Drug Class Review
on
Alzheimer's Drugs

Final Report

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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. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Richard A. Hansen, Ph.D.
Gerald Gartlehner, M.D., M.P.H.
Daniel J. Kaufer M.D.
Kathleen N. Lohr, Ph.D.
Leah C. Randolph, M.A.
Tim Carey, M.D., M.P.H.

RTI-UNC Evidence-based Practice Center
Cecil G. Sheps Center for Health Services Research
University of North Carolina at Chapel Hill
725 Airport Road, CB# 7590
Chapel Hill, NC 27599-7590
Tim Carey, M.D., M.P.H., Director

OHSU

Table of Contents

Introduction

A. Overview

Alzheimer's disease (AD), the most common adult form of dementia, is an age-associated neurodegenerative disorder pathologically characterized by the abnormal accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in selected brain regions. Primary clinical manifestations of AD include the insidious onset and gradual progression of cognitive impairment affecting multiple domains. Impaired recent memory (difficulty learning new information) is the clinical hallmark of AD; other associated cognitive signs include disturbances in language, visuospatial processes, and executive control functions such as insight and judgment. Alterations in behavior (e.g., irritability, paranoia), mood (e.g., depression), and personality (e.g., apathy) frequently occur in AD, are more variable than cognitive symptoms, and often contribute disproportionately to caregiver distress. Following the original case description in 1907 AD was initially viewed as a "pre-senile" dementia, with onset below age 65 years. Over time the term "senile dementia of the Alzheimer type" arose to acknowledge that dementia with AD-like clinical and pathological features occurred more commonly after age 65 years.

The historical distinction between pre-senile and senile forms of AD was abandoned in standard diagnostic criteria for AD developed over the last 25 years; the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-IV) and the National Institute of Neurological and Communicative Disorders and Stroke, and Alzheimer'sDisease and Related Disorders Association (NINCDS-ADRDA) have eliminated the historical distinction. The two main types of AD currently recognized are a generally later-onset sporadic form, representing about 95% of all cases, and autosomal-dominant familial forms involving specific mutations in one of three genetic loci (APP, presenilin 1, and presenilin 2) and typically associated with the early-onset of AD symptoms. Genetic polymorphism of the apolipoprotein epsilon locus (apo E4 allele) increases the risk of developing AD two to three-fold and is associated with an earlier age of onset in sporadic AD. Within the last decade, a syndrome referred to as "Mild Cognitive Impairment" (MCI) has gained recognition as a prodrome of AD in many but not all cases. [1] MCI is distinguished from AD by the presence of only short-term memory deficits and the absence of clear-cut functional limitations independent of memory difficulties.

Research diagnostic criteria for AD generally have been shown to be accurate and reliable based upon pathological confirmation studies;[2] nonetheless, the boundaries between MCI and early AD are not always clear. Furthermore, among all dementia cases with AD pathology a significant minority will have

concomitant cerebrovascular lesions (infarctions or small-vessel ischemic lesions of the white matter) or Lewy body pathology akin to Parkinson's disease (PD). The presence of multiple pathological substrates associated with AD also can contribute to diagnostic ambiguity. Further developments in structural and functional neuroimaging techniques, genetic susceptibility testing, and validating biomarker assays will help clarify diagnostic efforts and inform therapeutic drug testing and monitoring.

AD is estimated to affect 4.5 million individuals in the United States with an average course of about 8 to 10 years.[3] Of all individuals over age 65 years, an estimated 6% to 8% have AD or another form of dementia and this rate exceeds 30% at age 85 years and older. Although different estimates vary, roughly half of all AD patients are in the early or mild disease stage and the other half are in the moderate to severe range of severity.[4] The projected prevalence of AD will approximately double over the next 20 years, as a result of the aging of the post-WWII baby-boomer generation.

Since the total current economic burden posed by AD, including direct costs (medical, hospital, and nursing home care) and indirect costs (lost productivity of caregivers) is estimated to exceed $85 billion a year, the current and looming economic impact of AD is staggering.[5] The overall cost of managing AD is significantly greater for patients with severe disease than for those with mild to moderate; the reasons are largely greater dependency needs, higher resource utilization, and increased rate of institutionalization.

The comprehensive management of AD entails both nonpharmacologic and pharmacologic interventions. Nonpharmacologic interventions primarily address behavioral disturbances (e.g., task simplification, environmental modification, minimal excess stimulation, etc.) and other sources of cognitive impairment (e.g., treating comorbid medical conditions, minimizing or eliminating drugs with deleterious cognitive side effects).[6] Pharmacologic strategies have focused on modulating disease-associated neurotransmitter alterations; strategies can be characterized as symptomatic or neuroprotective. Although a symptomatic and a neuroprotective pharmacologic treatment may have similar outcome characteristics in a clinical trial, the key difference is that a neuroprotective therapy will have a cumulative benefit that persists after the treatment is discontinued. Currently available pharmacologic therapies, including cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists, are considered symptomatic treatments based on their ability to slow the clinical progression of symptoms across cognitive, behavioral, and functional domains.

Initial pharmacologic strategies for AD focused on increasing cholinergic transmission in the brain based on the "cholinergic hypothesis" of memory dysfunction. Among different strategies employed to increase synaptic levels of acetylcholine (ACh), blocking the breakdown of ACh by inhibiting acetylcholinesterase (AChE) has proven most successful to date. Inhibiting the enzyme butyrylcholinesterase (BuChE), which is a minor constituent in normal brains but in the brains of AD patients is increased in association with plaques and tangles, may also improve cholinergic transmission.[7]

Centrally active ChEIs, which differ in targeting AChE alone or affecting both AChE and BuChE, were the first class of drugs approved by the US Food and Drug Administration (FDA) for the treatment of AD. Currently available ChEIs include donepezil hydrochloride (donepezil), galantamine hydrochloride (galantamine), rivastigmine tartrate (rivastigmine), and tacrine hydrochloride (tacrine). Among these agents galantamine also acts as an allosteric nicotinic receptor modulator, which has been shown to stimulate the presynaptic release of acetylcholine and other neurotransmitters in laboratory preparations.[8] Because of their more favorable therapeutic profiles, greater convenience, and absence of liver toxicity, the second-generation ChEI agents (i.e., donepezil, galantamine, and rivastigmine) largely have supplanted the first approved drug in this class, tacrine. Neuropharmacologic and pharmacokinetic properties of the currently available ChEIs are summarized in Table 1.

More recent evidence implicates the excitatory neurotransmitter glutamate as playing a role in the pathophysiology of AD.[9, 10, 11] Currently, the only available drug targeting cognitive symptoms via a putative glutamatergic mechanism is memantine hydrochloride (memantine). Memantine has been widely used in Germany for more than two decades to treat a variety of conditions, including dementia, PD, neurogenic bladder, and neuropathic pain.[12,13] Memantine has been promoted as a treatment for dementia in Germany since 1989; in 2002 the European Union approved its use in AD. Memantine is a low-affinity noncompetitive NMDA receptor antagonist that blocks pathologic neural toxicity associated with prolonged glutamate release without interfering with the normal physiologic actions of glutamate required for learning and memory functions.[14, 15] Neuropharmacologic and pharmacokinetic properties of memantine are summarized in Table 1.

Other more poorly documented pharmacologic approaches include drugs like nicotine, selegiline, vitamin E, ginkgo biloba, piracetam, hormone replacement therapy, anti-inflammatory drugs, statins, and folic acid; [14, 16] these will not be considered in this review.

Table 1. Current drug treatments for Alzheimer's disease

Agent	Tacrine (Cognex®)	Donepezil (Aricept®)	Rivastigmine (Exelon®)	Galantamine (Reminyl®)	Memantine (Namenda™)
Manufacturer/ Distributor	West-Ward Horizon	Eisai Pfizer	Novartis	Janssen Shire	Merz Forest
Mechanism(s)	AChEI, BuChEI	AChEI	AChEI, BuChEI	AChEI, NRM	NMDA antagonist
Dose Forms (mg)	10, 20, 30, 40	5, 10	1.5, 3, 4.5, 6	4, 8, 12	5, 10
Dose Frequency	4x /day	1x /day	2x /day	2x /day	2x /day
Serum $T_{1/2}$ (hrs.)	1.3 – 2	70	2 – 8 [a]	6 – 8	60 – 80
Dose Range	40 – 160 mg/d	5 – 10 mg/d	3 – 12 mg/d	8 – 24 mg/d	5 – 20 mg/d
Target Dose	80 – 160 mg/d	5 – 10 mg/d	6 – 12 mg/d	16 – 24 mg/d	10 – 20 mg/d
Dose Titration	6 wks.	4 – 6 wks.	2 – 4 wks.	4 wks.	1 wk.
Metabolism [b]	CYP1A2	CYP2D6, 3A4	Non-hepatic	CYP2D6,3A4	Non-hepatic
Protein-binding	75%	96%	40%	19%	45%
Taken with food?	Yes	Not necessary	Yes	Yes	Not necessary
Hepatotoxicity?	Yes [c]	No	No	No	No

AChEI = Acetylcholinesterase inhibition
BuChEI = Butyrylcholinesterase inhibition
NRM = Nicotinicreceptor modulator
NMDA = N-methyl d-aspartate
[a] Pseudo-irreversible binding; upper range reflects duration of esterase inhibition
[b] Hepatic cytochrome p450 enzyme metabolism
[c] Requires periodic monitoring of serum liver transaminases (AST, ALT)

B. Scope and key questions

The purpose of this review is to help policy makers and clinicians make informed choices about the use of the four ChEIs and memantine in the treatment of AD. We compare the efficacy, effectiveness, and safety (adverse events) of donepezil, galantamine, rivastigmine, tacrine, and memantine in patients with mild to severe AD. Although we will emphasize *comparative* head-to-head studies, the few published ones do not allow for a comprehensive evaluation. Accordingly, we will also include supplementary data from individual placebo-controlled trials and observational studies.

The participating organizations of the Drug Effectiveness Review Project (DERP) are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to their constituencies. The Oregon Evidence-based Practice Center initially prepared preliminary key questions identifying the populations, interventions, and outcomes of interest, and we based the eligibility criteria for studies on these preliminary questions. Representatives of organizations participating in the DERP, in conjunction with experts in the fields of health policy, neurology, pharmacotherapy, and research methods reviewed, revised, and approved the questions and outcome measures. The participating organizations approved the following key questions:

1. How do donepezil, galantamine, rivastigmine, tacrine, and 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 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?

4. Does efficacy, effectiveness, or adverse events of donepezil, galantamine, rivastigmine, tacrine, or memantine 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?

The first key question addresses the issue of effectiveness: do drugs used to treat AD differ in their effects under real-life circumstances? This report addresses both efficacy (i.e., do AD drugs differ in their effects under ideal or highly controlled circumstances) and effectiveness. We distinguish between *efficacy* (*explanatory*) studies and *effectiveness (pragmatic)* studies; studies conducted in primary care or office-based settings that use less stringent eligibility criteria (i.e., broad range of population characteristics and disease severity) have long follow-up periods (i.e., greater than one year), and assess health outcomes are characterized as *effectiveness* studies. Studies conducted in more highly selected populations over shorter periods of time are characterized as *efficacy* studies. We summarize the results of efficacy and effectiveness studies separately as the results of effectiveness studies are more generalizable than results from highly selected populations (i.e., efficacy studies).

For assessing efficacy and effectiveness, our review includes methodologically valid comparative evidence from controlled clinical trials and fair- or good-quality systematic reviews. For evaluating safety we include controlled clinical trials, systematic reviews, and observational studies. A summary of outcome measures and study eligibility criteria can be found in Table 2; a more complete description of commonly used scales and outcome measures can be found in Appendix B.

The second key question specifically addresses the time to achieve statistical and clinical differences between available drugs. Although we searched for direct and indirect evidence addressing time to statistical and clinical differences, several points should be considered. In general, determining time to effect and time required to assess clinical response are both difficult tasks given the progressive nature of AD, the design of most trials, and the nature of measurement scales. Because limited evidence compares one AD drug to another and because placebo-controlled trials are too heterogeneous with respect to study design, outcomes assessment, and populations to allow any inferences about the comparative time to effect, drawing conclusions about one drug compared to another is similarly difficult. Furthermore, given the fact that changes in cognition and global assessment can be reached only with sustained treatment with ChEIs and memantine, the clinical significance of time to effect is likely to be of minimal importance to physicians and patients. We review the available evidence below, but we caution readers about interpretation given the nature of the evidence and questionable significance of any differences reported across trials.

Table 2: Outcome measures and study eligibility criteria

Outcome	Outcome Measures	Study Eligibility Criteria
Efficacy / Effectiveness	• 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) • Hospitalizations	• Head-to-head randomized controlled clinical trials or meta-analyses comparing one AD drug to another • When sufficient evidence was not available for head-to-head comparisons we evaluated placebo-controlled trials • Observational studies were reviewed for hospitalizations, an outcome measure rarely assessed in controlled trials for AD

Safety/ Tolerability	• Overall adverse effect reports
	• Withdrawals because of adverse effects
	• Serious adverse event reports
	• Discontinuations due to adverse events
	• Specific adverse events, including:
	- Gastrointestinal symptoms
	- Hepatotoxicity
	- Weight loss
		• Head-to-head randomized controlled clinical trials or meta-analyses comparing one AD drug to another
		• When sufficient evidence was not available for head-to-head trials, we evaluated:
		  • placebo-controlled trials
		  • observational studies

AD – Alzheimer's Disease

Given the progressive nature of AD it is important to note the distinction between clinical improvement and slowing the progression of disease. Although a treatment may not demonstrate clinical improvement from baseline over time, it may be able to slow the rate of cognitive or behavioral deterioration. In this review we use the term "improvement" to reflect the degree to which patients improve with respect to their comparator. Because most of the evidence for these drugs stems from placebo-controlled trials, "improvement" commonly reflects differences between active- and placebo-treated patients. These patients, in reality, may not be significantly better than they were when they started treatment, but have demonstrated slower deterioration than patients in the other study groups.

As equipotency among the reviewed antidementia drugs is not well established, we assume that dose comparisons made within the recommended daily dosing range are comparable (Table 1). Dose comparisons made outside the recommended daily dosing range are acknowledged in our report, but we do not use them to determine the quality of the evidence. Furthermore, we evaluate studies that assess only initial treatment with these drugs as independent agents; we do not consider the issue of switching from a ChEI to memantine or vice versa. Although some clinicians may use a combination of drugs in clinical practice, we do not specifically consider combination therapy in this report. However, because combination therapy has been addressed by at least one clinical trial, we contrast this trial with other available evidence.

Considerations governing our work on key question 1 and 2 (i.e., dose equivalency, operational definitions) pertain as well (as appropriate) to key questions 3 and 4.

METHODS

A. Literature search

We searched MEDLINE, Embase, The Cochrane Library, and the International Pharmaceutical Abstracts to identify articles relevant to each key question. We used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for the selected indication (Alzheimer's disease), drug interactions, and adverse events with a list of five specific Alzheimer's drugs (donepezil, galantamine, rivastigmine, tacrine, and memantine,). We limited the electronic searches to "human" and "English language", and searched sources from 1980 to 2004 (September) to identify literature relevant to the scope of our topic. We used the National Library of Medicine publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses. We manually searched reference lists of pertinent and relevant review articles and letters to the editor. All citations were imported into an electronic database (ProCite5.0).

Additionally, we hand-searched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the FDA. Finally, the Center for Evidence-based Policy at the Oregon Health and Science University (OHSU) contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations, using a protocol available at www.ohsu.edu/drugeffectiveness. We received dossiers from two pharmaceutical companies.

Our searches found 979 citations, unduplicated across databases. We found an additional 58 articles from manually reviewing the reference lists of pertinent review articles. We included no studies originating from pharmaceutical dossiers; all studies submitted from pharmaceutical dossiers were present in our other searches. The total number of citations included in the database was 1,037.

B. Study selection

Two persons independently reviewed abstracts; if both reviewers agreed that the trial did not meet eligibility criteria we excluded it; we obtained the full text of all remaining articles. Records were considered for exclusion if they did not meet pre-established eligibility criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons to Alzheimer's medications outside our scope of interest.

For this review, results from well-conducted, head-to-head trials provide the strongest evidence to compare drugs with respect to efficacy, effectiveness, and adverse events. We defined head-to-head trials

as those comparing one Alzheimer's drug with another. Included studies were RCTs lasting at least 12 weeks that had an outpatient study population with a total sample size greater than 100 participants.

If we could not find sufficient evidence of efficacy or effectiveness from at least one randomized, double-blinded, head-to-head trial, we reviewed randomized, controlled, open-label trials. For comparing different drugs, however, the strength of evidence must be rated lower for these results than for results from blinded trials.

If no head-to-head evidence was published, we reviewed placebo-controlled trials. We reviewed all placebo-controlled trials to provide an overview of efficacy without taking drug equivalency into account. Compared to placebo and all other things equal, higher dosages may yield greater treatment effects than do low or medium dosages. For that reason, we did not evaluate the dosage of one drug relative to the dosage of an alternative drug in a different trial. In addition, heterogeneity among study populations and placebo groups demand caution in making comparative judgments about treatment effects across trials.

We examined adverse events in both experimental and observational studies. For observational studies we included those with large sample sizes (> 100 patients) that lasted at least 1 year and reported an outcome of interest.

We initially reviewed studies with health outcomes as the primary outcome measures. Outcomes were institutionalizations, behavioral symptoms (e.g., aggression, agitation, mood disorders, psychosis), discontinuation effects, mortality, and changes in the rate of decline in day-to-day functioning and activities of daily living. Because health outcomes often were not reported, we also included intermediate outcomes (e.g., cognition, global assessment). Safety parameters included overall and specific adverse events (e.g., hepatotoxicity, weight loss, and gastrointestinal symptoms), withdrawals due to adverse events, and drug interactions.

We included meta-analyses in our evidence report if we found them to be relevant for a key question and methodologically sound (based on the QUORUM[17] statement); we did not review individual studies if they had been included in a high-quality meta-analysis. We excluded meta-analyses that were not based on a comprehensive systematic literature search or did not maintain the units of the studies in their statistical analyses. We included recent pooled analyses of RCTs if they covered all published trials and their methods were sound. We checked our database to ensure that our literature search had identified

trials included in any meta-analyses that we discarded; we then obtained any missing articles so that all constituent studies would be represented in this review.

If we could not find sufficient evidence of efficacy or effectiveness from at least one randomized, double-blinded, head-to-head trial, we reviewed placebo-controlled trials and randomized, controlled, open-label trials. For comparing different drugs, however, the strength of evidence must be rated lower for these results than for results from the preferred type of trial. Findings of placebo-controlled trials are hard to compare across studies because disparate populations may respond differently.

Overall, we reviewed 1,037 article abstracts and retrieved 173 of those as full text articles for background information or to be reviewed for inclusion into the evidence report.

C. Data abstraction

We designed and used a structured data abstraction form to ensure consistency in appraising each study. Trained reviewers abstracted data from each study and assigned an initial quality rating; a senior reviewer read each abstracted article, evaluated the completeness of the data abstraction, and confirmed the quality rating. We abstracted the following data from included trials: study design, eligibility criteria, intervention (drugs, dose, duration), additional medications allowed, methods of outcome assessment, population characteristics, sample size, loss to follow-up, withdrawals attributed to adverse events, results, and adverse events reported. We recorded intention-to-treat (ITT) results if available.

D. Quality assessment

We assessed the internal validity (quality) of trials based on predefined criteria (Appendix C). These criteria are based on those developed by the US Preventive Services Task Force (ratings: good, fair, or poor)[18] and the National Health Service Centre for Reviews and Dissemination.[19] We assessed external validity (generalizability) and reported on it, but these assessments did not influence our quality ratings.

Two independent reviewers assigned quality ratings; they resolved any disagreements by discussion and consensus or by consulting a third independent party. Elements of internal validity assessment included, among others, randomization and allocation concealment, similarity of compared groups at baseline, use of ITT analysis, and overall and differential loss to follow-up.

Loss to follow-up was defined as the number of persons randomized who did not reach the endpoint of the study, [20] independent of the reason and the use of ITT analysis. We adopted an overall loss to follow-up of 40% as a cut-off point for poor quality.

We rated trials that had a fatal flaw in one or more categories as poor quality; we did not include them in this analysis. We rated trials that met all criteria as good quality. The majority of trials received a quality rating of fair. This includes studies that presumably fulfilled all quality criteria but did not report their methodologies to an extent that answered all our questions. Thus, the "fair quality" category includes trials with quite different strengths and weaknesses and a range of validity.

The last observation carried forward (LOCF) method of data analysis is a particular issue in Alzheimer's disease. The reason is that the natural course of the disease leads to a gradual decline in cognition and daily functioning over time. Particularly in longer studies measurements carried forward can bias results towards an overestimation of the treatment effect. We took this potential bias into consideration when we appraised each study and highlighted possible bias in the text whenever appropriate.

RESULTS

We identified 1,037 citations from searches and reviews of reference lists; we identified no unpublished trials from dossiers submitted by pharmaceutical companies. In total we included 41 studies: 28 RCTs, 6 meta-analyses or systematic reviews, and 7 studies of other design. Furthermore, we retrieved 57 articles for background information. We could not retrieve six articles after multiple attempts.[21, 22, 23-26] For some studies, the investigators published more than a single article; therefore, numbers of referenced articles may not always sum to the number of studies (Figure 1, QUORUM Tree).

Reasons for exclusions were based on eligibility criteria or methodological criteria. We excluded nine studies that met the eligibility criteria but were later rated as poor quality for internal validity from the analysis (Appendix D). The main reasons for a poor quality rating were high study attrition rates among RCTs and lack of systematic literature search for meta-analyses. Lack of a systematic literature search leads to a selected spectrum of trials and biased results.

Of 41 included studies, 74 percent were supported financially by pharmaceutical companies; 17 percent were funded by governmental agencies or independent funds. We could not determine the funding source for 9 percent of included studies.

Studies reviewed for this report employed several different instruments for assessing symptoms, health status, or quality of life. Table 3 summarizes symptom assessment scales and health status or quality-of-life instruments encountered in this literature and used in this report.

Table 3: Abbreviations and full names of assessment scales and other instruments

Abbreviation	Full Name of Instrument
ADAS-cog	Alzheimer's Disease Assessment Scale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADFACS	Alzheimer's Disease Functional Assessment Change Scale
aRSS	Abridged Relative Stress Scale
BEHAVE-AD	Behavioral Symptoms in Alzheimer's Disease
BGP	Behavioral Rating Scale for Geriatric Patients
Bristol ADL	Bristol Activities of Daily Living Scale
CAS	Caregiver Activity Survey
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes
CGI-C	Clinical Global Impression of Change
CIBIC-plus	Clinician's Interview-Based Impression of Change scale
CMCS	Caregiver-rated Modified Crichton Scale
DAD	Disability Assessment for Dementia
FAST	Functional Assessment Staging Scale
GBS	Gottfries, Brane, and Steen Scale
GDS	Global Deterioration Scale
IADL	Instrumental Activities of Daily Living
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
MENFIS	Mental Function Impairment Scale
MMSE	Mini Mental State Examination
NOSGER	Nurse's Observational Scale for Geriatric Patients
NPI	Neuropsychiatric Inventory
PDS	Progressive Deterioration Scale
SCAG	Sandoz Clinical Assessment Geriatric Scale
SCGB	Screen for Caregiver Burden
SIB	Severe Impairment Battery

*More detail provided for some of these scales in Appendix B

KEY QUESTION 1

How do donepezil, galantamine, rivastigmine, tacrine, and memantine compare in their efficacy or effectiveness for stabilizing symptoms and treating behavioral disturbances in patients with Alzheimer's Disease?

We included 24 RCTs and 7 systematic reviews/meta-analyses. Of the RCTs, 3 were head-to-head trials; 21 were placebo-controlled trials. Only one trial was deemed to be an effectiveness trial.

A. Description of studies

We did not identify any head-to-head, randomized, double-blind, parallel-group study. Of the three head-to-head trials we identified,[27,28,29] all were open-label trials blinding only the rater to treatment allocation; two trials[27,28] compared donepezil to galantamine and one trial[29] compared donepezil to rivastigmine. We included one systematic review[30] that pooled placebo-controlled trials of donepezil, galantamine, and rivastigmine to represent ChEIs as a class. Several other systematic reviews pooled placebo-controlled trials for specific medications. [31-36]

Of the included placebo-controlled trials, 10 compared donepezil to placebo,[31,32,37-45,46] 5 compared galantamine to placebo,[47,48-50,51] 3 compared rivastigmine to placebo,[52,53,54] 1 compared tacrine to placebo,[55] and 2 compared memantine to placebo.[56,57] Most trials were 3 months to 1 year in duration; one trial followed patients for more than 3.5 years.[37] Only one trial was deemed to be an effectiveness trial. [37] Doses generally were given within the range of the approved package labeling (see Table 1), although several galantamine trials used doses above the recommended 24 mg/day and rivastigmine trials commonly included a low dose arm of 1-4 mg/day.

B. Study populations

We included studies with a sample size greater than 100; the largest trial included in our review randomized 978 patients with probable AD.[49] On average, the mean patient age was between 70 and 75 years; one trial was conducted in a nursing home population with a mean age of 86 years.[45] Most studies were conducted in patients with mild to moderate AD; one donepezil[39] and two memantine trials[56,57] were conducted in patients with moderate to severe AD. Most trials specifically excluded patients with vascular dementia and clinically significant neurologic disease other than AD. Some trials did not specify such exclusion criteria or report the proportion of patients with such comorbid disease. Most studies

allowed patients to use other medications except for drugs with cholinomimetic effects or anticholinergic medications.

C. Outcome measures

Studies commonly included measures to assess symptom stabilization (e.g., cognition, global assessment of change) and behavioral disturbances. Most studies included a measure of cognition (e.g., ADAS-cog) as the primary outcome; other commonly included measures of cognition were the MMSE and SIB. Global change often was measured using scales such as the CGI-C, CIBIC-plus, or GDS; functional status was commonly assessed using measures such as the ADCS-ADL, DAD, Bristol ADL, and PDS. Changes in mood, behavior, and personality were assessed with measures such as the NPI or BEHAVE-AD. Some studies included other instruments that assessed quality of life or caregiver burden.

D. Head-to-head comparisons

We did not identify any randomized, double-blind, comparative trials. We did identify three open-label head-to-head trials.[27,29,28] One trial compared donepezil to galantamine over 52 weeks,[27] one compared donepezil to galantamine over 12 weeks,[28] and one compared donepezil to rivastigmine over 12 weeks. [29] These trials blinded only the rater to treatment allocation. Although open-label trials are subject to "fatal flaws" for internal validity, we review their results because they provide the only comparative evidence. We do not provide quality ratings for these trials.

We included one meta-analysis[30] that evaluated evidence comparing donepezil, galantamine, and rivastigmine with placebo. Although this review does not make indirect comparisons among included ChEIs, the quantitative summary of placebo-controlled trials is useful for summarizing evidence for ChEIs in general.

Donepezil vs. Galantamine

One 52-week open-label trial compared donepezil 10 mg/day to galantamine 24 mg/day in 182 patients with probable AD and MMSE scores between 9 and 18 at screening.[27] Although raters were blinded to treatment allocation, patients, caregivers, and physicians were not blinded because of differences between the two study drugs in dosing frequency, escalation schedules, and physical appearance. On average, study participants were 73 years of age with a mean baseline MMSE score of 15. The primary study endpoint was based on function assessed by the Bristol ADL; cognitive outcome measures included the MMSE and ADAS-cog, behavioral disturbances were assessed with the NPI, and caregiver burden was measured using the SCGB scale. At endpoint no statistically significant differences were observed in

functional abilities, cognitive symptoms, behavioral disturbances, or caregiver burden between the donepezil and galantamine treatment groups. This trial was funded by the makers of galantamine.

One 12-week open-label trial compared flexible doses of donepezil 5-10mg/day (once daily) and galantamine 8-24mg/day (twice daily) in 120 patients with probable or possible AD;[28] as in the 52-week trial, only raters were blinded to treatment allocation. The mean age of study participants was 74 years with a mean baseline MMSE score of 21. On average, baseline MMSE scores for patients in this trial indicated less severe disease than in the 52-week trial. At baseline, patient demographics and disease characteristics were similar in both groups. The primary outcome measure was unblinded physician and caregiver satisfaction as measured on a scale specifically developed by the makers of donepezil for use in another head-to-head trial (presumably this instrument had not been previously validated). [29] Secondary outcome measures included cognition (ADAS-cog, MMSE) and disability (DAD). At 12 weeks, both physician and caregiver satisfaction ratings were significantly better for donepezil ($P < 0.001$ and $P < 0.01$, respectively). Furthermore, donepezil-treated patients demonstrated significantly more improvement on the ADAS-cog, MMSE, and DAD ($P < 0.05$). In contrast to the 52-week study that demonstrated no difference between donepezil and galantamine, this trial was funded by the makers of donepezil. Additionally, this trial demonstrated the worst reported galantamine response among all other clinical studies. Both trials utilized similar dosing protocols.

Donepezil vs. Rivastigmine

One 12-week open-label trial compared flexible doses (5-10 mg/day) of donepezil to flexible doses (6-12 mg/day) of rivastigmine in 111 patients with mild to moderate AD.[29] The mean age of study participants was 74 years with a mean baseline MMSE score of 20; 54% of donepezil-treated patients and 64% of rivastigmine-treated patients were female. With regard to baseline disease severity, patients in this trial most closely resembled the 12-week trial comparing donepezil to galantamine. Cognitive symptoms and disease severity were assessed with the ADAS-cog and MMSE, respectively. ADAS-cog raters were blinded to treatment allocation, but unblinded clinicians administered the MMSE. At 12 weeks no statistically significant differences in ADAS-cog or MMSE were reported for the two treatment groups. These investigators also administered an unidentified measure of clinician and caregiver satisfaction. Although physicians and caregivers reported significantly higher scores on the satisfaction measure for donepezil than for rivastigmine, this measure was designed and initially used in this trial and had not been previously validated. This trial was funded by the makers of donepezil.

E. Placebo-controlled trials

We identified 7 systematic reviews or meta-analyses of placebo-controlled trials and 21 RCTs that met the inclusion criteria for our review of placebo-controlled evidence. When good-rated systematic reviews provided comprehensive evidence for a specific drug-placebo comparison, we did not include individual trials already covered in the systematic review. However, in cases where individual trials were too heterogeneous or not adequately described by existing systematic reviews (i.e., donepezil and memantine), we include these trials in our review in addition to the pooled analysis.

Donepezil, Galantamine, and Rivastigmine vs. Placebo (Meta-Analysis)

One methodologically sound meta-analysis[30] evaluated placebo-controlled evidence for donepezil, galantamine, and rivastigmine. This review cannot be used to compare one drug to another directly, but quantitative analyses from this study are relevant to the question of the general effectiveness of ChEIs as a class. The authors defined "global responders" as subjects rated as minimally to very much improved on the CGIC or CIBIC-plus; "cognitive responders" were defined as patients with a 4-point or greater improvement (decrease) from baseline on the ADAS-cog. Compared to placebo the pooled number needed to treat (NNT) to yield one additional ChEI global responder was 12 (95% CI 9-16); the NNT to yield one additional cognitive responder was 10 (95% CI 8-15). Compared to patients receiving placebo, significantly more patients receiving ChEIs had adverse events (8%; 95% CI 5%-11%), dropped out (8%; 95% CI 5%-11%), or dropped out because of adverse events (7%; 95% CI 3%-10%). Pooled rates of dropouts and adverse events were not reported for each drug. However, adverse event rates in excess of those for placebo were lowest for donepezil (6%; 95% CI 2%-9%), followed by rivastigmine (8%; 95% CI 1%-10%), and galantamine (12%; 95% CI 7%-18%). Similarly, drop out rates in excess of the rate for placebo were lowest for donepezil (3%; 95% CI 1%-6%), followed by rivastigmine (9%; 95% CI 5%-12%), and galantamine (14%; 95% CI 8%-21%). Drop out rates due to adverse events demonstrated a similar trend.

Donepezil vs. placebo

We included two meta-analysis[32,58] and 10 trials[37,38,39-46]comparing donepezil to placebo.

A good meta-analysis pooled data from 13 trials lasting 12 or more weeks and involving 4,365 participants.[58] Pooled results demonstrated statistically significantly better ratings for 5mg/day and 10mg/day donepezil on all outcomes measures at 24 weeks. For 10mg/day doses, the global assessment with CIBIC-plus, dichotomized into those showing no change or decline and those showing improvement yielded an odds ratio (OR) of 2.18 (95% CI 1.53 – 3.11; P < 0.001) and assessment of cognition with MMSE a weighted mean difference (WMD) of 1.50, (95% CI 0.97 – 2.04; P < 0.0001) and with ADAS-Cog a WMD of -2.92 (95% CI -3.74 - -2.10; P < 0.001). The size of the effect was dose-related and did not differ by severity of the disease. Furthermore, pooled data from two trials assessing activities of daily living (DAD, IADL, PSMS, CMCS) presented a statistically significant benefit for 5mg/day and 10mg/day donepezil treatment at week 12 and week 24. No difference was reported on a patient-rated Quality of Life Scale between donepezil and placebo. These findings were consistent with those of a fair-rated meta-analysis using individual patient data of placebo-controlled trials.[32]

Of 10 placebo-controlled trials that we examined, all had been included in the meta-analysis by Birks et al. Because some[42,44,41] of these trials provide specific results on quality of life and activities of daily living we summarize results in Table 4. [37,39,43]

The only effectiveness study we identified was the only trial on donepezil that was not funded by the pharmaceutical industry.[37] This UK study enrolled 565 patients and assessed the effectiveness of long-term (3 years and 36 weeks) donepezil treatment in community-residents with mild to moderate AD with or without concomitant vascular dementia. Primary outcome measures were rate of institutionalism and functional capacity (Bristol ADL). No significant differences could be observed in the rates of institutionalism between donepezil and placebo at 1 year (9% vs. 14%; P = 0.15) and at 3 years (42% vs. 44%; P = 0.4). After 12 weeks until the end of the trial, the Bristol ADL scores of donepezil-treated patients were statistically significantly better, though the difference was modest (average +1.0 point, 95% CI 0.5 – 1.6; P = 0.0004). Similarly, MMSE scores were modestly but statistically significantly higher in donepezil- than in placebo-treated patients (average 0.8 points, 95% CI 0.5 – 1.2; P = 0.001); the clinical significance of these findings is questionable. No significant differences were detected in progression of disability (Bristol ADL) or behavioral and psychological symptoms (NPI).

