Approach to Dementia - 2012

Visions of Emerging Practice

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### Discussion Points

- When does Alzheimer’s disease begin?  
  - Early

- To screen or not to screen?

- The diagnosis of Alzheimer’s disease  
  - Middle

- When to medicate?  
  - Late

- Care and practice redesign.
<table>
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<th>Journal</th>
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<td>JAMA</td>
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<td>J Gen Intern Med</td>
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<td>J Amer Geriatrics Soc</td>
<td>279</td>
<td>171</td>
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Where are we?
Most of the randomized, double-blind, and placebo-controlled trials of hydergine were conducted and published before the advent of consensus-based diagnostic standards of dementia in 1984.

“Uncertainty remains regarding hydergine's efficacy in dementia.”
Diagnosis of Alzheimer’s Disease

1984 NINCDS-ADRDA criteria\(^1\), have been quite successful, surviving for over 27 years, to 2011

Reliable for the diagnosis of probable AD (possible, definite, with other features)

More than a dozen clinical pathological studies

Sensitivity of 81% and specificity of 70%.

Case 1: Worried surgeon

66 year old woman, currently working full time as a surgeon is seen for primary care. She is concerned about her memory as when working with residents she sometimes has difficulty recalling authors’ names on medical literature.

There have been no problems with her work, no quality or peer review concerns. She continues to receive excellent evaluations by her trainees.

Her father died of Alzheimer’s disease at age 75 and she is worried that she may also develop it.
PMH: Osteopenia, otherwise healthy.

Medications: calcium, vitamin D.

BP 135/70, BMI 27.2  physical examination normal. Basic laboratory testing has been normal.

Montreal Cognitive Assessment (MoCA) 29/30
Case 1

Which of the following is the most appropriate next step in managing this patient’s concerns?

A. Evaluate apolipoprotein E allele status
B. MRI of brain
C. Neuropsychiatric testing
D. Start an exercise program
E. Start donepezil
Case 2: Caring daughter

85 year old woman senior apartments is seen in follow up of HTN and mobility problems related to hip and knee DJD. She lives in senior apartments and reports that she is bored despite enjoying participating in many on site social activities.

Daughter visits weekly takes her shopping and assists with keeping finances and bill paying for the past 2 years. Pt had a business college education retired from work age 72 as an executive secretary.
Medicines: HCTZ, lisinopril, acetaminophen, calcium, vitamins.

BP 138/85, Examination normal other than DJD related changes and slow gait for which she uses a walker. No falls in past year.

Mini cog score 2/5 losing two points for memory, one point for abnormal clock drawing. PHQ-9 score is 1 Daughter in attendance during the visit believes her mother is “just fine for her age”.

Case 2

Which of the following is the most likely diagnosis?

A. Dementia
B. Mild cognitive impairment
C. Normal aging
D. Sub-syndromal depression
Case 3: Weight loss with dementia

78 year old man is seen for a 15 pound weight loss over the past two months. He has Alzheimer’s disease and lives for the past 2 years in a secured dementia unit of a nursing home. Staff report he is eating less than previously.

Both he and assisted living staff report no other symptoms. There has been no other change in his behavior. He requires assistance with many basic ADL’s, intermittently incontinent of urine, unchanged. He has never smoked.
Medications: Donepezil 5 mg once daily, calcium, multivitamins

Physical examination: Elderly man cooperative. Other than cognitive impairment his physical examination is normal. He walks without assistance.

MMSE 5/30. CBC, BMP, Hepatic panel, TSH are normal
Case # 3

Which of the following is the most appropriate next step in management?

A. CT of abdomen
B. Discontinue donepezil
C. Hospice consultation
D. Stool for occult blood
E. Upper endoscopy
Geriatric Health States

- Robust, healthy, successful aging
- Usual
- Frail
- Cognitive impairment
- End of life
The Aging Population

1960

1990

2020

Source: US Bureau of the Census.
Epidemiology of Alzheimer’s Disease

5 million people US
17 million world wide

Annual incidence:  1% age 60-70
                 ~ 7%   ≥ 85

Prevalence 1% age 65-69
           5%    ≥ 65

People live years with the disease,
prevalence doubles every 5 years after age 65
   18%   75-84
   30-50% ≥ 85
Dementia in Elderly

60-70% Alzheimer’s disease
women > men 20-50%

15-30% Other: Vascular (VaD)
Lewy Body (DLB)
Frontotemporal (FTD)

2 - 5% Drugs, metabolic, subdural, NPH, Parkinsons
<table>
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<tr>
<th>Condition</th>
<th>Description</th>
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<tbody>
<tr>
<td>Vascular dementia</td>
<td>Vascular risk factors even with non-suggestive neurological exam. Shared risk factors between AD and VaD</td>
</tr>
<tr>
<td>DLB</td>
<td>Dementia early in parkinsonism, hallucinations early, fluctuations resembling delirium, worsening with neuroleptics.</td>
</tr>
<tr>
<td>FTD</td>
<td>Personality changes predominate, younger.</td>
</tr>
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~ 1.5% moderate dementia is reversible.
Major risk factors for AD

