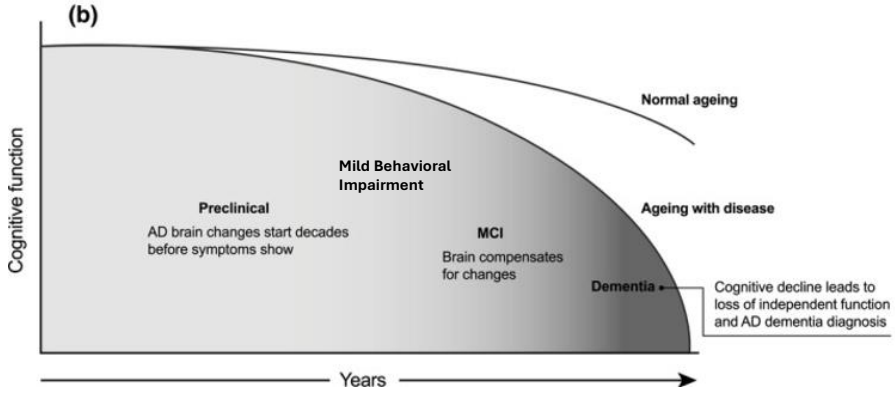
Dementia vs Mild Cognitive Impairment



Liss JL, et al. Practical recommendations for timely, accurate diagnosis of symptomatic Alzheimer's disease (MCI and dementia) in primary care: a review and synthesis. J Intern Med. 2021 Aug;290(2):310-334. doi: 10.1111/joim.13244. Epub 2021 Mar 31. PMID: 33458891

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Case 1

- **Mild Cognitive Impairment / Mild Behavioral Impairment**
  - Differential: Vascular, infectious, neoplastic, degenerative, toxin/medication, autoimmune, metabolic, psychiatric
  - Assess and Treat risk factors:
    - Depression and anxiety
    - Sleep apnea
    - Thyroid disease, vitamin deficiency
    - Blood pressure, cholesterol, diabetes
    - Substance use, high risk medications
    - Social isolation
    - Diet

→ Medications / Psychotherapy
Sleep medicine / c-PAP compliance

→ Treat metabolic syndrome
Avoid alcohol and tobacco
Community Centers, fitness center
MIND Diet / Mediterranean Diet

  - Serum Biomarkers for Alzheimer's Disease:
    - **p-tau 217= 1.34** (Ref. = or <0.15)
    - **B-amyloid 42/40= 0.09** (Ref. = or >0.170)

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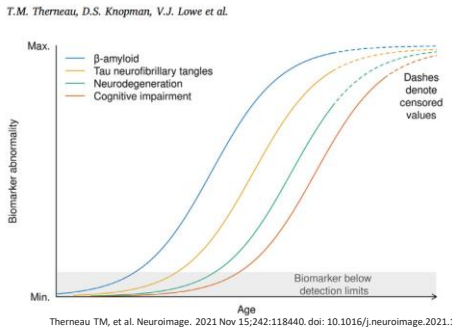
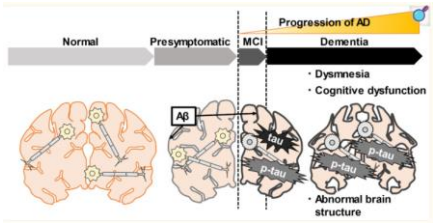
Alzheimer's Disease

- **Biomarkers** for Alzheimer's Disease
  - "A measurable or detectable biological characteristic that indicates the presence, progression, or risk of developing a disease" (NIH)

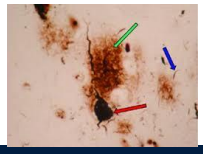


Therneau TM, et al. Neuroimage. 2021 Nov 15;242:118440. doi: 10.1016/j.neuroimage.2021.118440.

- Imaging biomarkers:
  - Amyloid PET CT of the brain
  - FDG-PET scan of the brain
- Abnormal proteins:
  - CSF / serum: amyloid, tau, NfL, 14-3-3



Gunes S,et al. Biomarkers for Alzheimer's Disease in the Current State: A Narrative Review. Int J Mol Sci. 2022 Apr 29;23(9):4962.



