

Drug Class Review

Alzheimer's Drugs

Preliminary Scan Report #5

August 2014

Last Report: June 2006

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations 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 to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. 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 Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, new systematic reviews, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Report

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

Date of Last Preliminary Update Scan Report

Preliminary Scan Report #4, October 2013

Scope and Key Questions

Researchers at the University of North Carolina Chapel Hill wrote preliminary key questions and the eligibility criteria for studies based on the populations, interventions, and outcomes of interest. These were reviewed by representatives of organizations participating in the Drug Effectiveness Review Project (DERP) and posted to the DERP website for public comment. 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

- Patients with Alzheimer's disease

Interventions

Table 1. Included interventions

Class	Generic Name	US Trade Name	Dosage Forms	Labeled Uses
AChEI	Donepezil	Aricept®	5, 10, 23 mg tabs 1x/day 5mg/5mL solution	Mild, moderate, and severe dementia of the Alzheimer's type
	Tacrine	Cognex®	discontinued by manufacturer	Mild to moderate dementia of the Alzheimer's type
AChEI, BuChEI	Rivastigmine	Exelon®	1.5, 3, 4.5, 6 mg tabs 2x/day 2 mg/mL solution 4.6 mg/24 hours or 9.5 mg/24 hours or 13.3 mg/24 hours patch 1x/day	Mild, moderate, and severe dementia of the Alzheimer's type
AChEI, NRM	Galantamine	Razadyne® Razadyne ER®	4, 8, 12 mg tabs 2x/day ^a 4mg/mL solution ^a 8, 16, 24 tabs 1x/day ^b	Mild to moderate dementia of the Alzheimer's type
NMDA antagonist	Memantine	Namenda™ Namenda XR®	5, 10 mg tabs 2x/day ^c 2 mg/mL solution ^c 7, 14, 21, 28 mg tabs 1x/day ^d	Moderate to severe dementia of the Alzheimer's type

Abbreviations: AChEI, acetylcholinesterase inhibition; BuChEI, butyrylcholinesterase inhibition; NRM, nicotinicreceptor modulator; NMDA, N-methyl d-aspartate

^a Razadyne

^b Razadyne ER

^c Namenda

^d Namenda XR

Study designs

- RCTs only
- Sample size $n \geq 100$
- Study duration ≥ 12 weeks

Comparators

- Any other Alzheimer's medication listed above
- Combination of any Alzheimer's medications listed above
- Placebo

Efficacy and 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

Harms/adverse events 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

METHODS

Literature Search

To identify relevant citations for randomized controlled trials published since the last full report, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from March 2005 through July 7, 2014 using terms for included drugs. We also searched the FDA website (<http://www.fda.gov/medwatch/safety.htm>) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>), the Canadian Agency for Drugs and Technology in Health (<http://www.cadth.ca/>), the VA Evidence-based Synthesis Program (<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>), and University of York Centre for Reviews and Dissemination (<http://www.york.ac.uk/inst/crd/crdreports.htm>). All citations were imported into an electronic database (EndNote X4) 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

New Drugs

New drugs identified in this Preliminary Update Scan

None identified.

New drugs identified in previous Preliminary Update Scan(s)

6/21/2010: Namenda XR™ (memantine), an extended release version of Namenda™, was approved for the treatment of moderate to severe dementia of the Alzheimer's type.

5/01/2012: Cognex® (tacrine), was discontinued by the manufacturer, Shionogi Inc., and withdrawn from the US market.

9/1/2012: Exelon® (rivastigmine), a higher dose of the rivastigmine transdermal patch was approved by the FDA, the transdermal patch is now available in 3 doses: 4.6 mg/24 hours or 9.5 mg/24 hours or 13.3 mg/24 hours.

New Indications

New indications identified in this Preliminary Update Scan

None identified.

New indications identified in previous Preliminary Update Scan(s)

6/27/2006: Exelon® (rivastigmine), a reversible cholinesterase inhibitor, was approved for the treatment of mild to moderate dementia associated with Parkinson's Disease.

10/13/2006: Aricept® (donepezil hydrochloride), an acetylcholinesterase inhibitor, was approved for the treatment of dementia of the Alzheimer's type in patients with severe Alzheimer's Disease.

New Safety Alerts

Identified in this Preliminary Update Scan

None identified.

Identified in previous Preliminary Update Scan(s)

None identified.

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

None identified.

Reviews identified in previous Preliminary Update Scan(s)

None identified.

Randomized Controlled Trials***Trials identified since the most recent Full Report***

We identified 17 new publications through recent Medline searches. After screening titles and abstracts, we identified 2 new potentially relevant placebo-controlled trials for one of the included medications (memantine). This increases the total of new citations for randomized controlled trials found through Medline searches to 313 since the last full report. Of those, there are 37 potentially relevant new publications, including 4 head-to-head trials, 32 publications of 26 placebo-controlled trials, and 1 subgroup or secondary analysis of 1 trial included in an existing report (see Appendix A for abstracts). Characteristics of these trials are shown in Tables 2, 3, and 4, below. Table 5 is a matrix showing head-to-head trials.

Table 2. New head-to-head trials

Study	N, Duration	Population	Comparison	Focus
Choi, 2011	172, 24 weeks	Mild-to-moderate AD	Rivastigmine vs. memantine + rivastigmine	Tolerability and efficacy of combination therapy of memantine plus rivastigmine patch compared to rivastigmine patch monotherapy in patients with mild-to-moderate AD
Han, 2012	206, 24 weeks	Probable AD	Rivastigmine vs. memantine + rivastigmine	Effect of the apolipoprotein E genotype on the clinical response to rivastigmine transdermal patch monotherapy or memantine plus rivastigmine patch in patients with mild-to-moderate AD
Parnetti, 2011	144, 1 year	AD	Rivastigmine vs. galantamine vs. donepezil	Cerebrospinal fluid activity of acetylcholinesterase and butyrylcholinesterase in patients with AD, before and after long-term treatment with different AChEIs
Howard, 2012	295, 52 weeks	Moderate or severe AD	Donepezil vs. memantine vs. donepezil + memantine	Treatment benefits of cholinesterase inhibitors after the progression to moderate-to-severe AD

Abbreviations: AD, Alzheimer's disease; AChEI, acetylcholinesterase inhibitor

Table 3. New placebo-controlled trials

Study	N, Duration	Population	Comparison	Focus
Andersen, 2012	187, 12 months	Recent diagnosis of mild or moderate AD	Donepezil vs. Placebo	Effect of stimulation therapy and donepezil on cognitive function in AD
Black, 2007	343, 24 weeks	Severe AD	Donepezil vs. Placebo	Efficacy and safety of donepezil for severe AD
Frolich, 2011	567, 12 weeks	Mild-to-moderate AD	Donepezil vs. Placebo	Effects of AZD3480 on cognition in patients with mild-to-moderate AD

Study	N, Duration	Population	Comparison	Focus
Gold, 2010	693, 24 weeks	Mild-to-moderate AD	Donepezil vs. Placebo	Efficacy and safety of rosiglitazone XR in mild-to-moderate AD
Homma, 2008	325, 24 weeks	Severe AD	Donepezil vs. Placebo	Efficacy and tolerability of donepezil in severe AD
Howard, 2007	272, 12 weeks	Patients with AD who had clinically significant agitation and no response to a brief psychosocial treatment program	Donepezil vs. Placebo	Benefits of cholinesterase inhibitors for behavioral disturbances in patients with AD
Mazza, 2006	NR, 24 weeks	Mild-to-moderate Alzheimer's dementia	Donepezil vs. Placebo	Efficacy of Ginkgo biloba special extract EGb 761 compared with second-generation cholinesterase inhibitors in the treatment of mild-to-moderate Alzheimer's dementia
Burns, 2009	407, NR	Severe AD	Galantamine vs. Placebo	Efficacy of galantamine in patients with severe AD
Rockwood, 2006	130, 4 months	Mild-to-moderate AD	Galantamine vs. Placebo	Clinical meaningfulness of cholinesterase inhibitors in AD
Scarpini, 2011	NR, 24 months	Mild-to-moderate AD	Galantamine vs. Placebo	Examination of long-term outcomes of galantamine treatment in patients with AD
Suh, 2008	138, 52 weeks	Mild-to-moderate AD	Galantamine vs. Placebo	Impact of galantamine treatment on the function, caregiver time, and resources used in the treatment of patients with mild-to-moderate AD
Ashford, 2011	NR, 52 weeks	Probable AD diagnosis with mild-to-moderate dementia	Memantine vs. Placebo	To test whether memantine would slow or prevent the loss of neurons in mild-to-moderate AD patients
Bakchine, 2007	470, 24 weeks	Mild-to-moderate AD	Memantine vs. Placebo	Efficacy and tolerability of 20mg/day memantine in patients with mild-to-moderate AD
Cummings, 2006	NR, 24 weeks	Moderate-to-severe AD on stable donepezil treatment	Memantine vs. Placebo	Investigation of the behavioral effects of memantine in moderate-to-severe AD
Dyksen, 2014	613, mean (SD) follow up 2.27 (1.22) years	Mild to moderate AD	Memantine vs. Placebo	To determine if vitamin E (alpha tocopherol), memantine, or both slow progression of mild to moderate AD in patients taking an acetylcholinesterase inhibitor
Fox, 2012	149, 12 weeks	Moderate-to-severe AD	Memantine vs. Placebo	Efficacy of memantine in treating clinically significant agitation in patients with moderate-to-severe AD
Grossberg, 2013	667, 24 weeks	Moderate-to-severe AD	Memantine XR vs. Placebo	Evaluate the efficacy, safety, and tolerability of a higher-dose, once-daily, extended-release formulation in patients with moderate-to-severe AD concurrently taking cholinesterase inhibitors

