Current Therapies for Alzheimer’s Disease
Do They Work?

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Disclosures

- Consultant: Acadia, Alkahest, Avanir, Axsome, Biogen, BioXcel, Genentech, Karuna, Lundbeck, Novartis, Otsuka, Roche, Takeda
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- Safety Monitoring Committee: Anavex, EryDel, Intra-Cellular Therapies, Merck, Newron
- Speaker’s Bureau: Acadia, Biogen
Learning Objectives

• Evaluate and contrast the pharmacologic therapies currently available for treating patients with mild-moderate to severe Alzheimer’s disease
• Assess the evidence for the benefits of combination therapies for improving cognition, activities of daily living, global outcome, and behavior

Outline

• Impact of antidementia therapies on activities of daily living (ADLs), behavior, and cognition in mild-moderate–severe Alzheimer’s disease (AD)
  – ChEIs (Cholinesterase inhibitors)
  – Memantine
  – Combination therapy
• Conclusions
Cholinesterase inhibitors and memantine (alone or in combination) produce statistically and clinically significant improvement in patients with moderate to severe AD when measured for:

A. Cognition
B. Activities of daily living
C. Global measures
D. All of the above
E. None of the above

Cochrane Review of Memantine Concluded

- A Low incidence of adverse events
- B Significant benefits in mild to severe AD & VaD
- C In mod to severe AD, patients taking memantine were less likely to develop agitation
- D All are correct
Comparison of FDA-Approved Agents for the Treatment of AD (Conventional Oral Tablets)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Donepezil</th>
<th>Galantamine</th>
<th>Galantamine ER</th>
<th>Memantine</th>
<th>Rivastigmine</th>
<th>Rivastigmine Transdermal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>Mild, moderate, severe</td>
<td>Mild to moderate</td>
<td>Mild to moderate</td>
<td>Moderate to severe</td>
<td>Mild to moderate</td>
<td>Mild to moderate*</td>
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<tr>
<td>MOA(s)</td>
<td>AChEI</td>
<td>AChEI</td>
<td>AChEI</td>
<td>NMDA receptor antagonist</td>
<td>AChEI BuChEI</td>
<td>AChEI BuChEI</td>
</tr>
<tr>
<td>Dose titration</td>
<td>2 steps</td>
<td>2 to 3 steps</td>
<td>2 to 3 steps</td>
<td>4 steps</td>
<td>3 to 4 steps</td>
<td>2 steps</td>
</tr>
<tr>
<td>Starting dose</td>
<td>5 mg 1 x daily</td>
<td>4 mg 2 x daily</td>
<td>8 mg 1 x daily</td>
<td>5 mg 1 x daily</td>
<td>1.5 mg 2 x daily</td>
<td>4.6 mg every 24 hours</td>
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<tr>
<td>Max dose</td>
<td>23 mg 1 x daily</td>
<td>24 mg 2 x daily</td>
<td>24 mg 1 x daily</td>
<td>10 mg 2 x daily XR 28 mg</td>
<td>6 mg 2 x daily</td>
<td>13.3 mg every 24 hours</td>
</tr>
</tbody>
</table>

* Tacrine is an FDA-approved therapy but is rarely used because of QID dosing and hepatotoxicity.
** Mild to Mod AD or PDD


Response to ChEI Therapy: Cognition

- ADAS-Cog data (shown) was statistically significant but did not show improvement in cognition clinically
- Clinically important improvements were seen using CIBIC-plus data (not shown)

Update on Pharmacologic Options for Patients With Moderate–Severe AD
George T. Grossberg, MD

ChEi Treatment and ADL in Mild-to-Moderate AD

Greater proportion of patients maintain ADL over 1 year.

Criteria-based definition of ADL preservation; intent-to-treat population.


Behavioral Responses in Mild to Moderate AD: Delayed Adverse Behaviors With Galantamine

NPI, neuropsychiatric inventory

Adapted with permission from Tariot PN et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. Neurology. 2000;54(12):2269-2276.
Treatment Responses With an NMDA Receptor Antagonist: Moderate to Severe AD


Combination Therapy in Moderate to Severe AD: Donepezil + Memantine (Cognitive)

Treatment With a ChEI Reduces Caregiver Burden

Donepezil (observed cases)

Mean Change From Baseline Time (min/d ± SE)

Week

0 4 12 24

Less Time

Baseline

More Time

P=0.015

IADL, instrumental activities of daily living; PSMS, physical self-maintenance scale