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Alzheimer's Disease

- Blood-Based Biomarkers (BBM)
  - Does **NOT** replace a comprehensive clinical evaluation
  - **ALWAYS** should be interpreted in a specific clinical context
- High sensitivity (>90% Sn and >75% Sp) blood-based biomarker for **triaging** patients
  - A negative test rules out AD with high probability
- High sensitivity and specificity (>90%) for **confirming** patients with AD
  - A negative test ruled out AD pathology while a positive test confirms AD with high probability
- Limitations of BBM:
  - Renal disease, acute brain injury, obesity, old age
  - NOT recommended in asymptomatic individuals

Received: 18 June 2025 | Revised: 11 July 2025 | Accepted: 14 July 2025
DOI: 10.1002/alz.70535

GUIDELINES

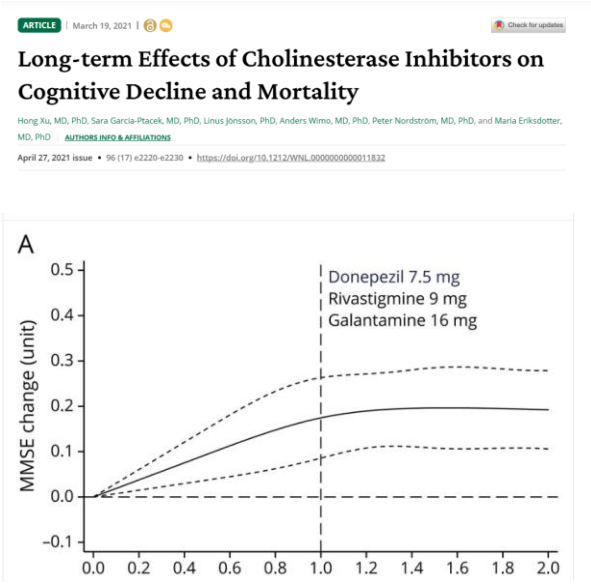
Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Alzheimer's Association Clinical Practice Guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings

Sebastian Palmqvist[1,2] | Heather E. Whitson[3,4] | Laura A. Allen[5] | Marc Suarez-Calvet[6,7] | Douglas Galasko[8] | Thomas K. Karikari[9,10,11] | Hamid R. Okrahvi[12] | Madeline Paczynski[13] | Suzanne E. Schindler[13] | Charlotte E. Teunissen[14] | Henrik Zetterberg[15] | Maria C. Carrillo[16] | Rebecca M. Edelmayer[16] | Simin Mahinrad[16] | Mary Beth McAteer[17] | Lara A. Kahale[18] | Sarah Pahlke[16] | Malavika P. Tampi[16]

Alzheimer's Disease

- Do cholinesterase inhibitors help?
  - Cognitive decline, risk for severe dementia, and delayed mortality
    - Galantamine demonstrated a reduction in the risk of severe dementia (MMSE <10)
    - ChEIs had 27% lower risk of death over 5 years, that risk was dose dependent
  - Lower risk of stroke
  - Neuropsychiatric symptoms



ARTICLE | March 19, 2021

Long-term Effects of Cholinesterase Inhibitors on Cognitive Decline and Mortality

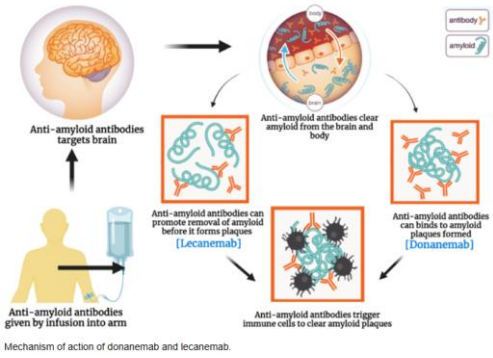
Hong Xu, MD, PhD, Sara Garcia-Ptacek, MD, PhD, Linus Jönsson, PhD, Anders Wimo, MD, PhD, Peter Nordström, MD, PhD, and Maria Eriksdotter, MD, PhD | AUTHORS INFO & AFFILIATIONS

