DIFFERENTIAL DIAGNOSIS OF EPISODIC MEMORY FAILURES: CASE PRESENTATIONS

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Learning objectives:
1. Understand the Alzheimer's disease pathophysiologic process.
2. Use the new diagnostic criteria to diagnose Alzheimer's disease dementia and mild cognitive impairment (MCI) due to the Alzheimer's disease pathophysiologic process.
3. Distinguish Alzheimer's disease from other common causes of cognitive impairment and dementia.
4. Treat Alzheimer's disease and other common causes of cognitive impairment and dementia.

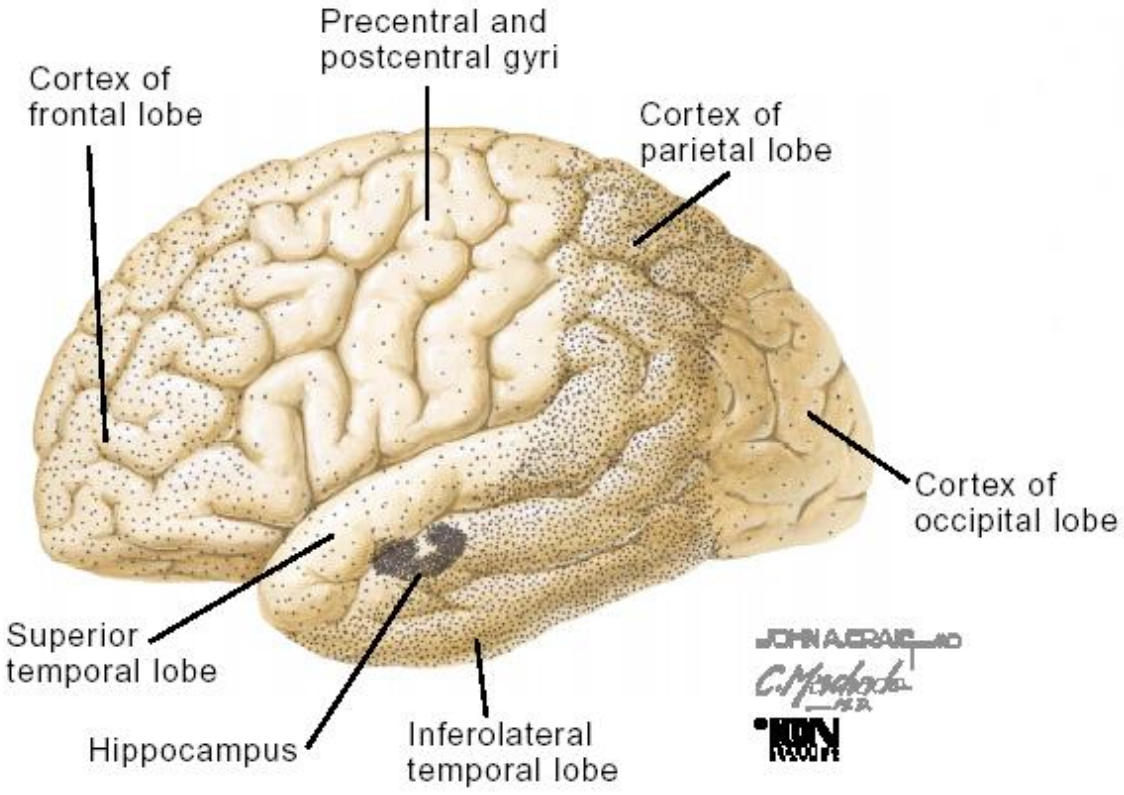
I. Dementia Prevalence

A. Increases geometrically with age
   1. 5-10% of individuals > age 65
   2. 50% of those > age 85

B. Alzheimer's disease is by far the most common form of dementia, affecting about 7 out of every 10 patients.

C. Distribution of pathology in Alzheimer's disease:

II.



Evaluation (to diagnose Alzheimer's disease vs. other dementia). For additional information see

Sections I & II of Budson & Solomon, *Memory Loss, Alzheimer's Disease, and Dementia: A Practical Guide for Clinicians*, Philadelphia: Elsevier Inc., 2016.

