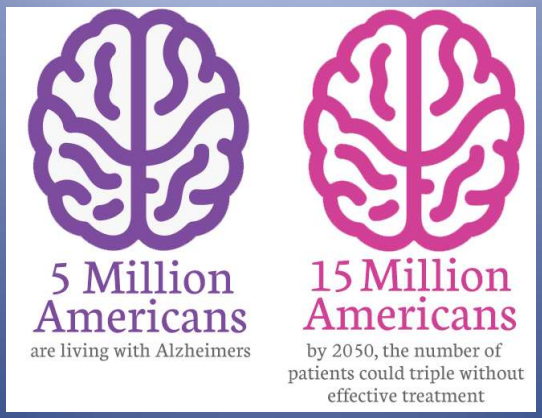
Mixed Dementia



Angela Hanson, MD

January 30, 2025

1

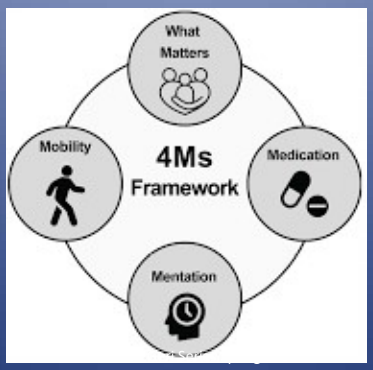
Learning Objectives

- Part 1: Not all cognitive impairment is dementia
- Part 2: Review the criteria for the most common forms of dementia
- Part 3: Review how often patients may have mixed dementia
- Part 4: Discuss how diagnosis affects management

2

Learning Objectives

- **Part 1: Not all cognitive impairment is dementia**
  - **Cognitive impairment is a geriatric syndrome**



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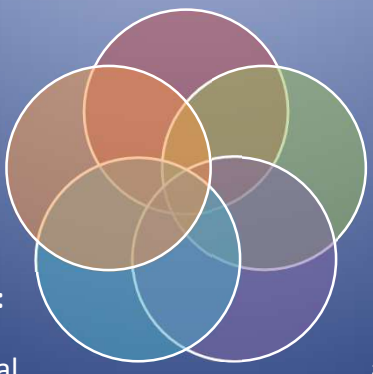
Contributors to Cog Impairment

Medical disease: Diabetes, kidney disease, thyroid, OSA

Neurologic disease: AD, LBD, stroke

Medications: anti-cholinergics, sedatives, EtOH, MJ



Psychosocial: Lack of caregiver/social supports

Psychiatric: Depression, anxiety, poor sleep

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Delirium vs Dementia

- Often thought about in setting of the hospital
- Can occur in conjunction with dementia
  - Might be the first time a dementia patient presents with cognitive impairment
- Can occur independent of dementia as it can take weeks/months to resolve in some cases
- Is the cause for delirium on-going: medication, poorly-controlled medical condition, etc?

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CAM: Confusion Assessment Method

- Feature 1: Acute onset or fluctuating course
- Feature 2: Inattention
  - Easily distractible, trouble paying attention
- Feature 3: Disorganized thinking
  - Rambling conversations, illogical flow of ideas
- Feature 4: altered level of consciousness
  - This includes hyperalert, lethargic, drowsy

1 and 2 and either 3 or 4

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What is normal aging?

- Wide variability in this!
  - A general slowing of cognitive performance
  - A decrease in mental flexibility
  - Some difficulties finding the right word
  - A mild decrease in short-term (working) memory
  - Intact memory for current events
  - Independence in ADL and IADL
  - Retention of verbal abilities and vocabulary
- Changes in perceptual systems or speed of processing associated with normal aging can influence cognitive processes such as attention and memory