A fair British study (n = 431) examined the functional decline of donepezil compared to placebo-treated patients over 1 year.[41] The primary endpoint was time to clinically evident decline in function (defined in study protocol). A higher proportion of placebo than of donepezil- treated patients reached the primary endpoint (56% vs. 41%; P < 0.005). The median time to clinically evident functional decline was significantly shorter for placebo than for donepezil-treated patients on donepezil (208 vs. 380 days; P = 0.0051).

Galantamine vs. placebo

One good-rated systematic review,[33] one good-rated RCT,[50] and four fair-rated RCTs[47,48,49,51] compared galantamine to placebo. We focus the majority of our discussion on the systematic review because it provides a comprehensive summary of the five RCTs identified in our search. However, for measures of behavior and functional capacity we focus our discussion on individual trials because data in these domains were not pooled in the systematic review.

Trials ranged from 12 to 52 weeks in duration. The most frequent galantamine dose tested was 24mg/day; in most trials patients began at 8 mg/day and increased over time to the daily maximum. Patients reached their maximum daily dose 2 to 8 weeks into the respective trials. All trials used the ADAS-cog to assess cognitive change; other measures of symptomatic change included the European adaptation of the ADAS scale, the expanded ADAS-cog, and the Digit Symbol Substitution Test. Most trials used global rating scales such as the CIBIC-plus or the ADCS-CGIC. Changes in behavior were assessed by the NPI and functional status was assessed using the PDS and DAD.

Overall, galantamine was significantly better than placebo for improving intermediate outcome measures of cognitive symptoms.[33] Pooled analyses of ADAS-cog scores from trials lasting 5 to 6 months revealed statistically significant differences for all doses of galantamine compared to placebo (8mg: WMD -1.3; 95% CI -2.6-0.3; 16mg: WMD -3.1; 95% CI -4.1- -2.1; 24mg/day: WMD -3.3; 95% CI -3.9- -2.7; 32mg/day: WMD -3.3; 95% CI -4.1- -2.4). Results from trials of 3 months' duration were similar. Pooled ITT analyses for global rating scales also favored galantamine over placebo. Trials lasting 5 to 6 months demonstrated similar differences (16mg/day: OR 2.04; 95% CI 1.4-2.9; 24mg/day: OR 1.82; 95% CI 1.4-2.3; 32mg/day: OR 1.79; 95% CI 1.3-2.4), except for the 8mg/day dose, which was not significantly different from placebo. Trials lasting 3 months demonstrated statistically significant differences between galantamine and placebo on global rating scales for doses of 18mg/day (OR 2.44; 95% CI 1.2-5.0), 24mg/day (OR 2.11; 95% CI 1.0-4.6), and 36 mg/day (OR 2.7; 95% CI 1.2-6.2).

Although most trials assessed behavior or functional status, the authors of the systematic review did not pool these data, presumably because of differences in study design and reporting. Evidence from individual trials is mixed. One good-rated trial assessed activities of daily living with the ADCS-ADL scale; ITT results statistically favored galantamine over placebo at 26 weeks.[50] Another trial that assessed activities of daily living using the PDS found no significant differences between galantamine and placebo.[51] Two trials assessed behavioral symptoms using the NPI; one reported no differences in NPI scores at 26 weeks[48] and the other reported statistically significant differences at 22 weeks for doses of 16mg/day and 24mg/day.[49] Three trials measured disability using the DAD scale; one reported statistically significant differences between galantamine and placebo for doses of 24mg/day and 32mg/day,[48] one reported statistically significant differences for doses of 32mg/day but not for 24mg/day,[50] and one reported no differences for doses of 24mg/day or 32mg/day.[47] One trial assessed sleep quality using the NPI sleep score and the PSQ1; no differences were found between galantamine and placebo on either measure.[59]

Rivastigmine vs. placebo

One good-rated systematic review,[58] one fair-rated systematic review,[34] and three placebo-controlled trials were included in our review of rivastigmine.[52-54] The good-rated systematic review included 3 published trials[52,54,60] and 5 unpublished phase II and phase III clinical trials involving 3,450 patients. All trials but one[60] were sponsored by rivastigmine's manufacturer. The fair-rated systematic review included data from two published trials[52,54] and one unpublished phase III clinical trial.

Although both systematic reviews included data from two of the same trials, we include them both because each study drew unique conclusions. However, because the Cochrane review received a better quality rating and was more comprehensive, we believe the good-rated Cochrane review gives the best overall summary.

The good-rated systematic review[58] included data from eight trials; studies ranged in duration from 9 to 26 weeks. In most trials, the mean baseline MMSE score was between 18 and 20. Analyses were stratified by dose, characterizing rivastigmine 1-4mg/day as low dose and rivastigmine 6-12mg/day as high dose. Common outcome measures included the ADAS-cog, CIBIC-plus, GDS, MMSE, and PDS. Caregiver activities also were assessed using the CAS. Pooled results suggest significantly greater improvement on the CIBIC-plus for all doses of rivastigmine compared to placebo. Significantly greater improvement also was found for high-dose rivastigmine (6-12mg/day) compared to placebo on the ADAS-cog, MMSE, GDS, and the PDS; pooled results were not significant for low-dose rivastigmine (1-

4mg/day) for these outcome measures. The high-dose regimen currently is the recommended dosing range for rivastigmine.

The fair-rated systematic review[34] included data from two published trials[52,54] and one unpublished trial (B351). In contrast to the good-rated Cochrane review,[58] this review reported statistically significant differences favoring *all* doses of rivastigmine compared to placebo. Statistically significant differences were reported for the ADAS-cog, CIBIC-plus, GDS, MMSE, and PDS. Although this pooled population includes data from the three largest placebo-controlled trials conducted by Novartis, it does not include a similarly designed phase III trial (i.e., B304). Furthermore, this review presents observed cases analyses for the ADAS-cog and CIBIC-plus but uses LOCF analyses for the PDS. The less conservative LOCF data may allow the natural course of the disease to overestimate treatment effect. This review was funded by Novartis, the makers of rivastigmine.

To contrast differences in the pooled evidence from these reviews, we review data from three published placebo-controlled trials that met the criteria for our review.[52,54,53] In contrast to the Cochrane review,[58] one trial found statistically significant differences in the ADAS-cog and GDS for *all* doses of rivastigmine compared to placebo;[52] a second reported statistically significant differences in these measures only for rivastigmine 6-12mg/day (but not 1-4mg/day).[54] A third trial[53] reported statistically significant differences in cognitive and behavioral measures between rivastigmine 6mg/day and placebo; similar differences were not observed for patients treated with rivastigmine 4mg/day.

Tacrine vs. placebo

A fair-rated meta-analysis pooled individual patient data on 1,984 patients with probable AD from 12 published and unpublished placebo-controlled trials.[35] Dosages in the component trials varied from 20 mg/day to 160 mg/day. Trials lasted 3 to 36 weeks. Pooled results at 12 weeks presented a small beneficial effect of tacrine over placebo for cognitive function (MMSE: + 0.62 points, 95% CI: 0.23 – 1.00; P = 0.002), clinical global impression (CGI: OR 1.58, 95% CI: 1.18-2.11; P = 0.002), and behavioral disturbance (ADAS: 0.58 points, 95% CI: 0.17-1.00; P = 0.006). No significant difference could be detected in functional autonomy at 6 weeks (PDS: 0.75 points, 95% CI: -0.34 – 1.93; P = 0.21). The authors did not report if the component studies were critically appraised for methodological quality before inclusion. In studies without a dose titration phase (i.e., no active drug run-in phase before randomization) before the efficacy study, significantly more patients on tacrine than on placebo withdrew from the study (OR: 3.63, 95% CI: 2.80 - 4.71; no absolute numbers reported).

Four placebo-controlled trials met our eligibility criteria.[61,62,55,63] We excluded three of these studies for poor methodological quality because of high overall[61,62] or high differential[63] loss to follow-up. In all three trials, the high attrition rate reflected frequent adverse events, in particular elevated liver function tests in tacrine-treated patients. The fourth study compared three fixed dosing regimens (20mg/day, 40mg/day, 80mg/day) to placebo in 468 patients with mild to moderate Alzheimer's disease.[55] We were unable to determine the differential loss to follow-up from the provided data. Thus, differential loss to follow-up may exceed our cut-off level of 15 percentage points. The differential loss to follow-up because of adverse events in this study was 18 percentage points (placebo: 7%; tacrine: 25%). Efficacy results reported statistically significant improvements only for tacrine at 80 mg/day on the CGIC (P = 0.015), ADAS-total (P = 0.029), and caregiver-rated CGIC (P = 0.028) compared to placebo. No significant differences could be detected for ADAS-cog, MMSE, PDS, or for dosages less than 80 mg/day on CGIC.

Memantine vs. placebo

Two fair-rated RCTs[56,57] comparing memantine to placebo met the inclusion criteria for our review. Although we identified one good-rated systematic review,[64] it included only one of the two RCTs that met our inclusion criteria so we do not discuss it further.

Both placebo-controlled trials randomized moderate to severe AD patients to memantine 20mg/day or placebo,[56,57] although one trial required patients to be receiving stable treatment with donepezil prior to randomization, making it difficult to assess the effect of memantine.[57] Population demographics were similar across trials. Outcome measures consistently used in both trials included the CIBIC-plus, SIB, ADCS-ADL, and NPI. In both trials, memantine-treated patients did significantly better on the SIB and ADCS-ADL than placebo-treated patients. However, only patients randomized to both memantine and donepezil faired significantly better on the CIBIC-plus and NPI than patients randomized to placebo plus donepezil.[57] In the memantine monotherapy study, no differences in MMSE, CIBIC-plus, GDS, or NPI were reported between memantine- and placebo-treated patients.

F. Summary of the evidence

Comparative evidence for drugs used to treat AD is limited to three open-label head-to-head efficacy trials; two trials compared donepezil to galantamine[27,28] and one compared donepezil to rivastigmine.[29] Evidence for the comparison of donepezil with galantamine is mixed. In one 52-week trial,[27] donepezil and galantimine did not differ in stabilizing symptoms or improving behavior and functional status. In a shorter trial (12 weeks),[28] donepezil was superior to galantamine in its effects on cognition, functional

status, and caregiver and clinician satisfaction. The comparison of donepezil to rivastigmine is limited to a single 12-week trial;[29] it produced similar improvement in cognitive scores for both drugs, although clinician and caregiver satisfaction ratings were significantly better for donepezil. Because of limitations in the quantity of evidence, design of available trials (i.e., open-label), use of outcome measures not previously validated in AD populations (e.g., caregiver satisfaction), suspicious directionality of findings favoring the funding drug company, and the minimal differences observed between compared drugs (i.e., clinical significance of differences is inconclusive), we conclude that the evidence is inadequate to draw conclusions about the effectiveness of one AD drug compared to another.

Evidence from placebo-controlled trials and systematic reviews of placebo-controlled trials provide general evidence of the efficacy and effectiveness of these drugs. Overall, the ChEIs as a class are modestly effective in reducing the rate of decline in cognition. The NNT to yield one additional ChEI (excluding tacrine) global responder is 12; the NNT to yield one additional cognitive responder is 10.[30]

Evidence from one placebo-controlled effectiveness trial[37] and 22 efficacy trials [31,46,41]supports modest effects on symptom stabilization, behavior, and functional status as measured by various scales. Although some trials did not support statistically significant differences between active treatment and placebo on all outcome measures,[37,38,41,44,47,48,51,65,55,56] most trials yielded data supporting a slower rate of decline or modest improvement in measures of cognition and global assessment. Fewer trials supported differences in measures of behavior or functioning.

The clinical significance of these statistical differences is controversial. Although some trials defined clinical and global responders *a priori*, inconsistencies in trial design and reporting make it difficult to assess the clinical relevance of differences across trials.

Overall, the quality of evidence of general efficacy of ChEIs and memantine is fair; the quality of evidence of effectiveness of ChEIs and memantine is limited to one study on donepezil[37] and therefore poor. On the basis of current evidence, we cannot demonstrate substantial differences in efficacy between one AD drug and another.

Table 4: Summary of trials assessing symptoms and behavioral disturbances

Author, Year	Mean Age (years)	N	Duration (weeks)	Disease Severity	Results	Quality Rating
Donepezil vs. Galantamine						
Wilcock et al., 2003[27]	73	188	52	NR	*Symptoms:* No significant differences in cognition *Behavior / function*: No significant differences in behavior, measures of daily functioning, or caregiver burden	N/A*
Jones et al., 2004[28]	74	120	12	Mild - moderate	*Symptoms:* significantly better cognitive scores for DON-treated patients *Behavior / function*: Significantly better physican & caregiver satisfaction and less disability for DON-treated patients	N/A*
Donepezil vs. Rivastigmine						
Wilkinson et al., 2002[29]	74	111	12	Mild - moderate	*Symptoms:* No significant differences in cognition *Behavior / function*: Clinician and caregiver satisfaction significantly better with DON	N/A*
Donepezil, Galantamine, and Rivastigmine vs. Placebo						
Lanctot et al., 2003 (MA)[30]	NR	7954	≥ 12 weeks	NR	*Symptoms:* Pooled NNT to yield one additional ChEI global responder was 12; NNT to yield one additional cognitive responder was 10 *Behavior / function*: NR	Good
Donepezil vs. Placebo						
Birks, 2004 (MA)[31]	NR	4365	≥ 12	Mild – moderate	Symptoms: significantly better cognitive and global assessment scores for DON *Behavior / function*: no differences in QoL and fuctional capacity	Good
Whitehead et al., 2004 (MA)[32]	NR	2376	12-24	Mild - moderate	Symptoms: significantly better ADAS-cog scores for DON treated patients *Behavior / function*: no difference in QoL	Fair
AD2000**[37]	76	565	192	Mild - moderate	Symptoms: significantly better cognition scores for DON *Behavior / function*: no differences in rates of institutionalization and progression of functional decline	Fair
Burns et al., 1999[38]	72	818	24	Mild - moderate	Symptoms: significantly better cognitive and global assessment scores for DON *Behavior / function*: no difference in QoL	Fair
Feldman et al., 2001[39]	74	290	24	Moderate - severe	Symptoms: significantly better cognitive and global assessment scores for DON *Behavior / function*: slower decline of measures of daily functioning for DON	Good
Homma et al., 2000[40]	70	268	24	Mild - moderate	Symptoms: significantly better cognitive and global assessment scores for DON *Behavior / function*: NR *Behavior / function*: slower decline of function in DON patients	Fair
Mohs et al. 2001 [41]	75	431	54	Mild-moderate	Significantly fewer people on DON than on placebo had clinically significant functional loss	Fair

Rogers et al., 1996[44]	72	161	12	Mild - moderate	Symptoms: significantly better cognitive and global assessment scores for DON *Behavior / function*: no significant differences in QoL and activities of daily living	Fair
Rogers et al., 1998[43]	73	473	24	Mild - moderate	Symptoms: significantly better cognitive and global assessment scores for DON *Behavior / function*: QoL scores significantly better with DON 5mg but not DON 10 mg	Fair
Rogers et al., 1998[42]	74	468	12	Mild - moderate	Symptoms: significantly better cognitive and global assessment scores for DON *Behavior / function*: QoL scores significantly better with DON 10mg but not DON 5 mg	Fair
Tariot et al., 2001[45]	86	208	20	Mild - moderate	Symptoms: significantly better cognitive and global assessment scores for DON *Behavior / function*: NR	Fair
Winblad et al., 2001[46]	73	286	52	Mild - moderate	Symptoms: significantly slower decline in cognitive and global assessment scores for DON *Behavior / function*: no difference in behavior and functional capacity	Fair
Galantamine vs. Placebo						
Olin & Schneider, 2004 (SR)[33]	NR	3,587	>4	NR	*Symptoms:* significantly slower decline in cognitive and global assessment scores for GAL 16-32mg/d *Behavior / function*: Mixed evidence for behavior and function; most trials reported statistically significant differences only at higher doses	Good
Raskind et al., 2000[47]	75	636	26	Mild - moderate	*Symptoms:* significantly slower decline in cognitive and global assessment scores for GAL *Behavior / function*: No significant difference in function	Fair
Rockwood et al., 2001[48]	75	386	26	Mild - moderate	*Symptoms:* significantly slower decline in cognitive and global assessment scores for GAL *Behavior / function*: significantly slower decline in function for GAL; no difference in behavior or sleep	Fair
Tairot et al., 2000[49][66]	77	978	22	Mild - moderate	*Symptoms:* significantly slower decline in cognitive and global assessment scores for GAL 16-24mg/d *Behavior / function*: slower decline of measures of daily function and behavior for GAL 16-24mg/d	Fair
Wilcock et al., 2000[50]	72	653	26	Mild - moderate	*Symptoms:* significantly slower decline in cognitive and global assessment scores for GAL 24-32mg/d *Behavior / function*: GAL 32mg/d (but not 24mg/d) patients had significantly less disability	Good

Wilkinson et al., 2001[51]	74	285	12	Mild - moderate	*Symptoms:* significantly more improvement in cognitive scores for GAL 24mg/d; no significant differences in global improvement *Behavior / function*: No differences in functioning	Fair
Rivastigmine vs. Placebo						
Birks et al., 2004 (SR)[36]	NR	3,450	> 2	NR	*Symptoms:* Pooled: RIV (all doses) significantly better than placebo on CIBIC-plus; only RIV 6-12mg/d significantly better on ADAS-cog, MMSE, and GDS *Behavior / function*: Pooled: RIV 6-12mg/d (but not RIV 1-4mg/d) better than placebo on measures of functioning	Good
Schneider et al., 1998 (SR) [34,67,68]	73	2,126	26	Mild - moderate	*Symptoms:* significantly more improvement in behavior and global function for RIV (all doses) *Behavior / function*: RIV (all doses) significantly better than placebo on measures of function	Fair
Agid et al., 1998 [53]	70	402	13	NR	*Symptoms:* RIV 6mg/day (but not 4mg/day) significantly better than placebo for clinical impression outcomes *Behavior / function*: RIV 6mg/d (but not 4mg/d) better than placebo on measures of behavior	Fair
Corey-Bloom et al., 1998 [52]	75	699	26	Mild - moderate	*Symptoms:* RIV (all doses) significantly better than placebo on measures of global function *Behavior / function*: RIV 6-12mg/d (but not RIV 1-4mg/d) better than placebo on measures of functioning	Fair
Rosler et al., 1999 [54]	NR	725	26	Mild - moderate	*Symptoms:* RIV 6-12mg/d significantly better on measures of global function; no differences between RIV 1-4mg/d and placebo *Behavior / function*: RIV 6-12mg/d (but not RIV 1-4mg/d) better than placebo for daily function	Fair
Tacrine vs. Placebo						
Qizilbash et al., 1998 (MA)[35]	NR	1,984	3-36	NR	*Symptoms*: small beneficial effect of TAC for cognitive and clinical impression outcomes *Behavior / function*: small beneficial effect of TAC for behavioral outcomes; no difference in functional capacity	Fair
Farlow et al., 1992 [55]	71	468	12	Mild-moderate	*Symptoms*: No differences compared to placebo except for TAC 80mg/d on CGI-C *Behavior / function*: NR	Fair

Memantine vs. Placebo						
Reisberg et al., 2003[56]	76	252	28	Moderate - severe	*Symptoms:* MEM significantly better than placebo on cognitive and global assessment measures	Fair
					Behavior / function: significantly better daily function and less caregiver time; no difference in behavior	
Tariot et al., 2004[57]	76	404	24	Moderate - severe	*Symptoms:* significantly slower decline in cognitive and global assessment scores for MEM	Fair
					Behavior / function: MEM significantly better than placebo on measures of function and behavior	

* This trial was open-label; in the absence of meeting all characteristics of an effectiveness trials, this trial would be given a poor quality rating for internal validity
** Effectiveness trial
MA = meta-analysis
SR = systematic review

KEY QUESTION 2

How do donepezil, galantamine, rivastigmine, tacrine, and memantine compare in their time to effect and in the time required to assess the clinical response?

We did not identify any study that directly compared the time to effect or time required to assess the clinical response of one AD drug compared to another. One open-label head-to-head trial provides evidence on the time to effect between donepezil and galantamine.[28] The study reports a trend favoring donepezil in cognition at weeks 4 and 8 that reached statistical significance at week 12 ($P < 0.05$).[28] DAD scores were significantly greater in donepezil-treated patients at weeks 4 and 12. Other head-to-head trials reported only long-term outcomes.

Placebo-controlled trials are too heterogeneous with respect to study design, outcomes assessment, and populations to allow any inferences about the comparative time to effect. Given that the overall placebo-controlled evidence indicates that long-term treatment with ChEIs and memantine will produce only modest beneficial effects on cognition and global assessment, the clinical significance of time to effect is likely to be of minimal importance to physicians and patients.

In general determining time to effect and time required to assess clinical response is difficult, given the design of most trials and the nature of measurement scales. First, trials commonly were not designed to measure the time required to produce a statistically different response. In most trials, the first follow-up visit was not conducted until 4 to 12 weeks after randomization. Given this relatively large and inconsistent gap in follow-up between randomization and first clinical assessment, comparison across placebo-controlled trials cannot provide accurate information. Second, different studies used different outcome scales that are not necessarily comparable to assess effect sizes. Third, the ability of a trial to detect statistically significant difference depends on the sample size of each respective trial; trials with large sample sizes have greater power to present statistically significant findings at earlier time points.

Interpretation of clinical response (and time to assess it) is also of concern. Three published studies have sought to shed light on the clinical significance of treatment effects in AD trials.[48,69,70] In one[69] the authors calculated standardized effect sizes from ChEI trials to assess clinically detectable responses. Effect sizes greater than 0.20 were considered to be clinically detectable, but one cannot determine from the article if this assumption was derived from validated evidence. In another study using a survey of

specialists, the investigators established a change in MMSE score of 3.72 points as a clinically significant difference.

Most of the included studies in this report have used arbitrary cut-off points on cognitive measures such as the ADAS-cog (≥ 4 points improvement from baseline) to define a clinical response. Others have considered any improvement on global assessment scales such as the CGI-C or the CIBIC-plus to define a clinical response. These definitions are arbitrary and have not been validated; consequently, comparisons across trials are impossible.

One generic indicator that influences time to effect is the time to titration of therapeutic dose. Given the recommended titration schedule for AD drugs (Table 1) and evidence regarding the dose-response curves for these drugs, a shorter time to therapeutic dose is expected for donepezil and rivastigmine than for the other ChEIs or memantine. Statistically significant differences between donepezil and placebo were reported in most trials for 5mg and 10mg daily doses; because the recommended starting dose of donepezil is 5mg/day (titrating to 10mg/day at 4 to 6 weeks), this finding suggests that donepezil-treated patients are given a therapeutic dose from day 1 of treatment (although steady state of therapeutic concentrations is not achieved for approximately 2 weeks). Titration of rivastigmine-treated patients to a therapeutic dose (i.e., 6mg to 12mg/day) is recommended at week 2, again inferring a relatively short time to therapeutic dose.

Conversely, patients treated with galantamine, tacrine, or memantine typically are not titrated to therapeutic doses until 4 weeks or later. Although titration schedules are designed to minimize potential adverse events, some patients may be titrated sooner than recommended. Furthermore, titration schedules do not reflect the time it takes to maintain steady state concentrations. Given the typically long natural course of disease and the modest treatment effects, the clinical significance of these differences is questionable, however.

KEY QUESTION 3

What are the comparative incidence and severity of complications of donepezil, galantamine, rivastigmine, tacrine, and memantine?

In general, adverse events depend on dose and mechanism of action for individual AD drugs. In most trials assessing a range of doses specific adverse events were reported more frequently among patients randomized to higher doses of study drugs.[42,43,47,49-52,54,55] In some trials the speed of dose titration also was believed to be related to greater reporting of adverse events.[52,54]

Based on three open-label head-to-head trials,[27-29] evidence suggests some differences between compared drugs. In one 12-week trial comparing donepezil with rivastigmine,[29] gastrointestinal-related adverse events were significantly more common among rivastigmine-treated patients; nausea and vomiting were reported by 41.8% and 23.6% of rivastigmine-treated patients compared to 10.7% and 7.1% of donepezil-treated patients, respectively (P = NR). Two trials compared donepezil to galantamine; the evidence is mixed. The incidence of gastrointestinal-related adverse events was not different in a 52-week trial comparing donepezil and galantamine.[27] In one 12-week trial gastrointestinal-related events were reported by 46.4% of patients in the galantamine group compared to 25% of patients in the donepezil group.[28]

Indirect comparisons based on evidence from placebo-controlled trials are difficult to make given differences in trial design, study populations, and assessment and reporting of specific events. Overall, adverse events were reported by 40% to 96% of randomized patients. In general ChEI- and memantine-treated patients appear to report a similar number of adverse events, although evidence is insufficient to compare the incidence of specific adverse events across drugs. Overall discontinuation rates are similar among memantine and ChEIs except for tacrine.

Table 5 presents the mean incidence of specific adverse events based on data provided by placebo-controlled trials of ChEIs and memantine. Statistics are descriptive only. Comparisons across different drugs are limited and should be made with caution. Large confidence intervals for some estimates indicate lack of precision due to a small number of component studies for some medications.

Table 5: Mean incidence of specific adverse events in placebo-controlled trials

Drug	Number of Studies	Diarrhea *Mean (95% CI)*	Vomiting *Mean (95% CI)*	Anorexia *Mean (95% CI)*	Dizziness *Mean (95% CI)*
Donepezil	10	10.5% (6.6 to 14.3)	7.1% (3.4 to 10.9)	5.2% (2.9 to 7.6)	7.2% (5.4 to 8.9)
Galantamine	5	9.4% (1.8 to 9.4)	13.0% (2.5 to 23.5)	10.8% (3.6 to 17.9)	11.9% (4.2 to 19.6)
Rivastigmine	2	NR	19% (0 to 44.4)*	11.2% (0 to 46.2)*	17.2% (0 to 45.8)*
Tacrine	4	8.6% (0 to 19.3)*	20.6% (0 to 43.7)*	NR	10.2% (0 to 22.6)*
Memantine	2	7.3% (0 to 42.2)	NR	NR	NR

*negative lower confidence interval

Some of the ChEIs appear to have a higher incidence of vomiting; this is likely attributable to their cholinergic mechanism of action. The highest incidence of nausea and vomiting was reported in rivastigmine trials, although these trials utilized a faster titration schedule than recommended by the product labeling and the rate of adverse events was also higher than normal in the placebo group. However, these estimates are consistent with available comparative evidence, which suggest that the risk of gastrointestinal-related adverse events is greater with rivastigmine and galantamine than with donepezil.

The incidence of specific adverse events reported by memantine-treated patients was generally low. From the single trial in our review that assessed only memantine[56] (rather than memantine plus donepezil),[57] the only adverse events reported by more than 10% of memantine-treated patients were agitation, diarrhea, somnolence, and urinary incontinence; no adverse event was reported in significantly more memantine-treated patients than in placebo-treated patients. The rate of agitation was significantly different in memantine-treated patients than in those on placebo, although significantly more placebo- than memantine-treated patients reported agitation (32% vs. 18%, respectively; P = NR). Urinary tract infections also were more common in placebo-treated patients than in memantine-treated patients (13% vs. 6%, respectively; P = NR).

Discontinuation rates varied across trials. Based on one trial that compared donepezil to rivastigmine,[29] more patients randomized to rivastigmine than donepezil discontinued treatment (30.9% vs. 10.7%, respectively; P = NR). Two open-label trials compared donepezil to galantamine;[27 28] overall discontinuation rates did not differ significantly. Trials assessing tacrine consistently reported

significantly higher discontinuation rates for tacrine than for placebo patients.[55,61-63] The high withdrawal rates were mainly attributable to elevated serum alanine aminotransferase (ALT; a feature of liver toxicity).

Withdrawals because of adverse events in donepezil, galantamine, rivastigmine, and memantine trials varied. Evidence from one open-label head-to-head comparison of donepezil and rivastigmine[29] suggests a higher number of withdrawals due to adverse events among rivastigmine-treated compared to donepezil-treated patients (21.8% vs. 10.7%, respectively; P = NR). Based on two open-label trials comparing donepezil and galantamine, withdrawals due to adverse events were higher among galantamine-treated patients than among donepezil-treated patients in one 12-week trial (21.4% vs. 9.4%, respectively; P = NR),[28] but not in a 52-week trial (13.4% vs. 13.2%, respectively; P not significant).[27] From placebo-controlled evidence, no obvious trend favored one drug over another. Patients treated with higher doses were more likely to discontinue because of an adverse event. A meta-analysis of discontinuation rates did not find a statistically significant difference between donepezil and placebo,[31] even though the incidence of anorexia, diarrhea, dizziness, fatigue, insomnia, muscle cramps, nausea, vomiting, tremor, vertigo, and weight loss were statistically significantly more common in the donepezil than in the placebo group.

We did not identify any study that assessed temporary or permanent adverse events due to discontinuation of donepezil, galantamine, rivastigmine, tacrine or memantine.

Specific adverse events

Hepatotoxicity

A major safety concern of tacrine treatment is hepatotoxic effects. A retrospective review of tacrine-trials involving 2,446 AD patients reported that 49% of tacrine-treated patients had elevated ALT levels.[71] Among all patients, 25% presented an ALT elevation three times the upper normal limit; 2% had ALT levels 20 times higher than normal. Patients with elevated ALT levels were generally asymptomatic, although sometimes they experienced eosinophilia, rash, and fever. Few patients developed signs of severe hepatocellular injury (e.g., jaundice); no death attributable to liver toxicity was reported.

Results of this retrospective analysis are consistent with individual trials included in this review. All four placebo-controlled RCTs of tacrine reported high elevations of ALT.[55,61-63] We excluded three of these

studies from the efficacy analysis on grounds of quality because of high overall[61,62] or differential[63] loss to follow-up. In all three trials the high drop-out rate was attributable to a high rate of elevated liver function tests in tacrine-treated patients. The differential loss to follow-up because of adverse events in the fourth study[55] was 18 percentage points (placebo: 7%; tacrine: 25%). Hepatotoxicity has not been reported for donepezil, galantamine, rivastigmine, or memantine.

Gastrointestinal adverse events and loss of body weight

ChEI trials commonly reported nausea and vomiting by more than 10% of patients (and as many as 50% of patients) randomized to active treatment. In the only memantine trial the incidence of nausea and vomiting did not differ between the active drug and placebo. Nausea, vomiting, and diarrhea are thought to reflect excessive activation of intestinal muscarinic cholinergic receptors and tend to be dose related. Anorexia and loss of body weight are associated gastrointestinal adverse events.

We did not find any trials directly comparing the incidence of gastrointestinal adverse events among ChEIs and memantine.

In a systematic review of donepezil, galantamine, and rivastigmine trials,[14] nausea and vomiting were 3 to 5 times more common in patients randomized to active treatment compared to placebo ($P < 0.0001$). The odds of having nausea or vomiting with rivastigmine compared to placebo (OR 5.28; 95% CI 4.19-6.65) were consistently higher than with donepezil or galantamine compared to placebo (donepezil OR 2.73; 95% CI 1.86-4.00; galantamine OR 3.01; 95% CI 2.15-4.21), although this finding could likely be attributed, at least in part, to the faster than recommended dose titration used in rivastigmine trials.[52,54]

Diarrhea was also common in the pooled analysis,[14] although the pooled odds ratio was significant for donepezil and rivastigmine (donepezil OR 2.83; 95% CI 2.01-4.00; rivastigmine OR 1.77; 95% CI 1.38-2.28) but not for galantamine (OR 1.37; 95% CI 0.91-2.05). The higher incidence of gastrointestinal events may be related to the significant loss of body weight commonly reported for donepezil-, galantamine-, and rivastigmine-treated patients. Pooled analysis suggests a 2- to 4-fold increase in the risk of anorexia for active treatment compared to placebo. Although tacrine was not included in this analysis, relative trends in gastrointestinal adverse events and loss of body weight reported in tacrine trials are consistent with those seen in donepezil, galantamine, and rivastigmine trials.[55,61-63]

A retrospective data review of the mean incidence rates of gastrointestinal adverse events of some RCTs shows that the following percentages of patients suffered nausea: donepezil, 11%; rivastigmine, 35%;

and tacrine, 28%.[72] Similarly, the relative proportions of patients who experienced vomiting were 5%, 21% and 28%, respectively; diarrhea occurred in 10%, 16% and 16%, respectively. Another review reported a loss of body weight of 0.5 to 2.5 kilogram for galantamine at doses of 16mg/day to 32mg/day and a loss of body weight of 1.39 to 1.78 kilogram for rivastigmine at doses of 6 mg/day to 12 mg/day.[73]

Cardiovascular adverse events

Bradycardia and subsequent dizziness or syncope originate from central and peripheral muscarinic cholinergic stimulation. Cardiovascular adverse events can lead to falls and other types of injury-causing accidents. We did not find any trials directly comparing the incidence of cardiovascular adverse events among ChEIs and memantine.

