

Drug Class Review on Alzheimer's Drugs

Update #2: Preliminary Scan Report #3

June 2009

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

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OBJECTIVE

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

Date of Last Report

June 2006 (searches through December 2005)

Dates of Previous Update Scans

Preliminary Update Scan #1: June 2007

Preliminary Update Scan #2: May 2008

Scope and Key Questions

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

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

Inclusion criteria**Populations**

- Study participants with Alzheimer's disease

Interventions

Five different treatments are currently available in the United States:

- Donepezil
- Galantamine
- Rivastigmine
- Tacrine
- Memantine

Effectiveness outcomes

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

Safety outcomes

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

Study design

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

METHODS

Literature Search

To identify relevant citations, we searched Medline from March 2005 through June 17, 2009 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/index_e.html) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X.02) and duplicate citations were removed.

Study Selection

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

RESULTS

Overview

Searches resulted in 152 citations. Of those, there are 20 new potentially relevant RCTs (Appendix A).

New Drugs

None at this time.

New Safety Alerts

None at this time.

Appendix A. Abstracts of potentially relevant new studies of Alzheimer's drugs

1. Aronson, S., B. Van Baelen, et al. (2009). "Optimal dosing of galantamine in patients with mild or moderate Alzheimer's disease: post Hoc analysis of a randomized, double-blind, placebo-controlled trial." *Drugs Aging* **26**(3): 231-9.

BACKGROUND: Galantamine (hydrobromide), a reversible acetylcholinesterase inhibitor and allosteric nicotinic receptor modulator, slows cognitive and functional decline in mild to moderate dementia of the Alzheimer's type. Although several drugs are indicated for mild to moderate Alzheimer's disease (AD), no published study has separately analysed mild and moderate AD subgroups to assess the effect of dosage. **OBJECTIVE:** To compare the efficacy and safety of galantamine 16 and 24 mg/day in patient subgroups with mild or moderate AD. **METHODS:** This post hoc analysis (n = 838) of a 5-month, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of galantamine 16 and 24 mg/day in a subgroup of patients with mild AD (Mini-Mental State Examination [MMSE] >18) and a subgroup with moderate AD (MMSE 10-18). Efficacy outcomes included the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) score and treatment response (ADAS-cog maintenance [≥ 0 -point improvement], improvement ≥ 4 points and improvement ≥ 7 points). **RESULTS:** Mean ADAS-cog scores of patients with mild AD demonstrated significant improvement from baseline with galantamine 16 and 24 mg/day ($p < 0.001$ for both), whereas cognitive function did not change significantly for placebo recipients ($p = 0.559$). Patients with moderate AD improved with galantamine 24 mg/day ($p = 0.009$) but not with 16 mg/day ($p = 0.768$); a decline occurred with placebo ($p < 0.001$). A greater proportion of patients treated with galantamine 16 mg/day (76% and 52% for mild and moderate AD, respectively) or 24 mg/day (69% and 61%, respectively) demonstrated a treatment response (i.e. ADAS-cog was maintained or improved) relative to placebo (55% and 28%, respectively; $p < 0.05$). Patients with moderate AD trended toward greater response with the 24 mg/day dosage than with the 16 mg/day dosage. Galantamine was well tolerated. Adverse events were comparable for all study groups with mild or moderate AD. **CONCLUSION:** This post hoc analysis suggests that galantamine 16 mg/day is the optimal dosage for patients with mild AD, as similar efficacy is observed with the 24 mg/day dose. However, patients with moderate AD appear to gain additional benefit from galantamine 24 mg/day.

2. Bakchine, S. and 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.

3. 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.

4. 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 adherence 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.

5. 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.

6. 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.

7. Feldman, H. H. and 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.

8. Holmes, C., D. Wilkinson, et al. (2007). "Risperidone and rivastigmine and agitated behaviour in severe Alzheimer's disease: a randomised double blind placebo controlled study." *Int J Geriatr Psychiatry* 22(4): 380-1.

9. 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 \geq 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.

10. Homma, A., Y. Imai, et al. (2009). "Long-term safety and efficacy of donepezil in patients with severe Alzheimer's disease: results from a 52-week, open-label, multicenter, extension study in Japan." *Dement Geriatr Cogn Disord* **27**(3): 232-9.

BACKGROUND/AIMS: A 6-month, randomized, double-blind, placebo-controlled study was extended to evaluate long-term safety and efficacy of donepezil in community-dwelling Japanese patients with severe Alzheimer's disease (AD). METHODS: 189 patients were enrolled from the double-blind study into a 52-week, open-label extension study. After a 2- to 8-week washout, donepezil was escalated within 6 weeks to 10 mg/day. Main outcomes were Severe Impairment Battery (SIB), Alzheimer's Disease Cooperative Study-Activities of Daily Living scale for severe AD (ADCS-ADL-sev) and Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). Safety parameters were monitored throughout. RESULTS: Overall, mean change from extension study baseline in SIB scores improved until week 24; however, scores were influenced by prior treatment during the double-blind study and by length of washout. Patients treated with donepezil retained some treatment benefits after a washout of 2-4 weeks but lost all treatment benefits after a washout of 4-8 weeks. There was no change in ADCS-ADL-sev or BEHAVE-AD scores. Adverse events were consistent with the known donepezil safety profile. CONCLUSION: Donepezil is effective and safe for symptomatic treatment of severe AD for at least 1 year. Patients who receive donepezil 10 mg daily with little or no interruption achieve the best long-term outcome.

11. 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].).

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

19. 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 $\geq 10\%$ 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.

20. 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-cm² rivastigmine patch (delivering 9.5 mg/24 hours); 20-cm² 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-cm² 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-cm² patch showed earlier improvement and numerically superior cognitive scores vs the 10-cm² 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.