Study	N, Duration	Population	Comparison	Focus
Peskind, 2006	403, 24 weeks	Mild-to-moderate AD	Memantine vs. Placebo	Efficacy and safety of memantine versus placebo in patients with mild-to-moderate AD
Porsteinsson, 2008	433, 24 weeks	Probable AD	Memantine vs. Placebo	Efficacy and safety of memantine in patients with mild-to-moderate AD receiving cholinesterase inhibitor treatment
Saxton, 2012	257, 12 weeks	AD	Memantine vs. Placebo	Communication-related benefits of memantine treatment in patients with AD
van Dyck, 2007	350, 24 weeks	Moderate-to-severe AD	Memantine vs. Placebo	Efficacy and safety of memantine monotherapy in patients with moderate-to-severe AD
Wilkinson, 2012	278, 52 weeks	Probable AD	Memantine vs. Placebo	Rate of total brain atrophy with serial magnetic resonance imaging using the Brain Boundary Shift Integral in patients with probable AD over the course of 52 weeks of treatment with memantine or placebo
Feldman, 2007	678, 26 weeks	Probable AD	Rivastigmine vs. Placebo	Efficacy and safety of rapidly titrated rivastigmine administered twice or three times daily in patients with mild-to-moderate AD
Grossberg, 2009	870, 28 weeks	AD	Rivastigmine vs. Placebo	Long-term safety and tolerability of a transdermal rivastigmine patch up to 1 year, as a novel approach to treatment in AD
Mowla, 2007	122, 12 weeks	Mild-to-moderate Alzheimer's dementia	Rivastigmine vs. Placebo	Survey of the effect of serotonin augmentation on cognition and activities of daily living in patients with AD
Blesa, 2007 Cummings, 2010 Grossberg, 2011 Grossberg, 2011 Lee, 2011 Winblad, 2007 Winblad, 2007 Winblad, 2007	1,195, 24 weeks	Probable AD	Rivastigmine vs. Placebo	Efficacy, safety and tolerability of a novel rivastigmine transdermal patch with conventional rivastigmine capsules and placebo in patients with AD

Abbreviations: AD, Alzheimer's disease

Table 4. Secondary analyses of included primary trial publications

Study	N, Duration	Population	Comparison	Focus
Gaudig, 1622	841, 6 weeks	Mild-to-moderate AD	Galantamine vs. placebo	Effects of galantamine withdrawal and comparison with uninterrupted therapy

Abbreviations: AD, Alzheimer's disease

Table 5. Breakdown of potentially relevant head-to-head comparisons by drug:

	Donepezil	Tacrine	Rivastigmine	Galantamine	Memantine	Memantine + donepezil	Memantine + rivastigmine
Donepezil			1	1	1	1	
Tacrine							
Rivastigmine	1			1			2
Galantamine	1		1				
Memantine	1					1	
Memantine + donepezil	1				1		
Memantine + rivastigmine			2				

Summary

We found 2 new placebo-controlled trials for one of the included medications (memantine) through recent searches. Cumulatively, all scans since the last full report identified 37 potentially relevant new publications (4 head-to-head trials, 26 placebo controlled trials [32 publications], and 1 subgroup or secondary analyses of 1 trial). Previous scans identified additional doses or formulations for two of the included medications (rivastigmine and memantine), and found that one included medication (tacrine) has been discontinued and withdrawn from the US market. The current scan yielded no new drugs, safety alerts, or systematic reviews.

Appendix A. Abstracts of potentially relevant new trials of second generation antidepressants

Head-to-head trials

Choi, S. H., K. W. Park, et al. (2011). "Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer's disease: a multicenter, randomized, open-label, parallel-group study." *Curr Med Res Opin* **27**(7): 1375-83.

OBJECTIVE: To compare the tolerability and efficacy of combination therapy of memantine plus rivastigmine patch with rivastigmine patch monotherapy in patients with mild to moderate Alzheimer's disease (AD). **RESEARCH DESIGN AND METHODS:** In this multicenter, randomized, open-label study, patients entered an 8-week run-in period (a 5 cm² rivastigmine patch for 4 weeks, then a 10 cm² patch for 4 weeks) followed by 16 weeks of memantine plus rivastigmine patch or rivastigmine patch monotherapy. The primary outcome measure was the retention rate at the end of the trial. Clinical trial registration: clinicaltrials.gov. NCT01025466. **RESULTS:** Overall, 88 and 84 patients received rivastigmine patch with and without memantine, respectively, and of these, 77 (87.5%) and 70 (83.3%) patients completed the study. The difference in retention rate was not significant (95% confidence interval: -6.3-14.7%). The incidence of adverse events (AEs) (53.4 vs. 50.6%) and discontinuation due to AEs (6.8 vs. 4.8%) were not different between patients with and without memantine. The most frequent AEs were skin irritation in patients with and without memantine (42.0 vs. 34.9%, $p = 0.71$), but discontinuation due to skin irritation was rare (4.5 vs. 2.4%, $p = 0.74$). The incidence of gastrointestinal AEs was very low in patients with and without memantine (nausea, 2.3 vs. 1.2%; vomiting, 1.1 vs. 1.2%). The Korean Version of the Cohen Mansfield Agitation Inventory scores favored rivastigmine patch monotherapy at the end of treatment ($p = 0.01$). Changes in other efficacy measures were similar between the groups.

CONCLUSION: There were no significant differences in tolerability and safety between the treatment groups. The combination therapy of memantine plus rivastigmine patch did not show an advantage over rivastigmine patch monotherapy on efficacy analyses. The sample size for comparing tolerability may have been too small to detect a difference of efficacy between the two groups.

Han, H. J., B. C. Kim, et al. (2012). "Response to rivastigmine transdermal patch or memantine plus rivastigmine patch is affected by apolipoprotein E genotype in Alzheimer patients." *Dement Geriatr Cogn Disord* **34**(3-4): 167-73.

BACKGROUND/AIMS: The apolipoprotein E (APOE) genotype in response to pharmacological treatments in patients with Alzheimer's disease (AD) remains a matter of controversy. This analysis investigated the effect of the APOE genotype on the clinical response to rivastigmine transdermal patch monotherapy or memantine plus rivastigmine patch in patients with mild to moderate AD. **METHODS:** Two hundred and six ($n = 206$) patients with probable AD and Mini-Mental State Examination (MMSE) scores of 10-20 were randomized to rivastigmine patch monotherapy or memantine plus rivastigmine patch for 24 weeks. Of the 206 patients with probable AD, 146 patients who consented to genetic testing for APOE were included and assessed for this subgroup study. **RESULTS:** There were no significant differences on MMSE, NPI, ADAS-cog, ADCS-ADL, CDR-

SB, NPI and FAB between rivastigmine patch monotherapy and memantine plus rivastigmine patch according to the APOE genotype. However, patients with moderately severe AD (MMSE ≤ 15) who were APOE epsilon4 carriers showed higher responder rates on ADCS-ADL with memantine plus rivastigmine patch compared to rivastigmine patch monotherapy. **CONCLUSION:** Moderately severe AD patients with the APOE epsilon4 allele may respond more favorably to memantine plus rivastigmine patch than epsilon4 noncarriers.

Howard, R., R. McShane, et al. (2012). "Donepezil and memantine for moderate-to-severe Alzheimer's disease." *N Engl J Med* **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.).

Parnetti, L., D. Chiasserini, et al. (2011). "Changes in CSF acetyl- and butyrylcholinesterase activity after long-term treatment with AChE inhibitors in Alzheimer's disease." *Acta Neurol Scand* **124**(2): 122-9.

OBJECTIVES: To measure cerebrospinal fluid (CSF) activity of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) in patients with Alzheimer's disease (AD) participating in randomized clinical trials from three European centers, before and after long-term treatment with different AChE inhibitors (AChEIs). **MATERIALS AND**

METHODS: Of the 144 patients included in the study, 104 were treated with donepezil, 15 with galantamine, 16 with rivastigmine, and nine with placebo. CSF AChE and BChE activities were measured at baseline and after 1- year treatment. **RESULTS:** Donepezil and galantamine groups showed a significant increase in CSF AChE activity at follow-up, while no changes for BChE activity were observed; in donepezil group, a positive correlation between plasma concentration and AChE activity was documented. Conversely, in rivastigmine group, a decrease in CSF activity of both enzymes was observed. CSF AChE and BChE activities were not correlated with the clinical outcome in any group considered. CSF biomarkers did not show any change after treatment. **CONCLUSIONS:** AChEIs differently influence the activity of target enzymes in CSF independent of their pharmacodynamic effects.

Placebo-controlled trials

Andersen, F., M. Viitanen, et al. (2012). "The effect of stimulation therapy and donepezil on cognitive function in Alzheimer's disease. A community based RCT with a two-by-two factorial design." *BMC Neurol* **12**(59).

