Original Research Article

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2004;18:217–226
DOI: 10.1159/000079388

Accepted after revision: January 8, 2004
Published online: June 28, 2004

Ginkgo biloba Compared with Cholinesterase Inhibitors in the Treatment of Dementia: A Review Based on Meta-Analyses by the Cochrane Collaboration

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Key Words

Ginkgo biloba · Cholinesterase inhibitors · Meta-analysis · Galantamine · Donepezil · Rivastigmine

Abstract

Data were derived from the Cochrane Collaboration meta-analyses of the efficacies of ginkgo, donepezil, rivastigmine and galantamine on changes in cognitive function in patients with dementia and, where necessary, were transformed to standardized mean differences. The proportion of patients discontinuing trials was used as a proxy measure of tolerability. Outcomes were assessed after 6 months of treatment. Trial data for cholinesterase inhibitors were more consistent than those for ginkgo, particularly regarding patient populations and outcome measures. Significant benefits on cognition vs. placebo were seen with donepezil, 5 and 10 mg, rivastigmine, 6–12 mg, and galantamine, 16 and 24 mg. Significant benefit vs. placebo with ginkgo was seen only when all doses were pooled. Similar proportions of patients discontinued treatment with ginkgo and placebo. Cholinesterase inhibitors were also well tolerated, although a significantly greater proportion of patients receiving active treatment discontinued vs. placebo with some doses. An evidence-based medicine approach, taking into account the quality of clinical trials, is essential when assessing the safety and efficacy of medications.

Introduction

Dementia is defined as a syndrome characterized by a decline in intellectual ability, including impaired memory, judgement and abstract thinking, accompanied by a progressive loss in activities of daily living, as well as personality changes. The incidence of dementia increases with increasing age, with its prevalence doubling for every 5-year increment in age after 65 years [1]. Overall, the prevalence of dementia in Europe and North America is around 6–10% in individuals over 65 years of age [1, 2]. The most common cause of dementia is Alzheimer's disease (AD), which accounts for two thirds of dementia cases. Cerebrovascular disease is the second most common aetiology of dementia, with an overall prevalence of 1.6% in individuals over 65 years of age [2]. In patients aged 70 years and older with dementia, AD and cerebrovascular disease are often combined (i.e. mixed dementia) [3].

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The cholinesterase inhibitors (donepezil, rivastigmine and galantamine) are currently licensed for the treatment of mild to moderate AD. In addition, other compounds have been promoted as beneficial in the treatment of AD and other dementias. *Ginkgo biloba* is an ancient Chinese tree, the seeds of which are widely used in traditional Chinese medicine for disorders such as asthma, bronchitis and tuberculosis [4]. More recently, ginkgo has been suggested as a treatment for cognitive impairment and dementia [4, 5]. Standardized preparations of ginkgo leaves, such as EGb 761 [6], are sold widely as prescription medicines in Europe, particularly in Germany and France [4]. Indeed, EGb 761 is one of the top five prescription products in Germany [7], where it is licensed both for prescription and over-the-counter sale as a symptomatic treatment for dementia syndromes in primary degenerative or vascular dementia, as well as for mixed dementia. Target symptoms include memory and concentration problems, depression, dizziness, tinnitus and headache. In the UK, USA and Canada, EGb 761 is marketed as a non-prescription food supplement for the improvement of mental alertness and is the top-selling herbal remedy in the USA [8].

Systematic, evidence-based evaluations are required when considering the efficacy and safety of medications. A key resource for such evaluations is the Cochrane Collaboration, which was founded in 1993 by scientists from 11 countries to provide independent, systematic reviews of randomized, controlled trials in all areas of health care. Central to the Cochrane methodology are the principles of minimizing bias and ensuring the quality of information available to physicians and other health care professionals. In addition to the reviews published by the Cochrane Collaboration, health technology assessments and treatment guidelines are also published by bodies such as the National Institute for Clinical Excellence in the UK [9], the Canadian Coordinating Office for Health Technology Assessment [10] and the American Academy of Neurology [11].

The purpose of this review is to compare the efficacies of *G. biloba* and cholinesterase inhibitors with regard to cognition on the basis of the extensive literature reviews and meta-analyses carried out by the Cochrane Collaboration [7, 12–14].

Methodology

When reviewing trials for the Cochrane Collaboration, the authors assessed the blinding and randomization of trials, as well as the design, assessment of outcomes and completion rate. Data for meta-analysis were based on reported summary statistics for each study. For studies using the same outcome measures, weighted mean differences (WMD) were calculated. As the WMD was calculated as an average over different trials, weighted with regard to the sample size of each trial, the WMD could still be interpreted in relation to the investigated scale. Where different outcome measures were used, data were converted to standardized mean differences (SMD) via the small sample bias-corrected method described by Deeks [15]. As the SMD was standardized using the different standard deviations observed in each trial, it had the advantage that it could be compared between different scales.