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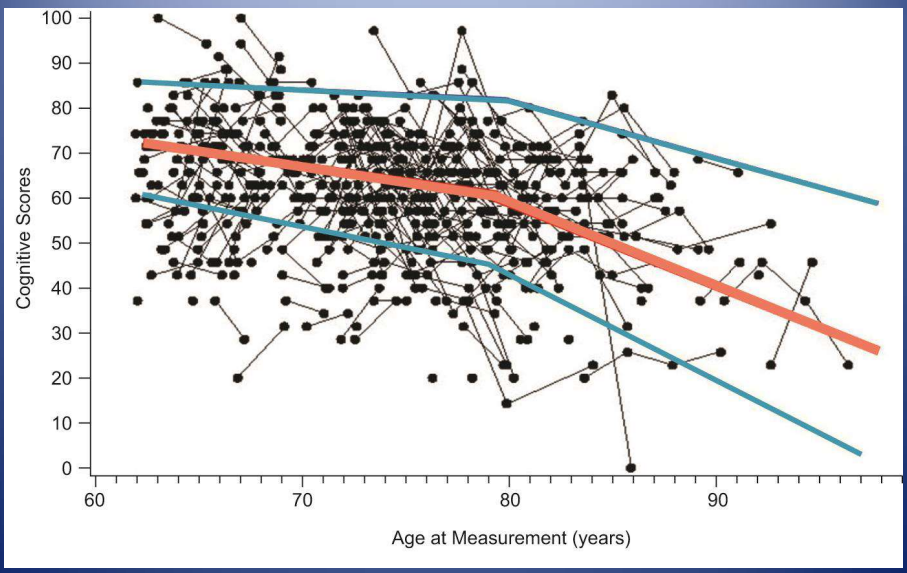
Cognitive composite score in a cohort study of 500 older adults



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Mild Cognitive Impairment

- MCI: problems with memory, language, judgment, and thinking—problems greater than expected for the age of the person, but less than is required for dementia diagnosis
- "Can still carry out everyday activities"
- Not all MCI progresses to dementia
  - About 10–20% a year will progress
- Treatable predictors associated with MCI include diabetes, prediabetes, metabolic syndrome, hypertension, hyperlipidemia, low B12 & folate, chronic alcohol abuse, renal failure, depression

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Cog Impairment and Renal Disease

- Prevalence: One study states 10% to 40%
- Screening: no specific guidelines (same as usual: MOCA, more testing if needed)
- Causes
  - Vascular disease – especially small vessel
  - Cerebral microbleeds – if on HD (Special imaging MRI)
  - Uremic metabolites
  - Anemia/proteinuria
- Management:
  - Treatment of traditional CVD risk factors
  - ACE/ARB to treat proteinuria
  - Kidney transplant
  - Avoiding polypharmacy, careful dosing of meds
  - Holistic approach: Sleep, diet, frequent visits, etc

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Other medical conditions

- Diabetes and cog impairment
  - Up to 20% of > 60 yo with T2DM may have dementia
  - Altered insulin signaling, hyperglycemia, advanced glycation, chronic low-grade inflammation
- COPD and cog impairment
  - A meta-analysis of 14 studies: ~32% of patients with COPD are affected by cognitive impairment and that 1 in 4 people with COPD suffer from mild cognitive impairment
  - Hypoxemia, sleep apnea, h/o smoking, ↓ exercise
- Importance of holistic non-siloed care, good geriatric principles for all adults at risk for cognitive impairment

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Summary Part 1

- Part 1: Not all cognitive impairment is dementia:
  - Cognitive impairment is a geriatric syndrome
  - Mild Cognitive Impairment does not always lead to dementia
  - Importance of good exam, med review, history, labs
  - Stop offending medications, rule out delirium
  - Excellent care of chronic medical conditions
  - Continue to do this throughout caring for patients with dementia

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Learning Objectives

- Part 1: Not all cognitive impairment is dementia
- **Part 2: Review the criteria for the most common forms of dementia**
- Part 3: Review how often patients may have mixed dementia
- Part 4: Discuss how diagnosis affects management

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When does it become dementia?

- Presence of cognitive impairment detected via history taking and cognitive assessment
- Decline from previous level of function
- Interference with the ability to function at work or usual activities
- Exclusion of delirium or major psych disorder
- Distinguish from normal aging

Alzheimer's & Dementia 7 (2011) 263–269

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Causes of Dementia [in older adults]

- #1: Alzheimer's disease
- #2: Vascular Dementia
- #3: Lewy Body Dementia/Parkinson's Disease Dementia
- Others to know about:
  - LATE: Limbic Predominant TDP-43 Encephalopathy
  - Frontotemporal dementia
  - EtoH related dementia
  - A bunch of others-esp if rapidly progressive
- **Mixed etiologies common (esp in older adults)**

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Things don't always match up...

Clinical diagnosis

- What domains are affected?
- What are the symptoms ?
- Age and rapidity of onset?

