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Challenges and Opportunities in Dementia Management:

2006 Update

June 12, 2006
St. Louis, Missouri

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Challenges and Opportunities in Dementia Management: 

2006 Update

Cynthia D. Steele, RN, MPH Program Chairperson
The Johns Hopkins University Schools of Medicine and Nursing
The Copper Ridge Institute
Baltimore, Maryland
Introduction and Symposium Goals

Cynthia D. Steele, RN, MPH Program Chairperson
Learning Objectives

• Identify signs and symptoms of dementia in patients to ensure early diagnosis

• Implement early and effective strategies for improved care in the long-term facility

• Understand improved outcomes in dementia management related to patient quality of life, caregiver burden, and cost

• Translate information presented into practical application in their facility
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Challenges and Opportunities in Dementia Management:

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Dementia Defined

- Decline of cognitive capacity (memory, language, judgment, etc)
- Multiple areas of cognition impaired (global)
- Occurs in a normal level of consciousness (absence of delirium)
Dementia Statistics

- Very common, affecting at least 4 to 5 million Americans
- By 2050, 12 million Americans will have Alzheimer’s disease (the most common cause of dementia)
Dementia in Long-Term Care (LTC)

- 70% to 80% LTC residents have symptoms consistent with dementia
- However, only 50% to 65% of LTC residents are actually diagnosed with dementia
Common Causes of Dementia

- Alzheimer’s Disease: 60%
- Vascular: 10%
- Lewy Body: 10%
- FTD: 10%
- Other: 10%

FTD=frontotemporal dementia.
Common Symptoms of Alzheimer’s Disease

• Amnesia (memory loss)
• Aphasia (language impairment)
• Apraxia (impairment in learned motor skills)
• Agnosia (loss of ability to recognize familiar people, objects, etc)
• Impairment in executive functioning
Recognizing the Common Signs of Alzheimer’s Disease

- Memory loss
- Difficulty performing familiar tasks
- Trouble finding words
- Problems naming common objects
- Substituting words
- Disorientation to time and place
- Misplacing or losing things a lot
- Trouble solving everyday problems
- Getting lost easily
- Impaired judgment
- Loss of initiative
- Changes in mood, personality, or behavior
Why Is It Important to Diagnose Dementia in LTC?

- Dementia is *not* a normal part of aging
- Increased costs of caring for residents with dementia (financial and emotional)
Why Is It Important to Diagnose Dementia in LTC?

- Gives caregivers (family/staff) an opportunity to adapt methods of communication and care.
- Treatment of cognitive/functional symptoms and mood/behavioral symptoms may ultimately affect a resident’s quality of life.
Screening for Dementia in LTC

• Assessment tools are helpful for screening, but are not diagnostic

• In order to diagnose dementia, residents should be referred for a comprehensive evaluation with their primary health care provider or a specialist (physician, nurse practitioner, neurologist, geriatric psychiatrist)
Common Methods of Screening for Dementia in Long Term Care

- Mini-Mental Status Examination (MMSE)
- Clock Drawing Test
- Items from the Minimum Data Set (MDS)
Dementia Screening: Mini Mental Status Examination

- Brief, structured
- Scores range from 0-30
- Limited by ceiling and floor effect
- Assesses:
  - orientation
  - registration
  - attention
  - recall
  - language/comprehension
  - praxis

Dementia Screening: Clock Drawing Test

- May help to detect deficits in cognition, such as attention, executive functioning, and visual spatial deficits
- Brief (1-5 minutes)
- Minimal language requirement
Screening for Dementia: MDS

- Data that is already required to be collected in the nursing homes
- Relevant sections for dementia screening include:
  - cognitive patterns
  - communication
  - behavioral symptoms
  - physical function
Screening for Dementia: Cognitive Performance Scale (CPS)

CPS is generated from 5 MDS items:

1. Comatose status
2. Short-term memory (the ability to recall information after 5 minutes)
3. Daily decision making (the ability to make everyday decisions about tasks or ADL)
4. Making self understood (able to communicate)
5. ADL self-performance in eating
Why Is Recognition and Treatment of Dementia Important?