BACKGROUND: Progressive neurodegeneration in Alzheimer's disease (AD) induces cognitive deterioration, and there is controversy regarding the optimal treatment strategy in early AD. Stimulation therapy, including physical exercise and cholinesterase inhibitors are both reported to postpone cognitive deterioration in separate studies. We aimed to study the effect of stimulation therapy and the additional effect of donepezil on cognitive function in early AD. **METHOD:** Design: A two-by-two factorial trial comprising stimulation therapy for one year compared to standard care to which a randomized double-blinded placebo controlled trial with donepezil was added. **Setting:** Nine rural municipalities in Northern Norway. **Participants:** 187 participants 65 years and older with a recent diagnosis of mild or moderate AD were included in the study of which 146 completed a one-year follow-up. **INTERVENTIONS:** In five municipalities the participants received stimulation therapy whereas participants in four received standard care. All participants were randomised double-blindly to donepezil or placebo and tested with three different cognitive tests four times during the one-year study period. **Main outcome:** Changes in MMSE sum score. **Secondary outcome:** Changes in ADAS-Cog and Clock Drawing Test. **RESULTS:** MMSE scores remained unchanged amongst AD participants receiving stimulation therapy and those receiving standard care. The results were consistent for ADAS-Cog and Clock Drawing Test. No time trend differences were found during one-year follow-up between groups receiving stimulation therapy versus standard care or between donepezil versus placebo. **CONCLUSION:** In rural AD patients non-pharmacological and pharmacological therapy did not improve outcome compared with standard care but all groups retained cognitive function during one year follow-up. Other studies are needed to confirm these results. **TRIAL REGISTRATION:** ClinicalTrials.gov (Identifier: NCT00443014). EudraCT database (no 2004-002613-37).

Ashford, J. W., M. Adamson, et al. (2011). "MR spectroscopy for assessment of memantine treatment in mild to moderate Alzheimer dementia." *J Alzheimers Dis* **26 Suppl 3**(331-6).

OBJECTIVES: Magnetic Resonance Spectroscopy (MRS) may provide a precise and reliable assessment of the extent and severity of neural tissue loss caused by various

diseases. In particular, the N-Acetyl Aspartate (NAA) and Creatine (Cr) ratio has been found to be an indicator of the degree of neuronal loss in Alzheimer's disease (AD). Memantine is thought to benefit the AD brain by stabilizing the NMDA receptors on neurons in turn reducing excitotoxicity. Despite its effectiveness in treating moderate to severe AD, memantine has not had similar success in the treatment of mildly demented AD patients. The objective of this study was to test whether memantine would slow or prevent the loss of neurons in mild to moderate AD patients. **METHODS:** A double-blind placebo-controlled study was designed to measure the effect of a year-long course of memantine in patients with a probable AD diagnosis with mild to moderate dementia. The primary outcome measure was stipulated to be change in MRS NAA/Cr ratio in inferior parietal cortex in memantine relative to the placebo treatment condition. The secondary outcome measures were changes in cognitive and function scale scores. **RESULTS:** This pilot study failed to demonstrate a benefit of memantine on the primary outcome measure, the inferior parietal NAA/Cr ratio, or the secondary outcome measures. **CONCLUSIONS:** More studies are needed to determine the effect of memantine on regions of the brain significantly affected by AD pathology.

Bakchine, S.H. Loft. (2007). "Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study." *J Alzheimers Dis* **11**(4): 471-9.

Memantine is a moderate affinity, uncompetitive NMDA receptor antagonist currently approved for the treatment of moderate to severe Alzheimer's disease (AD). A 24-week, double-blind, placebo-controlled, study (Study 99679) conducted in Europe evaluated the efficacy and tolerability of 20mg/day memantine in patients with mild to moderate AD. Patients were randomised to either memantine or placebo in a 2:1 ratio. Efficacy was primarily assessed as change from baseline in ADAS-cog and CIBIC-plus score. Of 470 patients randomised and treated (memantine, n=318; placebo, n=152), 85% and 91% completed the study. Memantine-treated patients showed statistically significant improvement relative to placebo at weeks 12 and 18, and numerical superiority at week 24 on both efficacy scales. The lack of significance at week 24 was attributed to an unexpectedly high placebo response. Memantine was well tolerated with an adverse event profile similar to placebo. The data presented support the efficacy of memantine in mild to moderate AD.

Black, S. E., R. Doody, et al. (2007). "Donepezil preserves cognition and global function in patients with severe Alzheimer disease." *Neurology* **69**(5): 459-69.

OBJECTIVE: To evaluate the efficacy and safety of donepezil for severe Alzheimer disease (AD). **METHODS:** Patients with severe AD (Mini-Mental State Examination [MMSE] scores 1 to 12 and Functional Assessment Staging [FAST] scores \geq or =6) were enrolled in this multinational, double-blind, placebo-controlled trial at 98 sites. Patients were randomized to donepezil 10 mg daily or placebo for 24 weeks. Primary endpoints were the Severe Impairment Battery (SIB) and Clinician's Interview-Based Impression of Change-Plus caregiver input (CIBIC-Plus). Secondary endpoints included the MMSE, the Alzheimer Disease Cooperative Study-Activities of Daily Living-severe version (ADCS-ADL-sev), the Neuropsychiatric Inventory (NPI), the Caregiver Burden Questionnaire (CBQ), and the Resource Utilization for Severe Alzheimer Disease

Patients (RUSP). Efficacy analyses were performed in the intent-to-treat (ITT) population using last post-baseline observation carried forward (LOCF). Safety assessments were performed for patients receiving \geq or $=1$ dose of donepezil or placebo. **RESULTS:** Patients were randomized to donepezil (n = 176) or placebo (n = 167). Donepezil was superior to placebo on SIB score change from baseline to endpoint (least squares mean difference 5.32; p = 0.0001). CIBIC-Plus and MMSE scores favored donepezil at endpoint (p = 0.0473 and p = 0.0267). Donepezil was not significantly different from placebo on the ADCS-ADL-sev, NPI, CBQ, or RUSP. Adverse events reported were consistent with the known cholinergic effects of donepezil and with the safety profile in patients with mild to moderate AD. **CONCLUSION:** Patients with severe AD demonstrated greater efficacy compared to placebo on measures of cognition and global function.

Blesa, R., C. Ballard, et al. (2007). "Caregiver preference for rivastigmine patches versus capsules for the treatment of Alzheimer disease." *Neurology* **69**(4 Suppl 1): S23-8.

Alzheimer disease (AD) has a significant impact on caregivers. Administering and managing medications is one of their many daily tasks. More effective modes of drug administration may benefit patient and caregiver, and may improve compliance. A prospective outcome of the IDEAL (Investigation of TransDermal Exelon in Alzheimer's disease) trial was to evaluate caregiver preference for rivastigmine patches compared with capsules. The 24-week, randomized, double-blind, double-dummy, placebo- and active-controlled IDEAL trial investigated once-daily rivastigmine patches vs twice-daily capsules in moderate AD patients. Caregivers rated patch adhesion throughout. The AD Caregiver Preference Questionnaire (ADCPQ) assessed patch vs capsule from caregivers' perspective, based on expectations, preferences, and satisfaction with treatment. A total of 1,059 caregivers completed the ADCPQ while their respective patients were on study drug. More than 70% of caregivers preferred the patch to capsules overall. The patch was preferred to capsules with respect to ease of use (p \leq 0.0001) and ease of following the schedule (p \leq 0.0001). Caregivers indicated greater satisfaction overall (p \leq 0.0001) and less interference with daily life (p \leq 0.01) with the patch vs capsules. The preference substudy of the IDEAL trial demonstrated that caregivers of AD patients preferred patches to capsules for drug delivery. Preference for the patch may indicate reduced caregiver stress, substantiated by greater satisfaction and less interference with daily life. These benefits may lead to improved compliance.

Burns, A., R. Bernabei, et al. (2009). "Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial." *Lancet Neurol* **8**(1): 39-47.

BACKGROUND: The efficacy of galantamine has been shown in patients with mild, moderate, and advanced moderate Alzheimer's disease (AD). Here we report its efficacy in patients with severe AD. **METHODS:** Between December, 2003, and March, 2007, patients aged 84 (SD 6) years with severe AD (mini-mental state examination [MMSE] score 5-12 points), in a nursing home setting were randomly assigned to receive galantamine (n=207), titrated initially to 24 mg/day, or placebo (n=200). Co-primary efficacy measures for cognitive function and ability to undertake normal daily activities were the severe impairment battery (SIB) and the seven-item minimum data set-activities

of daily living (MDS-ADL), respectively. Adverse events, vital signs, laboratory parameters, and electrocardiograms were monitored. This trial is registered with ClinicalTrials.gov, number NCT00216593. FINDINGS: 168 of 207 (81%) patients in the galantamine group and 161 of 200 (81%) in the placebo group completed the study. Mean SIB scores increased (improved) by 1.9 (95% CI -0.1 to 3.9) points with galantamine and decreased (worsened) by 3.0 (-5.6 to -0.5) points with placebo (between-group least squares mean difference 4.36, 1.3 to 7.5; $p=0.006$). Mean MDS-ADL self-performance score worsened by 1.2 (0.6 to 1.8) points and 1.6 (0.8 to 2.3) points, respectively (between-group least squares mean difference -0.41, -1.3 to 0.5; $p=0.383$). Nominally significant between-group differences in favour of galantamine occurred for the SIB domains of memory ($p=0.006$), praxis ($p=0.010$), and visuospatial ability ($p=0.002$), and for the MDS-ADL subitem locomotion on unit ($p=0.021$). 183 of 207 patients (88%) who received galantamine and 177 of 200 (89%) who received placebo had adverse events, which were mostly mild to moderate. Eight patients (4%) in the galantamine group and 21 patients (11%) in the placebo group died. ECG abnormalities were similar between the two groups. INTERPRETATION: Galantamine can be started and used safely in elderly patients with severe AD. Galantamine improved cognitive function but failed to significantly improve the co-primary parameter of overall activities of daily living.

