

Drug Class Review on Alzheimer's Drugs

Update #3: Preliminary Scan Report

June 2007

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 Update

February 2006 (searches through December 2005)

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

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from March 2005 through May 07, 2007 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 8.0) 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 313 citations. Of those, there are 49 new potentially relevant studies (see Appendix A, attached).

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. Ancoli-Israel, S., J. Amatniek, et al. (2005). "Effects of galantamine versus donepezil on sleep in patients with mild to moderate Alzheimer disease and their caregivers: a double-blind, head-to-head, randomized pilot study." *Alzheimer Dis Assoc Disord* **19**(4): 240-5.

OBJECTIVE: To examine the effects of galantamine and donepezil on patient and caregiver sleep. **METHODS:** In this randomized, 8-week, double-blind, parallel-group, multicenter, pilot comparison of galantamine and donepezil, safety and efficacy data were collected. Objective and subjective changes in sleep of patients (N = 63) and their caregivers were measured. Clinicians assessed changes in patient global function. As this was a pilot study, only descriptive statistics are presented. **RESULTS:** In general, neither galantamine nor donepezil, at stable doses, were associated with decrements in actigraphy sleep measurements. However, mean scores in all measures of sleep showed a tendency for minimal improvements in galantamine-treated patients and minimal decrements in the donepezil-treated patients. The same tendencies were present in caregiver sleep measures. Global function either improved or remained stable in a higher percentage of patients treated with galantamine than with donepezil. Galantamine and donepezil were both well tolerated and safe. **CONCLUSIONS:** This pilot study was the first to compare the effects of these drugs on sleep in patients or caregivers. Both drugs were safe and well tolerated. Neither galantamine nor donepezil negatively affected sleep; however, on every measure, there were suggestions of slightly more benefit associated with galantamine treatment. Although these results are suggestive of a differential effect of the drugs on sleep, further research is needed to confirm the clinical significance.

2. Aupperle, P. M., B. Koumaras, et al. (2004). "Long-term effects of rivastigmine treatment on neuropsychiatric and behavioral disturbances in nursing home residents with moderate to severe Alzheimer's disease: results of a 52-week open-label study." *Curr Med Res Opin* **20**(10): 1605-12.

OBJECTIVES: To evaluate the safety and efficacy of long-term treatment with rivastigmine (3-12 mg/day) and its effects on neuropsychiatric and behavioral disturbances in nursing home patients with moderate to severe probable Alzheimer's disease (AD). **METHODS:** A prospective, multicenter 26-week open-label extension to a 26-week open-label study (52 week results) of rivastigmine treatment in patients with Mini-Mental State Examination (MMSE) scores of 6-15 inclusive, residing in nursing homes at 13 centers in the US. Effects of treatment with rivastigmine for up to 52 weeks on neuropsychiatric and behavioral symptoms were examined using the Neuropsychiatric Inventory-Nursing Home (NPI-NH) scale. Cognitive function was assessed by the MMSE, and the Naming Objects and Fingers Test (NOFT) subset of the Alzheimer's Disease Assessment Scale -- Cognitive subscale (ADAS-Cog). Global functioning was assessed using the simplified Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus). **RESULTS:** Rivastigmine (3-12 mg/day) significantly improved neuropsychiatric and behavioral symptoms compared to baseline (in patients

with specific behavioral disturbances at baseline) in observed cases (OC) and last observation carried forward (LOCF) analyses. Over 52 weeks, treatment with rivastigmine significantly improved 10 of 12 individual NPI-NH domains from baseline in LOCF patients with symptoms present at baseline. Cognitive function was stable, indicated by the lack of decline in MMSE and the NOFT. Global function was stabilized or improved in greater than half of the patients as indicated by the simplified CIBIC-Plus scores. CONCLUSION: Rivastigmine showed potential benefit in the long-term treatment of behavioral symptoms as well as cognitive and global functioning in nursing home residents with moderate to severe AD with concurrent behavioral symptoms present at baseline. Although these results suggest that treatment with rivastigmine may have beneficial behavioral effects and cognitive benefits on patients with moderate to severe AD, they are subject to the limitations of an open-label study.

3. Babic, T., D. Mahovic Lakusic, et al. (2004). "ApoE genotyping and response to galanthamine in Alzheimer's disease--a real life retrospective study." *Coll Antropol* **28**(1): 199-204.

This study was undertaken to evaluate the effect of galanthamine, a new cholinesterase inhibitor on cognitive performances in 84 patients with various apoE genotype and Alzheimer's disease (AD) during the six-month treatment. The diagnosis of AD was made on the basis of NINCDS/ADRDN criteria. ApoE4 genotype was determined by PCR procedure. The cognitive performance was assessed MMSE at baseline and six months later. The difference among the groups was statistically analyzed by ANOVA model and Pearson's chi2-test. The MMSE at baseline in all completes was 18.0 +/- 3.73, whereas the mean value of MMSE after 6 months was 16.4 +/- 5.61 indicating significant deterioration ($p < 0.01$). Of the 84 patients, 14 (16.9%) were apoE4 homozygous, 41 (49%) were heterozygous, whereas 29 (35%) were apoE4 negative. The significant number of responders was observed among apoE4 homozygous patients (71%; $\chi^2 = 6.89$; $p = 0.032$). The subgroup of apoE4 homozygous patients with AD in its mild to moderate stage may be considered as responders to galanthamine.

4. Beusterien, K. M., S. K. Thomas, et al. (2004). "Impact of rivastigmine use on the risk of nursing home placement in a US sample." *CNS Drugs* **18**(15): 1143-8.

INTRODUCTION: Although numerous studies have evaluated predictors of nursing home placement (NHP), few have focused on the effects of cholinesterase inhibitor (ChEI) use on NHP. The objective of this study was to compare the risk of NHP between rivastigmine patients versus no-ChEI patients (control group), and secondly, between rivastigmine versus donepezil patients. METHODS: A retrospective analysis of a large US medical claims database was performed. Eligible subjects were identified from those who had continuous medical coverage from 1 April 2000 to 30 June 2002. Rivastigmine and donepezil subjects were new users, defined as having received no ChEI treatment during the initial 6 months of the study. Control subjects were diagnosed with Alzheimer's disease (AD) at some point after the initial 6-month period. All subjects were followed from baseline (initiation of ChEI therapy or initial AD diagnosis) to the date of NHP or 30 June 2002, whichever occurred first. RESULTS: In the rivastigmine (n=1181), donepezil (n=3864), and control (n=517) groups, 3.7%, 4.4% and 11.0% of

subjects, respectively, had an NHP ($p < 0.001$ for rivastigmine versus control). A Cox proportional hazard model, controlling for age, gender, comorbidities and behavioural disorders, showed that the control subjects were almost 3-fold more likely to have NHP than rivastigmine subjects (hazard ratio [HR]=2.71; 95% CI 1.82, 4.03). The difference in the risk of NHP was not significant between the rivastigmine and donepezil groups (HR=1.23; 95% CI 0.89, 1.71). **DISCUSSION:** This study demonstrated that rivastigmine decreased the risk of NHP in a large insured population.

5. Birks, J. (2006). "Cholinesterase inhibitors for Alzheimer's disease." Cochrane Database Syst Rev(1): CD005593.

BACKGROUND: Since the introduction of the first cholinesterase inhibitor (ChEI) in 1997, most clinicians and probably most patients would consider the cholinergic drugs, donepezil, galantamine and rivastigmine, to be the first line pharmacotherapy for mild to moderate Alzheimer's disease. The drugs have slightly different pharmacological properties, but they all work by inhibiting the breakdown of acetylcholine, an important neurotransmitter associated with memory, by blocking the enzyme acetylcholinesterase. The most that these drugs could achieve is to modify the manifestations of Alzheimer's disease. Cochrane reviews of each ChEI for Alzheimer's disease have been completed (Birks 2005, Birks 2005b and Loy 2005). Despite the evidence from the clinical studies and the intervening clinical experience the debate on whether ChEIs are effective continues. **OBJECTIVES:** To assess the effects of donepezil, galantamine and rivastigmine in people with mild, moderate or severe dementia due to Alzheimer's disease. **SEARCH STRATEGY:** The Cochrane Dementia and Cognitive Improvement Group's Specialized Register was searched using the terms 'donepezil', 'E2020', 'Aricept', galanthamin*, galantamin*, reminyl, rivastigmine, exelon, "ENA 713" and ENA-713 on 12 June 2005. This Register contains up-to-date records of all major health care databases and many ongoing trial databases. **SELECTION CRITERIA:** All unconfounded, blinded, randomized trials in which treatment with a ChEI was compared with placebo or another ChEI for patients with mild, moderate or severe dementia due to Alzheimer's disease. **DATA COLLECTION AND ANALYSIS:** Data were extracted by one reviewer (JSB), pooled where appropriate and possible, and the pooled treatment effects, or the risks and benefits of treatment estimated. **MAIN RESULTS:** The results of 13 randomized, double blind, placebo controlled trials demonstrate that treatment for periods of 6 months and one year, with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due to Alzheimer's disease produced improvements in cognitive function, on average -2.7 points (95%CI -3.0 to -2.3), in the midrange of the 70 point ADAS-Cog Scale. Study clinicians blind to other measures rated global clinical state more positively in treated patients. Benefits of treatment were also seen on measures of activities of daily living and behaviour. None of these treatment effects are large. There is nothing to suggest the effects are less for patients with severe dementia or mild dementia, although there is very little evidence for other than mild to moderate dementia. More patients leave ChEI treatment groups, approximately 29%, on account of adverse events than leave the placebo groups (18%). There is evidence of more adverse events in total in the patients treated with a ChEI than with placebo. Although

many types of adverse event were reported, nausea, vomiting, diarrhoea, were significantly more frequent in the ChEI groups than in placebo. There are four studies, all supported by one of the pharmaceutical companies, in which two ChEIs were compared, two studies of donepezil compared with galantamine, and two of donepezil compared with rivastigmine. In three studies the patients were not blinded to treatment, only the fourth, DON vs RIV/Bullock is double blind. Two of the studies provide little evidence, they are of 12 weeks duration, which is barely long enough to complete the drug titration. There is no evidence from DON vs GAL/Wilcock of a treatment difference between donepezil and galantamine at 52 weeks for cognition, activities of daily living, the numbers who leave the trial before the end of treatment, the number who suffer any adverse event, or any specific adverse event. There is no evidence from DON vs RIV/Bullock of a difference between donepezil and rivastigmine for cognitive function, activities of daily living and behavioural disturbance at two years. Fewer patients suffer adverse events on donepezil than rivastigmine. **AUTHORS' CONCLUSIONS:** The three cholinesterase inhibitors are efficacious for mild to moderate Alzheimer's disease. It is not possible to identify those who will respond to treatment prior to treatment. There is no evidence that treatment with a ChEI is not cost effective. Despite the slight variations in the mode of action of the three cholinesterase inhibitors there is no evidence of any differences between them with respect to efficacy. There appears to be less adverse effects associated with donepezil compared with rivastigmine. It may be that galantamine and rivastigmine match donepezil in tolerability if a careful and gradual titration routine over more than three months is used. Titration with donepezil is more straightforward and the lower dose may be worth consideration.