- Potential opportunity to:
  - Improve resident quality of life
  - Reduce or stabilize cognitive and/or functional decline
  - Reduce or stabilize behavioral deterioration
  - Decrease stress on caregiver/LTC staff
Dementia Treatment: Implementing Early and Effective Strategies for Improved Long-Term Care

Manju T. Beier, PharmD, FASCP
Geriatric Consultant Resources
University of Michigan
Ann Arbor, Michigan
Pharmacologic Treatment Success in AD

Treatment success may currently be defined as:

- **Improvement**
- **Stabilization**
- **Less-than-expected decline**
- **Untreated/natural course**

Graph showing:
- **Progression of Disease**
- **Change From Baseline**
- **Time**
Benefits of Treating Disease Progression

- Neurophysiologic pathways in patients with AD are still viable and are a target for treatment

- Opportunity to reduce:
  - functional decline
  - cognitive decline
  - behavioral symptoms
  - caregiver burden
FDA-Approved Pharmacotherapy in Alzheimer’s Disease

**Cholinesterase Inhibitors**

- Donepezil
- Galantamine
- Rivastigmine
- Approved for use in *mild to moderate AD*

**N-Methyl-D-Aspartate–Receptor Antagonist**

- Memantine
- Approved for use in *moderate to severe AD*

FDA=US Food and Drug Administration.
# Cholinesterase Inhibitors: Dosing Comparison

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Donepezil</th>
<th>Rivastigmine</th>
<th>Galantamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses per day</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Initial dose (mg/d)</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Dose escalation</td>
<td>4-6 weeks</td>
<td>Biweekly</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Clinically effective dose (mg/d)</td>
<td>5</td>
<td>6-12</td>
<td>16-24</td>
</tr>
<tr>
<td>Given with food</td>
<td>With/without</td>
<td>Yes</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

Aricept® (donepezil HCl) package insert. Pfizer Inc.
Razadyne® (rivastigmine tartrate) package insert. Ortho-McNeil Neurologics, Inc.
Exelon® (galantamine HBr) package insert. Novartis Pharmaceuticals Corp.
**Cholinesterase Inhibitors: Adverse Effect Profile**

- **Gastrointestinal**
  - Nausea, vomiting, diarrhea, abdominal pain
  - May result in anorexia and weight loss

- **Cardiovascular**
  - Bradycardia, tremor, and dizziness
  - May result in asthenia and fatigue

- **Neuromuscular**
  - Muscle cramps and weakness
  - May result in falls

- **Central nervous system**
  - Insomnia, nightmares, agitation, and a panic-like state

Potential Drug Interaction: Anticholinergics and Cholinesterase Inhibitors

- Opposing actions of drugs on the cholinergic system in CNS
- Anticholinergic agents effectively deplete the brain of acetylcholine
- Need to have increased awareness especially in the setting of incontinence
Memantine: Suggested Dosing

- Titrate memantine to 20 mg/d (10 mg bid):
  - start with 5 mg qd (5 → 10 → 15 → 20 mg) over 4-week titration
- Decrease dose (to 5 mg bid) in patients with severe renal impairment (CLcr: 5 – 29 mL/min)
Memantine: Adverse Events

- No clinically relevant differences between memantine- and placebo-treated groups were observed in:
  - adverse event profile
    - Most common AEs reported with memantine vs placebo (≥5% than placebo) were dizziness, confusion, headache, and constipation
  - vital signs
  - laboratory parameters
  - ECG values
AChE Inhibitors: Domains of Efficacy

- Cognition
- Function
- Behavior

Clinical improvement

- Pharmaco-economic benefit
- Reduced caregiver burden
- Delayed skilled nursing facility placement
# Reduced Caregiver Time

<table>
<thead>
<tr>
<th></th>
<th>Donepezil&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Galantamine&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Memantine&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Duration</strong></td>
<td>24 weeks</td>
<td>52 weeks</td>
<td>28 weeks</td>
</tr>
<tr>
<td><strong>Disease Severity</strong></td>
<td>Moderate-Severe</td>
<td>Mild-Moderate</td>
<td>Moderate-Severe</td>
</tr>
<tr>
<td><strong>Reduced Caregiver Time</strong></td>
<td>52.4 min/d</td>
<td>60 min/d</td>
<td>92 min/d</td>
</tr>
</tbody>
</table>

Note: Cholinesterase inhibitors are not indicated for treatment of severe AD.

Donepezil Significantly Improved Global Function in Nursing Home Patients

24-Week Clinical Trial of Nursing Home Patients

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*P<0.05 compared with placebo.
CDR-SB=Clinical Dementia Rating–Sum of Boxes.
Donepezil Monotherapy in Moderate to Severe AD*: Efficacy

*Cholinesterase inhibitors are not indicated for treatment of severe AD; †P<0.01; ‡P<0.001.
DAD = Disability Assessment in Dementia.
Donepezil in Patients With Severe AD: Study Design