For our comparison of data from the Cochrane review of ginkgo [7] with those from the reviews of donepezil [13], rivastigmine [12] and galantamine [14], it was necessary to transform WMD to SMD. This was because a range of tests and rating scales were used that applied varying methods to measure the different symptom domains of dementia. Transforming the data to SMD made the different scales numerically equivalent and allowed comparisons to be made. One drawback in doing this, however, is that it does not ensure that the underlying severity of disease being measured in each trial is the same.

Outcomes at 6 months were chosen for the comparison as this is a key time point for medication assessment by regulatory authorities, and thus most of the available trials lasted 6 months. The doses included in the analysis are the licensed maintenance doses for each agent: donepezil 5 and 10 mg/day, rivastigmine 6–12 mg/day and galantamine 16 and 24 mg/day. This review will focus on efficacy, measured by changes in cognitive function during treatment, and on tolerability, using the proportion of patients discontinuing a trial as a proxy measure.

Combined estimates of response to therapy formed across studies were calculated using the approach by DerSimonian and Laird [16]. The findings are summarized in tables as estimates with 95% confidence intervals (CIs), but are also displayed in graphs that include individual study findings as well as the combined estimate.

Efficacy

Ginkgo

The Cochrane review and meta-analysis of the safety and efficacy of *G. biloba,* 80–600 mg/day, included 33 studies [7]. These studies used a variety of outcome measures to assess the cognitive benefits of ginkgo treatment,

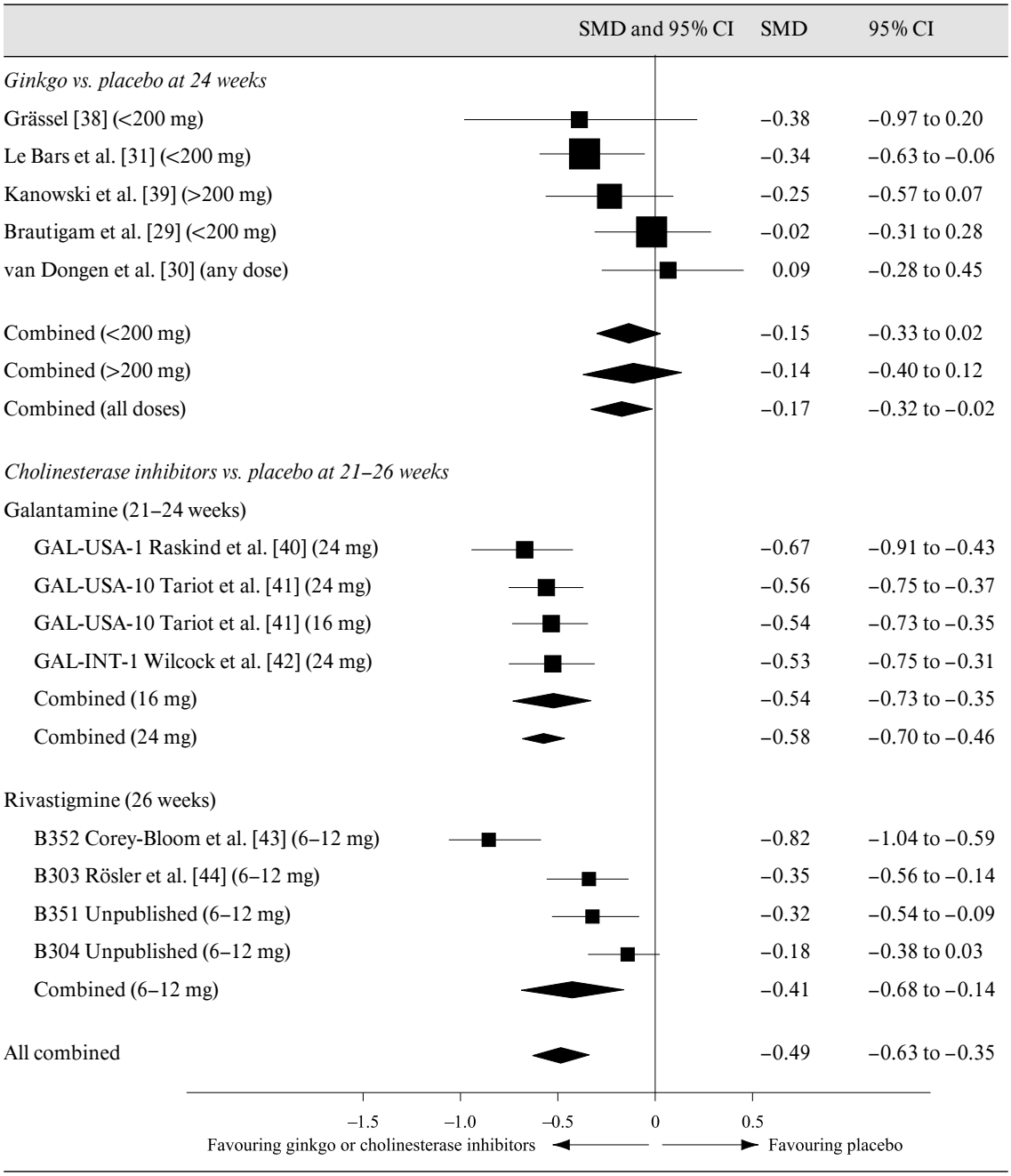


Fig. 1. SMD (±95% CI) vs. placebo for effects of *G. biloba* on measures of cognition and cholinesterase inhibitors on ADAS-cog (observed-case data) after 21–26 weeks of treatment. Based on data from Birks et al. [7, 12] and Olin and Schneider [14]. No observed-case analyses of ADAS-cog were included in the Cochrane review of donepezil [13].