6. Birks, J. and R. J. Harvey (2006). "Donepezil for dementia due to Alzheimer's disease." Cochrane Database Syst Rev(1): CD001190.

BACKGROUND: Alzheimer's disease is the most common cause of dementia in older people. One of the aims of therapy is to inhibit the breakdown of a chemical neurotransmitter, acetylcholine, by blocking the relevant enzyme. This can be done by a group of chemicals known as cholinesterase inhibitors. **OBJECTIVES:** The objective of this review is to assess whether donepezil improves the well-being of patients with dementia due to Alzheimer's disease. **SEARCH STRATEGY:** The Cochrane Dementia and Cognitive Improvement Group's Specialized Register was searched using the terms 'donepezil', 'E2020' and 'Aricept' on 12 June 2005. This Register contains up-to-date records of all major health care databases and many ongoing trial databases. Members of the Donepezil Study Group and Eisai Inc were contacted. **SELECTION CRITERIA:** All unconfounded, double-blind, randomized controlled trials in which treatment with donepezil was compared with placebo for patients with mild, moderate or severe dementia due to Alzheimer's disease. **DATA COLLECTION AND ANALYSIS:** Data were extracted by one reviewer (JSB), pooled where appropriate and possible, and the pooled treatment effects, or the risks and benefits of treatment estimated. **MAIN RESULTS:** 23 trials are included, involving 5272 participants. Most trials were of 6 months or less duration in selected patients. Available outcome data cover domains including cognitive function, activities of daily living, behaviour, global clinical state

and health care resource costs. For cognition there is a statistically significant improvement for both 5 and 10 mg/day of donepezil at 24 weeks compared with placebo on the ADAS-Cog scale (-2.01 points MD, 95% CI -2.69 to -1.34, $p < 0.00001$); -2.80 points, MD 95% CI -3.74 to -2.10, $p < 0.00001$) and for 10 mg/day donepezil compared with placebo at 52 weeks (1.84 MMSE points, 95% CI, 0.53 to 3.15, $p = 0.006$). The results show some improvement in global clinical state (assessed by a clinician) in people treated with 5 and 10 mg/day of donepezil compared with placebo at 24 weeks for the number of patients showing improvement or no change (OR 2.18, 95% CI 1.53 to 3.11, $p < 0.0001$, OR 2.38, 95% CI 1.78 to 3.19, $p < 0.00001$). Benefits of treatment were also seen on measures of activities of daily living and behaviour, but not on the quality of life score. There were significantly more withdrawals before the end of treatment from the 10 mg/day (but not the 5 mg/day) donepezil group compared with placebo which may have resulted in some overestimation of beneficial changes at 10 mg/day. Benefits on the 10 mg/day dose were marginally larger than on the 5 mg/day dose. Two studies presented results for health resource use, and the associated costs. There were no significant differences between treatment and placebo for any item, the cost of any item, and for the total costs, and total costs including the informal carer costs. A variety of adverse effects were recorded, with more incidents of nausea, vomiting, diarrhoea, muscle cramps, dizziness, fatigue and anorexia (significant risk associated with treatment) in the 10 mg/day group compared with placebo but very few patients left a trial as a direct result of the intervention. **AUTHORS' CONCLUSIONS:** People with mild, moderate or severe dementia due to Alzheimer's disease treated for periods of 12, 24 or 52 weeks with donepezil experienced benefits in cognitive function, activities of daily living and behaviour. Study clinicians rated global clinical state more positively in treated patients, and measured less decline in measures of global disease severity. There is some evidence that use of donepezil is neither more nor less expensive compared with placebo when assessing total health care resource costs. Benefits on the 10 mg/day dose were marginally larger than on the 5 mg/day dose. Taking into consideration the better tolerability of the 5 mg/day donepezil compared with the 10 mg/day dose, together with the lower cost, the lower dose may be the better option. The debate on whether donepezil is effective continues despite the evidence of efficacy from the clinical studies because the treatment effects are small and are not always apparent in practice.

7. Bullock, R., H. Bergman, et al. (2006). "Effect of age on response to rivastigmine or donepezil in patients with Alzheimer's disease." *Curr Med Res Opin* **22**(3): 483-94.

BACKGROUND: Younger Alzheimer's disease (AD) patients appear to differ genetically and neuropathologically from older AD patients, and may experience a more aggressive disease course compared with older patients. A randomised trial investigated the efficacy and tolerability of rivastigmine, an inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), and donepezil, an AChE-selective inhibitor, in patients with AD over a 2-year period. This retrospective analysis investigated whether younger and older patients showed differential tolerability and efficacy responses to cholinesterase inhibitor treatment. **METHODS:** For the current analysis, patients were divided according to age at baseline: those aged < 75 years and those aged ≥ 75 years.

Efficacy measures were the Severe Impairment Battery (SIB), Neuropsychiatric Inventory (NPI), Global Deterioration Scale (GDS), Mini-Mental State Examination (MMSE) and the AD Cooperative Study Activities of Daily Living scale (ADCS-ADL). Changes in efficacy parameters and adverse event frequencies were calculated for rivastigmine and donepezil-treated patients in both age groups. Exploratory analyses were also conducted on SIB, ADCS-ADL and NPI in patients who consented to pharmacogenetic testing at baseline. Genotyping of the apolipoprotein E (APOE) epsilon4 allele and the BuChE K-variant was conducted using the TaqMan assay. Main efficacy analyses were based on an intent-to-treat last observation carried forward (ITT-LOCF) population. RESULTS: Of the 994 patients who received the study drug, 362 (36.4%) were younger than 75 years and 632 (63.6%) were aged 75 years or over. Rivastigmine provided significant benefits in younger patients compared with donepezil on the NPI-10, NPI-12, NPI-D, GDS and ADCS-ADL (all $p < 0.05$, ITT-LOCF). With the exception of the NPI-D in favour of donepezil ($p < 0.05$, ITT-LOCF), no significant treatment differences were observed in older patients. Younger patients with two wild-type BuChE alleles had a significantly greater response to rivastigmine than donepezil on the ADCS-ADL ($p < 0.01$, ITT-LOCF) and SIB ($p < 0.05$, ITT-LOCF). The most common adverse events were nausea and vomiting and these were more frequent in rivastigmine-treated patients. CONCLUSION: In this sub group analysis, patients younger than 75 years of age showed greater treatment responses to rivastigmine than donepezil. Analysis of response by BuChE genotype suggests that this differential effect may be due to the inhibition of BuChE, in addition to AChE, by rivastigmine.

8. Bullock, R. and A. Dengiz (2005). "Cognitive performance in patients with Alzheimer's disease receiving cholinesterase inhibitors for up to 5 years." *Int J Clin Pract* **59**(7): 817-22.

The cholinesterase inhibitors (ChE-Is)--rivastigmine, donepezil and galantamine--demonstrated efficacy in large, 6-month, double-blind, placebo-controlled trials, and are widely used for the symptomatic treatment of patients with mild-to-moderate Alzheimer's disease (AD). Over the past few years, data have emerged, suggesting that these agents may have long-term benefits. These data have been summarized in this study, followed by an interpretation of clinical relevance. Data were identified by searches of Medline((R)) and references from relevant English-language articles. The search words 'Alzheimer', 'donepezil', 'rivastigmine', 'galantamine' and 'long term' were used. In addition, recent data presented at international congresses and/or provided by colleagues in this field of research were included in order to ensure maximum topicality. Data are available showing cognitive performance in patients remaining on rivastigmine for up to 5 years ($n = 83$), donepezil for up to 4.9 years ($n = 18$) and galantamine for up to 4 years ($n = 185$). Most of these data come from open-label studies and need to be interpreted with caution. The data appear to suggest that patients, caregivers and physicians will still see some decline on ChE-Is after a period of stabilization, but this may be slower and later than expected if the patients were left untreated. This applies across all domains of AD - not simply cognition - and function can be relatively preserved, even if cognitive scores are falling. Despite the limitations of current data, the information reviewed in this

study may help practising doctors assess the long-term value of ChE-Is in this consistently progressive disease.

9. Bullock, R., J. Touchon, et al. (2005). "Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period." *Curr Med Res Opin* **21**(8): 1317-27.

OBJECTIVES: Randomised controlled trials that directly compare cholinesterase inhibitors for the treatment of Alzheimer's disease have been characterised by significant methodological limitations. As a consequence, they have failed to establish whether there are differences between agents in this class. To help address this question, a double-blind, randomised, controlled, multicentre trial was designed to evaluate the efficacy and tolerability of cholinesterase inhibitor treatment in patients with moderate to moderately-severe Alzheimer's disease over a 2-year period. **METHODS:** Patients were randomly assigned to rivastigmine 3-12 mg/day or donepezil 5-10 mg/day. Efficacy measures comprised assessments of cognition, activities of daily living, global functioning and behavioural symptoms. Safety and tolerability assessments included adverse events and measurement of vital signs. **RESULTS:** In total, 994 patients received cholinesterase inhibitor treatment (rivastigmine, n = 495; donepezil, n = 499), and 57.9% of patients completed the study. The most frequent reason for premature discontinuation in both treatment groups was adverse events, primarily gastrointestinal. Adverse events were more frequent in the rivastigmine group during the titration phase, but similar in the maintenance phase. Serious adverse events were reported by 31.7% of rivastigmine- and 32.5% of donepezil-treated patients, respectively. Rivastigmine and donepezil had similar effects on measures of cognition and behaviour, but rivastigmine showed a statistically significant advantage on measures of activities of daily living and global functioning in the ITT-LOCF population. However, this was not maintained in the non-ITT-LOCF populations. In secondary subgroup analyses, AD patients who had genotypes that encoded for full expression of the butyrylcholinesterase enzyme (BuChE wt/wt; n = 226/340), who were < 75 years of age (n = 362/994) or who had symptoms suggestive of concomitant Lewy body disease (n = 49/994) showed significantly greater benefits from rivastigmine treatment. **CONCLUSIONS:** Cholinesterase inhibitor treatment may offer continued therapeutic benefit for up to 2 years in patients with moderate AD. Although both drugs performed similarly on cognition and behaviour, rivastigmine may provide greater benefit in activities of daily living and global functioning.

10. Caban-Holt, A., K. Bottiggi, et al. (2005). "Measuring treatment response in Alzheimer's disease clinical trials." *Geriatrics Suppl*: 3-8.

Alzheimer's disease (AD) is a progressive disorder that negatively impacts cognitive, behavioral, and functional abilities. Because of the complex nature of this disease, it is crucial to design assessment procedures that accurately track disease progression across a wide variety of symptom domains. One important use of such techniques is to assess the effectiveness of therapeutic compounds in AD clinical trials. A number of outcome measures that assess cognitive, behavioral, functional, or global ability have been developed for this purpose. This paper describes the assessment measures that are most

commonly used in AD trials. The inherent strengths and limitations of each evaluative technique are summarized, as well as how these outcome measures are useful to the practicing clinician.

11. 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.

12. Dantoine, T., S. Auriacombe, et al. (2006). "Rivastigmine monotherapy and combination therapy with memantine in patients with moderately severe Alzheimer's disease who failed to benefit from previous cholinesterase inhibitor treatment." *Int J Clin Pract* **60**(1): 110-8.