Cardiovascular adverse events may be of particular concern in patients with cardiac conduction disorders or a sick sinus syndrome. One head-to-head study reports no statistically significant differences in changes of heart rates between donepezil and galantamine.[28] Two open-label comparative trials reported no difference in cardiovascular events between donepezil and galantamine[28] and rivastigmine.[29] Most placebo-controlled trials revealed no other significant differences in cardiovascular events, vital signs, or electrocardiogram (ECG) findings. One trial described a statistically significantly larger reduction of heart rate in patients treated with donepezil than in those given placebo.[42] However, the incidence of bradycardia (heart rate < 50 beats per minute) was not significantly different among treatment groups. An analysis of prescription-event monitoring (n = 1,762) in general practice in the UK did not find evidence for cardiac arrythmias with donepezil treatment.[74]

One pooled data-analysis of RCTs including 2,791 patients evaluated ECG results from four clinical trials of rivastigmine;[75] rivastigmine had no apparent effect on heart rate. However, patients with underlying ECG abnormalities did not meet eligibility criteria of the RCTs.

Summary of the evidence

The overall grade of the evidence on comparative tolerability is poor to fair. Evidence of the comparative incidence of adverse events and tolerability comes from three open-label trials comparing donepezil with galantamine and rivastigmine. One 52-week trial[27] and one 12-week trial[28] compared donepezil to galantamine. Although the number of adverse events and loss to follow-up differed between trials, withdrawals and withdrawals because of adverse events were not significantly different in the 52-week trial and only minor differences favoring donepezil were observed in the 12-week trial. In one trial that compared donepezil to rivastigmine,[29] total withdrawals and withdrawals because of adverse events were

significantly greater among rivastigmine-treated patients. Gastrointestinal-related events were most commonly reported among rivastigmine-treated patients. Indirect comparison of the pooled mean incidence of adverse events from placebo-controlled trials also suggests a higher rate of gastrointestinal-related events among rivastigmine-treated patients. However, this comparison is limited by the tremendous variability observed among placebo-controlled evidence.

Evidence of hepatotoxity and cardiovascular events comes from comparative trials, meta-analyses, and indirect comparison of placebo controlled evidence. Evidence from one meta-analysis and four placebo-controlled trials indicate substantially higher rates of hepatotoxicity for tacrine.[71,61] Donepezil, galantamine, rivastigmine, and memantine did not present hepatotoxic effects in placebo controlled trials. Two open-label comparative trials reported no difference in cardiovascular events between donepezil and galantamine[28] and rivastigmine.[29] Placebo-controlled trials revealed no other significant differences in cardiovascular events.

Table 6: Summary of trials assessing adverse events

Author, Year	N	Study design	Results	Quality Rating
Hepatotoxicity				
Watkins et al., 1994[71]	2446	secondary data review	49% of tacrine-treated patients presented ALT elevations	N/A
Farlow et al., 1992[55]	468	RCT	25% of tacrine-treated patients had elevated ALT levels	Fair
Knapp et al., 1994[62]	663	RCT	54% of tacrine-treated patients had elevated ALT levels	Poor
Wong et al ., 1999[61]	100	RCT	51% of tacrine-treated patients had elevated ALT levels	Poor
Wood et al.,1994[63]	154	RCT	44% of tacrine-treated patients had elevated ALT levels	Poor
Gastrointestinal adverse events				
Evans et al., 2004[14]	NR	pooled analysis	Nausea, vomiting, and diarrhea 3 to 5 times more likely for donepezil, galantamine, and rivastigmine than for placebo	N/A
Cutler et al., 1994[72]	3350	pooled data analysis	Tacrine had a higher rate of adverse events than donepezil and rivastigmine	N/A
Gauthier et al. 2001[73]	NR	Retrospective data review	dose dependent rates of gastrointestinal adverse events for ChEIs	N/A
Cardiovascular adverse events				
Dunn et al., 2000[74]	1762	Prescription-event monitoring	No cardiac arrythmias were reported for donepezil	N/A
Morganroth et al. 2002[75]	2791	Pooled analysis of RCTs	No effect on heart rate for rivastigmine	Fair

KEY QUESTION 4

Does efficacy, effectiveness, or adverse events of donepezil, galantamine, rivastigmine, tacrine, or memantine differ in subgroups of patients with (1) different demographic profiles (age, race, or sex), (2) Parkinsonian features or vascular dementia, or (3) use of other commonly prescribed drugs?

A. Age

We did not identify any study specifically designed to compare the effect of donepezil, galantamine, rivastigmine, tacrine, or memantine in a younger versus an older population.

We did find age-related information in two sources: one subgroup analysis of rivastigmine-treated patients[34] and a placebo-controlled donepezil trial conducted in a population of nursing home residents who were, on average, older than the typical population for donepezil studies.[45] The subgroup analysis pooled data from four rivastigmine trials and reported an age-related treatment effect. Patients 75 years and older revealed a greater benefit of rivastigmine than did patients younger than 75 years; 15% of older patients and 6% of younger patients were considered responders on the ADAS-cog.[34]

A single trial[45] conducted in nursing home residents with a mean age of 85 years (range 64 to 102 years) provides indirect evidence about age effects when compared to findings from other similarly designed trials in which the mean age was less than 75 years.[39,40,42-44,46] Overall, no difference in efficacy or adverse events was apparent in the data on the older population compared to data from the trials in younger populations.

B. Race

We did not identify any study specifically designed to compare the effect of donepezil, galantamine, rivastigmine, tacrine, or memantine in one racial group compared to another. In general, trials were conducted predominantly in white populations.

One study used pooled data from 2,126 patients in three placebo-controlled rivastigmine trials to analyze differences in efficacy among racial subgroups.[34] The pooled population was 93.6% white, 4.4% black, and 2% other races. Treatment response did not differ across racial subgroups.

One donepezil trial[40] was conducted in a Japanese population and one tacrine trial[61] was conducted in a Chinese population. Overall, effect sizes observed in these trials are similar to effect sizes reported in trials conducted predominantly in non-Asian populations. However, the trial conducted in the Japanese population presented treatment effects on low-dose donepezil, which suggests ethnic differences in major enzymes that metabolize ChEIs.[30] This finding was supported by a meta-analysis of ChEIs.[30]

C. Sex

We did not identify any study specifically designed to compare the effect of donepezil, galantamine, rivastigmine, tacrine, or memantine in females compared to males. On average, study populations comprised more females than males; this fact reflects population and disease demographics and does not provide insight into treatment differences.

One review[34] of pooled data from rivastigmine trials conducted a subgroup analysis by sex but reported no differences. No other indirect evidence suggests that effectiveness or adverse events differ between females and males.

D. Parkinsonian features

Dementia with Parkinsonian features, or dementia with Lewy bodies (DLB), is characterized by abnormal protein inclusions (Lewy bodies) in selected areas of the brain. Because these structures, and many of the symptoms of dementia with Lewy bodies, are associated with Parkinson's and Alzheimer's diseases, it remains unclear whether DLB is a distinct clinical entity or perhaps a variant of Alzheimer's or Parkinson's disease.

We did not identify any trial conducted in patients with AD that compared effectiveness or adverse events in a population with Parkinsonian features to a population without Parkinsonian features. Although some trials specifically excluded patients with suspected PD, trials that did not specifically exclude patients with Parkinsonian features did not report differences among these patients.

Evidence from a recently published large-scale placebo-controlled study supports the general efficacy of rivastigmine in treating patients with PD dementia.[76] This 24-week multicenter European study enrolled 541 subjects with PD dementia (defined as the onset of cognitive symptoms 2 or more years after the onset of PD) who were randomized to either placebo or rivastigmine (1:2 ratio) beginning at 1.5mg twice a day and increased at 4-week intervals as tolerated up to 12 mg/day. Primary efficacy analyses showed better ADAS-cog scores and global ratings in the rivastigmine-treated group compared to placebo group.

E. Comorbid vascular dementia

Vascular dementia is the second most common form of dementia. In many patients with AD, vascular factors contribute to the development or expression of dementia. Mixed vascular dementia includes those patients that have clinical features of AD and clinically significant cerebrovascular disease. Most studies included in our review specifically excluded patients with mixed vascular dementia; studies that did not explicitly exclude patients with comorbid cerebrovascular disease often did not report the prevalence or stratify the results for this subgroup.

Although evidence is difficult to interpret given the inconsistencies in trial design and lack of differentiation between AD and vascular dementia, we discuss four studies that provide general evidence of the efficacy of donepezil,[37] galantamine,[77] rivastigmine,[78] and memantine[64] in populations with comorbid vascular dementia.

The only effectiveness study included in our review[37] randomized patients with or without a coexisting diagnosis of vascular dementia to long-term treatment with donepezil or placebo. Although results are not stratified by coexisting vascular dementia, results support the general efficacy of donepezil in this mixed population.

One placebo-controlled RCT[77] examined the effect of galantamine in patients with probable vascular dementia and AD with cerebrovascular disease. This 26-week trial randomized 592 patients to galantamine or placebo in a 2:1 ratio. Diagnosis of vascular dementia was based on National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) International Workshop criteria; computed tomography or magnetic resonance imaging was used to confirm evidence of cerebrovascular disease. Overall, galantamine was significantly better than placebo ($P < 0.05$) on cognitive, functional, behavioral, and global assessment measures. Treatment differences were of similar size to those seen in galantamine studies in patients with AD.[47,49,50] Galantamine was significantly better than placebo ($P < 0.05$) only in the subgroup of patients with AD and cerebrovascular disease. Although the study was not powered to detect treatment differences in the subgroups, differences between galantamine and placebo were not significant in patients with vascular dementia.

We identified one subgroup analysis of AD patients with concurrent vascular risk factors from a placebo-controlled RCT of rivastigmine.[78] Patients from this trial[52] were categorized by their Modified Hachinski

Ischemic Score (MHIS); MHIS scores greater than zero were used to identify the presence of vascular risk factors. At 26 weeks, rivastigmine was significantly better than placebo on cognitive, functional, and global assessment measures for patients with and without vascular risk factors. Larger treatment differences between rivastigmine and placebo were found for patients with vascular risk factors.

One systematic review[64] of placebo-controlled memantine trials included trials conducted in populations with AD, vascular dementia, and mixed or unspecified AD with vascular dementia. Although individual trials were different with regard to design, duration, dose, and outcome measures, comparison of evidence across populations suggests that results of trials conducted in populations with mixed or unspecified vascular dementia are similar to trials conducted in populations with AD only.

F. Other drugs

We did not identify any published study that specifically compared outcomes among subgroups of patients taking a ChEI or memantine concurrently with another drug to patients not concurrently taking the same medications. To characterize potential and known drug-drug interaction risks as much as possible in this situation, we summarize indirect evidence and pharmacokinetic properties.

In general, ChEIs (i.e., donepezil, galantamine, rivastigmine, tacrine) may interfere with the activity of anticholinergic medications. Likewise, a synergistic effect may be expected when ChEIs are given with cholinomimetics or other ChEIs. Concurrent use of such drugs should be approached with caution.

The NMDA antagonist memantine is believed to be safe when administered in combination with a ChEI. In a 24-week trial, memantine was safely administered in combination with donepezil[57] without evidence of altering the pharmacokinetic properties of either drug; evidence of additional benefit of this combination is not clear

The potential for other drug-drug interactions with donepezil, galantamine, rivastigmine, tacrine, and memantine should be evaluated on an individual basis. Pharmacokinetic parameters and information submitted to the FDA for approval provide useful information.

Donepezil

Donepezil is metabolized by CYP450 isoenzymes 2D6 and 3A4. Because other drugs may compete for or inhibit these metabolic enzymes, a potential for interaction exists with drugs metabolized by the same isoenzymes. Although to our knowledge no *in vivo* studies have been conducted, *in vitro* evidence suggests that donepezil has little effect on the metabolism of other drugs (e.g., theophylline, cimetidine, warfarin, digoxin, etc.). Drugs that inhibit 2D6 and 3A4 (e.g., ketoconazole, miconazole, quinidine, ritonavir, selective serotonin reuptake inhibitors [SSRIs], etc.) have been shown to inhibit donepezil metabolism but clinically significant interactions are rare. Patients taking donepezil in combination with other drugs metabolized by CYP450 isoenzymes 2D6 and 3A4 should be monitored closely.

Although donepezil is highly protein bound (96%) drug displacement studies performed *in vitro* have shown little effect of other highly bound drugs on the binding of donepezil to human albumin. Similarly, donepezil did not affect binding of other drugs to human albumin.

Galantamine

Like donepezil, galantamine is metabolized by CYP450 isoenzymes 2D6 and 3A4. *In vivo* studies have shown increased bioavailability of galantamine when it is administered together with inhibitors of these isoenzymes (e.g., cimetidine, ranitidine, ketoconazole, erythromycin, paroxetine). By contrast, galantamine is believed to have little effect on other drugs metabolized by the CYP system.

Rivastigmine

Because rivastigmine is metabolized primarily through hydrolysis by esterases, minimal interaction with drugs metabolized by CYP450 enzymes is anticipated. No other drug-drug interactions have been demonstrated.

In a subgroup analysis of nicotine users randomized to rivastigmine, a statistically significant relationship in the dose-response relationship was reported;[34] this analysis suggests that nicotine attenuates the benefits of rivastigmine. Another post-hoc analysis of 2,459 patients from 4 placebo-controlled rivastigmine trials evaluated drug interactions with 22 classes of medications.[79] This analysis did not reveal any significant pattern of increase in adverse events that would indicate a drug-drug interaction.

Tacrine

Tacrine is metabolized primarily by the CYP450 isoenzyme 1A2. Drug-drug interactions may occur with other medications metabolized by this enzyme (e.g., theophylline). Administration of tacrine and

theophylline has been shown to increase average plasma theophylline concentrations 2-fold. Likewise, administration of cimetidine with tacrine has been shown to increase plasma concentrations of tacrine.

Memantine

Because memantine is eliminated predominantly by the kidney, drugs that are inhibitors and/or substrates of the CYP450 system are not expected to interact with it. However, because memantine is eliminated via renal mechanisms, concurrent administration of drugs that use the same renal mechanisms (e.g., hydrochlorothiazide, triamterene, cimetidine, ranitidine, quinidine, nicotine) could alter the plasma levels of both agents. Additionally, drugs that make the urine alkaline (e.g., sodium bicarbonate, carbonic anhydrase inhibitors) may reduce the clearance of memantine. Patients using these drugs and memantine concurrently should be monitored closely.

Summary of the evidence

The overall grade of the evidence on efficacy and tolerability in subgroups is poor. We did not identify any study specifically designed to compare the effect of donepezil, galantamine, rivastigmine, tacrine, or memantine in one subgroup of patients compared to another. Subgroup analyses and indirect evidence from placebo controlled trials provide evidence for some AD drugs.

One subgroup analysis reported greater benefit for rivastigmine in patients older than 75 years. Indirect comparison of evidence from one donepezil trial conducted in nursing home residents to trials conducted in younger populations suggests no apparent difference in efficacy or adverse events.

Subgroup analyses of pooled data from four rivastigmine trials suggest no differences in efficacy or adverse events by sex or race.

No evidence addressed patients with comorbid PD.

Four studies provide general evidence of the efficacy of donepezil, galantamine, rivastigmine, and memantine in populations with comorbid vascular dementia. Only one study stratified patients by vascular risk factors; larger treatment differences between rivastigmine and placebo were found for patients with vascular risk factors compared to patients without vascular risk factors.

No study compared outcomes among subgroups of patients taking a ChEI or memantine concurrently with another drug to patients not concurrently taking the same medication.

Table 7: Summary of trials assessing subgroups

Author, Year	N	Study design	Results	Quality Rating
Age				
Schneider et al., 1998 [34]	2,126	Pooled Analysis	Better cognitive scores (ADAS-cog) for RIV in patients older than 75 years	Fair
Race				
Schneider et al., 1998 [34]	2,126	Pooled Analysis	No differences in response to RIV between black and white patients	Fair
Sex				
Schneider et al., 1998 [34]	2,126	Pooled Analysis	No differences in response to RIV between male and female patients	Fair
Comorbid Vascular Dementia				
Schneider L. AD2000 [37]	565	RCT	Results not stratified; general efficacy of DON supported in this mixed population	Good
Erkinjuntti et al., 2002 [77]	592	RCT	No comparison of patients with comorbid vascular disease to population with only AD; general evidence of GAL efficacy in population with comorbid vascular disease	Fair
Kumar et al., 2000 [78]	699	RCT subgroup	RIV better than placebo for patients with and without vascular risk factors; larger differences for patients with vascular risk factors	Fair

Table 8: Key questions and summary of the evidence

Key Question	Quality of Evidence	Conclusion
Key Question 1: Efficacy / Effectiveness	Poor to fair	No double-blind head-to-head trial compared one AD drug to another. Three open-label head-to-head trials compared the efficacy of one AD medication to another; two trials compared donepezil to galantamine and one trial compared donepezil to rivastigmine. Evidence for the comparison of donepezil with galantamine is mixed. In one 52-week trial, donepezil and galantimine did not differ in stabilizing symptoms or improving behavior and functional status. In a shorter trial (12 weeks), donepezil was superior to galantamine in its effects on cognition, functional status, and caregiver and clinician satisfaction. The comparison of donepezil to rivastigmine is limited to a single 12-week trial; similar improvements in cognitive scores were reported for both drugs, although clinician and caregiver satisfaction ratings were significantly better for donepezil. Both trials that reported significant differences were funded by the manufacturer of donepezil while the trial reporting no differences was funded by the manufacturer of galantamine. Evidence of general efficacy for donepezil, galantamine, rivastigmine, tacrine, and memantine is fair; 1 placebo-controlled effectiveness trial, 20 efficacy trials, and 7 systematic reviews [32,37-45,47,49-52,54-57,65] support modest effects on symptom stabilization, behavior, and functional status as measured by various scales. Although some trials did not support statistically significant differences between active treatment and placebo on all outcome measures,[38,41,44,47,48,51,56,65] most trials yielded data supporting modest improvement or a slower rate of decline in measures of cognition and global assessment. Fewer data supported differences in measures of behavior or functioning. Although evidence of general efficacy is fair, evidence of effectiveness is poor. We identified only one trial considered to demonstrate effectiveness.
Key Question 2: Time to Effect	Poor	We did not identify any study that directly compared the time to effect or time required to assess the clinical response of one AD drug compared to another. Placebo-controlled trials are too heterogeneous with respect to study design, outcomes assessment, and populations to allow any inferences about the comparative time to effect or time required to assess clinical response.
Key Question 3: Adverse events	Poor to Fair	Head-to-head trials did not present differences in adverse events between donepezil and galantamine, and donepezil and rivastigmine. Indirect evidence from placebo-controlled trials indicates a substantially higher risk of hepatotoxicity for tacrine than for donepezil, galantamine, rivastigmine, and memantine.
Key Question 4: Subgroups	Poor	We did not identify any study specifically designed to compare the effect of donepezil, galantamine, rivastigmine, tacrine, or memantine in one subgroup of patients compared to another. Subgroup analyses and indirect

		evidence from placebo controlled trials provide evidence for some AD drugs. One subgroup analysis reported greater benefit for rivastigmine in patients older than 75 years. Indirect comparison of evidence from one donepezil trial conducted in nursing home residents to trials conducted in younger populations suggests no apparent difference in efficacy or adverse events. Subgroup analyses of pooled data from four donepezil trials suggest no differences in efficacy or adverse events by sex or race. No evidence addressed patients with comorbid Parkinson's disease. Four studies provide general evidence of the efficacy of donepezil, galantamine, rivastigmine, and memantine in populations with comorbid vascular dementia. Only one study stratified patients by vascular risk factors; larger treatment differences between rivastigmine and placebo were found for patients with vascular risk factors compared to patients without vascular risk factors. No study compared outcomes among subgroups of patients taking a ChEI or memantine concurrently with another drug to patients not concurrently taking the same medication.

References

1. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56(9):1133-42.

2. Knopman D. Pharmacotheraphy for Alzheimer's disease. Curr Neurol Neurosci Rep 2001; 1(5):428-34.

3. Hebert L, Scherr P, Bienias J, Bennett D, Evans D. Alzheimer's disease in the US population: prevalence estimates using the 2000 Census. Arch Neurol 2003; 60:1119-22.

4. Sloane PD, Zimmerman S, Suchindran C *et al*. The public health impact of Alzheimer's disease, 2000-2050: potential implication of treatment advances. Annu Rev Public Health 2002; 23:213-31.

5. Wimo A, Winbald B. Health economical aspects of Alzheimer's and its treatment. Psychogeriatrics 2001; 1:189-93.

6. Cummings J, Frank J, Cherry D *et al*. Guidelines for managing Alzheimer's disease: Part II. Treatment. Am Fam Physician 2002; 65(12):2525-34.

7. Giacobini E ed. Cholinesterases and Cholinesterase-Inhibitors. London: Martin Dunitz, 2000.

8. Samochocki M, Zerlin M, Jostock R *et al*. Galantamine is an allosterically potentiating ligand of the human alpha4/beta2 nAChR. Acta Neurol Scand Suppl 2000; 176:68-73.

9. Greenamyre JT , Maragos WF, Albin RL, Penney JB, Young AB. Glutamate transmission and toxicity in Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 1988; 12(4):421-30.

10. Bowen D, Steele J, Lowe S, Palmer A. Tacrine in relation to amino acid transmitters in Alzheimer's disease. Adv Neurol 1990; 51:91-6.

11. Lipton SA, Rosenberg PA. Excitatory amino acids as a final common pathway for neurologic disorders. N Engl J Med 1994; 330(9):613-22.

12. Rogawski MA, Wenk GL. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. CNS Drug Rev 2003; 9(3):275-308.

13. Jarvis B, Figgitt D. Memantine. Drugs Aging 2003; 20(6):465-76; discussion 477-8.

14. Grimley Evans J, Wilcock G, Birks J. Evidence-based pharmacotherapy of AD. International Journal of Neuropsychopharmacology 2004; 7:351-69.

15. Standridge JB. Pharmacotherapeutic approaches to the treatment of Alzheimer's disease. Clin Ther 2004; 26(5):615-30.

16. Doody RS, Stevens JC, Beck C *et al*. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56(9):1154-66.

17. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999; 354(9193):1896-900.

18. Harris RP, Helfand M, Woolf SH *et al*. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001; 20(3 Suppl):21-35.

19. NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition) 2001.

20. Egger M, Smith GD, Altman DG. Systematic Reviews in Health Care (2nd edition). London, UK: BMJ Publishing Group, 2001.

21. Ebell M. Does donepezil help patients with moderate Alzheimer's dementia preserve their ability to function independently? Evidence-Based-Practice 2002.

22. Forette F, Hoover T, Gracon S *et al*. A double-blind, placebo-controlled, enriched population study of tacrine in patients with Alzheimer's disease. European Journal of Neurology 1995; 2:229-38.

23. Ibach B, Haen E. Acetylcholinesterase inhibition in Alzheimer's Disease. Curr Pharm Des 2004; 10(3):231-51.

24. Qizilbash N, Birks J, Lopez Arrieta J, Lewington S, Szeto S. Tacrine for Alzheimer's disease. Cochrane Database Syst Rev 2000; (3):CD000202.

25. Rogers S, Doody R, Mohs R *et al*. E2020 (Aricept TM) improves global and cognitive function in patients with Alzheimer's Disease. Results of a 30-week trial. Unpublished Paper 1996.

26. Salloway S. A double blind randomized pilot study to evaluate the effects of galantamine and donepezil on sleep and attention and gastrointestinal GI tolerance in patients with mild to moderate Alzheimer's disease AD. Clinical Trials Journal 2002; 1-2.

27. Wilcock G, Howe I, Coles H *et al*. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. Drugs Aging 2003; 20(10):777-89.

28. Jones R, Soininen H, Hager K *et al*. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. Int J Geriatr Psychiatry 2004; 19(1):58-67.

29. Wilkinson D, Passmore A, Bullock R *et al*. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. Int J Clin Pract 2002; 56(6):441-6.

30. Lanctot K, Herrmann N, Yau K *et al*. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ 2003; 169(6):557-64.

31. Birks J, Harvey R. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 2004; (3):CD001190.

32. Whitehead A, Perdomo C, Pratt RD, Birks J, Wilcock GK, Evans JG. Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer's disease: a meta-analysis of individual patient data from randomised controlled trials. Int J Geriatr Psychiatry 2004; 19(7):624-33.

33. Olin J, Schneider L. Galantamine for Alzheimer's disease. Cochrane Database Syst Rev 2004; (3):CD001747.

34. Schneider LS, Anand R, Farlow MR. Systematic review of the efficacy of rivastigmine for patients with Alzheimer's disease. International Journal of Geriatric Psychopharmacology 1998; 1(Suppl 1):S26-34.

35. Qizilbash N, Whitehead A, Higgins J, Wilcock G, Schneider L, Farlow M. Cholinesterase inhibition for Alzheimer disease: a meta-analysis of the tacrine trials. Dementia Trialists' Collaboration. JAMA 1998; 280(20):1777-82.

36. Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev 2004; (4):CD001191.

37. Schneider L. AD2000: donepezil in Alzheimer's disease. Lancet 2004; 363(9427):2100-1.

38. Burns A, Rossor M, Hecker J *et al*. The effects of donepezil in Alzheimer's disease - results from a multinational trial. Dement Geriatr Cogn Disord 1999; 10(3):237-44.

39. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E . A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001; 57(4):613-20.

40. Homma A, Takeda M, Imai Y *et al*. Clinical efficacy and safety of donepezil on cognitive and global function in patients with Alzheimer's disease. A 24-week, multicenter, double-blind, placebo-controlled study in Japan. E2020 Study Group. Dement Geriatr Cogn Disord 2000; 11(6):299-313.

41. Mohs R, Doody R, Morris J *et al*. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001; 57(3):481-8.

42. Rogers S, Doody R, Mohs R, Friedhoff L. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. Arch Intern Med 1998; 158(9):1021-31.

43. Rogers S, Farlow M, Doody R, Mohs R, Friedhoff L. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group.[see comment]. Neurology 1998; 50(1):136-45.

44. Rogers S, Friedhoff L. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial. The Donepezil Study Group. Dementia 1996; 7(6):293-303.

45. Tariot P, Cummings J, Katz I *et al*. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc 2001; 49(12):1590-9.

46. Winblad B, Engedal K, Soininen H *et al*. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001; 57(3):489-95.

47. Raskind M, Peskind E, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology 2000; 54(12):2261-8.

48. Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D. Effects of a flexible galantamine dose in Alzheimer's disease: a randomised, controlled trial. J Neurol Neurosurg Psychiatry 2001; 71(5):589-95.

49. Tariot P, Solomon P, Morris J, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 2000; 54(12):2269-76.

50. Wilcock G, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study

Group. BMJ 2000; 321(7274):1445-9.

51. Wilkinson D, Murray J. Galantamine: a randomized, double-blind, dose comparison in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2001; 16(9):852-7.

52. Corey-Bloom J, Anand J, Veach J, and E7BSG. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. International Journal of Geriatric Psychopharmacology 1998; 1:55-65.

53. Agid Y, Dubois B, Anand R, Gharabawi G. Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. Current Therapeutic Research, Clinical & Experimental 1998; 59(12):837-45.

54. Rosler M, Anand R, Cicin-Sain A *et al*. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999; 318(7184):633-8.

55. Farlow M, Gracon S, Hershey L, Lewis K, Sadowsky C, Dolan-Ureno J. A controlled trial of tacrine in Alzheimer's disease. The Tacrine Study Group. JAMA 1992; 268(18):2523-9.

56. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius H. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003; 348(14):1333-41.

57. Tariot P, Farlow M, Grossberg G, Graham S, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004; 291(3):317-24.

58. Birks J, Wilcock GGW. Velnacrine for Alzheimer's Disease (Cochrane Review). The Cochrane Library 2004; Issue 3.

59. Markowitz J, Gutterman E, Lilienfeld S, Papadopoulos G. Sleep-related outcomes in persons with mild to moderate Alzheimer disease in a placebo-controlled trial of galantamine. Sleep 2003; 26(5):602-6.

60. Tai C, Liu C, Sung S, Pai M, Hsu C. The safety and efficacy of Exelon in Alzheimers patients: A multicenter, randomized, 26 week study in Taiwan. International Journal of Neuropsychopharmacology 2000; 3 S 1:S 356.

61. Wong W, Liu H, Fuh J *et al*. A double-blind, placebo-controlled study of tacrine in Chinese patients with Alzheimer's disease. Dement Geriatr Cogn Disord 1999; 10(4):289-94.

62. Knapp M, Gracon S, Davis C, Solomon P, Pendlebury W, Knopman D. Efficacy and safety of high-dose tacrine: A 30-week evaluation. ALZHEIMER DIS ASSOC DISORD 1994; 8(SUPPL. 2):S22-S31.

63. Wood P, Castleden C. A double-blind, placebo controlled, multicentre study of tacrine for Alzheimer's disease. INT J GERIATR PSYCHIATRY 1994; 9(8):649-54.

64. Areosa S, Sherriff F. Memantine for dementia. Cochrane Database Syst Rev 2004; (1):CD003154.

65. Winblad B, Brodaty H, Gauthier S *et al*. Pharmacotherapy of Alzheimer's disease: is there a need to redefine treatment success? Int J Geriatr Psychiatry 2001; 16(7):653-66.

66. Cummings J, Schneider L, Tariot P, Kershaw P, Yuan W. Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. Am J Psychiatry 2004; 161(3):532-8.

67. Potkin S, Anand R, Hartman R, Veach J, Grossberg G. Impact of Alzheimer's disease and rivastigmine treatment on activities of daily living over the course of mild to moderately severe disease. Prog

Neuropsychopharmacol Biol Psychiatry 2002; 26(4):713-20.

68. Burns A, Spiegel R, Quarg P. Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease. Int J Geriatr Psychiatry 2004; 19(3):243-9.

69. Rockwood K. Size of the treatment effect on cognition of cholinesterase inhibition in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004; 75(5):677-85.

70. Burback D, Molnar F, St John P, Man-Son-Hing M. Key methodological features of randomized controlled trials of Alzheimer's disease therapy. Minimal clinically important difference, sample size and trial duration. Dement Geriatr Cogn Disord 1999; 10(6):534-40.

71. Watkins P, Zimmerman H, Knapp M, Gracon S, Lewis K. Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. JAMA 1994; 271(13):992-8.

72. Cutler NR, Sramek JJ. Tolerability profiles of AChEIs: a critical component of care for Alzheimer's disease patients. International Journal of Geriatric Psychopharmacology 1998; 1(Suppl 1):S20-S25.

73. Gauthier S. Cholinergic adverse effects of cholinesterase inhibitors in Alzheimer's disease: epidemiology and management. Drugs Aging 2001; 18(11):853-62.

74. Dunn N, Pearce G, Shakir S. Adverse effects associated with the use of donepezil in general practice in England. J Psychopharmacol 2000; 14(4):406-8.

75. Morganroth J , Graham S, Hartman R, Anand R. Electrocardiographic effects of rivastigmine. J Clin Pharmacol 2002; 42(5):558-68.

76. Emre M, Aarsland D, Albanese A *et al*. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 2004; 351(24):2509-18.

77. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju C. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet 2002; 359(9314):1283-90.

78. Kumar V, Anand R, Messina J, Hartman R, Veach J. An efficacy and safety analysis of Exelon in Alzheimer's disease patients with concurrent vascular risk factors. Eur J Neurol 2000; 7(2):159-69.

79. Grossberg G, Stahelin H, Messina J, Anand R, Veach J. Lack of adverse pharmacodynamic drug interactions with rivastigmine and twenty-two classes of medications. Int J Geriatr Psychiatry 2000; 15(3):242-7.

80. Gauthier S, Feldman H, Hecker J *et al*. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. Int Psychogeriatr 2002; 14(4):389-404.

81. Gauthier S, Feldman H, Hecker J, Vellas B, Emir B, Subbiah P. Functional, cognitive and behavioral effects of donepezil in patients with moderate Alzheimer's disease. Curr Med Res Opin 2002; 18(6):347-54.

82. Feldman H, Gauthier S, Hecker J *et al*. Efficacy of donepezil on maintenance of activities of daily living in patients with moderate to severe Alzheimer's disease and the effect on caregiver burden. J Am Geriatr Soc 2003; 51(6):737-44.

83. Rive B, Vercelletto M, Damier F, Cochran J, Francois C. Memantine enhances autonomy in moderate to severe Alzheimer's disease. Int J Geriatr Psychiatry 2004; 19(5):458-64.

84. Wimo A, Winblad B, Engedal K *et al*. An economic evaluation of donepezil in mild to moderate Alzheimer's disease: results of a 1-year, double-blind, randomized trial. Dement Geriatr Cogn Disord 2003;

15(1):44-54.