April 27, 2021 issue • 96 (17) e2220-e2230 • https://doi.org/10.1212/WNL.0000000000011832

Alzheimer's Disease

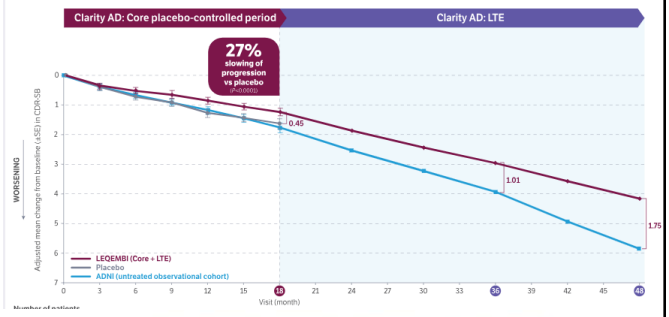
Lecanemab and **Donanemab**

Monoclonal antibody against B-amyloid



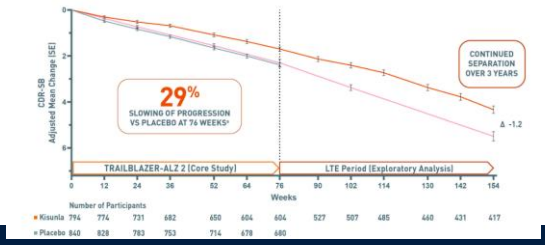
Mechanism of action of donanemab and lecanemab.

J, Nandhini & Keyan, Karthi. (2024). Translational Medicine in Alzheimer's Disease: The Journey of Donanemab From Discovery to Clinical Application. Chronic Diseases and Translational Medicine. 11. 105-116. 10



Including patients who completed treatment during the 18-month core trial[8]

CDR-SB CHANGE FROM BASELINE IN COGNITION AND FUNCTION THROUGH 3 YEARS: OVERALL POPULATION[1,8]



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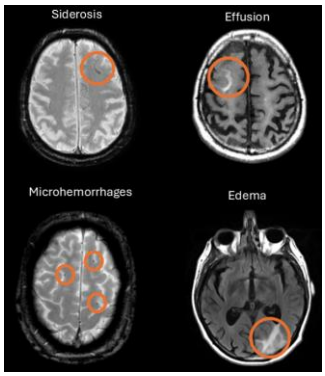
Alzheimer's Disease

- **Lecanemab** and **Donanemab**
  - CLARITY-AD / TRAILBLAZER-AD (Phase 3 clinical trials)
  - **Infusion-related reactions** (~26%)
    - Mostly mild-moderate, 75% occurred after the first dose
  - **Amyloid-Related Imaging-Abnormalities (ARIA)**
    - Hemorrhage (ARIA-H): 17% (L), 19% (D)
    - Edema (ARIA-E): 13% (L), 24% (D)
    - Mostly occur within the first 3-6 months
    - Majority were asymptomatic. Those with symptoms had mild-moderate symptoms
      - Headache, dizziness, confusion, visual disturbance
    - Highest risk with APOE e4 homozygous



ARIA Education, UCL, European Society for Neuroradiology

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Alzheimer's Disease

Treatment Logistics

Lecanemab

- **Administered IV every 2 weeks for 18 months, then monthly IV maintenance**
- Baseline amyloid PET or CSF Biomarkers
- Baseline labs including APOE
- Baseline MRI within 6-12 months of 1st treatment
- **MRI monitoring before the 3rd, 5th, 7th, 14th treatment**
- MRI PRN if concern for ARIA

Donanemab

- **Administered IV every 4 weeks for 18 months, then stop**
- Baseline amyloid PET or CSF Biomarkers
- Baseline labs including APOE
- Baseline MRI within 6-12 months of 1st treatment
- **MRI monitoring before the 2rd, 3th, 4th, 7th treatment**
- MRI PRN if concern for ARIA