including the Toulouse-Piéron Cancellation Test [17], the Crichton Memory Impairment Subtest [18], the Wechsler Memory Function Test [19] and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) [20]. These 33 studies also included patient populations with a wide range of aetiologies and disease severity. Some studies included patients with any type of dementia and patients with unspecified cognitive impairment, whereas others were more specific. Of the 33 studies, 5 were included in the meta-analysis of efficacy.

Table 1. WMD for change from baseline in ADAS-cog scores vs. placebo after 5–6 months of treatment in meta-analyses of donepezil, rivastigmine and galantamine

Product	Dose, mg	Observed-case analysis[1]			Intent-to-treat analysis[2]		
		WMD	95% CI	p value	WMD	95% CI	p value
Donepezil	5	–	–	–	–1.9	–2.6 to –1.1	<0.01
	10	–	–	–	–2.9	–3.7 to –2.2	<0.01
Rivastigmine	6–12	–2.6	–3.3 to –1.9	<0.00001	–2.1	–2.6 to –1.5	<0.00001
Galantamine	16	–3.3	–4.5 to –2.1	<0.0001	–3.3	–4.1 to –2.1	<0.01
	24	–3.5	–4.3 to –2.8	<0.0001	–3.3	–3.9 to –2.7	<0.0001

Data from Birks et al. [12, 13] and Olin and Schneider [14].

[1] No observed-case data were presented for donepezil in the Cochrane review.

[2] Classic intent-to-treat analysis for rivastigmine; 'last observation carried forward' for donepezil and galantamine.

No significant benefit of ginkgo vs. placebo with regard to cognition was seen with doses of either >200 mg/day (4 studies: SMD –0.14; 95% CI –0.40 to 0.12) or <200 mg/day (2 studies: SMD –0.15; 95% CI –0.33 to 0.02). When all doses were pooled (5 studies), a small but statistically significant benefit on cognition, relative to placebo, was seen for ginkgo (fig. 1; p = 0.03 vs. placebo).

Cholinesterase Inhibitors

From the meta-analysis of 8 donepezil studies, a significant benefit on cognitive function (assessed using ADAS-cog) vs. placebo was seen with the 5 and 10 mg doses at 24 weeks (2 studies, intent-to-treat analysis; table 1) [13]. Although no observed-case analysis was presented in the Cochrane review of donepezil, it seems likely that observed-case results will be similar to those seen with the intent-to-treat analysis.

Seven trials were included in the Cochrane review of rivastigmine, 6 of which contained efficacy data on cognition assessed using ADAS-cog [12]. Significant benefit in terms of improved ADAS-cog results was seen after 6 months of treatment with rivastigmine, 6–12 mg vs. placebo (4 studies, observed-case and intent-to-treat analyses; table 1).

Six studies were included in the Cochrane review of galantamine [14]. The observed-case and intent-to-treat analyses showed statistically significant benefits of galantamine, 16 and 24 mg, vs. placebo on cognitive function (assessed using ADAS-cog) at 6 months (4 studies; table 1).

