Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments

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[Intervention Review]

Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments: a network meta-analysis

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ABSTRACT

Background

Vascular cognitive impairment (VCI) describes a broad spectrum of cognitive impairments caused by cerebrovascular disease, ranging from mild cognitive impairment to dementia. There are currently no pharmacological treatments recommended for improving either cognition or function in people with VCI. Three cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) are licenced for the treatment of dementia due to Alzheimer's disease. They are thought to work by compensating for reduced cholinergic neurotransmission, which is also a feature of VCI. Through pairwise comparisons with placebo and a network meta-analysis, we sought to determine whether these medications are effective in VCI and whether there are differences between them with regard to efficacy or adverse events.

Objectives

(1) To assess the efficacy and safety of cholinesterase inhibitors in the treatment of adults with vascular dementia and other VCI.

(2) To compare the effects of different cholinesterase inhibitors on cognition and adverse events, using network meta-analysis.

Search methods

We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group's register, MEDLINE (OvidSP), Embase (OvidSP), PsycINFO (OvidSP), CINAHL (EBSCOhost), Web of Science Core Collection (ISI Web of Science), LILACS (BIREME), ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform on 19 August 2020.

Selection criteria

We included randomised controlled trials in which donepezil, galantamine, or rivastigmine was compared with placebo or in which the drugs were compared with each other in adults with vascular dementia or other VCI (excluding cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)). We included all drug doses and routes of administration.

Data collection and analysis

Two review authors independently identified eligible trials, extracted data, assessed risk of bias, and applied the GRADE approach to assess the certainty of the evidence. The primary outcomes were cognition, clinical global impression, function (performance of activities of daily living), and adverse events. Secondary outcomes were serious adverse events, incidence of development of new dementia, behavioural

disturbance, carer burden, institutionalisation, quality of life and death. For the pairwise analyses, we pooled outcome data at similar time points using random-effects methods. We also performed a network meta-analysis using Bayesian methods.

Main results

We included eight trials (4373 participants) in the review. Three trials studied donepezil 5 mg or 10 mg daily (n= 2193); three trials studied rivastigmine at a maximum daily dose of 3 to 12 mg (n= 800); and two trials studied galantamine at a maximum daily dose of 16 to 24 mg (n= 1380). The trials included participants with possible or probable vascular dementia or cognitive impairment following stroke. Mean ages were between 72.2 and 73.9 years. All of the trials were at low or unclear risk of bias in all domains, and the evidence ranged from very low to high level of certainty.

For cognition, the results showed that donepezil 5 mg improves cognition slightly, although the size of the effect is unlikely to be clinically important (mean difference (MD) −0.92 Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) points (range 0 to 70), 95% confidence interval (CI) −1.44 to −0.40; high-certainty evidence). Donepezil 10 mg (MD −2.21 ADAS-Cog points, 95% CI −3.07 to −1.35; moderate-certainty evidence) and galantamine 16 to 24 mg (MD −2.01 ADAS-Cog point, 95%CI −3.18 to −0.85; moderate-certainty evidence) probably also improve cognition, although the larger effect estimates still may not be clinically important. With low certainty, there may be little to no effect of rivastigmine 3 to 12 mg daily on cognition (MD 0.03 ADAS-Cog points, 95% CI −3.04 to 3.10; low-certainty evidence).

Adverse events reported in the studies included nausea and/or vomiting, diarrhoea, dizziness, headache, and hypertension. The results showed that there was probably little to no difference between donepezil 5 mg and placebo in the number of adverse events (odds ratio (OR) 1.22, 95% CI 0.94 to 1.58; moderate-certainty evidence), but there were slightly more adverse events with donepezil 10 mg than with placebo (OR 1.95, 95% CI 1.20 to 3.15; high-certainty evidence). The effect of rivastigmine 3 to 12 mg on adverse events was very uncertain (OR 3.21, 95% CI 0.36 to 28.88; very low-certainty evidence). Galantamine 16 to 24 mg is probably associated with a slight excess of adverse events over placebo (OR 1.57, 95% CI 1.02 to 2.43; moderate-certainty evidence).

In the network meta-analysis (NMA), we included cognition to represent benefit, and adverse events to represent harm. All drugs ranked above placebo for cognition and below placebo for adverse events. We found donepezil 10 mg to rank first in terms of benefit, but third in terms of harms, when considering the network estimates and quality of evidence. Galantamine was ranked second in terms of both benefit and harm. Rivastigmine had the lowest ranking of the cholinesterase inhibitors in both benefit and harm NMA estimates, but this may reflect possibly inadequate doses received by some trial participants and small trial sample sizes.

Authors' conclusions

We found moderate- to high-certainty evidence that donepezil 5 mg, donepezil 10 mg, and galantamine have a slight beneficial effect on cognition in people with VCI, although the size of the change is unlikely to be clinically important. Donepezil 10 mg and galantamine 16 to 24 mg are probably associated with more adverse events than placebo. The evidence for rivastigmine was less certain.

The data suggest that donepezil 10 mg has the greatest effect on cognition, but at the cost of adverse effects. The effect is modest, but in the absence of any other treatments, people living with VCI may still wish to consider the use of these agents. Further research into rivastigmine is needed, including the use of transdermal patches.

PLAIN LANGUAGE SUMMARY

Medicines to treat people with vascular dementia and other vascular cognitive impairments

Review question

What is the evidence for cholinesterase inhibitors (medicines designed to improve memory and thinking in people with dementia), when used with people who have vascular dementia?

Background

Vascular dementia (or vascular cognitive impairment) is a term used when a person has problems with memory and thinking that are caused by a disruption of blood supply. There are few drug treatments for vascular dementia.

In this review, we evaluated three drugs from the cholinesterase inhibitor family, donepezil, rivastigmine, and galantamine. These medications are widely used in Alzheimer's dementia but may also be useful in people with vascular dementia. Previous reviews of these cholinesterase inhibitor drugs could not draw definitive conclusions for people with vascular dementia.

Purpose of this review

We wanted to learn whether cholinesterase inhibitors benefit people with vascular dementia. We were interested in their effects on memory, thinking, and daily functioning. We wanted to learn of any harms associated with these drugs.

As some time has passed since the previous reviews, we wanted to update them by searching for new studies. We combined the three previous reviews on donepezil, rivastigmine and galantamine into one review.

What we did

We searched for studies that described the effects of donepezil, rivastigmine, and galantamine for people with vascular dementia. We searched databases of scientific studies and contacted drug manufacturers and experts in vascular dementia. Our search is current to 19 August 2020.