We investigated the efficacy and safety of rivastigmine alone and combined with memantine in Alzheimer's disease patients previously failing on donepezil or galantamine. This was a prospective, open-label, multicentre study. After stopping donepezil or galantamine, patients received rivastigmine 3-12 mg/day for 16 weeks. Non-responders to rivastigmine monotherapy at week 16 received memantine 5-20 mg/day plus rivastigmine for 12 weeks. The primary efficacy parameter was response (Mini-Mental State Examination equal or better than at week 16) to dual therapy at week 28. Secondary criteria were changes on cognitive and behavioural scales. Two hundred and two patients were included. Ninety-three (46.3%) patients responded to rivastigmine monotherapy. Of 86 patients receiving additional memantine for another 12 weeks, 67 (77.9%) responded. Combination therapy caused no apparent safety concerns. When

patients fail on donepezil or galantamine, switching to rivastigmine may improve cognition and behaviour. Should they continue to deteriorate, the addition of memantine may be beneficial.

13. Dunbar, F., Y. Zhu, et al. (2006). "Post hoc comparison of daily rates of nausea and vomiting with once- and twice-daily galantamine from a double-blind, placebo-controlled, parallel-group, 6-month study." *Clin Ther* **28**(3): 365-72.

BACKGROUND: A once-daily extended-release galantamine(GAL-ER) formulation has been designed to improve tolerability compared with twice-daily immediate-release galantamine (GAL-IR). **OBJECTIVE:** The aim of this study was to conduct a post hoc analysis of the clinical presentation of nausea and vomiting with GAL-ER compared with GAL-IR in subjects with mild to moderate Alzheimer's disease (AD). **METHODS:** This is the report of a post hoc analysis of a large, randomized, double-blind, placebo-controlled, multicenter trial of GAL-ER with GAL-IR as the active control in subjects with mild to moderate AD. Galantamine dose was titrated every 4 weeks by increments of 8 mg/d to a daily dose of 16 or 24 mg, based on tolerability. Daily rates of nausea and vomiting were compared for the GAL-ER and GAL-IR groups. AUCs of the daily percentage of subjects reporting nausea/vomiting during dose titration were calculated. Antiemetic use for nausea/vomiting was compared between GAL-ER and GAL-IR groups. **RESULTS:** Demographic characteristics were similar between the GAL-ER, GAL-IR, and placebo groups. Nausea was reported by 16.9% (54/319) of GAL-ER, 13.8% (45/326) of GAL-IR, and 5.0% (16/320) of placebo patients; vomiting was reported for 6.6% (21/319) of GAL-ER, 8.6% (28/326) of GAL-IR, and 2.2% (7/320) of placebo patients. The mean (SD) daily rate of nausea in the total population was 3.1 (13.43%) in the GAL-ER group and 5.2% (22.07%) in the GAL-IR group (P = NS); the mean (SD) daily rate of vomiting for the total population was 0.6% (4.14%) in the GAL-ER group and 1.6% (14.50%) in the GAL-IR group (P = NS). The mean (SD) daily rate of nausea or vomiting in the total population was 1.2 (8.46) and 0.4 (5.44) in the placebo group, respectively. For subjects reporting nausea, the mean (SD, SE) percentage of days with nausea was lower with GAL-ER than with GAL-IR (18.4% [28.22%, 5.31%] vs 38.0% [48.23%, 6.04%]; P = 0.014). AUC of the daily percentage of subjects reporting nausea/vomiting during dose titration was significantly higher in the GAL-IR group compared with the placebo group (320.9 vs 102.9; P = 0.01); there was no statistical difference between the GAL-ER group and placebo (171.1 vs 102.9; P = NS). Antiemetic use by subjects reporting nausea or vomiting was significantly lower in the GAL-ER group than the GAL-IR group (33.3% vs 53.4%; P = 0.028). **CONCLUSIONS:** In these subjects with AD, the daily percentage of subjects reporting nausea and vomiting, and the percentage of days with vomiting among subjects reporting vomiting, did not significantly differ between the GAL-ER and GAL-IR groups. However, GAL-ER was associated with a significantly lower percentage of days with nausea than GAL-IR among subjects reporting nausea. AUC of the daily percentage of subjects with nausea or vomiting during dose titration did not differ significantly between the GAL-ER and placebo groups but was significantly higher in the GAL-IR group than placebo. Subjects with nausea or vomiting who received GAL-ER reported significantly less antiemetic use

than those treated with GAL-IR. These results suggest the need for additional studies to explore the potential differences in the tolerability of these formulations.

14. Feldman, H. H., F. A. Schmitt, et al. (2006). "Activities of daily living in moderate-to-severe Alzheimer disease: an analysis of the treatment effects of memantine in patients receiving stable donepezil treatment." *Alzheimer Dis Assoc Disord* **20**(4): 263-8.

In moderate-to-severe Alzheimer disease (AD), there are significant losses of activities of daily living (ADL). In a recent prospective, randomized, placebo-controlled trial, memantine treatment lessened the overall functional decline in AD patients already on stable donepezil therapy. In this trial, patients (n=404) with Mini-Mental State Examination scores of 5 to 14 receiving stable donepezil treatment were randomized to double-blind treatment with memantine (10 mg b.i.d.; n=203) or placebo (n=201). A primary outcome measure was the 19-item Alzheimer's Disease Cooperative Study--Activities of Daily Living Inventory (ADCS-ADL(19)). To further evaluate the treatment effects of memantine on function, we performed post hoc analyses of ADCS-ADL(19) data from this trial, including ADL items and new subscales derived from factor analysis. Using mixed model analyses, patients receiving memantine had statistically significant less decline in total ADCS-ADL(19) scores compared with placebo. An item analysis revealed statistically significant benefits of memantine on grooming, toileting, conversing, watching television, and being left alone. Statistically significant improvements were noted in subscales evaluating higher-level functions and connectedness/autonomy with memantine compared with placebo. These post hoc analyses in moderate-to-severe AD patients receiving stable donepezil treatment suggest that memantine may impact overall functional levels, and some of the cognitive processing underlying ADL performance.

15. Frankfort, S. V., B. A. Appels, et al. (2006). "Treatment effects of rivastigmine on cognition, performance of daily living activities and behaviour in Alzheimer's disease in an outpatient geriatric setting." *Int J Clin Pract* **60**(6): 646-54.

We investigated rivastigmine effectiveness in 84 Alzheimer outpatients, with a special focus on behavioural problems. Cognition, activities in daily living (ADL) and behaviour were assessed during 30 months. Changes in test results between 6 months and baseline were compared with a historical control cohort of Alzheimer patients (n = 69) by performing t-tests and calculation of Cohen's d and standardised response mean (SRM). During 6 months, rivastigmine showed effect on cognition (p < 0.001, Cohen's d = 0.33, SRM = 0.78), ADL (p < 0.001, Cohen's d = -0.43, SRM = -0.54) and memory-related behaviour (p = 0.006, Cohen's d = -0.28, SRM = -0.28). Depressive behaviour worsened (p = 0.001, Cohen's d = 0.30, SRM = 0.37) and disruptive behaviour (p = 0.369, Cohen's d = -0.07, SRM = -0.09) was not effected by rivastigmine. During 30 months, a gradual decline was shown in most domains. Most RMBPC items showed stabilization during 30 months. Improvement on disruptive behaviour items and depression items was shown after 6 months of treatment in a large proportion of patients in whom behavioural problems were present at baseline. In conclusion, a huge discontinuation rate is experienced within the first half year of treatment. In the subpopulation of patients who

continued rivastigmine for 6 months, it shows modest effectiveness on cognition, functionality and memory-associated behaviour compared with historical control patients. Unfortunately, disruptive behaviour is not altered by rivastigmine therapy, and depressive behaviour worsened slightly after initial treatment. During 30 months, rivastigmine showed stabilization on numerous behaviour items as measured by the RMBPC.

16. Gasper, M. C., B. R. Ott, et al. (2005). "Is donepezil therapy associated with reduced mortality in nursing home residents with dementia?" Am J Geriatr Pharmacother **3**(1): 1-7.

BACKGROUND: Since cholinesterase inhibitors (CEIs) were approved for use in mild to moderate Alzheimer's disease, the therapeutic efficacy of this class of medications has largely centered on demonstration of short-term improvement in cognition and global function. Later evidence suggested that the beneficial effects of CEIs might be sustainable for at least 3 years and that CEIs may have a disease-modifying effect on Alzheimer's disease. These broad-ranging, long-term effects may explain the recent finding that the use of a CEI among nursing home residents with dementia was associated with lower mortality. **OBJECTIVE:** The goal of this study was to investigate whether donepezil treatment is associated with reduced mortality in nursing home residents who have dementia. **METHODS:** We performed a retrospective matched cohort study using the Systematic Assessment of Geriatric Drug Use via Epidemiology database, which contains data collected with the Minimum Data Set on a cross section of 915,469 nursing home residents aged > 65 years between 1998 and 2000 in 6 US states. We identified users of donepezil (5 and 10 mg) and an equal number of matched nonusers in the same facility, date of donepezil use, level of cognitive function, and dementia diagnosis. Comparisons of the 2 groups were made for sociodemographic variables, dementia severity, number of medications, and major comorbid illnesses (heart disease, cancer, diabetes mellitus, chronic obstructive pulmonary disease, and malnutrition), as well as survival over the 2-year study period. **RESULTS:** A total of 5423 users and 5423 nonusers of donepezil were identified. Based on Cox proportional hazards models, donepezil users showed a lower mortality rate than nonusers. The hazard rate ratio was 0.89 (95% CI, 0.83-0.95). After adjusting for the confounding variables, sociodemographic factors, other psychotropic drugs, and comorbid conditions, this survival advantage remained (hazard rate ratio, 0.90; 95% CI, 0.84-0.96). **CONCLUSIONS:** A relationship was observed between treatment of nursing home residents with donepezil and lower mortality. If the relationship was due to a direct effect of donepezil use, then this observation has implications for the socioeconomic impact of CEI therapy in those with advanced dementia in the nursing home. These implications deserve future investigation.

17. Hansen, R. A., G. Gartlehner, et al. (2007). "Functional outcomes of drug treatment in Alzheimer's disease: A systematic review and meta-analysis." Drugs Aging **24**(2): 155-67.

