Trinity Health
Alliance of Michigan

CHIEF COMPLAINT: MEMORY LOSS
A PRACTICAL AND USEABLE DEMENTIA UPDATE

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MEMORY AND AGING CHARACTERISTICS

- General slowing of cognitive performance.
- A decrease in mental flexibility and learning efficiency.
- Some difficulties finding the right word.
- Generally intact memory for current events.
- Normal retention of verbal abilities and vocabulary.
- Noticeable memory loss is not part of normal aging.
- Older adults with memory complaints may have normal cognition.

DEMENTIA DEFINITION

- Dementia describes a syndrome of cognitive impairment resulting in a specific and objective outcome:

  When a person's memory declines to a point that he/she is no longer self-sufficient and he/she requires ongoing hands-on help or supervision to manage **any** their usual responsibilities or personal care that he/she could once do independently (functional dependency), then he/she has dementia.

FUNCTIONAL ABILITIES

- Activities of daily living (ADLs) refer to daily functional self-care activities.
- ADLs are separated into basic ADLs and instrumental ADLs
  - Basic ADLs: Eating, bathing, dressing, toileting, continence, and transferring
  - IADLs: More complex activities such as using a telephone, shopping, preparing meals, doing housework, transportation, and managing finances

BACKGROUND

- Specific cognitive functions are divided into four systems: episodic memory (short term), semantic memory (facts and word meaning), working memory (multi-tasking), and procedural memory (overlearned memory e.g., tying shoes).
- Each system is linked to a separate anatomical area: temporal, parietal, and frontal lobes, hippocampus, cerebellum, etc.
- Diseases that cause dementia can be distinguished clinically based on memory tests that determine what systems are impaired and knowledge of disease characteristics.

FAMILIAL RISK FACTORS FOR DEMENTIA

- Most cases of dementia are sporadic and not “inherited”, even among early onset cases.
- Very high-risk genes (PSEN1 and 2 and APP) for early onset AD (age 35-65) are rare and account for 5–10% of EOAD cases.
- For late onset AD, a person's chance of having the disease may be higher if he or she has certain genes (ApoE) passed down from a parent. However, having a parent with Alzheimer's does not always mean that someone will develop it.
- E4/E4 homozygotes are not always destined to get dementia.

SCREENING FOR DEMENTIA

- Adults who manifest subjective signs and/or symptoms of cognitive impairment should undergo an evaluation.
- Initial evaluation typically involves administration of a brief objective standardized instrument to detect findings of cognitive impairment and determine if additional evaluation is warranted.
- All screening tests have limitations affecting sensitivity and specificity.
- Screening alone cannot diagnose dementia.

MILD COGNITIVE IMPAIRMENT

- Describes an outcome, but not a cause of cognitive impairment.
- If neurodegenerative, often precedes dementia (of all types).
- May be due to medical or psychiatric conditions (e.g., sleep apnea).
- Isolated memory impairment that does not affect daily routine.
- Noticeably forgetful, but self-sufficient.
- 10-15% convert to dementia per year (additive risk).
- Can improve if treatable condition found: 14 - 55% revert to normal.

COMMON CONDITIONS TO CONSIDER IN THE DIFFERENTIAL DIAGNOSIS

- Sleep disorders including sleep apnea
- Drug side effects (benzodiazepines, antihistamines, gabapentinoids, overactive bladder drugs)
- Mood disorders (depression, anxiety, stress)
- Other psychiatric disorders (e.g., late onset schizophrenia)
- Drug/alcohol abuse (including THC)
- COVID-19

CAUSES OF MCI AND DEMENTIA - NEURODEGENERATIVE

- Alzheimer's disease (75% of all cases of dementia)
- Frontotemporal lobar degeneration
- Dementia with Lewy bodies
- Parkinson's disease
- Diseases with associated with parkinsonism
  - Progressive supranuclear palsy
  - Corticobasal ganglionic degeneration
  - Multiple system atrophy

ALZHEIMER'S DEMENTIA CRITERIA

- Memory loss – usually short term – that affects daily routine (often manifests as frequent repeating).
- Impairments in speech (word finding or empty speech - anomia) and visual-spatial orientation.
- Loss of ability to recognize objects (agnosia), to use objects purposefully (apraxia), and to plan and execute complex tasks (executive dysfunction).
- Gradual onset and continuous decline.
- Other diseases, medical conditions, and delirium excluded.

