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Month/Year of Review: September 2013
PDL Classes: Alzheimer's Agents

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Current Status of PDL Class:

- Preferred Agents: DONEPEZIL TABLET, GALANTAMINE TABLET, MEMANTINE (NAMENDA®)
- Non-Preferred Agents: RIVASTIGMINE (EXELON PATCH®), DONEPEZIL ODT (ARICEPT ODT®), MEMANTINE XR (NAMENDA XR®)

Previous Conclusions and Recommendation:

- There is insufficient evidence that any one of the Alzheimer's disease (AD) drugs is superior to the others in terms of efficacy or effectiveness and there is no evidence that any drug prevents the progression of disability or delays institutionalization.
- Make Aricept 23 mg non-preferred due to increased adverse drug events.
- Add ProDUR edits to prevent duplicate therapy.

PA Criteria: Prior authorization criteria ensure that patients have an OHP covered diagnosis.

Conclusions and Recommendations:

- There remains insufficient evidence for the treatment of AD beyond 6 months and on important clinical outcomes such as mortality and 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.
- No further review or research needed at this time. Evaluate comparative costs in executive session.
- Based on costs comparisons, make rivastigmine (Exelon Patch) and galantamine XR preferred agents on the PDL.

Methods:

A Medline OVID search was conducted with the following search terms: Alzheimer disease, dementia, donepezil, galantamine, memantine, rivastigmine, Namenda, Aricept, and Exelon. The search was limited to English language articles of controlled trials conducted on humans published from February 2012 to August week one 2013. The Cochrane Collection, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ), Dynamed, and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

1. National Institute for Clinical Excellence (NICE) guidance does not recommend the use of memantine in combination with cholinesterase inhibitors due to a lack of evidence of additional clinical efficacy compared with monotherapy. A recent systematic review by Farrimond et al., compared the efficacy of cholinesterase inhibitor monotherapy with combination memantine and cholinesterase inhibitor in patients with moderate-to-severe AD

and examined the impact of including unpublished data in the results.[1] A literature search through May 2011 was conducted and randomized, double blind, placebo controlled trials were included. The outcomes of interest were clinical global impression, cognitive function, functional performance in activities of daily living (ADL) and mood and behavioral disturbance.

Five trials were identified and three were included in the meta-analysis. The risk of bias was judged to be low based on the Cochrane Collaboration assessment. The meta-analysis demonstrated a small improvement in clinical global impression (standardized mean difference [SMD] -0.20 95% CI -0.32 to -0.09; I^2=9%), cognition (SMD -0.25 95% CI -0.36 to -0.14; I^2=0%), but no significant difference in functioning (SMD -0.04 95% CI -0.21 to 0.13; I^2=58%) with the combination of memantine and a cholinesterase inhibitor compared to monotherapy, respectively. The authors concluded that there may be a small benefit of adding memantine to cholinersterase inhibitors; however the clinical relevance remains unknown. [1]

2. A systematic review and economic model from the Health Technology Assessment program reviewed the clinical effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of AD.[2] The literature review found trials of a maximum of 6 months and a lack of evidence from trials on key outcomes, such as mortality and institutionalization. Overall, the quality of the trials was moderate to poor. The authors concluded that the evidence continues to suggest clinical benefit from cholinesterase inhibitors in alleviating symptoms, although the magnitude of effect remains controversial. The evidence for the effectiveness of memantine remains weaker. In addition, for the treatment of mild to moderate AD, a sensitivity analysis suggested that donepezil is the most cost effective cholinesterase inhibitor.