Cummings, J. L., M. R. Farlow, et al. (2010). "Rivastigmine transdermal patch skin tolerability: results of a 1-year clinical trial in patients with mild-to-moderate Alzheimer's disease." *Clin Drug Investig* **30**(1): 41-9.

BACKGROUND AND OBJECTIVES: Transdermal patches provide non-invasive, continuous drug delivery, and offer significant potential advantages over oral treatments. With all transdermal treatments a proportion of patients will experience some form of skin reaction. The rivastigmine patch has been approved for the treatment of mild-to-moderate Alzheimer's disease (AD) since July 2007 in the US. The aim of the component of the trial reported here was to evaluate the skin tolerability of the rivastigmine transdermal patch in patients with mild-to-moderate AD. **METHODS:** The pivotal IDEAL trial was a 24-week, randomized, double-blind, placebo-controlled, multicentre trial of the efficacy and tolerability of the rivastigmine transdermal patch in 1195 patients with mild-to-moderate AD. This was followed by a 28-week open-label extension. Although not prospectively defined as a secondary assessment, during both phases of the study the condition of the patients' skin at the application site was evaluated. These data are reviewed in this article. **RESULTS:** During the 24-week, double-blind phase of the study, 89.6% of patients in the target 9.5 mg/24 h patch treatment group had recorded 'no, slight or mild' signs or symptoms for their most severe application-site reaction. Erythema and pruritus were the most commonly reported reactions. No patient in any patch treatment group experienced a skin reaction that was reported as a serious adverse event. In the 9.5 mg/24 h treatment group, 2.4% of patients discontinued treatment due to an application-site reaction. During the 28-week open-label extension, the skin tolerability profile was similar to that seen in the double-blind phase. Overall, 3.7% of patients discontinued treatment due to application-site skin reactions. There was no indication that the severity of the skin reactions increased over time. **CONCLUSION:** Overall, the data support a favourable skin tolerability profile for the rivastigmine

transdermal patch, and provide reassurance that the benefits of rivastigmine patch therapy for patients with AD are not confounded by significant skin irritation problems. Nevertheless, care should be taken to follow manufacturer's advice about patch application, such as daily rotation of the application site, to minimize the risk of skin reactions.

Cummings, J. L., E. Schneider, et al. (2006). "Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment." *Neurology* **67**(1): 57-63.

OBJECTIVE: To investigate the behavioral effects of memantine in moderate to severe Alzheimer disease (AD). **METHODS:** The authors conducted a hypothesis-generating, exploratory analysis of a 24-week, double-blind, placebo-controlled trial comparing memantine (20 mg/day) with placebo in subjects with moderate to severe AD on stable donepezil treatment. They employed the Neuropsychiatric Inventory (NPI; 12-item), administered at baseline, week 12, and week 24, to assess the effects of memantine on behavior. Global, cognitive, and functional measures were collected and relationships between these assessments and changes in behavior were determined. The intent-to-treat population was examined using last-observation-carried-forward and observed-cases approaches. **RESULTS:** Patients treated with memantine had significantly lower NPI total scores than patients treated with placebo. Analyses of the 12 NPI domains revealed significant effects in favor of memantine on agitation/aggression, eating/appetite, and irritability/lability. Of patients who exhibited agitation/aggression at baseline, those treated with memantine showed significant reduction of symptoms compared with placebo-treated patients. Memantine-treated patients without agitation/aggression at baseline evidenced significantly less emergence of this symptom compared with similar patients receiving placebo. Caregivers of patients receiving memantine registered significantly less agitation-related distress. There were significant relationships between the NPI and the global rating scale and performance of activities of daily living, but not between changes in the NPI and cognition. **CONCLUSION:** Treatment with memantine reduced agitation/aggression, irritability, and appetite/eating disturbances. Memantine reduced agitation/aggression in patients who were agitated at baseline and delayed its emergence in those who were free of agitation at baseline.

Dysken, M. W., et al. (2014). "Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial." *JAMA* **311**(1): 33-44.

IMPORTANCE: Although vitamin E and memantine have been shown to have beneficial effects in moderately severe Alzheimer disease (AD), evidence is limited in mild to moderate AD. **OBJECTIVE:** To determine if vitamin E (alpha tocopherol), memantine, or both slow progression of mild to moderate AD in patients taking an acetylcholinesterase inhibitor. **DESIGN, SETTING, AND PARTICIPANTS:** Double-blind, placebo-controlled, parallel-group, randomized clinical trial involving 613 patients with mild to moderate AD initiated in August 2007 and concluded in September 2012 at 14 Veterans Affairs medical centers. **INTERVENTIONS:** Participants received either 2000 IU/d of alpha tocopherol (n = 152), 20 mg/d of memantine (n = 155), the combination (n = 154), or placebo (n = 152). **MAIN OUTCOMES AND MEASURES:** Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory score (range, 0-78). Secondary outcomes included cognitive, neuropsychiatric,

functional, and caregiver measures. RESULTS: Data from 561 participants were analyzed (alpha tocopherol = 140, memantine = 142, combination = 139, placebo = 140), with 52 excluded because of a lack of any follow-up data. Over the mean (SD) follow-up of 2.27 (1.22) years, ADCS-ADL Inventory scores declined by 3.15 units (95% CI, 0.92 to 5.39; adjusted P = .03) less in the alpha tocopherol group compared with the placebo group. In the memantine group, these scores declined 1.98 units less (95% CI, -0.24 to 4.20; adjusted P = .40) than the placebo group's decline. This change in the alpha tocopherol group translates into a delay in clinical progression of 19% per year compared with placebo or a delay of approximately 6.2 months over the follow-up period. Caregiver time increased least in the alpha tocopherol group. All-cause mortality and safety analyses showed a difference only on the serious adverse event of "infections or infestations," with greater frequencies in the memantine (31 events in 23 participants) and combination groups (44 events in 31 participants) compared with placebo (13 events in 11 participants). CONCLUSIONS AND RELEVANCE: Among patients with mild to moderate AD, 2000 IU/d of alpha tocopherol compared with placebo resulted in slower functional decline. There were no significant differences in the groups receiving memantine alone or memantine plus alpha tocopherol. These findings suggest benefit of alpha tocopherol in mild to moderate AD by slowing functional decline and decreasing caregiver burden. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00235716.

Feldman, H. H.R. Lane. (2007). "Rivastigmine: a placebo controlled trial of twice daily and three times daily regimens in patients with Alzheimer's disease." *J Neurol Neurosurg Psychiatry* 78(10): 1056-63.

OBJECTIVE: To evaluate the efficacy and safety of rapidly titrated rivastigmine administered twice (BID) or three times (TID) daily in patients with mild to moderate Alzheimer's disease (AD). METHODS: This was a 26 week international, randomised, double blind, placebo controlled study in which 678 patients with probable AD received placebo or rivastigmine 2-12 mg/day BID or TID. Primary outcome measures included the cognitive subscale of the AD Assessment Scale (ADAS-cog) and categorical analysis of the Clinician Interview Based Impression of Change incorporating caregiver information (CIBIC-Plus). Secondary outcomes were the CIBIC-Plus change from baseline, Progressive Deterioration Scale, ADAS-cogA, Mini-Mental State Examination and Global Deterioration Scale. RESULTS: At week 26, mean rivastigmine dose was 9.6 (2.76) mg/day in the TID group and 8.9 (2.93) mg/day in the BID group. Mean ADAS-cog changes from baseline in the TID and BID rivastigmine treated groups were -0.2 (SD 7.3) and 1.2 (SD 7.2) versus 2.8 (SD 7.2) for the placebo group ($p < 0.05$). Differences between rivastigmine TID and placebo on the CIBIC-Plus categorical responder analysis were significant (31% vs 19%; $p < 0.05$, intention to treat). No significant differences were seen between BID and placebo for this outcome measure. Adverse events were predominantly gastrointestinal, occurring mainly during dose titration. Withdrawal because of adverse events accounted for 17% of BID, 11% of TID and 9% of placebo patients. CONCLUSIONS: Rivastigmine administered as a BID or TID regimen significantly benefited cognitive, function and global performances in AD patients. The TID regimen showed a tendency for superior tolerability and permitted titration to higher doses, an outcome that is significant as the efficacy of rivastigmine is dose related.