Pathologic diagnosis

- Plaques and tangles (AD)
- Tau only (FTD/TBI)
- Lewy Bodies
- Vascular strokes/damage

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Diagnosis of Alzheimer's Disease

- Pathology: plaques and tangles
- Probable AD: rare < age 60 (unless familial)
  - Meets criteria for general dementia
  - Insidious, gradual onset over months to **years**
    - Sometimes acute presentations are reported: post op,etc
  - Clear worsening of cognition
  - Typical presentation: Amnestic (↓ learning and recall)
- MRI: Medial Temporal Lobe atrophy (hippocampus)
- Newer tests: Amyloid in brain (PET, LP)

Alzheimer's & Dementia 7 (2011) 263–269

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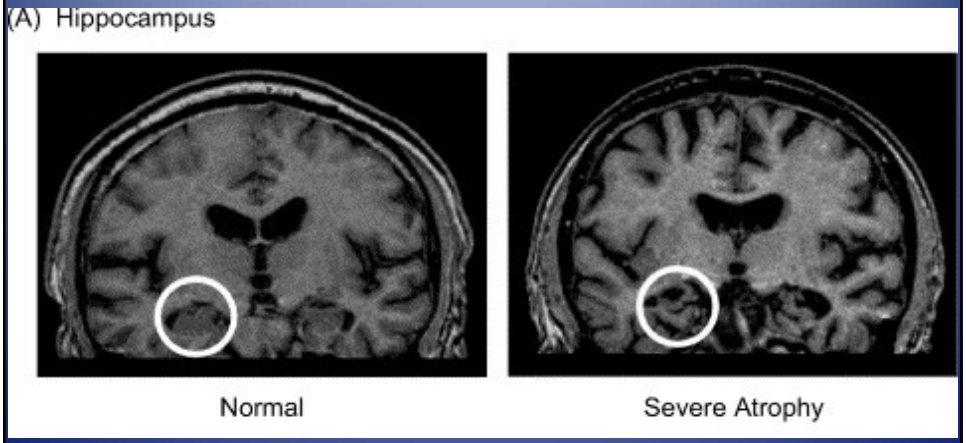
Hippocampal Atrophy in AD



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Vascular Dementia: NINDS criteria

- Large vessel stroke OR
- Small vessel strokes
  - Bilateral thalamic lesions OR
  - Multiple basal ganglia, thalamic and frontal WM lacunar stroke: need at least 2 in the BG area and at least 2 in the frontal white matter OR
  - "Extensive" periventricular WM lesions
- These patients may look more like AD in terms of progression (gradual rather than stepwise)

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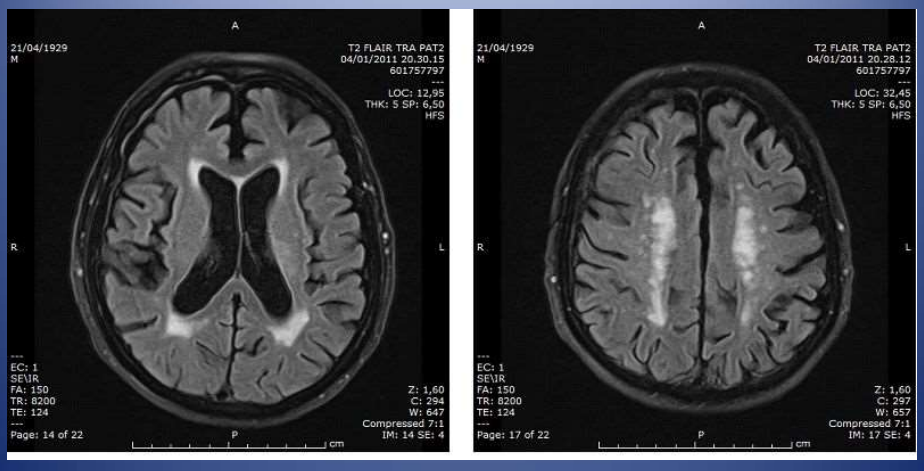
White Matter Disease



An 82 yo man with slowly progressive memory impairment

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Lewy Body/Parkinsons Dementia

- Consensus criteria for DLB 2017: Core features
  - Fluctuating cognition with pronounced variation in attention/alertness (Daytime sleep > 2 hours, staring for long periods, disorganized speech)
  - Recurrent well formed, visual hallucinations
  - REM sleep behavior disorder
  - Parkinsonism features (onset within 1 year of dementia, otherwise it's PDD)
- May respond better to Acetylcholinesterase Inhibitors
- Age of onset: range 50-85, Survival < AD, median<5y
- Pathology: Lewy body inclusions: Skin biopsy now avail!
- Cog testing: more impaired on attention, exec fxn, visuospatial skills

McKeith IG et al, Neurology 2005; 65:1863, *updated 2017*

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Frontotemporal Dementia

- As common as AD in younger patients
  - Mean age of onset: 58 (reports age 20-80)
- Up to 30% of cases are familial/genetic
  - Tau, TDP-43, FUS, others
  - Some overlap with ALS in families (TDP-43)
  - Pathology: tau/tdp43 tangles only
- Two main variants:
  - Behavioral: Often mistaken for mental illness
  - Language: can be subtle early on in the illness