To be included in our review, studies had to randomly assign people with vascular dementia to treatment with a cholinesterase inhibitor, or a dummy pill (placebo) and then compare the two groups. Studies comparing one cholinesterase inhibitor against another were also included. We combined the results of the included studies for each medicine to estimate how effective they were and how likely they were to cause side effects. We assessed how well the studies were conducted and how credible the results were.

We did not find studies which compared different cholinesterase inhibitors with each other. To see whether the different cholinesterase inhibitor drugs differed in their effects, we used a technique called network meta-analysis, which can provide an idea of how the medicines might perform if they were compared head-to-head.

What we found

We found 8 studies including a total of 4373 people with vascular dementia (or vascular cognitive impairment). The studies tested the drug donepezil at two different doses (5mg and 10mg daily), against each other and against placebo. Rivastigmine and galantamine were tested against placebo only. Rivastigmine is available as a skin patch, but the studies only tested the pill version. All eight studies evaluated participants when they first started taking the medicine or placebo and again six months later. Different tests were used to measure the effects. All studies included tests of memory, thinking and reported side effects.

People taking donepezil or galantamine had better scores on memory and thinking tests than people taking placebo, but the benefits were modest and may not be large enough to be evident in daily life. There was no evidence of a difference for rivastigmine, but the evidence was less certain, and the doses taken by some participants may have been too low to show an effect. We found evidence that when compared to placebo, side effects such as nausea and diarrhoea, were more common in people taking donepezil 10mg and galantamine, but probably not donepezil 5mg. We were unable to draw conclusions about side effects of rivastigmine from the studies.

No vascular dementia trials comparing the different cholinesterase against each other have been conducted. Using the information from the individual studies, we made indirect assessments of how the drugs would perform if tested head-to-head. The results suggested that donepezil 10 mg had the greatest effect on memory and thinking, but caused more side effects than donepezil 5 mg or galantamine.

There were only a small number of studies for each drug. Certainty in the results varied between drugs and between outcomes, from high to very low certainty. The studies showed only a small benefit at most; however, in the absence of any other treatments, people living with dementia may still wish to consider use of these drugs.

SUMMARY OF FINDINGS

Summary of findings 1. Donepezil 5 mg compared to placebo for vascular dementia and other vascular cognitive impairments

Donepezil 5 mg compared to placebo for vascular dementia and other vascular cognitive impairments

Patient or population: vascular dementia and other vascular cognitive impairments
Intervention: donepezil 5 mg
Comparison: placebo

Setting: outpatients

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with donepezil 5 mg				
Cognitive function: ADAS-Cog at 24 weeks Scale from: 0 to 70	Mean change from baseline ranged across control groups from −0.58 to 0.34. (Higher score indicates greater impairment.)	MD −0.92 (−1.44 to −0.40)	-	1601 (3 RCTs) Black 2003 Roman 2010 Wilkinson 2003	⊕⊕⊕⊕ HIGH	Small benefit of donepezil 5 mg, may not be clinically important
Clinical global impression: CIBIC-Plus (Improvement) at 24 weeks 7-point Likert scale	Study population 283 per 1000 (number demonstrating an improvement with placebo)	381 per 1000 (303 to 472)	OR 1.58 (1.10 to 2.27)	712 (2 RCTs) Black 2003 Wilkinson 2003	⊕⊕⊕⊕ HIGH	Small benefit of donepezil 5 mg, may not be clinically important
Functional performance and activities of daily living: ADFACS at 24 weeks 16-item score ranging from 0 to 54	Mean change from baseline ranged across control groups from 0.76 to 1.44. (Higher score indicates greater impairment.)	MD −0.73 (−1.52 to 0.06)	-	798 (2 RCTs) Black 2003 Wilkinson 2003	⊕⊕⊕⊖ MODERATE[1]	Probably no effect of donepezil 5 mg
Adverse events (all reported adverse events grouped) at 24 weeks	Study population 830 per 1000	856 per 1000 (821 to 885)	OR 1.22 (0.94 to 1.58)	1772 (3 RCTs) Black 2003	⊕⊕⊕⊖ MODERATE[1]	Probably no difference between donepezil 5 mg and placebo

				Roman 2010 Wilkinson 2003		
Serious adverse events (excluding death) at 24 weeks	Study population 163 per 1000	155 per 1000 (123 to 192)	OR 0.94 (0.72 to 1.22)	1772 (3 RCTs) Black 2003 Roman 2010 Wilkinson 2003	⊕⊕⊕⊖ MODERATE[1]	Probably no difference between donepezil 5 mg and placebo

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial; **ADAS-COG**: Alzheimer's Disease Assessment Scale - Cognitive subscale; **CIBIC-Plus:** Clinician's Interview-Based Impression of Change Plus Caregiver Input; **ADFACS:** Alzheimer's Disease Functional Assessment of Change Scale.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once due to imprecision: the 95% CI includes a result that would not be considered clinically important and a result that would be considered important.

Summary of findings 2. Donepezil 10 mg compared to placebo for vascular dementia and other vascular cognitive impairments

Donepezil 10 mg compared to placebo for vascular dementia and other vascular cognitive impairments

Patient or population: vascular dementia and other vascular cognitive impairments
Intervention: donepezil 10 mg
Comparison: placebo

Setting: outpatients

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with donepezil 10 mg				

Cognitive function: ADAS-Cog at 24 weeks Scale from: 0 to 70	Mean change from baseline ranged across control groups from −0.58 to 0.34. (Higher score indicates greater impairment.)	MD −2.21 (−3.07 to −1.35)	-	608 (2 RCTs) Black 2003 Wilkinson 2003	⊕⊕⊕⊖ MODERATE[1]	Probably a small benefit of donepezil 10 mg, may not be clinically important
Clinical global impression: CIBIC-Plus (Improvement) at 24 weeks 7-point Likert scale	Study population 283 per 1000	312 per 1000 (235 to 401)	OR 1.15 (0.78 to 1.70)	699 (2 RCTs) Black 2003 Wilkinson 2003	⊕⊕⊕⊖ MODERATE[1]	Probably no effect with donepezil 10 mg
Functional performance and activities of daily living: ADFACS at 24 weeks 16-item score ranging from 0 to 54	Mean change from baseline ranged across control groups from 0.76 to 1.44. (Higher score indicates greater impairment.)	MD −0.95 (−1.73 to −0.17)	-	813 (2 RCTs) Black 2003 Wilkinson 2003	⊕⊕⊕⊖ MODERATE[2]	Probably a small benefit of donepezil 10 mg, may not be clinically important
Adverse events (all adverse events) at 24 weeks	Study population 875 per 1000	932 per 1000 (894 to 957)	OR 1.95 (1.20 to 3.15)	813 (2 RCTs) Black 2003 Wilkinson 2003	⊕⊕⊕⊕ HIGH	A slight excess of adverse events with donepezil 10 mg over placebo
Serious adverse events (excluding death) at 24 weeks	Study population 179 per 1000	200 per 1000 (150 to 263)	OR 1.15 (0.81 to 1.64)	813 (2 RCTs) Black 2003 Wilkinson 2003	⊕⊕⊕⊖ MODERATE[1]	Probably no difference between donepezil 10 mg and placebo

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial; **ADAS-COG**: Alzheimer's Disease Assessment Scale - Cognitive subscale; **CIBIC-Plus:** Clinician's Interview-Based Impression of Change Plus Caregiver Input; **ADFACS:** Alzheimer's Disease Functional Assessment of Change Scale.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once due to imprecision: the 95% CI includes a result that would not be considered clinically important and a result that would be considered important.
[2]Downgraded once due to imprecision: different outcome measures used to assess functional performance.

