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**Oregon Health Resources Commission**



**Alzheimer's Drugs**

**Subcommittee Report**

**Update #1 October 2006**

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## Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission to advise the Department of Human Services on this Plan.

In the winter of 2003 the Oregon Health Resources Commission (HRC) appointed a subcommittee to perform an evidence-based review of the use of Alzheimer's drugs. Members of the subcommittee consisted of physicians, a PharmD, a pharmacist, a family Nurse Practitioner, a PhD, and other health care professionals. The subcommittee had three meetings. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) and Research Triangle Institute-University of North Carolina (RTI-UNC) EPC to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities.

Using standardized methods, the RTI-UNC EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The RTI-UNC EPC's report, "Drug Class Review Alzheimer's Drugs" was completed in April 2005, circulated to subcommittee members and posted on the web. The subcommittee met on May 9, 2005 to review the document and by consensus agreed to adopt the EPC report. The report was finalized at the June 13, 2005 meeting. Time was allotted for public comment, questions and testimony at each meeting.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the RTI-UNC EPC, the Alzheimer's Subcommittee or the Health Resources Commission. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the Health Resources Commission in providing recommendations to the Department of Human Services.

The Standing Update Committee of the Health Resources Commission, working together with the EPCs, Center, OMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. At least once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on

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the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. The Alzheimer's Drug report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene an Alzheimer's Drug Subcommittee.

The RTI-UNC EPC's report, "Drug Class Review Alzheimer's Drugs update 1" was completed in April 2006, circulated to Standing Update Committee members and posted on the web. The Standing Update Committee met on July 11, 2006 to review the document and by consensus agreed to adopt the EPC report. The report was finalized at the 10/20/06 HRC meeting. Time was allotted for public comment, questions and testimony at each meeting.

The full OHSU Evidence-based Practice Center's draft report, *Drug Class Review on Alzheimer's Drugs Update #1* is available on the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website: [http://egov.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence\\_based\\_reports.shtml](http://egov.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml) Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://egov.oregon.gov/DAS/OHPPR/ORRX/HRC/process.shtml>

You may request more information including copies of the draft report, minutes and tapes of subcommittee meetings, from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

Alison Knight, MD, Assistant Director for Health Projects  
Oregon Health & Science University  
Center for Evidence-based Policy  
2611 SW Third Avenue, MQ280  
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Phone: 503-494-2691

There will be a charge for copying and handling in providing documents both from the Office of Oregon Health Policy & Research and from the Center.

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## ***Critical Policy:***

### ■ *Senate Bill 819*

- “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

### ■ *Health Resources Commission*

- “Clinical outcomes are the most important indicators of comparative effectiveness”;
- “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

## ***Clinical Overview***

Alzheimer’s disease (AD) is the most common form of dementia in the elderly. Primary clinical manifestations of AD include the insidious onset and gradual progression of cognitive impairment affecting multiple domains. Amnesic type of memory impairment is the clinical hallmark of AD; other associated cognitive signs include deterioration of language, visuospatial deficits, and executive control functions such as insight and judgment. Alterations in behavior such as irritability, paranoia, depression, and apathy that frequently occur in AD contribute disproportionately to caregiver distress.

AD affects nearly 4.5 million people in the US with an average course of 8-10 years. The frequency in the population is age dependent with occurrence of 6-8% of all individuals <65, yet 30% of those >85. With the graying of America, the prevalence of AD will double over the next 20 years, compounding a current economic burden exceeding \$85 billion/year.

## ***Definition of Alzheimer’s Drugs***

The primary pharmacologic treatments used for treating patients with AD focus on modulating disease-associated neurotransmitter alterations such as cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists. Both memantine and ChEI drugs are considered symptomatic treatments for AD based on their ability to slow the clinical progression of symptoms across cognitive, behavioral, and functional domains. Centrally active ChEIs were the first class of drugs approved by the FDA for the treatment of AD. Currently, the only available drug targeting cognitive symptoms via a putative glutamatergic mechanism is memantine approved by the FDA in 2003, but widely used in Germany for more than two decades.<sup>1,2</sup>

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<sup>1</sup> Rogawski MA, Wenk GI. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer’s disease. *CNS Drug Rev* 2003; 9(3):275-308

<sup>2</sup> Jarvis B, Figgitt D, Memantine. *Drugs Aging* 2003; 20(6):465-76; discussion 477-8

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## ■ *Alzheimer's Drugs:*

<u>Generic</u>	<u>Brand(s)</u>
Donepezil	Aricept
Galantamine	Razadyne
Rivastigmine	Exelon
Tacrine	Cognex
Memantine	Nameda

## *Quality of the Evidence*

For quality of evidence the ICS subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period, and the end points of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency and power of the body of evidence relevant to that question.

## *Scope and Key Questions*

### **Key Question 1**

How do donepezil, galantamine, rivastigmine, tacrine and memantine or drug combinations (i.e. acetylcholinesterase inhibitor plus memantine) compare in their effectiveness for stabilizing symptoms and treating behavioral disturbance in patients with AD?