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BV FTD: Need 3 of 6 criteria:

- Early behavioral disinhibition: socially inappropriate behavior, loss of decorum, impulsivity
- Early apathy or inertia
- Loss of empathy: ↓ response to others' needs
- Early perseverative, stereotyped, compulsive behavior or speech
- Hyperorality, diet change: binge eating, pica
- Neuropsych profile: executive function deficits with relative sparing of episodic and visuospatial memory
- **Be skeptical of 'new onset' mood disorder in older adults!**

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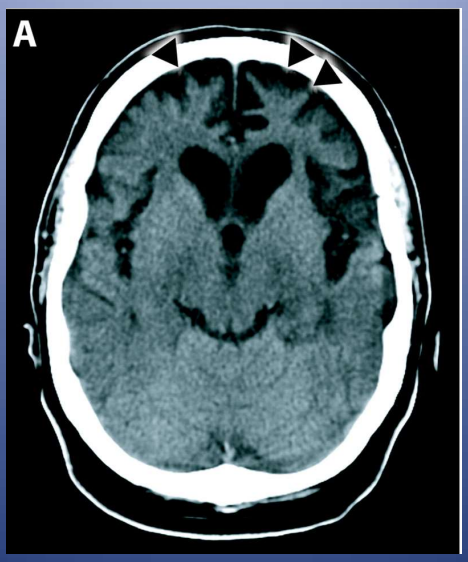
Frontotemporal Dementia

Note the jagged edges in frontal lobes, and the asymmetry

Relative sparing of hippocampus



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What is LATE?

- LATE: Limbic-Predominant Age-Related TDP-43 Encephalopathy
- First described in FTLD/ALS – then found prominent in aging and often (but not always) accomp + AD pathology
- This is an Alzheimer's mimic but some differences:
  - Problems with memory (less dramatic in other domains)
  - Age typically >75 yo (a bit older)
  - More indolent course than AD
- Diagnosis: Officially, only on autopsy
  - Unofficially: elevated inferior temporal/MTL ratio, and amyloid negative (unless you have both??)
  - Likely responsible for up to 90% cases of hippocampal sclerosis

Nelson PT, J Neuropathol Exp Neurol 2025
Schneider, JA. Continuum. 2022

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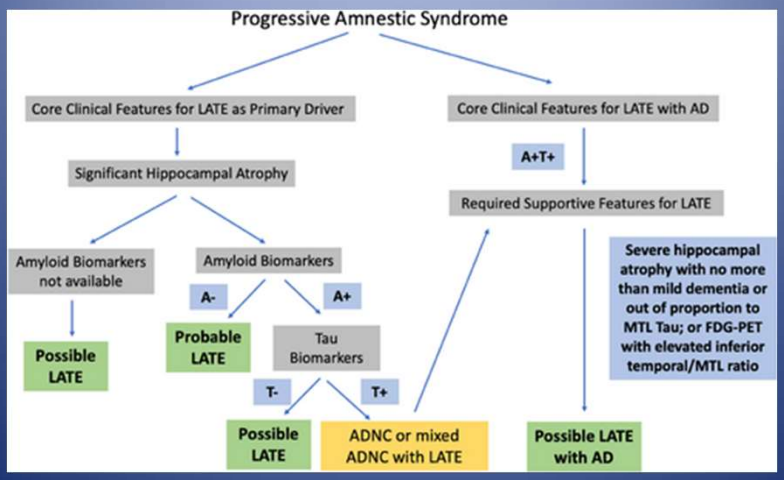
Flowchart: LATE vs AD



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Alcohol-Related Dementia

- 78% of patients with AUD have some brain pathology
  - Prominent white matter loss in prefrontal cortex, corpus callosum, cerebellum
  - Atrophy/neuronal loss in frontal lobes, hypothalamus, cerebellum
- Alcohol itself is neurotoxic, also causes thiamine deficiency (I.E. Wernicke-Korsakoff Syndrome)
- Many confounders exist in this population: head trauma, seizures, vascular co-pathology, hepatic encephalopathy
- Cog: somewhat preserved semantic (naming, category fluency) and verbal memory, whereas impaired in visuospacial, working memory, motor speed, exec fxn, antegrade amnesia and impaired recall
- **May be reversible in early stages**
- Tx: Abstinence is the key, thiamine and B12 supplementation