Summary of findings 3. Rivastigmine compared to placebo for vascular dementia and other vascular cognitive impairments

Rivastigmine compared to placebo for vascular dementia and other vascular cognitive impairments

Patient or population: vascular dementia and other vascular cognitive impairments
Intervention: rivastigmine (3 to 12 mg/day, oral preparation)
Comparison: placebo

Setting: outpatients

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with rivastigmine				
Cognitive function: ADAS-Cog at 24 to 26 weeks Scale from: 0 to 70	Mean change from baseline ranged across control groups from −2.8 to 0.4. (Higher score indicates greater impairment.)	MD 0.03 (−3.04 to 3.1)	-	748 (2 RCTs) Ballard 2008; Narasimhalu 2009	⊕⊕⊖⊖ LOW[1,2]	There may be no effect with rivastigmine.
Functional performance and activities of daily living at 24 to 26 weeks: ADCS-ADL and IADL scales	On the ADCS-ADL, the mean change from baseline ranged across the control groups from −0.7 to 5.2. The inverted mean change from baseline on the IADL: 0.1	SMD 0.02 (−0.12 to 0.16)	-	800 (3 RCTs) Ballard 2008 Mok 2007 Narasimhalu 2009	⊕⊕⊖⊖ LOW[2,3]	There may be no effect with rivastigmine.
Adverse events (all adverse events) at 24 to 26 weeks	Study population 287 per 1000	563 per 1000 (126 to 921)	OR 3.21 (0.36 to 28.88)	831 (3 RCTs) Ballard 2008 Mok 2007 Narasimhalu 2009	⊕⊖⊖⊖ VERY LOW[1,4]	Very uncertain evidence of no difference in number of adverse events with rivastigmine compared to placebo
Serious adverse events (excluding death) at 24 to 26 weeks	Study population		OR 1.42	622 (2 RCTs)	⊕⊕⊖⊖ LOW[4]	There may be no difference in number of serious adverse events

	118 per 1000	160 per 1000 (107 to 231)	(0.90 to 2.25)	Ballard 2008; Narasimhalu 2009	with rivastigmine compared to placebo.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial; **SD:** standard deviation; **SMD:** standardised mean difference; **ADAS-COG**: Alzheimer's Disease Assessment Scale - Cognitive subscale; **ADCS-ADL:** Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale; **IADL**: Instrumental Activities of Daily Living Scale.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once due to inconsistency in point estimates.
[2]Downgraded once due to imprecision: the 95% CI includes a result that would not be considered clinically important and a result that would be considered important.
[3]Downgraded once due to imprecision: different outcomes measures used to assess functional performance and activities of daily living. The ADCS-ADL is a 54-point scale, in which a lower score indicates a greater impairment. The IADL is a 0-to-8-point scale, in which a higher score indicates greater impairment. Consequently, the inverted mean change was used for IADL so that both scales would have the same direction for analysis.
[4]Downgraded twice due to imprecision: the 95% CI includes a result that would not be considered clinically important and a result that would be considered important.

Summary of findings 4. Galantamine compared to placebo for vascular dementia and other vascular cognitive impairments

Galantamine compared to placebo for vascular dementia and other vascular cognitive impairments

Patient or population: vascular dementia and other vascular cognitive impairments
Intervention: galantamine (16 to 24 mg/day)
Comparison: placebo

Setting: outpatients

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with galantamine				
Cognitive function: ADAS-Cog at 26 weeks	Mean change from baseline ranged across the control groups from 0.3 to 1.	MD −2.01 (−3.18 to −0.85)	-	1188 (2 RCTs)	⊕⊕⊕⊖ MODERATE[1]	Probably a small benefit of galantamine, may not be clinically important

Scale from: 0 to 70	(Higher score indicates greater impairment.)			Auchus 2007 Erkinjuntti 2002		
Clinical global impression: CIBIC-Plus (Improvement) at 26 weeks	Study population 268 per 1000	326 per 1000 (274 to 384)	OR 1.32 (1.03 to 1.70)	1326 (2 RCTs) Auchus 2007 Erkinjuntti 2002	⊕⊕⊕⊕ HIGH	Small benefit of galantamine, may not be clinically important
Functional performance and activities of daily living at 26 weeks ADCS-ADL and DAD	On the ADCS-ADL, the mean change from baseline in the control group was 1.3 (lower scores indicate greater impairment). The mean change from baseline on the DAD score was −4.4 (lower scores indicate greater impairment).	SMD 0.11 (−0.24 to 0.46)	-	1174 (2 RCTs) Auchus 2007 Erkinjuntti 2002	⊕⊕⊖⊖ LOW[2,3]	May be no effect of galantamine
Adverse events (all adverse events) at 26 weeks	Study population 701 per 1000	787 per 1000 (705 to 851)	OR 1.57 (1.02 to 2.43)	1378 (2 RCTs) Auchus 2007 Erkinjuntti 2002	⊕⊕⊕⊖ MODERATE[3]	Probably a slight excess of adverse events with galantamine over placebo
Serious adverse events (excluding deaths) at 26 weeks	Study population 185 per 1000	202 per 1000 (150 to 265)	OR 1.12 (0.78 to 1.59)	786 (1 RCT) Auchus 2007	⊕⊕⊕⊖ MODERATE[4]	Probably no difference between galantamine and placebo

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial; **SD:** standard deviation; **SMD:** standardised mean difference; **ADAS-COG**: Alzheimer's Disease Assessment Scale - Cognitive subscale; **CIBIC-Plus:** Clinician's Interview-Based Impression of Change Plus Caregiver Input; **ADCS-ADL:** Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale; **DAD:** Disability Assessment for Dementia Scale

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once due to inconsistency in point estimates.
[2]Downgraded once due to imprecision: two scales were combined for analysis for functional performance and activities of daily living. The ADCS-ADL is a 54-point scale, in which a lower score indicates a greater impairment. The DAD is a 100-point scale, in which a lower score indicates a greater impairment (downgraded once).
[3]Downgraded once due to imprecision: the 95% CI includes a result that would not be considered clinically important and a result that would be considered important.
[4]Downgraded once due to imprecision: only one trial included in result.

