New Treatments for Dementia Revisited: Are They Now Worth Remembering?
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Disclosure

• No disclosures to report
Learning Objectives

• *Describe epidemiology and cost*
• Define and differentiate dementia
• Discuss screening and evaluation of cognitive impairment
• Describe approach to prevention and treatment of dementia
• Management of behavioral problems
Epidemiology of Dementia

• Prevalence of dementia in community: 3% to 10% >65 yo, 30% to 50% >85 yo

• In primary care, 10-15% > 70 yo

• Incidence of dementia approx 3% among elderly >75 yo (Bronx Aging Study)

• 8th leading cause of mortality

• 75% of demented patients admitted to nursing homes for an average of 3 yrs
Cost of Dementia

• Five million elderly with dementia (twelve million by 2050)
• Formal and informal costs (includes value of unpaid caregivers) = $150-300 billion annually
• Delay onset by 5 years = 50% decline in prevalence

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Normal aging may be associated with which of the following:

1. Short term memory loss
2. Difficulty with calculations
3. Word finding difficulties
4. Difficulty remembering names
5. Reduction in vocabulary
“Normal” Aging Changes in Cognition

• Slowing in rate at which information can be received and processed

• Reduction in “explicit memory” (eg, the ability to recall a specific name, number, or location on demand)
DSM-IV Criteria for Dementia

- Acquired impairment of short- and long-term memory and at least 1 of the following: abstract thinking, judgment, language, praxis, visual recognition, constructional abilities, or personality
- Severe enough to interfere with daily function
- Gradual decline and progression (ie, absence of delirium)
Case Discussion

• 78 yo ex college professor complains that his memory just isn’t as good as it was. Daughter confirms that he has more difficulty remembering discussions that took place earlier in the day. He’s still paying bills and doing the crossword puzzles. He scores a 27/30 on the MMSE (education adjusted threshold 28/30).
Options

1. The patient has dementia
2. The patient is depressed
3. The patient is delirious
4. The patient had mild cognitive impairment (cognitive impairment, not dementia or CIND)
5. This patient is normal for his age
CIND

• Complaint of memory impairment
• Objective memory loss (adjusted for age and education)
• Preserved general cognitive function
• Intact activities of daily living
• High risk of developing dementia (15% annually)
Case Discussion

• 76 yo woman is brought to see you by her daughter who is concerned about her failing memory. 6 months ago, the daughter took over management of her mother’s checkbook after she failed to pay bills. Her mother seems unable to knit, something she enjoyed for years. She has difficulty finding the right words to complete a thought.
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DSM-IV Criteria for Alzheimer’s Disease

• Memory loss plus 1 or more: aphasia, apraxia, agnosia, executive dysfunction
• Usually few motor signs apparent early
• Subtle behavioral and personality changes early
• Accounts for at least 2/3s of dementia
Screening Questions for Alzheimer’s Dementia

- Aphasia: can’t come up with words, substitutes words, new words
- Apraxia: has difficulty using utensils, tools
- Agnosia: doesn’t recognize familiar people; gets lost in familiar surrounds
- Executive dysfunction: can’t manage checkbook
Distribution of Neurofibrillary Tangles and Amyloid Plaques

RED: heaviest
BLUE: lightest

Features Inconsistent With Alzheimer’s Disease

• Sudden onset
• Focal neurological findings
• Seizures, early marked change in personality/behavior
• Gait disorder early in disease course
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Should we screen for dementia?

• Under current Medicare Pay for Performance, PQRI measure 133: “Whether or not patient (>65 yo) was screened for cognitive impairment using a standardized tool”

• Affordable Care Act will require clinicians to assess for cognitive impairment as part of annual wellness visit

www.healthcare.gov/law/full/index.html
Screening for Dementia

• >50% of persons with dementia have not received a diagnosis of dementia

• Practical screening tools improve detection (eg, MMSE)
Mental Status Screening Tests

• Mini-Mental Status Exam (MMSE): 12-item, 30-point tool administered in 10-15 minutes

• St. Louis Univ Mental Status (SLUMS) 30-point; includes cutoffs for education/MCI
  [http://medschool.slu.edu/agingsuccessfully/pdf surveys/slumsexam_05.pdf](http://medschool.slu.edu/agingsuccessfully/pdf surveys/slumsexam_05.pdf) ($1.99 Iphone ap)