A. Structure of appointment:

- *With both patient & caregiver*: brief hx per patient's perspective, PMH, All, Meds, SHx including education & occupation, FHx (25-40% of AD patients have at least one other afflicted relative) (10 min)
- *Caregiver alone*: History per caregiver's perspective. Key questions: (1) What was the **first symptom** suggesting impairment, and (2) **when** did it occur? (3) What was the **pace** of the decline? Was it gradual or stepwise? (4) What cognitive areas are **currently** impaired & (5) which are the **most prominent**? (15 min)
- *Patient alone*: Physical, Neurological & Cognitive exam. (20 min)
- *Both patient & caregiver*: Assessment, further work-up and/or treatment plan. (15 min)
- Do in two visits if necessary. (An extra 10 minutes each on the history and cognitive exam is worth at least as much diagnostically as a PET or SPECT scan, neuropsychological testing, expert referral, etc., and is much more cost effective.)

B. History: (Although classically in neurology exam tells where, and history tells what, history often tells where as well as what in dementia.)

****Need to talk with caregiver/child/spouse alone****

General: Gradual and insidious onset over months to years, not stepwise (ask about when retired and why; keep checkbook; do taxes; continue community participation; etc.)

Hippocampal: Inability to learn new information, with striking preservation of older memories initially (repeats self; needs to be told information multiple times; misses appointments).

Temporal: Word finding difficulties. Disruption in the semantic storage and retrieval of linguistic information (anomia, not just for names of people; empty speech).

Parietal: Visuo-spatial deficits (difficulty planning routes; gets lost; cannot draw intersecting pentagons).

Frontal: (late) Dysexecutive syndrome (disinhibition; aggression; agitation; also much worse memory, attention and other cognitive functions).

C. General Exam: Check for cervical bruits; look for signs of systemic disease (COPD, liver failure, etc.)

D. Neuro exam:

Inconsistent: focal signs suggesting strokes, subdural fluid collections, tumors, etc.; signs suggesting Parkinson's (rigidity, tremor, etc.), PSP (no downgaze) or other neurodegenerative disease. (Note: some patients have both PD and AD.)

Supportive (early): none

Supportive (mid to late): Brisk reflexes, extensor plantars, snout, grasp, palmomental reflexes. (These are, however, not sensitive or specific.)

E. Cognitive exam:

Use one simple global cognitive exam to evaluate cognitive function.

Use the MMSE—but copyrights held by Psychological Assessments Resources.

Use the Montreal Cognitive Assessment (MoCA)—my new favorite—test & instructions below.

Useful for:

- Establishing the pattern of deficits
- Evaluation of drug effects (typical increases of 2-3 points are seen on both MoCA & MMSE)

- Annual comparisons (typical yearly decline of 2-3 points/year are seen on both MoCA & MMSE).

Pattern of deficits on the MoCA:

Delayed Recall tests new learning which is always impaired in early AD and MCI due to AD.

Orientation tests recent memory, which is generally impaired in early AD, particularly the date.

Other tests, including Visuospatial/Executive, Naming, Attention, Language, & Abstraction typically become more impaired as patients progress from early to moderate AD. These tests should be more or less intact in patients with MCI due to AD.

Other tests. Useful if the pattern from the MoCA is unclear:

Word Fluency: Intact individuals generate more words to categories (animals, vegetables, fruits; 12-15 or > for each), than letters (F, A, S; 10-12 or > for each); early AD patients show opposite pattern, i.e. can generate more words to letters than categories. (This is the only test that uses the patient as their own control.)

> Instructions: "Tell me all the words that you can think of in 1 minute that begin with a certain letter. You cannot use names or different forms of the same words. For example, if the letter was 'R' you could not say Richard or Roger or Rochester, because those are names. You could say 'run' but then you could not say 'runs,' 'running,' or 'ran' because those are different forms of the same word. The first letter is F…." Prompt patients if they do not give any words for any 15 second block. For efficiency, only do as many letters as needed to establish pattern or normality. For categories: "Now we're going to do the same thing only different. I want you to tell me all the words you can think of that are all in the same category (which I will give you). The words can begin with any letters. You can say both big subcategories, as well as small individual items. For example, if the category was 'furniture,' you could not only say 'tables,' 'desks,' and 'chairs,' but also 'armchair,' 'high chair,' 'rocker,' 'recliner,' etc. The first category is 'animals'…." Again, prompt patients after no response for 15 seconds, and only do as many categories as necessary to either establish a pattern or normality.