Alzheimer's Disease

- Lecanemab and Donanemab
  - **When to refer to a specialty cognitive clinic?**
    - MCI or mild dementia suspected to be due to Alzheimer's Disease
    - MoCA 17-30 / MMSE 22-30
    - No history of seizure or stroke within the past 12 months
    - Limited cerebrovascular disease on SWI
    - Less than 4 microhemorrhages
    - Limited neuropsychiatric symptoms
    - No anti-coagulation (Aspirin 81 mg okay)
    - No active cancer
    - Stable medical comorbidities
  - **Before you refer:**
    - Make sure the patient and family are interested!
    - Labs: CMP, CBC, TSH, vitamin B12, folate, PT/INR, PTT
    - MRI brain w/o contrast (must include SWI sequence)
    - Consider Amyloid PET CT and APOE genetic marker

Case 2

- 77 year old male presents to the clinic with his wife to discuss memory loss.
  - Past medical history
    - Hypertension
    - Hyperlipidemia
    - Type 2 diabetes
    - Chronic kidney disease

  Medications
  Donepezil 10 mg daily
  HCTZ-losartan 25-100 mg daily
  Sertraline 50 mg daily
  Metformin 1000 mg BID
- **Cognitive Symptoms**
  - **5 years** of **slowly progressive cognitive changes** initially in **memory andkeeping track of upcoming events**. Progressive **issues managing finances and getting confused**.
  - 1 year ago family noted **slowness getting up from the floor**
  - 8 months ago **changes in walking**, not picking up his feet, mild tremor
  - Progression of memory loss, issues multitasking, maintaining attention

Case 2

- **Neuropsychiatric Symptoms**
  - Notable **depression**, feels sad, like a burden to family. No suicidal ideation
  - **Apathy**, poor motivation, not wanting to do puzzles
  - 4-5 months of vivid **visual hallucinations**. Seeing bugs on the wall, running water on a chair
  - **Reduced appetite** and lost 30 pounds
  - Sleeping 15 hours a day, kicking in sleep
  - Urinary incontinence
- **Functioning**
  - Stopped driving due to **slow reaction times**
  - Unable to manage **finances and medications**
  - Needs help **showering, dressing, using toilet** due to physical issues

Case 2

- **Physical Exam**
  - + upper extremity rigidity
  - + upper and lower extremity bradykinesia
  - Hypomimia, Hypophonia
  - Small steps, reduced arm swing, imbalance with turns
- Labs normal
- CT head showed mild generalized atrophy
- MoCA= 18/30 (executive dysfunction, visuospatial, fluency, attention, serial 7s, memory)
- **Amyloid PET CT of the brain: diffuse cortical uptake of radiotracer obscuring the grey-white matter**

Case 2

- What is the most likely diagnosis?
  A. Mild Cognitive Impairment, probable Lewy Body Dementia
  B. Major Neurocognitive Disorder, due to Alzheimer's Disease
  C. Major Neurocognitive Disorder, probable Lewy Body Dementia mixed with Alzheimer's Disease
  D. Delirium due to urinary tract infection, with unspecified neurocognitive disorder

Lewy Body Dementia


Received: 17 December 2020 | Revised: 23 March 2021 | Accepted: 31 March 2021 | Published online: 13 May 2021
DOI: 10.1002/dad2.12189
RESEARCH ARTICLE

Clinico-pathological comparison of patients with autopsy-confirmed Alzheimer's disease, dementia with Lewy bodies, and mixed pathology

Atri Chatterjee[1] | Veronica Hirsch-Reinshagen[2] | Syed Ali Moussavi[1] | Blake Ducharme[1] | Ian R. Mackenzie[2] | Ging-Yuek Robin Hsiung[1]