WHAT IS EXECUTIVE FUNCTION?

- Executive function - a set of mental or cognitive skills believed to be controlled by the frontal lobe, anterior cingulate, prefrontal cortex, basal ganglia, and thalamus.
- Two main types of executive functions:
  - Organization: attention, managing time, planning and organizing, remembering details, sequencing, and working memory.
  - Regulation: self-control, emotional regulation, decision-making, and moral reasoning.

ATYPICAL PRESENTATIONS OF AD

- Anterograde amnestic type (most common)
- Posterior cortical atrophy (visual variant AD)
- Frontal variant Alzheimer’s disease (fvAD)
- Logopenic primary progressive aphasia (l-PPA)
- Down syndrome AD

CLINICAL PEARL – SUBSTANCE ABUSE

- Opinions differ on how much/long alcohol overuse will lead to cognitive impairment.
- Heavy and prolonged use can lead to Wernicke's encephalopathy from thiamine deficiency (potentially reversible confusion, ataxia, tremor, abnormal eye movements), then to Korsakoff syndrome (permanent damage to areas of the brain involved with memory).
- Alcoholic dementia is a separate term used to describe permanent memory loss due to direct toxic effects of alcohol.

CLINICAL PEARL – SUBSTANCE ABUSE

- The neurocognitive profile of alcoholic dementia is so like that of Alzheimer's dementia that differentiating them is difficult.
- With abstinence, cognition will plateau and may improve with time.
- Memory impairment from marijuana occurs because THC alters function of the hippocampus.
- Learning and memory problems caused by marijuana can persist for weeks after cessation of use.
- The long-term effect of cannabis on cognition is unclear.

COVID AND COGNITION

- COVID-19 is associated with neural damage; post-mortem studies show evidence of ischemic lesions and inflammation.
- Nearly 2/3 of COVID patients experience cognitive impairment (brain fog) even with mild disease. Most recover in 6-9 months.
- Cognitive dysfunction is one of the most common symptoms of long COVID (~70% of patients); unclear if permanent.
- There are no effective treatments for this condition.
- No good evidence that COVID vaccines cause memory loss.

CLINICAL PEARL – LAB TESTING

- The evidence that B12 deficiency causes isolated memory loss is incomplete. B12 replacement to reverse cognitive deficits alone, due to deficiency (unless severe), remains controversial. B12 testing and replacement therapy is however advised by the AAN to >300 pg/ml.
- Syphilis testing should only be done when clinical suspicion is high and not routinely as false positive tests can occur with non-treponemal tests.
- Genetic testing for ApoE is not recommended outside of clinical trials and is not covered by most insurance plans (family members who request testing should be referred to a medical genetics clinic).

NEUROIMAGING

- Brain imaging advised by American Academy of Neurology for initial evaluation of all patients with dementia. However, the yield from neuroimaging in identifying a potentially reversible cause of dementia is low such that there is controversy regarding the routine use of neuroimaging in the primary evaluation of dementia.
- Since only 14% of PCP's report high confidence in interpreting brain imaging findings and dementia specific scanning protocols may be unfamiliar to them, imaging decisions should be left to specialists if a neurology referral is anticipated.

NEUROIMAGING TIPS

- MRI is preferred over CT scanning; depicts anatomy in greater detail and no ionizing radiation - one head CT ~ 20 CXRs based on average mSv dose.
- Contrast is generally unnecessary.
- Radiologists differ in quantifying small vessel changes (mild, moderate, severe); > 25% of white matter must be affected to support VAD diagnosis if based on small vessel changes alone.
- Serial scans to estimate disease stage are not necessary.

ALZHEIMER'S IMAGING PEARLS

- Hippocampal atrophy is common imaging finding but not diagnostic.
- Cortical atrophy alone on imaging is also not diagnostic.
- Amyloid plaques cannot be seen with standard imaging.