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Summary Part 2

- Know the core features of common dementias
  - Imaging particularly useful for AD, Vascular
    - May not be able to diagnose LBD, LATE, or people in early stages of disease
  - **History often the most important piece**
  - Ok to diagnose over time
  - Assessment of cognition: MoCA vs formal neuropsych
  - Biomarkers of AD are here, others are coming fast (Skin biopsy for LBD, etc)

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Learning Objectives

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Mixed Dementias

- Common to have co-pathologies
  - AD + vascular: share risk factors
  - AD + LATE, AD+LBD also seen
- How common is it?
  - **Mixed dementia increases in frequency with age**
  - One study suggests <30% of dementia is "pure" AD in community-based cohorts
  - Limitation: almost all from autopsy studies (>80)
- So how do we advise our 'younger old' patients, and factor in comorbidities?

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Mixed Dementias

- NIA study: 94% Dx with AD: 54% had co-existing pathology: Vasc disease #1, Lewy body #2
- A study of the Mayo Clinic Brain Bank 2007-2016:
  - Majority of AD cases had co-existing pathologies
  - Comorbidities increased in frequency with age
  - Common co-pathologies: % not given
  - Vascular: common, heterogeneous: includes small vessel disease as well as cerebral amyloid angiopathy (CAA)
    - 13% of confirmed AD cases had mod-severe CAA
  - Lewy Body inclusions
  - LATE pathology

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Mixed Dementia

- Rush study: 946 older adults (398 with dementia), 2 cohorts combined, Ave age 89
- Those with AD:
  - 66.2% co-occurred with TDP-43
  - 54.4% co-occurred with arteriosclerosis
  - 34% with Lewy bodies
- "TDP-43 pathology was present in almost two-thirds of those with clinical AD-type dementia, being the second most common pathology after a pathologic diagnosis of Alzheimer's disease"

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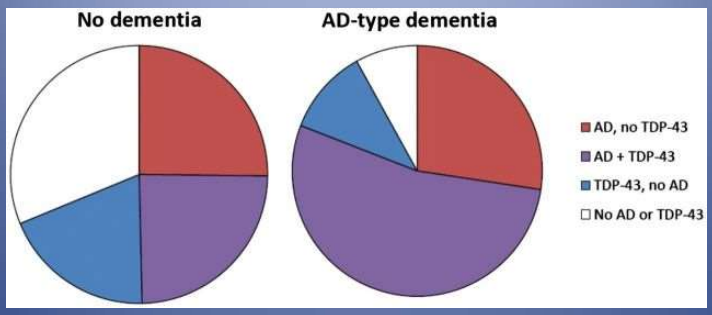
LATE: aka TDP-43



A high percentage of individuals with clinical diagnosis of AD had TDP-43 on pathology

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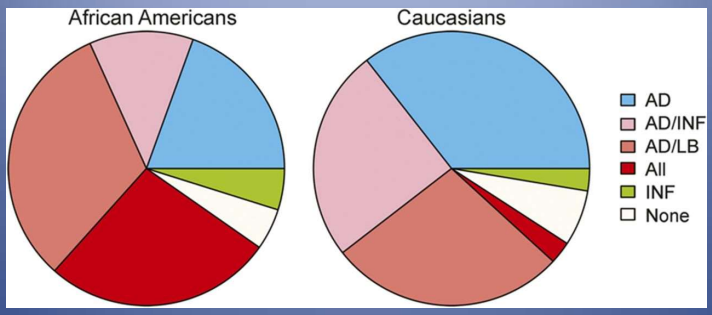
Mixed Dementia by Ethnicity



Pie chart shows proportions of individual and mixed pathologies in black and white decedents with Alzheimer disease (AD) dementia. INF = infarcts; LB = Lewy bodies. **TDP-43 not assessed in this cohort**

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Learning Objectives

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How diagnosis affects management

- Important treatments to consider:
  - Identify vascular/risk factors
  - CAA: Increased risk of bleeding, should avoid blood thinners, head trauma
  - Lewy body: PD aspect changes meds
  - LATE: less worse prognosis?
  - AD therapeutics: must have amyloid to get an anti-amyloid therapy
- Age of onset matters
- What to do with concurrent non-dementia conditions?
  - Delirium, concomitant medical conditions, meds, sleep

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How diagnosis affects management

- Important to establish or r/o neuropathologic changes
  - Brain MRI: atrophy, vascular disease
  - History and exam: parkinsonism, other issues
- Important to screen for and manage reversible causes and contributing factors
  - Labs, medication review, chronic disease management
- Still ok to try AD meds (donepezil, memantine)