BACKGROUND: Patient functioning is an important outcome in Alzheimer's disease, but treatment-related improvements in patient function are difficult to quantify because a number of different scales are used in its measurement. **OBJECTIVE:** To evaluate systematically the evidence relating to patient functioning as an outcome measure in the

drug treatment of Alzheimer's disease. Data were obtained by searching MEDLINE, EMBASE, The Cochrane Library and the International Pharmaceutical Abstracts from 1980 through to December 2005 for studies assessing functional outcomes with donepezil, galantamine, rivastigmine and memantine in Alzheimer's disease. Reference lists were searched manually and pharmaceutical manufacturers were invited to submit dossiers. Trained reviewers abstracted data and assessed the internal validity (quality) of trials using predefined criteria. Standardised effect sizes (i.e. Cohen's standardised mean difference [d]) for various functional outcome scales and pooled mean incidence and 95% CIs for adverse events were calculated and summarised qualitatively and quantitatively. Meta regression was used to explore potential heterogeneity. **RESULTS:** Overall, the standardised effect size for functional outcome measures was small ($d = 0.1-0.4$) among included studies. However, effect sizes consistently favoured drug treatment over placebo. For all drugs, pooled standardised effect sizes were consistent in both short (<24 weeks; $d = 0.25$; 95% CI 0.13, 0.37) and long trials (≥ 24 weeks; $d = 0.29$; 95% CI 0.22, 0.36). The pooled effect size was not significantly affected by parameters such as disease severity, age, gender and drug dose. Adverse events were generally limited to gastrointestinal problems, weight loss and dizziness, all of which were reported in $<20\%$ of patients on average. **CONCLUSIONS:** Standardised estimates of effect size across diverse functional outcome measures for drug treatment in patients with Alzheimer's disease were small and the data reflect only a modest trend favouring active treatment over placebo. However, given the current lack of other effective treatments for Alzheimer's disease, this trend supports the clinical benefits of these treatments with regard to this important health outcome.

18. Harry, R. D. and K. K. Zakzanis (2005). "A comparison of donepezil and galantamine in the treatment of cognitive symptoms of Alzheimer's disease: a meta-analysis." Hum Psychopharmacol **20**(3): 183-7.

This review was conducted in order to determine the efficacy of donepezil and galantamine in the treatment of cognitive symptoms of Alzheimer's disease, and also to determine whether galantamine was a superior pharmacological intervention. Meta-analytic methods were used to analyse the data from eight empirical studies which met the inclusion criteria specified. By finding the mean effect sizes of the treatment on the outcome measures of cognition, it was determined that neither drug was greatly efficacious. However, this result does not necessarily diminish the practical value of the drug. It was also found that galantamine was no better than donepezil at treating cognitive decline in AD.

19. Hatoum, H. T., S. J. Lin, et al. (2005). "The use of the occupational disruptiveness scale of the neuropsychiatric inventory-nursing home version to measure the impact of rivastigmine on the disruptive behavior of nursing home residents with Alzheimer's disease." J Am Med Dir Assoc **6**(4): 238-45.

OBJECTIVES: The Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) was used to study the impact of rivastigmine (Exelon; Novartis Pharmaceuticals Corporation, East Hanover, NJ), on occupational disruptiveness (OD), a proxy measure for

professional caregiver burden. **METHODS:** The study was a prospective, multicenter, open-label, single-arm trial with NH residents prescribed rivastigmine (up to 6 mg bid) for Alzheimer's disease (AD) treatment. The NPI-NH was completed by NH staff caregivers at time of initiation of treatment with rivastigmine (T1), at treatment weeks 10 to 14 (T2), at treatment weeks 24 to 28 (T3), and at treatment weeks 50 to 54 (T4). **RESULTS:** Observations ranged from 173 at baseline to 73 at week 52. All but one patient had either moderate or severe dementia. Total OD score means were 4.7 +/- 6.1, 3.9 +/- 5.0, 4.19 +/- 5.6, and 2.79 +/- 2.8 at baseline, and weeks 12, 26, and 52 (T1-T4), respectively, with significant difference found between T1 and T4. Except for euphoria and disinhibition at T3 and T4, all correlations between OD scores and the domain scores of the NPI, were significant. Rivastigmine dose was an independent variable that affected OD change. **CONCLUSION:** Treatment with rivastigmine was associated with a reduction in the self-reported professional caregiver burden, as assessed by the NPI-NH OD scale.

20. Heinen-Kammerer, T., H. Rulhoff, et al. (2006). "Added therapeutic value of memantine in the treatment of moderate to severe Alzheimer's disease." Clin Drug Investig **26**(6): 303-14.

When evaluating the added therapeutic value of a drug, evidence of greater overall benefit or at least an add-on benefit is increasingly being required. Therefore, cost-effectiveness in addition to clinical efficacy is an important consideration. The efficacy of a drug must be examined on the basis of clinical trials by measuring specific parameters that are affected by the drug (for example blood pressure with antihypertensive treatment). Today not only efficacy but also patient-relevant changes (patient benefits) must be demonstrated for a drug, often by measuring quality of life. In order to evaluate the benefit of monotherapy with the N-methyl-D-aspartate antagonist memantine in the management of moderate to severe Alzheimer's disease, a systematic literature review was conducted. The results showed a benefit for memantine in comparison with placebo in terms of a decrease in nursing care, a delay in care dependency and a delay in admission to nursing homes. In addition, an increase in quality of life has been observed.

21. Herrmann, N., K. Rabheru, et al. (2005). "Galantamine treatment of problematic behavior in Alzheimer disease: post-hoc analysis of pooled data from three large trials." Am J Geriatr Psychiatry **13**(6): 527-34.

OBJECTIVE: The authors explored the effect of galantamine on behavioral symptoms in Alzheimer disease (AD). **METHODS:** Data were pooled from 2,033 subjects with mild-to-moderate AD who had participated in one of three randomized, double-blind, placebo-controlled trials of 3-, 5-, and 6-month durations. Subjects included in this post hoc analysis had received treatment with either placebo (N=686) or galantamine (N=1347) in total daily doses of 16 mg, 24 mg, or 32 mg. Behavioral symptoms were measured on the 10-item Neuropsychiatric Inventory (NPI). Four symptom clusters were defined a priori: 1) delusions, hallucinations; 2) agitation, depression, anxiety, apathy, irritability; 3) disinhibition, elation, aberrant motor behavior; 4) hallucinations, anxiety, apathy, aberrant motor behavior. **RESULTS:** At endpoint, mean changes from baseline in NPI scores were significantly different between galantamine-treated subjects and placebo-

treated subjects, favoring galantamine for several measures: total NPI, individual domains of agitation/aggression, anxiety, disinhibition, and aberrant motor behavior, and Clusters 1, 3, and 4. The magnitude of the effect sizes was small. CONCLUSIONS: In this pooled sample of more than 2,000 subjects with mild-to-moderate AD, those who received galantamine therapy experienced modestly better, but statistically significant, outcomes in their behavioral symptoms than placebo-treated subjects. The cluster of hallucinations, anxiety, apathy and aberrant motor behaviors may represent a specific group of cholinergic-responsive behavioral symptoms.

22. Johannsen, P., E. Salmon, et al. (2006). "Assessing therapeutic efficacy in a progressive disease: a study of donepezil in Alzheimer's disease." *CNS Drugs* **20**(4): 311-25.

OBJECTIVE: To determine the value of continued donepezil treatment in patients with Alzheimer's disease for whom clinical benefit was initially judged to be uncertain.

METHODS: The study consisted of three phases: (i) a 12- to 24-week, pre-randomisation, open-label donepezil-treatment phase; (ii) a 12-week, randomised, double-blind, placebo-controlled phase; and (iii) a 12-week, single-blind (i.e. patient-blind) donepezil-treatment phase. Patients with mild to moderate Alzheimer's disease received open-label treatment with donepezil (5 mg/day for 4 weeks, then 10 mg/day for the remainder of the phase) for 12-24 weeks. Patients who exhibited a decline or no change from baseline on the Mini-Mental State Examination (MMSE) and whose physician was not sufficiently certain of clinical benefit to warrant continued treatment were randomised into the double-blind phase in which patients received 12 weeks of treatment with donepezil (10 mg/day) or placebo. At the end of the double-blind phase, donepezil-treated patients continued to receive donepezil, while placebo-treated patients were rechallenged with donepezil, in a 12-week single-blind phase. Patients were assessed at the start of the double-blind phase and at weeks 6 and 12 of this phase, and at the end of the single-blind phase. **RESULTS:** Six hundred and nineteen patients completed the open-label phase; 69% showed clear clinical benefit and 31% showed uncertain benefit. 202 patients were randomised to continued donepezil treatment (n = 99) or placebo (n = 103). Differences in favour of continued donepezil versus placebo were observed in cognition and behaviour. In addition, there was a non-significant trend favouring donepezil in activities of daily living (ADL) [week 12 observed case mean treatment differences: MMSE, 1.13 (p = 0.02); Alzheimer's Disease Assessment Scale - cognitive subscale, 0.57 (p = 0.5); the Neuropsychiatric Inventory, -3.16 (p = 0.02); Disability Assessment for Dementia scale, 3.67 (p = 0.1)]. **CONCLUSION:** Most patients showed clear clinical benefit during initial donepezil treatment. Among patients for whom clinical benefit was uncertain, improvement in cognition and behaviour were observed for those who continued donepezil treatment compared with the group switched to placebo. Initial decline or stabilisation does not necessarily indicate a lack of efficacy in Alzheimer's disease, and the decision to discontinue treatment should be based on an evaluation of all domains (cognition, behaviour and ADL) and performed at several timepoints.

23. Kaufer, D. I., S. Borson, et al. (2005). "Reduction of caregiver burden in Alzheimer's disease by treatment with galantamine." CNS Spectr **10**(6): 481-8.

Alzheimer's disease is a progressive condition characterized by a loss of cognition, altered behavior, and a loss of functional ability, such as bathing, dressing, toileting, and organizing finances. Family and friends provide nearly three quarters of all care for patients with Alzheimer's disease. This informal care results in significant burden to caregivers. Caregiver burden is the set of physical, psychological or emotional, social, and financial problems that family members may experience when caring for impaired older adults. Caregivers of Alzheimer's disease patients report higher rates of physical symptoms, mortality, depression, and fatigue, as well as adverse effects on employment compared with those who are not caregivers for Alzheimer's disease patients. In many cases, the same family members are responsible for both out-of-pocket expenditures and caregiving duties. For this article, a MEDLINE search using the key words "caregiver and Alzheimer's disease" and "cost and Alzheimer's disease" was performed. The purpose of this article is to review the literature on caregiver burden, the components of caregiver burden, effects of caregiving on the health of caregivers, the cost of Alzheimer's disease on the caregiver and society, and the benefits attainable with treatment.

24. Kirby, J., C. Green, et al. (2006). "A systematic review of the clinical and cost-effectiveness of memantine in patients with moderately severe to severe Alzheimer's disease." Drugs Aging **23**(3): 227-40.

Alzheimer's disease (AD) is the most common form of dementia and is characterised by a worsening of cognition, functional ability, and behaviour and mood. The objective of this study was to review the clinical and cost-effectiveness of memantine for the treatment of patients with moderately severe to severe AD. To achieve this, a systematic search and review of the clinical and cost effectiveness literature for memantine was undertaken. The literature search covered the period from the inception of MEDLINE, Cochrane Library, EMBASE and other electronic databases until July 2004. The search included randomised controlled trials (RCTs) and full economic evaluations that assessed the use of memantine in patients with moderately severe to severe AD. Two published RCTs were included in this review; in one of these trials the participants were already being treated with donepezil. The two RCTs showed benefit for patients receiving memantine compared with placebo on the outcome measures of the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia, the Clinician's Interview-Based Impression of Change Plus Caregiver Input, and the Severe Impairment Battery, and that memantine appeared to be slightly more effective in patients already receiving a stable dose of donepezil. Five cost-effectiveness studies were included in the review. Although these studies reported cost reductions and improved outcomes with memantine, the evaluations were based on a number of assumptions. In conclusion, memantine appears to be beneficial when assessed using functional and global measurements. However, the effect of memantine on cognitive scores and behaviour and mood outcomes is less clear. Cost-effectiveness is dependent upon assumptions surrounding clinical effect and context-specific cost data.