MESIAL TEMPORAL LOBE ATROPHY

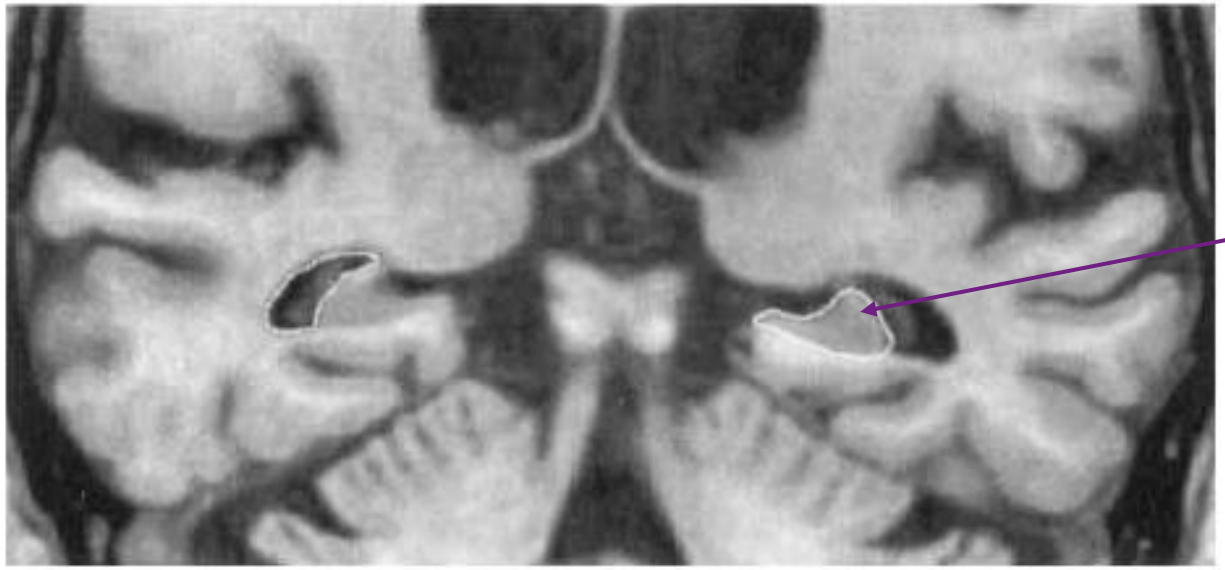
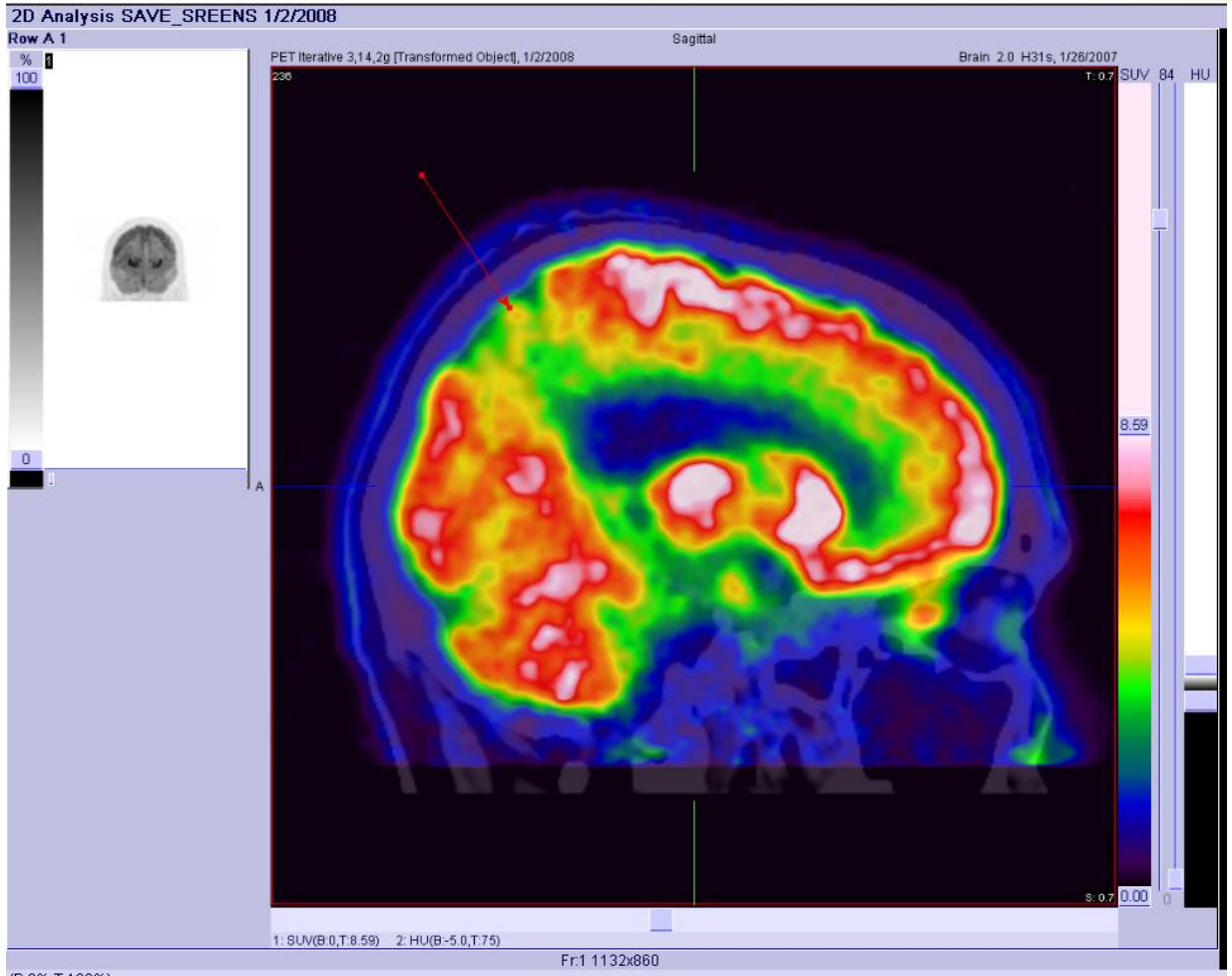