Attention: *Simple* (always intact in early AD): Digit span forwards, 1 to 20, months forwards, registration (remembering words etc. w/o distraction for 30-60 seconds).

Attention: *Complex* (may be impaired in early AD): Digit span backwards, 20 to 1, months backwards, calculations.

Memory (always impaired in early AD): (note: registration must be intact) drilled word span (= to 1 less than digit span forwards), story "Bill and Tom went fishing…", others. If they don't get the words on free recall, check cued recall and recognition.

Remote Memory (often intact in early AD): Presidents, personal information.

Language (usually intact early, except for naming): naming high and low frequency objects (watch & band, pencil & point), writing sentence, comprehension, repetition, (empty speech late).

Visuospatial (may be impaired in early AD): copy figure

F. Laboratory tests: TSH, B12, Vit D. Also screen for encephalopathy / delirium: CBC, lytes, BUN, Cr, glucose, LFTs, Ca, alb. If clinically indicated: RPR, Lyme titre.

G. Imaging: MR is better for judging atrophy (esp. hippocampal), better for small vessel disease, better for evaluating for unusual conditions. CT is adequate, and better for agitated patients. (Everyone deserves at least one image in the course of their disease. E.g. a subdural on top of AD may explain the patient's current presentation—AD patients don't remember their falls!)

H. Additional w/u:

Behavioral Neurology Evaluation: (1.5-2 hrs over 1-2 visits with neurologist who has additional training in dementias.) Review history, imaging, interviews with patient & caregiver, general and neurological examinations, 20-30 minute cognitive exam. Especially important for complicated patients or those seeking second opinion of specialist. (Will follow patient if you desire.)

Neuropsychological Evaluation: (1-1.5 hrs with neuropsychologist (Ph.D.) + 3-6 hrs with technician for cognitive testing, over 1-3 visits.) Helpful if after your own thorough w/u including 15-20 min cognitive exam it is necessary to better characterize the existing deficit to make a diagnosis. E.g. to help determine the contributions of depression to a memory disorder, or to help evaluate someone who has an above average IQ and educational background such that although they perform normally on your office tests, you still suspect they are impaired. [Caution: all neuropsychologists are NOT equal when it comes to diagnosing dementia; only refer your patients to ones with experience in dementias.]

Brain FDG PET or ^{99}Tc SPECT: Nuclear medicine tests. Useful for confirming diagnosis of atypical dementia, or AD in a young patient (< age 65). In AD Expect temporal and parietal hypoperfusion. Moderate sensitivity and specificity. In correct clinical setting, areas of medial temporal, temporal, or parietal hypoperfusion suggests AD *regardless of the official interpretation*. PET and SPECT scans (unlike MRI) will often show significant changes from one year to the next, making them a useful follow-up test in the setting of previous negative work-up. In frontotemporal dementia, PET and SPECT shows abnormalities in frontal lobes; in corticobasal degeneration there are abnormalities in parietal lobes; in Lewy body disease there are abnormalities similar to AD but also in occipital lobes; in primary progressive aphasia abnormalities are in left perisylvian areas. Some pathologies yield multifocal patterns: e.g., Lyme disease, cerebral vasculitis.

Florbetapir (Amyvid), flutemetamol (Vizamyl), or florbetaben (Neuraceq) PET: Nuclear medicine tests. Useful for confirming diagnosis of AD in a young patient (< age 65) or at any age when being sure that the patient has AD would significantly alter prognosis or treatment. About 90% sensitivity and specificity.

CSF Aβ & tau: laboratory study. Useful for confirming diagnosis of AD in a young patient (< age 65) or at any age when being sure that the patient has AD would significantly alter prognosis or treatment. About 85% sensitivity and specificity.