Fox, C., M. Crugel, et al. (2012). "Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial." *PLoS One* 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. **TRIAL REGISTRATION:** ClinicalTrials.gov NCT00371059. **TRIAL REGISTRATION:** International Standard Randomised Controlled Trial 24953404.

Frolich, L., T. Ashwood, et al. (2011). "Effects of AZD3480 on cognition in patients with mild-to-moderate Alzheimer's disease: a phase IIb dose-finding study." *J Alzheimers Dis* 24(2): 363-74.

AZD3480 is a selective agonist of the central alpha4beta2 and alpha2beta2 neuronal nicotinic cholinergic receptors (NNRs). Its effects on cognition were investigated in 567 patients with mild-to-moderate Alzheimer's disease (AD) (Mini Mental State Examination [MMSE] 12-26). Mean baseline MMSE was 21 (SD +/- 3.7), with 61% of patients having mild disease (MMSE 21-26). Mean age was 74 (range 58-85) years. Patients were randomized to one of 5 treatment groups: AZD3480 5 mg, 20 mg or 35/100 mg, donepezil 10 mg (active comparator) or placebo, and treated once daily for 12 weeks. The primary outcome measure was change from baseline at Week 12 on the AD Assessment Scale-Cognitive Subscale (ADAS-Cog). Neither AZD3480 nor donepezil showed a statistically significant improvement versus placebo on ADAS-Cog. Improvements in a number of secondary outcome measures (MMSE, AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) and Disability Assessment for Dementia [DAD]) were observed for AZD3480 and for donepezil. A post-hoc analysis on ADAS-Cog, excluding patients with very mild AD (MMSE 25-26) indicated

improvement versus placebo for AZD3480 20 mg (-1.4, 95% CI: -3.0; 0.2) and donepezil (-1.0, 95% CI: -2.3; 0.3). AZD3480 was well tolerated. The study did not meet proof of concept criteria: since neither AZD3480 nor donepezil were statistically significantly superior to placebo on ADAS-Cog and was considered to be inconclusive. Further studies are required to determine the therapeutic potential of stimulating alpha4beta2 receptors with NNRs in AD patients.

Gold, M., C. Alderton, et al. (2010). "Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study." *Dement Geriatr Cogn Disord* **30**(2): 131-46.

BACKGROUND/AIMS: A phase II study of the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone extended release (RSG XR) in mild-to-moderate Alzheimer's disease (AD) detected a treatment benefit to cognition in apolipoprotein E(APOE)-epsilon4-negative subjects. The current phase III study with prospective stratification by APOE genotype was conducted to confirm the efficacy and safety of RSG XR in mild-to-moderate AD. An open-label extension study assessed the long-term safety and tolerability of 8 mg RSG XR. **METHODS:** This double-blind, randomized, placebo-controlled study enrolled 693 subjects. Within 2 APOE allelic strata (epsilon4-positive, epsilon4-negative), subjects were randomized (2:2:2:1) to once-daily placebo, 2 mg RSG XR, 8 mg RSG XR or 10 mg donepezil (control). Coprimary endpoints were change from baseline to week 24 in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) score, and week 24 Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC+). **RESULTS:** At week 24, no significant differences from placebo in change from baseline in coprimary endpoints were detected with either the RSG XR dose in APOE-epsilon4-negative subjects or overall. For donepezil, no significant treatment difference was detected in ADAS-Cog; however, a significant difference was detected ($p = 0.009$) on the CIBIC+. Peripheral edema was the most common adverse event for 8 mg RSG XR (15%) and placebo (5%), and nasopharyngitis for 2 mg RSG XR (7%). **CONCLUSION:** No evidence of efficacy of 2 mg or 8 mg RSG XR monotherapy in cognition or global function was detected in the APOE-epsilon4-negative or other analysis populations. The safety and tolerability of RSG XR was consistent with its known pharmacology.

Grossberg, G., X. Meng, et al. (2011). "Impact of rivastigmine patch and capsules on activities of daily living in Alzheimer's disease." *Am J Alzheimers Dis Other Dement* **26**(1): 65-71.

BACKGROUND: Rivastigmine patches provide similar efficacy to rivastigmine capsules with a lower incidence of gastrointestinal side effects in patients with probable Alzheimer's disease (AD). **METHODS:** Post hoc analysis of a 24-week, prospective, international, randomized, double-blind, placebo- and active-controlled trial. Patients ($n = 892$) with probable AD received rivastigmine transdermal patches (9.5 mg/24 hours [10 cm(2)]), rivastigmine capsules (6 mg twice daily), or placebo, and impact on activities of daily living (ADLs) was assessed utilizing 3 subscales: basic, high-level function, and autonomy. **RESULTS:** At week 24, both rivastigmine groups demonstrated significantly superior performance in Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) Total Score versus placebo (rivastigmine patch, $P = .013$; capsules, $P = .039$). Overall, both rivastigmine formulations provided benefits in ADL subscales.

For basic ADLs, rivastigmine capsules performed significantly better than placebo ($P = .012$). For high-level function ADLs, rivastigmine patch performed better than placebo ($P = .056$). For autonomy ADLs, rivastigmine patch performed significantly better than placebo ($P = .017$). **CONCLUSION:** Rivastigmine patches and capsules provide significant effects in both total and subscale ADLs in patients with probable AD.

Grossberg, G., C. Sadowsky, et al. (2009). "Safety and tolerability of the rivastigmine patch: results of a 28-week open-label extension." *Alzheimer Dis Assoc Disord* **23**(2): 158-64.

The primary objective of the open-label extension was to evaluate the long-term safety and tolerability of a transdermal rivastigmine patch up to 1 year, as a novel approach to treatment in Alzheimer disease. This was a 28-week extension to a 24-week, double-blind, double-dummy, placebo-controlled, and active-controlled study evaluating rivastigmine patches [9.5 mg/24 h (10 cm²) and 17.4 mg/24 h (20 cm²)] and oral capsules (3 to 6 mg twice-daily). Patients entering the extension were switched directly to 9.5 mg/24 h rivastigmine patch and increased to 17.4 mg/24 h patch, irrespective of their double-blind study treatment. Primary measures included safety and tolerability assessments, including adverse events and serious adverse events. Of 1195 patients randomized to treatment, 870 (72.8%) completed the double-blind study and entered the open-label extension. During weeks 1 to 4 of the extension, 9.5 mg/24 h rivastigmine patch was well tolerated overall by patients formerly randomized to rivastigmine capsule or patch groups: $\leq 2.5\%$ reported nausea and $\leq 1.9\%$ reported vomiting. No unexpected safety issues arose, and skin tolerability was good; similar to the double-blind study. During the 28-week, open-label extension phase, the patch seemed to be well tolerated with a favorable safety profile.

Grossberg, G. T., J. T. Olin, et al. (2011). "Dose effects associated with rivastigmine transdermal patch in patients with mild-to-moderate Alzheimer's disease." *Int J Clin Pract* **65**(4): 465-71.

AIM: The cholinesterase inhibitor rivastigmine is available in both oral and transdermal forms. The efficacy of oral rivastigmine appears to be dose-dependent. The current analysis investigates the effect of dose on the efficacy of the rivastigmine transdermal patch. **METHODS:** This was a retrospective analysis of a large, international, 24-week, randomised, placebo- and active-controlled trial (IDEAL, CENA713D2320) of rivastigmine in patients with mild-to-moderate Alzheimer's disease (AD). Patients received the 9.5 mg/24 h rivastigmine patch, the 17.4 mg/24 h rivastigmine patch, 12 mg/day rivastigmine capsules or placebo. Changes from baseline at week 24 on the AD Assessment Scale-cognitive subscale (ADAS-cog), AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) and the AD Cooperative Study-Activities of Daily Living (ADCS-ADL) scale were calculated based on the patient's mode and last prescribed patch dose. The analysis included the 4.6 mg/24 h and 13.3 mg/24 h patch doses, for which efficacy data have not previously been reported. **RESULTS:** Significant differences ($p < 0.05$ vs. placebo) were seen on the ADAS-cog and ADCS-ADL for all mode rivastigmine patch doses (except 4.6 mg/24 h) and all last prescribed rivastigmine patch doses (except 4.6 mg/24 h and 13.3 mg/24 h). Patients with a last prescribed/mode patch dose of 9.5 mg/24 h and 13.3 mg/24 h showed significant improvements ($p < 0.05$ vs. placebo) on the ADCS-CGIC. **CONCLUSION:** Rivastigmine patch doses higher than

9.5 mg/24 h may offer additional benefits. The 13.3 mg/24 h patch is worthy of further investigation.

Grossberg, G. T., et al. (2013). "The safety, tolerability, and efficacy of once-daily memantine (28 mg): a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors." *CNS Drugs* **27**(6): 469-478.