BACKGROUND

Description of the condition

Vascular cognitive impairment (VCI) describes a broad spectrum of cognitive impairments caused by cerebrovascular disease, ranging from mild cognitive impairment to dementia (Dichgans 2017; van der Flier 2018). In 2017, the Vascular Impairment of Cognition Classification Consensus Study (VICCCS) led to a revised conceptualisation of VCI, in which VCI is divided into mild and major subtypes according to the level of impairment (Skrobot 2017). Mild VCI is not subdivided, but major VCI (or vascular dementia) has four subdivisions: post-stroke dementia, subcortical ischaemic vascular dementia, multi-infarct (cortical) dementia, and mixed dementias. For the purposes of this review, we treated VCI as an umbrella term that incorporates vascular dementia and other cognitive syndromes with a presumed vascular basis (i.e. all categories listed in the VICCCS definition, including mild VCI and all subdivisions of major VCI). Two criteria must be met for a diagnosis of VCI: firstly, a cognitive deficit demonstrated through neuropsychological testing, and secondly, the presence of cerebrovascular disease. VCI is further classified as ‘probable’ or ‘possible’, according to the level of evidence that there is a causal relationship between the cognitive impairment and the vascular disease (Dichgans 2017).

The clinical presentation of VCI depends on the type, extent, and location of the underlying cerebrovascular pathology. Possible symptoms of VCI are numerous and include memory problems, mental slowness, and problems with executive function (such as planning, sequencing, and problem solving). Patients often report difficulties with higher-order cognitive functions, such as planning, organising, and monitoring behaviour. Behavioural symptoms and psychological symptoms, including emotional lability, anxiety, depression, and apathy, are also commonly reported. Other neurological signs and symptoms often occur, including reflex asymmetry, dysarthria (difficulty with speech), gait disorders, and problems with balance, parkinsonism, rigidity, or urinary incontinence (O'Brien 2003; van der Flier 2018). VCI due to a single stroke presents abruptly, whilst symptoms and signs due to subcortical damage, such as lacunae and white matter disease (a progressive age-related decline in nerves that connect areas of brain to each other), typically develop more insidiously (Erkinjuntti 2004).

As life expectancy increases, VCI has become a growing public health issue. Approximately 36 million people have dementia worldwide, and this number is expected to reach 66 million by 2030 and 115 million by 2050 (Wortmann 2012). Vascular dementia is the second most common form of dementia after Alzheimer’s disease and accounts for at least 20% of dementia cases (Wu 2016). The prevalence of VCI is strongly age-related. In participants aged 65 to 84 years, the prevalence of mild forms of VCI that do not reach the criteria required for a diagnosis of dementia is higher than that of vascular dementia. Rates of conversion to dementia, institutionalisation, and mortality are significantly increased in these patients, suggesting that people with mild VCI are an important target population for the prevention of poor outcomes (Dichgans 2017).

Description of the intervention

Accurate assessment and management of vascular risk factors are a key priority in the treatment of VCI, particularly early in the disease when preventive strategies may prove to be most effective (Ritter 2015). Although primary prevention trials have suggested that treatment of hypertension, adherence to a Mediterranean diet, physical activity, and smoking cessation may reduce the risk of cognitive decline, there is limited evidence regarding these interventions for improving cognition in established VCI (Ritter 2015). There are currently no specific pharmacological treatments recommended for improving either cognition or function in VCI. Management strategies used for patients with VCI are similar to those for other forms of dementia. Key principles include treating psychological and behavioural comorbidities, providing information and support to the patient and caregivers, and maximising the patient's independence (Dichgans 2017).

Cholinesterase inhibitors are medicines recommended as options for managing mild-to-moderate dementia due to Alzheimer's disease in several clinical guidelines (e.g. Hort 2010; NICE 2018). Alzheimer's disease is the most common cause of dementia and is found in approximately 70% of autopsies of people with dementia (Qiu 2009). The three cholinesterase inhibitors currently marketed for the treatment of Alzheimer's disease are donepezil, rivastigmine, and galantamine. Cholinesterase inhibitors are taken orally once or twice a day; rivastigmine can also be applied transdermally. Tacrine is no longer licenced. Although memantine is often considered alongside cholinesterase inhibitors, it is a different drug class.

Previous Cochrane Reviews have reported modest cognitive benefit from cholinesterase inhibitors in mild-to-moderate dementia due to VCI (Malouf 2004; Craig 2006; Birks 2013), but a number of harms related to use of cholinesterase inhibitor treatment have also been reported, with evidence of more adverse events overall in people treated with a cholinesterase inhibitor than with placebo. Nausea, vomiting, and diarrhoea in particular were reported significantly more frequently in the cholinesterase inhibitor groups than in the placebo groups (Birks 2006). Serious adverse events have also been reported, including stroke, pneumonia, and myocardial infarction (Birks 2006).

How the intervention might work

Cholinesterase inhibitors inhibit the activity of the enzyme acetylcholinesterase, and increase acetylcholine levels by decreasing the rate at which the substance is broken down. The aim of prescribing cholinesterase inhibitors for Alzheimer's disease is to compensate for the loss of cholinergic brain cells and to boost cholinergic neurotransmission in forebrain regions (Colović 2013). Reductions in acetylcholine and acetyltransferase activity (markers of cholinergic neurotransmission) are common to both Alzheimer's disease and VCI, raising the possibility that these drugs may be beneficial for both conditions (Toghi 1996; Perry 1997). Donepezil is a second-generation cholinesterase inhibitor that is a non-competitive, reversible antagonist of cholinesterase and is highly selective for acetylcholinesterase compared to butyryl-cholinesterase (Dawbarn 2001). Rivastigmine is a 'pseudo-irreversible' inhibitor of acetylcholinesterase and also of butyryl-cholinesterase, which is a non-specific cholinesterase enzyme. Galantamine is a reversible, competitive inhibitor

of acetylcholinesterase with minimal butyryl-cholinesterase inhibitory activity (Lilienfeld 2002).

Why it is important to do this review

To date, the US Food and Drug Administration and the European Medicines Agency have not approved any pharmacological treatments for VCI or vascular dementia symptoms. Three previous Cochrane Reviews have investigated the efficacy and safety of individual cholinesterase inhibitors for VCI. The review of donepezil for VCI reported some improvements in cognitive function, activities of daily living, and global measures of change (Malouf 2004). The review investigating galantamine in VCI concluded that there were some advantages over placebo in the areas of cognition and global clinical state (Craig 2006). Similarly, rivastigmine had some benefit on cognitive function at 24 weeks in people with VCI (Birks 2013). However, these reviews did not investigate potential differences in efficacy between these medications, therefore a review that covered the evidence for all three cholinesterase inhibitors would be helpful to clinicians.