- **Mixed pathology with Alzheimer's Disease (amyloid + tau)**
  - 60% of patients with **Alzheimer's Dementia** have **Lewy Body Pathology**
  - 66% of patients with **Lewy Body Dementia** have **amyloid pathology**
  - Early stages can be a diagnostic challenge:
    - 50% of patients with underlying Lewy Body pathology can be clinically indistinguishable with Alzheimer-type dementia
- Co-pathology is associated with:
  - Earlier age of dementia
  - Faster progression

Co-pathologies

- Common!
  - "The rule rather than exception"
- Common co-pathologies:
  - Cerebrovascular disease / Alzheimer's Disease
  - Lewy Body Disease / Alzheimer's Disease
  - Alcohol use / bvFTD

Lewy Body Dementia

- Diagnosis:
  - Clinical
  - DAT scan
  - FDG-PET scan
  - **Alpha-synuclein biomarkers?** Skin biopsy?
- Management:
  - Physical therapy, occupational therapy
  - Cholinesterase inhibitors
  - Psychiatric management:
    - Mood, psychosis

Jolepalem P,et al. Complementary role of 18F-FDG PET and 123I-ioflupane SPECT in the diagnosis of Lewy body disease. J Nucl Med Technol. 2014 Sep;42(3):233-4. doi: 10.2967/jnmt.113.133199.

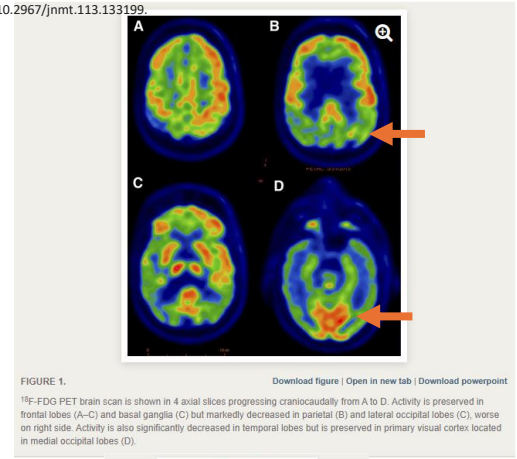
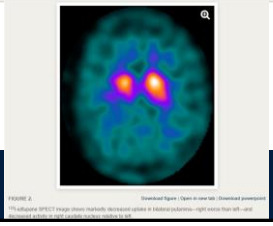


FIGURE 1. Download figure | Open in new tab | Download powerpoint

^{18}F-FDG PET brain scan is shown in 4 axial slices progressing craniocaudally from A to D. Activity is preserved in frontal lobes (A–C) and basal ganglia (C) but markedly decreased in parietal (B) and lateral occipital lobes (C), worse on right side. Activity is also significantly decreased in temporal lobes but is preserved in primary visual cortex located in medial occipital lobes (D).



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Case 3

- 84 year old female, PhD retired professor, history of hypertension, diabetes, osteoarthritis presents to the clinic with her husband for **8 years of worsening memory**
- **Cognitive symptoms:**
  - Husband first noticed **forgetfulness** of recent events
  - Went to the wrong airport for a trip she took every year with friends
  - **Patient has no recollection of this**
  - Losing her way driving to familiar places
- **Neuropsychiatric:**
  - No depression, apathy, loss of sympathy or empathy, hallucinations, delusions
- **Functioning:**
  - **No longer driving or managing medications**. Husband always managed finances, but she might have issues if she had to take over task
  - Requires more assistance for shopping and cooking, needs written reminders

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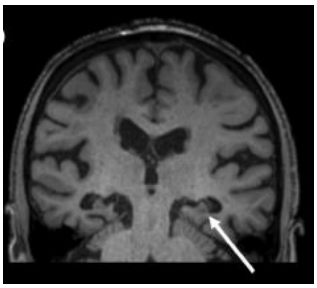
Case 3

MoCA= 19/30

- Impaired Trails, clock draw, serial 7s, fluency, delayed recall
- Amnestic presentation