INTRODUCTION: Immediate-release memantine (10 mg, twice daily) is approved in the USA for moderate-to-severe Alzheimer's disease (AD). This study evaluated the efficacy, safety, and tolerability of a higher-dose, once-daily, extended-release formulation in patients with moderate-to-severe AD concurrently taking cholinesterase inhibitors. **METHODS:** In this 24-week, double-blind, multinational study (NCT00322153), outpatients with AD (Mini-Mental State Examination scores of 3-14) were randomized to receive once-daily, 28-mg, extended-release memantine or placebo. Co-primary efficacy parameters were the baseline-to-endpoint score change on the Severe Impairment Battery (SIB) and the endpoint score on the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus). The secondary efficacy parameter was the baseline-to-endpoint score change on the 19-item Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL19); additional parameters included the baseline-to-endpoint score changes on the Neuropsychiatric Inventory (NPI) and verbal fluency test. Data were analyzed using a two-way analysis of covariance model, except for CIBIC-Plus (Cochran-Mantel-Haenszel test). Safety and tolerability were assessed through adverse events and physical and laboratory examinations. **RESULTS:** A total of 677 patients were randomized to receive extended-release memantine (n = 342) or placebo (n = 335); completion rates were 79.8 and 81.2 %, respectively. At endpoint (week 24, last observation carried forward), memantine-treated patients significantly outperformed placebo-treated patients on the SIB (least squares mean difference [95 % CI] 2.6 [1.0, 4.2]; p = 0.001), CIBIC-Plus (p = 0.008), NPI (p = 0.005), and verbal fluency test (p = 0.004); the effect did not achieve significance on ADCS-ADL19 (p = 0.177). Adverse events with a frequency of ≥ 5.0 % that were more prevalent in the memantine group were headache (5.6 vs. 5.1 %) and diarrhea (5.0 vs. 3.9 %). **CONCLUSION:** Extended-release memantine was efficacious, safe, and well tolerated in this population.

Homma, A., Y. Imai, et al. (2008). "Donepezil treatment of patients with severe Alzheimer's disease in a Japanese population: results from a 24-week, double-blind, placebo-controlled, randomized trial." *Dement Geriatr Cogn Disord* **25**(5): 399-407.

BACKGROUND/AIMS: A 24-week, randomized, parallel-group, double-blind placebo-controlled study was conducted to evaluate the efficacy and tolerability of donepezil in severe Alzheimer's disease (AD). **METHODS:** Patients with severe AD (Mini-Mental State Examination score 1-12; modified Hachinski Ischemic Score ≤ 6 ; Functional Assessment Staging ≥ 6) were enrolled in this study in Japan. A total of 325 patients were randomized to donepezil 5 mg/day (n = 110), donepezil 10 mg/day (n = 103) or placebo (n = 112). Primary outcome measures were change from baseline to endpoint in the Severe Impairment Battery (SIB) and Clinician's Interview-Based Impression of Change-plus caregiver input (CIBIC-plus) at the endpoint visit. **RESULTS:** Donepezil 5

mg/day and 10 mg/day were significantly superior to placebo on the SIB, with a least-squares mean treatment difference of 6.7 and 9.0, respectively ($p < 0.001$ compared with placebo). CIBIC-plus analyses showed significant differences in favor of donepezil 10 mg/day over placebo at endpoint ($p = 0.003$). A statistically significant dose-response relationship was demonstrated with the SIB and CIBIC-plus. Donepezil was well tolerated. CONCLUSION: This study confirmed the effectiveness of donepezil 10 mg/day in patients with severe AD and demonstrated a significant dose-response relationship. Donepezil at dosages of both 5 mg/day and 10 mg/day is safe and well tolerated in Japanese patients with severe AD.

Howard, R. J., E. Juszcak, et al. (2007). "Donepezil for the treatment of agitation in Alzheimer's disease." *N Engl J Med* **357**(14): 1382-92.

BACKGROUND: Agitation is a common and distressing symptom in patients with Alzheimer's disease. Cholinesterase inhibitors improve cognitive outcomes in such patients, but the benefits of these drugs for behavioral disturbances are unclear. **METHODS:** We randomly assigned 272 patients with Alzheimer's disease who had clinically significant agitation and no response to a brief psychosocial treatment program to receive 10 mg of donepezil per day (128 patients) or placebo (131 patients) for 12 weeks. The primary outcome was a change in the score on the Cohen-Mansfield Agitation Inventory (CMAI) (on a scale of 29 to 203, with higher scores indicating more agitation) at 12 weeks. **RESULTS:** There was no significant difference between the effects of donepezil and those of placebo on the basis of the change in CMAI scores from baseline to 12 weeks (estimated mean difference in change [the value for donepezil minus that for placebo], -0.06; 95% confidence interval [CI], -4.35 to 4.22). Twenty-two of 108 patients (20.4%) in the placebo group and 22 of 113 (19.5%) in the donepezil group had a reduction of 30% or greater in the CMAI score (the value for donepezil minus that for placebo, -0.9 percentage point; 95% CI, -11.4 to 9.6). There were also no significant differences between the placebo and donepezil groups in scores for the Neuropsychiatric Inventory, the Neuropsychiatric Inventory Caregiver Distress Scale, or the Clinician's Global Impression of Change. **CONCLUSIONS:** In this 12-week trial, donepezil was not more effective than placebo in treating agitation in patients with Alzheimer's disease. (ClinicalTrials.gov number, NCT00142324 [ClinicalTrials.gov].).

Lee, J. H.J. Sevigny. (2011). "Effects of body weight on tolerability of rivastigmine transdermal patch: a post-hoc analysis of a double-blind trial in patients with Alzheimer disease." *Alzheimer Dis Assoc Disord* **25**(1): 58-62.

The rationale for the development of the rivastigmine transdermal patch was to improve upon an efficacious therapy by mitigating certain adverse events, such as nausea and vomiting. This may be particularly important in Alzheimer disease patients with low body weights, who may be more susceptible to these adverse events. This analysis compared the effect of body weight on tolerability in Alzheimer disease patients receiving rivastigmine capsules or rivastigmine patch. Using data from a 24-week trial, adverse events and discontinuations were evaluated in patients stratified on the basis of extreme low weight (<50 kg), medium weight (50 to 80 kg), and high weight (>80 kg) at baseline. Rivastigmine patch was generally well tolerated, regardless of patient body weight. Among patients receiving rivastigmine patch, lower body weight, as stratified,

was not associated with a higher adverse event rate; however, there was an association between a higher adverse event rate and low body weight among patients receiving rivastigmine capsules. Discontinuations because of adverse events were not directly related to weight. A lower incidence of adverse events was apparent with transdermal delivery of rivastigmine compared with oral administration.

Mazza, M., A. Capuano, et al. (2006). "Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study." *Eur J Neurol* **13**(9): 981-5.

The Ginkgo biloba special extract EGb 761 seems to produce neuroprotective effects in neurodegenerative diseases of multifactorial origin. There is still debate about the efficacy of Ginkgo biloba special extract EGb 761 compared with second-generation cholinesterase inhibitors in the treatment of mild to moderate Alzheimer's dementia. Our aim is to assess the efficacy of the Ginkgo biloba special extract E.S. in patients with dementia of the Alzheimer type in slowing down the disease's degenerative progression and the patients' cognitive impairment compared with donepezil and placebo. The trial was designed as a 24-week randomized, placebo-controlled, double-blind study. Patients aged 50-80 years, suffering from mild to moderate dementia, were allocated into one of the three treatments: Ginkgo biloba (160 mg daily dose), donepezil (5 mg daily dose), or placebo group. The degree of severity of dementia was assessed by the Syndrom Kurz test and the Mini-Mental State Examination. Clinical Global Impression score was recorded to assess the change in the patients' conditions and the therapeutic efficacy of tested medications. Our results confirm the clinical efficacy of Ginkgo biloba E.S. (Flavogin) in the dementia of the Alzheimer type, comparable with donepezil clinical efficacy. There are few published trials that have directly compared a cholinesterase inhibitor with Ginkgo for dementia. This study directly compares a cholinesterase inhibitor with Ginkgo biloba for dementia of the Alzheimer type and could be a valid contribution in this debate. Our study suggests that there is no evidence of relevant differences in the efficacy of EGb 761 and donepezil in the treatment of mild to moderate Alzheimer's dementia, so the use of both substances can be justified. In addition, this study contributes to establish the efficacy and tolerability of the Ginkgo biloba special extract E.S. in the dementia of the Alzheimer type with special respect to moderately severe stages.

Mowla, A., M. Mosavinasab, et al. (2007). "Does serotonin augmentation have any effect on cognition and activities of daily living in Alzheimer's dementia? A double-blind, placebo-controlled clinical trial." *J Clin Psychopharmacol* **27**(5): 484-7.

OBJECTIVE: Recent studies suggest that cholinergic dysfunction does not provide a complete account of age-related cognitive deficits, and other neuronal systems like monoaminergic hypofunction are involved. In several studies, selective serotonin reuptake inhibitors demonstrated promotion in neurogenesis in the hippocampus and enhanced memory and cognition. The aim of this study is to survey the effect of serotonin augmentation on cognition and activities of daily living in patients with Alzheimer's disease. **METHOD:** The trial was designed as a 12-week randomized, placebo-controlled, double-blind study. One hundred twenty-two patients aged 55 to 85 years with mild-to-moderate Alzheimer's dementia were randomly allocated in 1 of the 3 treatment groups:

fluoxetine plus rivastigmine, rivastigmine alone, or placebo group. Efficacy measures comprised assessments of cognition, activities of daily living, and global functioning. Hamilton Depression Scale also was used to assess changes in mood throughout the study. **RESULT:** Fluoxetine plus rivastigmine and rivastigmine groups demonstrated improvement on measures of cognitive and memory without any significant difference; however, the former group did better in their activities of daily living and global functioning. Patients taking placebo had significant deterioration in all the efficacy measures. Patients taking rivastigmine or rivastigmine plus fluoxetine had improvements in Hamilton Depression Scale without significant differences. **CONCLUSIONS:** Concomitant use of selective serotonin-enhancing agents and acetyl cholinesterase inhibitors can provide greater benefit in activities of daily living and global functioning in patients with cognitive impairment. Because our study is preliminary, larger double-blind studies are needed to confirm the results.