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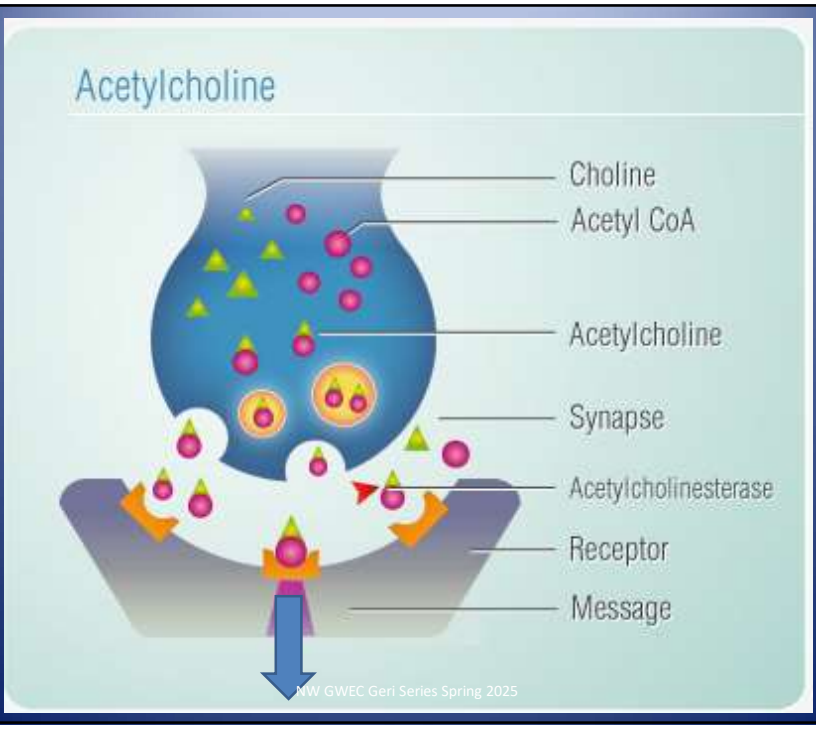

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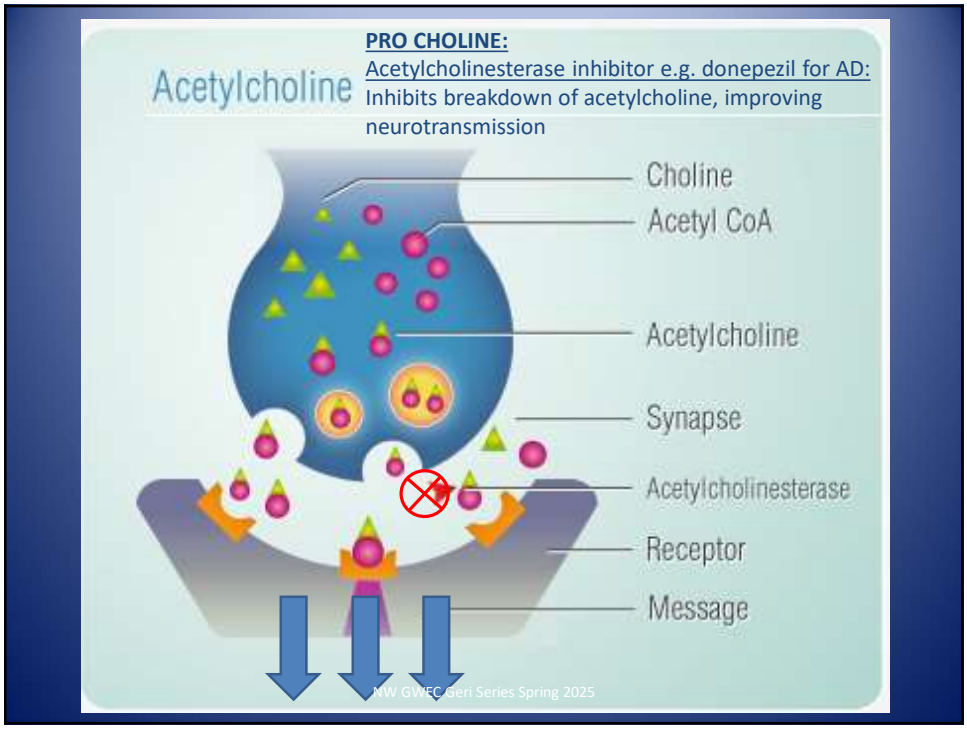
Acetylcholine
PRO CHOLINE:
Acetylcholinesterase inhibitor e.g. donepezil for AD:
Inhibits breakdown of acetylcholine, improving neurotransmission
Choline
Acetyl CoA
Acetylcholine
Synapse
Acetylcholinesterase
Receptor
Message
NW GWEC Geri Series Spring 2025

