Current Management of Alzheimer’s Disease

William Petrie, MD

Risk factors for Alzheimer’s disease

- Increased systolic B/P(>160)
- Increased cholesterol
- Noted in 21 year followup
  
  Kivipelto et al 2001
Canadian Study of Health and Aging-5 year followup

- Increased Age
- Fewer years of Education
- Apoliprotein E4

Canadian study of health and aging

- Reduced Risk:
  - Wine drinking
  - Use of NSAIDS
  - Coffee
  - Regular Physical Activity
**Canadian study of health and aging - no association**

- Family history of dementia
- History of depression
- Estrogen replacement
- Head injury
- Smoking
- High blood pressure
- Heart disease
- Stroke

Lindsay et al. 2002

**Dutch Study**

- Risk: Smoking
- Low Education

- No Risk:
  - Family History
  - Head injury

Launer et al. 1999
SLEEP

- Increased rate of MCI and AD in both short and long sleepers (<6 hours, >9 hrs)

Chen et al. 2015

GAIT

- Gait speed
- Gait Variability

Both predicted dementia

Gillain et al 2015
2015 Risk Factors

- Age
- Family history
- Susceptibility genes (ApoE)
- Diabetes (>12 studies)
- Mid life obesity (6 studies)
- Mid life hypertension
- Current Smoking

Other Risk Factors

- Years of formal education
- TBI, esp repetitive
- Depression, esp recurrent
- Impaired sleep
- Hyperlipidemia (+/-)
Progression from MCI to AD

- Phosphorylated tau
- Hippocampal atrophy
- Medial temporal lobe atrophy
- Entorhinal atrophy
- Total tau
- WMI

Progression from MCI to AD

- Depression
- Diabetes
- Hypertension
- Age
DIET

- Mediterranean Diet reduced risk of AD by 54% (comparing top 1/3 to bottom 1/3)
- Hypertension Diet (DASH) reduced AD by 39% compared to bottom third
- MIND (Med-DASH Intervention for Neurodegenerative Delay)

Good foods

- Green leafy vegetables
- Other vegetables
- Nuts/ Berries
- Beans
- Whole grains
- Fish/Poultry
- Olive oil
- Wine
Bad Foods

- Red Meat
- Butter/ stick margarine
- Cheese
- Pastries
- Sweets
- Fried food
- Fast foods

Treatment of Alzheimer’s Disease

![Graph showing prevalence, diagnosed, treated, and treated with AChEIs](image)

* Any drug treatment, not limited to acetylcholinesterase inhibitors.


Winton, M.J. August 2012: Treatment Algorithms in Alzheimer's Disease
CLINICAL MANAGEMENT

Managing Alzheimer’s disease requires the skillful combination of:

- Nonpharmacologic interventions
- Medications to enhance and/or maintain cognitive functioning
- Medications to address behavioral symptomatology
- Support/education for caregivers

Nursing Home Placement
Impact of Support Programs

Cumulative proportion of patients surviving

<table>
<thead>
<tr>
<th>Survival time from baseline (year)</th>
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Major Changes in the Cholinergic System in Alzheimer’s Disease

- Depletion of acetylcholine (ACh)
- ↓ in choline acetyltransferase (ChAT) activity
- Loss of cholinergic neurons
- ↓ Acetylcholinesterase (AChE)
- ↑ Butyrylcholinesterase (BuChE)
- Loss of muscarinic & nicotinic receptors
FDA-Approved ChEI Treatments for Mild to Moderate Alzheimer’s Disease

- Mild to moderate AD
  - Cognex® tacrine (Sept 1993)
  - Aricept® donepezil (Jan 1997)
  - Exelon® rivastigmine (June 2000)
  - Reminyl® galantamine (Feb 2001)

Cognex is a registered trademark of Warner-Lambert Company.
Aricept is a registered trademark of Eisai Company Ltd.
Exelon is a registered trademark of Novartis AG.
Reminyl is a registered trademark of Janssen Pharmaceutica.
Commonly used ChE inhibitors in AD