Age

1st degree relative

↑ 10-30%, esp. with earlier onset

APOE genotype

Cardiovascular risk factors
AD Phases – 2011 Research and Diagnostic Criteria

Asymptomatic – pre-clincal (biomarkers)

Symptomatic- pre-dementia (MCI)

Dementia

McKhann GM. Changing concepts of Alzheimer’s Disease. JAMA 2011;305:2458-59
Figure 1. Sequence of Pathological, Clinical, Physiological, and Radiologic Changes from Normal Aging to Early Alzheimer’s Disease.

Biomarkers

Accumulation of Amyloid Beta peptide (Aβ):
1. ↑ brain amyloid PET imaging (florbetapir)
2. ↓ CSF levels

Neuronal injury:
1. ↑ CSF Tau levels (tangles)
   Total, phosphorylated
   less specific than Aβ
2. ↓ Metabolism FDG PET uptake in temporoparietal cortex
3. MR atrophy specific areas (medial, basal, lateral temporal lobes, medial parietal cortex)
Possible clinical roles for amyloid scanning

Enhance certainty of AD

Estimate likelihood of progression from one stage to the next (MCI to AD)
Florbetapir – PET

**AMYVID - THE FIRST AND ONLY...**

The first-and-only FDA-approved diagnostic PET tracer for estimation of beta-amyloid neuritic plaque density when evaluating for Alzheimer’s Disease (AD) and other causes of cognitive decline.

Amyloid scans are interpreted using a binary visual read methodology (negative/positive). Amyloid images should be interpreted only by readers who successfully complete a special training program.
Pre-clinical Alzheimer’s disease
When does it begin?
Implications for future drug therapy

Dominantly inherited Alzheimer’s Network (DIAN) 1% AD

3 gene mutations: APP, PSEN1, PSEN2
Autosomal dominant, complete penetrance

Similar age of onset between generations
Can estimate year to onset of clinical disease

Estimated years to onset = Parent age of onset – study participant age

Years prior to expected symptom onset

25 years
  ↓ CSF Aβ
  ↑ Aβ brain deposition via PET

15 years
  ↑ CSF tau
  specific anatomic brain atrophy

10 years
  ↓ FDG metabolism, episodic memory

5 years
  Cognitive impairment (? Define this or too much)

3 years after expected symptom onset
  Diagnostic criteria

B  Mini–Mental State Examination

Score

Estimated Yr from Symptom Onset
A Clinical Dementia Rating–Sum of Boxes

Score vs. Estimated Yr from Symptom Onset
F  $A\beta$ Deposition in the Precuneus

Estimated Yr from Symptom Onset

SUVR
E  Glucose Metabolism in the Precuneus

SUVR

Estimated Yr from Symptom Onset
Differences between carriers and non carriers

Figure 2. Comparison of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes as a Function of Estimated Years from Expected Symptom Onset.
Apo-lipoprotein E genotype

Genetic alles: $\epsilon$ 2, 3, 4

Lifetime risk: 9% w/o $\epsilon4$, 29% w/one $\epsilon4$

$\epsilon$ 4/4 ↑ risk (RR 30, CI 11-84)

15% overall $\epsilon$ prevalence in US.

? Earlier onset
? Risk for other dementias

40% AD do not have $\epsilon$ 4 gene

Currently not recommended by consensus
? Harm of disclosure.
Risk Evaluation and Education for Alzheimer’s disease, REVEAL

Hypothesis: Persons learning about their APOE genotype through an education and disclosure protocol would not have greater psychological symptoms than those not receiving.

162 asymptomatic adults, parent with AD

Consented to be 1. APOE genotyped
2. Randomly assigned to receive or not receive results of the test

Outcomes: psychological scores: anxiety, depression, “test related distress”

6 weeks, 6 months, 1 year

Results:

ε4-positive and showed no more anxiety, depression, or test-related distress except for transient test related distress among ε4-positive subjects at 6 months.

Significant, but not clinically meaningful reduced distress among ε4-negative subjects compared to ε4-positive at 6 months and 12 months.
Clinical implications: “Withering” critique

1. Short term
2. Circumscribed study population
   None had baseline high anxiety or depression
   Variation in care giving to parent with AD
   Acceptance of randomization
3. Generalization relative to implications of a + test

   predictive value

   personal actions

Potential for “delayed emotional repercussions and injudicious life decisions”

Risk of precipitous actions
Avoid changes
Personal finances
Social opportunities
Insurance
  long term care, disability, life

Heightened distress later
“...perhaps the social effects of genetic testing will be less worrisome by the time a clinical rationale for the test becomes apparent”.