25. Koontz, J. and A. Baskys (2005). "Effects of galantamine on working memory and global functioning in patients with mild cognitive impairment: a double-blind placebo-controlled study." Am J Alzheimers Dis Other Demen **20**(5): 295-302.

Mild cognitive impairment (MCI) causes memory impairment and executive function deficits in those with the condition. There is also some evidence that MCI patients are impaired in their daily functioning. Cholinesterase inhibitors have been widely used for patients with Alzheimer's disease (AD), with evidence of improving cognitive function. There is currently no established treatment for MCI, and cholinesterase inhibitors are beginning to be studied in these patients. Galantamine is a cholinesterase inhibitor that also has nicotinic receptor-modulating properties that has been successful in improving AD patients. This study examined the effects of galantamine in patients with MCI in areas of memory, executive functioning, and global functioning. There was a significant improvement in scores on the Functional Activities Questionnaire, which is a measure of global functioning. There were also improvements in the galantamine group on two of six measures in the Cambridge Automated Neuropsychiatric Test Assessment Battery and in immediate free recall on the California Verbal Learning Test.

26. Lingler, J. H., L. M. Martire, et al. (2005). "Caregiver-specific outcomes in antidementia clinical drug trials: a systematic review and meta-analysis." J Am Geriatr Soc **53**(6): 983-90.

OBJECTIVES: To describe the range of caregiver-specific outcomes and approaches to their study within antidementia drug trials and to quantify the effect of cholinesterase inhibitors on burden and active time use of caregivers of persons with Alzheimer's disease (AD). **DESIGN:** Systematic review of English-language publications and unpublished reports of antidementia clinical drug trials that included caregiver-specific outcomes. Study characteristics and methodological quality were summarized. Random effects meta-analyses were conducted for the outcomes of caregiver burden and active time use. **SETTING:** Community. **PARTICIPANTS:** Informal caregivers of participants in clinical trials of antidementia drugs. **MEASUREMENTS:** Burden, time use, psychological well-being, healthcare costs, and ease of use of or satisfaction with intervention. **RESULTS:** Seventeen studies involving 4,744 subjects were identified. Four trials (n=1,594) met criteria for inclusion in the burden analysis, and six trials (n=2,286) met criteria for inclusion in the time-use analysis. Most investigations involved drugs now approved by the Food and Drug Administration for the treatment of AD; donepezil was the most frequently studied intervention in the set of studies. Methodological quality varied across trials. The weighted average effect sizes were Cohen's d=0.18 (95% confidence interval (CI)=0.04-0.32) and d=0.15 (95% CI=0.07-0.24) for the outcomes of caregiver burden and time use, respectively. **CONCLUSION:** Cholinesterase inhibitors have a small beneficial effect on burden and active time use among caregivers of persons with AD. Recommendations to enhance the quality and interpretability of AD clinical trials that involve caregiver-specific outcomes are presented.

27. Loveman, E., C. Green, et al. (2006). "The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease." Health Technol Assess **10**(1): iii-iv, ix-xi, 1-160.

OBJECTIVES: To provide an update review of the best quality evidence for the clinical effectiveness and cost-effectiveness of donepezil, rivastigmine and galantamine for mild to moderately severe Alzheimer's disease (AD) and of memantine for moderately severe to severe AD. **DATA SOURCES:** Electronic databases, experts in the field and manufacturer submissions to the National Institute for Health and Clinical Excellence (NICE). **REVIEW METHODS:** A systematic review of the literature and an economic evaluation were undertaken. The quality of included randomised controlled trials (RCTs) was assessed using criteria developed by the NHS Centre for Reviews and Dissemination. An outline assessment of economic evaluations was undertaken using a standard checklist. The clinical and cost-effectiveness data were synthesised through a narrative review with full tabulation of the results of included studies. Where appropriate, meta-analysis of data was undertaken. **RESULTS:** For mild to moderately severe AD, the results of the study suggested that all three treatments were beneficial when assessed using cognitive outcome measures. Global outcome measures were positive for donepezil and rivastigmine, but mixed for galantamine. Results for measures of function were mixed for donepezil and rivastigmine, but positive for galantamine. Behaviour and mood measures were mixed for donepezil and galantamine, but showed no benefit for rivastigmine. For memantine, two published RCTs were included; in one of these trials the participants were already being treated with donepezil. The results suggest that memantine is beneficial when assessed using functional and global measurements. The effect of memantine on cognitive and behaviour and mood outcomes is, however, less clear. Literature on the cost-effectiveness of donepezil, rivastigmine and galantamine was dominated by industry-sponsored studies, and studies varied in methods and results. Of the three UK studies, two report donepezil as not cost-effective, whereas a third study reports an additional cost (1996 pounds sterling) of between 1200 pounds sterling and 7000 pounds sterling per year in a non-severe AD health state (concerns over these estimates are raised, suggesting that they may underestimate the true cost-effectiveness of donepezil). Cost-effectiveness analysis undertaken in this review suggests that donepezil treatment has a cost per quality-adjusted life-year (QALY) in excess of 80,000 pounds sterling, with donepezil treatment reducing the mean time spent in full-time care (delays progression of AD) by 1.42-1.59 months (over a 5-year period). From four published cost-effectiveness studies, two UK studies report additional costs associated with rivastigmine treatment. Cost-effectiveness analysis undertaken in the current review suggests that rivastigmine treatment has a cost per QALY in excess of 57,000 pounds sterling, with rivastigmine treatment reducing the mean time spent in full-time care (delays progression) by 1.43-1.63 months (over a 5-year period). From five published cost-effectiveness studies, one UK study reports a cost per QALY of 8693 pounds sterling for 16-mg galantamine treatment and 10,051 pounds sterling for 24-mg galantamine treatment (concerns raised suggest that this may underestimate the true cost-effectiveness of galantamine). Cost-effectiveness analysis undertaken in the present review suggests that galantamine treatment has a cost per QALY in excess of 68,000

pounds sterling, with galantamine reducing the time spent in full-time care (delays progression) by 1.42-1.73 months (over a 5-year period). From two published cost-effectiveness studies, one reports analysis for the UK, finding that memantine treatment results in cost savings and benefits in terms of delaying disease progression (concerns raised suggest that this may underestimate the true cost-effectiveness of memantine). In the current review, the cost-effectiveness of memantine has not been modelled separately, but where alternative parameter inputs on the cost structure and utility values have been used in a reanalysis using the industry model, the cost-effectiveness is reported at between 37,000 pounds sterling and 52,000 pounds sterling per QALY, with this alternative analysis still based on what is regarded as an optimistic or favourable effectiveness profile for memantine. CONCLUSIONS: Although results from the clinical effectiveness review suggest that these treatments may be beneficial, a number of issues need to be considered when assessing the results of the present review, such as the characteristics of the participants included in the individual trials, the outcome measures used, the length of study duration, the effects of attrition and the relationship between statistical significance and clinical significance. Many included trials were sponsored by industry. For donepezil, rivastigmine and galantamine, the cost savings associated with reducing the mean time spent in full-time care do not offset the cost of treatment sufficiently to bring estimated cost-effectiveness to levels generally considered acceptable by NHS policy makers. It is difficult to draw conclusions on the cost-effectiveness of memantine; it is suggested that further amendments to the potentially optimistic industry model (measure of effect) would offer higher cost per QALY estimates. Future research should include: information on the quality of the outcome measures used; development of quality of life instruments for patients and carers; studies assessing the effects of these interventions of durations longer than 12 months; comparisons of benefits between interventions; and research on the prediction of disease progression.

28. Loy, C. and L. Schneider (2006). "Galantamine for Alzheimer's disease and mild cognitive impairment." Cochrane Database Syst Rev(1): CD001747.

BACKGROUND: Galantamine is a specific, competitive, and reversible acetylcholinesterase inhibitor. **OBJECTIVES:** To assess the clinical effects of galantamine in patients with mild cognitive impairment (MCI), probable or possible Alzheimer's disease (AD), and potential moderators of effect. **SEARCH STRATEGY:** The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group, last updated on 25 April 2005 using the terms galanthamin*, galantamin* and Reminyl. Published reviews were inspected for further sources. Additional information was collected from unpublished clinical research reports for galantamine obtained from Janssen and from <http://www.clinicalstudyresults.org/>. **SELECTION CRITERIA:** Trials selected were randomised, double-blind, parallel-group comparisons of galantamine with placebo for a treatment duration of greater than 4 weeks in subjects with MCI or AD. **DATA COLLECTION AND ANALYSIS:** Data were extracted independently by the reviewers and pooled where appropriate and possible. Outcomes of interest include the clinical global impression of change (CIBIC-plus or CGIC), Alzheimer's Disease Assessment

Scale-cognitive sub scale (ADAS-cog), Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL), Disability Assessment for Dementia scale (DAD) and Neuropsychiatric Inventory (NPI). Potential moderating variables of treatment effect assessed included trial duration, dose, and diagnosis of possible versus probable Alzheimer's disease. MAIN RESULTS: Ten trials with a total 6805 subjects were included in the analysis. Treatment with galantamine led to a significantly greater proportion of subjects with improved or unchanged global rating scale rating (k = 8 studies), at all dosing levels except for 8 mg/d . Confidence intervals for the ORs overlapped across the dose range of 16 mg to 36 mg per day, with point estimates of 1.6 - 1.8 when analysed with the intention-to-treat sample. Treatment with galantamine also led to significantly greater reduction in ADAS-cog score at all dosing levels (k = 8), with greater effect over six months compared to three months. Confidence intervals again overlapped. Point estimate of effect was lower for 8 mg/d but similar for 16 mg to 36 mg per day. For example, treatment effect for 24 mg/d over six months was 3.1 point reduction in ADAS-cog (95%CI 2.6-3.7, k = 4, ITT).ADCS-ADL, DAD and NPI were reported only in a small proportion of trials: all showed significant treatment effect in some individual trials at least. Confidence interval of treatment effect for the one trial recruiting patients with possible AD overlapped with the other seven recruiting patients with probable AD. Galantamine's adverse effects appeared similar to those of other cholinesterase inhibitors and to be dose related. Prolong release / once daily formulation of galantamine at 16 - 24mg/d was found to have similar efficacy and side-effect profile as the equivalent twice-daily regime. Data from the two MCI trials suggest marginal clinical benefit, but a yet unexplained excess in death rate. AUTHORS' CONCLUSIONS: Subjects in these trials were similar to those seen in earlier anti dementia AD trials, consisting primarily of mildly to moderately impaired outpatients. Galantamine's effect on more severely impaired subjects has not yet been assessed. Nevertheless, this review shows consistent positive effects for galantamine for trials of three to six months' duration. Although there was not a statistically significant dose-response effect, doses above 8 mg/d were, for the most part, consistently statistically significant. Galantamine's safety profile in AD is similar to that of other cholinesterase inhibitors with respect to cholinergically mediated gastrointestinal symptoms. It appears that doses of 16 mg/d were best tolerated in the single trial where medication was titrated over a four week period, and because this dose showed statistically indistinguishable efficacy with higher doses, it is probably most preferable initially. Longer term use of galantamine has not been assessed in a controlled fashion. Galantamine use in MCI is not recommended due to its association with an excess death rate.