Guidelines:

The Canadian Neurological Society:

A 2012 update on the guidelines for AD were completed using the AGREE methodology.[3] Specific recommendations on the treatment of AD are as followed:

- Cholinesterase inhibitors are recommended as a treatment option for AD with cerebrovascular disease (Grade 1B).
- All cholinesterase inhibitors have demonstrated efficacy for mild to severe AD (Grade 1A).
- Direct comparisons do not suggest differences between cholinesterase inhibitors (Grade 2B). Selection should be based on adverse effect profile, ease of use, and differences in pharmacokinetics and mechanism of action.
- Combination therapy of a cholinesterase inhibitor and memantine is rational and appears to be safe, but there is insufficient evidence to recommend for or against this combination (Grade 2B).
- When a decision has been made to discontinue therapy because of a perceived lack of effectiveness, it is suggested that the dose be tapered before stopping the agent and the patient be monitored over the next 1-3 months for evidence of an observable decline. If this occurs, it is suggested that consideration be given to reinstating therapy (Grade 2C).

New drugs:

None

New Formulations/Indications:

None

New FDA safety alerts:

None

New Trials (Appendix 2):

A total of 121 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, five relevant clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Study	Comparison	Population	Primary Outcome	Results
Howard et al.[4] 2012	Continue donepezil monotherapy vs. Donepezil + memantine (n=295)	Patients who had been treated with donepezil for at least 3 months with moderate-severe AD.	Cognitive function (SMMSE scores) and activities of daily living (BADLS scores)	There was no significant benefit of adding memantine to donepezil, with respect to scores on the SMMSE (0.8 points higher with memantine than with placebo; 95% CI, −0.1 to 1.6; P = 0.07) or with respect to scores on the BADLS (0.5 points lower with memantine than with placebo; 95% CI, −2.2 to 1.2; P = 0.57). Patients assigned to continue donepezil, as compared to discontinuing donepezil, had improved cognition scores
Fox et al.[5] 2012	Memantine 10 mg vs. placebo (n=149)	AD with clinically significant agitation	Cohen-Mansfield Agitation Inventory (CMAI) at 6 weeks	No significant difference between memantine and placebo of CMAI scores at 6 weeks (mean difference -3.0, 95% CI -8.3 to 2.2; p=0.26).
Farlow et al.[6] 2013	Rivastigmine patch 13.3 mg/24 hr vs. rivastigmine patch 4.6 mg/24 hr	Patients with severe AD (n=716)	Cognition, as measured by the severe impairment battery (SIB) score and function (activities of daily living scale) at week 24	The 13.3 mg/ 24 h patch was significantly superior to 4.6 mg/24 h patch on cognition (SIB) and function (ADCS-ADL-SIV) at Week 24 (P < 0.0001 and P = 0.025).
Doody et al.[7] 2013	Semagacestat 100mg vs. semagacestat 140 mg vs. placebo	Patients with mild to moderate AD (n=1537)	Changes in cognition from baseline to week 76 (ADAS-cog scale) and changes in functioning (ADCS-ADL scale)	The trial was terminated early. Cognition worsened in all three groups (mean change, 6.4 points placebo, 7.5 points 100mg, 7.8 points 140mg; p=0.15 and p=0.07 vs. placebo). Functioning also worsened. Patients on semagacestat lost more weight and had more infections, treatment discontinuations due to adverse events, and serious adverse events (P<0.001 for all comparisons).

Tariot et al.[8] 2012	1 year Open-label safety and tolerability extension trial of donepezil 23mg/day	Adults with moderate to severe AD previously on donepezil 10mg who were then started on 23 mg/day	Adverse events	74.7% of patients reported at least one AE, of which 47.5% were considered related to the study drug. Most common were weight decrease (11.2%), fall, agitation, UTI, and aggression. Patients had higher rates of AE's during the first 4 weeks of the study, then in the extension phase. Serious AE occurred in 15.1% of patients.

References:

1. Farrimond LE, Roberts E, McShane R. Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review. *BMJ Open*. 2012;2(3). doi:10.1136/bmjopen-2012-000917.

2. Bond M, Rogers G, Peters J, et al. The Effectiveness and Cost-Effectiveness of Donepezil, Galantamine, Rivastigmine and Memantine for the Treatment of Alzheimer's Disease (Review of Technology Appraisal No. 111): A Systematic Review and Economic Model. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0047569/. Accessed August 28, 2013.

