EXHIBIT E

Governor's Advisory Council on Alzheimer's Disease

Alzheimer Disease: Management

Mark Pippenger, MD
Behavioral Neurology
Associate Clinical Professor
Director, Walker Memory Clinic
UAMS

Dementia

- A syndrome in which there is decline in memory, general cognition, or behavior to the point that it interferes with function

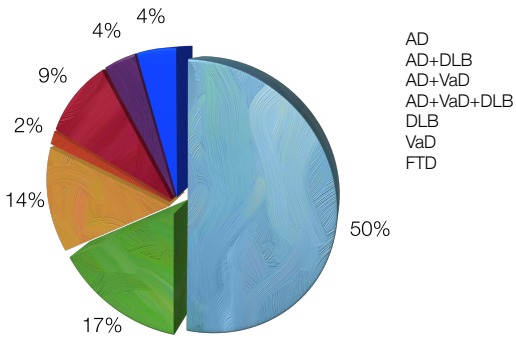
Common Causes of Dementia

- Alzheimer Disease (AD)
- Dementia with Lewy Bodies (DLB)
- Vascular Dementia (VaD)
- Fronto-Temporal Dementia (FTD)

Uncommon Causes of Dementia

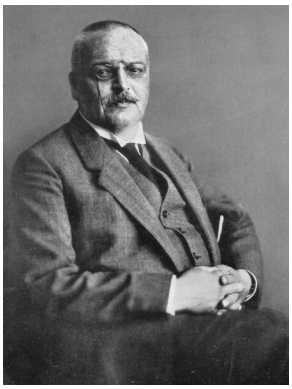
- Parkinson Disease
- Normal Pressure Hydrocephalus
- Creutzfeldt-Jakob Disease

Cause of Dementia at Autopsy



Barker et al, Alz Dis Assoc Dis 2002;16:203-212

Alois Alzheimer



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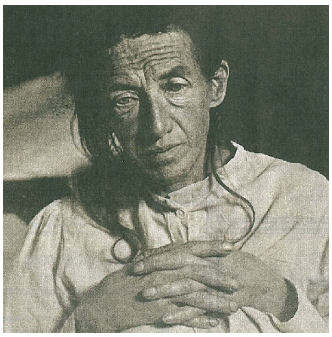


Alzheimer Disease (NINCDS/ADRDA)

- Dementia of insidious onset
- Steady progression of dementia
- Memory is prominently affected
- Onset after age 60
- Neurological exam otherwise normal
- Family history of dementia is supportive

Probable Alzheimer Disease (NIA/AA)

- Meets criteria for dementia
- Insidious onset
- Evidence of progression
- Not due to another condition

Presentations of AD

- Amnestic presentation
- Non-amnestic presentations
  - Language presentation
    - Most prominent findings are word-finding difficulty
  - Visuospatial presentation
    - Most prominent deficits are in spatial cognition, simultanagnosia, prosopagnosia
  - Executive presentation
    - Impaired reasoning, judgement, problem solving

Possible Alzheimer Disease

- Atypical course
  - Sudden onset or no evidence of progression
- Etiologically mixed presentation
  - Evidence of significant vascular disease, Lewy body disease, or other medical conditions

How Is Dementia Diagnosed?

- Diagnosis of dementia is clinical:
  - Depends on history of cognitive decline
  - Cognitive decline demonstrated on exam
  - History of functional impairment or decline
- Lab tests and scans used to exclude other disease
- Cause of dementia determined clinically:
  - No scan or lab test can make the diagnosis

Diagnostic Testing in Dementia

- Lab tests
  - General metabolic labs
  - Complete Blood Count (CBC)
  - Thyroid functions
  - Vitamin B12
- Imaging tests
  - To exclude (or "rule out") structural disease that would change treatment (like tumors)
  - In most cases, CT without contrast is best

Non-routine Tests in Dementia

- Syphilis serology (RPR, VDRL)
- EEG
- Neuropsychological Testing
- PET imaging
- Genetic testing (eg, ApoE genotyping)

Management of Dementia

- Diagnostic disclosure and discussion
- Referral to support services (Alzheimer's Arkansas)
- Address safety issues or concerns
- Address legal and financial concerns
- Medications for dementia
- Management of behavioral symptoms

General Statements about Drug Treatment for AD

- All approved drugs are symptomatic only
- All drugs show only modest effects in delaying symptomatic progression
- No drugs have been found which are neuroprotective
- No drugs slow disease progression