Figure 1. Structure boundaries. Boundaries of the hippocampus indicated on the patient's left, and the temporal horn on the right.

FDG PET


2D Analysis SAVE_SREENS 1/2/2008
Row A 1
Sagittal
PET Iterative 3,14,2g [Transformed Object], 1/2/2008
Brain 2.0 H31s, 1/26/2007
SUV 84 HU
8.59
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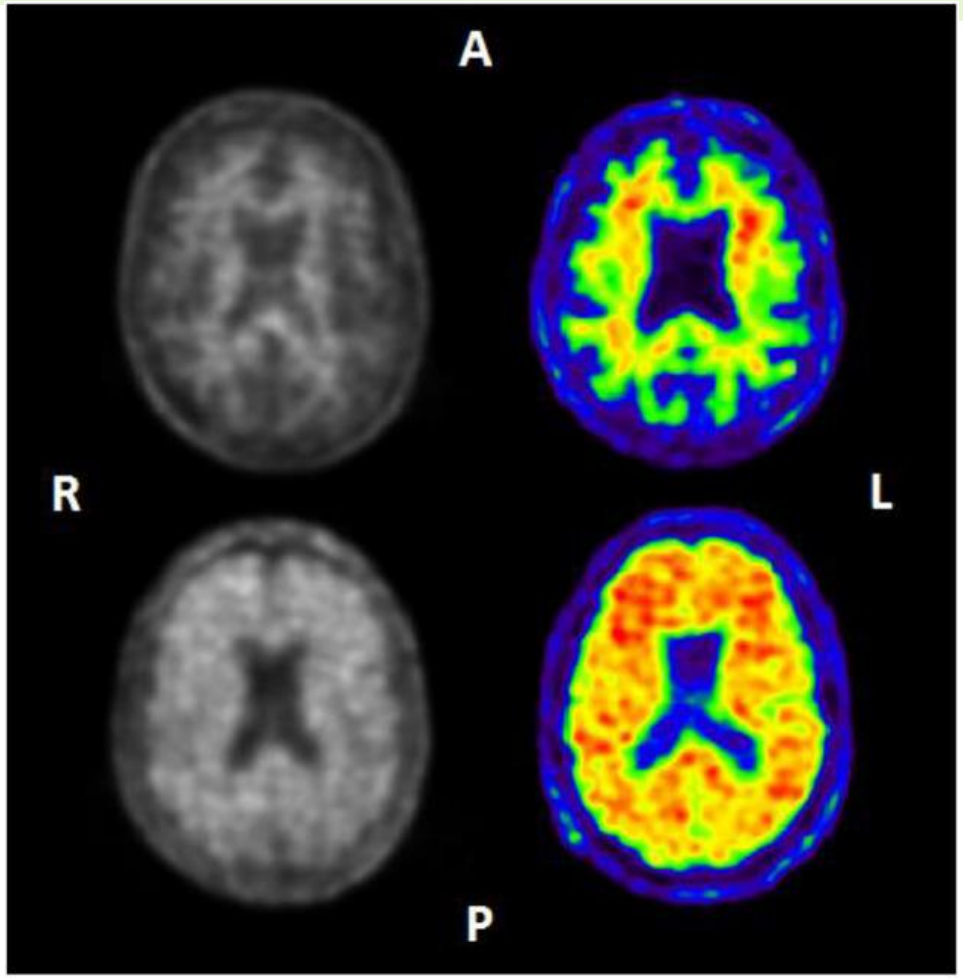
1: SUV(B:0,T:8.59) 2: HU(B:-5.0,T:75)
Fr:1 1132x860