How do we recognize, diagnose?

How good a job do we do with this?
Estimated > 50% with dementia have not been diagnosed by a physician, many with mild, some with moderate disease

What about more subtle forms?

Undiagnosed patients may account for 50-60% of dementia in primary care populations studied
When do we recognize?

Family, caregiver, neighbor concerns, behavioral crisis

(Patient NOT - anosognosia)

Functional decline  -  Keep a high index of suspicion
   ↓Hygiene
   Medication adherence
New psychiatric symptoms
Barriers to early diagnosis

Familiarity with early symptoms

Time, perceived complexity, resources

Knowledge of screening tools
Should we increase our recognition?

What are patient and family expectations for diagnosis of this potentially serious illness?

Potential for unabated morbidity

Finance, public/private safety, social isolation, independence, quality of life.

Informal care provider burden, cost
Counterpoints

How effective are pharmacologic / non pharmacologic interventions in mild to moderate dementia?

Does earlier diagnosis improve patient and family planning for future medical care or safety?

What are the adverse effects of screening and early treatment? Depression, anxiety, time, cost of screening, labeling effects?

Complexity: Screening followed by diagnostic interview/examination, likely referral from primary care for specialty evaluation.
The U.S. Preventive Services Task Force (USPSTF) June 2003

Good evidence that some screening tests have good sensitivity but only fair specificity in detecting cognitive impairment and dementia.

Fair to good evidence that several drug therapies have a beneficial effect on cognitive function (equivalent to delaying the natural progression of Alzheimer's disease from 2 to 7 months)

Evidence of their beneficial effects on instrumental activities of daily living is mixed, with the benefit being small, at best.

http://www.uspreventiveservicestaskforce.org/3rduspstf/dementia/dementrr.htm
Insufficient evidence to determine whether the benefits observed in drug trials are generalizable to patients whose disease would be detected by screening in primary care settings.

Accuracy of diagnosis, the feasibility of screening and treatment in routine clinical practice, and the potential harms of screening (e.g., labeling effects) are also unknown.

Could not determine whether the benefits of screening for dementia outweigh the harms.

http://www.uspreventiveservicestaskforce.org/3rdusptf/dementia/dementrr.htm
Early recognition of cognitive impairment

Diagnostic and treatment decisions for this illness and others (goals of treatment).

Anticipate problems patients may have in understanding and adhering to recommended therapy.

May also be useful to the patient's caregiver(s) and family member(s) in helping anticipate and plan for future problems.
Clinicians should assess cognitive function whenever cognitive impairment or deterioration is suspected based on direct observation, patient report, or concerns raised by family members, friends, or caretakers.
Consider secondary case-finding measures for dementia in elderly patients:

- Unexplained (any) functional decline
- Deterioration in hygiene
- Questionable adherence to medication regimens
- New-onset psychiatric symptoms.

Patients referred to dementia specialists after “screening” have been diagnosed at an earlier stage of illness than those referred from physicians or families.
January 1, 2011 Medicare Annual Wellness Visit

“...assessment of an individual’s cognitive function by direct observation, with due consideration of information obtained by way of patient report, concerns raised by family members, friends, caretakers, or others.”

Who does this currently?

How?
Finding dementia in primary care: the results of a clinical demonstration project
J Am Geriatr Soc 2012; 60: 210-17

8,063 veterans > 70 w/o prior dx cognitive impairment offered Mini-cog screening
Routine primary care visit
7 VA centers
Mini-cog, followed by additional detailed evaluation

11% Newly documented cognitive impairment vs 4% in similar clinics without screening
The mini cog: a cognitive vital signs measure for dementia screening in multilingual elderly


Memory

3 words at 3 minutes

Clock drawing hands set to 10 after 11 numbers correct, time correct

3 minutes vs 7 minutes for MMSE
Screening test score ≠ diagnosis of dementia
Box 1: General criteria for diagnosing dementia

A. The development of multiple cognitive deficits manifested by both:
   1. Memory impairment (impaired ability to learn new information or to recall previously learned information).
   2. One or more of the following cognitive disturbances:
      - aphasia (language disturbance)
      - apraxia (impaired ability to carry out motor activities despite intact motor function)
      - agnosia (failure to recognize or identify objects despite intact sensory function)
      - disturbance in executive function (e.g., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause major impairment in social or occupational functioning and represent a substantial decline from a previous level of functioning.