• Mini-cog: Draw clock face and 3-word recall

• MOCA: [www.mocatest.org](http://www.mocatest.org)
U.S. Preventive Medicine Task Force

“No direct evidence linking screening and improved health outcomes”

Potential Benefits of Screening

• Clarify advance directives while patient still competent
• Begin discussion about alternatives to driving, housing alternatives
• Prevent financial victimization or self-neglect; remove firearms
• Participate in research
Case Discussion

• An 80 yo has slowly progressive memory loss and word finding difficulties. Family took over his finances two months ago. His physical exam is unremarkable. No focal findings on neurological exam.
The next step mostly likely to result in improvement in his function:

1. MRI of brain
2. CBC, metabolic panel, TSH, B12
3. EEG
4. PET scan
5. Medication review
How to Work Up the Elderly Demented Patient?

• Once cognitive impairment is identified, what tests should be included to rule out a “reversible dementia”? 
‘Average’ Dementia Evaluation

- History, PE, mental status testing, comprehensive neuropsychological testing
- CBC, SMA 6, TSH, VDRL, B12, folate, calcium, U/A
- Genetic testing?
- Brain imaging (CT or MRI)
“Reversible” Dementia

• 1970s: Reversible dementia said to be 5%-10% of all dementia

• Early studies flawed; often done in hospital setting (confounded by delirium) and no follow-up to document reversibility

• Outpatient studies with follow-up suggest 1% or less are reversible
“Structural neuroimaging with either a noncontrast CT or MR scan in the initial evaluation of patients with dementia is appropriate. (Guideline)”.... “Screening for depression, B12 deficiency, and hypothyroidism should be performed (Guideline).”
Incidence and Causes of Dementia

(Incidence and Causes of Dementia (Knopman et al, Arch Neurol 63:218, 2006)

• Record review of 560 consecutive patients newly diagnosed with dementia

• No cases of dementia due to NPH, subdural hematoma, B12 deficiency, hypothyroidism, or neurosyphilis

• Conclusion: “None of the patients with dementia reverted to normal with treatment of the putative reversible cause.”
# Potentially Reversible Dementias


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<td><strong>TOTAL</strong></td>
<td><strong>31 (10%)</strong></td>
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Reversibility of Drug-Induced Dementia

• >50% who stop medication will improve
• Often a single medication implicated
• Patients with drug-induced cognitive impairment were also 3 times more likely to fall
• Most offending drugs taken for several years prior to diagnosis
Medications Impairing Cognition

• Everything we prescribe ... except acetaminophen and docusate
• Most often psychoactive meds or those with anticholinergic side effects
• “Discontinue amitriptyline” is always the correct answer on boards.
Drugs Impairing Cognition

- Anticholinergics (eg, diphenhydramine, trihexyphenidyl, oxybutynin, etc)
- Anticonvulsants (phenytoin, gabapentin, valproate)
- Muscle relaxers (carisoprodol [Soma], cyclobenzaprine [Flexeril])
- Antiemetics (prochlorperazine, metoclopramide)
- Digoxin, clonidine, amantadine, amiodarone
- Benzodiazepines, antipsychotics
What about Statins?

• “The post-marketing adverse event reports generally described individuals over the age of 50 years who experienced notable, but ill-defined memory loss or impairment that was reversible upon discontinuation of statin therapy. Time to onset of the event was highly variable, ranging from one day to years after statin exposure. The cases did not appear to be associated with fixed or progressive dementia.”

• [www.fda.gov/drugs/drugsafety/ucm293101.htm](http://www.fda.gov/drugs/drugsafety/ucm293101.htm)
Case Discussion

The most likely diagnosis is:

1. Alzheimer’s Disease
2. Pick’s Disease
3. Huntington’s Disease
4. Parkinson’s Disease
5. Vascular dementia
Vascular Dementia

• Subcortical or mixed dementia
• Stepwise progression, prior strokes, focal neuro symptoms/signs
• preserved personality but “emotional incontinence” or apathy common
• Definitive diagnosis difficult
Types of Dementia

- CORTICAL (60%-70%): short-term memory loss + apraxia, etc, without motor signs (eg, Alzheimer’s disease)
- SUBCORTICAL (10%-20%): memory loss plus mental slowing, inertia, mood disturbances, motor signs (focal or gait disorder)
- MIXED (10%-20%)
- METABOLIC (eg, B12) mimic subcortical
Vascular Dementia: Is it Preventable and/or Treatable?
Cardiovascular Risk Factors and Risk of Dementia  

- Retrospective cohort study of midlife cardiovascular risk and late-life risk of dementia
- Hypertension, hyperlipidemia, diabetes mellitus, and smoking associated with 20% to 40% increased risk for dementia
Does Treatment of Vascular Risk Factors Prevent Dementia?