PET AMYLOID CT



NPH

- NPH is a rare disorder - common causes of memory loss are more likely in patients with large ventricles.
- More likely when associated with CNS injury, bleeding, or infection, Idiopathic cases are believed to be most common.
- The clinical triad is not specific to NPH but must be present to diagnose NPH. A “magnetic gait” is common.
- Ventricular enlargement is more often due to central atrophic changes (from AD) mimicking NPH (hydrocephalus ex-vacuo).
- Improvement in gait is far more likely than cognition after shunting.

NEUROPSYCHOLOGICAL TESTING

- History, neurological examination, and screening tests of cognition with additional cognitive tests are often sufficient to meet the diagnostic criteria for a suspected dementia.
- Neuropsychological testing is appropriate when clinicians are unfamiliar with specific diagnostic criteria, an atypical presentation is evident, or if a patient's true functional status is unclear (functional dependency required for dementia diagnosis).
- Tests results are often invalid in adults who do not speak English and/or have no formal education.

PHARMACOLOGIC THERAPY

- Cognitive decline from AD has been shown to be associated with depletion of acetylcholine.
- Other mechanisms have been identified over time that challenge the relevance of this finding as a treatment target.
- Cholinesterase Inhibitors – increase acetylcholine. concentrations in brain. Clinical trials involving AD subjects conducted in the 1990’s reported a modest slowing of cognitive and functional decline over several months in comparison to placebo.

PHARMACOLOGIC THERAPY

- 12 trials used the ADAS-cog (score range 0 lowest to 70 highest) as the primary outcome measure; significant differences between cholinesterase inhibitor and placebo groups were reported, always favoring the treatment groups. The mean differences between treatment and placebo groups ranged from 1.5 to 3.9 points.
- No studies have investigated the benefits of cholinesterase inhibitors beyond a year or the risks/benefits of long-term therapy.

COGNITION STABILIZERS

- Donepezil given full disease spectrum approval by FDA.
- Galantamine and rivastigmine are approved for mild to moderate stage.
- Memantine approved for moderate to severe stage, effect in mild stage is doubtful based on published trials.
- Benefit of combination therapy (AChEI + Memantine) is uncertain as clinical trial results are inconsistent.

MEMANTINE

- NMDA-receptor antagonist.
- FDA approved for treatment of *moderate to severe* AD (MMSE score ≤ 14) based on 3 monotherapy and 1 combination study with donepezil.
- Effects modest (magnitude of effect on the Severe Impairment Battery (1–100 point scale) 4.46 points (95% CI 1.87-7.04).
- Actual mechanism of action unclear.
- Can be used alone or in conjunction with an AChE inhibitor.

TREATMENT EMERGENT SIDE EFFECTS/ADVERSE REACTIONS

- Cholinesterase inhibitors – Nausea, vomiting, diarrhea, insomnia appetite suppression leading to weight loss, vivid dreams/nightmares, rhinorrhea, leg cramps, dizziness and syncope (from increased vagal tone).
  - ➢ May increase incidence of falls + hip fractures due to syncope
  - ➢ Use with caution in patients with asthma or COPD
- Memantine – confusion, dizziness, headache, somnolence.