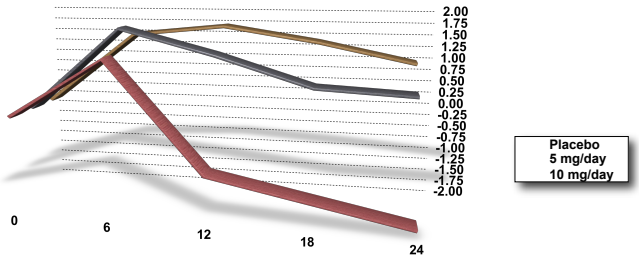
Drug Treatments for Alzheimer Disease

- Cholinesterase inhibitors (CEIs)
  - Donepezil (Aricept®)
  - Rivastigmine (Exelon®)
  - Galantamine (Razadyne®)
- NMDA Antagonists
  - Memantine (Namenda®)
- Combination Drugs
  - Namzaric® (donepezil + memantine)

Donepezil (Aricept®)

- Two dose forms, regular and ODT (orally disintegrating tablet)
- Three doses, 5 mg, 10 mg, 23 mg*
- Once daily dosing
- Approved for mild, moderate, or severe AD

ADAS-Cog on Donepezil



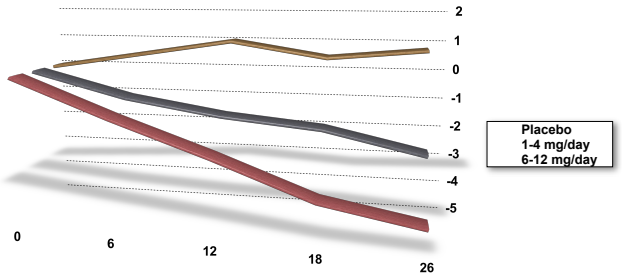
Weeks

Rogers et al, Neurology 1998;50:136-145

Rivastigmine (Exelon®)

- Available as oral capsules or transdermal patch
- Capsules are BID dosing, 1.5 mg, 3 mg, 4.5 mg, and 6 mg
- Patch: 4.6 mg/24 hrs; 9.5 mg/24hrs, and 13.3 mg/24 hrs
- Approved for mild, moderate, or severe AD

ADAS-Cog on Rivastigmine



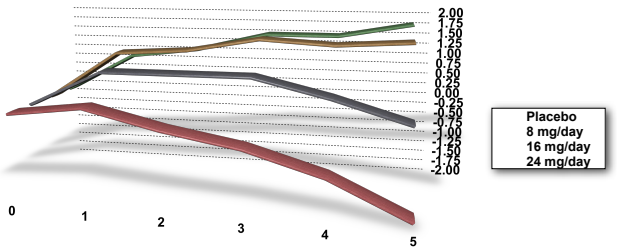
Weeks

Corey-Bloom et al 1998, Int J Ger Psychopharm 1:55-65

Galantamine (Razadyne®)

- Immediate-release (4 mg, 8 mg, 12 mg)
  - Twice-daily dosing
- Extended-release tablets (8 mg, 16 mg, 24 mg)
  - Once-daily dosing
- Approved for mild or moderate AD

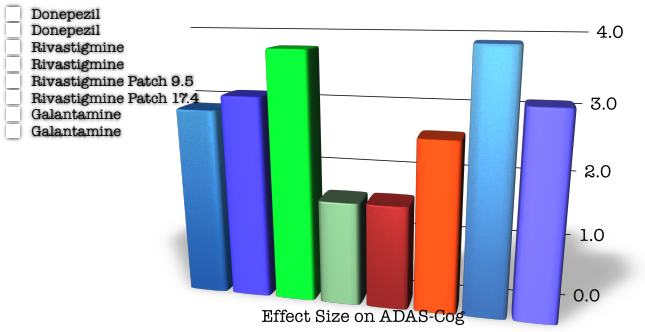
ADAS-Cog on Galantamine



Months

Tariot et al, Neurology 2000;54:2269-2276

CEI Effect Sizes



Summary on CEIs

- Efficacy very similar at high doses, except for rivastigmine transdermal and possibly extended-release galantamine
- Adverse effects similar for all drugs, least for donepezil and galantamine, most for oral rivastigmine
- Cost is (currently) wildly different