I. Apply new criteria for AD and MCI due to AD (see review from Budson & Solomon, 2012, at end of handout)

III. Treatment For additional information see Section III of Budson & Solomon, *Memory Loss, Alzheimer's Disease, and Dementia: A Practical Guide for Clinicians*, Philadelphia: Elsevier Inc., 2016.

A. D/c or change anticholinergic agents, sedatives, etc.

B. To enhance cognition:

1. donepezil (generic & as Aricept). Cholinesterase inhibitor. Main side effects are: anorexia, nausea, & diarrhea (occur infrequently, <1 out of 10), also vivid dreams. (Additionally, need to use non-cholinergic paralytic agent for anesthesia; i.e. no succinyl choline) Start with 5mg QD, increase to 10 mg after 4-6 weeks if tolerated. 23 mg tablet available for moderate to severe AD; data suggests it may improve cognition but side-effects (anorexia, nausea, vomiting, diarrhea) also more common. Low income assistance program available. Produces a noticeable improvement in most patients. FDA approved for mild, moderate, and severe AD.

2. rivastigmine (Exelon). Cholinesterase inhibitor. Side-effects are more than donepezil in capsule form, but rivastigmine is now available in a QD patch which has comparable efficacy and fewer side-effects than any drug in this class. Start 4.6 mg/24 hr patch; can increase to 9.5 mg/24 hr patch after one month, and 13.3 mg/24 hr patch after that. Note: 13.3 mg/24 hr patch has more side-effects than 9.5 mg/24 hr patch; most patients do best with the 9.5 mg/24 hr patch. The rivastigmine patch is FDA approved for mild to moderate AD and mild to moderate dementia associated with Parkinson's disease (Lewy Body Dementia).
3. galantamine (now generic, formerly Razadyne, formerly Reminyl). Cholinesterase inhibitor. Similar to Donepezil. Immediate release (IR) and extended release (ER) formulations available; ER is both easier to use and has fewer side-effects (due to lower serum peak levels). ER: Start with 8 mg QD and increase after 4 weeks to 16 mg QD. Can also go to 24 mg QD. IR: 4 mg bid and increase after 4 weeks to 8 mg bid. Can also go to 12 mg bid.

References for cholinesterase inhibitors:

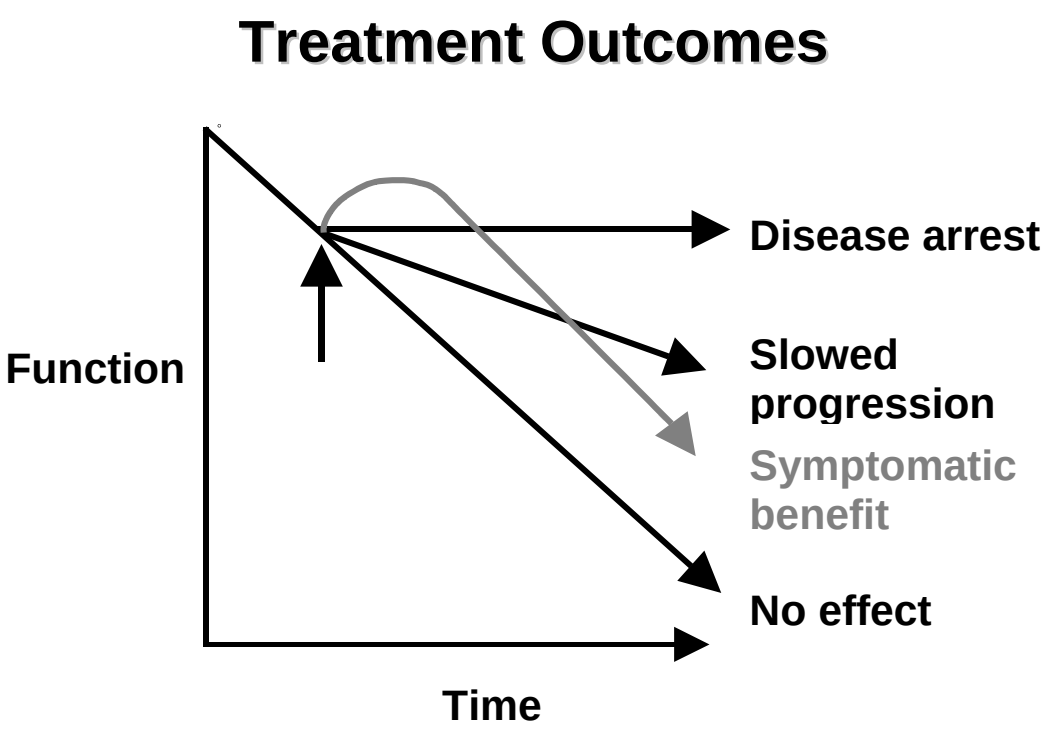
- Improves cognition, participation in activities of daily living, & global function in mild to moderate patients with AD:
  - Donepezil: Neurology 1998;50:136
  - Rivastigmine: BMJ 1999;318:633
  - Rivastigmine patch: Int J Geriatr Psychiatry 2007;22:456
  - Galantamine: Neurology 2000;54:2261
- Improves cognition & behavior in mild to moderate and moderate to severe patients with AD
  - Donepezil: Neurology 2001;57:613 & Lancet 2006;367:1057
  - Donepezil 23 mg: Clin Ther. 2010 Jul;32(7):1234-51.
  - Galantamine: Neurology 2000;54:2269
- Delay to nursing home placement by up to 2 years:
  - Donepezil: J Am Ger Soc 2003;51:937
- Reduces healthcare expenditures because treatment costs are offset by reductions in other healthcare expenditures.
  - Galantamine: Neurology 2000;57:972
  - Donepezil: Dementia and Geriatric Cognitive Disorders 2003;15:44
- Reduces caregiver time by over 1 hour per day
  - Galantamine: Int J Geriatr Psychiatry 2003;18:942
- Mild Cognitive Impairment
  - Donepezil: Neurology 2004;63:651 & NEJM 2005;352:23
- Vascular Dementia
  - Galantamine: Lancet 2002;359:1283
  - Donepezil: Neurology 2003;61:479
- Lewy Body Dementia
  - Rivastigmine: Lancet 2000;356:2031
- Neuropsychiatric inventory meta-analysis
  - JAMA 2003;289:210
- Responders and non-responders
  - 25-30% show an improvement equivalent to a 1 year reversal of symptoms

- 50-60% show an improvement equivalent to a 6-month reversal of symptoms
- 10-15% show either less than a 6-month reversal of symptoms or no significant improvement
- NEJM 2004;351:56.

- How long to use them?
  - Studies suggest at least 4 to 5 years (CNS Drugs 2004;18:757)
  - Recommend: continue as long as there is quality of life to preserve.
  - In patients with moderate or severe Alzheimer's disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months. (NEJM 2012; 366: 893-903)

See Figure below for Treatment outcomes curves.

Treatment expectations for cholinesterase inhibitors:
•Small but noticeable improvements:
–Less time spent looking for keys, glasses, etc.
–Repeats self less often
–Dwells in past less
–Easier time keeping track of conversation
–More engaged, outgoing
•Will decline over time even if the cholinesterase is working.



Treatment side effects:

•Gastrointestinal effects
–anorexia
–nausea/vomiting
–diarrhea
•Vivid dreams
–take in AM or earlier PM dose
•Other cholinergic symptoms
–rarely slows heart rate
-muscle cramps
-increased salivation
-rhinorrhea
-can exacerbate existing ulcers (but not known to cause them)