Ginkgo vs. Cholinesterase Inhibitors

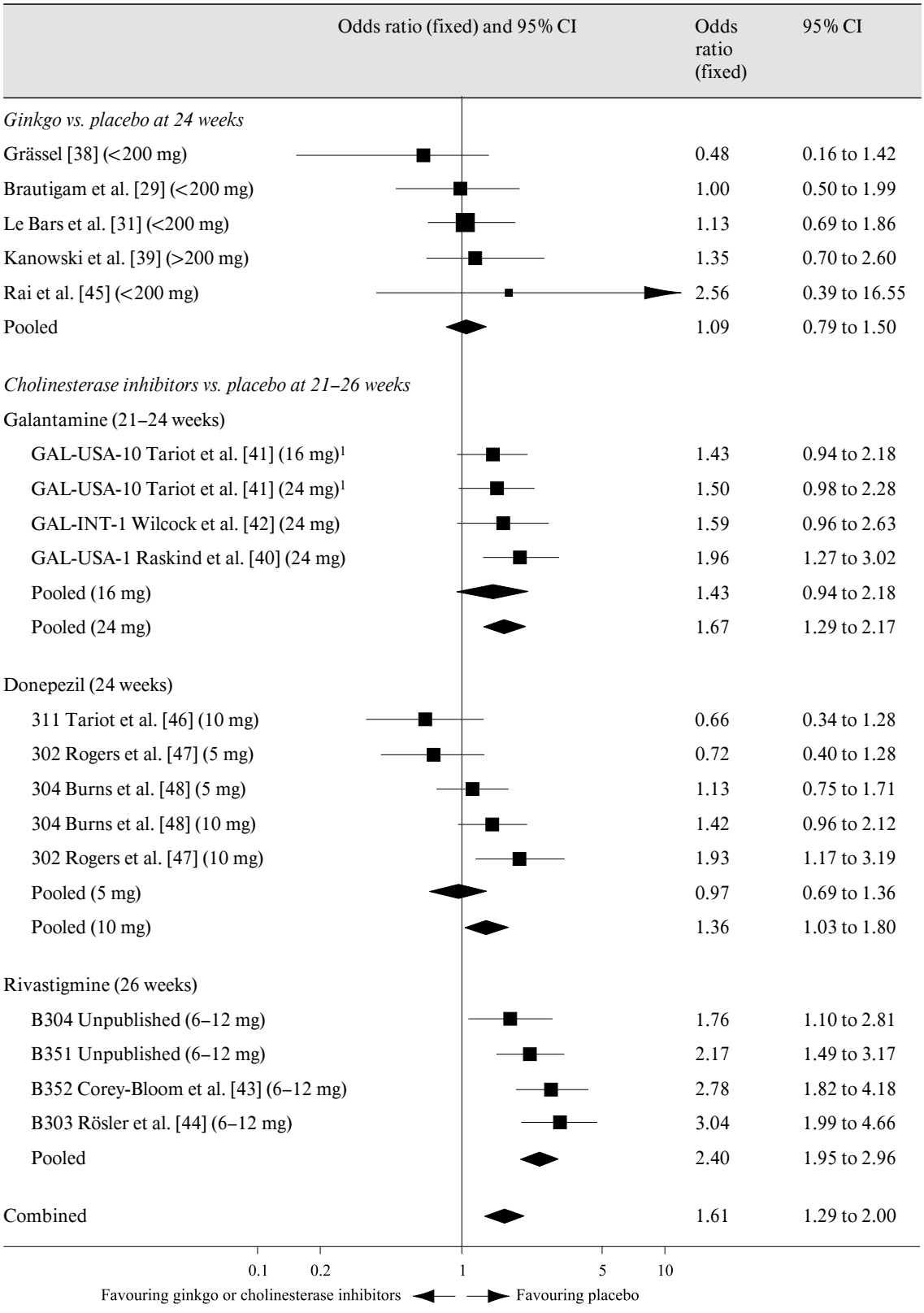
Overall, SMD between active treatment and placebo were larger and more consistent in the trials of cholinesterase inhibitors than in the ginkgo trials (table 2; fig. 1). In particular, as described above, significant differences between ginkgo and placebo were only seen when the 6-month data for different doses were pooled, whereas significant results were seen for all typical maintenance doses of the cholinesterase inhibitors.

Safety

Ginkgo

Ginkgo was well tolerated in clinical trials. Overall, there were no significant differences between ginkgo and placebo with regard to the proportion of patients who discontinued the trials for any reason (fig. 2) and the proportion of patients who experienced adverse events [7]. No data on the proportion of patients who discontinued the trial due to adverse events were provided in the Cochrane review of ginkgo [7].

Fig. 2. Odds ratios vs. placebo for patients discontinuing treatment for any reason during trials of ginkgo and cholinesterase inhibitors. Adapted from Birks et al. [7, 12, 13] and Olin and Schneider [14].



[1] Using recommended 4-week titration schedule in product label.

Table 2. SMD between active treatment and placebo for cognition (ginkgo trials) and ADAS-cog scores (cholinesterase inhibitors) after 24–26 weeks of treatment

Product	Dose, mg	Observed-case analysis[1]		Intent-to-treat analysis	
		SMD	95% CI	SMD	95% CI
Ginkgo	<200	–0.15	–0.33 to 0.02	–	–
	>200	–0.14	–0.40 to 0.12	–	–
	All doses	–0.17	–0.34 to 0.01	–	–
Donepezil	5	–	–	–0.34	–0.47 to –0.20
	10	–	–	–0.53	–0.67 to –0.39
Rivastigmine	6–12	–0.41	–0.68 to –0.14	–0.34	–0.43 to –0.25
Galantamine	16	–0.54	–0.73 to –0.35	–0.52	–0.70 to –0.35
	24	–0.58	–0.70 to –0.45	–0.55	–0.66 to –0.44

Based on data from Birks et al. [7, 12, 13] and Olin and Schneider [14].

[1] No observed-case data were presented in the Cochrane review of donepezil. It is assumed that data for *G. biloba* are analysed on an observed-case basis.

Cholinesterase Inhibitors

The cholinesterase inhibitors were also well tolerated in clinical trials [12–14]. In the Cochrane reviews, tolerability was assessed in terms of the percentage of patients completing the trials, and the percentage of patients withdrawing as a result of adverse events. For donepezil 10 mg, galantamine 24 mg and rivastigmine 6–12 mg, the meta-analysis demonstrated superior tolerability for placebo – both overall trial discontinuations (fig. 2) and discontinuations for adverse events (fig. 3) were generally greater in patients receiving active treatment. For donepezil 5 mg and galantamine 16 mg, overall trial discontinuations and discontinuations for adverse events were not significantly different from placebo.