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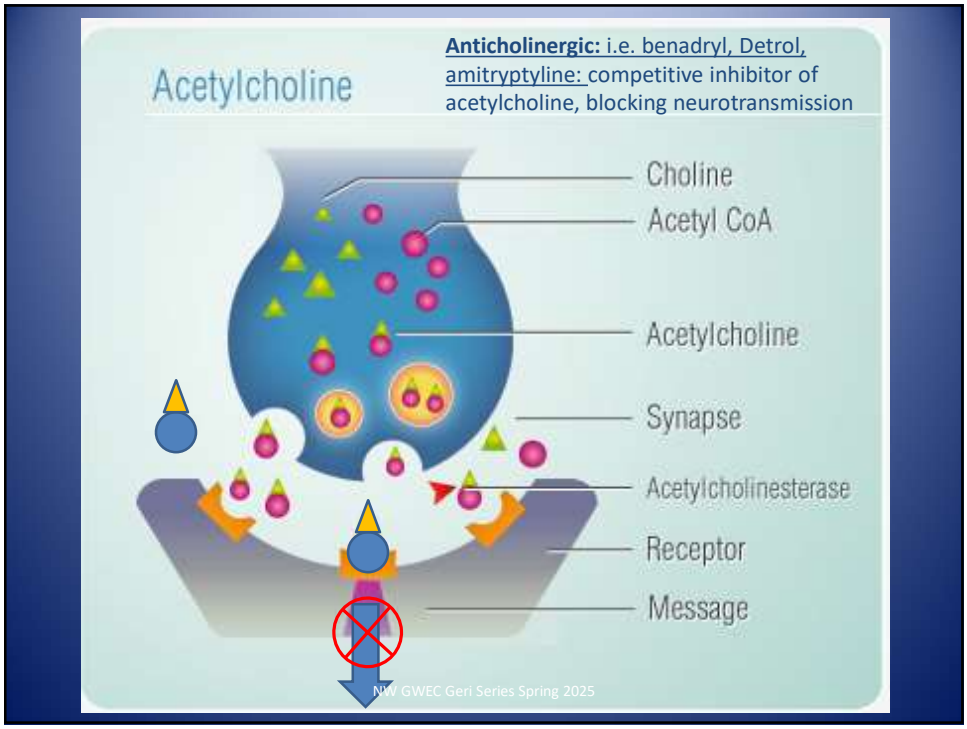
Acetylcholine
Anticholinergic: i.e. benadryl, Detrol, amitryptyline: competitive inhibitor of acetylcholine, blocking neurotransmission
Choline
Acetyl CoA
Acetylcholine
Synapse
Acetylcholinesterase
Receptor
Message
NW GWEC Geri Series Spring 2025

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Anticholinergics and Cog Impairment

- Multiple studies now show a fairly strong positive association with these drugs and the following:
  - Development of cognitive impairment/MCI
  - Risk factor for actually developing dementia
- Recommendations:
  - Reduce or stop as many definite anticholinergics as you can
  - Consider stopping "possible" ones: review need
  - Remember that new drugs won't be on these lists

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Drugs with anti-cholinergic properties→

https://www.acbcalc.com/

^ Use this to look up new meds

ACB Score 2 (moderate)	ACB Score 3 (severe)
Amantadine	Amitriptyline
Belladonna alkaloids	Amoxapine
Carbamazepine	Atropine
Cyclobenzaprine	Benztropine
Cyproheptadine	Chlorpheniramine
Loxapine	Chlorpromazine
Meperidine	Clemastine
Methotrimeprazine	Clomipramine
Molindone	Clozapine
Oxcarbazepine	Darifenacin
Pethidine hydrochloride	Desipramine
Pimozide	Dicyclomine
	Diphenhydramine
	Doxepin
	Flavoxate
	Hydroxyzine
	Hyoscyamine
	Imipramine
	Meclizine
	Nortriptyline
	Orphenadrine
	Oxybutynin
	Paroxetine
	Perphenazine
	Procyclidine
	Promazine
	Promethazine
	Propentheline
	Pyrilamine
	Scopolamine
	Thioridazine (withdrawn)
	Tolterodine
	Trifluoperazine
	Trihexyphenidyl
	Trimipramine

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FDA Approved Oral Meds for Dementia

- Acetylcholinesterase inhibitors "aka choline boosters"
  - Donepezil (Aricept)
  - Galantamine (Razadyne)
  - Rivastigmine (Exelon)
- Memantine (Namenda): NMDA receptor antagonist aka glutamate regulator
- Namzaric: Combo pill with donepezil and memantine together

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Summary Part 3 and 4

- Mixed dementias very common
  - Particularly in older people
  - Leading pathologies: TDP43 (AD mimic), Vascular, Lewy body changes
- Mixed pathologies affect diagnosis, prognosis, treatment
  - Ok to diagnose lightly, over time, order testing if will change management
  - Many dementias treated similarly: exceptions: FTD, LBD, CAA

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Time for questions!