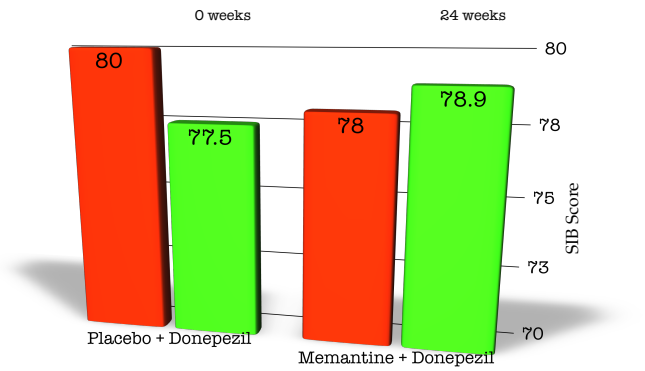
Memantine (Namenda®)

- Standard formulation is twice-daily, will become available generically in April 2015
- Namenda XR® is once-daily
- Target dose is 10 mg BID (standard), or 28 mg once daily (XR)
- Approved for moderate or severe AD

Memantine for Mod-Sev AD: Add-On to Donepezil

- 404 patients with moderate-severe AD, already on donepezil, with MMSE 5-14
- Randomized to continue donepezil and add memantine 20 mg/day or continue donepezil with placebo, for 24 weeks
- Primary efficacy measures: SIB, ADCS-ADL19

Memantine for Mod-Sev AD: Add-On to Donepezil

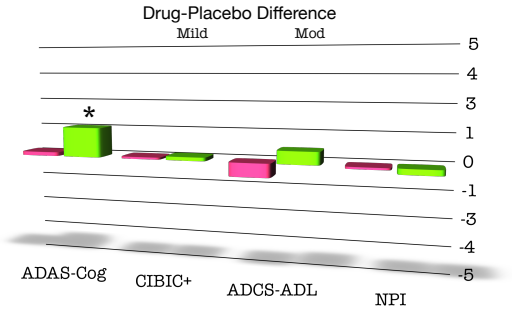


Tariot et al, JAMA 2004; 291:317-324

Memantine for Mild-to-Moderate AD

- Schneider et al performed meta-analysis of mild-moderate AD trials using memantine
- 3 trials, total of 431 mild (MMSE 20-23) AD patients and 697 moderate (MMSE 10-19) AD patients

Memantine for Mild-Mod AD



Schneider et al, Arch Neurol 2011; 68:991-998

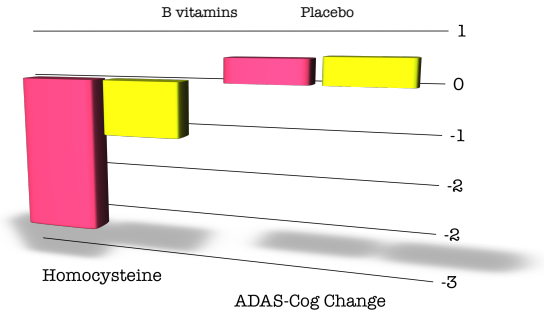
Memantine Summary

- May give small additional benefit in moderate-severe dementia
- Ineffective in mild dementia and MCI
- No behavioral benefits in any monotherapy study
- No neuroprotective effect

B Vitamins for AD

- 409 patients with AD randomized to receive folate/B6/B12 supplement or placebo for 18 months
- Main outcome was ADAS-Cog change

B Vitamins for AD

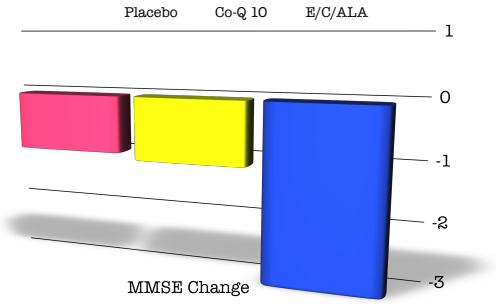


Aisen et al, JAMA 2008;300:1774-1783

Antioxidant Vitamins for AD

- 78 AD patients randomized to Vitamin E 800 IU daily/Vitamin C 500 mg daily/alpha-lipoic acid 900 mg daily, or Co-enzyme Q10 400 mg TID, or placebo
- CSF markers and cognitive scores followed for 16 weeks