85. Evans JG, Wilcock G, Birks J. Evidence-based pharmacotherapy of Alzheimer's disease. Int J Neuropsychopharmacol 2004; 7(3):351-69.

86. Knapp M, Knopman D, Solomon P, Pendlebury W, Davis C, Gracon S. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. JAMA 1994; 271(13):985-91.

87. Farlow M, Brashear A, Hui S, Schneider L, Unverzagt F, and TSG. The effects of tacrine in patients with mild versus moderate stage Alzheimer's disease. Research Advances in Alzheimer's Disease and Related Disorders 1995; 283-92.

88. Knopman D, Schneider L, Davis K *et al*. Long-term tacrine (Cognex) treatment: effects on nursing home placement and mortality, Tacrine Study Group. Neurology 1996; 47(1):166-77.

89. Farlow M, Lahiri D, Poirier J, Davignon J, Schneider L, Hui S. Treatment outcome of tacrine therapy depends on apolipoprotein genotype and gender of the subjects with Alzheimer's disease. Neurology 1998; 50(3):669-77.

90. Anand R, Gharabawi G, Enz A. Efficacy and safety results of the early phase studies with Exelon (ENA-713) in Alzheimer's disease: an overview. J Drug Dev Clin Pract 1996; 8:109-16.

91. Farlow M, Potkin S, Koumaras B, Veach J, Mirski D. Analysis of outcome in retrieved dropout patients in a rivastigmine vs placebo, 26-week, Alzheimer disease trial. Arch Neurol 2003; 60(6):843-8.

92. Forette F, Anand R, Gharabawi G. A phase II study in patients with Alzheimer's disease to assess the preliminary efficacy and maximum tolerated dose of rivastigmine (Exelon). Eur J Neurol 1999; 6(4):423-9.

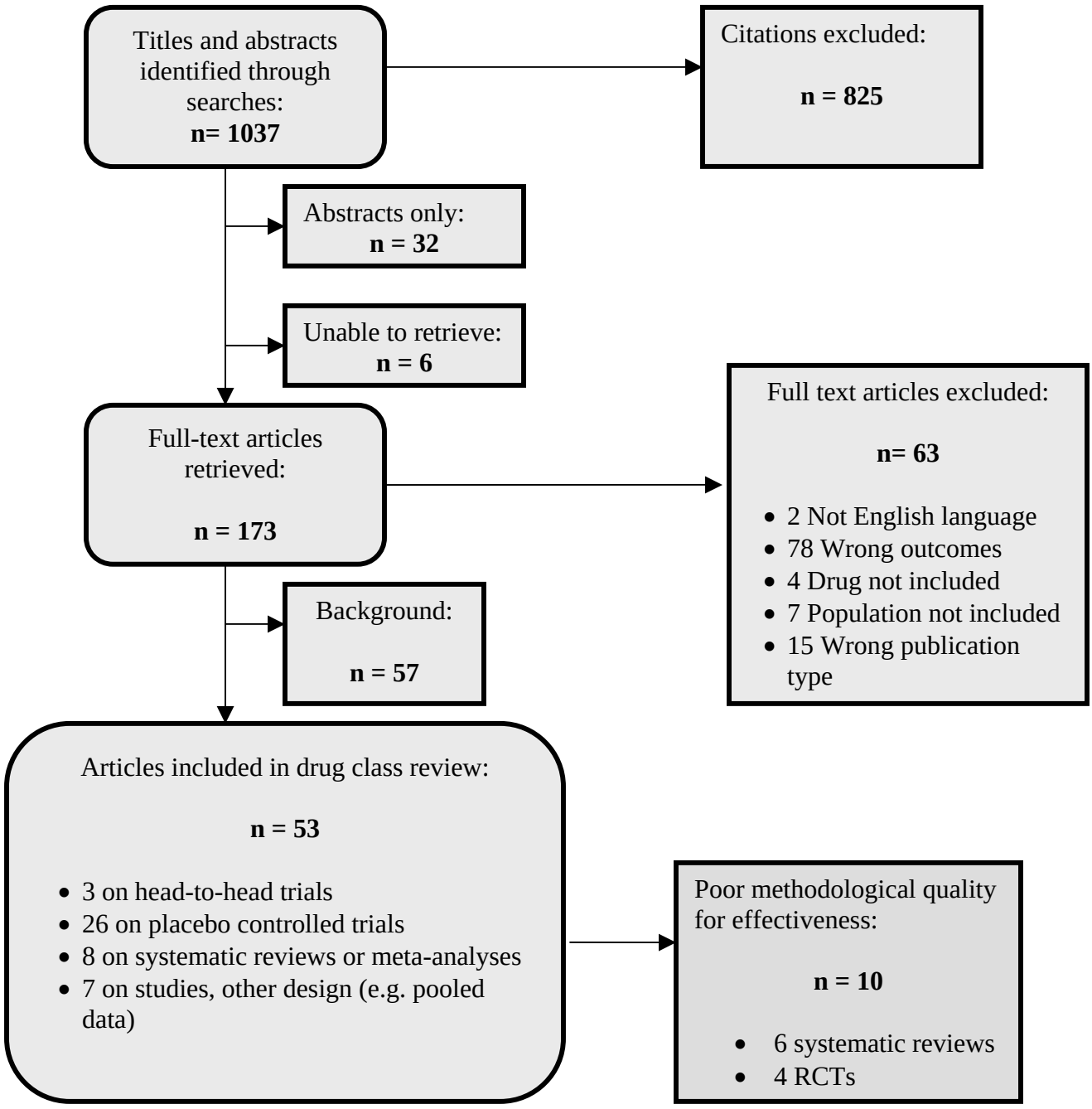
93. Geldmacher D , Provenzano G, McRae T, Mastey V, Ieni J. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc 2003; 51(7):937-44.

94. Pratt R, Perdomo C, Surick I, Ieni J. Donepezil: tolerability and safety in Alzheimer's disease . Int J Clin Pract 2002; 56(9):710-7.

95. Sano M, Wilcock G, van Baelen B, Kavanagh S. The effects of galantamine treatment on caregiver time in Alzheimer's disease. Int J Geriatr Psychiatry 2003; 18(10):942-50.

96. Stahl S, Markowitz J, Papadopoulos G, Sadik K. Examination of nighttime sleep-related problems during double-blind, placebo-controlled trials of galantamine in patients with Alzheimer's disease. Curr Med Res Opin 2004; 20(4):517-24.

Figure 1: Results of literature search



Evidence Tables

Table 9: Abbreviations for Evidence Tables

ACh	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer's disease
ADAS	Alzheimer's Disease Assessment Scale
ADAS-Cog	cognitive subscale of Alzheimer's Disease Assessment Scale
ADAS-Cog 11	cognitive portion of ADAS 11-item cognitive subscale
ADAS-Cog 13	cognitive portion of ADAS 13-item cognitive subscale
ADAS-J-Cog	Japanese version of ADAS-Cog
ADAS-Noncog	noncognitive component of ADAS
ADCS/ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living
ADFACS	Alzheimer's Disease Functional Assessment and Change Scale
ADL	Activities of Daily Living
ADS	Alzheimer's Deficit Scale
ALT	alanine aminotransferase
AMTS	Abbreviated Mental Test Score
APOE	apolipoprotein E
BADLS	Bristol Activities of Daily Living Scale
BDS	Blessed Dementia Scale
BDT	Block Design Test
BGP	Behavioural Rating Scale for Geriatric Patients
BS-AS	Behavioral Scale for Alzheimer's Disease
BVR	Benton Visual Retention
CAMCOG	Cambridge Cognitive Examination
CASI	Cognitive Abilities Screening Instrument
CAUST	Canadian Utilization of Services Tracking questionnaire
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Sum of the Boxes
CGIC	Clinical Global Impression Change
CGRS	Clinicians Global Rating Score
ChE	cholinesterase
CI	confidence interval
CIBI	Clinician Interview-Based Impression
CIBIC	Clinician Interview-Based Impression of Chanage
CIBIC-plus	CIBIC plus Caregiver Input
CMCS	Caregiver-rated modified Chrichton Scale
CSS	Caregiver Stress Scale
CST	Color Slide Test
CT	computed tomography
CVD	cerebrovascular disease
DAD	Disability Assessment for Dementia scale
DON	donepezil
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, version III
DSM-III-R	
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, version IV
DST	Digit Span Test
FAST	Functional Assessment Staging Scale
FCCA	Final Comprehensive Consensus Assessment
FLS	Functional Life Scale
FOME	Fuld Object Memory Evaluation
FRS	Functional Rating Scale
GAL	galantamine
GBS	Gottfried, Brane and Steel Scale
GDS	Global Deterioration Scale
GERRI	Geriatric Evaluation by Relative's Rating Instrument
HDS	Hierarchic Dementia Scale
HIS	Hachinski Ischemia Scale
HUI	Health Utilities Index
IADL	Instrumental activities of daily living
ICD-10	International Classification of Diseases 10th revision
IDDD	Interview for Deterioration in Daily Living Activities in Dementia

IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
ITT	intention-to-treat
LFT	Liver Function Test
LMT	Logical Memory Test
MCID	Minimal clinically important difference
MEM	memantine
MENFIS	Mental Function Impairment Scale
MHIS	Modified Hachinski Ischemic Score
MMSE	Mini-Mental State Examination
3MS	Modified MMSE
MSQ	Mental Status Questionnaire
N/A	not applicable
NINCDS/ADRDA	National Institute of Neurological & Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche l'Enseignement en Neurosciences
NMDA	N-methyl-D-aspartate
NOSIE	Nurse Observation Scale for Inpatient Evaluation
NOSGER	Nurse Observation Scale for Geriatric Patients (also abbreviated as NOSGP)
NOSGP	See NOSGER
NPI	Neuropsychiatric Inventory
NPI-NH	NPI-Nursing Home version
NR	not reported
OR	odds ratio
PDS	Progressive Deterioration Scale
PSMS	Physical Self-Maintenance Scale
PSQI	Pittsburgh Sleep Quality Index
PWT	Paired Words Test
QALY	Quality-adjusted-life-year
QOL	quality of life
RDRS-II	Rapid Disability Rating Scale II
RGRS	Relatives Global Rating Scale
RIV	rivastigmine
RR	relative risk
SCAG	Sandoz Clinical Assessment Geriatric Scale
SGRS	Stockton Geriatric Rating Scale
SIB	Severe Impairment Battery
sMMSE	Screening standardized MMSE
TAC	tacrine
UTI	urinary tract infection
VaD	Vascular dementia
VAS	Visual Analogue Scales
VRF	vascular risk factors
WFT	Word Fluency Test
WMD	weighted mean difference

Efficacy/Effectiveness ***Alzheimer Drugs***

STUDY:	**Authors: AD2000 Collaborative Group**[37] **Year: 2004** **Country:** UK		
FUNDING:	NHS Executive R&D and Health Authorities in the West Midlands, East Lancashire, Iechyrd Morgannwg, and North Nottingham		
RESEARCH OBJECTIVE:	To determine whether long-term DON treatment produces worthwhile improvements in disability, dependency, behavioral, and psychological symptoms or delay in institutionalism		
DESIGN:	**Study design:** RCT **Effectiveness trial** **Setting:** Multi-center (22 memory clinics) **Sample size:** 565		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil** 5 or 10 mg/d 192 weeks 282	**placebo** N/A 192 weeks 283	
INCLUSION:	Community residents referred by treating doctor; DSM-IV diagnosis of AD with or without co-existing VaD; regular caretaker		
EXCLUSION:	Taking a ChE inhibitor or a contraindication against DON		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	All medications except other AChE inhibitors		

<table>
<tr><td colspan="4">Authors: AD2000 Collaborative Group
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild to moderate</td></tr>
<tr><td></td><td><u>donepezil</u></td><td><u>placebo</u></td><td></td></tr>
<tr><td>Median age (years):</td><td>76</td><td>75</td><td></td></tr>
<tr><td>Sex (% female):</td><td>58</td><td>60</td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• VaD</td><td>18%</td><td>15%</td><td></td></tr>
<tr><td>• Parkinsonism</td><td>4%</td><td>4%</td><td></td></tr>
<tr><td>• Median baseline MMSE</td><td>19</td><td>19</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Entry to institutionalized care; progression of disability defined by loss of 2 of 4 basic or 6 of 11 instrumental activities on the BADLS

Secondary Outcome Measures: Functional ability measured by the BADLS; NPI; MMSE; compliance (defined as dropouts); death from AD

Timing of assessments: Baseline and every 12 weeks during treatment</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No significant difference observed between DON and placebo in rates of institutionalism (9% vs. 14% at 1 year; P = 0.15; 42% vs. 44% at 3 years; P = 0.4)*
• Progression of disability similar between DON and placebo (13% vs. 19% at 1 year; P = 0.3; 55% vs. 53% at 3 years; P = 0.9)
• No significant difference in BADLS at 12 weeks, but thereafter DON was significantly better than placebo (average difference: 1.0 points, 95% CI: 0.5 – 1.6; P = 0.0004)*
• The number of severe adverse events and deaths in both groups were similar
• No differences found between DON and placebo on the NPI (P = 0.4)
• No significant differences in behavioral or psychological differences at any point in time

Intermediate Outcome Measures:
• MMSE was significantly better in DON group than placebo group at 2 years (+ 0.8 points 95% CI: 0.5 – 1.2; P < 0.0001)</td></tr>
</table>

Authors: AD2000 Collaborative Group **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported:** **Specific adverse effects reported:**	**donepezil** NR NR	**placebo** NR NR	
Significant differences in adverse events:	Significantly more DON than placebo-treated patients withdrew because of adverse events after 12 weeks (13% vs. 7%; P = 0.02) and between 13 and 60 weeks (7% vs. 3%; P = 0.05)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (at least 1)		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 17% after 60 weeks of treatment **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up (60 weeks):** **Withdrawals due to adverse events:**	**donepezil** 17% 7%	**placebo** 18% 3%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Agid et al.** [53] **Year: 1998** **Country:** Multinational		
FUNDING:	Novartis Pharma AG		
RESEARCH OBJECTIVE:	To investigate the efficacy and tolerability of two different dosages of RIV in elderly patients with probable AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (Europe, 54 centers) **Sample size:** 402		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**rivastigmine** 4 mg/d 13 weeks 136	**rivastigmine** 6 mg/d 13 weeks 133	**placebo** N/A 13 weeks 133
INCLUSION:	Diagnosis of mild-to-moderate dementia using DSM-IV and DSM-III-R criteria and diagnosis of probable AD according to NINCDS/ADRDA criteria		
EXCLUSION:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Medications for non-cognitive aspects of AD such as hypnotics provided they were not long-acting agents; drugs for other concomitant conditions at continued dosage		

<table>
<tr><td colspan="4">Authors: Agid et al.
Year: 1998</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: NR
Alzheimer classification: Mild-moderate</td></tr>
<tr><td></td><td><u>rivastigmine 4 mg/d</u></td><td><u>rivastigmine 6 mg/d</u></td><td><u>placebo</u></td></tr>
<tr><td></td><td>Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:</td><td>68.62
NR
NR
NR</td><td>68.68
NR
NR
NR</td><td>70.80
NR
NR
NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: CGIC

Secondary Outcome Measures: FOME; Digit Symbol Substitution test; BVR; Trail Making test; NOSGER; MMSE

Timing of assessments: Baseline and weeks 7 and 13</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No statistically significant differences between RIV and placebo for NOSGER

Intermediate Outcome Measures:
• Significantly more patients on RIV 6 mg/d than on placebo had marked or moderate improvements on CGIC (42.7% vs. 29.9%; P = 0.05); 4 mg/d differences not significant
• At week 13, patients on RIV 6 mg/d had significantly better scores on Digit Symbol Substitution test and FOME (P < 0.05) than placebo-treated patients; 4 mg/d differences not significant
• No statistically significant differences between RIV and placebo for MMSE, BVR, and Trail Making test
• Patients on RIV 4 mg/d presented statistically significant difference to placebo only on FOME</td></tr>
</table>

Authors: Agid et al. **Year: 1998**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea • Vomiting • Diarrhea • Dizziness • Headache	**rivastigmine 4 mg/d** NR 17% 10% 7% 6% 4%	**rivastigmine 6 mg/d** NR 31% 18% 12% 20% 13%	**placebo** NR 6% 3% 2% 7% 6%
Significant differences in adverse events:	Significantly more patients suffered from nausea, vomiting, diarrhea, dizziness, and headache in RIV groups especially at higher doses; P = NR		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 11.2% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**rivastigmine 4 mg/d** 12.5% 10%	**rivastigmine 6 mg/d** 15% 12%	**placebo** 6% 4%
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness ***Alzheimer Drugs***

STUDY:	**Authors: Birks et al.** [31] **Year: 2004** **Country:** Multinational
FUNDING:	Review funded by NHS R&D UK
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 17 trials contributed 4,365 participants; studies ranged from 12 - 566 participants
AIMS OF REVIEW:	To assess whether DON improves the well-being of patients with dementia due to AD
STUDIES INCLUDED IN META-ANALYSIS	A total of 17 placebo-controlled RCT studies were included, 13 of which provide sufficient details for analysis
TIME PERIOD COVERED:	Trials completed before October 9, 2002 that were included in the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group
CHARACTERISTICS OF INCLUDED STUDIES:	Unconfounded, randomized trials of patients with dementia due to AD in which treatment with DON was administered for more than a day compared with a placebo group; trials in which allocation of treatment or control was not randomized, or in which treatment allocation was not concealed were excluded; all studies were multi-center, randomized, and double-blind
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients diagnosed with probable AD using accepted criteria such as ICD-10; DSM; and NINCDS/ADRDA

Authors: Birks et al. **Year: 2004**	
CHARACTERISTICS OF INTERVENTIONS:	DON given at any dose for more than one day with parallel concomitant placebo group; outcome measures included: Global assessment (CIBIC-plus, GBS, MENFIS, CDR-SB, ADAS-Cog, MMSE); ADL's (PDS, DAD, IADL, PSMS, CMCS); behavioral disturbances; QOL; caregiver stress; side effects
MAIN RESULTS:	**Quality of life** • No significant difference between DON and placebo for QOL and behavioral disturbance **Activities of daily living** • Pooled data from 2 studies provided evidence of benefit of DON at 12 and 24 weeks ($P < 0.01$) **Global assessment** • The CIBIC-plus scale was dichotomized into those showing no change or decline against those showing improvement; overall there are benefits associated with 5 and 10 mg/d DON compared with placebo at 12 and 24 weeks ($P < 0.005$) as shown by the ITT-LOC analyses: 24 weeks, 10 mg/d: OR 2.18; 95% CI: 1.53 – 3.11; $P < 0.001$ 24 weeks 5 mg/d: OR 2.38; 95% CI: 1.78 – 3.19; $P < 0.001$ • The CDR-SB showed a benefit with 5 and 10 mg/d of DON compared with placebo at 12 weeks and 10 mg/d of DON compared with placebo at 24 weeks 24 weeks, 10 mg/d: WMD -0.53; 95% CI: -0.73 – -0.33; $P < 0.001$ 24 weeks 5 mg/d: WMD -0.51; 95% CI: -0.70 – -0.32; $P < 0.001$ **Cognitive function** • Evidence of benefits associated with 5 and 10 mg/d of DON compared with placebo on cognitive function was shown by improvement in the ADAS-Cog and MMSE test scores at 12 and 24 weeks ($P < 0.005$) • ADAS-Cog: 24 weeks, 10 mg/d: WMD -2.92; 95% CI: -3.74 – -2.10; $P < 0.001$ 24 weeks 5 mg/d: WMD -2.02; 95% CI: -2.77 – -1.26; $P < 0.001$ • MMSE: 24 weeks, 10 mg/d: WMD 1.50; 95%: 0.97 – 2.04; $P < 0.00001$ 24 weeks 5 mg/d: WMD 1.44; 95% CI: 0.64 – 2.24; $P < 0.001$

Authors: Birks et al. **Year: 2004**	
ADVERSE EVENTS:	**Withdrawals due to adverse events:** A meta-analysis of withdrawals before the end of treatment showed no significant differences between the 5 mg/d group and the placebo group at 12 and 24 weeks; there were significant differences for the 10 mg/d group in favor of placebo at 12, but not at 24 and 52 weeks (29/184 DON, 13/178 placebo) (OR 2.31; 95% CI: 1.21 – 4.40, P = 0.01) Anorexia, diarrhea, dizziness, fatigue, insomnia, muscle cramps, nausea, vomiting, tremor, vertigo, and weight loss were statistically significantly more common in the DON than in the placebo group
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Trials were selected from Specialized Register of the Cochrane Dementia and Cognitive Improvement Group
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Efficacy/Effectiveness ***Alzheimer Drugs***

STUDY:	**Authors: Birks et al.**[36] **Year: 2004** **Country:** Multinational
FUNDING:	NHS R&D Executive UK
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 8 trials involving 3,450 participants
AIMS OF REVIEW:	To determine the clinical efficacy and safety of RIV for patients with dementia of Alzheimer's type
STUDIES INCLUDED IN META-ANALYSIS	A total of 8 studies: Agid et al., 1998; Anand et al. B104, 1996; Anand et al. B105, 1996; Rösler et al., 1999; ADENA Programme B304 (published and unpublished data), 1998; ADENA Programme B351 (published and unpublished data), 1998; Corey-Bloom et al., 1998; Tai, 2000; Tai et al., 2000
TIME PERIOD COVERED:	Trials completed before October 21, 2003
CHARACTERISTICS OF INCLUDED STUDIES:	All trials were randomized, double-blind, parallel group, and placebo-controlled in which RIV was administered for longer than 2 weeks
CHARACTERISTICS OF INCLUDED POPULATIONS:	Diagnostic criteria for all studies were DSM-IV and probable AD according to NINCDS/ADRDA except Tai 2000 which provided none

Authors: Birks et al. **Year: 2004**	
CHARACTERISTICS OF INTERVENTIONS:	RIV given at any dose with parallel placebo control; outcome measures included: dependency, global impression, functional performance, cognitive function, behavioral disturbance, QOL, effect on caregiver, death, institutionalization rates, withdrawals, incidence of adverse events
MAIN RESULTS:	• Meta-analysis of ADAS-Cog WMDs reveals statistically significant benefit of RIV 6/12 mg/d over placebo at 26 weeks (WMD -2.1; 95% CI: -2.6 – -1.5), and for RIV 1- 4 mg/d (WMD -0.8; 95% CI: -1.5 – -0.2); pooled results across doses not presented • ITT meta-analysis of ADAS-Cog dichotomized into those showing < 4 points improvement and those showing ≥ 4 points improvement at 26 weeks shows benefit of cognitive function for RIV 6-12 mg/d (83%, 878/1054 did not show 4 points improvement compared to 89%, 787/863; OR 0.6; 95% CI: 0.4 – 0.8), but NOT for the 1-4 mg/d (88%, 571/650 did not show 4 points improvement compared to 90%, 576/643; OR 0.84; 95% CI: 0.60 – 1.19); pooled results across does not presented. • ITT meta-analysis for MMSE shows similar results to ADAS-Cog at 26 weeks; 6-12 mg/d WMD -0.83; 95% CI: -1.12 – -0.53 and 1-4 mg/d WMD -0.43; 95% CI: -0.78 – -0.08 • ITT analysis of CIBIC-plus dichotomized into those showing no change or decline against those showing improvement shows there are benefits to 1-4 mg/d at 26 weeks (74%, 457/614 showed no improvement compared with 80%, 500/623; OR 0.71; 95% CI: 0.55 – 0.93), and for 6-12 mg/d (73%, 715/973 showed no improvement compared to 80%, 675/839; OR 0.68; 95% CI: 0.55 – 0.85); pooled results across does not presented • ITT analysis of PDS at 26 weeks revealed significant improvement in RIV 6-12 mg/d versus placebo (WMD -2.2; 95% CI: -3.2 – -1.1), but not with 1-4 mg/d (WMD 0.4; 95% CI: -0.9 – 1.6); pooled results across does not presented • ITT analysis of GDS dichotomized counting those showing moderately severe, severe, or very severe dementia against those showing moderate or mild dementia revealed significant benefit at 26 weeks for RIV 6-12 mg/d (55%, 579/1056 showed the worse condition compared to 59%, 511/868; OR 0.78; 95% CI: 0.64 – 0.94); results did not differ between 1-4 mg/d and placebo (P = NR)

Authors: Birks et al. **Year: 2004**	
ADVERSE EVENTS:	• Withdrawals for any reason before the end of treatment show that there are no significant differences between withdrawals in the 1-4 mg/d RIV group and placebo group at 12 and 26 weeks; there are significant differences for the 6-12 mg/d group in favor of placebo at 12, 18 and 26 weeks; (20/133 vs. 8/133, 16/45 vs. 2/24, 367/1052 vs. 145/868; OR 2.60; 95% CI: 1.19 – 5.68; OR 4.02; 95% CI: 1.31 – 12.32; OR 2.40; 95% CI: 1.95 – 2.96) • Withdrawals by week 26 for adverse events showed no significant differences between the 1-4 mg/d RIV and placebo groups (55/645 vs. 54/646; OR 1.01; 95% CI: 0.75 – 1.34); however, there are significant differences between the 6-12 mg/d and placebo groups in favor of the latter (257/1052 vs. 74/868; OR 2.97; 95% CI: 2.33 – 3.79) • Meta-analyses overall adverse event rates show no significant differences by the end of the titration period between 1-4 mg/d RIV and placebo groups (440/644 vs. 437/646; OR 1.04; 95% CI: 0.82 – 1.31); the same is true at 26 weeks (509/644 vs 518/646; OR 0.93; 95% CI: 0.71 – 1.23); however, there were significant differences between the 6-12 mg/d RIV and placebo groups in favor of the latter by the end of the titration period (920/1071 vs. 584/878; OR 2.98; 95% CI: 2.40 – 3.70) and by 26 weeks (960/1052 vs 687/868; OR 2.67; 95% CI: 2.05 – 3.46); the pattern is similar for the number of patients with at least one severe adverse event; the 1-4 mg/d group did not differ significantly from the placebo group, but there were significant differences between 6-12 mg/d and placebo groups in favor of the latter; results for the titration period were 130/1052 vs. 61/868; OR 1.88; 95% CI: 1.39 – 2.55) and by 26 weeks 166/1052 vs. 114/868 (OR 1.29; 95% CI: 1.00 –1.67) • There are significant differences in favor of placebo for number of patients suffering nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain and dizziness;

Authors: Birks et al. **Year: 2004**	
COMPREHENSIVE LITERATURE SEARCH STRATEGY	Refers to Cochrane Dementia and Cognitive Improvement Group search strategy; trials were selected from Specialized Register of the Cochrane Dementia and Cognitive Improvement Group, containing records from a number of published and unpublished electronic databases (e.g., MEDLINE, CCTR/Central, EMBASE)
STANDARD METHOD OF APPRAISAL OF STUDIES:	Cochrane Collaboration approach
QUALITY RATING:	**Good**

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Burns et al.** [38] **Year: 1999** **Country:** Multinational (9 countries)		
FUNDING:	Eisai Inc., Teaneck, NJ and Eisai Co. Ltd., Tokyo, Japan		
RESEARCH OBJECTIVE:	To investigate the efficacy and safety of DON in a multinational setting in patients with mild to moderately severe AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (82 clinical centers) **Sample size:** 818		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil 5 mg** 5 mg/d 24 weeks 271	**donepezil 10 mg** 10 mg/d 24 weeks 273	**placebo** N/A 24 weeks 274
INCLUSION:	Fifty years of age or older; met DSM-III-R criteria for AD; met NINCDS/ADRDA for probable AD; MMSE scores between 10 and 26 (inclusive); CDR scores of 1 or 2		
EXCLUSION:	Patients with structural lesions or significant vascular changes in a recent CT or MRI scan; patients with other neurological or psychiatric disorders; patients with asthma or significant uncontrolled gastrointestinal, renal, hepatic, endocrine or oncological disorders		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR; patients taking “prohibited” study medications were excluded		

<table>
<tr><td colspan="4">Authors: Burns et al.
Year: 1999</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild to moderate</td></tr>
<tr><td></td><td><u>donepezil 5 mg</u></td><td><u>donepezil 10 mg</u></td><td><u>placebo</u></td></tr>
<tr><td></td><td>Mean age (years):</td><td>72</td><td>72</td><td>71</td></tr>
<tr><td></td><td>Sex (% female):</td><td>61</td><td>57</td><td>55</td></tr>
<tr><td></td><td>Ethnicity:</td><td></td><td></td><td></td></tr>
<tr><td></td><td>• White</td><td>100%</td><td>99%</td><td>99%</td></tr>
<tr><td></td><td>• Other</td><td><1%</td><td>1%</td><td>1%</td></tr>
<tr><td></td><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td></td><td>• Baseline mean MMSE</td><td>20</td><td>20</td><td>20</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADAS-Cog; CIBIC-plus

Secondary Outcome Measures: CDR-SB; patient rated quality of life (scale not specified but reported in Rogers et al., 1998); modified IDDD

Timing of assessments: Baseline and weeks 6, 12, 18, 24 and 30 (endpoint = 24 weeks; placebo washout phase = 30 weeks; outcome measures reported for 24 weeks)</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No significant differences in quality of life scores at any time during the study; authors note significant variability in scale scores and inherent problems with measurement
• Mean improvement in IDDD total score and self-care score NR; statistically significant improvement in IDDD-complex tasks score for DON 10 mg/d (P = 0.0072) but not for DON 5 mg/d

Intermediate Outcome Measures:
• Statistically significant improvement in ADAS-Cog scores for both DON groups compared to placebo; P = 0.0021 for 5 mg/d; P < 0.001 for 10 mg/d*
• Statistically significant improvement in CIBIC-plus scores for both DON groups compared to placebo; P = 0.0072 for 5 mg/d; P = 0.0002 for 10 mg/d*
• Statistically significant improvement in CDR-SB scores for both DON groups compared to placebo; P = 0.0344 for 5 mg/d; P = 0.0033 for 10 mg/d</td></tr>
</table>

Authors: Burns et al. **Year: 1999**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea • Diarrhea • Vomiting • Nervous system	**donepezil 5 mg** 79% 7% 10% 4% 36%	**donepezil 10 mg** 86% 24% 16% 16% 40%	**placebo** 76% 7% 4% 4% 29%
Significant differences in adverse events:	Patients taking DON had significantly more adverse digestive and nervous system events (dizziness, confusion, insomnia: incidence < 10%) than placebo; P ≤ 0.05		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 132 (24%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**donepezil 5 mg** 22% 9%	**donepezil 10 mg** 26% 18%	**placebo** 20% 10%
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Corey-Bloom et al.** [52] **Year: 1998** **Country:** USA		
FUNDING:	Novartis		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of RIV tartrate for patients with AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (22) **Sample size:** 699		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**placebo** N/A 26 weeks 235	**rivastigmine** 1-4 mg/d 26 weeks 233	**rivastigmine** 6-12 mg/d 26 weeks 231
INCLUSION:	Age between 45 and 89 years; non-childbearing potential for females; criteria for AD according to DSM-IV; probable AD according to NINCDS/ADRDA criteria; mild-to-moderate impairment based on MMSE score between 10 and 26; head CT or MRI consistent with AD within 12 months of inclusion; responsible caregiver who provided written consent		
EXCLUSION:	Severe and unstable medical illnesses; use of anticholinergics ACh precursor health food supplements, memory enhancers, insulin, and psychotic drugs must be discontinued		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Occasional use of chloral hydrate for agitation or insomnia		

Authors: Corey-Bloom et al. **Year: 1998**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No (more females in high dose RIV group) **Alzheimer classification:** Mild-moderate		
	placebo	**rivastigmine (low)**	**rivastigmine (high)**
Mean age (years):	74.8	74.9	73.8
Sex (% female):	58	57	68
Ethnicity:			
• **White**	94%	95%	97%
• **Black**	4%	4%	3%
• **Asian**	1%	0%	0%
• **Other**	< 1%	1%	0%
Other germane population qualities:			
• Mean dementia duration (months)	40.4	39.3	38.4
• Mean MMSE score	20	19.5	19.62
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ADAS-Cog; CIBIC-plus; PDS **Secondary Outcome Measures:** MMSE; GDS **Timing of assessments:** Baseline and weeks 12, 18, 26 or early termination		
RESULTS:	**Health Outcome Measures:** • PDS: high-dose RIV vs. placebo difference was significant ($P < 0.05$); only the high dose RIV group had a significantly greater number of treatment responders than placebo on the PDS ($P < 0.01$) **Intermediate Outcome Measures:** • ADAS-Cog, CIBIC-plus: for both doses of RIV, the mean changes from baseline on ADAS-Cog and CIBIC-plus were significantly better than those for placebo ($P < 0.05$) • MMSE: both high dose and low dose RIV MMSE scores were better than placebo, but only high dose RIV was statistically significant ($P < 0.05$) • GDS: both high and low dose RIV were significantly more improved than placebo ($P < 0.05$)		