### **Key Question 2**

How do donepezil, galantamine, rivastigmine, tacrine and memantine or drug combinations compare in their

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- time to effect and in the time required to assess the clinical response?
- Key Question 3** What are the comparative incidence and severity of complications of donepezil, galantamine, rivastigmine, tacrine and memantine or drug combinations?
- Key Question 4** Do the included drugs or drug combinations differ in effectiveness or adverse events in the following subgroups?
- different racial groups, genders, or age groups?
  - patients with Parkinsonian features or vascular dementia?
  - patients taking other commonly prescribed drugs?

## *Time to achieve clinical differences*

The second key question specifically addresses the time to achieve statistical and clinical differences between available drugs. Because of the progressive nature of AD, the design of the trials, and the nature of the assessment scales, determining time effect are difficult at best. The EPC report cautions readers about interpretation of results given the nature of the evidence and the questionable significance of any differences reported across trials.

## *Clinical Improvement*

In considering all four key questions, it is important to make distinction between clinical improvement and slowing the progression of AD. Because AD is progressive in nature, a treatment may not demonstrate clinical improvement from baseline over time, but it may be able to slow the rate of cognitive or behavioral deterioration. Because most of the evidence for these drugs stems from placebo-controlled trials, *improvement* reflects differences between active- and placebo-treated patients. These patients may be worse than they were when they started treatment, but have demonstrated slower deterioration than patients in the other study groups.

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## *Clinical Scales*

Evaluation and comparison of the literature is made difficult because there are at least 12 validated in addition to some non-validated scales used. These scales have not been compared to each other. The validated scales are: *cognition* - Mini Mental State Exam (MMSE), Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog); *global change* - Clinical Global Impression of Change (CGIC), Clinicians Interview-Based Impression of Change Plus caregiver input (CIBIC-plus), Global Deterioration Scale (CDS); *function* - Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL), Disability Assessment for Dementia (DAD), Bristol Activities of Daily Living scale (Bristol ADL); and *behavior* - Neuropsychiatric inventory (NPI), and Behavioral symptoms in Alzheimer's Disease (BEHAVE-AD).

## *Summary of Results*

### **Key Question 1**

How do donepezil, galantamine, rivastigmine, tacrine and memantine or drug combinations (i.e. acetylcholinesterase inhibitor plus memantine) compare in their effectiveness for stabilizing symptoms and treating behavioral disturbance in patients with AD?

No double-blind head-to head trial compared one AD drug to another. Three open-label head-to-head trials of patients compared the efficacy of one AD medication to another. The fair evidence from two trials comparing donepezil to galantamine were mixed. In one 52-week trial, donepezil and galantamine did not differ in stabilizing symptoms or improving behavior and functional status. In a shorter (12 week) trial donepezil was superior to galantamine in its effects on cognition, functional status and caregiver and clinician satisfaction. The comparison of donepezil to rivastigmine was limited to a single 12 week trial with similar improvements in cognitive scores reported for both drugs, although clinician and caregiver satisfaction ratings were significantly better for donepezil. Both trials that reported significant differences were funded by the manufacturer of donepezil and used a non-validated scale to report clinician and caregiver satisfaction. The trial reporting no differences was funded by the manufacturer of galantamine.

Evidence of general efficacy for donepezil, galantamine, rivastigmine, tacrine, and memantine is fair; 1 placebo-controlled effectiveness trial, 20 efficacy trials, and 7 systematic reviews support modest effects on symptom stabilization, behavior, and functional status as measured on various scales that are difficult to compare. Most trials yielded data supporting a slower rate of decline in measures of cognition and global assessment. Fewer data supported differences in measures of behavior or functioning.

Key Question 1 addresses the issue of effectiveness: do drugs used to treat AD differ in their effects under real -life circumstances? The RIT-UNC EPC report on Alzheimer's Drugs distinguished *effectiveness* studies as those that were conducted in primary care or office-

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based settings that used less stringent eligibility criteria, that had follow-up periods of > 1 year, and that assessed health outcomes. In contrast, *efficacy* studies were conducted under highly controlled circumstances.

Although evidence of general efficacy is fair, evidence of effectiveness is poor due to the identification of only one trial that demonstrates effectiveness. The trial that compared donepezil to placebo for 565 community-resident patients over 3 years showed significantly better cognitive scale (MMSE) and functionality scores (Bristol ADL) for donepezil, although the clinical differences were modest. There were no differences in progression of disability or rate of institutionalization.

## Consensus

The AD Subcommittee agrees by consensus that:

- There is insufficient evidence that any of the AD drugs, donepezil, galantamine, rivastigmine, tacrine and memantine is superior for even modest efficacy of stabilizing symptoms and slowing the rate of decline in measures of cognition and global assessment in patients with AD.
- There is limited evidence that donepezil demonstrates *effectiveness* in cognition and functionality in patients with AD in a long term ( $\geq 1$  year) primary care setting; however, there was no difference in progression of disability or institutionalization.
- Although there is evidence for *efficacy* for galantamine, rivastigmine, tacrine and memantine, there is no evidence for *effectiveness* with these drugs in patients with AD.