4. huperzine A (Cerebra). Available w/o prescription as a nutritional product. Cholinesterase inhibitor. Similar (perhaps fewer) side effects. 100 mcg of huperzine A BID is equivalent to 5 mg donepezil QHS. Effects are somewhat less impressive. (Obviously, this drug should not be used with other cholinesterase inhibitors.) http://www.nutrapharm.com/
5. Memantine (Namenda). Two mechanisms: 1. Uncompetitive antagonist at the NMDA glutamate receptor. 2. Dopamine agonist. Approved for use in moderate to severe patients (MMSE 15/Blessed 15 or worse). Works well with cholinesterase inhibitors—both are better than either one alone. Improves both cognition and behavior—particularly agitation. Side-effects uncommon, < 1 out of 10. Main side-effect is drowsiness, confusion, and dizziness which is dose related, often transient, and worse in milder patients. A few patients have experienced changes in blood pressure. Old pills are 10 mg. Start at half a pill, then increase weekly by half a pill: ½ qd, then ½ bid, then ½ in AM and 1 in PM, then 1 bid. Can prescribe memantine "titration pack" disp #1 sig. Use as directed, followed by memantine 10 mg BID disp #60. New pills are 7 mg extended release. Start 7 mg QAM, then increase by 7 mg QAM weekly until 28 mg QAM. Latest retrospective data analysis suggest that combination therapy, memantine plus a cholinesterase inhibitor, is superior to either medication alone.
    - References for memantine:
        - N Engl J Med 2003; 348:1333
        - Int J Geriatr Psychiatry 1999;14:135
        - JAMA 2004; 291:317
        - Alzheimer Dis Assoc Disord. 2008 Jul-Sep;22(3):209-21
6. Gingko Biloba. Doesn't work: JAMA 2002;288:835.
7. Ritalin. A useful stimulant when attention or encoding deficits are prominent, or when fatigue, somnolence, and poor energy are issues. Also great when there is a problem with napping during the day and consequent wandering at night—much better to use a stimulant in the morning than a sleeper at night. I use the 20 mg of the sustained release formulation. Can also use Concerta 18 mg or modafinil 100 mg.
8. On-going clinical trials.

C. To slow down disease progression:
1. Lower homocysteine: Folate, B6, B12 (NEJM 2002;346:476) Can use Folgard (Folate 0.8 mg, B6 10 mg, B12 115 mcg)
2. Statins

3. Clinical trials.

D. Managing Agitaion. For additional information see Section IV of Budson & Solomon, *Memory Loss, Alzheimer's Disease, and Dementia: A Practical Guide for Clinicians*, Philadelphia: Elsevier Inc., 2016. Try to determine the underlying cause of agitation:
    1. Use non-pharmacologic approaches first!!!
        i. Educate Caregiver.
        ii. Teach 3Rs: Reassure, Reconsider, Redirect
    2. Agitation is often due to anxiety
        i. Start with sertraline (Zoloft) 50 to 100 mg or citalopram (Celexa) 10 to 20 mg [but watch for increased QTc] (others not as good.)
    3. Manage sleep cycle disturbances
        i. Limit naps
        ii. Methylphenidate (Ritalin) SR 20 mg or modafanil (Provigil) in AM if needed.
    4. Daytime agitation
        i. Risperidone (Risperdal) start 0.25 mg QD
    5. Nighttime agitation
        i. Trazodone start 50 mg QHS
        ii. Quetiapine (Seroquel) start 25 mg QHS
    6. Studies underway to evaluate prazosin & carbamazepine. (Corbett A, Smith J, Creese B, Ballard C. Treatment of behavioral and psychological symptoms of Alzheimer's disease. Curr Treat Options Neurol. 2012 Apr;14(2):113-25.)
    7. Consider 20 mg Dextromethorphan HBr / 10 mg Quinidine sulfate (Nuedexta)
        i. Cummings et al., JAMA. 2015;314:1242-54
        ii. Dosage: Weeks 1: 20/10 QD, 2-3: 20/10 BID, 4+: 30/10 BID
        iii. Need more dextromethorphan? Add 10 mg/5 ml BID to Nuedexta BID
        iv. Common adverse reactions: falls, diarrhea, UTI, dizziness, cough, vomiting, asthenia, peripheral edema, influenza, ⇧GGT, & flatulence
    8. Consider pimavanserin (Nuplazid) 40 mg QD. FDA approved to treat hallucinations and delusions associated with psychosis of Parkinson's disease. Clinical trials of AD on-going now. (Cummings et al., Lancet. 2014 383(9916):533-40)
    9. Inform families of cardiovascular risk of neuroleptics along with side-effects of drowsiness and Parkinsonism.
    10. Refer to psychiatry if needed.