Ginkgo vs. Cholinesterase Inhibitors

Overall, ginkgo appeared to be better tolerated than the cholinesterase inhibitors: the odds ratio of trial discontinuations (for any reason) for ginkgo was lower than those for the pooled results from the trials of cholinesterase inhibitors (fig. 2) with the exception of the donepezil 5 mg and galantamine 16 mg doses.

Limitations of the Trials

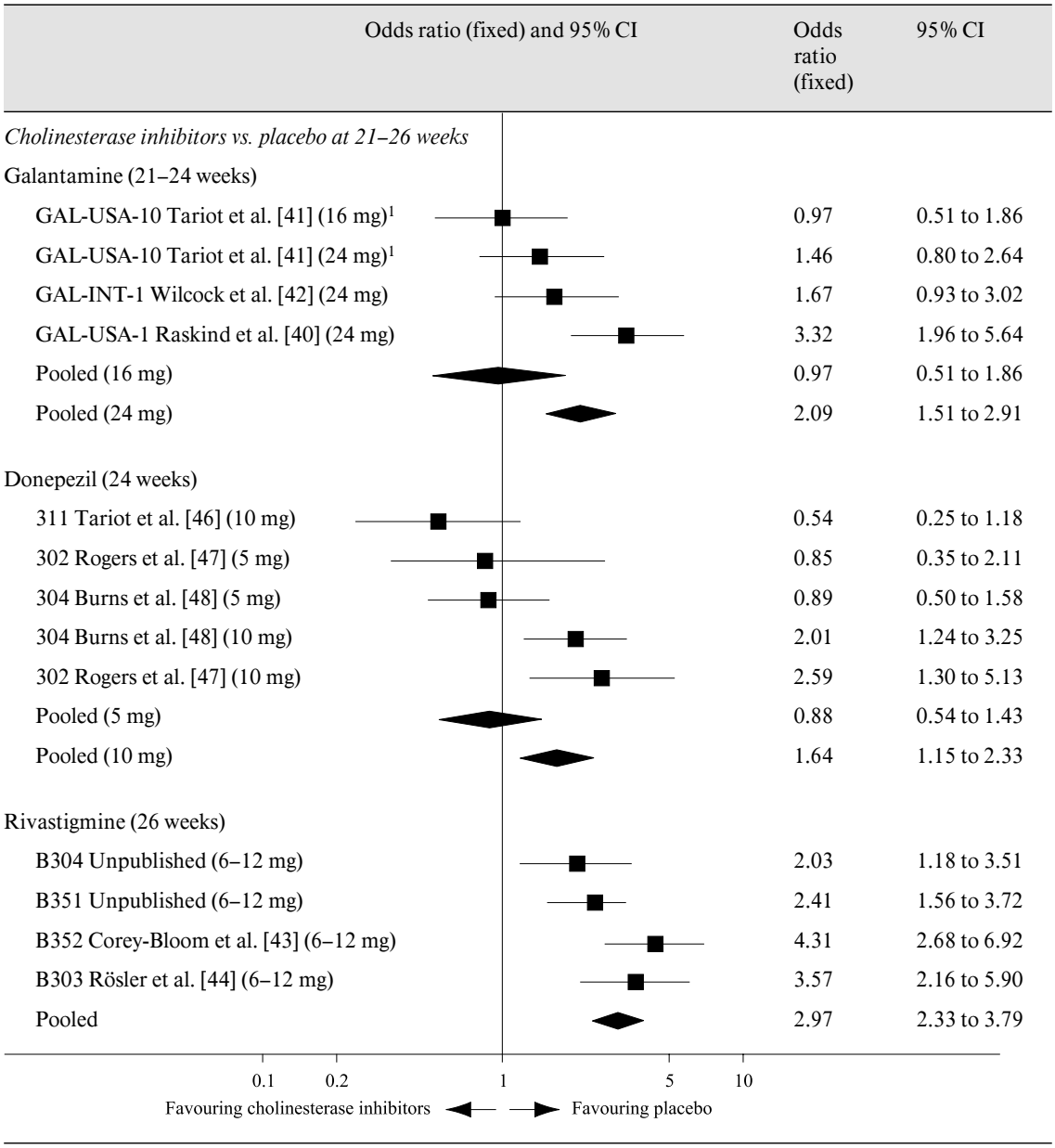
Ginkgo

Of the studies included in the Cochrane review of ginkgo, many are older trials that used methods described by the reviewers as 'unsatisfactory' [7]. Thus, randomization procedures may not have been entirely unbiased. Moreover, a wide variety of outcome measures were used, many of which were not well validated. Indeed, assessment of symptom severity and change in condition was determined in many ginkgo studies by simple questioning of the patients, who were asked to grade their symptoms on a scale from 'none' to 'severe'. The precise details of the questioning were not described, and thus the Cochrane reviewers compared the procedure to using 'an invalidated, unpublished rating scale' [7]. In the individual studies, it is not always clear what form the data take, how they were analysed with regard to the statistical tests used, and whether observed-case or intent-to-treat analyses were performed. Despite these limitations, the Cochrane review remains the best and most comprehensive, independent evidence available for decision making.