C. The deficits do not occur exclusively during the course of a delirium.
The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease


Interferes with ability to function at work or at usual activities
Decline from prior levels
No delirium or major psychiatric disorder

History taking from the patient and a knowledgeable informant

Objective cognitive assessment, “bedside” mental status examination or neuropsychological testing

Neuropsychological testing should be done when the routine history and bedside mental status examination cannot provide a confident diagnosis.
Memory

Impaired ability to acquire and remember new information:

- repetitive questions or conversations
- misplacing personal belongings
- forgetting events or appointments
- getting lost on a familiar route
Manipulation of acquired knowledge, executive function

Impaired reasoning and handling of complex tasks, poor judgment:

- poor understanding of safety risks
- inability to manage finances
- poor decision-making ability
- inability to plan complex or sequential activities
Trail Making Test “B”
Stroop word color test 1

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Stroop word color test 2

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</table>
The Stroop color word test: influence of age, sex, and education; normative data for a large sample across the adult age range. Assessment 2006;13:62-69
Wisconsin Card Sort Test - 128 cards
Abstract reasoning, change problem solving strategies
time to learn new rules, correct mistakes
ages 6 ½ - 89
Language

Impaired language functions: speaking, reading, writing

- Difficulty thinking of common words while speaking
- Hesitations
- Speech, spelling, and writing errors, wrong word use (aphasia).
Spatial organization

Impaired visuospatial abilities

inability to:

- recognize faces or common objects.
- find objects in direct view despite good acuity (agnosia).
- inability to operate simple implements.
- orient clothing to the body (apraxia).
Personality/behavior

Changes in personality, behavior, or comportment:

- Uncharacteristic mood fluctuations, erratic agitation
- Impaired motivation, initiative, apathy
- Loss of drive, social withdrawal
- Decreased interest in previous activities
- Loss of empathy
- Compulsive or obsessive behaviors
- Socially unacceptable behaviors
Probable AD dementia

Insidious onset. Gradual onset over months to years, not sudden over hours or days

Clear-cut history of worsening of cognition by report or observation
4 major presentations

Amnestic:  most common

Non-amnestic:
  Language -  + other fx

  Visuospatial  - object agnosia, impaired face recognition, alexia, simultanagnosia, + other fx

  Executive - reasoning, judgment, problem solving + other fx

  “ME and three A’s”
Mild Cognitive Impairment

Symptomatic pre clinical phase of AD

Intermediate state of cognitive function between changes associated with aging and dementia

Other causes of MCI
Mild cognitive impairment

Successful aging: 1/100, no memory impairment

Usual: minor memory difficulties, no functional impairment

MCI: further decline in memory, recognized by the person, sometimes others

Amnestic, non amnestic

MCI

Prevalence: 10-20% > 65

  Prospective population study 70-89 y.o.
    11.1% amnestic MCI
    4.9% non amnestic MCI

General incidence of dementia >65, 1%/yr
  MCI 5-10%, up to 10-15% in specialty clinics

Up to 25% reversal of MCI, likely lower
Normal Aging: Misplacing objects, forgetting words

Not normal aging: Forgetting important information

Degree of functional impairment
spectrum of inefficiencies
retention of independence
Mild Cognitive Impairment

Preservation of independence in functional abilities

Mild problems performing complex functional tasks which they previously performed:
   paying bills, preparing a meal, shopping.

More time, less efficient, more errors performing such activities than in the past.

Generally maintain independence of function in daily life, minimal aids or assistance.

Diagnosis requires knowledge about an individual’s level of function at the current phase of their life.

Similar information is also necessary to determine whether a person is demented.
Figure 1. Diagnostic Algorithm for Amnestic and Nonamnestic Mild Cognitive Impairment.
MCI denotes mild cognitive impairment.
## Clinical Dementia Rating Scale

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<th>Impairment</th>
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<tr>
<td></td>
<td>None (0)</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td>No memory loss or slight inconsistent forgetfulness</td>
</tr>
<tr>
<td><strong>Orientation</strong></td>
<td>Fully oriented</td>
</tr>
<tr>
<td><strong>Judgment &amp; Problem Solving</strong></td>
<td>Solves everyday problems &amp; handles business &amp; financial affairs well; judgment good in relation to past performance</td>
</tr>
<tr>
<td><strong>Community Affairs</strong></td>
<td>Independent function at usual level in job, shopping, volunteer and social groups</td>
</tr>
<tr>
<td><strong>Home and Hobbies</strong></td>
<td>Life at home, hobbies, and intellectual interests well maintained</td>
</tr>
<tr>
<td><strong>Personal Care</strong></td>
<td>Fully capable of self-care</td>
</tr>
</tbody>
</table>

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.
ITEM

ORIENTATION
What is the (year) (season) (date) (day) (month)?
Where are we: (state) (city) (hospital)?
What (street) do you live on? What (county)?

REGISTRATION
Name 3 objects (apple, penny, table): 1 second to say each. Then ask patient all three after you have said them. Give 1 point for each correct answer. Then repeat them until all three are learned (for later checking).