A number of years have passed since the publication of the original reviews. This new, overarching review ensured that any new trials were included. It also allowed the use of contemporary approaches to evidence synthesis (e.g. use of GRADE methods to assess evidence quality) that were not in use when the previous reviews were written. For the first time, we have included all cholinesterase inhibitors in a network meta-analysis (NMA) in order to address the question of which cholinesterase inhibitor, if any, is the most efficacious and safest in the management of VCI (Salanti 2012).

OBJECTIVES

- To assess the efficacy and safety of cholinesterase inhibitors in the treatment of adults with vascular dementia and other VCI.
- To compare the effects of different cholinesterase inhibitors on cognition and adverse events in adults with vascular dementia and other VCI, using network meta-analysis.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel-group, randomised controlled trials (RCTs) in which participants with VCI are assigned to treatment with a cholinesterase inhibitor or placebo, or to alternative cholinesterase inhibitors. We included any identified trial regardless of publication status. Restricting eligibility to RCTs meant that there were no differences in study design between interventions, satisfying the transitivity assumption for the NMA.

Types of participants

We included participants diagnosed as having vascular dementia on the basis of any validated and internationally recognised diagnostic framework for dementia, including the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), APA 2013, and the ICD-11 Classification of Mental and Behavioural Disorders: Clinical Description and Diagnostic Guidelines (WHO 1992), and any classification systems specific to VCI, such as the National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l' Enseignement en Neurosciences (NINDS/AIREN) (Roman 1993). Diagnosis of VCI with no dementia (sometimes labelled VCIND) was based on cognitive test scores and a clinical diagnosis to ensure the distinction between vascular and non-vascular impairment. We considered that all participants identified by these criteria would be equally likely to be treated with any of the cholinesterase inhibitors, thus satisfying the transitivity assumption for the NMA.

We made an a priori decision that we would not include monogenic conditions such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in this review. This early-onset familial form of dementia may not be a good model of the common forms of VCI seen in older age. CADASIL is included in another Cochrane Review covering cholinesterase inhibitors for rarer dementias (Li 2015).

If studies were conducted in a population with a mixture of dementia subtypes, we included the data if the proportion of participants with VCI was 80% or more. We excluded studies in which the population was described as having undifferentiated dementia, or where dementia subtype was not described, because based on general population frequencies it would be unlikely that more than 80% would have VCI.

Types of interventions

We included any cholinesterase inhibitor licenced for the treatment of Alzheimer's disease or another form of dementia, that is donepezil, galantamine, and rivastigmine.

These medications can be administered orally or, in the case of rivastigmine, transdermally. All routes of administration were eligible for inclusion.

The licenced cholinesterase inhibitors are available in a range of doses. The drugs usually have a dose-titration period. We considered the final dose achieved in our analyses. Reviews in non-vascular dementias suggest that doses may differ in efficacy and adverse events. All doses were eligible for inclusion, but we intended to consider studies using a final dose within the manufacturer's recommended range separately from other studies. For donepezil, we planned to include studies where the final dose was a licenced oral dose of 5 mg, 10 mg, or 23 mg daily; we planned to consider each of these doses separately. For rivastigmine, we planned to assess the manufacturer's recommended final dose of 6 to 12 mg daily for the oral preparation, or 4.6 mg/24 hours or 9.5 mg/24 hours for the transdermal preparation; any other doses that were studied would be considered separately. For galantamine, we planned to assess the manufacturer's recommended oral dose of 16 to 24 mg (standard or modified-release); any other doses that were studied would be considered separately.

Eligible comparator interventions were placebo, or, for the network meta-analysis only, an alternative cholinesterase inhibitor.

Types of outcome measures

Primary outcomes

- Cognitive function (e.g. the cognitive part of the Alzheimer's Disease Assessment Scale, ADAS-Cog; Syndrom-Kurz test)
- Clinical global impression (e.g. Clinician's Interview-Based Impression of Change scale, CIBIC-Plus; Clinical Global

Impression of Change, CGIC; Clinical Global Impression, CGI (which measures of symptom severity, treatment response, and treatment efficacy); Sandoz Clinical Assessment Geriatric Scale, SCAG)
- Functional performance in activities of daily living (e.g. Alzheimer's Disease Cooperative Study-Activities of Daily Living, ADCS-ADL; Behavioural Rating Scale for Geriatric Patients, BGP)
- Number of adverse events (including nausea and/or vomiting, diarrhoea, dizziness, loss of appetite and/or anorexia, headache and hypertension). If the number of adverse events was not presented, we used the number of participants with any adverse events (one or more) in a study. We accepted adverse events as defined in the included studies.

Secondary outcomes

- Serious adverse events (SAEs) (including death, transient ischaemic attack or stroke, focal motor seizures, pneumonia, and myocardial infarction or congestive heart failure)
- Incidence of development of new dementia: if any studies were concerned exclusively with vascular mild cognitive impairments or related syndromes, then we described rates of incident dementia as an outcome. This outcome was considered separately to the other outcomes of interest to the dementia population.
- Behavioural disturbance (e.g. Neuropsychiatric Inventory, NPI)
- Carer burden (e.g. Carer - Dementia Quality of Life Instrument)
- Institutionalisation
- Quality of life (e.g. Dementia Quality of life Instrument, Alzheimer's Disease-Related Quality of Life Measure)
- Death

NMA outcomes

We used cognition to represent benefit outcomes and adverse events to represent harms in the NMA. We selected these outcomes as they were the most consistently reported in the included studies.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's (CDCIG) specialised register on 19 August 2020.

ALOIS is maintained by the Information Specialists for the Cochrane Dementia and Cognitive Improvement Group, and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy elderly populations. The studies are identified through searching:

- a number of major healthcare databases: MEDLINE, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO;
- a number of trial registers: US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov and the World Health Organization International Clinical Trials Register Platform (WHO ICTRP), which covers ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials; and the Netherlands National Trials Register, plus others;
- the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library);
- grey literature sources: ISI Web of Science Core Collection.

To view a list of all sources searched for ALOIS, visit the ALOIS website (www.medicine.ox.ac.uk/alois).

Details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement, and cognitive enhancement trials, can be viewed on the Cochrane Dementia and Cognitive Improvement Group's website (dementia.cochrane.org/searches).