Authors: Corey-Bloom et al. **Year: 1998**			
ADVERSE EVENTS:	**placebo**	**rivastigmine (low)**	**rivastigmine (high)**
Overall adverse effects reported:	NR	NR	NR
Titration Phase			
• Fatigue	4%	5%	10%
• Asthenia	2%	2%	10%
• Dizziness	13%	15%	24%
• Somnolence	2%	7%	9%
• Nausea	11%	14%	48%
• Vomiting	3%	7%	27%
• Anorexia		8%	20%
Maintenance Phase			
• Dizziness	4%	8%	14%
• Nausea	3%	8%	20%
• Vomiting	2%	5%	16%
Significant differences in adverse events:	Titration Phase: sweating, fatigue, asthenia, weight decrease, malaise, dizziness, somnolence, nausea, vomiting, anorexia, flatulence ($P < 0.05$) Maintenance Phase: dizziness, nausea, vomiting, dyspepsia, sinusitis ($P < 0.05$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes (independent firm cited, along with voice responses system for randomization code assignment)		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 22% **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*):	**placebo**	**rivastigmine (low)**	**rivastigmine (high)**
Loss to follow-up:	16.6%	14.6%	35.5%
Withdrawals due to adverse events:	7.2%	8.2%	29%
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Farlow et al.** [55] **Year: 1992** **Country:** US and Canada		
FUNDING:	Warner-Lambert		
RESEARCH OBJECTIVE:	To compare efficacy and safety of TAC with placebo in patients with probable AD		
DESIGN:	**Study design:** RCT **Setting:** 23 centers (21 US and 2 Canada) **Sample size:** 468		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**tacrine** 20 to 80 mg/d 12 weeks 310	**placebo** NA 12 weeks 158	
INCLUSION:	Men and women with probable AD based on NINCDS criteria and symptoms for 1 year; MMSE 10-26; age ≥ 50 years; mild to moderate AD; without other significant medical conditions		
EXCLUSION:	Patients with stroke, tumor, subdural hematoma, hydrocephalus, or VaD		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concurrent medications with cognitive properties such as anticholinergics, anticonvulsants, antidepressants, antipsychotics, anxiolytics, and stimulants were prohibited		

Authors: Farlow et al. **Year: 1992**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Alzheimer classification:** Mild-moderate		
	tacrine 20; 40; 60; 80 mg/d	**placebo** placebo; placebo/20 mg/d	**total** (n = 468)
Mean age (years):	70.7; 71.9; 72.1; 70.8	71; 71.6	71.3
Sex (% female):	49; 50; 55; 47	49; 59	52
Ethnicity: (% white)	97; 97; 96; 99	91; 99	97
Other germane population qualities:			
• MMSE	18.8, 18.4, 17.9, 19.2	18.2; 18.8	18.5
• HIS	0.8, 0.5, 0.7, 0.6	0.5; 0.6	0.6
• ADAS-Cog	27, 28.4, 27.7, 26.6	28.1; 27	27.5
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ADAS-Cog; CGIC **Secondary Outcome Measures:** ADAS-Noncog; ADAS total score; MMSE; caregiver-rated CGIC; PDS **Timing of assessments:** Weeks 4, 6, 10 and 12		
RESULTS:	**Health Outcome Measures:** • Significantly better PDS score only for TAC 40 mg/d compared to placebo (P = 0.046) **Intermediate Outcome Measures: (observed cases)** • Significant improvement in ADAS-Cog and CGIC at 12 weeks for TAC compared to placebo only for 80 mg/d (P = 0.015 for both)* • No significant differences in ADAS-Noncog or MMSE at 12 weeks • Significantly greater improvement in ADAS total score only for 80 mg/d TAC (P = 0.029) • Significantly greater improvement in caregiver-rated CGIC for TAC 40 mg/d and 80 mg/d compared to placebo (P = 0.034 and P = 0.028, respectively)		

Authors: Farlow et al. **Year: 1992**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Elevated transaminases • Nausea/Vomiting • Diarrhea	**<u>tacrine 20, 40, 80 mg/d</u>** 51% (mean treatment-related) 19.8%; 19.8%; 11.7% 4.7%; 5.9%; 11.7% 3.4%; 3.2%; 10%	**<u>placebo</u>** 34% (treatment-related) 1.9% 3.2% 3.2%	
Significant differences in adverse events:	Significance NR, although clearly significant differences in adverse events noted above		
ANALYSIS:	**ITT:** No; ITT results available upon request and "generally" consistent **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Unable to assess method of randomization; groups adequately balanced		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 41.7% (not included in analysis) **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**<u>tacrine</u>** NR 25%	**<u>placebo</u>** NR 7%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors and year: Feldman et al. 2001 [39]; Gauthier et al. 2002 [80]; Gauthier et al. 2002 [81]; Feldman et al. 2003 [82]** **Country:** Multinational (Canada, Australia, France)		
FUNDING:	Eisai, Inc. and Pfizer, Inc.		
RESEARCH OBJECTIVE:	To examine the efficacy and safety of DON in patients with moderate to severe AD; subgroup analyses focus on behavioral symptoms and patients with moderate severity		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (32) **Sample size:** 290		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil** 5-10 mg/d 24 weeks 144	**placebo** N/A 24 weeks 146	
INCLUSION:	All of the following criteria: probable or possible AD according to DSM-IV and the NINCDS; a screening standardized MMSE score of 5-17; Functional Assessment Staging Test of ≤ 6 at baseline; ambulatory; CT or MRI scan within past 24 months consistent with AD		
EXCLUSION:	Patients requiring total nursing care; evidence of other cause of dementia; complicating delirium, depression, or other concurrent diagnosis that might interfere with study participation; history of drug or alcohol misuse; hypersensitivity to AChE inhibitors; significant COPD, asthma, hematologic or oncologic disorders; B_{12} or folate deficiency; active GI, renal, hepatic, endocrine, or cardiovascular system disease		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Most concomitant medications were allowed except for those with anticholinergic effects and investigational drugs		

<table>
<tr><td colspan="4">Authors: Feldman et al.
Year: 2001</td></tr>
<tr><td rowspan="4">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Moderate-Severe</td></tr>
<tr><td></td><td><u>donepezil</u></td><td><u>placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>73.3</td><td>74.0</td></tr>
<tr><td>Sex (% female):</td><td>61.1</td><td>61.0</td></tr>
<tr><td>Other germane population qualities:
• Mean baseline sMMSE score</td><td>11.72</td><td>11.97</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: CIBIC-plus

Secondary Outcome Measures: sMMSE; SIB; DAD; ADL; IADL; modified IADL (IADL+); PSMS+; NPI; FRS; CSS; Caregiver SF-36; CAUST

Timing of assessments: Baseline and weeks 4, 8, 12, 18 and 24</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• DON-treated patients had a significantly slower decline of measures of daily functioning than placebo-treated patients; differences were +6.83 (P < 0.001) in IADL, +1.32 (P = 0.0015) in PSMS, and 8.24 in DAD (P<0.0001) at week 24
• Behavioral and neuropsychiatric symptoms, as measured by NPI 12 item, showed significant differences in favor of DON (mean difference = 6.64 at 24 weeks); significant differences in favor of DON were found in depression/dysphoria (P = 0.0166), anxiety (P = 0.0128), and apathy/indifference (P = 0.0018)

Intermediate Outcome Measures:
• There were significant differences in favor of DON in the CIBIC-plus scores at all visits (mean difference = 0.54 at 24 weeks); at 24 weeks 63% of DON and 42% of placebo were rated as improved or no decline (P < 0.0001)*
• There were significant mean improvements in favor of DON on both the sMMSE and SIB (mean difference = 1.79 on sMMSE (P < 0.0001); mean difference = 5.62 on SIB (P < 0.0001))</td></tr>
</table>

Authors: Feldman et al. **Year: 2001**			
RESULTS:	**Intermediate Outcome Measures (Cont'd.):** • Stabilization of global function, as measured by FRS, showed significant differences in favor of DON (mean difference = 1.28 at 24 weeks; P = 0.0002) • A subgroup analysis of patients with moderate AD (MMSE 10-17) presented significant drug-placebo differences in CIBIC-plus scores (mean treatment difference = 0.53, P = 0.0003); improvement in MMSE and SIB (mean treatment difference = 2.06, -4.44; P = 0.0002, 0.0026); improvement on IADL+ and PSMS (P = 0.0002, 0.001)		
ADVERSE EVENTS: **Overall adverse effects reported:** • Diarrhea • Headache • Respiratory tract infection	**donepezil** 83% 12.5% 11.8% 11.1%	**placebo** 80% 4.8% 4.1% 11.1%	
Significant differences in adverse events:	Significance not reported; mild, moderate, and severe AEs were similar between treatment groups		
ANALYSIS:	**ITT:** ITT/LOCF **Post randomization exclusions:** Unable to determine		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes (identical appearing blister packs)		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 14.8 % **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**donepezil** 16.0% 8%	**placebo** 13.7% 6%	
QUALITY RATING:	**Good**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Homma et al.** [40] **Year: 2000** **Country:** Japan		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To evaluate efficacy and safety of DON at 5 mg/d in patients with mild to moderate AD over 24 weeks		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (54) **Sample size:** 268		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil** 5 mg/d 24 weeks 116	**placebo** N/A 24 weeks 112	
INCLUSION:	Outpatients diagnosed as having AD by the diagnostic criteria of DSM-IV; CDR of (1) mild or (2) moderate; MMSE score of 10-26 points; ADAS-J-Cog score of at least 15 points		
EXCLUSION:	Patients with neurological signs such as parkinsonism; patients with definite symptoms of depression, and patients with old had trauma associated with disturbances of consciousness; patients with visual or hearing impairment or with aphasia who could not undergo the cognitive performance test and patients with no caregivers to provide assistance in outpatient examinations; patients with serious complications; patients with peptic ulcers		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concomitant use of choline activators, anticholinergics, cerebral vasodilators, activators of cerebral metabolism, psychotropic drugs, hypnotics, antiparkinsonism agents, and nonsteroidal anti-inflammatory drugs was prohibited; initiation of rehabilitation was prohibited but patients could continue existing rehabilitation		

Authors: Homma et al. **Year: 2000**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Alzheimer classification:** Mild-moderate		
	donepezil	**placebo**	
Mean age (years):	70.1	69.4	
Sex (% female):	68	66	
Ethnicity (% Japanese):	100	100	
Other germane population qualities:			
• CDR 1,2	68%, 32%	62%, 38%	
• Mean baseline MMSE	17.8	16.6	
• Mean ADAS-J-Cog	22.91	26.90	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ADAS-J-Cog; J-CGIC **Secondary Outcome Measures:** CDR-SB; MENFIS; CMCS **Timing of assessments:** Baseline and every 4 weeks		
RESULTS:	**Health Outcome Measures:** • Significantly more improvement in CMCS for DON-treated patients (P=0.01) at endpoint **Intermediate Outcome Measures:** • DON was significantly better than placebo on ADAS-J-Cog (P = 0.003) and J-CGIC (P < 0.001)* • Significantly more improvement in CDR-SB for DON-treated patients (P < 0.001) at endpoint • Significantly more improvement in MENFIS for DON-treated patients (P = 0.004) at endpoint		

Authors: Homma et al. **Year: 2000**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Cold syndrome	**donepezil** 40% (at least 3 incidences/event) 7%	**placebo** 25% (at least 3 incidences/event) 2%	
Significant differences in adverse events:	Cold syndrome was reported more frequently in DON-treated patients ($P < 0.05$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (5)		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 15% **Loss to follow-up differential high:** Unable to assess		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**donepezil** NR 1%	**placebo** NR 5%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Jones et al.** [28] **Year: 2004** **Country:** Multinational (UK, Finland, Germany, Norway)		
FUNDING:	Eisai Inc., Pfizer Inc.		
RESEARCH OBJECTIVE:	To directly compare the effectiveness and tolerability of DON and GAL in the treatment of AD and investigate effects of both treatments on cognition and activities of daily living		
DESIGN:	**Study design:** RCT (open-label) **Setting:** Multi-center (14 centers) **Sample size:** 120		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil** 5-10 mg once daily 12 weeks 64	**galantamine** 4-12 mg twice daily 12 weeks 56	
INCLUSION:	At least 50 years of age diagnosed with probable or possible mild to moderate AD consistent with NINCDS/ADRDA and DSM-IV criteria; MMSE score at screening within range 10-24 inclusive; results of CT or MRI scan within past 18 months consistent with AD diagnosis; availability of caregiver to provide information on patient's status and ensure compliance		
EXCLUSION:	Previous treatment with ChE inhibitor or with known hypersensitivity to ChE inhibitors; clinically significant obstructive pulmonary disease, asthma, gastrointestinal, endocrine, or cardiovascular disease; known sensitivity to piperidine or alkaloid derivatives or any investigational drug therapy within 30 days of screening visit; medications with pronounced anticholinergic effects such as drugs used for Parkinson's disease, neuroleptics, or tricyclic antidepressants within 1 month of study entry		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Jones et al.
Year: 2004</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:

Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• Mean age onset AD diagnosis
• Months since diagnosis (median)</td><td colspan="3">Groups similar at baseline: No (gender distribution differed significantly)
Alzheimer classification: Mild-moderate</td></tr>
<tr><td><u>donepezil</u>
73.8
51.6
NR

73.5
3.1</td><td><u>galantamine</u>
75.1
71.4
NR

74.6
3.2</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Physician’s and Caregiver’s Satisfaction Questionnaires (developed by Pfizer and Eisai)

Secondary Outcome Measures: ADAS-Cog 11; ADAS-Cog 13; MMSE; DAD (40-item)

Timing of assessments: Weeks 4, 8 and 12; cognitive assessments at screening, weeks 4, 8 and 12</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• DON-treated patients had significantly better physician and caregiver satisfaction scores at endpoint ($P < 0.01$).
• Significantly greater improvement of DAD scores for DON than GAL- treated patients ($P < 0.05$) at endpoint
Intermediate Outcome Measures:
• At endpoint DON-treated patients had significantly greater improvements on ADAS-Cog 11 ($P < 0.05$) and ADAS-Cog 13 ($P < 0.05$) than GAL-treated patients
• Significantly better MMSE scores for DON-treated patients at endpoint ($P < 0.05$)
• Significantly more DON than GAL-treated patients had a substantial response (i.e., ≥ 7 points; 28.3% vs. 11.5%; $P < 0.029$) or a good response (i.e., ≥ 4 points; 53.3% vs. 28.8%; $P < 0.009$)</td></tr>
</table>

Authors: Jones et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea • Diarrhea • Anorexia • Vomiting • Headache • UTI • Dizziness	**donepezil** 67.2% 15.6% 9.4% 4.7% 0.0% 6.3% 3.1% 1.6%	**galantamine** 73.2% 23.2% 14.3% 8.9% 12.5% 5.4% 7.1% 5.4%	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Open-label; only cognitive assessments were implemented by independent raters who were blinded to patient assignment;		
ATTRITION (*overall*):	**Overall loss to follow-up:** 6.7% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**donepezil** 4.7% 4.7%	**galantamine** 8.9% 7.1%	
QUALITY RATING:	**N/A**		

*primary outcome measures

Efficacy/Effectiveness ***Alzheimer Drugs***

STUDY:	**Authors: Lanctot et al.** [30] **Year: 2003** **Country:** Canada
FUNDING:	NR; several authors have received speaker fees or honoraria from pharmaceutical companies; two authors are employed by pharmaceutical companies
DESIGN:	**Study design:** Meta analysis of placebo-controlled trials **Number of patients:** 7,954
AIMS OF REVIEW:	To quantitatively summarize data on the efficacy and safety of ChE inhibitors in AD
STUDIES INCLUDED IN META-ANALYSIS	Rogers 1996; Rogers 1998a; Rogers 1998b; Burns 1999; Winblad 2001; Homma 2000; Mohs 2001; Feldman 2001; Agid 1998; Rösler 1999; Corey-Bloom 1998; Raskind 2000; Wilcock 2000; Tariot 2000; Rockwood 2001; Wilkinson
TIME PERIOD COVERED:	Studies published through May, 2002
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs of currently marketed ChE inhibitors (DON, GAL, and RIV) used in therapeutic doses for at least 12 weeks; a cognitive outcome was measured (and reported) on any validated scale
CHARACTERISTICS OF INCLUDED POPULATIONS:	AD diagnosed on basis of DSM-IV or NINCDS; therapeutic doses for at least 12 weeks of any available second-generation ChE inhibitors; cognitive measure must have been measured; original reports of RCTs

Authors: Lanctot et al. **Year: 2003**	
CHARACTERISTICS OF INTERVENTIONS:	DON 1-10 mg/d given for 12-54 weeks; RIV 1-12 mg/d given for 13-26 weeks; GAL 8-36 mg/d given for 3-6 months; outcome measures included CGIC; CIBIC; ADAS-Cog, MMSE, NPI, DAD, FRS, PDS, unspecified QOL scale, IDDD; global response defined as improved on a global assessment scale (CGIC or CIBIC plus) and cognitive responders were defined as subjects with a 4-point or greater improvement in ADAS-Cog
MAIN RESULTS:	Global responders extracted from 9 studies: pooled mean proportion of global responders to ChE inhibitor treatment in excess of that for placebo treatment was 9% (95% CI: 6% – 10%) excluding one study because of heterogeneity; proportion of cognitive responders could be extracted from 5 studies: pooled mean proportion of cognitive responders to ChE inhibitor treatment in excess of that for placebo treatment was 10% (95% CI: 4% – 17%)
ADVERSE EVENTS:	Compared with those receiving placebo, significantly more subjects receiving ChE inhibitor treatment had adverse advents (8%) (95% CI: 5% – 11%), dropped out (8%) (95% CI: 5% – 11%) and dropped out because of adverse events (7%) (95% CI: 3% – 10%)
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	MEDLINE and EMBASE searches from January 1980 to May 2002; key words ChE inhibitor and AD, and the limits were RCT, English and human; Cochrane library also searched
STANDARD METHOD OF APPRAISAL OF STUDIES:	Trials included if they were randomized, double-blind, placebo-controlled, parallel group studies and if patients satisfied inclusion criteria; study quality rated on Jadad scale but quality was not identified as an exclusion criteria; no other methods were discussed as to how trials were evaluated to be included in the meta analysis
QUALITY RATING:	**Good**

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Mohs et al.** [41] **Year: 2001** **Country:** USA		
FUNDING:	Eisai, Inc. and Pfizer, Inc.		
RESEARCH OBJECTIVE:	To examine the effects of DON compared to placebo on the preservation of function in patients with AD over a 1-year period		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (31) **Sample size:** 431		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil** 10 mg/d (28 day escalation) 54 weeks 214	**placebo** N/A 54 weeks 217	
INCLUSION:	Probable AD according to DSM-IV and the NINCDS; a MMSE score of 12-20; CDR score of 1 (mild) or 2 (moderate); MHIS ≤ 4 at both screening and baseline; protocol amendment allowed patients to enroll with MMSE scores of 21 at baseline if their scores at screening were 20; subjects were also required to be able to perform 8 of 10 instrumental ADL (each score ≤ 2) on the ADFACS at both screening and baseline		
EXCLUSION:	Evidence of stroke; Parkinson's Disease; schizophrenia; dementia complicated by other organic disease; delirium; depression; AD with significant delusions; history of alcoholism or drug misuse; hypersensitivity to ChE inhibitors; use of any investigational drug or TAC within 1 month of screening; concomitant use of anticholinergics, cholinomimetics, tricyclic antidepressants, antiparkinsonian agents, and neuroleptics were not permitted; no reliable caregiver		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Vitamin E; Gingko biloba; NSAIDs; and estrogens		

<table>
<tr><td colspan="4">Authors: Mohs et al.
Year: 2001</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild-moderate</td></tr>
<tr><td></td><td><u>donepezil</u></td><td><u>placebo</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>75.4</td><td>75.3</td><td></td></tr>
<tr><td>Sex (% female):</td><td>61.3</td><td>64.5</td><td></td></tr>
<tr><td>Ethnicity:</td><td></td><td></td><td></td></tr>
<tr><td>• White</td><td>94.9%</td><td>89.4%</td><td></td></tr>
<tr><td>• Black</td><td>0.9%</td><td>4.6%</td><td></td></tr>
<tr><td>• Other</td><td>4.2%</td><td>6.0%</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Baseline MMSE score</td><td>17.1</td><td>17.1</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADFACS; CDR
Clinically evident <u>functional</u> decline, defined as any of the following:
1) Decline <u>≥</u> 1 point on ADFACS basic ADLs present at baseline, except that a decline from 0 (no impairment) to 1 (mild impairment) was not considered clinically significant
2) Decline in ability to perform 20% or more of ADFAC instrumental ADLs; a decline from 0 (no impairment) to 1 (mild impairment) was not considered clinically significant but other declines of one or more were
3) Increase in global CDR score <u>≥</u> 1 point compared to baseline

Secondary Outcome Measures: ADL; CDR; MMSE

Timing of assessments: Baseline and weeks 6, 12, 18, 24, 30, 36, 42 and 48</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Higher proportion of placebo patients (56%, n = 116 of ITT population) compared with DON patients (41%, n = 84) met criteria for clinically evident functional decline (P < 0.005)*
• Median time (in days) to clinically evident functional decline was shorter in placebo group (208 days) compared to DON (357 days)*
• No difference in adjusted mean change from baseline scores on ADFACS at endpoint*</td></tr>
</table>

Authors: Mohs et al. **Year: 2001**			
RESULTS:	**Intermediate Outcome Measures:** • Differences in mean change from baseline to endpoint for DON differed from placebo for both instrumental ADL (P = 0.001) and basic ADL (P = 0.007) • No significant differences in CDR-SB or MMSE scores at endpoint, although significant differences in favor of DON were observed at weeks 6, 18, 24, 36 and 42		
ADVERSE EVENTS: **Overall adverse effects reported:** • Diarrhea • Agitation • Rhinitis • UTI	**donepezil** NR 17% 12% 13% 12%	**placebo** NR 5% 10% 7% 7%	
Significant differences in adverse events:	Frequency of adverse event was significantly higher in DON compared to placebo for headache, UTI, and those associated with digestive systems (anorexia, diarrhea, dyspepsia, nausea)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes; 5.1% placebo and 6.5% DON		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Method NR		
BLINDING OF OUTCOME ASSESSORS:	Yes, but method NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 27% **Loss to follow-up differential high:** Yes but inherent differential in study design		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**donepezil** 28% 10.7%	**placebo** 26% 7.4%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness ***Alzheimer Drugs***

STUDY:	**Authors: Olin et al.**[33] **Year: 2002** **Country:** Multinational
FUNDING:	NIMH; NIA; NIMH Clinical Antipsychotic Trials of Interventions Effectiveness
DESIGN:	**Study design:** Meta-analysis **Number of patients:** Seven trials with the number of participants ranging from 95 - 978
AIMS OF REVIEW:	To assess the clinical effects of GAL in patients with probable AD, and to assess possible moderators of an effect.
STUDIES INCLUDED IN META-ANALYSIS	A total of 7 placebo-controlled RCT studies were included, 6 of which were Phase II or III industry-sponsored multi-center trials: Wilkinson et al. 2001; GAL Investigator's Brochure; Wilcock 2000; Rockwood et al. 2001; Raskind et al. 2000; Tariot et al. 2000; and Kewitt et al. 1994
TIME PERIOD COVERED:	Trials completed before May 15, 2002 included in the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group.
CHARACTERISTICS OF INCLUDED STUDIES:	Double-blind, parallel-group, placebo-controlled with randomized and unconfounded treatment assignment to placebo or GAL; other inclusion criteria: sample selection criteria, outcome instruments or duration specified; most of the trials of acceptable methodological quality having been designed as Phase II or III clinical trials; five trials had quality ratings of 'A,' the remainder had quality ratings of B because randomization schemes were not reported
CHARACTERISTICS OF INCLUDED POPULATIONS:	Elderly patients who met criteria for NINCDS/ADRDA 'probable AD' or DSM-III-R primary degenerative dementia of the Alzheimer's type

Authors: Olin et al. **Year: 2004**	
CHARACTERISTICS OF INTERVENTIONS:	Any oral dose of GAL versus placebo for a duration greater than 4 weeks; outcome measures included ADAS-Cog, CIBIC-plus, ADCS-CGIC, ADCS-ADL, DAD, and NPI)
MAIN RESULTS:	• **Global Rating Scales** (CIBIC-plus k = 2; ADCS-CGIC k = 4; unspecified physician global rating k = 1) Data were dichotomized into those that had no change or improvement versus those that worsened; for ITT analyses trials of 3 months duration, doses of 18 mg/d (OR 2.44; 95% CI: 1.2 – 5.0), 24 mg/d (OR 2.11; 95% CI: 1.0 – 4.6) and 36 mg/d (OR 2.7; 95% CI: 1.2 – 6.2) revealed statistically significant benefit of GAL versus placebo; for trials of 6 months duration, 8 mg/d failed to have an effect whereas other doses demonstrated significant benefit of GAL over placebo (16mg: OR 2.04; 95% CI: 1.4 – 2.9; 24mg: OR 1.82; 95% CI: 1.4 – 2.3; 32 mg: OR 1.79; 95% CI: 1.3 – 2.4); no apparent dose-response relationship between GAL and global rating • **Cognitive tests (ADAS-Cog)** ITT analyses of 6 months data revealed statistically significant benefit of GAL over placebo (8 mg: WMD -1.3; 95% CI: -2.6 – 0.03; 16 mg WMD -3.1; 95% CI: -4.1 – -2.1; 24 mg WMD -3.3; 95% CI: -3.9 – -2.7; 32 mg WMD -3.3; 95% CI: -4.1 – -2.4); the two 3 month trials also show significant benefit of GAL over placebo • **Activities of Daily Living (ADCS-ADL, DAD**) One trial provided data using the ADCS-ADL scale; observed case analysis revealed statistically significant benefits of GAL (16 mg: WMD -3.5; 95% CI: -5.2 – -1.8; 24 mg: WMD -2.4; 95% CI: -4.1 – -0.07); ITT results revealed statistically significant benefit of GAL (MD = NR; OR = NR; P = NR) Two trials provided data using DAD; in one 3 month trial, ITT results revealed statistically significant benefit of GAL (32mg: WMD 4.8; 95% CI: 2.0 – 7.5); in the 6 month trial, ITT results revealed statistically significant benefit of GAL (32 mg: WMD 3.5; 95% CI: 0.5 – 6.5) • **Behavior (NPI)** Two trials provided data using the NPI; observed case analysis revealed statistically significant benefits of GAL (16 mg: WMD -2.4; 95% CI: -4.5 – -1.3; 24 mg: WMD -2.4; 95% CI: -4.6 – -0.01); ITT results revealed statistically significant benefit of GAL (MD = NR; OR = NR; P = NR)

Authors: Olin et al. **Year: 2004**	
ADVERSE EVENTS:	Three 6-month studies reported those adverse events appearing at least 5% of the time occurred more frequently in GAL versus placebo; the proportion of subjects with those adverse events was analyzed; OR >1 indicates greater adverse events for GAL; adverse events recorded (in order of magnitude of the greatest effect size by daily dose): tremor, anorexia, vomiting, nausea, weight loss, headache, abdominal pain diarrhea, dizziness, and agitation; at 8 mg/d, the differences between GAL and placebo were not significant; at 16 mg/d nausea, vomiting, and diarrhea were statistically more frequent in GAL (P = NR); at 24 mg/d nausea, vomiting, dizziness, weight loss, anorexia, tremor and headache were statistically more frequent in GAL (P = NR); at 32 mg/d nausea, vomiting, dizziness, weight loss, anorexia, abdominal pain, tremor, and headache were statistically more frequent in GAL
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Refers to Cochrane Dementia and Cognitive Improvement Group search strategy; trials were selected from the Trial-based Specialized Register of the Cochrane Dementia and Cognitive Improvement Group, containing records from a number of published and unpublished electronic databases (e.g., MEDLINE, CCTR/Central, EMBASE)
STANDARD METHOD OF APPRAISAL OF STUDIES:	Cochrane Collaboration guidelines (Mulrow 1997)
QUALITY RATING:	**Good**

Efficacy/Effectiveness ***Alzheimer Drugs***

STUDY:	**Authors: Qizilbash et al.** [35] **Year: 1998** **Country:** NR
FUNDING:	Some authors were supported by Parke-Davis and SmithKline Beecham
DESIGN:	**Study design:** Meta-analysis of individual patient data **Number of patients:** 1,984
AIMS OF REVIEW:	To determine the effects of TAC on the symptoms of AD in terms of cognitive performance, clinical global impression, behavior, and functional autonomy
STUDIES INCLUDED IN META-ANALYSIS	A total of 12 published and unpublished studies identified from the Cochrane registry; 6 crossover studies and 6 parallel group designs
TIME PERIOD COVERED:	Trials completed before January 1, 1996
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized, double-blind, placebo-controlled trials in which TAC had been given for more than 1 day; treatment comparisons of TAC vs. placebo or TAC plus lecithin vs. lecithin were considered
CHARACTERISTICS OF INCLUDED POPULATIONS:	All patients were diagnosed as having “probable” AD according to NINCDS/ADRDA criteria

Authors: Qizilbash et al. **Year: 1998**	
CHARACTERISTICS OF INTERVENTIONS:	The trials involved dosages varying from 20 to 160 mg/d, varying duration of treatment (3-36 wks), and varying times and frequencies of assessment; two studies contained more than 1 TAC group with fixed dosage regimens; in 3 of the remaining 10 studies, patients were given their "best dose" based on pre-randomization dose titration, and in the other 7 studies, patients were titrated to their best does by the clinician after randomization, giving possible maximum dosages between 80 and 120 mg/d
MAIN RESULTS:	• In pooled ITT analysis for MMSE scores at 12 weeks, there was a 0.62 point difference in favor of TAC relative to placebo (95% CI: 0.23 – 1.00; P = 0.002) • The CGIC and CIBI revealed an improvement for TAC compared to placebo: OR 1.58; 95% CI: 1.18 – 2.11; P = 0.002) • ADAS-Noncog used as a measure of behavioral disturbance showed a 0.58 difference in favor of TAC at 12 weeks (95% CI: 0.17 – 1.00; P = 0.006) • The PDS, used in 4 studies, did not differ significantly at 6 weeks between treatment and control (difference = 0.75; 95% CI: -0.43 – 1.93; P = 0.21)
ADVERSE EVENTS:	In 5 studies with no dose titration phase prior to the main efficacy phase patients receiving TAC were significantly more likely to withdraw (OR for withdrawal from TAC compared with placebo was 3.63; 95% CI: 2.80 – 4.71; P < 0.001); reason for withdrawal was not available for all patients, but in two studies elevated transaminase levels was given as the main reason (NNT for withdrawal = 4)
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Studies were identified from the Cochrane Dementia Group database of trials by searching the terms TAC and tetrahydroaminoacridine
STANDARD METHOD OF APPRAISAL OF STUDIES:	NR
QUALITY RATING:	**Fair**

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Raskind et al.** [47] **Year: 2000** **Country:** US		
FUNDING:	Janssen Research Foundation		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of two doses of galantamine compared with placebo over 6 months in patients with mild to moderate AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (33 sites) **Sample size:** 636		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**galantamine** 24 or 32 mg/d 6 months 212/211 (423 total)	**placebo** N/A 6 months 213	
INCLUSION:	History of cognitive decline that had been gradual in onset and progressive over a period of at least 6 months; diagnosis of probable AD according to the criteria of the NINCDS-ARDA; presence of mild to moderate dementia; MMSE score of 11 to 24 and a score of ≥ 12 on the standard cognitive subscale of the ADAS-Cog; responsible caregiver		
EXCLUSION:	Patients with evidence of any neurodegenerative disorders other than AD; cardiovascular disease thought likely to prevent completion of the study; clinically significant CVD; active major psychiatric disorders; hepatic, renal, pulmonary, metabolic or endocrine conditions or urinary outflow obstruction; active peptic ulcer; any history of epilepsy, drug abuse, or alcohol abuse; treatment for AD with a ChE inhibitor in the preceding 3 months		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	All drugs except sedative-hypnotics and sedating cough and cold remedies, which were discontinued, if possible, 48 hours before the cognitive evaluation; anticholinergic and cholinomimetic drugs avoided		

<table>
<tr><td colspan="4">Authors: Raskind et al.
Year: 2000</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild-moderate</td></tr>
<tr><td></td><td><u>galantamine 24 mg/d</u></td><td><u>galantamine 32 mg/d</u></td><td><u>placebo</u></td></tr>
<tr><td></td><td>Mean age (years):
Sex (% female):
Ethnicity (% white):
Other germane population qualities:
• Other medical conditions
• MMSE score</td><td>75.9
65.6
92

94.3%
19.5</td><td>75.0
58.8
90

91.9%
19.1</td><td>75.3
61.5
92

95.3%
19.2</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADAS-Cog 11; CIBIC-plus

Secondary Outcome Measures: ADAS-Cog 13; ADAS-Cog 11 responders (≥ 4 point improvement); DAD

Timing of assessments: Baseline and 3 weeks, 3 months, 6 months</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No significant differences between treatment groups in the mean change in total DAD score from baseline

Intermediate Outcome Measures:
• ADAS-Cog 13: NR
• GAL-treated patients showed significantly improved cognitive function relative to placebo (3.9 pts (lower dose) and 3.8 (higher dose) on the ADAS-Cog 11 (P < 0.001) for observed cases analysis); ITT analysis also was significant but showed smaller differences 0.1 pts (lower dose) and 3.4 pts (higher dose) difference relative to placebo
• Significantly more ADAS-Cog 11 responders for both doses of GAL compared to placebo (P < 0.001)
• Better outcome on CIBIC-plus than placebo (P < 0.05)</td></tr>
</table>