Vit E/C/ALA, Co-Q10 for AD

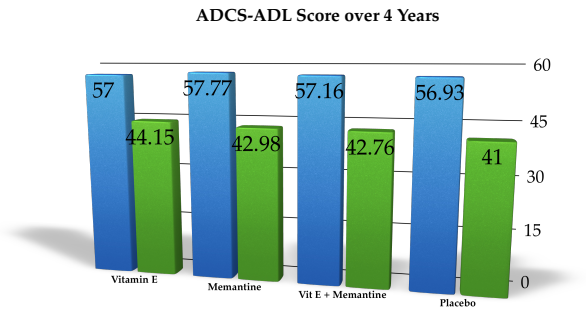


Galasko et al, Arch Neurol 2012;69:836-841

Vitamin E for AD

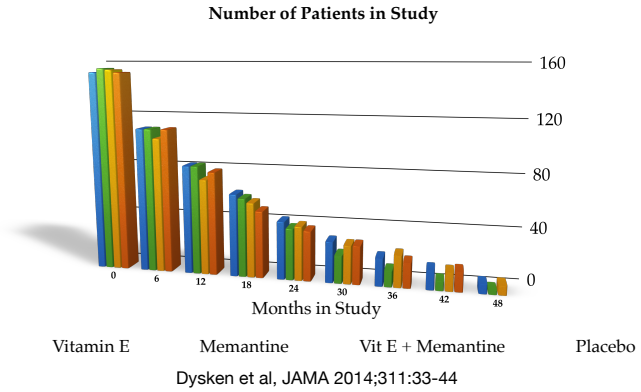
- 613 AD patients randomized to Vitamin E 1000 IU twice daily, 10 mg of memantine twice daily, the combination, or placebo, for four years
- Main endpoint was ADCS-ADL (a measure of function)

Vitamin E plus Memantine for AD



Dysken et al, JAMA 2014;311:33-44

Vitamin E plus Memantine for AD



Dysken et al, JAMA 2014;311:33-44

Future Treatments for AD?

- Anti-amyloid treatments: monoclonal antibodies (solenazumab), BACE inhibitors (MK-8931)
- Anti-tau treatments now being studied (AADvac1)
- Anti-inflammation drugs
- 5-HT6 receptor antagonist (idalopirdine)
- Insulin-receptor-mediated treatments now being studied (eg, Glucagon-Like Peptide 1 analogs)

Behavioral Symptoms

- Behavioral and Psychological Symptoms of Dementia (BPSD) refer to non-cognitive symptoms of dementia
- 95% of persons with dementia will have BPSD at some point during their life
- More common as dementia progresses
- Often the cause of significant distress, increased caregiver burden, and may lead directly to institutionalization, greatly increasing cost of care

What are BPSD?

- Apathy
- Depression/anxiety
- Elation/euphoria, moria
- Sleep disturbances
- Psychosis (delusions, hallucinations)
- Agitation
- Wandering

Drugs Proven Effective for BPSD

- None

Drugs Often Used for BPSD

- Antipsychotics
  - Risperidone (Risperdal®), haloperidol (Haldol®), olanzapine (Zyprexa®), aripiprazole (Abilify®)
  - Quetiapine (Seroquel®)
- Benzodiazepines
  - Alprazolam (Xanax®), lorazepam (Ativan®), clonazepam (Klonopin®)
- Antidepressants
  - Sertraline (Zoloft®), citalopram (Celexa®), escitalopram (Lexapro®)
- Anticonvulsants
  - Divalproex (Depakote®)

Nonpharmacological BPSD Management

- Environmental modification
- Sleep hygiene
- Physical exercise
- Music therapy
- Caregiver education

Caregiver Approach

- Always use calm, kind voice
- Avoid correction, scolding, argument
- Practice distraction and redirection
- Develop patience--if necessary to repetitively answer questions, do so without irritation
- Give instructions clearly, one step at a time
- Always explain before doing things like dressing, undressing, etc.

When to Resort to Medications

- Behavior is dangerous, distressing

  AND
- Behavior does not respond to non-pharmacological management

  OR
- Behavior requires emergency treatment to allow for more time to evaluate

Using Medications for BPSD

- Pick the most problematic behavior
- Select a drug to address this symptom
- Start at a low dose
- Titrate the dose upward until the symptom is controlled or side effects occur
- If BPSD respond, then consider withdrawal of drug after a few months