29. Lu, S., J. Hill, et al. (2005). "Impact of donepezil use in routine clinical practice on health care costs in patients with Alzheimer's disease and related dementias enrolled in a large medicare managed care plan: a case-control study." *Am J Geriatr Pharmacother* 3(2): 92-102.

BACKGROUND: Clinical studies have shown efficacy of cholinesterase inhibitors (eg, donepezil) in mild to moderate Alzheimer's disease (AD). However, there are limited studies examining the impact on health care costs of cholinesterase inhibitors prescribed

in routine clinical practice. **OBJECTIVE:** The purpose of this study was to estimate the impact of donepezil use on health care costs and utilization in patients with mild to moderate AD and related dementias. **METHODS:** This case-control study was conducted using data from the Health Insurance Plan of Greater New York (New York, New York). Data from patients with predominantly mild to moderate AD and related dementias who were enrolled in this Medicare managed care plan from January 1, 1999, to December 31, 2002, were included. The health care costs and utilization of patients who had received donepezil prescribed in routine clinical practice were compared with those of patients who had never received donepezil or other cholinesterase inhibitors (control group). The 2 study groups were matched for age, sex, number of comorbid conditions, and presence of complications of late-stage dementia. Regression analysis was used to estimate the impact of donepezil use on health care costs and utilization during a 12-month follow-up period, controlling for characteristics associated with the outcomes. The analyses did not use a direct measure of disease severity but instead used proxy measures of severity based on medical conditions associated with late-stage dementia. **RESULTS:** Data from 687 patients were included in the study. The donepezil group comprised 229 patients (140 women, 89 men; mean age, 79.6 years); the control group, 458 patients (280 women, 178 men; mean age, 80.0 years). The mean costs of medical services per year in the donepezil group were US \$2500 (95% CI, \$300-\$4671) less than those in the control group ($P = 0.024$). Lower medical costs in the donepezil group (\$3325; 95% CI, \$1163-\$5486; $P < 0.003$ vs controls) were largely attributable to the lower costs of services performed in the hospital (\$2594; 95% CI, \$846-\$4341; $P < 0.004$ vs controls) and postacute skilled nursing facility (SNF) (\$1012; 95% CI, \$444-\$1579; $P < 0.001$ vs controls), which were partially offset by \$1241 in higher prescription, physician's office, and outpatient hospital costs. Patients receiving donepezil had shorter mean lengths of stay in the hospital (3.00 vs 5.43 days; 95% CI, 0.66-4.19; $P < 0.008$) and postacute SNF (0.42 vs 3.40 days; 95% CI, 1.28-4.69; $P < 0.001$) but a higher mean number of physician's office visits (10.91 vs 7.91 visits; 95% CI, 1.63-4.36; $P < 0.001$) compared with controls. **CONCLUSIONS:** In this case-control study in patients with predominantly mild to moderate AD and related dementias, donepezil therapy prescribed in routine clinical practice was associated with reduced health care costs to the Medicare managed care plan studied. The findings support previous pharmacoeconomic studies with larger sample sizes obtained over a longer period of time, and with improved case-matching criteria.

30. Marder, K. (2006). "Donepezil in patients with severe Alzheimer's disease: double-blind parallel-group, placebo controlled study." Curr Neurol Neurosci Rep **6**(5): 364-3.

31. Marin, D., K. Amaya, et al. (2003). "Impact of rivastigmine on costs and on time spent in caregiving for families of patients with Alzheimer's disease." Int Psychogeriatr **15**(4): 385-98.

BACKGROUND: Alzheimer's disease (AD) places a significant burden on health care systems worldwide. As new treatments are developed, their cost-effectiveness is often assessed to help health care professionals make informed decisions. In addition to the more common practice of assessing direct medical costs, indirect costs, including time

spent in caregiving, should be evaluated. **METHODS:** This study examined the potential effects of the dual cholinesterase inhibitor rivastigmine (Exelon) on caregivers of patients with AD. Results from two 26-week, placebo-controlled trials have demonstrated the clinically relevant and statistically significant efficacy of rivastigmine (6-12 mg/day) compared to placebo, on cognition, activities of daily living, and global functioning. By delaying progression of AD, significant savings in caregiver burden are anticipated, as measured by time spent caregiving and its related costs. Data collected in a prospective, observational study of AD patients and their caregivers were used to establish the relationship between disease severity (based on Mini-Mental State Examination [MMSE] score) and time spent caregiving (according to the 5-item Caregivers Activity Survey score). A significant correlation was observed between the two scores ($N = 43$, $r = -.56$, $p < .0001$), demonstrating that more time for supervision from caregivers is required as the disease progresses. This finding was used to estimate the reduced caregiver burden resulting from the delay in disease progression that was demonstrated with use of rivastigmine. **RESULTS:** Over a 2-year period, the reduction in time spent in caregiving reached 691 hours for caregivers of patients with mild AD (MMSE score 21-30), resulting in a total savings of approximately 11,253 dollars. Treatment of patients with moderately severe AD was also evaluated. The trend was similar but the impact was less, suggesting an economic benefit to early therapy. **CONCLUSION:** Early diagnosis and a pharmacologic intervention that allows the patients to remain at home longer by delaying disease progression would have a beneficial impact on patients, caregivers, and payers, and should therefore be encouraged through initiatives designed to identify and treat patients early in the course of disease.

32. Mauskopf, J. A., C. Paramore, et al. (2005). "Drug persistency patterns for patients treated with rivastigmine or donepezil in usual care settings." *J Manag Care Pharm* **11**(3): 231-51.

OBJECTIVE: To compare levels of persistency with 2 cholinesterase (ChE) inhibitors--rivastigmine and donepezil--for the treatment of Alzheimer's disease (AD) through the use of administrative claims data. **METHODS:** This retrospective cohort study identified treatment-naïve, community-based AD patients having an initial prescription (index event) for rivastigmine or donepezil between June and December 2000, in the United States, from pharmacy claims in a proprietary administrative claims database. Patients were excluded if they received either drug during the 180 days prior to their index prescription or if they did not have continuous plan enrollment during this period and for at least 90 days following the index date. The probability of treatment discontinuation within the first 60 days of treatment was estimated. Time to treatment discontinuation was analyzed for the cohort of patients that remained on therapy $>$ or $=60$ days as well as for subgroups of the cohort reaching either approved or maximum recommended doses of donepezil or rivastigmine. Treatment discontinuation was defined as either a stop of therapy (no prescription refill within 60 days of estimated completion of prior prescription) or a switch to an alternative AD drug. Kaplan-Meier survival and proportional hazard model analyses were performed. Proportion of days covered (PDC) by an AD therapy was also evaluated in each quarter during the first year of follow-up. **RESULTS:** Of the newly treated AD study population, 30.4% (171/563) of rivastigmine

patients and 31.2% (583/1,871) of donepezil patients discontinued treatment within 60 days of starting therapy ($P = 0.72$). For the cohort of patients that remained on therapy $>$ or $=60$ days, the mean time to treatment discontinuation was 331 days (95% confidence interval [CI], 307-355) for rivastigmine patients ($n = 392$) versus 337 days (95% CI, 322-352) for donepezil patients ($n = 1288$). The proportion of patients with a PDC $>$ or $=80\%$ after 12 months of follow-up was 23% for the donepezil group and 19% for the rivastigmine group ($P = 0.34$). For the cohort subgroup that reached an approved dose, the mean time to treatment discontinuation was 346 days (95% CI, 318-374) for rivastigmine patients ($n = 282$) versus 338 days (95% CI, 323-353) for donepezil patients ($n = 1,283$). For the cohort subgroup that reached the maximum recommended dose, the mean time to treatment discontinuation was 396 days (95% CI, 343-449) for rivastigmine patients ($n = 61$) versus 364 days (95% CI, 344-384) for donepezil patients ($n = 712$).
CONCLUSION: Newly treated AD patients in a usual care setting who initiate therapy with either rivastigmine or donepezil have similar levels of persistency with treatment.

33. 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.

34. 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.

35. Pomara, N., B. R. Ott, et al. (2007). "Memantine treatment of cognitive symptoms in mild to moderate Alzheimer disease: secondary analyses from a placebo-controlled randomized trial." Alzheimer Dis Assoc Disord **21**(1): 60-4.

Memantine, an N-methyl-D-aspartate receptor antagonist, is approved in the United States and Europe for the treatment of moderate to severe Alzheimer disease (AD) and has also been investigated in patients with mild to moderate AD. To characterize the specific cognitive benefits of memantine in patients with mild to moderate AD, a post hoc analysis was conducted of a 24-week randomized, double-blind, placebo-controlled, clinical trial comparing memantine (10 mg twice daily) to placebo. Cognition was assessed using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) total score, individual items, and aggregated subscales, using a mixed model repeated measures analysis. As assessed by the ADAS-cog total score, participants in the placebo group demonstrated significantly more cognitive decline from baseline than participants treated with memantine at all visits beginning at week 8. Subjects treated with placebo also declined significantly more than individuals in the memantine group on 5 of 11 ADAS-cog individual items: orientation, language, comprehension, word finding, and recall of test instructions. Out of 3 ADAS-cog aggregated item subscales (language, memory, and praxis), outcomes in 2 (language and memory) favored memantine. Consistent with findings from trials conducted in moderate to severe AD patients, this

post hoc analysis of a randomized clinical trial suggests that memantine benefits core aspects of language and some aspects of memory in patients with mild to moderate AD.