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Supplementary slides (if time)

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Choline boosters

- Examples:
  - Donepezil (Aricept)
  - Galantamine (Razadyne)
  - Rivastigmine (Exelon): also comes as a patch
- Who are they for:
  - Mild, moderate or severe Alzheimer's
  - Also effective for Lewy Body Dementia, especially for hallucinations
  - May be used in other dementias as well
- What does it do: "Donepezil delays the progressive worsening of cognitive symptoms of Alzheimer's disease"

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Choline boosters

- Cautions:
  - Caution if you have had a "GI bleed" or have any low heart rate problems, problems falling
- Side effects:
  - Passing out (syncope): 2%
  - GI: Nausea (3-19%), diarrhea (5-15%), vomiting (3-9%), loss of appetite (2-8%)
  - Low heart rate: higher if already on heart rate blockers (beta blockers like metoprolol)
  - Others: vivid dreams, cramping, dizziness, headache, urinary incontinence

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Memantine (Namenda)

- Complex drug that probably does several things (blocks NMDA receptor which lessens effects of excitotoxic glutamate)
  - One study: "improved delusion, hallucinations, agitation, aggression, and irritability"
  - Another study: "modestly improved attention, global well-being, daily function, and independence"
- For mod to severe AD, off label for other dementias, not shown to help MCI
- Ok to be on this alongside choline drugs

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Memantine (Namenda)

- Complicated up-taper: 5 mg for 1 week, then 5 mg twice a day 1 week, then 5 mg and 10 mg, then 10 and 10. Clear as mud, right?
  - **Hanson pearl: I start people at 'half dosing' then check in after 2-3 weeks**
- Side effects: especially when starting or titrating up
  - Nausea/vomiting
  - Diarrhea OR constipation (up to 5%)
  - Dizziness (5-7%)
  - Headache (6%)
- Cautions: Kidney problems - ↓ dose

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Memantine (Namenda)

- Side effects: especially when starting or titrating up
  - Nausea/vomiting
  - Diarrhea OR constipation (up to 5%)
  - Dizziness (5-7%)
  - Headache (6%)
  - *Stroke listed but placebo group was higher*
- Cautions: Kidney problems - ↓ dose
- No black box warnings with this medicine

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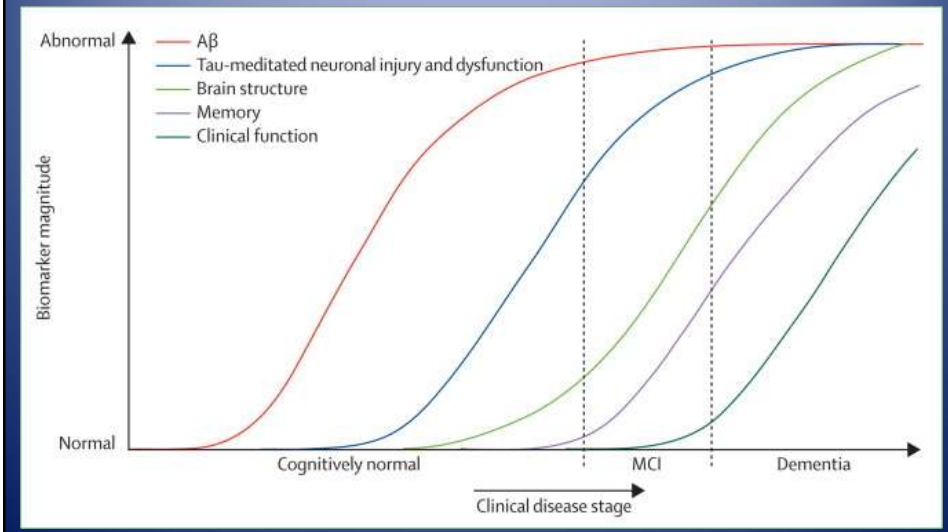
Course of Alzheimer's Disease:



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