We ran additional searches in MEDLINE, Embase, CINAHL, PsycINFO, LILACS (Latin American and Caribbean Health Science Information database), ClinicalTrials.gov, and the WHO ICTRP from inception to ensure that the searches for this review were as comprehensive and as up-to-date as possible. The search strategies used are shown in Appendix 1.

Searching other resources

We checked the reference lists of eligible studies and previous systematic reviews to identify additional studies. We contacted pharmaceutical companies (Eisai and Pfizer for donepezil (Aricept); Shire for galantamine (Reminyl); Lundbeck for rivastigmine (Exelon)) and searched their press releases pertaining to cholinesterase inhibitors. We requested all conference posters presented by relevant authors and those sponsored by the pharmaceutical companies. We sought other grey literature through handsearching of reference lists of retrieved relevant trials and systematic reviews. We also handsearched relevant conference abstracts that are not covered in ALOIS, specifically; International Stroke Conference 2017 to 2019 (published in *Stroke*); European Stroke Organisation Conference 2017 to 2019 (published in *European Stroke Journal*); and Alzheimer's Association International Conference 2017 to 2019 (published in *Alzheimer's & Dementia*).

Data collection and analysis

Selection of studies

We used Cochrane's Screen4Me workflow to help in the assessment of the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened by Cochrane Crowd (Cochrane's citizen science platform) and have been labelled as an RCT or not an RCT; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs; and Cochrane Crowd - Cochrane's crowd-sourcing platform where contributors help to identify RCTs and other study types.

For more information about Screen4Me and the evaluations that have been done, visit the Screen4Me web page on the Cochrane Information Specialists Portal (community.cochrane.org/organizational-info/resources/resources-groups/information-specialists-portal). More detailed information regarding evaluations of the Screen4Me components can also be found in the following publications: McDonald 2017; Thomas 2017; Marshall 2018; Noel-Storr 2018.

After the results had been through the Screen4Me workflow, two review authors (CEB and AHAR) independently assessed the

remainder. Any disagreements were resolved through discussion and consultation with a third review author (TJQ). We created a PRISMA flow diagram to map out the number of records identified, included, and excluded (Figure 1). We listed all studies excluded after full-text assessment and their reasons for exclusion in a 'Characteristics of excluded studies' table.

Figure 1. Study flow diagram.

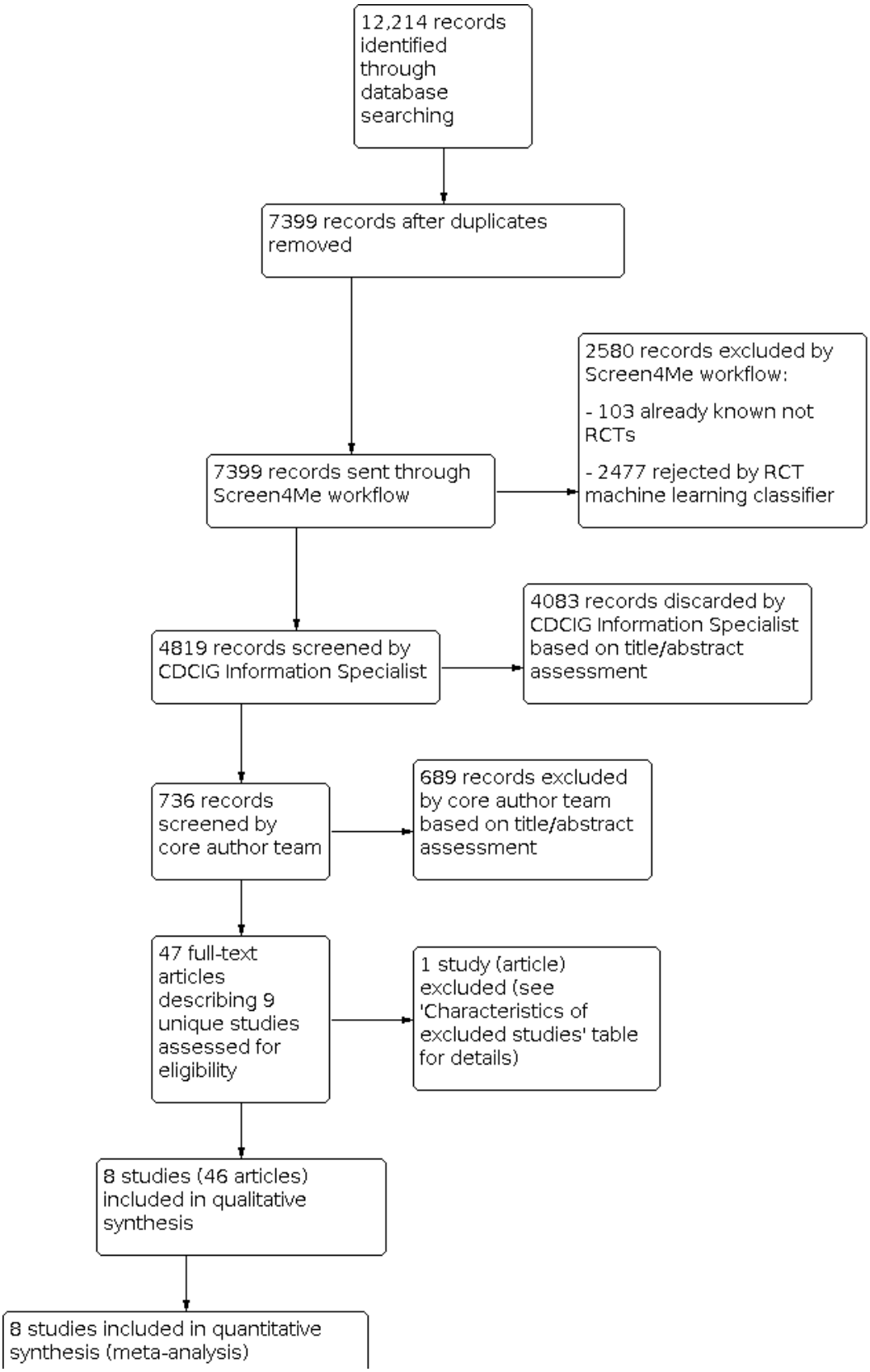
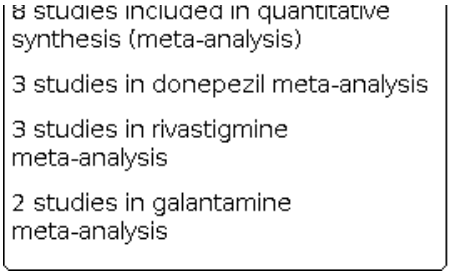


Figure 1. (Continued)



Data extraction and management

Two review authors independently extracted data using a standardised data extraction form.

