

Drug Class Review on Alzheimer's Drugs

Update #2: Preliminary Scan Report #4

September 2010

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. RTI-UNC Evidence-based Practice Center does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Washington State Health Care Authority with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with the Washington State Health Care Authority's consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Washington State Health Care Authority ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Dates of Previous Reports

Original Report: April 2005

Update #1: June 2006 (searches through December 2005)

Dates of Previous Update Scans

Update #2 Preliminary Update Scan #1: June 2007

Update #2 Preliminary Update Scan #2: May 2008

Update #2 Preliminary Update Scan #3: June 2009

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. How do donepezil, galantamine, rivastigmine, tacrine, and memantine or combinations of these drugs (i.e., acetylcholinesterase inhibitor plus memantine) compare in their efficacy or effectiveness for stabilizing symptoms and treating behavioral disturbances in patients with AD?
2. How do donepezil, galantamine, rivastigmine, tacrine, and memantine (or combinations of these drugs) compare in their time to effect and in the time required to assess the clinical response?
3. What are the comparative incidence and severity of complications of donepezil, galantamine, rivastigmine, tacrine, and memantine (or combinations of these drugs)?
4. Does efficacy, effectiveness, or adverse events of donepezil, galantamine, rivastigmine, tacrine, or memantine (or combinations of these drugs) differ in subgroups of patients with (1) different demographic profiles (age, race, or gender), (2) Parkinsonian features or vascular dementia, or (3) use of other commonly prescribed drugs?

Inclusion criteria**Populations**

- Study participants with Alzheimer's disease

Interventions

Five different treatments are currently available in the United States:

- Donepezil (Aricept)
- Galantamine (Razadyne, formerly Reminyl)
- Memantine (Namenda)
- Rivastigmine (Exelon)
- Tacrine (Cognex)

Effectiveness outcomes

- Stabilizing or slowing the rate of decline in *health outcome* measures:
 - Activities of daily living
 - Instrumental activities of daily living
 - Level of care changes
 - Quality of life
 - Behavioral symptoms (e.g., aggression, agitation, psychosis, mood disorders)
- Stabilizing or slowing the rate of decline in *intermediate outcome* measures:
 - Cognition
 - Global assessment
- Discontinuation effects (i.e., temporary or permanent changes in behavioral symptoms, functional capacity, or cognition as a result of discontinuing treatment)
- Reducing caregiver burden
- Hospitalizations or nursing home placement
- Mortality

Safety outcomes

- Overall adverse effect reports
- Withdrawals because of adverse effects
- Serious adverse event reports
- Adverse events due to discontinuation
- Specific adverse events, including:
 - Gastrointestinal symptoms
 - Hepatotoxicity
 - Weight loss

Study design

- RCTs only
- Sample size ≥ 100
- Study duration ≥ 12 weeks

METHODS

Literature Search

To identify relevant citations, we searched Medline from June 2009 through August 31, 2010 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (<http://www.hc-sc.gc.ca/dhp-mpps/medeff/advisories-avis/prof/index-eng.php>) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X.02) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 75 citations. Of those, there are 3 new potentially relevant RCTs (Appendix A). These include one publication describing a head-to-head trial of donepezil and memantine in progress (Jones 2009); this trial has not yet been completed. Another trial evaluated the effect of switching from donepezil tablets to the rivastigmine transdermal patch (Sadowsky 2009). The third publication describes pooled data from 3 randomized, placebo-controlled controlled trials of donepezil (Wilkinson 2009).

Taken together with 85 potentially relevant new trials identified in the 3 previous scans, the total number of potentially relevant RCTs for this topic now totals 88.

New Drugs

6/21/2010: Namenda XR (memantine hydrochloride) 7 mg, 14 mg, 21 mg, & 28 mg extended release capsules were FDA-approved for the treatment of moderate to severe dementia of the Alzheimer's type.

7/6/2007: Exelon Patch (rivastigmine transdermal system) was FDA-approved for treatment of mild to moderate dementia of the Alzheimer's type and treatment of mild to moderate dementia associated with Parkinson's disease.

New Safety Alerts

None identified.

Appendix A. Abstracts of potentially relevant new studies of Alzheimer's drugs (N=3)

Jones, R., B. Sheehan, et al. (2009). "DOMINO-AD protocol: donepezil and memantine in moderate to severe Alzheimer's disease - a multicentre RCT." [Trials \[Electronic Resource\]](#) **10**: 57.