• 1 of 3 large studies suggests treating hypertension in patients >60 yo may prevent vascular dementia; no other treatment proven effect

• No randomized trials to determine effect of antiplatelet (aspirin, clopidogrel, etc) or anticoagulation (warfarin) on reducing risk of dementia
Is Vascular Dementia Treatable?

- Two 6-month trials of donepezil (Aricept) in patients with NINDS probable or possible vascular dementia
- One 6-month trial of galantamine (Razadyne) in (VD or VD + Alzheimer’s disease)
- Efficacy similar to pure Alzheimer’s disease
Other Forms of Dementia

- Frontotemporal dementias
- Lewy body dementia and dementia of Parkinson’s disease
- “Normal pressure” hydrocephalus
- Creutzfeldt-Jakob disease
Does the diagnosis of a specific type of dementia really matter?
Prevention: exercise you mind and body?

• 170 participants with MCI in randomized, controlled, 24-week trial of home-based physical activity intervention (70,000 steps/week) vs “usual care” showed modest improvement in cognition (JAMA. 2008;300:1027-1037.)
Case Discussion

• An 80 yo woman has short term memory loss consistent with Alzheimer Dementia. She scores 20/30 on the MMSE. Her family asks about starting donepezil (Aricept).
You should tell them:

1. It will reverse her dementia
2. It will delay nursing home placement
3. It will increase life expectancy
4. It may have modest effects on scales measuring cognition and function
5. It will have major side effects and should be avoided
Prevention and Treatment of Dementia: the Dismal Failure of Medical Science

- No current intervention will prevent or delay the onset of dementia (consensus.nih.gov/2010)
- Treatment for dementia (cholinesterase inhibitors and NMDA receptor antagonist) are minimally effective *Ann Intern Med.* 2008;148:370-378.
Going “over the fiscal cliff”?: Not if you have Aricept 23

- Aricept 5 and 10 mg grossed 2 billions dollars from 1996-2010 (patent expired); four months before expiration, FDA approved Aricept 23
- Trial of 1400 patients, 2 point improvement in 100 point cognitive scale but no benefit in global functioning scale; far more nausea & vomiting
- Approved over objections of FDA’s reviewers by FDA division director
Memantine

- 3 RCTs in 1317 subjects, 28 weeks; most had moderate to severe dementia
- Patients on stable doses of cholinesterase inh
- Cognitive, behavioral and global scales, but not ADL scales, modestly better; clinical relevance “not robustly demonstrated”.
- Caregiver burden not measured
- ADR: No different than placebo

www.bmjopen.bmj.com/content/2/3/e000917.full.pdf+html
Current Cost of Alzheimer’s Treatment

- Donepezil (Aricept) @ $60/90 day
- Galantamine (Razadyne) & rivastigmine (Exelon) @ $300/90 day
- Exelon patch $823/90 day, Aricept 23mg @$825/90 day
- Memantine (Namenda) $688/90 day
Potential Future Disease Modifying Treatments?

- Amyloid precursor proteins (APP) cleaved by secretases, releasing toxic beta proteins
- 8/17/10 Eli Lilly halts development of semagacestat, a gamma secretase inhibitor; does not slow disease and patients clinically worse
National Alzheimer’s Project Act

• Signed by President Obama January 2011
• Increases research and education programs for clinicians and caregivers
• Two major NIH trials:
  – Prevention: Medellin study ($16 million)
  – Treatment: Inhaled insulin ($8 million)
Medellin Study

• Autosomal dominant presenilin 1 mutation leads to early, severe Alzheimer’s dementia

• Two hundred asymptomatic Colombian citizens with mutation will be randomized; also 100 without mutation included

• Crenezumab is monoclonal Ab to Beta amyloid 40 and 42
Intranasal insulin

(Arch Neurol 2012, 69:29)

- Insulin important in normal brain function; reduced insulin activity noted in AD
- Insulin has close relationship with Beta amyloid peptide; insulin modulates levels and protects against detrimental effects of Abeta
- In a four month pilot study, intranasal insulin (20 or 40IU) in 104 patients with MCI or mild dementia showed promising effects on scales and PET scan
New Treatments for Dementia: Are They Worth Remembering?