3. Gauthier S, Patterson C, Chertkow H, et al. 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia. *Can J Neurol Sci*. 2012;39(6 Suppl 5):S1–8.

4. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366(10):893–903. doi:10.1056/NEJMoa1106668.

5. Fox C, Crugel M, Maidment I, et al. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. *PLoS ONE*. 2012;7(5):e35185. doi:10.1371/journal.pone.0035185.

6. Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M. A 24-Week, Randomized, Controlled Trial of Rivastigmine Patch 13.3 mg/24 h Versus 4.6 mg/24 h in Severe Alzheimer's Dementia. *CNS Neurosci Ther*. 2013. doi:10.1111/cns.12158.

7. Doody RS, Raman R, Farlow M, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med*. 2013;369(4):341–350. doi:10.1056/NEJMoa1210951.

8. Tariot P, Salloway S, Yardley J, Mackell J, Moline M. Long-term safety and tolerability of donepezil 23 mg in patients with moderate to severe Alzheimer's disease. *BMC Res Notes*. 2012;5:283. doi:10.1186/1756-0500-5-283.

Abstract 1: Abstracts of Randomized Controlled Trials

Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366(10):893–903

BACKGROUND: Clinical trials have shown the benefits of cholinesterase inhibitors for the treatment of mild-to-moderate Alzheimer's disease. It is not known whether treatment benefits continue after the progression to moderate-to-severe disease.

METHODS: We assigned 295 community-dwelling patients who had been treated with donepezil for at least 3 months and who had moderate or severe Alzheimer's disease (a score of 5 to 13 on the Standardized Mini-Mental State Examination [SMMSE, on which scores range from 0 to 30, with higher scores indicating better cognitive function]) to continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine. Patients received the study treatment for 52 weeks. The coprimary outcomes were scores on the SMMSE and on the Bristol Activities of Daily Living Scale (BADLS, on which scores range from 0 to 60, with higher scores indicating greater impairment). The minimum clinically important differences were 1.4 points on the SMMSE and 3.5 points on the BADLS.

RESULTS: Patients assigned to continue donepezil, as compared with those assigned to discontinue donepezil, had a score on the SMMSE that was higher by an average of 1.9 points (95% confidence interval [CI], 1.3 to 2.5) and a score on the BADLS that was lower (indicating less impairment) by 3.0 points (95% CI, 1.8 to 4.3) (P<0.001 for both comparisons). Patients assigned to receive memantine, as compared with those assigned to receive memantine placebo, had a score on the SMMSE that was an average of 1.2 points higher (95% CI, 0.6 to 1.8; P<0.001) and a score on the BADLS that was 1.5 points lower (95% CI, 0.3 to 2.8; P=0.02). The efficacy of donepezil and of memantine did not differ significantly in the presence or absence of the other. There were no significant benefits of the combination of donepezil and memantine over donepezil alone.

CONCLUSIONS: In patients with moderate or severe Alzheimer's disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months. (Funded by the U.K. Medical Research Council and the U.K. Alzheimer's Society; Current Controlled Trials number, ISRCTN49545035.).

Fox C, Crugel M, Maidment I, et al. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. *PLoS ONE*. 2012;7(5):e35185