We extracted results for the primary outcome measures at the following time points, where reported: up to 3 months, from 3 months to 6 months, from 6 months to 18 months, and more than 18 months. We extracted data from more than one time point, if such information was available.

We extracted the following data that may act as effect modifiers from each included study:

- population: diagnostic criteria; baseline mean age; male-to-female ratio; comorbidities; concurrent medications; ethnicity and socioeconomic status;
- interventions: duration of the intervention, including duration of any wash-out, run-in, or titration period; dosage regimen, including during any titration period; route of administration;
- outcome measures: measure used, time point completed;
- 'Risk of bias' domains (see Assessment of risk of bias in included studies);
- funding sources.

Assessment of risk of bias in included studies

Two review authors (CEB and AHAR) independently assessed the risk of bias in each study. Any disagreements were resolved by discussion to reach consensus, involving a third review author (TJQ) when necessary. Using the Cochrane 'Risk of bias' tool (Higgins 2017), we assessed the risk of bias of each included study based on the following domains: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. We judged the level of risk of bias within each study explicitly for each domain as being at 'low', 'high', or 'unclear' risk of bias. We described all judgements fully and presented our conclusions in the 'Risk of bias' tables.

We judged studies as being at low risk of bias for the incomplete outcome data domain when numbers of and causes for dropouts were balanced between arms. For continuous outcomes, we considered the following factors: the level of missing data, the difference between groups, and the reasons for missingness. We also took into account whether the approach to missing data (e.g. observed case (OC) or last observation carried forward (LOCF)) gave different effect estimates. For dichotomous outcomes, we compared the proportions missing in each group with each other and with the adverse event risk, by visual inspection. If there was a substantial difference in missing data between groups, or the proportion of missing data was comparable with the adverse events risk, we rated the risk of attrition bias as high. We assessed selective outcome reporting by comparing the outcomes the trialists intended to analyse against the published study results. Where no trial protocol was available, we assigned a judgement of high risk of bias when study results did not include the primary outcome measures set out in their methods section.

Measures of treatment effect

For binary outcomes, we used odds ratios (ORs) with 95% confidence intervals (CIs) as the measure of treatment effect. For continuous outcomes, we used mean differences (MDs) with 95% CI. If different instruments were used to measure the same continuous outcome, we used the standardised mean difference (SMD) with 95% CIs. If outcomes were reported both as binary and continuous outcomes, we analysed binary outcomes in one analysis and continuous outcomes in another analysis. For time-to-event outcomes, we planned to use hazard ratios (HRs) and their 95% CIs.

We presented results from the network meta-analysis (NMA) as summary relative effect sizes for each possible pair of treatments. For each study intervention, we also estimated the ranking probabilities for all treatments of being at each possible rank. We then obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks (Salanti 2011).

Unit of analysis issues

We did not find any cluster-randomised or cross-over trials for inclusion in the review.

For multi-arm trials, we included all intervention groups meeting the criteria for inclusion in pairwise comparisons.

Dealing with missing data

We reported the amount of missing data for each study in the 'Characteristics of included studies' tables.

We used observed case (OC) data wherever possible. If OC data were not available, we used data imputed using the last observation carried forward (LOCF). This was made explicit in the accompanying text. We assessed the impact of this approach in a sensitivity analysis, by comparing the results of analyses based on the two main approaches (OC and LOCF). Where mixed methods or area under the curve methods were reported by study authors, we extracted the results from these analyses, only if OC results were unavailable.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

To evaluate the presence of heterogeneity deriving from different trial designs or different clinical characteristics of study participants, we generated descriptive statistics for trial and study population characteristics across all eligible trials that compared each pair of interventions. Two review authors assessed the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics. We assessed statistical heterogeneity using the I^2 statistic and its 95% CI, which measures variability that cannot be attributed to random error. We considered an I^2 of more than 50% as indicative of substantial heterogeneity (Higgins 2017), and reported this in the results.

Assessment of transitivity across treatment comparisons

We expected that the transitivity assumption would hold, with the assumption that all pairwise comparisons would not differ with respect to the distribution of effect modifiers (e.g. rivastigmine, galantamine, and donepezil would have been administered in a similar way across all included trials).

We evaluated the assumption of transitivity by comparing the clinical and methodological characteristics (potential effect modifiers) across the different pairwise comparisons.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise the potential impact of these biases by ensuring a comprehensive search for eligible studies and being alert to duplication of data. If there were 10 or more studies in the pairwise meta-analysis, we used a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies) and account for the fact that studies estimate effects for different comparisons. The funnel plots would be aggregate combining all relevant studies.

Data synthesis

Methods for direct treatment comparisons

Our primary analyses compared each cholinesterase inhibitor separately with placebo.

We conducted separate analyses for different daily doses as follows: donepezil 5 mg, 10 mg, and 23 mg; galantamine 16 to 24 mg and other doses; rivastigmine 6 to 12 mg orally or 4.6 mg or 9.5 mg transdermally and other doses. We planned that for rivastigmine, we would combine both oral and transdermal routes, and compare their efficacy and tolerability in subgroup analyses. In practice, we identified no eligible trials of transdermal rivastigmine, and it was not possible to separate doses of oral rivastigmine < 6 mg/day from other doses, so all doses of oral rivastigmine were pooled (see Differences between protocol and review).

We conducted separate analyses for treatment durations up to and including 3 months, 3 to 6 months, 6 to 18 months, and > 18 months.

We performed standard pairwise meta-analyses in Review Manager 5 using a random-effects model, due to variable levels of heterogeneity, for every treatment comparison where the summary analysis included at least two studies (Review Manager 2014).

Methods for indirect and mixed comparisons

Network meta-analysis (NMA) is a method used to synthesise information from a network of trials that address the same question, but involve different interventions. NMA combines direct and indirect evidence across a network of randomised trials into a single effect size, and, under certain assumptions, can increase the precision of the estimates whilst respecting randomisation. The model enabled us to estimate the probability that each intervention is the best for each outcome, given the relative effect sizes as estimated in NMA.

Each cholinesterase inhibitor was considered as a separate (intervention) node in the analysis, with donepezil included as two separate nodes for the two different doses investigated (5 mg and 10 mg daily). Data on different doses were not available for galantamine or rivastigmine, so both of these drugs were included as a single node encompassing all doses investigated. For galantamine, the range of doses was within the manufacturer's recommended range (for treatment of Alzheimer's disease dementia); however, this was not the case for rivastigmine. The decision set in the NMA was donepezil 5 mg daily, donepezil 10 mg daily, rivastigmine 3 to 12 mg daily, and galantamine 16 to 24 mg daily. The supplementary set was placebo.