• 4 FDA approved medications for Rx of dementia; no evidence yet of clinically significant alteration in disease course
• Stop the amitriptyline (et al)
• Read while you exercise
• “Searching for a breakthrough, settling for less”
Learning Objectives

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Are we better at treating the behavioral complications of dementia than the cognitive decline?
Case Discussion

• An 81 yo patient with advanced dementia is agitated, hoarding food at her assisted living facility and repeatedly leaving her room wearing only her underwear. She uses vulgar language when visitors are present. The administrator asks you to “do something” to control these behaviors.
You should:

1. Begin sertraline 50 mg daily
2. Begin haloperidol 0.5 mg bid
3. Begin olanzapine (Zyprexa) 2.5 mg hs
4. Begin Valproate 250 mg tid
5. Offer to help the staff find ways to manage the behaviors non-pharmacologically
Treatment of Behavior Problems

• *Use nonpharmacological interventions first* (JAMA 2012, 308:2020)

• Evaluate for precipitating factors and eliminate them

• Choose medication based on specific behavioral disturbance and patient’s comorbid illnesses
Which Behaviors “Responsive” to Medication?

• RESPONSIVE: Agitation, depression, delusions, hallucinations, aggression
• REFRACTORY: Wandering, hoarding/hiding objects, repetitive questioning, apathy, social inappropriateness
• Behavioral approach to refractory sx
Do Cholinesterase Inhibitors Treat Neuropsychiatric Symptoms?

- 272 pts in 12-week trial of donepezil (Aricept) for treatment of agitation in Alzheimer’s disease (avg MMSE 8/30)
- Donepezil no more effective than placebo
“Popular Drugs for Dementia Tied to Deaths”  NY TIMES 4/12/05

• FDA reviewed ALL atypical antipsychotics in dementia
• 17 placebo controlled studies, 5106 elderly subjects with dementia, average duration of Rx 10 weeks
• Deaths: 4.5% (Rx) vs 2.6% (placebo)
Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotics


- Retrospective evaluation of Medicare data suggests that death rate in nursing home residents on typical antipsychotics is the same, if not greater than, the atypical antipsychotics
CATIE-D RESULTS
Schneider L et al, NEJM 355:1525: 10/12/06

• 421 pts with psychosis, agitation or aggression; mean time to discontinuation of assigned drug eight weeks - Olanzapine (Zyprexa), risperidone (Risperdal) or quetiapine (Seroquel)

• ‘Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer disease’
Cost of Antipsychotics

- Haloperidol 0.5 mg bid $4/mo
- Risperdal 0.5 mg bid $13/mo
- Seroquel 25 mg bid $175/mo
- Zyprexa 2.5 mg bedtime $240/mo
- Geodon 20 mg bedtime $270/mo
- Abilify 2mg bedtime $624/mo
Choosing Antipsychotics

• If no parkinsonism, start haloperidol (Haldol) trial 0.5-1.0 mg bid

• If parkinsonism or history of EPS, use Seroquel 12.5 bid (titrate up q 2-3 days) or risperidone (Risperdal) 0.5 hs or bid

• Zyprexa begin 2.5 mg - 5 mg hs, max 10 mg/day (sedating, weight gain, diabetes)

• Ziprasidone (Geodon), aripiprazole (Abilify), etc, little data in elderly)
Other Drugs for Agitation

• Carbamazepine (Tegretol) may be effective in controlling chronic agitation (median dose 300 mg/day, blood level around 5)
• Sodium valproic acid (Depakote), gabapentin (Neurontin) anecdotally helpful
• SSRIs might reduce agitation, anxiety, hypersexuality
• Benzodiazepines (eg, lorazepam [Ativan]) use cautiously; buspirone (Buspar)?
Summary: Drugs for Behavior Problems in Dementia

• Few randomized, double blind studies emerging in relevant population
• Newer ‘atypical’ antipsychotics expensive; ?? more effective than haloperidol; less EPS
• Anticonvulsants (valproate) may be helpful for chronic, severe agitation but evidence of effectiveness is limited
Answers

• 1D, 2D, 3A, 4E, 5E, 6D, 7E
Caregiver/Practitioner Resources

• Alzheimer’s Association 1-800-272-3900 or www.alz.org

• Government funded clinical trials in AD can be found at http://clinicaltrials.gov
Additional Reading