In addition to the variation in trial protocols and outcome measures described above, the patient populations included in ginkgo studies vary from trial to trial [7, 12–14]. Some studies specify inclusion criteria on the basis of the Mini-Mental State Examination (MMSE) – a general assessment of cognition with scores ranging from 0 to 30 [21] – whereas others base inclusion on the presence of certain symptoms such as loss of memory or impaired learning ability. The severity and type of cognitive impairment also vary from trial to trial; for example, some protocols included only patients with 'slight' or 'mild' age-related memory impairment [22, 23], whereas others specified AD [24, 25], vascular dementia [26] or both [27].

Cholinesterase Inhibitors

A limitation common to many placebo-controlled trials is that the participants may not be representative of the wider patient population who are treated in clinical practice. For example, patients in the trials of cholinesterase inhibitors were generally required to be in good physi-



[1] Using recommended 4-week titration schedule in product label.

Fig. 3. Odds ratios vs. placebo for patients discontinuing medication due to adverse events during 6 months of treatment with donepezil, rivastigmine or galantamine. Adapted from Birks et al. [12, 13] and Olin and Schneider [14]. ©The Cochrane Library. Permission is granted by John Wiley & Sons Ltd. on behalf of the Cochrane Collaboration. No data were provided in the Cochrane review of ginkgo [7].

cal health, although those with stable and well-controlled concomitant conditions such as hypertension or heart failure were also included.

The severity of dementia in the patients included in the trials was also restricted by the inclusion criteria. The trials discussed in the Cochrane reviews were limited to patients with mild to moderate AD, which was defined in terms of the patient's score on the MMSE. The precise ranges used varied between trials, but usually involved patients with an MMSE score greater than 10–12, with an

Table 3. Strengths and weaknesses of trials of ginkgo compared with trials of cholinesterase inhibitors

	Ginkgo	Cholinesterase inhibitors
Strengths	Real-life trials	Robust trial designs Clearly defined patient populations Clear, statistically significant benefits over placebo
Weaknesses	Heterogeneous patient populations Mixed and non-validated outcome measures Minimal benefit over placebo	Not representative of the full range of patients who will receive treatment

upper limit of 22–26. Some of the trials also used an ADAS-cog assessment as part of the inclusion criteria, with the lower cut-off point being in the range 12–18.

Discussion

The Cochrane review of ginkgo suggests 'modest improvement' with regard to cognition [7], with efficacy at 6 months seen only when data were pooled across all doses.

One striking feature of ginkgo trials is the inclusion of patients with a wide range of aetiologies and disease severities. Although this could be seen as contributing to a strong evidence base for ginkgo, it should be noted that the natural course of cognitive decline varies depending on the underlying aetiology [28]. The ginkgo evidence base is so scattered in terms of patient population and outcome measures, that overall conclusions based on these heterogeneous studies are difficult to draw and are unlikely to be valid. Moreover, at the time of writing, the manufacture of ginkgo is not standardized, unlike that of the cholinesterase inhibitors, and thus the activity of ginkgo may vary from one preparation to another.

In reviewing more recent and methodologically sound ginkgo studies, the Cochrane reviewers comment that 2 studies – those by Brautigam et al. [29] and van Dongen et al. [30] – show little or no benefit for ginkgo. Furthermore, they were highly critical of the study by Le Bars et al. [31], noting that the option for investigators to withdraw patients who deteriorated from double-blind treatment in favour of 'humanitarian' open-label treatment with ginkgo 120 mg/day is 'not a satisfactory procedure in a randomized trial'. Given the high discontinuation rate, the reviewers are still awaiting further information before deciding whether or not to omit the trial from their meta-analysis [7], noting that the omission of these data would alter their conclusions on the efficacy of ginkgo to report less benefit.

In contrast, the methodological quality of the trials of cholinesterase inhibitors is generally good [32], all the studies being randomized, double-blind, placebo-controlled phase II or phase III studies [12–14] (table 3). When classified according to the criteria of Jadad et al. [33], 12 of the 15 trials were good quality, with only 2 of poor quality. Galantamine trials were particularly robust, in terms of both magnitude and consistency of effect sizes at the recommended dose [32].

In as far as comparisons can be made, the degree of cognitive improvement in patients receiving cholinesterase inhibitors is greater and more consistent than that seen in those receiving ginkgo. The efficacy of cholinesterase inhibitors is noted in treatment guidelines from the American Academy of Neurology, Canadian Coordinating Office for Health Technology Assessment and National Institute for Clinical Excellence, which recommend routine prescription for patients with mild to moderate AD [10, 11, 34]. The health technology assessments supporting these guidelines also noted benefits in other domains [9, 11, 35]. More recently, benefits for donepezil and galantamine have been observed in patients with advanced AD [36] and other forms of dementia, particularly vascular and mixed dementia [28, 37]. In many ginkgo studies, symptom severity was determined using an invalidated method of patient questioning or not reported in sufficient detail to enable a subgroup analysis, based on disease severity, to be conducted. Consequently, it is impossible to establish whether the effects of ginkgo are dependent on disease severity.