**Design**
6-month, double-blind, parallel group, placebo-controlled study

**Population**
248 patients with severe AD living in LTC facilities (Sweden)
*(MMSE range, 1 - 10)*

**Treatment**
Donepezil 5 mg/d for 30 days then 10 mg/d (n=128)
Matched placebo (n=120)

**Endpoints**
Primary: SIB, ADCS-ADL-severe
Secondary: MMSE, NPI, CGI-I

Donepezil in Patients With Severe AD: SIB Results


Donepezil (n=109) 109 95 (109)
Placebo (n=107) 107 98 (107)

Clinical improvement
Clinical decline
# Pivotal Trials: Memantine

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Monotherapy in Moderate to Severe AD&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Combination Memantine and Donepezil&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Nursing Home Patients With Dementia&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine dose</td>
<td>10 mg bid</td>
<td>10 mg bid (plus donepezil)</td>
<td>10 mg qd</td>
</tr>
<tr>
<td>Duration in weeks</td>
<td>28</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>MMSE range</td>
<td>3-14</td>
<td>5-14</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

**Principal Efficacy Measures**

<table>
<thead>
<tr>
<th>Global change</th>
<th>CIBIC-Plus</th>
<th>CIBIC-Plus</th>
<th>CGI-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td>SIB</td>
<td>SIB</td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>ADCS-ADL&lt;sub&gt;19&lt;/sub&gt;</td>
<td>ADCS-ADL&lt;sub&gt;19&lt;/sub&gt;</td>
<td>BGP-Care</td>
</tr>
</tbody>
</table>

Combination Therapy for AD?

Would memantine and ChEIs work together?
Memantine in Patients Receiving Ongoing Donepezil: Efficacy

**Design**
US phase 3, multicenter (37), randomized, double-blind, placebo-controlled study

**Population**
404 outpatients with moderate to severe AD on stable donepezil *(MMSE range, 5-14)*

**Treatment**
Memantine 20 mg/d (10 mg bid) 4-week titration (5→10→15→20 mg)

**Duration**
24 weeks

Memantine in Patients Receiving Ongoing Donepezil: Behavior

**NPI Single-Item Domains**

- Delusions
- Hallucinations
- Agitation/Aggression
- Depression/Dysphoria
- Anxiety
- Elation/Euphoria
- Apathy/Indifference
- Disinhibition
- Irritability/Lability
- Aberrant Motor Behavior
- Nighttime Behavior
- Appetite/Eating Change

LOCF analysis; *P=0.045; **P=0.005; ***P=0.001. Cummings J et al. Presented at: 56th Annual Meeting of the American Academy of Neurology; April 24–May 1, 2004; San Francisco, Calif.
**Interventions for Dementia-Related Behavioral Symptoms**

<table>
<thead>
<tr>
<th>Nonpharmacologic</th>
<th>Pharmacologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Remove trigger</td>
<td>• Antidepressants</td>
</tr>
<tr>
<td>• Caregiver/family education</td>
<td>• Mood stabilizers</td>
</tr>
<tr>
<td>• Caregiver support</td>
<td>• Antipsychotics*</td>
</tr>
<tr>
<td>• Increase staffing ratio</td>
<td>• Cholinesterase inhibitors</td>
</tr>
<tr>
<td>• Activity programs</td>
<td>• NMDA-receptor antagonist (memantine)</td>
</tr>
<tr>
<td>• Adult day care</td>
<td></td>
</tr>
</tbody>
</table>

*Public health advisory from FDA (April 2005): Clinical trials of antipsychotic drugs to treat behavioral disorders in elderly patients with dementia have shown a higher death rate compared to placebo. Specific causes of death were primarily due to heart-related events (eg, heart failure, sudden death) or infections (mostly pneumonia).*
Treatment Consideration: When to Stop?

- May not tolerate cholinergic side effects despite slow and careful escalation
- When medication is prescribed, give it time to work
- Studies suggest that most subjects benefit and that long-term treatment is useful
- May see some deterioration when medication is stopped, so slow taper and monitor
Is Drug Treatment Working?

Is the patient better, worse, or the same compared to the last assessment?

Cognition  
Function  
Behavior
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Objectives

- What is improvement in a progressive disease?
- How do we approach the QOL outcomes for the patient, family and staff?
- When do we use medications? Which ones?
- How can we approach end-of-life issues?
Nonpharmacologic Treatments May Help Caregivers Manage Symptoms

- Sensory stimulation\(^1\)
  - Music therapy
  - Light therapy
- Social contact\(^1,2\)
  - One-to-one contact
  - Pet therapy
- Environment\(^1\)
  - Provide a safe environment
  - Reduce excess stimulation

- Rehabilitation\(^2,3\)
  - Develop a predictable daily routine
  - Simplify tasks
  - Allow independence