36. Raschetti, R., M. Maggini, et al. (2005). "A cohort study of effectiveness of acetylcholinesterase inhibitors in Alzheimer's disease." *Eur J Clin Pharmacol* **61**(5-6): 361-8.
- OBJECTIVES:** To characterise the population of Alzheimer's disease patients treated with acetylcholinesterase inhibitors, to analyse effectiveness and drug safety in the clinical practice, and to identify variables that may predict the response to therapy.
- METHODS:** From September 2000 to December 2001, a total of 5,462 patients diagnosed with mild to moderate Alzheimer's disease were enrolled at the time of their first prescription of the study drugs and followed up for an average of 10.5 months. Responders were defined as patients with a mini-mental state examination (MMSE) score improvement of 2 or more points from baseline after 9 months of therapy. **RESULTS:** At 9 months, 2,853 patients (52.2%) completed the study. The mean change from baseline in MMSE scores was an improvement of 0.5 points (+/-3.0). The proportion of responders to the therapy was 15.7% at 9 months. A greater probability of response at 9 months was observed among patients without concomitant diseases at baseline [odds ratio (OR)=2.1, 95% confidence interval (CI) 1.5-2.9] and among those with a response at 3 months (OR=20.6, 95% CI 17.2-24.6). During the study period, 285 patients (5.2%) discontinued the treatment because of an adverse drug reaction. **CONCLUSIONS:** Effectiveness of acetylcholinesterase inhibitors on cognitive symptoms of patients with mild to moderate Alzheimer's disease is modest. At 9 months, improvement was evident only in a subgroup of patients without concomitant diseases and who had demonstrated a response at 3 months.
37. Raskind, M. A., E. R. Peskind, et al. (2004). "The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial." *Arch Neurol* **61**(2): 252-6.
- BACKGROUND:** Alzheimer disease (AD) causes progressive cognitive and functional decline over years. Although cholinesterase inhibitors have demonstrated efficacy in studies lasting 3 to 6 months, little is known about long-term therapy. **OBJECTIVE:** To report the long-term cognitive effects of galantamine hydrobromide given continuously for 36 months in AD patients. **PARTICIPANTS:** Subjects were 194 US patients with mild to moderate AD who had been randomized to continuous galantamine therapy in either of 2 double-blind placebo-controlled trials. Subjects subsequently received open-label continuous galantamine therapy for up to 36 months. **MAIN OUTCOME MEASURES:** Effects on cognition were analyzed as change from study enrollment baseline in scores on the Alzheimer's Disease Assessment Scale-11-item cognitive subscale. Cognitive decline in galantamine-treated subjects was compared with that in a clinically similar historical control sample of AD patients who had received placebo for 12 months and with the mathematically predicted decline of untreated patients over 36 months. The rate of cognitive decline of patients who completed the entire 36-month trial (n = 119) was compared with that of patients who withdrew for any reason during the long-term open-label extension (n = 75). An inverted responder analysis was also performed in 36-month completers. **RESULTS:** Patients treated continuously with

galantamine for 36 months increased a mean +/- SE of 10.2 +/- 0.9 points on the Alzheimer's Disease Assessment Scale-11-item cognitive subscale—a substantially smaller cognitive decline (approximately 50%) than that predicted for untreated patients. Patients discontinuing galantamine therapy before 36 months had declined at a similar rate before discontinuation as those completing 36 months of treatment. Almost 80% of patients who received galantamine continuously for up to 36 months seemed to demonstrate cognitive benefits compared with those predicted for untreated patients. **CONCLUSIONS:** Cognitive decline over 36 months of continuous galantamine treatment was substantially less than the predicted cognitive decline of untreated patients with mild to moderate dementia. Thus, the cognitive benefits of galantamine seemed to be sustained for at least 36 months. These findings suggest that galantamine slows the clinical progression of AD.

38. Rockwood, K., S. Fay, et al. (2007). "Effect of galantamine on verbal repetition in AD: a secondary analysis of the VISTA trial." *Neurology* **68**(14): 1116-21.

OBJECTIVES: To understand how commonly diminution of verbal repetition was a goal of treatment in patients with Alzheimer disease (AD), how commonly that goal was achieved, whether goal attainment might be attributable to galantamine treatment, and whether change in verbal repetition is a marker of the overall treatment response.

METHODS: This is a secondary analysis of the Video-Imaging Synthesis of Treating Alzheimer's Disease study, a 4-month, double-blind, randomized, placebo-controlled trial of galantamine in 130 community-dwelling patients with mild to moderate AD. The primary outcome was Goal Attainment Scaling, in which individualized problems identified by patients/caregivers and treating physicians were assessed bimonthly.

RESULTS: Reduction of verbal repetition was set as a treatment goal in 44% (n = 57) of randomized patients. More patients/caregivers (32%) set repetition goals than did physicians (18%). After 4 months, more galantamine-treated patients showed diminution of verbal repetition (58%) than did placebo-treated patients (24%; p < 0.01). Reduction of verbal repetition correlated with improvement in clinical measures, but not in standardized ones. **CONCLUSIONS:** Reduction of verbal repetition is a common goal of Alzheimer disease treatment. After 4 months, patients treated with galantamine were more likely to experience a reduction of verbal repetition than those treated with placebo. Diminution of verbal repetition was associated with other improvements, suggesting it might be a clinical marker of a positive treatment response.

39. 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.

40. Rozzini, L., B. Vicini Chilovi, et al. (2005). "Effects of cholinesterase inhibitors appear greater in patients on established antihypertensive therapy." *Int J Geriatr Psychiatry* 20(6): 547-51.

INTRODUCTION: There is increasing evidence that hypertension may contribute to development of dementia. Studies show that blood pressure lowering therapy might protect against cognitive deterioration and that antihypertensive treatment reduce the incidence of dementia. AIM: We hypothesize that administration of cholinesterase inhibitors (AChEis) to patients with Alzheimer's Disease (AD) receiving antihypertensive medications therapy would result in clinical benefits for a period of 40 weeks in routine clinical practice. METHODS AND MATERIALS: Patients with possible or probable AD were enrolled from 16 Alzheimer evaluation units (UVA) of Brescia and Cremona (Northern Italy). Patients treated with donepezil, rivastigmine and galantamine for 40 weeks independently of dosages were selected. Patients were evaluated at baseline (T0), 4 weeks (T1), 16 weeks (T2) and 40 weeks (T3). RESULTS: 416 patients completed the study at 40 weeks; of these 255 were 'non users' while 161 utilized antihypertensive drugs ('users'). The mean change in MMSE score from baseline to week 40 demonstrate that antihypertensive-treated patients improved by 0.7 points while patients receiving only AChEis remain stables. Analyzing separately patients (n = 183) that ameliorate (responders) on cognition at T3 (\geq 1 point MMSE score increase) a significant

differences in favor of 'users' antihypertensive drugs over 'non users' on cognition at weeks 16 and 40 has been demonstrated. In particular, at T2 the mean change of MMSE from baseline in 'users' was 3.2 +/- 2.6 vs 'non users' 2.2 +/- 2.3 (p = 0.016) and at T3 was 3.5 +/- 2.5 vs 'non users' 2.0.2.7+/-1.6 (p = 0.018). Antihypertensive drugs were independently associated with cognitive improvement in responder patients treated with AChEis (95% CI: 0.41-1.79; p = 0.002). CONCLUSION: Antihypertensive medications in AD patients treated with AChEis are associated with an independent improvement on cognition after 40 weeks of treatment.

41. Schmitt, F. A., C. H. van Dyck, et al. (2006). "Cognitive response to memantine in moderate to severe Alzheimer disease patients already receiving donepezil: an exploratory reanalysis." Alzheimer Dis Assoc Disord **20**(4): 255-62.

OBJECTIVE: To investigate the cognitive effects of the N-methyl-D-aspartate receptor antagonist, memantine, with a post-hoc exploratory reanalysis of a 24-week randomized, double-blind, placebo-controlled, parallel group clinical trial comparing memantine (20 mg per day) to placebo in patients with moderate to severe Alzheimer disease (AD) receiving treatment with the cholinesterase inhibitor, donepezil. **METHODS:** The effects of memantine on individual items of the Severe Impairment Battery (SIB), subscale performance, and 3 post-hoc-derived aggregate subscales were investigated. Analyses were based on the intention-to-treat population using last observation carried forward and observed cases approaches. The SIB components were assessed at baseline, weeks 4, 8, 12, 18, and 24. **RESULTS:** The mean change from baseline by visit and at study end point on the SIB showed statistically significant differences between the memantine and placebo groups at all visits beginning at week 8 (last observation carried forward and observed cases). The SIB subscale analysis showed statistically significantly greater effects of memantine than placebo on memory, language, and praxis. When the SIB domains were aggregated using a face valid approach to create 3 higher-order subscales, memantine treatment resulted in statistically significant differences on memory, language, and praxis compared with placebo. **CONCLUSIONS:** These post-hoc analyses support the beneficial effects of memantine on cognition observed in a previously reported clinical trial. The results presented here suggest an effect of memantine on memory, language, and praxis in patients with moderate to severe AD and support the efficacy of memantine for the treatment of cognitive deficits in AD.

42. Suh, D. C., S. K. Thomas, et al. (2005). "Drug persistency of two cholinesterase inhibitors: rivastigmine versus donepezil in elderly patients with Alzheimer's disease." Drugs Aging **22**(8): 695-707.

OBJECTIVES: To compare persistency rates and persistency days in patients with Alzheimer's disease (AD) who initiated therapy with either rivastigmine or donepezil, and to identify factors influencing persistency in a real-world setting. **DESIGN AND METHODS:** This study used data collected by MarketScan from 1 January 1999 to 31 December 2002. Patients were included if they were newly diagnosed with AD and filled at least one prescription for rivastigmine or donepezil between 1 July 2000 and 30 June 2001, were > or =65 years of age on the index prescription date, and had continuous

health and prescription insurance during the entire study period. Patients were excluded if they filled a prescription for any cholinesterase inhibitor during the 18 months prior to initiation of the study drugs. Patients who refilled their initial cholinesterase inhibitor prescription within a permissible gap of 60 days after depleting the drug supply from the prior prescription were considered to be persistent. Sensitivity analysis was performed to test the robustness of the persistency definition. The Kaplan-Meier method was used to determine persistency rates across time and Cox proportional hazards models were used to estimate relative risks of discontinuation or switch with adjustment for other covariates, and to identify factors significantly influencing persistency of the study drugs. RESULTS: Of the newly treated AD patients, the proportion of rivastigmine and donepezil patients who continued their medication was the same (47%; $p = 0.5$). On average, rivastigmine users continuously used their medication for 234 days (median 312 days) while those taking donepezil used their medication for 235 days (median 315 days) [$p = 0.91$]. Patients were more likely to discontinue or switch their initial cholinesterase inhibitor if they used a central nervous system (CNS) medication before initiation of therapy (relative risk [RR] = 1.23; 95% CI 1.01, 1.51 without adjustment for study variables; RR = 1.30; 95% CI 1.05, 1.60 with adjustment for study variables). On the other hand, patients were less likely to discontinue their cholinesterase inhibitor if they visited their physician office frequently (RR = 0.24; 95% CI 0.18, 0.32 without adjustment; RR = 0.23; 95% CI 0.17, 0.30 with adjustment) or if they were hospitalised after initiation of their cholinesterase inhibitor therapy (RR = 0.60; 95% CI 0.39, 0.91 without adjustment; RR = 0.65; 95% CI 0.42, 0.99 with adjustment). CONCLUSION: Patients who were newly diagnosed with AD and initiated therapy with either rivastigmine or donepezil had similar levels of persistency with their initial AD therapy in a real-world setting.

43. Takeda, A., E. Loveman, et al. (2006). "A systematic review of the clinical effectiveness of donepezil, rivastigmine and galantamine on cognition, quality of life and adverse events in Alzheimer's disease." *Int J Geriatr Psychiatry* **21**(1): 17-28.

