

Literature Scan: Alzheimer's Drugs

Date of Review: September 2015

PDL Class: Alzheimer's disease (AD) Drugs

Date of Last Review: September 2014

Literature Search: July 2015

Current Status of PDL Class:

See **Appendix 1**.

Conclusions:

- While acetylcholinesterase inhibitors and memantine have demonstrated modest but persistent improvements in cognition, activities of daily living, and behavior, none of the approved medications have been shown to stop or reverse the underlying process or any impact on important clinical outcomes such as mortality, disability, or institutionalization in patients with moderate to severe Alzheimer's disease (AD).
- There is low quality evidence that cholinesterase inhibitors can reduce neuropsychiatric symptoms in patients with AD but there is no effect with memantine.¹
- There was moderate quality evidence that rivastigmine is associated with better outcomes for cognitive function, activities of daily living (SMD 0.20; 95% CI 0.13 to 0.27), and deterioration (OR 0.68; 95% CI 0.58 to 0.80) compared to placebo. However, these effects were small and of uncertain clinical significance. There is moderate level evidence of no difference in behavioral change or impact on caregivers with rivastigmine compared to placebo.²
- There is moderate quality evidence of a small but significant benefit of combination therapy with cholinesterase inhibitors and memantine on behavior and cognitive functions, with no difference in activities of daily living or serious adverse events.³
- There is moderate quality evidence that the new fixed-dose combination of memantine ER and donepezil (Namzaric[®]) is bioequivalent to co-administered memantine ER and donepezil but no clinical efficacy data are available. Generic formulations of both individual products are currently available.

Recommendations:

- There is no new comparative efficacy or safety data resulting in changes to the current PDL; maintain Namzaric[®] (memantine ER/donepezil) as non-preferred.
- No further changes recommended to the PDL at this time.

Previous Conclusions and Recommendations:

- There remains insufficient evidence for the treatment of AD beyond 6 months and on important clinical outcomes such as mortality, disability, or institutionalization.
- There is moderate quality evidence that cholinesterase inhibitors can alleviate AD symptoms and there is no strong evidence that one agent is more efficacious or safer than others.

- There is low quality and conflicting evidence that the combination of memantine with cholinesterase inhibitors may provide a small improvement in cognition and behavior. However, the magnitude of effect is low and the clinical significance is unknown. There is no evidence of an improvement in function with the combination compared to monotherapy.
- Make Aricept 23 mg non-preferred due to an increased risk of adverse drug events.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A recent systematic review from the Cochrane Collaboration was completed to determine the clinical efficacy and safety of rivastigmine for patients with Alzheimer's dementia.² A total of 7 randomized, double-blind trials of 12 weeks or more were included in the review (n=3450). The main comparison was rivastigmine 6 to 12 mg/day orally or 9.5 mg/day transdermally to placebo. All of the studies included patients with mild to moderate disease with a mean age of about 75 years. There was moderate level evidence that rivastigmine was associated with better outcomes for cognitive function measured with the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score (mean difference [MD] -1.79; 95% CI -2.21 to -1.37) and the mini mental state examination (MMSE) score (MD 0.74; 95% CI 0.52 to 0.97), activities of daily living (SMD 0.20; 95% CI 0.13 to 0.27), and deterioration (OR 0.68; 95% CI 0.58 to 0.80) compared to placebo. However, these effects were small and of uncertain clinical significance. A standard mean difference of 0.2 in the activities of daily living scale is considered a small effect size, as well as the differences in the cognitive function scores. There were no differences found in behavioral change with rivastigmine compared to placebo (SMD -0.04; 95% CI -0.14 to 0.06). There was no difference in impact on caregivers or in the clinician's global assessment. Patients taking rivastigmine were more likely to withdraw from trials (OR 2.01; 95% CI 1.71 to 2.37) or experience an adverse event (OR 2.16; 95% CI 1.82 to 2.57), but no significant difference in withdrawals due to adverse events (OR 1.20; 95% CI 0.68 to 2.13) was found. There was a significant difference between oral rivastigmine and the patch, favoring the patch, in total adverse events (OR 0.59; 95% CI 0.43 to 0.82). There is insufficient data beyond 12 months on the long term treatment outcomes of AD.