BACKGROUND: Agitation in Alzheimer's disease (AD) is common and associated with poor patient life-quality and carer distress. The best evidence-based pharmacological treatments are antipsychotics which have limited benefits with increased morbidity and mortality. There are no memantine trials in clinically significant agitation but post-hoc analyses in other populations found reduced agitation. We tested the primary hypothesis, memantine is superior to placebo for clinically significant agitation, in patients with moderate-to-severe AD.
METHODS AND FINDINGS: We recruited 153 participants with AD and clinically significant agitation from care-homes or hospitals for a double-blind randomised-controlled trial and 149 people started the trial of memantine versus placebo. The primary outcome was 6 weeks mixed model autoregressive analysis of Cohen-Mansfield Agitation Inventory (CMAI). Secondary outcomes were: 12 weeks CMAI; 6 and 12 weeks Neuropsychiatric symptoms (NPI), Clinical Global Impression Change (CGI-C), Standardised Mini Mental State Examination, Severe Impairment Battery. Using a mixed effects model we found no significant differences in the primary outcome, 6 weeks CMAI, between memantine and placebo (memantine lower -3.0; -8.3 to 2.2, p = 0.26); or 12 weeks CMAI; or CGI-C or adverse events at 6 or 12 weeks. NPI mean difference favoured memantine at weeks 6 (-6.9; -12.2 to -1.6; p = 0.012) and 12 (-9.6; -15.0 to -4.3 p = 0.0005). Memantine was significantly better than placebo for cognition. The main study limitation is that it still remains to be determined whether memantine has a role in milder agitation in AD.
CONCLUSIONS: Memantine did not improve significant agitation in people with in moderate-to-severe AD. Future studies are urgently needed to test other pharmacological candidates in this group and memantine for neuropsychiatric symptoms.

Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M. A 24-Week, Randomized, Controlled Trial of Rivastigmine Patch 13.3 mg/24 h Versus 4.6 mg/24 h in Severe Alzheimer's Dementia. *CNS Neurosci Ther*. 2013.

AIMS: The 24-week, prospective, randomized, double-blind ACTION study investigated the efficacy, safety, and tolerability of 13.3 versus 4.6 mg/24 h rivastigmine patch in patients with severe Alzheimer's disease (AD).

METHODS: Patients had probable AD and Mini-Mental State Examination scores ≥3-≤12. Primary outcome measures were as follows: Severe Impairment Battery (SIB) and AD Cooperative Study-Activities of Daily Living scale-Severe Impairment Version (ADCS-ADL-SIV). Secondary outcomes were as follows: ADCS-Clinical Global Impression of Change (ADCS-CGIC), 12-item Neuropsychiatric Inventory (NPI-12), and safety/tolerability.

RESULTS: Of 1014 patients screened, 716 were randomized to 13.3 mg/24 h (N = 356) or 4.6 mg/24 h (N = 360) patch. Baseline characteristics/demographics were comparable. Completion rates were as follows: 64.3% (N = 229) with 13.3 mg/24 h and 65.0% (N = 234) with 4.6 mg/24 h patch. The 13.3 mg/24 h patch was significantly superior to 4.6 mg/24 h patch on cognition (SIB) and function (ADCS-ADL-SIV) at Week 16 ($P < 0.0001$ and $P = 0.049$, respectively) and 24 (primary endpoint; $P < 0.0001$ and $P = 0.025$). Significant between-group differences (Week 24) were observed on the ADCS-CGIC ($P = 0.0023$), not NPI-12 ($P = 0.1437$). A similar proportion of the 13.3 mg/24 h and 4.6 mg/24 h patch groups reported adverse events (AEs; 74.6% and 73.3%, respectively) and serious AEs (14.9% and 13.6%).

CONCLUSIONS: The 13.3 mg/24 h patch demonstrated superior efficacy to 4.6 mg/24 h patch on SIB and ADCS-ADL-SIV, without marked increase in AEs, suggesting higher-dose patch has a favorable benefit-to-risk profile in severe AD.

Doody RS, Raman R, Farlow M, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med*. 2013;369(4):341–350.

BACKGROUND: Alzheimer's disease is characterized by the presence of cortical amyloid-beta (Aβ) protein plaques, which result from the sequential action of β-secretase and γ-secretase on amyloid precursor protein. Semagacestat is a small-molecule γ-secretase inhibitor that was developed as a potential treatment for Alzheimer's disease.

METHODS: We conducted a double-blind, placebo-controlled trial in which 1537 patients with probable Alzheimer's disease underwent randomization to receive 100 mg of semagacestat, 140 mg of semagacestat, or placebo daily. Changes in cognition from baseline to week 76 were assessed with the use of the cognitive subscale of the Alzheimer's Disease Assessment Scale for cognition (ADAS-cog), on which scores range from 0 to 70 and higher scores indicate greater cognitive impairment, and changes in functioning were assessed with the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale, on which scores range from 0 to 78 and higher scores indicate better functioning. A mixed-model repeated-measures analysis was used.