BACKGROUND: The use of cholinesterase inhibitors for Alzheimer's disease (AD) is currently being appraised by the National Institute for Clinical Evidence (NICE). This article provides the latest evidence that NICE will be using as part of this appraisal process. OBJECTIVE: To provide a systematic review of the best quality evidence of the effects of donepezil, rivastigmine and galantamine on cognition, quality of life and adverse events in people with mild to moderately-severe AD. DESIGN: Electronic databases were searched, references of all retrieved articles were checked, and experts were contacted for advice, peer review and to identify additional references. Randomised controlled trials (RCTs) were included if they fulfilled pre-specified criteria. Data were synthesised through a narrative review. RESULTS: Twenty-six RCTs that compared any one of the cholinesterase inhibitors with either a control group or with another cholinesterase inhibitor were included. The quality of reporting and methodology was varied. Treatment with donepezil, rivastigmine or galantamine resulted in significantly better cognitive performance using the ADAS-cog scale when compared with placebo. These findings were generally supported using the MMSE scale. Results from head to

head comparisons were limited by the low number of studies and the study quality; generally showing no robust support for any one drug. Few studies evaluated quality of life. Adverse events were generally related to the gastrointestinal system, with a tendency for these to be more common in the treatment arms. **CONCLUSIONS:** The cholinesterase inhibitors donepezil, rivastigmine, and galantamine can delay cognitive impairment in patients with mild to moderately-severe AD for at least 6 months duration.

44. van Dyck, C. H., F. A. Schmitt, et al. (2006). "A responder analysis of memantine treatment in patients with Alzheimer disease maintained on donepezil." *Am J Geriatr Psychiatry* **14**(5): 428-37.

OBJECTIVE: The objective of this study was to examine the clinical utility of memantine for moderate-to-severe Alzheimer disease (AD) using responder analyses. **METHOD:** Data from a previously published 24-week, randomized, double-blind, placebo-controlled trial of 10 mg memantine twice a day in patients with moderate-to-severe AD (N = 404) on stable donepezil therapy were evaluated using three sets of responder criteria. Response rates were calculated and analyzed for the intention-to-treat population using a generalized estimating equations model. The following outcomes were examined separately and in combination: the Alzheimer's Disease Cooperative Study-Activities of Daily Living 19-Item Inventory (ADCS-ADL19), Severe Impairment Battery (SIB), Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), and Neuropsychiatric Inventory (NPI). **RESULTS:** When treatment response required cognitive improvement relative to baseline, memantine yielded higher response rates than placebo. When treatment response was defined as stabilization of individual outcomes, memantine resulted in significantly higher response rates than placebo for all outcomes, with number needed to treat (NNT) ranging from 8-10. More conservative definitions of response that required simultaneous stabilization on multiple outcome measures again favored memantine treatment for six of 10 combinatorial definitions. **CONCLUSIONS:** These responder analyses may assist clinicians in evaluating the impact of memantine in a relevant clinical scenario, i.e., in patients with AD previously stabilized on a cholinesterase inhibitor. The current results indicate that in this setting, memantine produces both improvement and stabilization of symptoms, across multiple outcomes, and thus provides a clinically important treatment benefit for patients with moderate-to-severe AD.

45. Vellas, B., L. Cunha, et al. (2005). "Early onset effects of galantamine treatment on attention in patients with Alzheimer's disease." *Curr Med Res Opin* **21**(9): 1423-9.

INTRODUCTION: Exploratory pilot studies and knowledge of its mode of action suggested that galantamine, a cholinesterase inhibitor and modulator of nicotinic receptors, can improve attention. This study was designed to test the effects of galantamine on attention in patients with mild-to-moderate Alzheimer's disease (AD) and to see how changes in attention affected their caregivers. **METHODS:** This was an open-label, multicentre study. Patients received galantamine (up to 24 mg/day) for 12 weeks. Attention was assessed after 1, 4, 8 and 12 weeks using computerized tests including Choice Reaction Time (CRT), and caregiver, physician and patient ratings. **RESULTS:**

Data were available from 373 patients (mean age 75 years, mean baseline MMSE score 21). Attention as measured by CRT improved significantly from baseline to study endpoint ($p < 0.001$), improvements were observed after 1 week and statistical significance was maintained from 8 weeks. Physicians rated 67% of patients as globally improved and 5% as worsened. Caregivers reported improved attention in 57% of patients and worsening in 6%; 62% of patients considered they had improved and 3% considered themselves to be worse. Caregiver stress, time spent caring for patients and patients' interactions with others all improved from baseline to endpoint. Galantamine was generally well tolerated; the most common adverse events were gastrointestinal. **CONCLUSION:** Previous controlled trials have demonstrated that galantamine has a positive effect on cognition, activities of daily living, behaviour and global condition, but this is the first study to suggest that galantamine may specifically improve attention (according to both objective and subjective measures) in patients with AD. These effects may be a consequence of galantamine's potentiating action at nicotinic receptors.

46. Wallin, A. K., N. Andreasen, et al. (2007). "Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting." *Dement Geriatr Cogn Disord* **23**(3): 150-60.

BACKGROUND/AIMS: Clinical short-term trials have shown positive effects of donepezil treatment in patients with Alzheimer's disease. The outcome of continuous long-term treatment in the routine clinical settings remains to be investigated. **METHODS:** The Swedish Alzheimer Treatment Study (SATS) is a descriptive, prospective, longitudinal, multicentre study. Four hundred and thirty-five outpatients with the clinical diagnosis of Alzheimer's disease, received treatment with donepezil. Patients were assessed with Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), global rating (CIBIC) and Instrumental Activities of Daily Living (IADL) at baseline and every 6 months for a total period of 3 years. **RESULTS:** The mean MMSE change from baseline was positive for more than 6 months and in subgroups of patients for 12 months. After 3 years of treatment the mean change from baseline in MMSE-score was 3.8 points (95% CI, 3.0-4.7) and the ADAS-cog rise was 8.2 points (95% CI, 6.4-10.1). This is better than expected in untreated historical cohorts, and better than the ADAS-cog rise calculated by the Stern equation (15.6 points; 95% CI, 14.5-16.6). After 3 years with 38% of the patients remaining, 30% of the them were unchanged or improved in the global assessment. **CONCLUSION:** Three-year donepezil treatment showed a positive global and cognitive outcome in the routine clinical setting.

47. Wimo, A., B. Winblad, et al. (2004). "Impact of donepezil treatment for Alzheimer's disease on caregiver time." *Curr Med Res Opin* **20**(8): 1221-5.

OBJECTIVE: To assess the impact of donepezil treatment compared with placebo on caregiver time spent assisting patients with Alzheimer's disease (AD). **RESEARCH DESIGN AND METHODS:** Patient and caregiver data were collected as part of a 1-year, prospective, double-blind, randomized, placebo-controlled trial. The Resource Utilization in Dementia (RUD) questionnaire was used to record caregiver time at study baseline and

at Weeks 12, 24, 36, and 52. This analysis focuses solely on those caregivers who were actively (> 0 h/day reported on the RUD) providing care at study baseline. **MAIN OUTCOME MEASURES:** The change in time relative to baseline that caregivers spent assisting patients over the course of the study. **RESULTS:** The active caregiver population was composed of 96 caregivers of donepezil-treated patients and 94 caregivers of patients receiving placebo. Over the course of the 1-year study, and as the condition of the AD patients deteriorated, it was expected that caregiver time would increase. As expected, after 52 weeks, caregivers of placebo patients were providing almost 2 h each day (106.8 min) more care than they had done at study baseline. For those caregivers of donepezil-treated patients, although they were spending more time caring than they had done at study baseline, their time burden had only increased by 42.6 min more each day. This difference in caring time between the 2 groups, relative to baseline at Week 52, was 1.1 h (64.2 min) each day, and was significant ($p = 0.03$). **CONCLUSION:** Caregiver time devoted to helping an AD patient typically increases with the severity of the disease. By helping the patient maintain his/her ability to perform activities of daily living for longer, treatment with donepezil is not only beneficial to the patient, but also has positive time-burden implications for the caregiver.

48. Winblad, B., L. Kilander, et al. (2006). "Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study." *Lancet* **367**(9516): 1057-65. **BACKGROUND:** The cholinesterase inhibitor donepezil is used to treat mild-to-moderate Alzheimer's disease. Its efficacy in severe dementia has not been assessed and is controversial. Our aim was to ascertain the effectiveness of donepezil in patients with severe Alzheimer's disease, by focusing primarily on cognition and activities of daily living. **METHODS:** We did a 6-month, double-blind, parallel-group, placebo-controlled study in 248 patients with severe Alzheimer's disease (mini mental state examination score 1-10) who were living in assisted care nursing homes ran by trained staff in Sweden. We assigned patients oral donepezil (5 mg per day for 30 days then up to 10 mg per day thereafter, $n=128$) or matched placebo ($n=120$). Our primary endpoints were change from baseline to month 6 in the severe impairment battery (SIB) and modified Alzheimer's Disease Cooperative Study activities of daily living inventory for severe Alzheimer's disease (ADCS-ADL-severe). We analysed outcomes for patients with data at baseline and at one or more other timepoints (modified intent-to-treat population) with last observation carried forward used to replace missing data. **FINDINGS:** 95 patients assigned donepezil and 99 patients assigned placebo completed the study. Patients treated with donepezil improved more in SIB scores and declined less in ADCS-ADL-severe scores at 6 months after initiation of treatment compared with baseline than did controls (least squares [LS] mean difference, 5.7, 95% CI 1.5-9.8; $p=0.008$, and 1.7, 0.2-3.2; $p=0.03$, respectively). The incidence of adverse events was comparable between groups (donepezil 82% [$n=105$] vs placebo 76% [$n=91$]), with most being transient and mild or moderate in severity. More patients discontinued treatment because of adverse events in the donepezil group ($n=20$) than in the placebo group ($n=8$). **INTERPRETATION:** Donepezil improves cognition and preserves function in individuals with severe Alzheimer's disease who live in nursing homes.

49. Winblad, B., A. Wimo, et al. (2006). "3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy." Dement Geriatr Cogn Disord **21**(5-6): 353-63.

Delays in the diagnosis of Alzheimer's disease, and, therefore, delays in treatment, may have a detrimental effect on a patient's long-term well-being. This study assessed the effects of postponing donepezil treatment for 1 year by comparing patients treated continuously for 3 years with those who received placebo for 1 year followed by open-label donepezil for 2 years. Patients (n = 286) with possible or probable Alzheimer's disease (according to DSM-IV, NINCDS-ADRDA, and Mini-Mental State Examination criteria; see text) were randomized to receive donepezil (5 mg/day for 4 weeks, 10 mg/day thereafter) or placebo (delayed-start group) for 1 year. Of the 192 completers, 157 began a 2-year, open-label phase of donepezil treatment. Outcome measures were the Gottfries-Brane-Steen scale, the Mini-Mental State Examination, the Global Deterioration Scale, the Progressive Deterioration Scale, the Neuropsychiatric Inventory, and safety (adverse events). Mixed regression analysis was used to compare changes between the groups over 3 years on the efficacy measures. There was a trend for patients receiving continuous therapy to have less global deterioration (Gottfries-Brane-Steen scale) than those who had delayed treatment (p = 0.056). Small but statistically significant differences between the groups were observed for the secondary measures of cognitive function (Mini-Mental State Examination; p = 0.004) and cognitive and functional abilities (Global Deterioration Scale; p = 0.0231) in favor of continuous donepezil therapy. Over 90% of the patients in both cohorts experienced one treatment-emergent adverse event; most were considered mild or moderate. In conclusion, patients in whom the start of treatment is delayed may demonstrate slightly reduced benefits as compared with those seen in patients starting donepezil therapy early in the course of Alzheimer's disease. These data support the long-term efficacy and safety of donepezil.