ATTENTION AND CALCULATION
Serial 7s. Give 1 point for each correct answer. Stop after 5 answers. Spell "WORLD" backwards "DLROW". Score whichever is highest.

RECALL
Ask for the three objects repeated above. Give 1 point for each correct

LANGUAGE
Show 2 objects (pencil and watch); ask for their names.
Repeat the following: "No ifs, ands, or buts."
Follow a 3-stage command: "Take a paper in your right hand, fold it in half, and put it on the floor."
Have the patient read and obey the following:

"CLOSE YOUR EYES"
Have the patient write a sentence of his or her own choice.
Have the patient copy the following design.

TOTAL SCORE

30 ( )
<table>
<thead>
<tr>
<th>MoCA scores</th>
<th>Normal Controls (NC)</th>
<th>Mild Cognitive Impairment (MCI)</th>
<th>Alzheimer’s Disease (AD)</th>
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</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>90</td>
<td>94</td>
<td>93</td>
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<tr>
<td>MoCA average score</td>
<td>27.4</td>
<td>22.1</td>
<td>16.2</td>
</tr>
<tr>
<td>MoCA standard deviation</td>
<td>2.2</td>
<td>3.1</td>
<td>4.8</td>
</tr>
<tr>
<td>MoCA score range</td>
<td>25.2 - 29.6</td>
<td>19.0 - 25.2</td>
<td>21.0 - 11.4</td>
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<tr>
<td>Suggested cut-off score</td>
<td>≥26</td>
<td>&lt;26</td>
<td>&lt;26</td>
</tr>
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</table>

* Although the average MoCA score for the AD group is much lower than the MCI group, there is overlap between them. The suggested MoCA cut-off score is thus the same for both. The distinction between AD and MCI is mostly dependent on the presence of associated functional impairment and not on a specific score on the MoCA test.
MoCA vs MMSE for MCI

ROC curves showing MoCA® superiority to MMSE in distinguishing Normal Controls from MCI. The areas under ROC curves were compared with the method of Delong, DeLong and Clarke-Pearson (1988) for correlated curves. The difference was statistically significant $\chi^2(1, N=132)=11.66, p<0.001$. 
Pharmacotherapy.
To what extent do current medications work, for what?


Abstract Results: Cholinesterase inhibitors benefit patients with AD (Standard), although the average benefit appears small
Alzheimer’s Disease Assessment Scale (ADAS –cog) 70 points

Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment.
Subjective Functional Scale

Figure 3. Frequency Distribution of CIBIC plus Scores at Week 24.
Pharmacologic treatment of AD:

Cholinesterase inhibitors should be **considered** in patients with mild to moderate AD (Standard), although studies suggest a small average degree of benefit.
Translated to:

“Cholinesterase inhibitors are the only medications approved by the US Food and Drug Administration as treatment for AD.

Sufficient evidence has accumulated for these to be recommended as standard therapy for AD.”

Referencing the Neurology practice parameter

“significant but clinically marginal benefits with respect to cognition, daily function, and behavior” (ACHEI’s)

No significant differences between the (various) medications with respect to cognition.

Donepezil modestly but significantly better than rivastigmine and galantamine on daily function.

~ ½ discontinue ACHEI’s with one year

Perceived lack of efficacy
Anorexia
Weight loss
Agitation
Bradycardia
Syncope
23 mg donepezil
Moderate to severe AD (MMSE 1-20)
Clinician Interview Based Impression of Change

(7 point scale: No change, mild, moderate, marked improvement or deterioration)
May 18, 2011

Margaret A. Hamburg, M.D.
Commissioner
U.S. Food and Drug Administration
Department of Health and Human Services
W0 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Hamburg:

Public Citizen, representing more than 225,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act 21 U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately remove from the market the 23 milligram (mg) dose of Aricept (donepezil; Eisai Co., Ltd; Pfizer Inc.) because in the primary clinical trial:

1) The 23 mg dose of Aricept failed to meet the two efficacy criteria required by FDA as a condition of approval of drugs for dementia, specifically required for Aricept 23 in this case.

2) The 23 mg dose of Aricept significantly increased adverse events compared with the previously approved 10 mg dose, including increased risks for nausea, vomiting, diarrhea, anorexia, and confusion.

3) The 23 mg dose of Aricept received negative reviews from both the FDA clinical and statistical reviewers.
Figure 5: Time course of the change from baseline in ADCS-ADL score for patients completing 24 weeks of treatment.