Due to recent conflicting evidence for the efficacy and safety of pharmacological agents used for the treatment of neuropsychiatric symptoms in patients with AD, a systematic review and meta-analysis of RCTs was done to compare agents on Neuropsychiatric Inventory (NPI) and safety outcomes in patients with AD and neuropsychiatric symptoms.¹ The NPI is a validated inventory used to assess neuropsychiatric symptoms and behavioral disturbances in patients with AD.⁴ Thirty two studies were included in the review; 8 evaluating memantine and 15 with cholinesterase inhibitors. The remaining trials included atypical antipsychotics and antidepressants. All of the included trials were randomized, double-blinded, and placebo-controlled. Meta-analysis data demonstrated a significant benefit on neuropsychiatric symptoms with cholinesterase inhibitors compared to placebo (standard mean difference [SMD] -0.12; 95% CI -0.23 to -

0.02) and no difference between memantine and placebo (SMD -0.12; 95% CI -0.27 to 0.03). In the donepezil subgroup, there were no significant effects seen on neuropsychiatric symptoms. There were no significant differences in the number of dropouts for any reason between any treatment group and placebo but a significantly higher number of withdrawals due to adverse events in the cholinesterase inhibitor treatment group compared to placebo (RR 1.64; 95% CI 1.12 to 2.42).

A good quality systematic review and meta-analysis by Tan, et al. evaluated the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease.⁵ A systematic literature search through 2013 for double-blind, placebo-controlled RCTs identified 23 trials that met inclusion criteria. Trials were assessed for quality using the GRADE tool and demonstrated poor reporting of allocation concealment and randomization methods. Of these, 10 donepezil, 4 galantamine, 3 rivastigmine, and 6 memantine trials were included. There was a statistically significant benefit in cognitive outcomes on the ADAS-cog subscale with all agents compared to placebo, with a pooled weighted MD between intervention and placebo ranging from -1.29 points (95% CI -2.30 to -0.28) in the memantine trials to -3.20 points (95% CI -3.28 to -3.12) in the galantamine group. However, both memantine and galantamine had no effect on the Clinicians' Global Impression of Change scale. Overall, there was no significant difference on behavioral outcomes.

New Guidelines:

The European Federation of Neurological Societies (EFNS) and European Neurological Society (ENS) developed guidelines for the concomitant use of cholinesterase inhibitors and memantine in AD.³ Results of their meta-analysis showed moderate level evidence of significant overall benefits of combination therapy over cholinesterase inhibitor therapy alone for behavior (SMD -0.19; 95% CI -0.31 to -0.07), cognitive function (SMD -0.27; 95% CI -0.37 to -0.17) and global clinical impression (SMD -0.20; 95% CI -0.31 to -0.09). There was low level evidence of no overall differences between combination and monotherapy in activities of daily living (SMD -0.08; 95% CI -0.18; 95% CI 0.02). Overall, the guideline panel gave a weak recommendation for the combination therapy in patients with moderate to severe AD.

New FDA Drug Approvals:

In December 2014, the FDA approved a fixed-dose combination of extended-release (ER) memantine 28 mg, an NMDA-receptor antagonist, and donepezil 10 mg, an acetylcholinesterase inhibitor for the treatment of moderate to severe Alzheimer's type dementia in patients previously stabilized on both drugs.^{6,7} Generic formulations of both individual products are currently available.⁸ Previous trials of combination therapy with both agents have had conflicting results. Some have shown an improvement in measures of cognition and function compared to treatment with an acetylcholinesterase inhibitor alone, while others have not.

No efficacy data were required for approval of the combination product. Two single-dose, randomized, open-label, cross over studies in 74 healthy volunteers 18-45 years of age evaluated the combination capsule formulation for bioequivalence with co-administered memantine ER and donepezil.⁹ Both studies demonstrated that the combination capsule was bioequivalent. The most common adverse events were nausea, dizziness, vomiting, headache, and abdominal discomfort.

New FDA Safety Alerts:

None Identified.

References:

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2. Birks JS, Grimley Evans J. Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev*. 2015;4:CD001191. doi:10.1002/14651858.CD001191.pub3.
3. Schmidt R, Hofer E, Bouwman FH, et al. EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease. *Eur J Neurol*. 2015;22(6):889-898. doi:10.1111/ene.12707.
4. Trzepacz PT, Saykin A, Yu P, et al. Subscale validation of the neuropsychiatric inventory questionnaire: comparison of Alzheimer's disease neuroimaging initiative and national Alzheimer's coordinating center cohorts. *Am J Geriatr Psychiatry*. 2013;21(7):607-622. doi:10.1016/j.jagp.2012.10.027.
5. Tan C-C, Yu J-T, Wang H-F, et al. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. [Review]. *Journal of Alzheimer*. 2014;41(2):615-631. doi:10.3233/JAD-132690.
6. FDA Center for Drug Evaluation and Research. Application Number: 206439Orig1s000. Namzaric Summary Review. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#applist.
7. Namzaric Prescribing Information. Forest Pharmaceuticals, In. 12/2014.
8. Namzaric--a combination of 2 old drugs for Alzheimer's disease. *Med Lett Drugs Ther*. 2015;57(1473):105-106.
9. Boinpally R, Chen L, Zukin SR, McClure N, Hofbauer RK, Periclou A. A Novel Once-Daily Fixed-Dose Combination of Memantine Extended Release and Donepezil for the Treatment of Moderate to Severe Alzheimer's Disease: Two Phase I Studies in Healthy Volunteers. *Clin Drug Investig*. 2015;35(7):427-435. doi:10.1007/s40261-015-0296-4.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND NAME	GENERIC NAME	PDL
ORAL	CAP24H PEL	GALANTAMINE HBR	GALANTAMINE HBR	Y
ORAL	CAP24H PEL	RAZADYNE ER	GALANTAMINE HBR	Y
ORAL	SOLUTION	NAMENDA	MEMANTINE HCL	Y
ORAL	TAB DS PK	NAMENDA	MEMANTINE HCL	Y
ORAL	TABLET	ARICEPT	DONEPEZIL HCL	Y
ORAL	TABLET	DONEPEZIL HCL	DONEPEZIL HCL	Y
ORAL	TABLET	GALANTAMINE HBR	GALANTAMINE HBR	Y
ORAL	TABLET	NAMENDA	MEMANTINE HCL	Y
ORAL	TABLET	RAZADYNE	GALANTAMINE HBR	Y
TRANSDERM	PATCH TD24	EXELON	RIVASTIGMINE	Y
ORAL	CAP SPR 24	NAMENDA XR	MEMANTINE HCL	N
ORAL	CAP24 DSPK	NAMENDA XR	MEMANTINE HCL	N
ORAL	CAPSULE	EXELON	RIVASTIGMINE TARTRATE	N
ORAL	CAPSULE	RIVASTIGMINE	RIVASTIGMINE TARTRATE	N
ORAL	SOLUTION	GALANTAMINE HYDROBROMIDE	GALANTAMINE HBR	N
ORAL	TAB RAPDIS	DONEPEZIL HCL ODT	DONEPEZIL HCL	N
ORAL	TABLET	ARICEPT	DONEPEZIL HCL	N
ORAL	TABLET	DONEPEZIL HCL	DONEPEZIL HCL	N
ORAL	TABLET	DONEPEZIL HCL	DONEPEZIL HCL	N

Appendix 2: New Clinical Trials

Thirty potentially relevant clinical trials were evaluated from the literature search. After further review, all trials were excluded due to irrelevant outcomes, comparisons, and study design.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2014

1 donepezil.mp 2519

2 galantamine.mp or Galantamine/ 1269

3 memantine.mp or Memantine/ 2159

4 rivastigmine.mp 1271

5 alzheimer's disease.mp or Alzheimer Disease/ 74868

6 1 or 2 or 3 or 4 5727

7 5 and 6 3083

Limit 7 to (English language and humans and yr="2014 – Current" and (controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)) 30

Appendix 4: Prior Authorization Criteria for Donepezil 23 mg only

Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes

Goal(s):

- The purpose of this prior authorization policy is to ensure that non-preferred drugs are used appropriately for an OHP-funded condition.

Initiative:

- PDL: Preferred Drug List

Length of Authorization:

Up to 6 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at <http://www.orpdl.org/drugs/>

Note:

A complete list of PDL classes is available at <http://www.orpdl.org/drugs/>

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an FDA approved indication?	Yes: Go to #3	No: Pass to RPh. Deny for medical appropriateness
3. Is this an OHP-funded diagnosis?	Yes: Go to #4.	No: Go to #5.

Approval Criteria

4. Will the prescriber consider a change to a preferred product?

Message:

Preferred products do not generally require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.

Yes: Inform provider of covered alternatives in class.

No: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.

5. RPH only: All other indications need to be evaluated as to whether they are a funded diagnosis on the OHP prioritized list.

- If funded and clinic provides supporting literature: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.
- If not funded: Deny; not funded by the OHP.

P&T / DUR Review: 7/15 (RC), 9/10; 9/09; 5/09
Implementation: TBD; 1/1/11, 9/16/10