MRI brain w/o contrast: hippocampal atrophy



Labs

- A1c 6.6
- Normal CBC, CMP, TSH, B12, folate
- **Serum p-tau 217= 0.08** (Ref. = or <0.15)
- **Serum B-amyloid 42/40= 0.23** (Ref. = or >0.170)
- **Liklihood ratio= 0.0006** (Ref low likelihood <0.3254)

- Amyloid PET CT head -- **negative**

Case 3

- What is the most likely diagnosis?
  A. Atypical Alzheimer-type dementia
  B. Limbic-Predominant Age-Related TDP43 Encephalopathy (LATE)
  C. Autoimmune encephalitis
  D. Obstructive Sleep apnea

Limbic-Predominant Age-Related TDP43 Encephalopathy (LATE)

Alzheimers Dement. 2025 Jan;21(1):e14202. doi: 10.1002/alz.14202. Epub 2025 Jan 14.

Clinical criteria for limbic-predominant age-related TDP-43 encephalopathy

David A Wolk [1], Peter T Nelson [2], Liana Apostolova [3], Konstantinos Arfanakis [4 5],

- 25-40% of people >85 years
- TDP-43 accumulation in mesial temporal lobes
- Memory-predominant
- Slower cognitive decline
- More common above 75 years

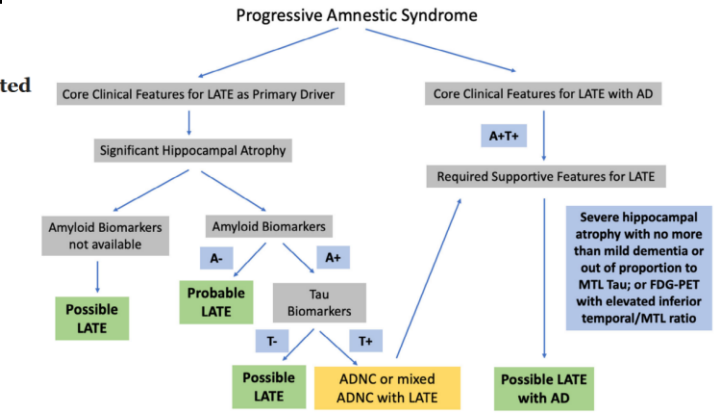


FIGURE 1 Flow for decisions about diagnosis of of LATE. A- , amyloid negative biomarker; A+ , amyloid positive biomarker; T- , tau negative biomarker; T+, tau positive biomarker; LATE.

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Case 5

- 79 year old male veteran with hyperlipidemia and PTSD presents to the clinic for 1-2 years of progressive memory impairment
  - Cognitive symptoms:
    - **Trouble remembering words**
    - Wife says she asked him to get the cooler in the basement, and he **didn't understand what she meant by "cooler"**
    - **Paraphasias**: "I saw a lion" when he meant a deer in the yard
    - Slow onset, NOT acute
  - Neuropsychiatric symptoms:
    - **Very frustrating** to the patient causing mild anxiety and depression
  - Functioning:
    - **Difficulty reading** and understand books articles

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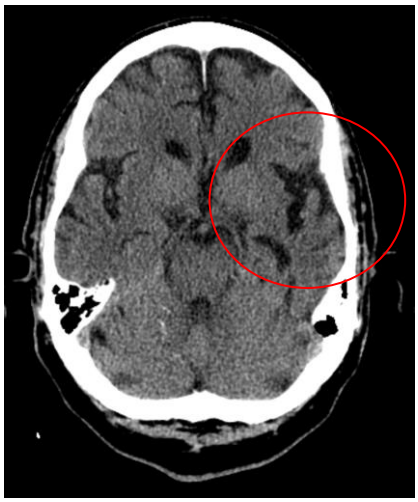
Case 5

- MoCA= 21/30
  - 1/3 for naming, 0/5 for memory **with excellent recognition**
- No parkinsonism, no apraxia, no focal weakness or sensory loss
- Normal labs
- Cognitive examination:
  - **Severe impairment in confrontation naming**
  - **Loss of object knowledge**
  - Sentence repetition intact
  - **Fluent speech**, no hesitations or pauses