Donepezil + Memantine

FDA approved for moderate to severe AD, MMSE 1-10. (many physicians use combination “off label”)

UK physicians 3 choices:
   a. Continue donepezil
   b. Discontinue
   c. Discontinue donepezil and switch to memantine

No NHS approval for combined drugs

2012 UK trial    MMSE 5-13
   1. Continue donepezil vs discontinue
   2. Start memantine vs do not start

One year follow up
   Continuing donepezil > discontinue (cognition + ADL)

Switching to memantine when donepezil stopped > not switching to memantine

Adding memantine to donepezil not better than continuing donepezil alone

Findings conflict with FDA approval

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Common Adverse Side Effects</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Donepezil (Aricept)</td>
<td>5 mg/day at bedtime with or without food for 4 to 6 weeks; 10 mg/day there-after, if tolerated</td>
<td>Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, muscle cramps, insomnia and vivid dreams</td>
<td>Available in a single daily dose</td>
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<td>Rivastigmine (Exelon)</td>
<td>3 mg daily, split into morning and evening doses with meals; dose increased by 3 mg/day every 4 weeks as tolerated, with a maximum daily dose of 12 mg</td>
<td>Nausea, vomiting, loss of appetite, weight loss, diarrhea, indigestion, dizziness, drowsiness, headache, diaphoresis, weakness</td>
<td>Available as a patch</td>
</tr>
<tr>
<td>Galantamine (Razadyne)</td>
<td>8 mg daily, split into morning and evening doses with meals; dose increased by 4 mg every 4 weeks, as tolerated, with a maximum daily dose of 16 to 24 mg</td>
<td>Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, headache, fatigue</td>
<td>Available as an extended-release capsule</td>
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<tr>
<td>Memantine (Namenda)</td>
<td>5 mg/day with or without food; dose increased by 5 mg every week, with a maximum daily dose of 20 mg</td>
<td>Constipation, dizziness, headache, pain (nonspecific)</td>
<td>Often used as an adjunct to cholinesterase inhibitors; not recommended alone for treatment of early disease</td>
</tr>
</tbody>
</table>
### Cost

<table>
<thead>
<tr>
<th>Tablets (Aricept)</th>
<th>Capsules (Exelon)</th>
<th>Capsule, 24-hour (Galantamine Hydrobromide)</th>
<th>Tablets (Namenda)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg (30): $304.91</td>
<td>1.5 mg (60): $266.86</td>
<td>8 mg (30): $118.99</td>
<td>5 mg (60): $240.00</td>
</tr>
<tr>
<td>10 mg (30): $302.74</td>
<td>3 mg (60): $256.82</td>
<td>16 mg (30): $119.99</td>
<td>10 mg (60): $240.84</td>
</tr>
<tr>
<td>23 mg (30): $277.99</td>
<td>4.5 mg (60): $258.37</td>
<td></td>
<td>Tablets (Namenda Titratio Pak)</td>
</tr>
<tr>
<td></td>
<td>6 mg (60): $256.96</td>
<td></td>
<td>(49): $188.00</td>
</tr>
<tr>
<td>Tablets (Donepezil HCl)</td>
<td>Patch, 24-hour (Exelon)</td>
<td>Capsule, 24-hour (Razadyne ER)</td>
<td></td>
</tr>
<tr>
<td>5 mg (30): $179.99</td>
<td>4.6 mg/24 hrs (30): $275.00</td>
<td>8 mg (30): $225.98</td>
<td></td>
</tr>
<tr>
<td>10 mg (30): $188.00</td>
<td>9.5 mg/24 hrs (30): $277.99</td>
<td>16 mg (30): $225.98</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 mg (30): $225.98</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tablets (Galantamine Hydrobromide)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 mg (30): $69.99</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Tablets (Razadyne)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 mg (30): $109.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 mg (30): $112.16</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 mg (30): $112.16</td>
<td></td>
</tr>
</tbody>
</table>
Cholinesterase inhibitors for mild cognitive impairment
Russ TC, Morling JR. Cochrane Database Syst Rev. 2012 Sep 12;9

Very little evidence that cholinesterase inhibitors affect progression to dementia or cognitive test scores in mild cognitive impairment.

Weak evidence is overwhelmed by the increased risk of adverse events, particularly gastrointestinal.

Cholinesterase inhibitors should not be recommended for mild cognitive impairment.
Envisioning better approaches for dementia care


Caregivers as the dominant focus of effective management

Much of the care cannot be delivered in the office setting

Interdisciplinary team models
Care of Persons with Dementia in their Environments (COPE) trial

Nonpharmacologic, biobehavioral approach to support physical function

Quality of life for patients with dementia and the well-being of their caregivers.

Targeted modifiable environmental stressors to decrease sensorial, physical, cognitive demands

Align with patient capabilities that could lead to reduced patient functioning.

Re-engage patients in daily activities, increase functionality, Alleviate caregiver burden.

Living at home MMSE 1-24, not bed bound

Improved caregiver well being

Gitlin LN et al. A bio-behavioral home based intervention and the well being of patients with dementia and their caregivers. JAMA 2010;304(9):983-991
Meta-analysis of non-pharmacologic interventions for neuropsychiatric symptoms of dementia.

