TITLE: Memantine in Combination with Cholinesterase Inhibitors for Alzheimer’s Disease: Clinical Effectiveness and Safety

DATE: 17 May 2012

RESEARCH QUESTIONS

1. What is the clinical effectiveness of using memantine in combination with a cholinesterase inhibitor for the treatment of Alzheimer’s disease?

2. What is the clinical evidence on the safety of using memantine in combination with a cholinesterase inhibitor for the treatment of Alzheimer’s disease?

KEY MESSAGE

Seven studies were identified regarding the clinical effectiveness and safety of using memantine in combination with a cholinesterase inhibitor for the treatment of Alzheimer’s disease.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated lists of major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between October 1, 2008 and May 4, 2012. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.
RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, and non-randomized studies.

One systematic review, two randomized controlled trials, and four non-randomized studies were identified regarding the clinical effectiveness and safety of memantine in combination with a cholinesterase inhibitor for the treatment of Alzheimer’s disease. No relevant health technology assessments were identified. Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

Seven studies\(^1\)\(^-\)\(^7\) were identified that examined the clinical effectiveness or safety of the use of memantine in combination with cholinesterase inhibitors for Alzheimer’s disease. Clinical effectiveness results were mixed among the included studies.\(^1\)\(^-\)\(^5\) No major safety or tolerability issues associated with memantine were identified in the included studies. The most commonly reported adverse events were confusion, headache, nausea, vomiting, and dizziness.\(^1\)\(^,\)\(^6\) More details of these studies are provided in Table 1.

<table>
<thead>
<tr>
<th>Author, Year, Study Type</th>
<th>Intervention</th>
<th>Severity of Alzheimer’s Disease</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Swedish Council on Technology Assessment in Health Care (2008)(^1)</td>
<td>donepezil + memantine or donepezil + placebo</td>
<td>moderate to severe</td>
<td>A small but significant benefit was observed in the memantine group on global functioning, cognitive function, ADL function, and BPSD. Confusion and headache were more common in the memantine group.</td>
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<tr>
<td>Choi et al. (2011)(^2)</td>
<td>rivastigmine patch + memantine or rivastigmine patch alone</td>
<td>mild to moderate</td>
<td>Changes in efficacy measures were mostly similar between groups. At the end of treatment, the Korean version of the CMAI scores favored rivastigmine monotherapy. Incidence of AEs and discontinuation due to AEs were similar between treatment groups.</td>
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<tr>
<td>Farlow et al. (2010)(^3)</td>
<td>rivastigmine patch + memantine or rivastigmine patch alone</td>
<td>mild to moderate</td>
<td>ADL scores were lowered in both groups but were significant in patients in the memantine group. Changes in cognitive and global functioning were similar between groups. Incidence of AEs and SAEs was slightly higher in the memantine group but the difference was not statistically significant. Incidence of GI-related AEs was low in both groups.</td>
</tr>
<tr>
<td>Howard et al.</td>
<td>no treatment,</td>
<td>moderate to severe</td>
<td>The efficacy of memantine and donezepil did</td>
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</table>
### Table 1: Summary of Included Studies

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Weiner et al. (2011)⁵ NRS</td>
<td>cholinesterase inhibitor + open label memantine</td>
<td>not specified</td>
<td>Treatment with memantine was associated with significantly slower right hippocampal atrophy, superior performance on the Boston Naming Test and the Trail Making Test, but more errors on the California Verbal Learning Test. No major safety or tolerability issues were reported to be associated with memantine.</td>
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<tr>
<td>Olin et al. (2010)⁶ NRS</td>
<td>rivastigmine + open-label memantine</td>
<td>moderate</td>
<td>Incidence of nausea and vomiting was lower in the combination therapy group as compared to the recorded incidence with rivastigmine alone. The most common AEs were nausea, vomiting, and dizziness.</td>
</tr>
<tr>
<td>Lopez et al. (2009)⁷ NRS</td>
<td>cholinesterase inhibitors + memantine</td>
<td>not specified</td>
<td>Patients receiving cholinesterase inhibitors had a significant delay in nursing home admission when compared to patients who had never received cholinesterase inhibitors. Patients receiving combination therapy with memantine showed an even more significant delay in nursing home admission.</td>
</tr>
</tbody>
</table>

ADL = activity of daily living; AE = adverse event; BALDS = Bristol Activities of Daily Living Scale; BPSD = Behavioral and Psychological Symptoms of Dementia; CMAI = Cohen Mansfield Agitation Inventory; GI = gastrointestinal; NRS = non-randomized study; RCT = randomized controlled trial; SAE = serious adverse event; SR = systematic review; SMMSE = Standardized Mini-Mental State Examination
REFERENCES SUMMARIZED

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses

   See: Combined memantine and donepezil treatment, page 315

Randomized Controlled Trials

   PubMed: PM21561398

   PubMed: PM19929593

Non-Randomized Studies

   PubMed: PM22397651

   PubMed: PM21646051

   PubMed: PM19670390

   Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2823571
   PubMed: PM19204022
APPENDIX – FURTHER INFORMATION:

Guidelines and Consensus Statements


Review Articles


Additional References