ESTIMATE OF BENEFIT

- In pooled analyses, those taking AchEI or memantine compared to placebo ranged from 1 - 2.5 points on the ADAS-cog (0 - 70) over 3 mos to 3 years of follow up.
- Changes of this magnitude generally are not considered clinically important/meaningful.
- Follow-up beyond 1 year in these trials was infrequent.

BALANCING RISK VERSUS HARM

- Benefit must be carefully estimated compared to potential harm for every treatment candidate.
- A meta-analysis published in *CMAJ* determined that the numbers needed to treat for 1 additional patient to benefit were 7 (95% CI 6-9) for stabilization or better, 12 (95% CI 9-16) for minimal improvement or better and 42 (95% CI 26-114) for marked improvement; the number needed to treat for 1 additional patient to experience an adverse event was 12 (95% CI 10–18).

COGNITION STABILIZERS TIPS

- Treatment trials to “improve” memory are not recommended as this outcome is unlikely and stabilization is the goal of treatment.
- Cognition stabilizers should be prescribed according to disease stage approved by the FDA.
- Based on published evidence, cholinesterase inhibitors and memantine are not indicated for treatment subjective memory complaints or MCI due to any cause.
- Despite FDA labeling, donepezil should not be given at bedtime as it can significantly increase risk of insomnia.

COGNITION STABILIZERS TIPS

- There is no convincing evidence that high dose treatment (donepezil 23mg, rivastigmine 13.3mg/24h, galantamine 24mg) provides additional benefit over 10mg, 9.5mg, 16mg respectively and side effect rates are doubled at higher dosages.
- When stopping treatment, tapering of dose and close monitoring for cognitive, functional, and neuropsychiatric symptoms is advised as case reports suggest that a discontinuation syndrome can occur from abrupt discontinuation of cholinesterase inhibitors / memantine.

PHARMACOLOGIC THERAPY - OTHER

- Aducanumab (Aduhelm®)
  - IV amyloid beta-directed monoclonal antibody infused monthly.
  - Controversial FDA approval for treatment of mild cognitive impairment due to AD or mild AD.
  - Reduces amyloid plaques in brain, but no evidence this results in meaningful clinical benefit.
  - CMS decided to pay for it if patient enrolled in qualifying clinical trial.
  - Adverse effects can include cerebral edema (35%) and microhemorrhages (19%).
  - Due to unending controversy, marketing of drug stopped June 2022.

PHARMACOLOGIC THERAPY - OTHER

- Lecanumab (Leqembi®)
  - IV amyloid beta-directed monoclonal antibody infused biweekly.
  - For treatment of mild cognitive impairment due to AD or mild AD.
  - Also reduces amyloid plaques in brain; evidence this results in meaningful clinical benefit is unclear (only 1 trial published).
  - Approved by CMS with same conditions as aducanumab.
  - Adverse effects can include cerebral edema (12.6%) and microhemorrhages (17%), mostly asymptomatic.
  - May not be safe to administer to patients on antithrombotic drugs.

DEMENTIA OUTCOMES

- Rates of decline vary between individuals, even with the same disease, making prognostication very difficult.
- Trajectory of decline is non-linear, natural plateaus of cognitive stability have been measured up to two years.
- Poor prognostic factors - rapid decline, aphasia, hallucinations, wandering, incontinence, falls.
- Published statistics report survival between <1 to 20+ years.
- Most older adults with dementia die of concomitant chronic illness or infections/injuries.

KEY DEMENTIA MANAGEMENT GOALS

- Provide a clear and specific diagnosis.
- Ensure basic care needs are met and well.
- Monitor safety (driving, wandering, falls).
- Identify and treat mood/behavioral problems.
- Ensure that health in general is optimized.
- Alleviate boredom and maintain sense of self-purpose.
- Address medical-financial proxy planning (POA's).
- Assist caregivers in making difficult decisions and help to relieve their guilt.

CAREGIVER SUPPORT

- Being caregiver is extremely taxing, both physically and emotionally. Validate caregivers often.
- Common caregiver symptoms include guilt, anger, grief, fatigue, loneliness, demoralization, and depression.
- Assess the well-being of the caregiver at every visit.
- Provide caregiver education and skills training (e.g., Savvy Caregiver® program).
- Alzheimer’s Association, Area Agency on Aging, support groups.

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