Non pharmacologic interventions delivered by family caregivers have the potential to:

- ↓ frequency and severity of behavioral and psychologic symptoms of dementia, effect size 0.34 (CI = 0.20-0.48)
- ↓ caregiver reactions to behaviors, effect size 0.15 (CI=0.04-0.26)

Effect sizes at least equal those of pharmacotherapy

9-12 home based sessions tailored to the needs of the pt and caregiver delivered individually in the home multiple components over 3–6 months with periodic follow-up
1. Skills training for caregivers
   Managing behavioral and psychological symptoms of dementia
   Communicating better with care recipient
   Using role play, videos modeling behavior management strategies, cognitive-behavioral interventions, vignettes, live interviews
   Enhancing care recipients quality of life, e.g., improving daily activities, increasing pleasant events

2. Education for caregivers
   Psychoeducation
   Improving home care
   Tailored advice and recommendations
   Problem-solving methods
   Improving support network
   Computer-mediated automated interactive voice response
   Planning: emergencies, legal, financial

3. Activity planning and environmental redesign
   Planning activities with caregiver for care recipient
   Modifying care recipient’s physical and social environment

4. Enhancing support for caregivers
   Social support
   Web or telephone support
   Strategies on how to access support
   Family counseling

5. Self-care techniques for caregivers
   Health management
   Stress management
   Coping with change as a result of caregiving
   Music therapy
   Counseling

6. Miscellaneous
   Collaborative care with a health professional or care manager
   Exercise for care recipient


New memory impairment
Assess cognition
Review medications

New dementia
Neuro exam
Screen for depression
Lab testing

Manage dementia
Assess functional state
Discuss ACHEI
Screen for behavioral sx
Discuss risk/benefits antipsychotics
Driving counseling
Surrogate decision making
Alzheimer’s Assoc referral
Family care and counseling.

The 36-Hour Day

A Family Guide to Caring for Persons with Alzheimer Disease, Related Dementing Illnesses, and Memory Loss in Later Life

NANCY L. MACE, M.A.
PETER V. KABINS, M.D., M.P.H.

A JOHNS HOPKINS PRESS HEALTH BOOK
36 Hour Day contents

1. Getting medical help for the person who has dementia
2. Characteristic behavioral symptoms
3. Problems in independent living
4. Problems arising in daily care
5. Medical problems
6. Behavioral symptoms of dementia
7. Symptoms that appear as changes in mood
8. Special arrangements if you become ill
9. Getting outside help
36 Hour Day

10. You and the person who has dementia as parts of a family
11. How caring for a person who has dementia affects you
12. Caring for yourself
13. For children and teenagers
14. Financial and legal issues
15. Nursing home and other living arrangements
16. Preventing or delaying cognitive decline
17. Brain disorders and the causes of dementia
18. Research in dementia
Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults

Benefits and harms vary among agents

Small, but statistically significant differences in global behavioral scores associated with dementia
  aripiprazole, olanzapine and risperidone

Delusions, hallucinations, dysphoria, anxiety, agitation or aggression, euphoria, disinhibition, irritability, apathy, aberrant motor activity, behavioral disturbances.
Slightly above threshold for 30% improvement, minimum clinical observable change (A,O,R)
Study analysis: Adverse events associated with use of atypical antipsychotic medications compared with placebo in elderly patients.

Cardiovascular events and stroke
↑ appetite and weight
Anticholinergic
Sedation
Extrapyramidal
Urinary

Sudden cardiac deaths 2-9-3.3 / 1,000 pt-yrs
+ other potential adverse effects

Mortality with antipsychotics ~ 1.6 X placebo
NNH =87
Black box warning.

Compared to
6.8/ 1000 pt yrs clozaril agranulocytosis
Deaths due to clozaril agranulocytosis 0.2/1000 pt yrs
Relapse after discontinuation of risperidone in Alzheimer’s disease.


Open label, 180 pts mean dose 0.97 mg
4-8 months stable dose
↓ psychosis, agitation
Mild ↑ parkinsonism

Discontinuation of risperidone associated with ↑ risk of relapse of sx
? Bias
Functional Assessment Staging for Dementia

1. No difficulty subjectively or objectively
2. Subjective work difficulties
3. ↓ job fx evident to co-workers
4. ↓ ability to perform complex tasks
5. Assistance with choosing clothing
6. ↓ Dress, bathe, toilet
   Subcategories, urinary, fecal incontinence

Reisberg, B. Psychopharmacol Bulletin 1988;22(4):653-659
Functional Assessment Staging (FAST) + complication = hospice eligible