The Cochrane review noted that ginkgo is well tolerated in patients with dementia [7], with the incidence of adverse events not significantly different from placebo. Studies of donepezil, rivastigmine and galantamine have consistently shown that these agents are well tolerated by elderly patients with AD [12–14]. Adverse events are generally gastrointestinal and mild in severity.

The current evidence base on the efficacy of ginkgo would be improved greatly by one or more well-conducted, large-scale, double-blind, placebo-controlled clinical trials in a patient population with a well-defined diagnosis, such as mild to moderate AD. Should such a trial show benefit for ginkgo, then the logical next step would be to compare the efficacy of ginkgo with a cholinesterase inhibitor in a similarly well-designed head to head study.

Based on current evidence of its efficacy, the case for routine prescription of ginkgo is unconvincing. Ginkgo may have a place in the treatment of AD as a 'last resort' in patients who do not tolerate cholinesterase inhibitors. It may also act as a substitute in patients in whom cholinesterase inhibitor treatment is contraindicated, such as those with a history of seizures, gastric or duodenal ulcer, or bradycardia. Patients receiving ginkgo should be monitored as closely and critically, both for a therapeutic response and for adverse events, as those receiving cholinesterase inhibitors.

Conclusions

Overall, the clinical trial data for the cholinesterase inhibitors donepezil, rivastigmine and galantamine, reported in reviews by the Cochrane Collaboration, appear to be more consistent and robust than those for ginkgo, and also show greater effects on cognition. Considering the evidence, it is suggested that cholinesterase inhibitors should be used in preference to ginkgo in patients with mild to moderate AD [11]. When assessing the safety and efficacy of medications, an evidence-based approach requires that, in addition to evaluation of the main outcomes, consideration must be given to the quality of the clinical trials and the specific outcomes that are being assessed.

References

1 Hendrie HC: Epidemiology of dementia and Alzheimer's disease. Am J Geriatr Psychiatry 1998;6:S3–S18.
2 Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, Copeland JR, Dartigues JF, Jagger C, Martinez-Lage J, Soininen H, Hofman A: Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54:S4–S9.
3 Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS): Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet 2001;357:169–175.
4 McKenna DJ, Jones K, Hughes K: Efficacy, safety, and use of *Ginkgo biloba* in clinical and preclinical applications. Altern Ther Health Med 2001;7:70–90.
5 Yoshikawa T, Naito Y, Kondo M: *Ginkgo biloba* leaf extract: Review of biological actions and clinical applications. Antioxid Redox Signal 1999;1:469–480.
6 Christen Y, Maixent JM: What is *Ginkgo biloba* extract EGb 761? An overview – From molecular biology to clinical medicine. Cell Mol Biol 2002;48:601–611.
7 Birks J, Grimley Evans J, Van Dongen M: *Ginkgo biloba* for cognitive impairment and dementia (Cochrane Review); in: Cochrane Library, Issue 2, 2003. Update Software.
8 Watkins RW: Herbal therapeutics: The top 12 remedies. Emerg Med 2002;34:12–19.
9 Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, Waugh N: Clinical and Cost-Effectiveness of Donepezil, Rivastigmine and Galantamine for Alzheimer's Disease. London, National Institute for Clinical Excellence, 2001.
10 Husereau D, Wolfson C, Shukla VK: Drug Treatments for Alzheimer's Disease: Efficacy, Outcome Measurements and Cost-Effectiveness. Technology Overview No 4. Ottawa, Canadian Coordinating Office for Health Technology Assessment (CCOHTA), 2001.
11 Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, Gwyther L, Mohs RC, Thal LJ, Whitehouse PJ, DeKosky ST, Cummings JL: Practice parameter: Management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56:1154–1166.
12 Birks J, Grimley Evans J, Iakovidou V, Tsolaki M: Rivastigmine for Alzheimer's disease (Cochrane Review); in: Cochrane Library, Issue 2, 2003. Update Software.
13 Birks JS, Melzer D, Beppu H: Donepezil for mild and moderate Alzheimer's disease (Cochrane Review); in: Cochrane Library, Issue 2, 2003. Update Software.
14 Olin J, Schneider L: Galantamine for Alzheimer's disease (Cochrane Review); in: Cochrane Library, Issue 2, 2003. Update Software.
15 Deeks J: Statistical Methods Programmed in MetaView. Oxford, Cochrane Library, 1999.
16 DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.
17 Toulouse E, Piéron H: Toulouse-Piéron. Prueba Perceptiva y de Atención. Madrid, TEA Ediciones, 1986.
18 Robinson RA: Current Achievements in Geriatrics. London, Cassell, 1964, pp 190–203.
19 Wechsler D: A standardized memory scale for clinical use. J Psychol 1945;19:87–95.
20 Rosen WG, Mohs RC, Davis KL: A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364.
21 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
22 Allain H, Raoul P, Lieury A, LeCoz F, Gandon JM, d'Arbigny P: Effect of two doses of *Ginkgo biloba* extract (EGb 761) on the dual-coding test in elderly subjects. Clin Ther 1993;15:549–558.
23 Chartres JP, Bonnan P, Martin G: Reduction de posologie de médicaments psychotropes chez des personnes agées vivant en institution. Etude à double-insu chez des patients prenant soit de l'extrait de *Ginko biloba* 761 soit du placebo. Psychol Med 1987;19:1365–1375.
24 Hofferberth B: The efficacy of EGb 761 in patients with senile dementia of the Alzheimer type. A double-blind, placebo-controlled study on different levels of investigation. Hum Psychopharmacol 1994;9:215–222.
25 Maurer K, Ihl R, Dierks T, Frolich L: Clinical efficacy of *Ginkgo biloba* special extract EGb 761 in dementia of the Alzheimer type. J Psychiatr Res 1997;31:645–655.