Authors: Raskind et al. **Year: 2000**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea • Vomiting • Dizziness • Diarrhea • Anorexia • Weight loss • Abdominal pain	**galantamine 24 mg/d** 92.0% 37.3% 20.8% 13.7% 12.3% 13.7% 12.3% 6.6%	**galantamine 32 mg/d** 92.4% 43.6% 25.6% 18.5% 19.4% 20.4% 10.9% 10.9%	**placebo** 78.9% 13.1% 7.5% 11.3% 9.9% 5.6% 4.7% 4.2%
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 31.1% **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**galantamine 24 mg/d** 32.1% 23.1%	**galantamine 32 mg/d** 42.2% 31.8%	**placebo** 19.2% 7.5%
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Author and Year: Reisberg et al. 2003 [56]; Rive et al. 2004 [83]** **Country:** US		
FUNDING:	Merz Pharmaceuticals; NIH		
RESEARCH OBJECTIVE:	To assess the efficacy of MEM in outpatients with moderate to severe AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (32) **Sample size:** 252		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**memantine** 20 mg/d 28 weeks 126	**placebo** N/A 28 weeks 126	
INCLUSION:	Probable AD according to DSM-IV and NINCDS/ARDA criteria; baseline MMSE scores of 3 - 14; stage of 5 or 6 on the GDS; stage of 6a or greater on the Functional Assessment Staging Instrument; reliable caregivers; CT or MRI of the brain within previous 12 months		
EXCLUSION:	VaD; clinically significant neurological or medical diseases; clinically significant co-existing medical conditions		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Antidepressive treatment and chloral hydrate allowed; anticonvulsant, antiparkinson, hypnotic, anxiolytic, and neuroleptic agents not allowed		

Authors and Year: Reisberg et al. 2003; Rive et al. 2004			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Alzheimer classification:** Moderate-severe		
	memantine	**placebo**	**total**
Mean age (years):	NR	NR	76.1
Sex (% female):	72	62.7	67.5
Ethnicity:			
• **White**	88.9%	91.3%	90.0%
• **Black**	4.0%	4.8%	4.4%
• **Other**	7.1%	3.9%	5.6%
Other germane population qualities:			
• MMSE score	NR	NR	7.9
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** CIBIC-Plus; ADCS-ADL modified for severe dementia (ADCS-ADLsev) **Secondary Outcome Measures:** SIB; MMSE; GDS; FAST; NPI; Resource Utilization in Dementia **Timing of assessments:** Baseline and weeks 12 and 28		
RESULTS:	**Health Outcome Measures:** • MEM patients had significantly less deterioration on ADCS/ADL (difference 2.1; P = 0.02) • Caregivers spent significantly less time (45.8 hours/mo) with patients receiving MEM (P = 0.01) • FAST (P = 0.02) was significantly less deteriorated for MEM patients • No significant differences in NPI **Intermediate Outcome Measures:** • No significant differences in GDS between placebo- and MEM-treated patients • MEM was not significantly different from placebo on the CIBIC-PLUS (difference 0.3; P = 0.06)* • SIB (P = 0.002) was significantly less deteriorated for MEM patients • No significant differences in MMSE		
ADVERSE EVENTS:	**memantine**	**placebo**	
Overall adverse effects reported:	84%	87%	
• Agitation	18%	32%	
• Insomnia	10%	8%	
• Diarrhea	10%	8%	
Significant differences in adverse events:	No significant differences in adverse events		

Authors and Year: Reisberg et al. 2003; Rive et al. 2004			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Method not reported		
ATTRITION (*overall*):	**Overall loss to follow-up:** 28.2% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**memantine**	**placebo**	
Loss to follow-up:	23.0%	33.3%	
Withdrawals due to adverse events:	10%	17%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors and Year: Rockwood et al. 2001[48]; Markowitz et al. 2003[59]** **Country:** Multinational		
FUNDING:	Janssen Research Foundation		
RESEARCH OBJECTIVE:	To assess the efficacy and safety of GAL in AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (43 centers in 6 countries) **Sample size:** 386		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**galantamine** 24 – 32 mg/d 3 months 261	**placebo** N/A 3 months 125	
INCLUSION:	History of cognitive decline over the last 6 months; diagnosis of probable AD according to NINCDS/ADRDA; presence of mild to moderate dementia; MMSE of 11- 24; $\geq$ 2 on ADAS-Cog; contact with a responsible caregiver		
EXCLUSION:	Concomitant medical disease; other neurodegenerative disorder; previously treated with cholinomimetic agents except muscarinic agonists		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	All drugs except anticholinergic or cholinomimetic drugs were permitted; psychotropic drugs had to be discontinued 48 hours before cognitive evaluation		

<table>
<tr><td colspan="4">Authors and Year: Rockwood et al. 2001; Markowitz et al. 2003</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:

Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• Other medical conditions
• MMSE score</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild-moderate</td></tr>
<tr><td><u>galantamine</u>
75.2
56.7
NR

90.0%
19.6</td><td><u>placebo</u>
74.6
53.6
NR

89.6%
19.7</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADAS-Cog 11; CIBIC-plus

Secondary Outcome Measures: ADAS-Cog 13; ADAS-Cog 11 responders (≥ 4 point improvement); NPI; DAD; PSQI; NPI sleep score

Timing of assessments: Baseline and months 1 and 3</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Activities of daily living were significantly better in GAL group than in placebo group (DAD score: +4.3 points; P = 0.004)
• No significant differences in sleep quality between groups (PSQI: P = 0.929; NPI sleep score: P = 0.929)
• No significant differences in behavioral symptoms between GAL and placebo (NPI mean change)

Intermediate Outcome Measures:
• GAL-treated patients showed significantly superior cognitive functions compared to placebo (ADAS-Cog 11: +1.6 points; P < 0.001; ADAS-Cog 13: P = 0.004)*
• Overall clinical response was significantly better in GAL group than in placebo group (CIBIC-plus: P = 0.003)*
• No significant differences in the number of ADAS-Cog 11 responders for ITT analysis; significantly more responders for observed cases analysis (P = 0.02)</td></tr>
</table>

Authors and Year: Rockwood et al. 2001; Markowitz et al. 2003			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea • Vomiting • Dizziness • Anorexia	**galantamine** 86.2% 32.2% 14.6% 14.9% 11.9%	**placebo** 63.2% 11.2% 4.0% 4.0% 2.4%	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (4)		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 25% **Loss to follow-up differential high:** Yes (23.3 percentage point difference)		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**galantamine** 32.9% 25.3%	**placebo** 9.6% 4.0%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness ***Alzheimer Drugs***

STUDY:	**Authors: Rogers et al.** [44] **Year: 1996** **Country:** USA			
FUNDING:	Eisai America, Inc., Teaneck, NJ, USA and Eisai Co Ltd., Tokyo, Japan			
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of DON in patients with mild to moderately severe AD and to examine the relationships between plasma DON concentration, red blood cell AChE activity and clinical response			
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size:** 161			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil** 1 mg 12 weeks 42	**donepezil** 3 mg 12 weeks 40	**donepezil** 5 mg 12 weeks 39	**placebo** N/A 12 weeks 40
INCLUSION:	Male and female subjects ages 55-85 with established diagnosis of mild to moderately severe AD for at least 1 year prior to study; MMSE between 18 and 26 and CDR of 1 or 2; fully ambulatory or able to walk with assistive device and had vision and hearing sufficient for compliance with test procedures; females at least 2 years post-menopausal or surgically sterile; presence of AD supported by CT or MRI			
EXCLUSION:	Patients with other psychiatric or neurological disorders who had had clinically significant or active gastrointestinal, renal, hepatic, endocrine or cardiovascular diseases or any form of diabetes, obstructive pulmonary disease, hematologic or oncologic disorders of recent onset ($\leq$ 2 years); vitamin B_{12} or folate deficiency; alcohol or drug abuse; hypersensitivity to ChE inhibitor; used investigational drug			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR			

<table>
<tr><td colspan="5">Authors: Rogers et al.
Year: 1996</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="4">Groups similar at baseline: Yes
Alzheimer classification: Mild to moderately severe</td></tr>
<tr><td></td><td><u>donepezil 1mg</u></td><td><u>donepezil 3mg</u></td><td><u>donepezil 5 mg</u></td><td><u>placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>72.6</td><td>71.0</td><td>72.9</td><td>70.6</td></tr>
<tr><td>Sex (% female):</td><td>72.5</td><td>55</td><td>62.5</td><td>52.5</td></tr>
<tr><td>Ethnicity:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>• White</td><td>97.6%</td><td>92.5%</td><td>94.9%</td><td>100%</td></tr>
<tr><td>• Black</td><td>2.4%</td><td>7.5%</td><td>2.6%</td><td>0%</td></tr>
<tr><td>• Other</td><td>0%</td><td>0%</td><td>2.6%</td><td>0%</td></tr>
<tr><td>Other germane population qualities:</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">Primary Outcome Measures: ADAS-Cog; CGIC

Secondary Outcome Measures: ADL; MMSE; CDR-SB; QOL-P (patient); QOL-C (caregiver)

Timing of assessments: Screening visit, baseline, and weeks 1, 3, 6, 9, 12 and 14</td></tr>
<tr><td>RESULTS:</td><td colspan="4">Health Outcome Measures:
• No significant differences between DON and placebo in quality of life (patient and caregiver) and activities of daily living measures

Intermediate Outcome Measures:
• DON 3 mg/d and 5 mg/d treated patients showed statistically significantly better ADAS-Cog scores than placebo-treated patients at endpoint (P = 0.036 and P = 0.002, respectively)*; significant differences observed beginning at week 3
• No significant differences between DON and placebo in CGIC at endpoint*
• No significant differences between DON and placebo on MMSE and CDR-SB</td></tr>
</table>

Authors: Rogers et al. **Year: 1996**				
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea/vomiting • Diarrhea • Dizziness • Nasal congestion • Common cold • Headache • Flushing • Coughing	**donepezil 1mg** 64% 7% 0% 5% 2% 10% 10% 10% 2% 2%	**donepezil 3mg** 68% 0% 3% 3% 13% 5% 5% 3% 10% 3%	**donepezil 5 mg** 67% 10% 10% 8% 5% 5% 3% 3% 3% 10%	**placebo** 65% 5% 3% 10% 8% 5% 8% 3% 5% 3%
Significant differences in adverse events:	NR			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR			
ADEQUATE RANDOMIZATION:	Method not reported but groups well balanced			
ADEQUATE ALLOCATION CONCEALMENT:	Method not reported			
BLINDING OF OUTCOME ASSESSORS:	Yes			
ATTRITION (*overall*):	**Overall loss to follow-up:** 12.4% **Loss to follow-up differential high:** No			
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**donepezil 1mg** 19% 11.9%	**donepezil 3mg** 5% 5%	**donepezil 5 mg** 12.8% 7.7%	**placebo** 12.5% 5%
QUALITY RATING:	**Fair**			

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Rogers et al.** [42] **Year: 1998** **Country:** USA		
FUNDING:	Eisai Inc, Teaneck NJ and Eisai Co Ltd, Tokyo Japan		
RESEARCH OBJECTIVE:	To examine the efficacy and safety of DON in treatment of mild to moderately severe AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (23 clinical centers) **Sample size:** 468		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil 5 mg** 5 mg/d 12 weeks 157	**donepezil 10 mg** 10 mg/d 12 weeks 158	**placebo** N/A 12 weeks 153
INCLUSION:	≥50 yrs old; diagnosis of probable AD consistent with NINCDS and DSM-IV criteria; mild to moderately severe disease based on MMSE scores of 10-26; CDR scores of 1 or 2		
EXCLUSION:	Major medical illness – diabetes, COPD, asthma, hematologic or oncologic disorders; vitamin B_{12} or folate deficiency; gastrointestinal, renal, hepatic, endocrine, or cardiovascular disease; evidence of other psychiatric or neurological disorders; HIS score ≥ 5; known hypersensitivity to ChE inhibitors		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Occasional use of hypnotics and cold preparations allowed; concomitant medications that could affect the central nervous system or interfere with efficacy assessments (anticholinergic, cholinomimetic, anticonvulsant, antidepressant, antipsychotic, antianxiety, stimulating agents, anti-Parkinsonian) and certain antihypertensives were prohibited		

Authors: Rogers et al. **Year: 1998**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Alzheimer classification:** Mild to moderate		
	donepezil 5 mg	**donepezil 10 mg**	**placebo**
Mean age (years):	73.8	73.4	74.0
Sex (% female):	69	61	61
Ethnicity:			
• **White**	95%	96%	96%
• **Black**	4%	1%	4%
• **Other**	1%	3%	0%
Other germane population qualities:			
• Mean baseline MMSE	19.39	19.35	19.8
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ADAS-Cog; CIBIC-plus **Secondary Outcome Measures:** MMSE; CDR-SB; unspecified 7-item QOL scale **Timing of assessments:** Baseline and three week intervals throughout trial		
RESULTS:	**Health Outcome Measures:** • Mean QOL score was significantly better than placebo for DON 10 mg/d (P = 0.02) but not 5 mg/d **Intermediate Outcome Measures:** • Mean change in ADAS-Cog: -2.1 for the 5 mg/d DON group (95% CI: -3.59 – -1.29) and -2.7 for the 10 mg/d DON group (95% CI: -4.22 – -1.92); both were significantly better than the mean change for placebo (0.4, P < 0.001)* • CIBIC-plus was 3.9 for the 5 mg/d DON group and 3.8.for the 10 mg/d DON group; both were significantly better than placebo score of 4.2. (P = 0.003 for 5 mg/d and P = 0.08 for 10 mg/d)* • MMSE significantly better for DON (both doses) compared to placebo (P < 0.004) • No differences in CDR-SB at endpoint		

Authors: Rogers et al. **Year: 1998**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea • Insomnia • Diarrhea • UTI	**donepezil 5 mg** 68% 7% 8% 6% 6%	**donepezil 10 mg** 78% 22% 18% 13% 4%	**placebo** 69% 8% 5% 3% 13%
Significant differences in adverse events:	Nausea, insomnia and diarrhea were significantly more common in patients taking high dose DON than patients taking placebo (P < 0.001); placebo treated patients had significantly more UTI's (P = 0.009)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Method not reported		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 56 (12%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**donepezil 5 mg** 16 (10%) 7 (4%)	**donepezil 10 mg** 29 (18%) 16 (10%)	**placebo** 11 (7%) 3 (2%)
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Rogers et al.** [43] **Year: 1998** **Country:** US		
FUNDING:	Eisai Inc.		
RESEARCH OBJECTIVE:	To study the efficacy and safety of DON for patients with mild to moderate AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (20 sites) **Sample size:** 473		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil** 5 mg/d 24 weeks 154	**donepezil** 10 mg/d 24 weeks 157	**placebo** N/A 24 weeks 162
INCLUSION:	Men and women of any race ≥ 50 yrs old diagnosed with uncomplicated AD; probable AD diagnosed by NINCDS guidelines; MMSE score of 10 – 26; CDR score of 1 or 2		
EXCLUSION:	Patients with evidence of insulin dependent diabetes, mellitus or other endocrine disorders; asthma, obstructive pulmonary disease or clinically significant uncontrolled gastrointestinal, hepatic, or cardiovascular diseases; patients with hypersensitivity to ChE inhibitors or taking TAC within 1 month of baseline were excluded		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concomitant medications such as anticholinergics, anticonvulsants, antidepressants, and antipsychotics were not allowed; drugs with central nervous system activity were either prohibited or partially prohibited; all other drugs allowed		

<table>
<tr><td colspan="4">Authors: Rogers et al.
Year: 1998</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No; mean age of DON 10 mg/d group was 2 years older than placebo (P = 0.03)
Alzheimer classification: Mild-moderate</td></tr>
<tr><td></td><td><u>donepezil 5mg</u></td><td><u>donepezil 10mg</u></td><td><u>placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>72.9</td><td>74.6</td><td>72.6</td></tr>
<tr><td>Sex (% female):</td><td>63</td><td>62</td><td>61</td></tr>
<tr><td>Ethnicity:</td><td></td><td></td><td></td></tr>
<tr><td>• White</td><td>95%</td><td>96%</td><td>94%</td></tr>
<tr><td>• Black</td><td>3%</td><td>2%</td><td>4%</td></tr>
<tr><td>• Other</td><td>2%</td><td>3%</td><td>2%</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Mean baseline MMSE</td><td>19.0</td><td>18.9</td><td>19.2</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADAS-Cog; CIBIC-plus

Secondary Outcome Measures: MMSE; QOL; CDR-SB

Timing of assessments: Baseline and every 6 weeks</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• 5 mg/d DON-treated patients showed significant improvement in QOL score compared to placebo at week-24 (P < 0.05); no statistically significant differences for DON 10 mg/d

Intermediate Outcome Measures:
• 5 mg/d and 10mg/d DON-treated patients had significantly less ADAS-Cog deterioration than placebo at 24 weeks (mean difference of -2.49 and -2.88, respectively; P < 0.0001)*
• 5 mg/d and 10 mg/d DON-treated patients had significantly better CIBIC-plus scores than placebo at 24 weeks (mean difference of 0.36 and 0.44, respectively; P < 0.005)*
• 5 mg/d and 10 mg/d DON-treated patients had significantly better MMSE scores than placebo at 24 weeks (mean difference of 1.21 and 1.36, respectively; P < 0.001)
• 5 mg/d and 10 mg/d DON-treated patients had significantly better CDR-SB scores than placebo at 24 weeks (mean difference of 0.59 and 0.60, respectively; P < 0.001)</td></tr>
</table>

Authors: Rogers et al. **Year:1998**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Fatigue • Diarrhea • Nausea • Vomiting • Muscle cramps • Dizziness	**donepezil 5mg** NR 5% 9% 4% 3% 6% 10%	**donepezil 10mg** NR 8% 17% 17% 10% 7% 8%	**placebo** NR 2% 7% 4% 2% 2% 1%
Significant differences in adverse events:	Yes; DON 10 mg/d had significantly more reports of fatigue, diarrhea, nausea, vomiting and muscle cramps ($P \leq 0.05$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 22% **Loss to follow-up differential high:** No (< 15 percentage point differential)		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**donepezil 5mg** 15% 6%	**donepezil 10mg** 32% 16%	**placebo** 20% 7%
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Rösler et al.** [54] **Year: 1999** **Country:** Europe and North America		
FUNDING:	Novartis Pharma AG, Basle, Switzerland		
RESEARCH OBJECTIVE:	To assess the effects of RIV on the core domains of AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (45 centers in North America and Europe) **Sample size:** 725		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**rivastigmine 1-4 mg/d** 1-4 mg/d 26 weeks 243	**rivastigmine 6-12 mg/d** 6-12 mg/d 26 weeks 243	**placebo** N/A 26 weeks 239
INCLUSION:	50-85 years of age; not able to bear children; met DSM-IV criteria for Alzheimer's type dementia; met criteria for probable AD according to NINCDS/ADRDA; MMSE scores of 10-26; had a responsible caregiver		
EXCLUSION:	Severe and unstable cardiac disease; severe COPD; life threatening conditions		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Drugs for coexisting diseases allowed except anticholinergic drugs, health food supplements containing ACh precursors, putative memory enhancers, insulin, and psychotropic drugs		

<table>
<tr><td colspan="4">Authors: Rösler et al.
Year: 1999</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild to moderately severe</td></tr>
<tr><td><u>rivastigmine 1-4 mg/d</u></td><td><u>rivastigmine 6-12 mg/d</u></td><td><u>placebo</u></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• Baseline ADAS-Cog
• Baseline PDS</td><td>NR
NR
NR

23.87
53.8</td><td>NR
NR
NR

23.57
55.22</td><td>NR
NR
NR

23.29
54.1</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADAS-Cog; PDS; CIBIC

Secondary Outcome Measures: MMSE; GDS

Timing of assessments: Primary outcome measures at baseline and weeks 12, 18 and 26; secondary outcome measures at baseline and week 26</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Scores on PDS improved in patients taking high dose RIV when compared with placebo, P < 0.05 (LOCF analysis); no significant difference observed between low dose RIV and placebo, P > 0.05*
• PDS scores significantly more improved for high dose RIV compared to placebo (P < 0.05) but not for low dose RIV

Intermediate Outcome Measures:
• Scores on ADAS-Cog improved in patients taking high dose RIV (6-12 mg/d) when compared with placebo, P < 0.05 (LOCF analysis); no significant difference observed between low dose RIV (1-4 mg/d) and placebo, P > 0.05*
• Scores on CIBIC improved in patients taking high dose RIV when compared to placebo, P < 0.001; no significant difference observed between low dose RIV and placebo, P > 0.05*
• MMSE scores significantly more improved for high dose RIV compared to placebo (P < 0.05) but not for low dose RIV</td></tr>
</table>

Authors: Rösler et al. **Year: 1999**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea • Vomiting • Dizziness • Headache • Diarrhea • Anorexia • Abdominal Pain • Fatigue • Malaise	**rivastigmine 1-4 mg/d** 71% 17% 8% 10% 7% 10% 3% 5% 2% 1%	**rivastigmine 6-12 mg/d** 91% 50% 34% 20% 19% 17% 14% 12% 10% 10%	**placebo** 72% 10% 6% 7% 8% 9% 2% 3% 3% 2%
Significant differences in adverse events:	All adverse events occurred significantly more often for high dose RIV than placebo ($P < 0.05$); nausea occurred significantly more often for low dose RIV than placebo ($P < 0.05$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes, computer generated		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes, but method not described		
ATTRITION (*overall*):	**Overall loss to follow-up:** 144 (20%) **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*):	**rivastigmine 1-4 mg/d**	**rivastigmine 6-12 mg/d**	**placebo**
Loss to follow-up:	14%	33%	13%
Withdrawals due to adverse events:	7%	23%	7%
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors and Year: Tairot et al. 2000[49]; Cummings et al. 2004[66]** **Country:** US		
FUNDING:	Janssen Research Foundation		
RESEARCH OBJECTIVE:	To investigate the efficacy and tolerability of GAL using slow dose escalating schedule of up to 8 weeks in 978 patients with mild to moderate AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size:** 978		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**galantamine** 8; 16; 24 mg/d 5 months 140; 279; 273	**placebo** N/A 5 months 286	
INCLUSION:	History of cognitive decline gradual in onset and progressive over a period of at least 6 months; diagnosis of probable AD according to NINCDS/ADRDA; MMSE score 10 – 22; ADAS-Cog 11 score of ≥18		
EXCLUSION:	Any other neurodegenerative disorders; cardiovascular disease; clinically significant psychiatric, hepatic, renal pulmonary, metabolic, or endocrine conditions, or urinary outflow obstruction; active peptide ulcer; history of epilepsy or significant drug or alcohol abuse; treated for AD with a cholinomemetic agent in preceding 60 days		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concomitant medications with the exception of sedative-hypnotics and sedating cough and cold remedies; drugs with anticholinergic or cholinomimetic effects were not allowed		

<table>
<tr><td colspan="4">Authors and Year: Tairot et al. 2000; Cummings et al. 2004</td></tr>
<tr><td rowspan="6">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild-moderate</td></tr>
<tr><td><u>galantamine 8; 16; 24 mg/d</u></td><td><u>placebo</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>76; 76.3; 77.7</td><td>77.1</td><td></td></tr>
<tr><td>Sex (% female):</td><td>64.2; 62.3; 67</td><td>62.2</td><td></td></tr>
<tr><td>Ethnicity (% white):</td><td>94; 93; 91</td><td>93</td><td></td></tr>
<tr><td>Other germane population qualities:
• MMSE
• ADAS-Cog</td><td>18; 17.8; 17.7
27.8; 29.4; 29</td><td>17.7
29.4</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADAS-Cog 11; CIBIC-plus

Secondary Outcome Measures: ADAS-Cog 11 responders (improvement ≥ 4 points) and ADAS-Cog11 improvers (≥ 7 points); ADCS/ADL; NPI

Timing of assessments: Baseline, weeks 4 and 13, and at 5 months</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Significantly less reduction in ADCS/ADL for 16 mg/d GAL (-0.7 vs. -3.8 mean reduction; P < 0.001) and 24 mg/d GAL (-1.5 vs. -3.8 mean reduction; P < 0.01) compared to placebo
• Significantly less reduction in mean NPI change from baseline for GAL 16 mg/d (-0.1 vs. 2.0 mean change; P < 0.05) and 24 mg/d GAL (0.0 vs. 2.0 mean change; P < 0.05) compared to placebo

Intermediate Outcome Measures:
• (ITT) ADAS-Cog improvement in cognitive function in GAL treated patients compared with placebo: 1.3 points (8 mg/d; P value not significant), 3.1 points (16 mg/d; P < 0.001), and 3.1 points (24 mg/d; P < 0.001)
• (ITT) CIBIC-plus improvement greater than placebo for 16 mg/d GAL (66% vs. 49% improved; P < 0.001) and for 24 mg/d GAL (64% vs. 49% improved; P < 0.001)
• Proportion of responders and significant improvers significantly better than placebo for GAL 16 mg/d and GAL 24 mg/d</td></tr>
</table>

Authors and Year: Tariot et al. 2000; Cummings et al. 2004			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea • Agitation • Diarrhea	**galantamine 8; 16; 24 mg/d** 75.5%; 73.8%; 80.2% 5.7%; 13.3%; 16.5% 15%;10%; 8.1% 5%; 12%; 5.5%	**placebo** 72.0% 4.5% 9.4% 5.9%	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall loss to follow-up:** 20.7% **Loss to follow-up differential high:** Yes		
	galantamine 8; 16; 24 mg/d	**placebo**	
Loss to follow-up: **Withdrawals due to adverse events:**	22.8%; 21.5%; 22.3% 6.4%; 6%; 9.8%	16% 6.9%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Tariot et al.** [45] **Year: 2001** **Country:** US		
FUNDING:	Eisai, Inc; Pfizer, Inc		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of DON in the management of patients with AD residing in nursing home facilities		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (27) **Sample size:** 208		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil** 5 mg/d; 10 mg/d 4 weeks; 20 weeks 103	**placebo** N/A 24 weeks 105	
INCLUSION:	Diagnosis of possible or probable AD with CVD according to NINCDS/ADRDA; MMSE score between 5 and 26 inclusive; reported frequency of a symptom at least several times a week from NPI-NH; sufficient vision and hearing; resided in nursing home for at least 1 month before study		
EXCLUSION:	Parkinson's, VaD or other neurological diseases that could be responsible for the dementia; clinically significant obstructive pulmonary disease; asthma; vitamin B_{12} deficiency; recent hematological/oncological disorders, hemiparesis or aphasia due to cerebrovascular accident; unstable medical illnesses; undergone medical/surgical hospitalization within 3 months before study; dementia secondary to alcohol abuse; alcohol or drug dependence; know ChE hypersensitivity		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concomitant medications except those with anticholinergic effects and investigational drugs; patients treated with TAC must have discontinued use of the agent at least 30 days before screening visit		

<table>
<tr><td colspan="4">Authors: Tariot et al.
Year: 2001</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild-moderate</td></tr>
<tr><td></td><td><u>donepezil</u></td><td><u>placebo</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>85.4</td><td>85.9</td><td></td></tr>
<tr><td>Sex (% female):</td><td>83</td><td>82</td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• MMSE</td><td>14.4</td><td>14.4</td><td></td></tr>
<tr><td>• NPI-NH</td><td>21.0</td><td>20.5</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: NPI-NH

Secondary Outcome Measures: MMSE; CDR-SB; PSMS

Timing of assessments: Screening, baseline, and 4 week intervals throughout study</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No significant differences in PSMS change from baseline between DON and placebo
• No statistical or clinically significant differences in mean NPI-NH total scores observed between DON and placebo at any time points*

Intermediate Outcome Measures:
• No statistically significant differences in mean MMSE change from baseline at endpoint
• Significantly greater improvement in CDR-SB total score and cognitive subscale for DON compared to placebo ($P < 0.05$)</td></tr>
</table>

Authors: Tariot et al. **Year: 2001**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Diarrhea • Vomiting • Nausea • Anorexia	**donepezil** 96% 15% 15% 9% 9%	**placebo** 97% 10% 14% 4% 5%	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:**	**Overall loss to follow-up:** 46 (22.2%) **Loss to follow-up differential high:** No **donepezil** 18% 11%	**placebo** 26% 18%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness ***Alzheimer Drugs***

STUDY:	**Authors: Tariot et al.** [57] **Year: 2004** **Country:** US		
FUNDING:	Forest Research Institute, a division of Forest Laboratories		
RESEARCH OBJECTIVE:	To compare the efficacy and safety of MEM in patients with moderate to severe AD already receiving DON treatment		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (37 sites) **Sample size:** 404		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**memantine** 20mg/d titrated in 5 mg/d doses 24 weeks 203	**placebo** N/A 24 weeks 201	
INCLUSION:	Probable AD by NINCDS; MMSE score of 5 – 14; ≥ 50 yrs old; recent (within 12 months) MRI or CT scan consistent with probable AD; ongoing ChE inhibitor with DON for more than 6 months before entrance into trial and as stable dose (5-10 mg/d) for at least 3 months; reliable caregiver; ambulatory aided ability; residence in community; stable medical condition		
EXCLUSION:	Significant B_{12} or folate deficiency; active pulmonary, gastrointestinal, renal, hepatic, endocrine or cardiovascular disease; psychiatric or central nervous system disorders other than AD; dementia complicated by other organic disease; modified HIS score > 4 at screening		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	All concomitant medications were allowed; DON maintained at current dose throughout the study		

Authors: Tariot et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Alzheimer classification:** Moderate-severe		
	memantine	**placebo**	
Mean age (years):	75.5	75.5	
Sex (% female):	63	67	
Ethnicity (% white):	90.1	92.5	
Other germane population qualities:			
• Baseline MMSE	9.9	10.2	
• Duration of DON treatment	126 weeks	129 weeks	
• DON dose (mg)	9.25	9.49	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** SIB; ADCS-ADL **Secondary Outcome Measures:** CIBIC-plus; NPI; BGP **Timing of assessments:** Baseline, and weeks 4, 8, 12, 18 and 24		
RESULTS:	**Health Outcome Measures:** • Statistically significant benefit of MEM compared to placebo on ADCS-ADL (P = 0.03), NPI (P = 0.01), and BGP (P = 0.001) **Intermediate Outcome Measures:** • Statistically significant benefit of MEM compared to placebo on SIB (P < 0.001), and CIBIC-plus (55% of MEM improved compared to 45% of placebo improved (P = 0.03))		

Authors: Tariot et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Agitation	**memantine** 78% 9.4%	**placebo** 72% 11.9%	
Significant differences in adverse events:	Significant differences favoring placebo: confusion 7.9% vs. 2% (P = 0.01); headache 6.4% vs. 2.5% (P = 0.09); significant differences favoring MEM: diarrhea 4.5% vs. 8.5% (P = NR) and fecal incontinence 2% vs. 5% (P = NR)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 20% **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**memantine** 14.9% 7.4%	**placebo** 25.4% 12.4%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness ***Alzheimer Drugs***

STUDY:	**Authors: Whitehead et al.** [32] **Year: 2004**
FUNDING:	Medical Research Council
DESIGN:	**Study design:** Meta-analysis (individual patient data) **Number of patients:** 2,376
AIMS OF REVIEW:	To evaluate the efficacy and tolerability of DON (5 and 10 mg/d) compared with placebo in alleviating manifestations of mild to moderate AD
STUDIES INCLUDED IN META-ANALYSIS	Published and unpublished data of 10 RCTs
TIME PERIOD COVERED:	Up to 1999
CHARACTERISTICS OF INCLUDED STUDIES:	All randomized, double-blind, placebo-controlled, parallel-group studies from the DON clinical development program undertaken and completed as of 20 December 1999, in which DON was administered for more than one day at 5 and 10 mg/d
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients satisfied a diagnosis of probable AD as defined by the validated diagnostic criteria of the International Classification of Diseases (WHO), DSM and/or NINCDS/ADRDA; patients were required to have mild to moderate AD at screening as defined by MMSE with scores between 10 and 26 inclusive and CDR scores of 1 (mild) or 2 (moderate)

Authors: Whitehead et al. **Year: 2004**	
CHARACTERISTICS OF INTERVENTIONS:	10 trials comparing either 5 or 10 mg/d over 12 to 24 weeks in patients with mild to moderate AD; primary outcome measures included ADAS-Cog treatment difference; ADAS-Cog response (improvement of 4 or 7 points); CIBIC-plus; MMSE; CDR-SB
MAIN RESULTS:	ADAS-Cog score statistically significantly better for 5 or 10 mg/d DON at all time points compared with placebo ($P < 0.001$); odds of improvement in CIBIC-plus scores were twice as great with DON 5 or 10 mg/d as with placebo and statistically significant ($P < 0.001$)
ADVERSE EVENTS:	Adverse events occurred in 65% and 83% of patients treated with 5 or 10 mg/d DON respectively, compared with 62% of placebo treated patients; discontinuations due to adverse events were higher in DON 10 mg/d (13.9%) than in DON 5 mg/d (6.3%) or placebo (5.8%) group; significantly greater incidence of nausea, diarrhea, vomiting, headache and insomnia in DON 10 mg/d than DON 5 mg/d or placebo group
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No systematic search was reported; the trials were provided by the DON clinical Development Program
STANDARD METHOD OF APPRAISAL OF STUDIES:	Blindly accepted trials if they were randomized, double-blind, placebo-controlled, parallel group studies and if patients satisfied inclusion criteria; no other methods were discussed as to how trials were evaluated to be included in the meta-analysis
QUALITY RATING:	**Fair**