*Donepezil*
- Mechanism: AChE-I
- Inhibition: reversible

*Acetylcholine*

*Galantamine*
- Mechanism: AChE-I
- Inhibition: reversible

*Rivastigmine*
- Mechanism: AChE-I/BuChE-I
- Inhibition: very slowly reversible

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In Alzheimer’s disease, cognitive decline is expected over time

If untreated, the expected decline in MMSE scores of mild to moderate AD patients ranges from 2 to 4 points annually

![Graph showing MMSE score decline over time](image)

Becker, Huff, Nebes et al, 1998,
Time-course of the Change from Baseline in SIB Score for Patients Completing 24 Weeks of Treatment.

MMSE: 0-20; Mod to severe
Stable dose of ARICEPT 10 mg/day>3 months
1434 patients
36% on memantine

Donepezil HCl (ARICEPT®)
Side Effects

- Placebo (N = 315)
- ARICEPT® 5 mg/d (N = 311)
- ARICEPT® 10 mg/d (N = 315) (1-wk titration)
- ARICEPT® 10 mg/d (N = 269) (6-wk titration)

% of Patients

Nausea  Diarrhea  Insomnia  Fatigue  Vomiting  Muscle cramps  Anorexia

From ARICEPT® (donepezil hydrochloride) package insert.
DONEPEZIL IN PURE VASCULAR DEMENTIA

Study Week


Role of Nicotinic Receptors in Alzheimer’s Disease

- Presynaptic nicotinic receptors control the release of neurotransmitters important for memory and mood\(^1\)
  - ACh, glutamate, serotonin, noradrenaline
- Blocking nicotinic receptors impairs cognition\(^2\)
- Stimulating nicotinic receptors improves memory\(^3\)

Acetylcholine can affect pre- and postsynaptic nicotinic receptors.

ACh = acetylcholine
M = muscarinic
N = nicotinic

Nicotine Patch in Mild Cognitive Impairment

A 6-month double-blind pilot clinical trial.
N=34 - Nicotine Patch: 5 mg → 10 mg → 15 mg
N=33 - Placebo:
MMSE=24 – 30

Reminyl → Razadyne (galantamine)

- Enhances cholinergic function
- Stimulates the nicotinic receptor
- Extracted from the dewdrops of Amaryllidaceae (daffodils)
Reminyl® (galantamine HBr) Proposed Mechanism of Action

Reminyl inhibits AChE*

Reminyl binds to allosteric site on nicotinic receptor*

Acetic acid

Choline

Muscarnic receptor

ACh

Postsynaptic nerve terminal

Presynaptic nerve terminal

Nicotinic receptor

AChE

* Clinical significance of this mechanism is unknown.


LONG TERM EFFECTS OF EXELON® ON COGNITION:
MEAN CHANGE IN ADAS-COG FROM BASELINE
THROUGH WEEK 52

ADAS-Cog Mean Change
from Baseline

6-12 mg
1-4 mg
Placebo
Proj. PBO

All Patients Taking Exelon

Study Week

0 10 20 30 40 50 60

0 1 2 3 4 5 6 7

* * * * * * * * *

Adapted from Proceedings, Satellite Symposium, FDA 3rd Cong. Aug. 96, P11
*p < .05 vs projected placebo
Causes of Dementia

Rivastigmine International Lewy Body Dementia Trial: Behavioral Changes

NPI 10-item Score—Mean Change from Baseline (OC)

- Rivastigmine
- Placebo

*P<0.01 vs placebo (ANOV/ANCOVA)
Efficacy of Aricept: Three Year Study

Eisai Data on File: Nordic Study, with 2-Year Open Label Extension

Effects of long-term ChE inhibition on AChE levels

Donepezil and galantamine increase CSF AChE activity\(^1\) (assessed by enzyme antigen immunoassay)

Sustained inhibition of CSF AChE activity by rivastigmine\(^2\) (assessed colorimetrically)

\(^1\)Adapted from Davidsson et al. 2001
\(^2\)Adapted from Darreh-Shori et al. 2002