Case 5

- **Be specific** with imaging request!
  - "Slowly progressive language-predominant syndrome. Please assess for vascular and degenerative pathology in the L-temporal lobe"
- CT of the head w/o contrast
  - L anterior temporal atrophy



Case 5

- What is the most likely pathologic diagnosis?
  - A. Alzheimer's Disease
  - B. Pick's Disease
  - C. 4R Tau
  - D. TDP-Type C

Frontotemporal dementia

The Association for Frontotemporal Degeneration
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- Primary Progressive Aphasia
  - **Non-fluent / agrammatic variant** → TDP-43/Tau
    - Impaired grammar, halting and hesitating speech
    - Insight usually intact
  - **Logopenic variant** → Alzheimer's Disease
    - Impaired repetition and confrontation naming
  - **Semantic variant** → TDP-43-Type C
    - Loss of object knowledge, surface dyslexia
- **Behavioral Variant FTD** → Tau
  - Loss of comportment, apathy/disinhibition, loss of sympathy and empathy

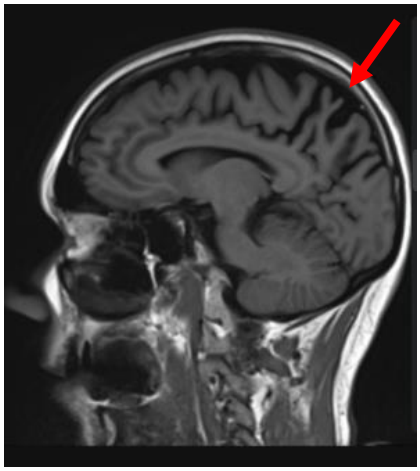
Most Common Pathology

Case 6

- 61 year old female, history of depression and anxiety presenting to the clinic for cognitive concerns.
  - Cognitive symptoms:
    - 3-4 years ago had **worsening anxiety** when her mother was sick: overwhelmed, **trouble with finances and calculations**
    - **Couldn't find her car** in a parking lot and trouble navigating out of the lot
    - Trouble **pairing socks**, getting stuck in clothing
    - More issues with **short term memory**
  - Neuropsychiatric:
    - **Mild depression and anxiety**, on citalopram
    - No hallucinations or delusions
  - Functioning:
    - **No longer driving**, cannot perform **calculations or manage finances**

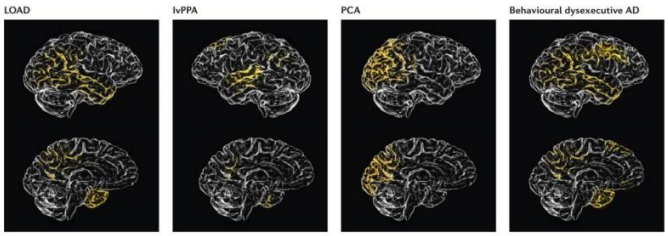
Case 6

- MRI brain w/ and w/o contrast
- Normal metabolic labs
- AD Biomarkers
  - Serum p-tau 217= **2.02** (reference <0.15)
  - Serum B-Amyloid 42/40= **0.148** (reference >0.170)



Case 6

- 4 types of dementia due to **Alzheimer's Disease**
  - Amnestic (Alzheimer-type dementia)
  - Logopenic PPA (Primary Progressive Aphasia)
    - Impaired repetition, impaired confrontation naming with intact object knowledge and grammar
  - **Visuospatial impairment (Posterior Cortical Atrophy)**
  - Dysexecutive / behavioral variant



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Summary

- **Don't delay a clinical diagnosis**
  - Cognitive assessment
  - Ask detailed questions related to daily functioning
  - Think about differential diagnosis and **comorbidities/risk factors**:
    - Sleep apnea, mood/anxiety, vascular contributors, diet, exercise, substances, degenerative syndromes
- Consider anti-amyloid therapies
  - **Inclusion and exclusion criteria**
- **Early and on-going prevention and risk factor optimization**