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Wilcock et al.** [50] **Year: 2000** **Country:** Multinational (Canada, Finland, France, Germany, Norway, Sweden, Netherlands, UK)		
FUNDING:	Janssen Research Foundation		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of GAL in the treatment of AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (86) **Sample size:** 653 randomized (525 completed)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**galantamine** 24 mg/d 6 months 220	**galantamine** 32 mg/d 6 months 218	**placebo** N/A 6 months 215
INCLUSION:	Probable AD according to the NINCDS; MMSE score of 11-24; ADAS-Cog score $\geq$ 12; FAST $\leq$ 6 at baseline		
EXCLUSION:	Had no responsible caregiver; neurogenerative disorder; multi-infarct dementia or clinically active CVD; cardiovascular disease thought to prevent study completion; clinically important cerebrovascular, psychiatric, hepatic, renal, pulmonary, metabolic, or endocrine conditions or urinary outflow obstruction; active peptic ulcer; any history of epilepsy or serious drug or alcohol misuse; history of treatment with ChE inhibitor		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Most concomitant medications were allowed except for those with anticholinergic effects; sedative-hypnotic drugs and sedating cough and cold remedies must have been discontinued in 48 hours before cognitive evaluation		

<table>
<tr><td colspan="4">Authors: Wilcock et al.
Year: 2000</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild-Moderate</td></tr>
<tr><td></td><td><u>galantamine 24 mg</u></td><td><u>galantamine 32 mg</u></td><td><u>placebo</u></td></tr>
<tr><td></td><td>Mean age (years):
Sex (% female):
Other germane population qualities:
• MMSE score</td><td>71.9
63.2

19.5</td><td>72.1
63.3

19.0</td><td>72.7
61.4

19.3</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADAS-Cog; CIBIC-plus

Secondary Outcome Measures: Proportion of patients with improvements from baseline on the ADAS-Cog of ≥ 0 and ≥ 4; DAD

Timing of assessments: Baseline and weeks 3 (ADAS-Cog only), 12 and 24</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• ITT analysis of DAD at 6 months revealed significant benefit of GAL only at 32 mg/d; mean difference = 3.4; 95% CI: 0.1 – 6.7; P < 0.05; 24 mg/d mean difference = 2.8; P value not significant

Intermediate Outcome Measures:
• ITT analysis of ADAS-Cog scores at 6 months revealed significant benefit of GAL over placebo (24 mg/d mean difference = 2.9; 95% CI: 1.6 – 4.1; P < 0.001); (32 mg/d mean difference = 3.1; 95%: CI 1.9 – 4.4; P < 0.001)*
• ITT analysis of CIBIC-plus at 6 months revealed significant benefit of GAL over placebo (P < 0.05); more patients in the GAL groups (weighted % = 63.6) improved or remained stable than in the placebo group (49.5%)*
• ITT analysis of ADAS-Cog improvement (≥0 and ≥4 points) showed significant benefit for GAL 24 mg/d and 32 mg/d (P < 0.001 for all comparisons with placebo)</td></tr>
</table>

Authors: Wilcock et al. **Year: 2000**			
ADVERSE EVENTS	**galantamine 24mg**	**galantamine 32mg**	**placebo**
Overall adverse effects reported:	83%	89%	77%
• Nausea	37%	40%	12%
• Vomiting	20%	17%	4%
• Diarrhea	7%	13%	7%
• Dizziness	11%	12%	5%
• Headache	10%	11%	3%
• Anorexia	10%	11%	0%
Significant differences in adverse events:	Nausea (P = NR); vomiting (P = NR); dizziness (P = NR); headache (P = NR); anorexia (P < 0.001)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 19.6 % **Loss to follow-up differential high:** No (< 15 percentage points difference)		
ATTRITION (*treatment specific*):	**galantamine 24mg**	**galantamine 32mg**	**placebo**
Loss to follow-up:	20%	25.2%	13.5%
Withdrawals due to adverse events:	14%	22%	9%
QUALITY RATING:	**Good**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Wilcock et al.** [27] **Year: 2003** **Country:** UK		
FUNDING:	Janssen-Cilag UK, Janssen Pharmaceutica Products L.P., Shire Pharmaceuticals Ltd.		
RESEARCH OBJECTIVE:	To compare the long-term efficacy and safety of GAL 24 mg/d and DON 10 mg/d in patients with AD		
DESIGN:	**Study design:** Randomized, rater-blinded trial **Setting:** Multi-center (18) **Sample size:** 182		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**galantamine** 24 mg/d 52 weeks 94	**donepezil** 10 mg/d 52 weeks 88	
INCLUSION:	Diagnosis of probable AD (NINCDS/ADRDA); MMSE score 9 – 18 at screening; history of cognitive decline gradual onset over last 12 months; caregiver who lived with subject or visited at least 5 days/week and could assist with medication, attend assessments and provide information about the subject; MRI/high resolution CAT scan after diagnosis and consistent with AD		
EXCLUSION:	Use of AChE inhibitor within 30 days prior to study entry (other dementia Rx can be discontinued at enrollment); previous GAL or DON use; neurodegenerative disorders other than AD; multi-infarct dementia or clinically active CVD; other conditions possibly resulting in cognitive impairment, such as post-traumatic brain injury, hypoxic cerebral damage, or neoplasia; coexisting medical conditions that would compromise patient's ability to complete the trial		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

<table>
<tr><td colspan="4">Authors: Wilcock et al.
Year: 2003</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No; significantly more females randomized to DON
Alzheimer classification: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>galantamine</u></td><td><u>donepezil</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>74.1</td><td>72.8</td><td></td></tr>
<tr><td>Sex (% female):</td><td>56.4</td><td>68.2</td><td></td></tr>
<tr><td>Ethnicity (% white):</td><td>100</td><td>98.9</td><td></td></tr>
<tr><td>Other germane population qualities:
• Mean screening MMSE</td><td>15.1</td><td>14.8</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: BADLS

Secondary Outcome Measures: MMSE; ADAS-Cog 11; NPI; SCGB

Timing of assessments: Baseline and weeks 13, 26 and 52</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• BADLS scores showed no significant difference between treatment groups in mean change from baseline to week 52
• Changes from baseline in NPI similar for both treatments
• At endpoint, a higher percentage of GAL than DON patients reported maintenance or improvement of objective and subjective caregiver burden (SCGB); 67.1% and 68.3% respectively for GAL, and 51.3% and 49.4% respectively for DON; significance NR

Intermediate Outcome Measures:
• GAL patients showed no significant improvement in MMSE scores ($P > 0.05$), whereas DON patients scores were significantly lower at week 52 compared to baseline ($P < 0.0005$); total between group differences in MMSE not significant
• ADAS-Cog 11 analysis between-group differences for total population not significant, although both groups demonstrated significant decline from baseline; $P < 0.05$ for GAL and $P < 0.0005$ for DON</td></tr>
</table>

Authors: Wilcock et al. **Year: 2003**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Severe adverse events • Nausea • Agitation • Vomiting • Headache • Falls	**galantamine** 90.7% 18.6% 19.6% 18.6% 17.5% 16.5% 16.5%	**donepezil** 93.4% 19.8% 17.6% 12.1% 14.3% 12.1% 8.8%	
Significant differences in adverse events:	None		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	No; different treatment regimens precluded allocation concealment		
BLINDING OF OUTCOME ASSESSORS:	Method NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 21% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**galantamine**	**donepezil**	
Loss to follow-up:	19.6%	22%	
Withdrawals due to adverse events:	13.4%	13.2%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness *Alzheimer Drugs*

STUDY:	**Authors: Wilkinson et al.** [51] **Year: 2001** **Country:** UK		
FUNDING:	Shire Phamaceuticals		
RESEARCH OBJECTIVE:	To investigate whether GAL significantly improves the core symptoms of AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size:** 285		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**galantamine** 18; 24; 36 mg/d 3 months 88; 56; 54	**placebo** N/A 3 months 87	
INCLUSION:	Male and female outpatients with mild to moderate AD as defined by NINCDS/ADRDA and MMSE (score 13-24) aged >45 years who were attending memory clinics; required to have appropriate caregiver		
EXCLUSION:	Dementia secondary to causes other than AD or any condition considered likely to interfere with the trial in the opinion of the investigator		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Antidepressants; antipsychotic drugs; antiparkinsonian drugs; insulin; anticonvulsants; sedatives; antihypertensive agents (except ACE inhibitors and diuretics); other cholinergic or anticholinergic agents (except inhaled drugs for asthma)		

<table>
<tr><td colspan="4">Authors: Wilkinson et al.
Year: 2001</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild-moderate</td></tr>
<tr><td></td><td><u>galantamine 18; 24; 36 mg/d</u></td><td><u>placebo</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>72.7; 72.9; 75.4</td><td>74.2</td><td></td></tr>
<tr><td>Sex (% female):</td><td>56; 59; 57</td><td>59</td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Baseline MMSE</td><td>18.8, 18.2, 18.8</td><td>18.7</td><td></td></tr>
<tr><td>• Baseline ADAS-Cog</td><td>26.0, 26.7, 25.7</td><td>26.9</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADAS-Cog

Secondary Outcome Measures: CGIC; PDS-1 (quality of life measure)

Timing of assessments: Baseline and weeks 6 and 12</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No significant differences in PDS-1 score for any dose of GAL compared to placebo (ITT)

Intermediate Outcome Measures:
• GAL 24 mg/d produced greater improvement in ADAS-Cog change compared to placebo (P = 0.01); mean change from baseline for GAL 18 mg/d and GAL 32 mg/d not statistically different from placebo
• No significant differences in CGIC for any dose of GAL compared to placebo (ITT)</td></tr>
</table>

Authors: Wilkinson et al. **Year:2001**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Vomiting • Nausea • Headache	**galantamine 18; 24; 36 mg/d** 55.7%; 58.9%; 70.4% 17%; 7.1%; 16.7% 17%; 17.9%; 37% 5.7%; 10.7%; 14.8%	**placebo** 43.7% 4.6% 3.4% 4.6%	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 27.7% **Loss to follow-up differential high:** Yes; highest between high dose GAL and placebo		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**galantamine 18; 24; 36 mg/d** 28%; 25%; 48% 21.6%; 17.9%; 44.4%	**placebo** 16% 9.2%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Efficacy/Effectiveness ***Alzheimer Drugs***

STUDY:	**Authors: Wilkinson et al.** [29] **Year: 2002** **Country:** Multinational (UK, South Africa, Switzerland)		
FUNDING:	Eisai, Inc. and Pfizer, Inc.		
RESEARCH OBJECTIVE:	To compare the tolerability and cognitive effects of DON vs. RIV in patients with mild to moderate AD		
DESIGN:	**Study design:** RCT (open label) **Setting:** Multi-center (19) **Sample size:** 111		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil** 5-10 mg/d (flexible) 12 weeks 56	**rivastigmine** 6-12 mg/d (flexible) 12 weeks 55	
INCLUSION:	Patients ≥ 50 yrs; probable or possible AD according to DSM-IV and NINCDS; MMSE score of 10-26; CT or MRI scan within past 12 months consistent with diagnosis of AD; available caregiver		
EXCLUSION:	History of DON or RIV use; concomitant use of anticholinergics		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	SSRIs; small daily doses of neuroleptics and short-acting benzodiazepines provided they were given in stable doses for at least one month prior to study entry		

<table>
<tr><td colspan="4">Authors: Wilkinson et al.
Year: 2002</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild-moderate</td></tr>
<tr><td><u>donepezil</u></td><td><u>rivastigmine</u></td><td></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Other germane population qualities:
• Mean baseline MMSE score
• Mean baseline ADAS-Cog
• Taking ≥ 1 concomitant med</td><td>74.0
54

21.5
20.4
48%</td><td>74.9
64

20.7
20.8
50%</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADAS-Cog (blinded rater); MMSE (un-blinded clinician)

Secondary Outcome Measures: Satisfaction/ease of use as measured by questionnaire developed by Pfizer and Eisai (clinician and caregiver satisfaction/ease of use)

Timing of assessments: Baseline and weeks 4 and 12</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Physicians reported better mean total satisfaction/ease of use with DON than with RIV at 12 weeks ($P < 0.0001$)
• Caregivers reported better mean total satisfaction/ease of use with DON than with RIV at 12 weeks ($P < 0.05$)

Intermediate Outcome Measures:
• No statistically significant differences between DON and RIV as measured by ADAS-Cog (blinded rater) and MMSE (un-blinded clinician)*</td></tr>
</table>

Authors: Wilkinson et al. **Year: 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea • Vomiting • Headache	**donepezil** 42.9% 10.7% 7.1% 7.1%	**rivastigmine** 58.2% 41.8% 23.6% 18.2%	
Significant differences in adverse events:	Percentage of patients experiencing at least one adverse event was lower in DON than in RIV (42.9% vs. 58.2%; P = NR); nausea, vomiting, and headache were more frequent in RIV than DON patients, although significance NR		
ANALYSIS:	**ITT:** No; authors note ITT was conducted but not reported because of high differential loss to follow-up **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Method not reported		
ADEQUATE ALLOCATION CONCEALMENT:	N/A (open-label)		
BLINDING OF OUTCOME ASSESSORS:	Yes (ADAS-Cog); No (MMSE)		
ATTRITION (*overall*):	**Overall loss to follow-up:** 20.7 % **Loss to follow-up differential high:** Yes (20% differential)		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**donepezil** 10.7% 10.7%	**rivastigmine** 30.9% 21.8%	
QUALITY RATING:	**N/A**		

*primary outcome measures

Efficacy/Effectiveness ***Alzheimer Drugs***

STUDY:	**Authors and Year: Winblad et al. 2001[46]; Wimo et al. 2003[84]** **Country:** Multinational (Northern European countries)		
FUNDING:	Pfizer Pharmaceuticals Group, Pfizer, Inc.		
RESEARCH OBJECTIVE:	To evaluate the long-term clinical efficacy and safety of DON versus placebo over 1 year in patients with mild to moderate AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (52 sites in 5 countries: Denmark, Finland, Norway, Sweden, The Netherlands) **Sample size:** 286		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil** 10 mg/d (8.5% on 5mg/d) 52 week 142	**placebo** N/A (2.8% did not escalate dose) 52 week 144	
INCLUSION:	Diagnosis of AD consistent with NINCDS/ADRDA and DSM-IV; age 40 to 90 years; mild to moderate AD confirmed by MMSE score of 10 – 26; CT or MRI scans were obtained at screenings if not performed in last 12 months; healthy and ambulatory or ambulatory aided, with vision and hearing sufficient for compliance with testing procedures; laboratory test values had to be within normal limits or considered to be clinically insignificant by the investigator; reliable care giver		
EXCLUSION:	Clinically significant and unstable, active gastrointestinal, renal, hepatic, endocrine, or cardiovascular system disease; primary neurologic or psychiatric disease other than AD; newly treated hypothyroidism; drug abuse or alcoholism; neoplasm, insulin-dependent diabetes or diabetes not stabilized by diet or oral hyploglycemic agents; obstructive pulmonary disease or asthma; recent hematologic/oncologic disorders; pernicious anemia; vitamin B_{12} or folate deficiency as evidenced by blood concentrations below the lower normal limit; known hypersensitivity to ChE inhibitors; cholinomimetic treatment within 30 days		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Serotonin reuptake inhibitors, low dose neuroleptics, and benzodiazepines permitted if started within 2 months; anticholinergics, high dose neuroleptics, tricyclic antidepressants, medications for Parkinson's were not permitted		

<table>
<tr><td colspan="4">Authors and Year: Winblad et al. 2001; Wimo et al. 2003</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes, although 10 percentage point difference in sex
Alzheimer classification: Mild-moderate</td></tr>
<tr><td><u>donepezil</u></td><td><u>placebo</u></td><td></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity (% white):
Other germane population qualities:
• Mean baseline MMSE
• Mean baseline GBS
• Mean baseline GDS
• Mean baseline NPI</td><td>72.1
69.7
100

19.37
29.51
4.15
13.05</td><td>72.9
59
100

19.26
29.77
4.16
11.78</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: GBS total score plus the 4 domains: GBS-I (intellectual), GBS-ADL (activities of daily living), GBS-E (reasoning), GBS-S (behavior)

Secondary Outcome Measures: MMSE; ADL; PDS; NPI; GDS

Timing of assessments: Weeks 4, 12, 36 and 52</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No significant differences in GBS-ADL, GBS-E, or GBS-S subtotals at endpoint
• Treatment response to DON was not predicted by APOE genotype or sex
• Significantly slower decline in PDS total score for DON-treated patients (P < 0.05); specific differences noted on telephone use (P < 0.01), memory (P < 0.01), and self care (P < 0.05)
• No significant differences in NPI at endpoint
Outcome Measures:
• Significantly slower decline in MMSE for DON-treated patients (P < 0.001)
• Significantly slower decline in GBS total score at weeks 24, 36, and 52 for observed cases of DON-treated patients (P < 0.05) but no statistically significant difference in ITT analysis (P = 0.054)
• Significantly slower decline in GBS-I for DON-treated patients compared to placebo (P = 0.004)
• Significantly greater improvement for DON-treated patients on GDS (P < 0.05)</td></tr>
</table>

Authors: Winblad et al. 2001; Wimo et al. 2003			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea • Depression • Anxiety	**donepezil** 81.7% 11.3% 11.3% 10.6%	**placebo** 75.7% 9.0% 7.6% 5.6%	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:**	**Overall loss to follow-up:** 32.9% **Loss to follow-up differential high:** No **donepezil** 33.1% 7%	**placebo** 32.6% 6.3%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Adverse Events ***Alzheimer Drugs***

STUDY:	**Authors: Cutler et al.** [72] **Year: 1998**
FUNDING:	NR
DESIGN:	**Study design:** Pooled data analysis **Number of patients:** 3,350
AIMS OF REVIEW:	To determine the incidence rates of adverse events for TAC, DON, and RIV
STUDIES INCLUDED IN REVIEW	NR
TIME PERIOD COVERED:	NR
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs
CHARACTERISTICS OF INCLUDED POPULATIONS:	NR

Authors: Cutler et al. **Year: 1998**				
CHARACTERISTICS OF INTERVENTIONS:	Placebo-controlled trials of TAC, DON, and RIV			
MAIN RESULTS: **TAC 40-160 mg/d** **DON 10 mg/d** **RIV ≤ 9 mg/d**	**Discontinuation** 55% 8% 18%	**Vomiting** 28% 5% 21%	**Diarrhea** 16% 10% 16%	**Nausea** 28% 11% 35%
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No			
STANDARD METHOD OF APPRAISAL OF STUDIES:	No			
QUALITY RATING:	**N/A**			

Adverse Events ***Alzheimer Drugs***

STUDY:	**Authors: Dunn et al.** [74] **Year: 2000** **Country:** UK		
FUNDING:	Drug and Safety Research Unit		
RESEARCH OBJECTIVE:	To report the incidence of adverse events associated with DON		
DESIGN:	**Study design:** Observational cohort pharmacovigilance study (prescription event monitoring) **Setting:** Questionnaires to general practitioners in the UK **Sample size:** 3,356 questionnaires sent; 1,762 returned		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**donepezil** N/A N/A 1,762		
INCLUSION:	Patients who received DON within the first few months of its launch		
EXCLUSION:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Dunn et al.
Year: 2000</td></tr>
<tr><td>POPULATION CHARACTERISTICS:

Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:</td><td colspan="3">Groups similar at baseline: N/A
Alzheimer classification: NR

<u>donepezil</u>
72.9
58
NR
NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Adverse events noted during 6 months after first prescription for DON

Secondary Outcome Measures: NR

Timing of assessments: 6 months after first prescription for the drug</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• See adverse events (incidence > 5% reported)

Intermediate Outcome Measures:
• NR</td></tr>
</table>

Authors: Dunn et al. **Year:2000**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea/Vomiting • Diarrhea • Malaise/lassitude • Respiratory tract infection • Dizziness • Insomnia • Micturition disorder	**donepezil** 16.1 15.5 7.4 5.6 5.0 5.0 5.0 5.0		
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	N/A		
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**donepezil** N/A N/A		
QUALITY RATING:	**N/A**		

*primary outcome measures

Adverse Events ***Alzheimer Drugs***

STUDY:	**Authors: Evans et al.** [85] **Year: 2004**
FUNDING:	NR
DESIGN:	**Study design:** Pooled data analysis **Number of patients:** NR
AIMS OF REVIEW:	To determine the incidence rates of adverse events for DON, GAL, and RIV
STUDIES INCLUDED IN REVIEW	29 RCTs
TIME PERIOD COVERED:	NR
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs
CHARACTERISTICS OF INCLUDED POPULATIONS:	NR

Authors: Evans et al. **Year: 2004**				
CHARACTERISTICS OF INTERVENTIONS:	Placebo-controlled and head-to-head trials of DON, GAL and RIV			
MAIN RESULTS:	**Weight loss**	**Vomiting**	**Diarrhea**	**Nausea**
GAL 8-50mg/d	10%	16%	8%	29%
DON 1-10mg/d	12%	12%	16%	17%
RIV 1-12mg/d	NR	31%	19%	47%
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No			
STANDARD METHOD OF APPRAISAL OF STUDIES:	No			
QUALITY RATING:	**N/A**			

Adverse Events ***Alzheimer Drugs***

STUDY:	**Authors: Gauthier**[73] **Year: 2001**
FUNDING:	Canadian Institute for Health Research
DESIGN:	**Study design:** Retrospective data review of published RCTs **Number of patients:** NR
AIMS OF REVIEW:	To determine the incidence rates of adverse events for DON, GAL, and RIV
STUDIES INCLUDED IN REVIEW	9 RCTs
TIME PERIOD COVERED:	NR
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs
CHARACTERISTICS OF INCLUDED POPULATIONS:	NR

Authors: Gauthier **Year: 2001**				
CHARACTERISTICS OF INTERVENTIONS:	Placebo-controlled trials of DON, GAL, and RIV			
MAIN RESULTS:	**Discontinuation**	**Vomiting**	**Diarrhea**	**Nausea**
DON 5mg/d	7%	3-10%	6-10%	4-10%
DON 10mg/d	15%	6-16%	13-17%	17-22%
GAL 16mg/d	7%	6%	12%	13%
GAL 24mg/d	16%			
GAL 32mg/d	27%	17-26%	13-19%	40-44%
RIV 6-12mg/d	26%	27-34%	17%	48-50%
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No			
STANDARD METHOD OF APPRAISAL OF STUDIES:	No			
QUALITY RATING:	**N/A**			

Adverse Events ***Alzheimer Drugs***

STUDY:	**Authors: Knapp et al. 1994 [86]; Farlow et al. 1995 [87]; Knopman et al 1996 [88]; Farlow 1998 [89]** **Country:** US		
FUNDING:	Warner Lambert		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of high dose TAC over 30 weeks in patients with probable AD		
DESIGN:	**Study design:** RCT **Setting:** Outpatients at 33 centers **Sample size:** 653		
INTERVENTION: **Dose (mg/d):** **Duration (weeks):** **Sample size:**	**tacrine** 40-80; 40-60-120; 40-80-120-160 6-24; 6-6-18; 6-6-6-12 472	**placebo** N/A 30 181	
INCLUSION:	Men and women ≥ 50 yrs old with mild to moderate AD and otherwise in good health; met NINCDS criteria for AD with symptoms of AD for 1 year		
EXCLUSION:	Patients with prior exposure to TAC or other analogues; unhealthy patients		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Medications known to effect the central nervous system and likely to interfere with assessment of efficacy and medications likely to mask the cholinergic side effects of TAC were prohibited; those taking citmetidine or therophylline were excluded		

<table>
<tr><td colspan="4">Authors: Knapp et al.
Year: 1994</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild-moderate</td></tr>
<tr><td></td><td><u>tacrine</u>
40- 80; 40-60-120; 40-80-120-160 mg/d</td><td><u>placebo</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>73; 73; 72.8</td><td>72.7</td><td></td></tr>
<tr><td>Sex (% female):</td><td>48; 55; 51</td><td>53</td><td></td></tr>
<tr><td>Ethnicity: NR</td><td></td><td></td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• MMSE</td><td>17.1; 18.7; 18.8</td><td>18.2</td><td></td></tr>
<tr><td>• ADAS-Cog</td><td>30.9; 28.5; 28</td><td>29.2</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: CIBI; ADAS-Cog; FCCA

Secondary Outcome Measures: ADAS-Noncog; ADAS-Total score; MMSE; GDS

Timing of assessments: Baseline and every 6 weeks</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• At week 30 significantly more patients in the placebo group were placed in a nursing home or had died than in the TAC 160 mg/d group (7% vs. 4%; OR 2.8; 95% CI: 1.0 – 7.8; P = 0.046); no significant differences between placebo and TAC 80 mg/d group (7% vs. 7%)

Intermediate Outcome Measures:
• Significant differences in favor of 160 mg/d TAC vs. placebo for CIBI (P = 0.002) and ADAS-Cog (P < 0.001)
• A subgroup analysis revealed that patients with higher MMSE scores (18-26) did not benefit more from treatment than patients with lower scores (10-17)
• No interaction between gender and TAC treatment on the ADAS-Cog score could be detected
• Patients with an APOE-[epsilon]4 genotype had less response to treatment than patients with an APOE-[epsilon]2-3 genotype</td></tr>
</table>

<table>
<tr><td colspan="4">Authors: Knapp et al.
Year: 1994</td></tr>
<tr><td>ADVERSE EVENTS:</td><td colspan="3">54% of TAC treated patients had elevated ALT levels
29% of TAC treated patients had three times the upper limit of normal (120 U/L)
90% of elevations occurred within the first 12 weeks</td></tr>
<tr><td>Significant differences in adverse events:</td><td colspan="3">Significantly higher rate of ALT elevations in TAC group</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes
Post randomization exclusions:</td></tr>
<tr><td>ADEQUATE RANDOMIZATION:</td><td colspan="3">Yes</td></tr>
<tr><td>ADEQUATE ALLOCATION CONCEALMENT:</td><td colspan="3">NR</td></tr>
<tr><td>BLINDING OF OUTCOME ASSESSORS:</td><td colspan="3">Yes</td></tr>
<tr><td>ATTRITION (overall):

ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:</td><td colspan="3">Overall loss to follow-up: 58%
Loss to follow-up differential high:
<table><tr><td><u>tacrine</u>

55%
Primary reason: ALT elevations; also gastrointestinal symptoms (16%)</td><td><u>placebo</u>

11%</td><td></td></tr></table></td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Poor</td></tr>
</table>

*primary outcome measures

Adverse Events ***Alzheimer Drugs***

STUDY:	**Authors: Morganroth et al.**[75] **Year: 2002** **Country:** USA
FUNDING:	eResearch Technology, Philadelphia, PA and Novartis Pharmaceuticals Corporation, East Hanover, NJ
DESIGN:	**Study design:** Pooled data-analysis **Number of patients:** 2,791
AIMS OF REVIEW:	To determine if RIV has adverse cardiac effects by analysis of recorded ECGs
STUDIES INCLUDED IN META-ANALYSIS	Four phase III clinical trials in AD patients reported in: Corey-Bloom et al. 1998; Rosler et al. 1999; Schneider et al. 1998
TIME PERIOD COVERED:	1998
CHARACTERISTICS OF INCLUDED STUDIES:	Four placebo-controlled trials of RIV (26 weeks) at outpatient research centers in 10 countries; doses of 1-12 mg/day titrated over 7 to 12 weeks
CHARACTERISTICS OF INCLUDED POPULATIONS:	$\geq$ 50 years old; not of childbearing potential; met DSM-IV and NINCDS/ADRDA criteria for AD; had responsible caregiver; admitted with coexisting disease unless condition was severe; patients excluded if abnormality identified by physical exam, ECG, lab test, or abnormal vital signs

Authors: Morganroth et al. **Year: 2002**	
CHARACTERISTICS OF INTERVENTIONS:	Patients randomly assigned to either placebo or RIV for 26 weeks; dosage could be fixed, partially flexible, or fully flexible; standard 12-lead ECG performed at screening, baseline, and weeks 2, 4, 8, 12, 16, 18, 22 and 26, or early termination; ECG abnormalities characterized as “new or worsened”, “no change”, or “improved”; ECG variables included heart rate, PQ or PR interval, QRS interval, and corrected and uncorrected QT intervals
MAIN RESULTS:	No clinically meaningful differences were apparent between RIV and placebo-treated patients with regard to mean change from baseline in heart rate, PQ or PR interval, QRS interval, QT interval uncorrected, or QT interval corrected
ADVERSE EVENTS:	No clinically meaningful differences in treatment-emergent ECG abnormalities, bradycardia, or tachycardia were observed between groups
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No; review focused on four specific studies
STANDARD METHOD OF APPRAISAL OF STUDIES:	NR
QUALITY RATING:	**Fair**

Adverse Events ***Alzheimer Drugs***

STUDY:	**Authors: Watkins et al.** [71] **Year: 1994** **Country:** USA
FUNDING:	Alzheimer's Association Inc., Chicago, IL; National Institute on Aging, Washington, DC; Parke-Davis/Warner-Lambert Co, Ann Arbor, MI; Advanced Nutritional Technologies, Elizabeth, NJ
DESIGN:	**Study design:** Retrospective data-analysis of RCTs **Number of patients**: 2,446
AIMS OF REVIEW:	To analyze the hepatic effects of TAC treatment in patients with AD
STUDIES INCLUDED IN META-ANALYSIS	Three published trials: Davis et al. 1992; Farlow et al. 1992; Knapp et al 1994 Data from two unpublished trials by coauthor Knapp also included
TIME PERIOD COVERED:	1992-1994
CHARACTERISTICS OF INCLUDED STUDIES:	Placebo-controlled trials of TAC in the US, France, and Canada of at least 6 weeks; in one study patients were also administered lecithin as 9 g of phosphatidylcholine
CHARACTERISTICS OF INCLUDED POPULATIONS:	2,468 patients $\geq$ 50 yrs old; met NINCDS/ADRDA criteria for AD of mild to moderate severity for at least 1 year; good health without significant hepatic, cardiovascular or renal disease; required to have serum ALT, AST, total bilirubin, and creatinine levels within normal limits at entry

Authors: Watkins et al. **Year: 1994**	
CHARACTERISTICS OF INTERVENTIONS:	Patients assigned to either placebo or TAC, with weekly to biweekly measurement of serum hepatic enzymes
MAIN RESULTS:	• ALT levels elevated above normal limit at least once in 49% of patients taking TAC • ALT levels elevated by more than three times normal limit observed in 25% of patients • ALT levels greater than twenty times normal limit observed in 2% of patients • Serum AST changes generally mirrored ALT elevations • Elevations appeared to occur abruptly (i.e., within 50 days) and discontinuation of TAC completely reversed elevations in ALT
ADVERSE EVENTS:	Elevated ALT levels were associated with increased eosinophilia, fever, and rash
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No; review focused on five specific studies
STANDARD METHOD OF APPRAISAL OF STUDIES:	NR
QUALITY RATING:	**N/A**

Adverse Events ***Alzheimer Drugs***

STUDY:	**Authors: Wong et al.** [61] **Year: 1999** **Country:** Taiwan		
FUNDING:	Parke-Davis Pharmaceutical Division of Warner-Lambert Company		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of TAC in Chinese patients with probable AD		
DESIGN:	**Study design:** RCT **Setting:** NR **Sample size:** 100		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**tacrine** 120 mg/d titrated at 30 mg/d 30 weeks 75	**placebo** N/A 30 weeks 25	
INCLUSION:	≥ 50 yrs old; met NINCDS criteria for probable AD with the presence of symptoms for at least 1 year; dementia was mild to moderate as determined by CDR; baseline MMSE score of 10 - 26		
EXCLUSION:	Cardiac disease; stroke; diabetes; hepatic or renal insufficiency; any malignancy; prior exposure to TAC; probable VaD with HIS > 4; CT or MRI of a focal brain lesion; evidence of vitamin B_{12} deficiency; hypothyroidism; neurosyphilis		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concomitant medications except nootropics, anti-depressants, antipsychotics, and sedative-hypnotics; patients taking concomitant medications had to discontinue use for at least 10 days before the study		

<table>
<tr><td colspan="4">Authors: Wong et al.
Year: 1999</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild-to-moderate</td></tr>
<tr><td></td><td><u>tacrine</u></td><td><u>placebo</u></td></tr>
<tr><td></td><td>Mean age (years):
Sex (% female):
Ethnicity (% Chinese):
Other germane population qualities:
• Baseline HIS
• Baseline MMSE</td><td>73.6
48.6
100

0.66
15.8</td><td>74.0
58.3
100

0.71
17.3</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: CASI; CGIC; IQCODE

Secondary Outcome Measures: MMSE; ADS; CGIC rated by caregivers

Timing of assessments: Baseline and every 6 weeks</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• NR

Intermediate Outcome Measures:
• Significantly more improvement on the CASI for TAC compared to placebo (P = 0.05)*
• No significant differences in patient or caregiver rated CGIC (P > 0.5)*
• No significant differences in IQCODE between TAC and placebo (P > 0.5)*
• Marginally significant improvement in MMSE for TAC-treated patients compared to placebo (P = 0.057)
• No significant differences in ADS between TAC and placebo (P > 0.5)</td></tr>
</table>

Authors: Wong et al. **Year: 1999**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Elevated ALT • Anorexia • Nausea/Vomiting	**tacrine** NR 51% 30% 14%	**placebo** NR 12.5% 8% 0%	
Significant differences in adverse events:	Yes, but significance not reported		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (6)		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 44% **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**tacrine** 52% NR	**placebo** 20% NR	
QUALITY RATING:	**Poor**		

*primary outcome measures

Adverse Events ***Alzheimer Drugs***

STUDY:	**Authors: Wood et al.** [63] **Year: 1994** **Country:** UK		
FUNDING:	Shire Pharmaceuticals and Parke-Davis Research Laboratories		
RESEARCH OBJECTIVE:	To determine whether oral TAC improves the symptoms of patients with mild to moderate AD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (memory and psychogeriatric clinics) **Sample size:** 154		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**tacrine** 80 mg/d 12 weeks 78	**placebo** N/A 12 weeks 76	
INCLUSION:	AD diagnosed by NINCDS/ADRDA; MMSE $\geq$ 10; CDRS of 1 or 2		
EXCLUSION:	Evidence of concurrent illness (cerebral infarction, including evidence on CT scan, hepatic disease, clinical depression or other psychiatric diagnoses); lacked a reliable caregiver		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Other medications allowed if they were not likely to interfere with or confuse the interpretation of the expected actions of TAC		

<table>
<tr><td colspan="4">Authors: Wood et al.
Year: 1994</td></tr>
<tr><td rowspan="5">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: Mild-moderate</td></tr>
<tr><td></td><td><u>tacrine</u></td><td><u>placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>76</td><td>73</td></tr>
<tr><td>Sex (% female):</td><td>66</td><td>62</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: MMSE; CGRS

Secondary Outcome Measures: RGRS; GBS; ADAS-Noncog

Timing of assessments: Baseline and weeks 4, 8 and 12</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• NR

Intermediate Outcome Measures:
• No significant differences in MMSE scores between groups (P = 0.55)
• CGRS and RGRS scores significantly better in TAC compared to placebo (P = 0.012 and P = 0.013)</td></tr>
</table>

Authors: Wood et al. **Year:1994**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Raised LFTs • Nausea/Vomiting • Dizziness	**tacrine** NR 44% 33% 10%	**placebo** NR 4% 7% 0%	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 20.1% **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**tacrine** 29.5% 23%	**placebo** 10.5% 6.5%	
QUALITY RATING:	**Poor**		

*primary outcome measures

Subgroups ***Alzheimer Drugs***

STUDY:	**Authors: Areosa et al.** [64] **Year: 2004** **Country:** Multinational (Germany, France, Belgium, Sweden, UK, USA, Latvia).
FUNDING:	Funding for review NR; all included studies were funded by Merz Pharma KGaA, Frankfurt, Germany
DESIGN:	**Study design:** Systematic review of MEM trials **Number of patients:** Ranged from 60 – 579
AIMS OF REVIEW:	To determine the clinical efficacy and safety of MEM for people with AD, or vascular or mixed dementia
STUDIES INCLUDED IN META-ANALYSIS	7 placebo-controlled RCT studies were included: Ditzler 1991; Gortelmeyer 1992; MMM300 (Orgogozo) 2000; MMM500 (Wilcock) 2000; Pantev 1993; Reisberg 2000; Winblad 1999
TIME PERIOD COVERED:	Trials completed before April 2003 that were included in the Trial-based Specialized Register of the Cochrane Dementia and Cognitive Improvement Group
CHARACTERISTICS OF INCLUDED STUDIES:	Diagnosis of dementia established using DSM-III-R, DSM-III, and DSM-IV; 2 studies involved only people with VaD (MMM300, MMM500); one study was restricted to people with AD; 3 studies included both types of dementia
CHARACTERISTICS OF INCLUDED POPULATIONS:	Sample size ranges: 60 (Pantev 1993) to 579 (MMM 500); range of mean ages: 71.5-77.0 yrs.