Peskind, E. R., S. G. Potkin, et al. (2006). "Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial." *Am J Geriatr Psychiatry* **14**(8): 704-15.

OBJECTIVE: The objective of this study was to compare the efficacy and safety of the moderate-affinity, uncompetitive N-methyl-d-aspartate receptor antagonist, memantine, versus placebo in patients with mild to moderate Alzheimer disease (AD). **METHOD:** This was a randomized, double-blind, placebo-controlled clinical trial conducted at 42 U.S. sites. Participants were 403 outpatients with mild to moderate AD and Mini-Mental State Examination scores of 10-22 randomized to memantine (20 mg/day; N=201) or placebo (N=202) for 24 weeks. Primary outcomes were change from baseline at 24 weeks on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), a measure of cognition, and on the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), a global measure. Secondary outcomes included change on the Neuropsychiatric Inventory (NPI) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL(23)), measures of behavior and function, respectively. **RESULTS:** Most (82.4%) participants completed the trial. Memantine resulted in significantly better outcomes than placebo on measures of cognition, global status, and behavior when based on the protocol-specified primary last observation carried forward imputation as well as a mixed-models repeated-measures approach applied to the continuous outcomes. Treatment discontinuations because of adverse events for memantine versus placebo were 19 (9.5%) and 10 (5.0%), respectively. **CONCLUSIONS:** These results support the safety and efficacy of memantine for the treatment of mild to moderate AD.

Porsteinsson, A. P., G. T. Grossberg, et al. (2008). "Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial." *Curr Alzheimer Res* **5**(1): 83-9.

OBJECTIVE: To evaluate the efficacy and safety of memantine in patients with mild to moderate Alzheimer's disease (AD) receiving cholinesterase inhibitor (ChEI) treatment. **METHODS:** Participants (N= 433) with probable AD, Mini-Mental State Exam (MMSE) scores between 10-22 (inclusive), and concurrent stable use of ChEIs (donepezil, rivastigmine, galantamine) were randomized to placebo or memantine (20 mg once daily) for 24 weeks. Primary outcomes were changes from baseline on the Alzheimer's Disease

Assessment Scale-cognitive subscale (ADAS-cog) and on Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) score. Secondary measures comprised the 23-item Alzheimer Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL(23)), Neuropsychiatric Inventory (NPI), and MMSE. RESULTS: At the end of the trial, there were no statistically significant differences between the memantine- and placebo group on primary and secondary outcome measures. The incidence of adverse events (AEs) was similar between the two groups, with no AE occurring in more than 5% of memantine-treated patients and at a rate twice that of the placebo group. CONCLUSIONS: In this trial, memantine did not show an advantage over placebo based on protocol-specified primary or secondary analyses in patients with mild to moderate AD on stable ChEI regimens. There were no significant differences in tolerability and safety between the memantine- and placebo groups.

Rockwood, K., S. Fay, et al. (2006). "Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial." *Cmaj* **174**(8): 1099-105.

BACKGROUND: Although cholinesterase inhibitors have produced statistically significant treatment effects, their clinical meaningfulness in Alzheimer's disease is disputed. An important aspect of clinical meaningfulness is the extent to which an intervention meets the goals of treatment. METHODS: In this randomized controlled trial, patients with mild to moderate Alzheimer's disease were treated with either galantamine or placebo for 4 months, followed by a 4-month open-label extension during which all patients received galantamine. The primary outcome measures were Goal Attainment Scaling (GAS) scores from assessments by clinicians and by patients or caregivers of treatment goals set before treatment and evaluated every 2 months. Secondary outcome measures included the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), the Clinician's Interview-based Impression of Change plus Caregiver Input (CIBIC-plus), the Disability Assessment for Dementia (DAD) and the Caregiving Burden Scale (CBS). To evaluate treatment effect, we calculated effect sizes (as standardized response means [SRMs]) and p values. RESULTS: Of 159 patients screened, 130 (mean age 77 [standard deviation (SD) 7.7]; 63% women) were enrolled in the study (64 in the galantamine group and 66 in the placebo group); 128 were included in the analysis because they had at least one post-baseline evaluation. In the intention-to-treat analysis, the clinician-rated GAS scores showed a significantly greater improvement in goal attainment among patients in the galantamine group than among those in the placebo group (change from baseline score 4.8 [SD 9.6] v. 0.9 [SD 9.5] respectively; SRM = 0.41, p = 0.02). The patient- caregiver-rated GAS scores showed a similar improvement in the galantamine group (change from baseline score 4.2 [SD 10.6]); however, because of the improvement also seen in the placebo group (2.3 [SD 9.0]), the difference between groups was not statistically significant (SRM = 0.20, p = 0.27). Of the secondary outcome measures, the ADAS-cog scores differed significantly between groups (SRM = -0.36, p = 0.04), as did the CIBIC-plus scores (SRM = -0.40, p = 0.03); no significant differences were in either the DAD scores (SRM = 0.28, p = 0.13) or the CBS scores (SRM = -0.17, p = 0.38). INTERPRETATION: Clinicians, but not patients and caregivers, observed a significantly greater improvement in goal attainment among patients with mild to moderate Alzheimer's disease who were taking galantamine than among those who were taking placebo.

Saxton, J., R. K. Hofbauer, et al. (2012). "Memantine and functional communication in Alzheimer's disease: results of a 12-week, international, randomized clinical trial." *J Alzheimers Dis* **28**(1): 109-18.

Post hoc analyses suggest that memantine treatment may provide communication-related benefits in patients with Alzheimer's disease (AD). In this 12-week, international, randomized, double-blind, placebo-controlled trial of memantine (10 mg bid), the functional communication abilities of patients with AD (MMSE range: 10-19) were assessed using the Functional Linguistic Communication Inventory (FLCI; primary measure). Two combined subscales (Social Communication and Communication of Basic Needs) from the American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults (ASHA FACS; secondary measure) were administered to caregivers. Treatment-emergent adverse events were also recorded. After 12 weeks, memantine-treated patients (n = 133) demonstrated a non-significant improvement on the FLCI (placebo: -0.6; memantine: 0.7; p = 0.070, LOCF) and a significant improvement on the ASHA FACS (placebo: -5.3; memantine: 0.5; p = 0.022), compared with placebo-treated patients (n = 124). Memantine had a low incidence of adverse events. In patients with moderate AD, memantine treatment improved functional communication, as recognized by caregivers.

Scarpini, E., G. Bruno, et al. (2011). "Cessation versus continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: a randomized, double blind, placebo controlled withdrawal trial." *J Alzheimers Dis* **26**(2): 211-20.

Galantamine improved symptoms in Alzheimer's disease (AD) patients after 5 to 6 months of treatment. To examine long-term outcomes, this study assessed if continuing of galantamine treatment beyond 12 months delayed further cognitive deterioration. It consisted of two phases: an open label (OL) phase (12 months), followed by a double blind, randomized, placebo controlled withdrawal phase (up to 24 months). Subjects with mild to moderate AD were included in the study and titrated up to 16 mg/day of galantamine. Subjects were eligible to enter the double blind phase if a cognitive decline of <4 points on AD Assessment Scale-cognitive subscale (ADAS-cog)/11 was recorded at the end of the OL phase. The differences between galantamine and placebo in time to dropout were estimated using the Cox proportional hazard model. 47.4% of galantamine and 31.7% of placebo subjects completed the double blind phase. Placebo subjects were more likely to discontinue prematurely than galantamine subjects for any reason (hazard ratio [HR] 1.76, 95% confidence interval [CI] 1.10-2.81, p = 0.02), or lack of efficacy (HR 1.80, 95% CI 1.02-3.18, p = 0.04); no statistically significant difference was seen for a change in ADAS-cog \geq 4 between treatment groups (HR 1.66, 95% CI 0.78-3.54, p = 0.19). Subjects who responded to 12 months of galantamine treatment benefited from continued drug therapy for up to 36 months. Galantamine was effective in delaying time to cognitive deterioration in subjects with mild to moderate AD. Treatment was generally safe and well tolerated.

Suh, G. H., H. Y. Jung, et al. (2008). "Economic and clinical benefits of galantamine in the treatment of mild to moderate Alzheimer's disease in a Korean population: a 52-week prospective study." *J Korean Med Sci* **23**(1): 10-7.