- Recreation\(^4-6\)
  - Exercise
  - Sorting
  - Games

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Donepezil Significantly Preserved Global Function: CIBIC-Plus

MSAD Study = Moderate to Severe Alzheimer’s Disease Study;
CIBIC-Plus = Clinician’s Interview-Based Impression of Change with caregiver input.
Results: Global Change—CGI-C

Memantine in Moderate to Severe Dementia Study

Change From Baseline

<table>
<thead>
<tr>
<th>Treatment Week</th>
<th>Improvement</th>
<th>Worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.4</td>
<td>3.0</td>
</tr>
<tr>
<td>4</td>
<td>2.6</td>
<td>3.2</td>
</tr>
<tr>
<td>12</td>
<td>2.8</td>
<td>3.4</td>
</tr>
<tr>
<td>End Point</td>
<td>3.0</td>
<td>3.6</td>
</tr>
</tbody>
</table>

n = 82
n = 84
n = 78
n = 80
n = 82
n = 84

P = .006  *P < .001  †P < .001

*OC analysis. †LOCF analysis.
Memantine + Donepezil in MSAD Study

Results: Global Change—CIBIC-Plus

<table>
<thead>
<tr>
<th>Treatment Week</th>
<th>Memantine+Donepezil</th>
<th>Placebo+Donepezil</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.6</td>
<td>4.8</td>
</tr>
<tr>
<td>4</td>
<td>3.8</td>
<td>4.6</td>
</tr>
<tr>
<td>8</td>
<td>4.0</td>
<td>4.4</td>
</tr>
<tr>
<td>12</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>18</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>24</td>
<td>3.8</td>
<td>3.8</td>
</tr>
<tr>
<td>End Point</td>
<td>3.6</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Mean CIBIC-Plus Score

- $P = 0.032$
- $P = 0.014$
- $P = 0.123$
- $P = 0.008$
- *$P = 0.028$
- †$P = 0.027$

*n = 198 197 190 182 180 172 198
n = 196 194 181 170 164 152 196

*OC analysis. †LOCF analysis.
Adapted from Tariot P et al. JAMA. 2004;291:317-324.
Data on file, Forest Laboratories, Inc.
Alzheimer’s Disease and Treatment

Cognitive Function

Early

Moderate

Severe

Cholinesterase inhibitors

Memantine

Time
Behavioral Symptoms of AD Evolve Over Time

Medical and Psychiatric History: Causes and Aggravators

D – Drugs
E – Emotional illness (including depression)
M – Metabolic/Endocrine disorders
E – Eye/Ear/Environment
N – Nutrition/Neurologic
T – Tumors/Trauma
I – Infection
A – Alcoholism/Anemia/Atherosclerosis/AD

Prescription Medication with Anticholinergic Effects

<table>
<thead>
<tr>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
</tr>
<tr>
<td>Ranitidine</td>
</tr>
<tr>
<td>Prednisolone</td>
</tr>
<tr>
<td>Theophylline</td>
</tr>
<tr>
<td>Warfarin</td>
</tr>
<tr>
<td>Dipyridamole</td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Nifedipine</td>
</tr>
<tr>
<td>Isosorbide</td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>Furosemide</td>
</tr>
<tr>
<td>Triamterene and hydrochlorothiazide</td>
</tr>
<tr>
<td>Captopril</td>
</tr>
</tbody>
</table>

Psychotropic Medications With Anticholinergic Effects

- **Tricyclic antidepressants**
  - Amitriptyline
  - Doxepin
  - Imipramine

- **Antipsychotics**
  - Thioridazine
  - Chlorpromazine
  - Clozapine
  - Olanzapine
FDA and Atypicals in Dementia

- The FDA has determined an increased risk of mortality based on a review of 17 placebo-controlled studies of atypicals in older dementia patients with behavioral disorders.

- The odds ratios showed a 1.6-1.7 increase.

- The death rates were 4.5% on drug and 2.6% on placebo.

- There was no indication that one drug was safer than the others.

- None of these agents are approved for use by the FDA in this condition.
Final Stages of Dementia

- Personal space = “cocoon”
- Goals of treatment
- Diminishing space
- Behavior disturbances and respecting space
- Activity reduction
- Food and water
- “Benefits of dehydration”
Final Progression of AD

- **Timeline**
  - Average course of AD = 6-8 years
  - Range of course = 2-20 years

- Most AD patients die from some form of sepsis or “failure to thrive”

- Autopsy finds plaques and tangles  
  (per Dr. Alzheimer’s 1907 findings)
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Putting Knowledge into Practice:

A Panel Discussion
Concluding Remarks

Cynthia D. Steele, RN, MPH
Program Chairperson
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