Stage 7

a. Speaking limited to 6 words
b. Single word or repetition
c. Cannot walk w/o assistance
d. Cannot sit w/o assistance
e. Cannot smile
f. Cannot hold head up
Clinical course of advanced dementia

322 patients, stage 7 dementia, mean age 85.3, 22 nursing homes, 18 month follow up

54.8% died

41.1% pneumonia
52.6% febrile episode
85% eating problem

Adjusted 6 month mortality rate
46.7% pneumonia
44.5% febrile episode
38.6% eating problem

54.8% died

41.1% developed pneumonia

52.6% febrile episode

85% eating problem

Symptoms last 3 months
46% dyspnea
39.1% pain

Co morbidities: 57% heart failure, 36% COPD, 4% active cancer
Interventions

- 40.7% hospitalization, ER visit, IV therapy, enteral feeding
- 29% IV
- 12.4% Hospital
- 2.8% ER
- 7.3% enteral feeding

Pt’s with proxies having understanding of prognosis and complications were less likely to have the above interventions
Figure 1. Overall Mortality and the Cumulative Incidences of Pneumonia, Febrile Episodes, and Eating Problems among Nursing Home Residents with Advanced Dementia.
Dementia with eating problem
Figure 3. Proportion of Nursing Home Residents Who Had Distressing Symptoms at Various Intervals before Death.
Use of Feeding Tubes in Nursing Home Residents With Severe Cognitive Impairment.
JAMA. 2002;287(24):3211-3212
Association of incident dementia with hospitalizations.

3019 pt > 65 w/o dementia, health plan, 13 yr follow up

494 developed dementia, 86% hosp at least once
   419 admissions/100 pt yrs

2525   No dementia, 59% hosp at least once
   200 admissions/100 pt yrs

Adjusted Admission ratio: All cause 1.41 (1.23-1.61)*  
   ACSC 1.78 (1.38-2.31)*

Dementia = Higher adjusted admission rates for all types of ACSCs, bacterial pneumonia, congestive heart failure, dehydration, duodenal ulcer, and urinary tract infection,

Call for health system redesign:  
   effective ambulatory care for proactive dementia detection and management

Clinical Case 1  Worried surgeon

66 year old woman, currently working full time as a surgeon is seen for primary care. She is concerned about her memory as when working with residents she sometimes has difficulty recalling authors’ names on medical literature.

There have been no problems with her work, no quality or peer review concerns. She continues to receive excellent evaluations by her trainees.

Her father died of Alzheimer’s disease at age 75 and she is worried that she may also develop it.
PMH: Osteopenia, otherwise healthy.

Medications: calcium, vitamin D.

BP 135/70, BMI 27.2  physical examination normal. Basic laboratory testing has been normal.

Montreal Cognitive Assessment (MoCA) 29/30
Clinical Case 1

Which of the following is the most appropriate next step in managing this patient’s concerns?

A. Evaluate apolipoprotein E allele status
B. MRI of brain
C. Neuropsychiatric testing
D. Start an exercise program
E. Start donepezil
Clinical Case 2: Caring daughter

85 year old woman senior apartments is seen in follow up of HTN and mobility problems related to hip and knee DJD. She lives in senior apartments and reports that she is bored despite enjoying participating in many on site social activities.

Daughter visits weekly takes her shopping and assists with keeping finances and bill paying for the past 2 years. Pt had a business college education retired from work age 72 as an executive secretary.
Medicines: HCTZ, lisinopril, acetaminophen, calcium, vitamins.

BP 138/85, Examination normal other than DJD related changes and slow gait for which she uses a walker. No falls in past year.

Mini cog score 2/5 losing two points for memory, one point for abnormal clock drawing. PHQ-9 score is 1 Daughter in attendance during the visit believes her mother is “just fine for her age”.

Clinical Case 2

Which of the following is the most likely diagnosis?

A. Dementia
B. Mild cognitive impairment
C. Normal aging
D. Sub-syndromal depression
Clinical Case 3: Weight loss with dementia

78 year old man is seen for a 15 pound weight loss over the past two months. He has Alzheimer’s disease and lives for the past 2 years in a secured dementia unit of a nursing home. Staff report he is eating less than previously.

Both he and assisted living staff report no other symptoms. There has been no other change in his behavior. He requires assistance with many basic ADL’s, intermittently incontinent of urine, unchanged. He has never smoked.
Medications: Donepezil 5 mg once daily, calcium, multivitamins

Physical examination: Elderly man cooperative. Other than cognitive impairment his physical examination is normal. He walks without assistance.

MMSE 5/30. CBC, BMP, Hepatic panel, TSH are normal
Clinical Case 3

Which of the following is the most appropriate next step in management?

A. CT of abdomen
B. Discontinue donepezil
C. Hospice consultation
D. Stool for occult blood
E. Upper endoscopy
Questions?

Thank you