To evaluate the impact of galantamine treatment on the function, caregiver time, and resource used in the treatment of patients with mild to moderate Alzheimer's disease (AD), costs and outcomes were evaluated during a 52-week prospective, randomized, double-blind, community-controlled trial of galantamine. Patients received either galantamine treatment (n=72) or no treatment (n=66). The analysis was performed from a societal perspective. Galantamine treatment reduced time spent caring for the patients and maintained improved functional capacity, whereas, when no treatments were given, a great increase in caregiver time and progressive functional deteriorations were observed. Saved caregiver time was equivalent to 113 working days per year. After 52 weeks, mean total annual costs per patient were 14,735,000 Korea Won (KRW) (USD 12,315) for patients with galantamine treatment and 25,325,000 KRW (USD 21,166) for patients without treatment. Adjusted annual cost saving of galantamine treatment was 6,428,000 KRW (USD 5,372) when compared to no treatment (p=0.0089). Galantamine had a beneficial effect not only to slow functional decline in patients with mild to moderate AD, but also to save a substantial amount of costs, closely related to reduction in caregiver burden and decrease in caregiver time.

van Dyck, C. H., P. N. Tariot, et al. (2007). "A 24-week randomized, controlled trial of memantine in patients with moderate-to-severe Alzheimer disease." *Alzheimer Dis Assoc Disord* **21**(2): 136-43.

This study examined the efficacy and safety of memantine monotherapy in patients with moderate-to-severe Alzheimer disease (AD). Patients not receiving a cholinesterase inhibitor (N=350) were randomized to receive memantine (20 mg/d) or placebo during this 24-week, double-blind, placebo-controlled trial. Prospectively defined analyses failed to demonstrate a statistically significant benefit of memantine treatment compared with placebo on the Severe Impairment Battery (SIB) at week 24 end point, although a significant advantage was observed for memantine at weeks 12 and 18. The 19-item Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL19) did not differ significantly between groups in any analysis. Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-Plus) did not significantly favor memantine at week 24 despite a significant advantage for memantine at weeks 12 and 18. Other secondary outcomes showed no significant treatment differences. Post hoc analyses of potentially confounding covariates and alternative methods of imputing missing data did not substantially alter the results. Because of the violations of normality assumptions for the SIB and ADCS-ADL19, nonparametric analyses were performed; statistically significant benefit of memantine over placebo was demonstrated at week 24 for the SIB but not the ADCS-ADL19. The type and incidence of adverse events were similar in both groups.

Wilkinson, D., N. C. Fox, et al. (2012). "Memantine and brain atrophy in Alzheimer's disease: a 1-year randomized controlled trial." *J Alzheimers Dis* **29**(2): 459-69.

The primary objective of this study was to evaluate the rate of total brain atrophy (TBA) with serial magnetic resonance imaging (MRI), using the Brain Boundary Shift Integral (BBSI), in patients with probable Alzheimer's disease (AD) over the course of 52 weeks of treatment with memantine or placebo. This was a multi-national, randomized, double-blind, placebo-controlled, fixed-dose 1-year study. Patients were randomized (1 : 1) to

treatment with placebo or memantine. Patients randomized to memantine were up-titrated to the target dose of 20 mg/day over 4 weeks. MRI scans were collected at screening and at Weeks 4, 42, and 52. Secondary efficacy assessments included several cognitive and behavioral scales. 518 patients were screened, 278 patients were randomized, and 217 patients completed the study. In the primary efficacy analysis, the differences in TBA rates between memantine (15.2 mL/year) and placebo (15.3 mL/year) were not statistically significant (-0.04 mL/year [(95% CI: -2.60, 2.52), $p = 0.98$]). There was a statistically significant correlation between change in TBA and change in most cognitive and behavioral scale scores. Patients who were not treated with acetyl cholinesterase inhibitors (AChEIs) showed a significantly lower TBA rate than patients treated with AChEIs. Memantine had a placebo-level incidence of adverse events. There were no statistically significant differences between memantine and placebo in total brain or hippocampal atrophy rates in patients with probable AD treated for 1 year. The biological relevance of cerebral atrophy was supported by a significant correlation between rate of atrophy and decline in cognitive and behavioral outcomes.

Winblad, B., J. Cummings, et al. (2007). "A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease--rivastigmine patch versus capsule." *Int J Geriatr Psychiatry* **22**(5): 456-67.

OBJECTIVES: To compare the efficacy, safety and tolerability of a novel rivastigmine transdermal patch with conventional rivastigmine capsules and placebo in patients with Alzheimer's disease (AD). **METHODS:** In this 24-week, multicenter, double-blind, double-dummy, placebo- and active-controlled trial, patients with probable AD were randomized to one of four treatment groups: 12 mg/day rivastigmine capsules; 10 cm² (9.5 mg/24 h) rivastigmine patch; 20 cm² (17.4 mg/24 h) rivastigmine patch; or placebo. Primary efficacy measures were the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and Alzheimer's Disease Cooperative Study--Clinical Global Impression of Change (ADCS-CGIC). **RESULTS:** One thousand one hundred and ninety five AD patients from 21 countries participated in the study. Treatment differences (vs placebo) on the ADAS-Cog at Week 24 in 10 cm² patch, 20 cm² patch and capsule groups were 1.6 ($p=0.005$), 2.6 ($p<0.001$) and 1.6 ($p=0.003$). Treatment differences on the ADCS-CGIC were 0.3 ($p=0.01$), 0.2 ($p=0.054$) and 0.3 ($p=0.009$). Comparison between the 10 cm² patch and the capsule revealed non-inferiority. Rates of nausea in the 10 cm² patch and capsule groups were 7.2% and 23.1%, respectively; rates of vomiting were 6.2% and 17.0%, respectively. Moderate or severe skin irritation occurred in 10% patients across the four patch sizes (5, 10, 15 and 20 cm²). **CONCLUSIONS:** The target dose of 10 cm² rivastigmine patch provides efficacy similar to the highest doses of capsules with a superior tolerability profile. The transdermal patch with rivastigmine may offer convenience important to many caregivers and patients.

Winblad, B., G. Grossberg, et al. (2007). "IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease." *Neurology* **69**(4 Suppl 1): S14-22.

The rivastigmine patch is the first transdermal treatment for Alzheimer disease (AD). By providing continuous delivery of drug into the bloodstream over 24 hours, transdermal delivery may offer benefits superior to those of oral administration. This study compared the efficacy, safety and tolerability of rivastigmine patches with capsules and placebo.

IDEAL (Investigation of transDermal Exelon in ALzheimer's disease) was a 24-week, double-blind, double-dummy, placebo- and active-controlled study. Patients with AD were randomized to placebo or one of three active treatment target dose groups: 10-cm(2) rivastigmine patch (delivering 9.5 mg/24 hours); 20-cm(2) rivastigmine patch (17.4 mg/24 hours); or 6-mg BID rivastigmine capsules. Primary efficacy measures were the Alzheimer's Disease Assessment Scale-Cognitive subscale and Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. Secondary outcome measures assessed a range of domains, including behavior, cognitive performance, attention, executive functions, and activities of daily living. A total of 1,195 AD patients participated. All rivastigmine treatment groups showed significant improvement relative to placebo. The 10-cm(2) patch showed similar efficacy to capsules, with approximately two-thirds fewer reports of nausea (7.2% vs 23.1%) and vomiting (6.2% vs 17.0%), incidences statistically not significantly different from placebo (5.0% and 3.3% for nausea and vomiting, respectively). The 20-cm(2) patch showed earlier improvement and numerically superior cognitive scores vs the 10-cm(2) patch with similar tolerability to capsules. Local skin tolerability was good. The transdermal patch with rivastigmine may offer additional therapeutic benefits and may prove to be the best delivery system for this drug to treat AD.

Secondary analyses of included primary trial publications

Gaudig, M., U. Richarz, et al. (2011). "Effects of galantamine in Alzheimer's disease: double-blind withdrawal studies evaluating sustained versus interrupted treatment." *Curr Alzheimer Res* 8(7): 771-80.

To evaluate the effects of galantamine withdrawal, and compare this with uninterrupted therapy, two 6-week double-blind withdrawal studies (Studies 1 and 2) were performed. These enrolled individuals who had completed one of two 3- or 5-month randomized clinical trials (parent trials) involving patients with mild to moderate Alzheimer's disease (AD). In Study 1 (GAL-USA-11; n=723), patients continuously treated with galantamine 16 mg/day exhibited a mean (+/- standard error [SE]) improvement in 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale score of 1.8 (+/- 0.46) points at Week 6 compared with the parent trial baseline, ($p < 0.001$ vs placebo; observed cases analysis). Over the same period, patients switched from galantamine to placebo and those who had received continuous placebo, exhibited mean (+/- SE) deteriorations of 0.7 (+/- 0.49) and 1.2 (+/- 0.49) points, respectively. Similar trends were apparent in Study 2 (GAL-USA-5; n=118). In Study 1, subgroup analyses demonstrated cognitive benefits with continuing galantamine treatment and deterioration associated with galantamine withdrawal in patients with advanced moderate AD (baseline Mini-Mental State Examination score ≤ 14) and in individuals deemed non-responsive in terms of Clinician's Interview-Based Impression of Change-plus Caregiver Input (CIBIC-plus) evaluation at the end of the parent trial (CIBIC-plus score > 4). No safety issues were identified. In patients with mild to moderate AD who have exhibited cognitive benefits from up to 5 months' galantamine treatment, continuing therapy reinforces previously achieved benefit, whereas in patients in whom galantamine is discontinued, although no safety concerns arise, the natural progression of AD is apparent.