26 Hartmann A, Frick M: Wirkung eines Ginkgo-Spezial-Extraktes auf psychometrische Parameter bei Patienten mit vaskulär bedingter Demenz. Münch Med Wochenschr 1991;133: S23–S25.
27 Haase J, Halama P, Horr R: Effectiveness of brief infusions with *Ginkgo biloba* special extract EGb 761 in dementia of the vascular and Alzheimer type. Z Gerontol Geriatr 1996;29: 302–309.
28 Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV: Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: A randomised trial. Lancet 2002; 359:1283–1290.
29 Brautigam MRH, Blommaert FA, Verleye G, Castermans J, Jansen Steur ENH, Kleijnen J: Treatment of age-related memory complaints with *Ginkgo biloba* extract: A randomized, placebo-controlled study. Phytomedicine 1998;5: 425–434.
30 van Dongen MC, van Rossum E, Kessels AG, Sielhorst HJ, Knipschild PG: The efficacy of Ginkgo for elderly people with dementia and age-associated memory impairment: New results of a randomized clinical trial. J Am Geriatr Soc 2000;48:1183–1194.
31 Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF: A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. JAMA 1997;278:1327–1332.
32 Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, Waugh N: Clinical and cost-effectiveness of donepezil, rivastigmine, and galantamine for Alzheimer's disease. A systematic review. Int J Technol Assess Health Care 2002;18:497–507.
33 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1–12.
34 National Institute for Clinical Excellence: Guidance on the use of Donepezil, Rivastigmine and Galantamine for the Treatment of Alzheimer's Disease. London, National Institute for Clinical Excellence, 2001.
35 Wolfson C, Oremus M, Shukla V, Momoli F, Demers L, Perrault A, Moride Y: Donepezil and rivastigmine in the treatment of Alzheimer's disease: A best-evidence synthesis of the published data on their efficacy and cost-effectiveness. Clin Ther 2002;24:862–886.
36 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; 57:613–620.
37 Meyer JS, Chowdhury MH, Xu G, Li YS, Quach M: Donepezil treatment of vascular dementia. Ann NY Acad Sci 2002;977:482–486.
38 Grässel E: Einfluß von Ginkgo-biloba-Extrakt auf die geistige Leistungsfähigkeit. Fortschr Med 1992;110:73–76.
39 Kanowski S, Herrmann WM, Stephan K, Wierich W, Hörr R: Proof of efficacy of the Ginkgo biloba special extract EGb 761 in outpatients suffering from primary degenerative dementia of the Alzheimer type and multi-infarct dementia. Pharmacopsychiat 1996;29:47–56.
40 Raskind MA, Peskind ER, Wessel T, Yuan W: Galantamine in AD. A 6-month randomized, placebo-controlled trial with a 6-month extension. Neurology 2000;54:2261–2268.
41 Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Parys W, Ding C: A 5-month, randomized, placebo-controlled trial of galantamine in Alzheimer's disease. Neurology 2000;54:2269–2276.
42 Wilcock GK, Lilienfeld S, Gaens E: Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: Multicentre randomised controlled trial. BMJ 2000;321:1445–1449.
43 Corey-Bloom J, Anand R, Veach J: A randomized trial evaluating the efficacy and safety of ENA-713 (Rivastigmine tartrate), a new cholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. Int J Geriatr Psychopharmacol 1998;1:55–65.
44 Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, Stähelin HB, Hartmann R, Gharabawi M: Efficacy and safety of rivastigmine in patients with Alzheimer's disease: International randomised controlled trial. BMJ 1999;318:633–640.
45 Rai GS, Shovlin C, Wesnes KA: A double-blind, placebo-controlled study of Ginkgo biloba extract ("Tanakan") in elderly outpatients with mild to moderate memory impairment. Curr Med Res Opin 1991;12:350–355.
46 Tariot P, Perdomo CA, Whalen E, Sovel MA, Scham EM: Age is not a barrier to donepezil treatment of Alzheimer's disease in the long-term care setting. Int Psychogeriatr 1999;11 (suppl 1):134.
47 Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT: A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 1998;50:136–145.
48 Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Möller HJ, Rogers SL, Friedhoff LT: The effects of donepezil in Alzheimer's disease – results from a multinational trial. Dement Geriatr Cogn Disord 1999;10:237–244.