Cognitive Efficacy at 5 Years

Data presented are from 2 large open-label extension studies enrolling patients from 4 phase III, randomized, placebo-controlled trials. All patients who were enrolled in the open-label extension studies received up to 12 mg/day rivastigmine. The baseline values used for patients treated with rivastigmine from the outset of the double-blind trials were those from Week 0; for patients treated with placebo in the double-blind trials, the baseline values used for the current analysis were those from the week immediately preceding the beginning of rivastigmine treatment in the open-label extension. The cognitive decline of projected untreated patients was estimated using the algorithm, proposed by Mendiondo et al, a baseline-dependent mathematical model designed to estimate cognitive decline.

Data on file, Novartis Pharmaceuticals Corp.
Exelon (rivastigmine) ‘Patch’ Transdermal System

Role of Glutamate in AD

- The normal activity of the neurotransmitter glutamate plays an integral role in the neural pathways associated with learning and memory
- In AD, abnormal glutamatergic activity can cause neuronal toxicity and may impair learning

Glutamate Hypothesis of Cognitive Deficit

Abnormal glutamatergic activity leads to sustained low-level activation of NMDA receptors

Cognitive deficit

Neuronal damage/loss following chronic insult


Pharmacology of Memantine

- Uncompetitive (open channel) NMDA-receptor antagonist
- Improves performance in learning-impaired animals
- Does not alter AChE activity in the presence or absence of AChEIs
- Antagonistic effects at the 5HT₃ receptor

Memantine Voltage Dependency in Alzheimer’s Disease

Memantine in Moderate to Severe AD Study
(Mean age = 76 ± 8; MMSE = 7.9 ± 3.6 (3-14); GDS = 5-6

Results: Cognition—SIB

The Memantine Group Exhibited Significantly Superior Cognitive Function Compared With the Placebo Group

Reprinted from Neuropharmacology, Vol 38, CG Parsons, W Danysz, G Quack. Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist—a review of preclinical data, pages 735-767, copyright 1999, with permission from Elsevier.
Memantine + Donepezil in Moderate to Severe AD Study

Results: Cognition—SIB

Memantine + Donepezil Produced Sustained Improvement in Cognition Above Baseline Compared With Donepezil Alone

*OC analysis. †LOCF analysis.
Data on file, Forest Laboratories, Inc.

Memantine + Donepezil in Moderate to Severe AD (5 -13 MMSE)

295 Subjects
(MMSE=5-13)

Howard et al. 366;10 nejm.org march 8, 2012
Treatment Expectations

- In Alzheimer’s Disease, clinical success may be:
  - Short-term improvement (<20%)
  - Stabilization (30%, but only for 12-18 months)
  - Less than expected decline (75%)
Mini-Mental Status Examination

**Mini-Mental State Examination (MMSE)**

- **Orientation**
  - Name
  - City
  - Date
  - Month

- **Registration**
  - Name 3 common objects (e.g., apple, bicycle, pen)
  - Write 3 numbers in order (e.g., 1, 2, 3)

- **Attention and Calculation**
  - Serial 7s (7-4)
  - Copy 3-digit number

- **Recall**
  - Ask the subject to recall 3 words

- **Language**
  - Name a "pencil" and a "clock" (2 points)
  - Repeat the following: "Do you wash, eat, or talk?"

**Score Ranges**

- 24-26: Normal
- 20-23: Mild dementia
- 17-19: Moderate dementia
- <12: Severe dementia

**Total Score**

No confusion problem

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St. Louis University Mental Status Examination (SLUMS)

- **Takes ~ 7 min to complete**
- **Detects Mild Neurocognitive Impairment (MNCD)**
- **Higher Specificity than MMSE**

**MCI:**
- <High School = 23.5
- MCI: >High School = 25.5

**Dementia:**
- <High School = 19.5
- Dementia: >High School = 21.5

Clock Drawing Test (CDT) Scoring

- Draws closed circle: Score 1 point
- Places numbers in correct positions: Score 1 point
- Includes all 12 correct numbers: Score 1 point
- Places hands in correct positions: Score 1 point