RESULTS: The trial was terminated before completion on the basis of a recommendation by the data and safety monitoring board. At termination, there were 189 patients in the group receiving placebo, 153 patients in the group receiving 100 mg of semagacestat, and 121 patients in the group receiving 140 mg of semagacestat. The ADAS-cog scores worsened in all three groups (mean change, 6.4 points in the placebo group, 7.5 points in the group receiving 100 mg of the study drug, and 7.8 points in the group receiving 140 mg; $P=0.15$ and $P=0.07$, respectively, for the comparison with placebo). The ADCS-ADL scores also worsened in all groups (mean change at week 76, -9.0 points in the placebo group, -10.5 points in the 100-mg group, and -12.6 points in the 140-mg group; $P=0.14$ and $P<0.001$, respectively, for the comparison with placebo). Patients treated with semagacestat lost more weight and had more skin cancers and infections, treatment discontinuations due to adverse events, and serious adverse events ($P<0.001$ for all comparisons with placebo). Laboratory abnormalities included reduced levels of lymphocytes, T cells, immunoglobulins, albumin, total protein, and uric acid and elevated levels of eosinophils, monocytes, and cholesterol; the urine pH was also elevated.

CONCLUSIONS: As compared with placebo, semagacestat did not improve cognitive status, and patients receiving the higher dose had significant worsening of functional ability. Semagacestat was associated with more adverse events, including skin cancers and infections. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT00594568.)

Tariot P, Salloway S, Yardley J, Mackell J, Moline M. Long-term safety and tolerability of donepezil 23 mg in patients with moderate to severe Alzheimer's disease. *BMC Res Notes*. 2012;5:283. doi:10.1186/1756-0500-5-283

BACKGROUND: Donepezil (23 mg/day) is approved by the US Food and Drug Administration for the treatment of patients with moderate to severe Alzheimer's disease (AD). Approval was based on results from a 24-week, randomized, double-blind study of patients who were stable on donepezil 10 mg/day and randomized 2:1 to either increase their donepezil dose to 23 mg/day or continue taking 10 mg/day. The objective of this study was to assess the long-term safety and tolerability of donepezil 23 mg/day in patients with moderate to severe AD.

METHODS: Patients who completed the double-blind study and were eligible could enroll into a 12-month extension study of open-label donepezil 23 mg/day. Clinic visits took place at open-label baseline and at months 3, 6, 9, and 12. Safety analyses comprised examination of the incidence,

severity, and timing of treatment-emergent adverse events (AEs); changes in weight, electrocardiogram, vital signs, and laboratory parameters; and discontinuation due to AEs.

RESULTS: 915 double-blind study completers were enrolled in the open-label extension study and 902 comprised the safety population. Mean treatment duration in this study was 10.3 ± 3.5 months. In total, 674 patients (74.7%) reported at least one AE; in 320 of these patients (47.5%) at least one AE was considered to be possibly or probably study drug related. The majority of patients reporting AEs (81.9%) had AEs of mild or moderate severity. There were 268 patients (29.7%) who discontinued early, of which 123 (13.6%) were due to AEs.Patients increasing donepezil dose from 10 mg/day in the double-blind study to 23 mg/day in the extension study had slightly higher rates of AEs and SAEs than patients who were already receiving 23 mg (78.0% and 16.9% vs 72.8% and 14.0%, respectively). The incidence of new AEs declined rapidly after the first 2 weeks and remained low throughout the duration of the study.

CONCLUSION: This study shows that long-term treatment with donepezil 23 mg/day is associated with no new safety signals. The elevated incidence of AEs in patients increasing the dose of donepezil from 10 mg/day to 23 mg/day was limited to the initial weeks of the study