E. Pseudobulbar Affect
    1. What it is: Crying, laughing, or showing other strong emotions for little or no reason. Crying out of proportion to mood is particularly common in AD and vascular dementia.
    2. New Medication FDA approved to treat pseudobulbar affect:
        i. 20 mg Dextromethorphan HBr / 10 mg Quinidine sulfate (Nuedexta)
        ii. 1 capsule daily x 7 days, then 1 capsule Q12H
        iii. Common adverse reactions: diarrhea, dizziness, cough, vomiting, asthenia, peripheral edema, UTI, influenza, ⇧GGT, & flatulence
        iv. Serious side-effects & contraindications mainly related to quinidine

F. Social Work referral often helpful for helping patients and families deal with diagnosis, day programs, nursing home and other long term care placement.

G. Early on, Cognitive Occupational Therapy can be especially helpful for those with a bit of insight, to provide alternative strategies.

H. Driving. For additional information see Section V of Budson & Solomon, *Memory Loss, Alzheimer's Disease, and Dementia: A Practical Guide for Clinicians*, Philadelphia: Elsevier Inc., 2016.

1. Patients with very mild AD have accident rates similar to 16 to 19 year old drivers (Neurology 2000;54:2205)
2. Have family members ride as passengers; when they feel uncomfortable patient is not safe to drive.
3. Rehabilitation hospitals have driving evaluations ($250 to $500)

I. Non-pharmacologic approaches

1. Aerobic exercise has been proven to improve memory in healthy older adults and patients with mild Alzheimer's disease likely related to increased production of growth factors in the brain which stimulates hippocampal stem cells.
2. Social activities have also been shown to improve cognition in healthy older adults and patients with mild Alzheimer's disease
3. Use of habit can be helpful. Habit learning (procedural memory, learning by doing) is intact in mild Alzheimer's disease and therefore these patients can learn new routines and improve their lives.

J. Alzheimer's Association: www.alz.org, is a great resource for patients and families.

K. Chronic Traumatic Encephalopathy For additional information see Chapter 13 of Budson & Solomon, *Memory Loss, Alzheimer's Disease, and Dementia: A Practical Guide for Clinicians*, Philadelphia: Elsevier Inc., 2016.

Definition & etiology	• Chronic traumatic encephalopathy is a progressive neurodegenerative disease associated with repetitive brain trauma.
Cognitive and behavioral symptoms, in order of prevalence at presentation	• Memory impairment • Executive dysfunction • Attention & concentration difficulties • Sadness/depression • Hopelessness • Explosivity • Language impairment • Visuospatial difficulties • "Out of control" • Physically violent • Verbally violent • Impulse control problems • Suicidal ideation/attempts
Summary of diagnostic criteria	**General Criteria for Traumatic Encephalopathy Syndrome:** *All five criteria must be met* 1) History of multiple impacts to the head. 2) No other neurological disorder present that likely accounts for all clinical features 3) Clinical features must be present for a minimum of 12 months 4) At least 1 Core Clinical Features must be present and considered a change from baseline 5) At least 2 Supportive Features must be present

	Core Clinical Features of Traumatic Encephalopathy Syndrome: *At least 1 must be met:* 1) *Cognitive*. Difficulties in cognition substantiated by impairment on standardized tests 2) *Behavioral*. Emotionally explosive, physically and/or verbally violent 3) *Mood*. Feeling overly sad, depressed, and/or hopeless **Supportive Features of Traumatic Encephalopathy Syndrome**: *At least 2 must be present:* (1) *Impulsivity*, (2) *Anxiety*, (3) *Apathy*, (4) *Paranoia*, (5) *Suicidality*, (6) *Headache*, (7) *Motor Signs*, including dysarthria & features of parkinsonism, (8) *Documented Decline*, for a minimum of one year, (9) *Delayed Onset*, at least 2 years **Traumatic encephalopathy syndrome diagnostic subtypes:** (1) Behavioral/Mood Variant, (2) Cognitive Variant, (3) Mixed Variant, (4) Dementia.
Imaging findings	• Cavum septum pellucidum is commonly seen on MRI or CT. Atrophy and hypofunction is typically observed in medial temporal and in frontal lobes.
Treatment	• Treatment is supportive. Cholinesterase inhibitors, memantine, and SSRIs can be tried.
Top differential diagnoses	• Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, vascular dementia, progressive supranuclear palsy, corticobasal degeneration, and normal pressure hydrocephalus.