## Key Question 2

How do donepezil, galantamine, rivastigmine, tacrine and memantine **or drug combinations** compare in their time to effect and in the time required to assess the clinical response?

No studies were identified that directly compared the time to effect or time required to assess the clinical response of one AD drug compared to another. Placebo-controlled trials are too heterogeneous to make comparisons.

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## Consensus

- There is insufficient evidence to determine the time to effect for donepezil, galantamine, rivastigmine, tacrine and memantine.
- The heterogeneity of the placebo-controlled trials do not allow pragmatic determination of the time required to assess the clinical response for any of the AD drugs reviewed.

### Key Question 3

What are the comparative incidence and severity of complications of donepezil, galantamine, rivastigmine, tacrine and memantine or drug combinations?

Overall among placebo-controlled trials, adverse events were reported by 40-96% of randomized patients. In general, ChEI- and memantine-treated patients appear to report a similar number of adverse events, although evidence is insufficient to compare the incidence of specific adverse events across drugs. Overall discontinuation rates are similar among memantine and ChEIs except for tacrine. Trials assessing tacrine consistently reported significantly higher discontinuation rates for tacrine than for placebo patients. The high withdrawal rates were mainly attributable to elevated serum alanine aminotransferase (ALT), a feature of liver toxicity.

Gastrointestinal-related adverse events may be greater with rivastigmine or galantamine than with donepezil. The highest incidence of nausea and vomiting was reported in rivastigmine trials, although these trials used a faster titration schedule than recommended by the product labeling. No trials were found that directly compared the incidence of gastrointestinal adverse events among ChEIs and memantine.

Indirect evidence from placebo-controlled trials indicates a substantially higher risk of hepatotoxicity for tacrine than for donepezil, galantamine, rivastigmine, and memantine. A retrospective review of tacrine-trials involving 2,446 AD patients reported 49% of tacrine-treated patients had elevated ALT levels, 25% had ALT 3x normal, 2% had ALT levels 20X normal, although few patients developed jaundice, and there were no deaths attributable to liver toxicity.

Two open-label comparative trials reported no difference in cardiovascular events between donepezil and galantamine and rivastigmine.

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## Consensus

- Tacrine appears to have significantly more liver toxicity than the other AD drugs based on available data.
- Evidence is insufficient to compare the incidence of specific adverse events across drugs.

### Key Question 4

Do the included drugs or drug combinations differ in effectiveness or adverse events in the following subgroups?

- (a) Different demographic profiles (age, race, or gender),
- (b) Parkinsonian features or vascular dementia,
- (c) or use of other commonly prescribed drugs?

No studies were specifically designed to compare the effect of donepezil, galantamine, rivastigmine, tacrine or memantine in one subgroup of patients compared to another. Only by evaluating subgroups analyses and indirect evidence from placebo-controlled trials can evidence regarding subgroups be inferred.

One subgroup analysis reported greater benefit for rivastigmine in patients older than 75 years. Indirect comparison of evidence from one donepezil trial conducted in nursing home residents to trials conducted in younger populations, suggested no apparent difference in efficacy or adverse event rates.

No evidence addressed patient's comorbid with Parkinson's disease.

Four studies provided general evidence of the efficacy of donepezil, galantamine, rivastigmine, and memantine in populations with comorbid vascular dementia. Only one study stratified patients by vascular risk factors. Patients were categorized by their Modified Hachinski Ischemic Score (MHIS). MHIS scores > 0 were used to identify the presence of vascular risk factors. At 26 weeks, rivastigmine was significantly better than placebo on cognitive, functional, and global assessment measures for patients with and without vascular risk factors. Larger treatment differences between rivastigmine and placebo were found for patients with vascular risk factors compared to patients without vascular risk factors.

No study compared outcomes among subgroups of patients taking a ChEI or memantine concurrently with another drug to patients not concurrently taking the same medication.

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## Consensus

- There is insufficient evidence to conclude that there is superior efficacy or adverse effects of donepezil, galantamine, rivastigmine, tacrine or memantine in one subgroup of patients based on demographic profiles of age, race, or gender.

## Conclusion

**It is the decision of the AD Subcommittee that:**

- **There is insufficient evidence that any one of the AD drugs, donepezil, galantamine, rivastigmine, tacrine, or memantine is superior to the others in terms of efficacy or effectiveness.**
- **There is no evidence that any of the AD drugs prevent the progression of disability or delay institutionalization.**
- **Tacrine has an increased incidence of liver enzyme elevation compared to the other AD drugs.**
- **There is insufficient evidence that donepezil, galantamine, rivastigmine, or memantine has less adverse effects than each other.**
- **Memantine may have some pharmacological differences from the other medications, but there is inadequate data to conclude that these are clinically significant differences.**

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## Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.