Data on Combination Therapy for AD

• NIH-sponsored analysis of 382 patients over the course of 15 years

• Study supports the benefits of combination therapy

NIH, National Institute of Health


Long-term Course and Effectiveness of Combination Therapy in Alzheimer’s Disease

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From the Department of Neurology and Massachusetts Alzheimer’s Disease Research Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA USA, U.S.A. 02115, and the Massachusetts School of Professional Psychology, West Roxbury, MA USA.
**Objectives**

- To compare the real-world clinical effectiveness and long-term clinical trajectory in patients with AD who received:
  - No treatment
  - Cholinesterase inhibitor (ChEI) alone
  - Memantine HCl + ChEI (combo)
- To compare the cognitive and functional differences between the 3 treatment groups

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**Results: Cognitive Performance* Over Time†**

- Patients receiving combination therapy may experience significantly slower cognitive decline.
- The data show that the mean deterioration for an untreated patient is 3 to 4 errors per year; combination therapy decreased the deterioration by 2 errors per year.

*Based on predictive values from regression models of actual patient data. Actual patient data were used in a statistical model to generate these predicted values that account for patient differences such as duration of illness, time entering study, education, and baseline BDS and ADL scores.
†Mean cumulative medication treatment time was 1.3 years.
‡Blessed Dementia Scale (Information-Memory-Concentration subscale) is a brief mental status best administered by a physician to assess cognitive impairment.
Results: Functional Dependence* Over Time†

- Patients receiving combination therapy may experience less dependence compared with a ChEI alone and not treatment

*Based on predictive values from regression models of actual patient data. Actual patient data were used in a statistical model to generate these predicted values that account for patient differences such as duration of illness, time entering study, education, and baseline BDS and ADL scores.

†Mean cumulative medication treatment time was 1.9 years.

‡Weintraub ADL Scale (Weintraub Activities of Daily Living scale) is a 31-item questionnaire on both basic and instrumental ADLs.

Behavioral Effects of Combination Therapy

Memantine + donepezil produced significant improvements in behavior compared with placebo + donepezil.

*Statistically significant; †OC analysis; ‡LOCF analysis.

LS, least square; SE, standard error
### Persistent Treatment With ChEI and/or Memantine Slows Clinical Progression of AD

- 641 AD patients followed over 20 years
- Persistent drug treatment produced statistically and clinically significant impact on AD progression as assessed by measures of:
  - Cognition
  - ADLs
  - Global measures
- Positive treatment effects even seen in advanced AD


### Management of Neuropsychiatric Symptoms

- Nonpharmacologic
  - Behavioral
  - Environmental
- Psychotropics
  - Antidepressants (SSRIs, SNRIs)
  - Atypical antipsychotics, conventional neuroleptics
  - Mood-stabilizing anticonvulsants (valproate, gabapentin)
- Antidementia agents
  - Cholinesterase inhibitors
  - Memantine

SSRI, selective serotonin reuptake inhibitor; SSNI, selective norepinephrine reuptake inhibitor
Outline of Presentation

- Use of cholinesterase inhibitors
- Use of memantine

Outline of Presentation

- Use of neuroleptics
- Use of cholinesterase inhibitors
- Use of memantine
Behavioral Symptoms


*P<0.05 vs placebo

Mean (± SE) Change In NPI Score From Baseline

Deterioration

Baseline 1 2 3 4 5

Time (months)

NPI Individual Item Analysis in Patients Treated With Donepezil or Placebo (MMSE 5–11)

Outline of Presentation

• Use of neuroleptics
• Use of cholinesterase inhibitors
• Use of memantine

Cochrane Review of Memantine

Objectives
• To determine efficacy and safety of memantine for people with AD, vascular dementia (VaD), and mixed dementia

Conclusions
Moderate to severe AD:
• Pooled data indicate a beneficial effect of memantine at 6 months on cognition, ADLs, and behavior
• Supported by a significant improvement in the clinical impression of change
• Patients taking memantine appeared to be less likely to develop agitation

Mild to severe dementia (AD, VaD):
• Significant benefit of memantine on global impression, cognition, function, and behavior

Tolerability:
• Memantine is well tolerated and the incidence of adverse effects is low
Effects of Memantine on Behavior

Meta-analysis, six studies:
• Memantine produced a statistically significant beneficial effect on behavior (P=0.01 vs placebo) in patients with moderate to severe AD (MMSE <20)

Pooled data, six studies in moderate to severe AD:
• Memantine significantly improved NPI scores (vs placebo) from week 12 onwards

Conclusions

- ChEIs and memantine (alone or in combination) produce statistically and clinically significant improvement in patients with mild-to-severe AD when measured for cognition, ADLs, behavior, and global measures.