BACKGROUND: Alzheimer's disease (AD) is the commonest cause of dementia. Cholinesterase inhibitors, such as donepezil, are the drug class with the best evidence of efficacy, licensed for mild to moderate AD, while the glutamate antagonist memantine has been widely prescribed, often in the later stages of AD. Memantine is licensed for moderate to severe dementia in AD but is not recommended by the England and Wales National Institute for Health and Clinical Excellence. However, there is little evidence to guide clinicians as to what to prescribe as AD advances; in particular, what to do as the condition progresses from moderate to severe. Options include continuing cholinesterase inhibitors irrespective of decline, adding memantine to cholinesterase inhibitors, or prescribing memantine instead of cholinesterase inhibitors. The aim of this trial is to establish the most effective drug option for people with AD who are progressing from moderate to severe dementia despite treatment with donepezil. **METHOD:** DOMINO-AD is a pragmatic, 15 centre, double-blind, randomized, placebo controlled trial. Patients with AD, currently living at home, receiving donepezil 10 mg daily, and with Standardized Mini-Mental State Examination (SMMSE) scores between 5 and 13 are being recruited. Each is randomized to one of four treatment options: continuation of donepezil with memantine placebo added; switch to memantine with donepezil placebo added; donepezil and memantine together; or donepezil placebo with memantine placebo. 800 participants are being recruited and treatment continues for one year. Primary outcome measures are cognition (SMMSE) and activities of daily living (Bristol Activities of Daily Living Scale). Secondary outcomes are non-cognitive dementia symptoms (Neuropsychiatric Inventory), health related quality of life (EQ-5D and DEMQOL-proxy), carer burden (General Health Questionnaire-12), cost effectiveness (using Client Service Receipt Inventory) and institutionalization. These outcomes are assessed at baseline, 6, 18, 30 and 52 weeks. All participants will be subsequently followed for 3 years by telephone interview to record institutionalization. **DISCUSSION:** There is considerable debate about the clinical and cost effectiveness of anti-dementia drugs. DOMINO-AD seeks to provide clear evidence on the best treatment strategies for those managing patients at a particularly important clinical transition point. **TRIAL REGISTRATION:** Current controlled trials ISRCTN49545035.

Sadowsky, C. H., A. Dengiz, et al. (2009). "Switching from donepezil tablets to rivastigmine transdermal patch in Alzheimer's disease." [American Journal of Alzheimer's Disease & Other Dementias](#) **24**(3): 267-75.

OBJECTIVE: Evaluate safety and tolerability of switching from donepezil to rivastigmine transdermal patch in patients with mild to moderate Alzheimer's disease. **METHODS:** Prospective, parallel-group, open-label study to evaluate immediate or delayed switch from 5-10 mg/day donepezil to 4.6 mg/24 h rivastigmine following a 4-week treatment period. **RESULTS:** Rates of discontinuation due to any reason or adverse

events were similar between groups. Incidences of gastrointestinal adverse events were 3.8% in the immediate and 0.8% in the delayed switch group. No patients discontinued secondary to nausea and vomiting. Discontinuations due to application site reactions were low (2.3%). Asymptomatic bradycardia was more common following the immediate switch (2.3% vs 0%); however, these patients had coexisting cardiac comorbidities. **CONCLUSION:** Both switch strategies were safe and well tolerated. The majority of patients may be able to switch directly to rivastigmine patches without a withdrawal period. Appropriate clinical judgment should be used for patients with existing bradycardia or receiving beta blockers.

Wilkinson, D., R. Schindler, et al. (2009). "Effectiveness of donepezil in reducing clinical worsening in patients with mild-to-moderate alzheimer's disease." Dementia & Geriatric Cognitive Disorders **28**(3): 244-51.

BACKGROUND: Therapeutic endpoints based on reduced clinical worsening represent clinically relevant and realistic goals for patients suffering from progressive neurodegenerative disorders such as Alzheimer's disease (AD). **METHODS:** Data from 906 patients (388 receiving placebo; 518 receiving donepezil) with mild-to-moderate AD [Mini-Mental State Examination (MMSE) score 10-27] were pooled from 3 randomized, double-blind placebo-controlled studies. Clinical worsening was defined as decline in (1) cognition (MMSE), (2) cognition and global ratings (Clinician's Interview-Based Impression of Change plus Caregiver Input/Gottfries-Brane-Steen scale) or (3) cognition, global ratings and function (various functional measures). **RESULTS:** At week 24, lower percentages of donepezil-treated patients than placebo patients met the criteria for clinical worsening, regardless of the definition. The odds of declining were significantly reduced for donepezil-treated versus placebo patients ($p < 0.0001$; all definitions). Among patients meeting criteria for clinical worsening, mean declines in MMSE scores were greater for placebo than donepezil-treated patients. **CONCLUSION:** In this population, donepezil treatment was associated with reduced odds of clinical worsening of AD symptoms. Moreover, patients worsening on donepezil were likely to experience less cognitive decline than expected if left untreated. This suggests that AD patients showing clinical worsening on donepezil may still derive benefits compared with placebo/untreated patients. Copyright 2009 S. Karger AG, Basel.