**TOTAL SCORE ( 0 - 4 )**

**EXAMPLES OF CLOCK DRAWING:**

Mini-Cog: Relationship to MMSE

- Mini-Cog Cognitive Assessment:
  - Scoring:
    - Results of the 3-item recall: [ ]/3 e.g. [2]/3
    - Results of The Clock Drawing Test
      - ( ) Draws circle
      - ( ) places numbers in correct positions
      - ( ) includes all 12 correct numbers
      - ( ) places hands in correct positions
    - Results of the clock drawing test score [ ]/4 e.g. [3]/4
  - Total Mini-Cog score [ ]/7 e.g. [5]/7
  - For equivalency with Mini-mental status exam, multiply numerator by 4.3. MMSE ~ [ ]/30 e.g. [20–22]/30

Treatment Options

- Stop donepezil; start another cholinesterase inhibitor
  - e.g. Exelon Patch
- Continue current therapy
- Increase dosage
- Add memantine
- Discontinue therapy
Other Pharmacological Options

- **NSAIDs**—Clinical trials of COX-2 inhibitors rofecoxib (Vioxx) and celecoxib (Celebrex) failed to show benefit in AD. Nonselective NSAIDs (ibuprofen, naproxen) have thus far failed to show a benefit.

- **Estrogen (hormone)**—Women's Health Initiative: a small increased risk of clinically meaningful cognitive decline.

- **Statins**—HMG-CoA reductase inhibition of cholesterol synthesis may reduce microvascular dementias due to reduced stroke. May also modulate APP processing.

- **Vitamin E (tocopherol)**—Antioxidant scavenges toxic free radicals; safe and well tolerated.

- **Selegiline (MAO-B inhibitor)**—Some evidence of improvement with selegiline in the short term in cognition and activities of daily living; magnitude did not reach clinical importance. No evidence of long-term effects.

Alzheimer Immunotherapy: State of the Art

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<tr>
<th>Discovery</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Market</th>
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<td><strong>AFFiRiS:</strong></td>
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Modified from B. Permanne
Bapineusumab in Apo-E4 Carriers – Change in ADAS-Cog

Presentation: EFNS (European Federation of Neurological Societies), Stockholm, Sweden, Sept. 8-11, 2012:

www.alz.uci.edu
Age-Related Cognitive Impairment

Virginia Cognitive Aging Project


Does Aricept Prevent Onset of Dementia in MCI?

P=0.004 P=0.04

N=259 PBO
N=253 DPL

PBO=Placebo
DPL=Donepezil
APO-E genotype and AD onset

- e2  --  7% of the population
- e3  --  78% of the population
- e4  --  15% of the population

- e3/3 - average age of onset = 74 y/o
- e3/4 and e4/4  average age = 69 y/o

Prevention of MCI → Dementia in APO-E4 Carriers

N=136 PBO
N=147 DPL
N=141 Vit E

P=0.04

PBO=Placebo
DPL=Donepezil
Apolipoprotein E and AD Pathology

- Apolipoprotein E (APOE) genotype is associated with AD risk
- APOE-epsilon2 may be protective—APOE-epsilon4 is associated with increased risk
- The role of APOE-epsilon2 and APOE-epsilon4 in pathogenesis is not known
- APOE is found in β-amyloid plaques and neurofibrillary tangles and may affect protein-protein interactions

Bexarotene (Targretin)

Nuclear receptor PPAR receptor γ and retinoid X receptor (RXR) Agonist.

Mild Cognitive Impairment
WHO PROGRESSES?

• Small hippocampal volumes (order Neuroquant with MRI)
• Decreased blood flow to posterior cingulate gyrus
• Increased CSF tau protein and decreased beta-amyloid (1-42)

Hippocampal Neurogenesis With Aerobic Activity

(a, b) running animals have significantly more dividing cells (BrdU+) than controls.
(c, d) Immunofluorescent confocal Microscopy identify the newly born neurons, neuronal phenotype (NeuN+) appears orange.