Authors: Areosa et al. **Year: 2004**	
CHARACTERISTICS OF INTERVENTIONS:	The trials studied different dosages of MEM with placebo. The doses ranged from 10 to 30 mg/day but the most common was 20mg/day. Most of the trials started with low doses progressively increased to target levels. Outcome measures included ADAS-Cog, Syndrom-Kurz test, SIB, CIBIC-plus, CGIC, SCAG, NOSIE, ADCS-ADL, ADL, BGP, NOSGER
MAIN RESULTS:	**Note: This study stratifies results by the randomized population (i.e., AD, VaD, or AD+VaD)** • **Cognition:** *Moderate-Severe AD*: Significant improvement in SIB at 28 weeks (1 trial; *MD = 6.1; 95% CI: 2.99 – 9.21; P = 0.0001) *Mild-moderate VaD*: Significant improvement in ADAS-Cog at 28 weeks (2 trials; **WMD = -2.19; 95% CI: -3.16 – -1.21; P < 0.0001) *Mixed AD + VaD*: Effect size NR at 12 weeks (1 trial) **Activities of Daily Living**: *Moderate-Severe AD*: Significant improvement in activities of daily living at 28 weeks (1 trial; WMD=0.32; 95% CI: 0.07 – 0.73; P = 0.01) *Mild-moderate VaD*: No significant differences in activities of daily living (NOSGER) (1 trial; MD = 0.21; 95% CI: -4.65 – 5.07) *Mixed AD + VaD*: No significant differences at 12 weeks using BGP care dependence sub score (1 trial; effect size NR) • **Behavior:** *Moderate-Severe AD*: No significant differences in NPI at 28 weeks (1 trial; WMD = -3.30; 95% CI: -7.33 – 0.73, P = 0.11) *Mild-moderate VaD*: NR *Mixed AD + VaD*: NR (1 trial; effect size not reported) • **Global scales:** *Moderate-Severe AD*: Significant difference in CIBIC-plus score at 28 weeks (1 trial; MD = -0.30; 95% CI: -0.058 – -0.02, P = 0.04) *Mild-moderate VaD*: No significant differences in GBS scores at 28 weeks (2 trials; WMD = -1.81; 95% CI: -4.21 – 0.58, P = 0.14); no differences in NOSGER at 28 weeks (2 trials; WMD = -0.92; 95% CI: -2.90 – 1.05; P = 0.4) *Mixed AD + VaD*: Significant improvement in numbers at 12 weeks (1 trial; 60/82 compared with 38/84, OR 3.30; 95% CI 1.72 – 6.33; P = 0.0003)

Authors: Areosa et al. **Year: 2004**	
ADVERSE EVENTS:	Not stratified by population
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes: trials selected from the Trial-based Specialized Register of the Cochrane Dementia and Cognitive Improvement Group, containing records from a number of published and unpublished electronic databases (e.g., MEDLINE, CCTR/Central, EMBASE)
STANDARD METHOD OF APPRAISAL OF STUDIES:	Cochrane Collaboration guidelines (Mulrow 1997)
QUALITY RATING:	**Good**

*Mean difference (MD)
**Weighted mean difference (WMD)

Subgroups ***Alzheimer Drugs***

STUDY:	**Authors: Erkinjuntti et al.**[77] **Year: 2002** **Country:** Multinational (10 countries)		
FUNDING:	Janssen Research Foundation		
RESEARCH OBJECTIVE:	To determine the effect of GAL on patients with probable VaD or AD combined with CVD		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (number of centers NR) **Sample size:** 592		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**galantamine** 24 mg/d 6 months 396	**placebo** N/A 6 months 196	
INCLUSION:	Met clinical criteria for probable VaD based on NINDS-AIREN guidelines or AD based on NINCDS/ADRDA; significant radiological evidence of CVD; MMSE score of 10-25: ADAS-Cog score > 12; have a reliable caregiver; evidence of relevant focal neurological signs consistent with previous stroke or CVD		
EXCLUSION:	Evidence of neurodegenerative disorders other than AD; cognitive impairment resulting from cerebral trauma; hypoxic cerebral damage; vitamin deficiency; other clinically significant disease; patients who received investigational medication within 30 days of trial		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Other antidementia medications not allowed; others NR		

<table>
<tr><td colspan="4">Authors: Erkinjuntti et al.
Year: 2002</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Alzheimer classification: NR</td></tr>
<tr><td><u>galantamine</u></td><td><u>placebo</u></td><td></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity:
• Black
• White
• Asian
Other germane population qualities:
• ADAS-Cog score
• MMSE</td><td>75.0
48

0.5%
99.5%
0%

22.3
20.7</td><td>75.2
46

0%
99.8%
0.2%

24.1
20.2</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADAS-Cog 11; CIBIC-plus (only primary outcome measures reported in the subgroup analysis of patients with AD & CVD)

Secondary Outcome Measures: ADAS-Cog 13; NPI; DAD

Timing of assessments: ADAS-Cog 11 performed at screening, baseline, 6 weeks, and months 3 and 6; CIBIC-plus, NPI, and DAD performed at baseline, and months 3 and 6</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Subgroup analysis for AD-patients with CVD (ADAS-Cog & CIBIC-plus only):

Health Outcome Measures: N/A

Intermediate Outcome Measures:
• At 6 months patients taking GAL had a significantly greater improvement in ADAS-Cog scores compared with patients on placebo (treatment difference 2.7 points; $P < 0.0005$)*
• At 6 months a greater proportion of GAL-treated patients improved on the CIBIC-plus compared to placebo (32% vs. 19%; $P = 0.019$)
• These outcome measures were not significant for the subgroup of patients with VaD</td></tr>
</table>

Authors: Erkinjuntti et al. **Year: 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Nausea for AD subgroup	**galantamine** NR for subgroup 19.7%	**placebo** NR for subgroup 10.3%	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 135 (23%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**galantamine** 26% 20%	**placebo** 17% 8%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Subgroups ***Alzheimer Drugs***

STUDY:	**Authors: Grossberg et al.** [79] **Year: 2000** **Country:** NR (authors from Switzerland and the US; trials not reported in detail)		
FUNDING:	Novartis		
RESEARCH OBJECTIVE:	To conduct a pharmacodynamic analysis of potential drug interactions between RIV and other medications commonly prescribed in the elderly AD population		
DESIGN:	**Study design:** Post-hoc analysis of data from 4 RCTs **Setting:** NR **Sample size:** 2,459		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**rivastigmine** 1 to 12 mg/d 6 months 1,696	**placebo** N/A 6 months 763	
INCLUSION:	Patients randomized in placebo-controlled trials of RIV		
EXCLUSION:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

<table>
<tr><td colspan="4">Authors: Grossberg et al.
Year: 2000</td></tr>
<tr><td>POPULATION CHARACTERISTICS:

Mean age (years):
Sex (% female):
Ethnicity: (% white)
Other germane population qualities:
• MMSE</td><td colspan="3">Groups similar at baseline: No substantive differences between the groups
Alzheimer classification: NR
<u>pooled population</u>
73.1
58
94

19.5</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Breslow-Day test assessing the homogeneity of ORs for the incidence of AE in RIV/placebo receiving and not receiving a concomitant medication

Secondary Outcome Measures: NR

Timing of assessments: NR</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• None

Intermediate Outcome Measures:
• No clinically significant pattern of increased incidence of AEs associated with RIV and concomitant medication use compared with placebo; 31 statistically significant ORs were not homogenous; 21 of these differences exhibited a higher incidence in the placebo group; in cases where higher incidence was observed for RIV (salicylates and diuretics) significant differences were attributed to placebo group differences</td></tr>
</table>

<table>
<tr><td colspan="4">Authors: Grossberg et al
Year: 2000</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
• N/A</td><td><u>rivastigmine</u>
N/A</td><td><u>placebo</u>
N/A</td><td></td></tr>
<tr><td>Significant differences in adverse events:</td><td colspan="3">Significant differences in the odds ratios (AEs RIV/AEs placebo) were noted across concomitant use of anticholinergics, diabetic drugs, cardiac drugs, diuretics, estrogens, salicylic acid, psycholeptics, and aldehydes and derivatives</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: NR
Post randomization exclusions: NR</td></tr>
<tr><td>ADEQUATE RANDOMIZATION:</td><td colspan="3">NR</td></tr>
<tr><td>ADEQUATE ALLOCATION CONCEALMENT:</td><td colspan="3">NR</td></tr>
<tr><td>BLINDING OF OUTCOME ASSESSORS:</td><td colspan="3">NR</td></tr>
<tr><td rowspan="2">ATTRITION (overall):

ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:</td><td colspan="3">Overall loss to follow-up: NR
Loss to follow-up differential high: NR</td></tr>
<tr><td><u>rivastigmine</u>
NR
NR</td><td><u>placebo</u>
NR
NR</td><td></td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">N/A</td></tr>
</table>

*primary outcome measures

Subgroups ***Alzheimer Drugs***

STUDY:	**Authors: Kumar et al. (Subgroup analysis of Corey-Bloom et al.)** [78] **Year: 2000** **Country:** USA		
FUNDING:	Novartis		
RESEARCH OBJECTIVE:	Evaluate the efficacy and safety of the centrally acting ChE inhibitor RIV tartrate for patients with mild to moderately severe AD with or without concurrent VRF		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (22) **Sample size:** 699		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**rivastigmine** 1-4 mg/d 26 weeks 233	**rivastigmine** 6-12 mg/d 26 weeks 231	**placebo** N/A 26 weeks 235
INCLUSION:	Age between 45 and 89 years; non-childbearing potential for females; criteria for AD according to DSM-IV; probable AD according to NINCDS/ADRDA criteria; mild-to-moderate impairment based on MMSE score between 10 and 26; head CT or MRI consistent with AD within 12 months of inclusion; responsible caregiver provided written consent [Note: see Corey-Bloom et al., 1998]		
EXCLUSION:	Severe and unstable medical illnesses; use of anticholinergics AChE precursor health food supplements, memory enhancers, insulin, and psychotic drugs [Note: see Corey-Bloom et al., 1998]; patients with MHIS $\geq$ 5 were excluded from this analysis		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Occasional use of chloral hydrate for agitation or insomnia [Note: authors refer to previous study design description in Corey-Bloom et al., 1998]		

<table>
<tr><td colspan="4">Authors: Kumar et al.
Year: 2000</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No (more females in high dose RIV group)
Alzheimer classification: Mild-moderate</td></tr>
<tr><td></td><td><u>placebo</u></td><td><u>rivastigmine (1-4 mg/d)</u></td><td><u>rivastigmine (6-12 mg/d)</u></td></tr>
<tr><td>Mean age (years):</td><td>74.8</td><td>74.9</td><td>73.8</td></tr>
<tr><td>Sex (% female):</td><td>58</td><td>57</td><td>68</td></tr>
<tr><td>Ethnicity:</td><td></td><td></td><td></td></tr>
<tr><td>• White</td><td>94%</td><td>95%</td><td>97%</td></tr>
<tr><td>• Black</td><td>4%</td><td>4%</td><td>3%</td></tr>
<tr><td>• Other</td><td>2%</td><td>1%</td><td>0%</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Mean MMSE score</td><td>20</td><td>19.5</td><td>19.62</td></tr>
<tr><td>• % with MHIS > 0 (VRF)</td><td>44%</td><td>47%</td><td>47%</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ADAS-Cog; CIBIC-plus; PDS (all stratified by baseline MHIS score category; MHIS > 0 means VRF are present)

Secondary Outcome Measures: MMSE; GDS (all stratified by baseline MHIS score category)

Timing of assessments: Baseline, and weeks 12, 18 and 26 or early termination</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Treatment differences in PDS scores between high dose RIV and placebo were greater in the MHIS > 0 group than the MHIS = 0 group (5.9 vs 3.5)

Intermediate Outcome Measures:
• Treatment differences in ADAS-Cog scores between RIV 6-12 mg/d and placebo greater in the MHIS > 0 group than the MHIS = 0 group (6.15 vs 4.03); significant difference also observed in the MHIS > 0 for RIV 1-4 mg/day (difference = 2.3 points, P = 0.02)
• Both RIV treatment groups had higher percentages of responders on CIBIC-plus compared with the placebo treatment groups in the MHIS = 0 category (P < 0.05) but not the MHIS > 0 group
• In both MHIS categories the MMSE mean change from baseline scores were higher indicating less deterioration in the 6-12 mg/day group compared with the placebo group (MHIS = 0, P = 0.086; MHIS > 0, P = 0.005); the treatment difference was larger in the MHIS > 0 category
• At week 26 the mean change from baseline GDS score for patients receiving RIV 6-12 mg/day indicated less disease worsening in the MHIS > 0 category (P = 0.032)</td></tr>
</table>

Authors: Kumar et al. **Year: 2000**			
ADVERSE EVENTS: ***[See table for Corey-Bloom et al (1998)]*** **Overall adverse effects reported:** • All gastrointestinal • Nausea • Vomiting • Diarrhea • Anorexia	**rivastigmine MHIS = 0** NR 67% 41% 16% 23% 15%	**rivastigmine MHIS > 0** NR 54% 25% 16% 17% 12%	
Significant differences in adverse events:	Treatment with RIV not associated with any increase in mortality, serious adverse events, effects on laboratory measures, ECGs or cardiovascular vital signs in either MHIS category		
ANALYSIS:	**ITT:** No; observed cases used for this analysis **Post randomization exclusions:** Yes (2 patients with no MHIS score were excluded)		
ADEQUATE RANDOMIZATION:	Yes (independent firm cited, along with voice responses system for randomization code assignment)		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 22% **Loss to follow-up differential high:** No (between treatment groups, stratified by MHIS status)		
ATTRITION (*MHIS score-specific*): **Loss to follow-up:** **Placebo** **RIV (low)** **RIV (high)** **Withdrawals due to adverse events:**	**MHIS = 0** 22% 16% 14% 37% NR	**MHIS > 0** 21% 17% 15% 33% NR	
QUALITY RATING:	**Fair**		

*primary outcome measures

APPENDICES

APPENDIX A. Search Strategy

#2	Search "Alzheimer Disease"[MeSH]	32571
#11	Search "Cholinesterase Inhibitors"[MeSH] OR "Cholinesterase Inhibitors"[Pharmacological Action] OR "Galantamine"[MeSH] OR "Tacrine"[MeSH] OR "Memantine"[MeSH]	30351
#12	Search "donepezil hydrochloride" OR aricept OR "rivastigmine tartrate" OR exelon OR reminyl OR cognex OR namenda	2242
#13	Search #11 OR #12	30378
#14	Search #2 AND #13	1720
#15	Search #2 AND #13 Field: All Fields, Limits: Randomized Controlled Trial	210
#16	Search #2 AND #13 Field: All Fields, Limits: Review	508
#18	Search "Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Organizational Case Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Multicenter Studies"[MeSH] OR "Single-Blind Method"[MeSH] OR "Evaluation Studies"[MeSH] OR "Double-Blind Method"[MeSH]	1245441
#19	Search #14 AND #18	603
#20	Search #15 OR #16 OR #19	988
#21	Search #15 OR #16 OR #19 Field: All Fields, Limits: English, Human	843

Cochrane Search Strategy
(Alzheimer OR Alzheimers) AND (Acetylcholinesterase OR Donezepil OR Rivastigmine OR Galantamine OR Tacrine OR Memantine) = 39

EMBASE Search Strategy
(Alzheimer OR Alzheimers) AND (Acetylcholinesterase OR Donezepil OR Rivastigmine OR Galantamine OR Tacrine OR Memantine) = 466

International Pharmaceutical Abstracts Search Strategy

(Alzheimer OR Alzheimers) AND (Acetylcholinesterase OR Donezepil OR Rivastigmine OR Galantamine OR Tacrine OR Memantine) = 50

After removing letters, editorials, notices, foreign languages, etc, and editing for duplicates, final numbers are:

MEDLINE = 843

Cochrane = 15

EMBASE = 355

IPA = 40

And total database (with duplicates marked) = 979.

APPENDIX B. Clinical Assessment Scales Commonly Used in AD Therapeutic Trials

Domain / Scale	Description
Cognition	Memory, orientation, language, praxis, etc.
Mini-Mental State Exam (MMSE)	30-pt. scale (higher scores better) Clinician administered patient evaluation Mostly used for eligibility screening and dementia staging
Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)	70-pt. scale (higher scores worse) Clinician administered patient evaluation Standard cognitive outcome measure in mild-moderate AD
Severe Impairment Battery (SIB)	100-pt. scale (higher scores better) Clinician administered patient evaluation Cognitive outcome measure used in moderate-severe AD
Global Change	Summary outcome assessment from baseline to endpoint
Clinical Global Impression of Change (CGI-C)	7-pt. scale (1 = very much improved, 4 = no change, 7 = very much worse) Clinician rated, based on patient +/- informant interview
Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus)	7-pt. scale (1 = very much improved, 4 = no change, 7 = very much worse) Clinician rated (with caregiver input), based on semi-structured interview covering cognition, behavior, function

Global Deterioration Scale (GDS)	7-pt. scale (1 = no decline, 7 = very severe decline) Clinician rated based on cognitive change only
Function	Activities of daily living (basic and instrumental)
Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL)	54-pt. scale (higher scores better) Informant rated interview of 27 basic and instrumental ADL's used in mild – moderate AD; a subgroup of 19 validated items has been used in moderate-severe AD
Disability Assessment for Dementia (DAD)	100-pt. scale (higher scores better) Informant rated interview of 17 basic and 23 instrumental ADL's; initiation, organization, and planning distinguished
Bristol Activities of Daily Living Scale (Bristol ADL)	60-pt. scale (higher scores worse) Informant rated interview of 20 items (10 ADL's, 10 IADL's) each rated on a 0-3 pt. scale
Behavior	Mood , behavior, personality alterations, etc.
Neuropsychiatric Inventory (NPI)	144-pt. scale (higher scores worse) Informant interview of 12 symptom domains rated on a 12-pt. scale based on Frequency (0-4) x Severity (0-3)
Behavioral symptoms in Alzheimer's disease (BEHAVE-AD)	75-pt. scale (higher scores worse) Informant interview of 25 behavioral symptoms rated on a 0-3 pt. scale

APPENDIX C. Quality Criteria

Assessment of Internal Validity
To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the US Preventive Services Task Force and the NHS Centre for Reviews and Dissemination.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alteration, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alteration, case record numbers, birth dates or week days
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
    - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition.)

APPENDIX D. Characteristics of Excluded Studies

Study	Design	Sample size	Intervention	Reason for exclusion
Anand et al., 1996[90]	pooled data analysis	566	RIV vs. placebo	no systematic literature search
Farlow et al., 2003[91]	pooled analysis of 3 placebo-controlled trials	3550	RIV vs. placebo	selection bias
Forette et al., 1999[92]	RCT	114	RIV vs. placebo	high differential loss to follow up; no ITT analysis
Geldmacher et al., 2003[93]	pooled data analysis	1115	DON vs. placebo	no systematic literature search
Knapp et al., 1994[86]	randomized, double-blind, placebo-controlled, parallel group trial	663	TAC vs. placebo	high loss to follow up
Pratt et al., 2002[94]	pooled data analysis	1920	DON vs. placebo	no systematic literature search
Sano et al., 2003[95]	pooled data analysis	825	GAL vs. placebo	pooled data, trials not identical; no systematic literature search
Stahl et al., 2004[96]	pooled data analysis	1698	GAL vs. placebo	no systematic literature search
Wong et al., 1999[61]	RCT	100	TAC vs. placebo	high loss to follow up
Wood et al., 1994[63]	RCT	154	TAC vs. placebo	high loss to follow up

APPENDIX E. Abstract-only Studies (not included)

Reference List

1. Bayer A, Rossor M, Hecker J *et al*. DONEPEZIL IMPROVES FUNCTIONAL ACTIVITY IN PATIENTS WITH ALZHEIMER'S DISEASE. XXIst Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, Scotland. 12th-16th July, 1998. 1998; (ABSTRACT REF: PW11015).

2. Cummings J, Anand R, Koumaras B, Hartman R. Rivastigmine provides behavioral benefits to Alzheimer's disease patients residing in a nursing home: findings from a 26-week trial. Neurology 2000; 54(Suppl 3):A468-69.

3. Doody R, Clark C, Farlow Mao. Chronic Donepezil Treatment is Associated with Slowed Cognitive Decline in Alzheimer's disease patients. Neurobiology of Aging 1998; 19(Suppl 4):S303.

4. Doraiswamy P, Anand R, and HR. Cognitive effects of rivastigmine in patients with mild to moderate alzheimer's disease compared to those with moderately-severe to severe AD. Clinical Neuropsychological Assessment 2000; 1 (6):12.

5. Doraiswamy P, Anand R, and HR. Long term cognitive effects in alzheimer's disease patients stratified by vascular risk score and treated for 1 year with rivastigmine. Clinical Neuropsychological Assessment 2000; 1(6):14.

6. Engedal K, Soininen H, Verhey F *et al*. Donepezil improved or stabilized cognition over one year in patients with mild and moderate alzheimer's disease. Journal of the European College of Neuropsychopharmacology (Abstracts of the 13th ECNP Congress, Munich, September 9-13, 2000) 2000; 10(Supplement 3):S368.

7. Farlow M, Tariot P, Grossberg G, Gergel I, Graham S, Jin J. Memantine/donepezil dual therapy is superior to placebo/donepezil therapy for treatment of moderate to severe Alzheimer's disease. Neurology 2003; 60(Suppl 1):A412.

8. Feldman H, Gauthier S, Hecker J *et al*. Benefits of Donepezil on global function, behavior, cognition and ADLs in patients with moderate to severe Alzheimer's disease. Neurology 2000; 54(Suppl 3):A469.

9. Froelich L, Gertz H-J, Heun R *et al*. Donepezil for alzheimer's disease - the donald study - a multicenter 24 weeks clinical trial in germany. Journal of the European College of Neuropsychopharmacology (Abstracts of the 13th ECNP Congress, Munich, September 9-13, 2000) 2000; 10(Supplement 3):S360.

10. Grimley EJ, Wilcock G, Whitehead A, Birks J, Perdomo C, Pratt R. Donepezil: a meta-analysis of individual patient data from randomised controlled trials in the treatment of patients with mild to moderate alzheimer's disease. JNS 2001; 187(Suppl. 1).

11. Mastey V, Wimo A, Winblad B *et al*. Donepezil reduces the time caregivers spend providing care: results of a one-year, double-blind, randomized trial in patients with mild to moderate Alzheimer's disease. 14th Annual Meeting of the American Association for Geriatric Psychiatry; 2001 23rd-26th February; San Francisco, CA, USA 2001.

12. McRae T, Knopman D, Duttagupta S, Ieni J, Provenzano G. Donepezil delays time to nursing home placement in patients with Alzheimer's disease. 14th Annual Meeting of the American Association for Geriatric Psychiatry; 2001 23rd-26th February; San Francisco, CA, USA 2001.

13. McRae T, Knopman D, Mastey V, Ieni J, Provenzano G. Donepezil is strongly associated with delayed nursing home placement in patients with alzheimer's disease. JNS 2001; 187(Suppl. 1).

14. Mohs R, Doody R, Morris J *et al*. Donepezil preserves activities of daily living in alzheimer's disease patients: results from a one-year placebo-controlled functional survival study. Neurology 2000; 54(Suppl 3):A415.

15. Mohs R, Doody R, Morris J *et al*. Donepezil preserves functional status and improves cognition in alzheimer's disease patients: results from a 1-year propective placebo-controlled study. Journal of the American Geriatrics Society 2000; 48(8):S46.

16. Mohs R, Doody R, Morris J *et al*. Donepezil preserves functional status in Alzheimer's disease patients: results from a 1-year prospective placebo-controlled attrition study. Journal of the European College of Neuropsychopharmacology 1999; 9(Supplement 5):S328.

17. Petit H, Doody R, Pratt R. Donepezil improves cognition and global function in Alzheimer's disease: Results from us and multinational phase III clinical trials CONFERENCE ABSTRACT. 11th European College of Neuropsychopharmacology Congress. Paris, France. 31st October - 4th November 1998. 1998; Abstract: P.4.008.

18. Pratt R, Perdomo C, Ieni J. Long-term safety and tolerability of donepezil: results from a phase iii extension trial of patients with mild to moderately severe alzheimer's disease. European Journal of Neurology (Abstracts of the 4th Congress of the European Federation of Neurological Sciences, September 7-11, Lisbon, Portugal 1999) 1999; 6(Supplement 3):116.

19. Raskind M, Peskind E, Parys W, Wessel T. Galantamine produces long-term cognitive and functional benefits in patients with Alzheimer's disease. Neurology 2000; 54(Suppl 3):A468.

20. Reisberg B, Ferris S, Sahin K, Windscheif U, Möbius H. Results of a placebo-controlled 6-month trial with memantine in moderate to severe alzheimer's disease (ad). Journal of the European College of Neuropsychopharmacology (Abstracts of the 13th ECNP Congress, Munich, September 9-13, 2000) 2000; 10(Supplement 3):S363.

21. Robert P, Lebert F, Goni S, Touchon J. The impact of caregiver distress of donepezil treatment of patients with mild alzheimer's disease. 152nd Annual Meeting of the American Psychiatric Association. Washington DC, USA. 15-20th May, 1999. 1999.

22. Rockwood K, Kershaw P. Galantamine's clinical benefits are not offset by sleep disturbance: a 3-month placebo-controlled study in patients with Alzheimer's disease. Neurobiology of Aging 2000; 21:S239.

23. Rogers S, Perdomo C, Friedhoff L. Clinical Benefits are Maintained During Long-term Treatment of Alzheimer's Disease with the Acetylcholinesterase Inhibitor, E2020 CONFERENCE ABSTRACT. 8th European College of Neuropsychopharmacology Congress. Venice, Italy. 30th September - 4th October, 1995. 1995.

24. Rogers S, Friedhoff L. Donepezil improves cognition in patients with mild to moderate AD: Results of ADAS-COG analysis in a 30-week phase III study. 10th European College of Neuropsychopharmacology Congress. Vienna, Austria. 13th-17th September 1997. 1997.

25. Rogers S, Friedhoff L. Donepezil is well tolerated at clinically effective doses for the treatment of Alzheimer's disease (AD). 10th European College of Neuropsychopharmacology Congress. Vienna, Austria. 13th-17th September 1997. 1997.

26. Rogers S, Friedhoff L. Donepezil provides long-term clinical benefits for patients with alzheimer's Disease (AD) [Abstract]. Journal of the Neurological Sciences 1997; (Sept):S296.

27. Small G, Mendiondo M, Quarg P, and SR. Efficacy of rivastigmine treatment in Alzheimer's disease over 5

years. 42nd American College of Neuropsychopharmacology Annual Meeting, San Juan, Puerto Rico, 7-11 December 2003 2003.

28. Smith F, Gracon S, Knopman D, and SL. Survival Analysis to Evaluate the Effect of Long-Term Tacrine (Cognex) Treatment on Nursing Home Placement in Alzheimer Patients. Journal of Neurology 1997; 244(Suppl 3):S88.

29. Tariot P, Cummings J, Katz I *et al*. Donepezil was well-tolerated and enhanced cognition in nursing home patients with alzheimer's disease. Journal of the American Geriatrics Society 1999; 47:S3.

30. Tiseo P, Rogers S, Friedhoff L. Co-administration of donepezil and digoxin produces no pharmacokinetic or pharmacodynamic interactions. 10th European College of Neuropsychopharmacology Congress. Vienna, Austria. 13th-17th September 1997. 1997.

31. Tiseo P, Rogers S, Friedhoff L. The pharmacokinetics and pharmacodynamics of (R)- and (S)-Warfarin are unaffected by co-administration of donepezil. 10th European College of Neuropsychopharmacology Congress. Vienna, Austria. 13th-17th September 1997. 1997.

32. Triau E, Boada M, Sakka P, et. al. Efficacy and safety of donepezil hydrochloride in patients with AD: preliminary findings from a large, multinational experience study. Journal of Neurology 2001; 248(suppl 2):II/133.

33. Tune L, Tiseo P, Hoffman J *et al*. PET in AD: Donepezil HCl (E2020) maintains functional brain activity in patients with Alzheimer's disease: results of a 24-week study. 14th Annual Meeting of the American Association for Geriatric Psychiatry; 2001 23rd-26th February; San Francisco, CA, USA 2001.

34. Tune L, Tiseo P, Ieni J *et al*. Donepezil HCl (E2020) maintains functional brain activity in patients with Alzheimer disease: results of a 24-week, double-blind, placebo-controlled study. Am J Geriatr Psychiatry 2003; 11(2):169-77.

35. Tune L, Tiseo P, Hoffman J *et al*. Functional Brain Activity in Alzheimer's Disease. 151st Annual Meeting of the American Psychiatric Association. Toronto, Ontario, Canada. 30th May-4th June 1998. 1998; (NR345).

36. Veach K, SM, Doraiswamy P. Rivastigmine slows stage-specific global deterioration in alzheimer's disease. 152nd Annual Meeting of the American Psychiatric Association. Washington DC, USA. 15-20th May, 1999. 1999.

37. Waldemar G, Winblad B, Engedal K *et al*. Donepezil benefits patients with either mild of moderate Alzheimer's disease over one year. Neurology 2000; 54(Suppl 3):A470.

38. Wilkinson D, Passmore P, Potocnik F, Maud C, Hock C. Donepezil compared to rivastigmine in Alzheimer's disease: similar efficacy but better tolerability and physician and caregiver satisfaction in a multinational randomized trial. 14th Annual Meeting of the American Association for Geriatric Psychiatry; 2001 23rd-26th February; San Francisco, CA, USA 2001.