We assumed that the three cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are directly comparable treatments. In other words, we assumed that the distribution of important characteristics (effect modifiers) is the same across all treatment comparisons (Salanti 2012). We defined the placebo node as any drug intervention that did not contain an active ingredient, or any trial arm that contained no investigator-intended treatment. We used Bayesian analysis for the NMA for its flexibility and more natural interpretation. The Bayesian approach allows ranking of the treatments according to their comparative effectiveness (Mills 2013; Kibret 2014; Rücker 2015).

We performed NMA for each primary outcome measure using MetaInsight (bespoke NMA tool developed by the University of Leicester) (Owen 2019). The free web-based tool (Owen 2019) is supported by the National Institute for Health Research Complex Reviews Support Unit (NIHR-CRSU). We also received support in the design, analyses and interpretation of the NMA from NIHR-CRSU.

Subgroup analysis and investigation of heterogeneity

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity

As there were only two to four studies in each direct comparison, in standard pairwise meta-analysis we assumed a common heterogeneity variance for all direct comparisons. In NMA we assumed a common estimate for the heterogeneity variance across the different comparisons.

Measures and tests for heterogeneity

We based the assessment of statistical heterogeneity in the entire network on the magnitude of the heterogeneity variance parameter (T^2) estimated from the NMA models. For dichotomous outcomes, we compared the magnitude of the heterogeneity variance with

the empirical distribution as derived by Turner (Turner 2012). We also estimated a total I^2 value for heterogeneity in the network as described elsewhere (Jackson 2014).

Assessment of statistical inconsistency

Local approaches for evaluating inconsistency

To evaluate the presence of inconsistency locally, we used the loop-specific approach. This method assesses the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor) (Veroniki 2013). The magnitude of the inconsistency factors and their 95% CIs can then be used to infer information about the presence of inconsistency in each loop. We assumed a common heterogeneity estimate within each loop. We presented the results of this approach graphically in a forest plot using MetaInsight (University of Leicester) (Owen 2019)

Global approaches for evaluating inconsistency

To check the assumption of consistency in the entire network, we used the 'design-by-treatment' model, as described by Higgins 2017. This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results, as well as disagreements between direct and indirect evidence. Using this approach, we have drawn inferences about the presence of inconsistency from any source in the entire network based on a Chi^2 test. Inconsistency and heterogeneity are interwoven; in order to distinguish between these two sources of variability, we employed the I^2 or between-study standard deviation for inconsistency, as it measures variability that cannot be attributed to random error or heterogeneity (within comparison variability). We also sought guidance from the NIHR-CRSU to address any inconsistencies.

Investigation of heterogeneity and inconsistency

Due to insufficient studies we were unable to perform network meta-regression or subgroup analyses.

Sensitivity analysis

We conducted sensitivity analyses to compare results obtained with OC data or intention-to-treat/LOCF data when both were reported. We identified too few studies within each comparison to conduct planned sensitivity analyses related to risk of bias and severity of VCI.

Summary of findings and assessment of the certainty of the evidence

We summarised our results in 'Summary of findings' tables using the online GRADEpro GDT application (GRADEpro GDT). We reported the estimated treatment effects for the primary outcomes in the tables, using the GRADE approach to rate our confidence that the estimate was correct (Schünemann 2011). GRADE categorises quality using four possible ratings: high, moderate, low, and very low. Results of RCTs rated high certainty will generally have no limitations. Evidence from RCTs is downgraded due to several factors, including: imprecision of effect estimates, risk of bias in included studies, inconsistency of results, indirectness of evidence, and publication bias (Schünemann 2011). These factors are described in the footnotes below the 'Summary of findings' tables.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The search identified a total of 12,214 citations. These citations were assessed initially in Cochrane's Screen4Me workflow to identify potential reports of randomised trials and then by the Information Specialist of the Cochrane Dementia and Cognitive Improvement Group to exclude obviously irrelevant titles. A total of 736 citations were then passed to the review authors for further assessment. We excluded 689 of these on the basis of titles and abstracts, identifying 47 citations that were related to potentially eligible trials. We assessed these in full-text where available. These 47 citations described nine unique trials. We included eight trials (46 citations) and excluded one trial (one citation) because participants had CADASIL (see Characteristics of excluded studies table). We identified no further trials through scanning reference lists of the included studies. We identified no ongoing studies. The study identification process is illustrated in Figure 1.

Included studies

We included eight trials in the review (for details see Characteristics of included studies). Three trials investigated donepezil (Black 2003; Wilkinson 2003; Roman 2010); three trials investigated rivastigmine (Mok 2007; Ballard 2008; Narasimhalu 2009); and two trials investigated galantamine (Erkinjuntti 2002; Auchus 2007).

In the three donepezil trials, 2193 participants provided data for one or more of the outcomes. All participants had probable or possible vascular dementia according to the NINDS-AIREN criteria. Their mean age was 73.9 years. All trials were of 24 weeks' duration. Two trials compared 5 mg and 10 mg of donepezil to placebo and to each other (Black 2003; Wilkinson 2003), and one trial compared 5 mg of donepezil to placebo (Roman 2010).

In the three rivastigmine trials, 800 participants provided data for one or more of the outcomes. Two trials included participants with probable vascular dementia (Mok 2007; Ballard 2008), and one trial included participants with cognitive impairment, no dementia (CIND) following a cerebrovascular accident (Narasimhalu 2009). Mean age of participants was 72.2 years. Two trials ran for 24 weeks (Ballard 2008; Narasimhalu 2009), whilst the third trial ran for 26 weeks (Mok 2007). All trials compared oral rivastigmine with placebo, but final doses of rivastigmine varied across the trials: 3 to 12 mg/day in Ballard 2008; mean of 6 mg/day in Mok 2007; and maximum 9 mg/day in Narasimhalu 2009. No trial reported the proportions of participants receiving different doses. No trial studied transdermal rivastigmine.

In the two galantamine trials (Erkinjuntti 2002; Auchus 2007), 1380 participants provided data for one or more outcomes. Both trials included individuals with probable vascular dementia as defined by the NINDS-AIREN criteria. The mean age of participants was 73.7 years. Both trials lasted 26 weeks. The final daily doses of galantamine were 16 to 24 mg/day in Auchus 2007 and 24 mg/day in Erkinjuntti 2002.

All included trials were sponsored by pharmaceutical companies.

Excluded studies

We excluded one trial of cholinesterase inhibitors for people with CADASIL (see Characteristics of excluded studies) (Dichgans 2008).

Risk of bias in included studies

Risk of bias in the included studies is summarised in Characteristics of included studies and Figure 2 and Figure 3. We considered only two studies to be at low risk across all domains (Ballard 2008; Narasimhalu 2009). We judged the remaining trials to be at unclear risk of bias across one or more domains.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

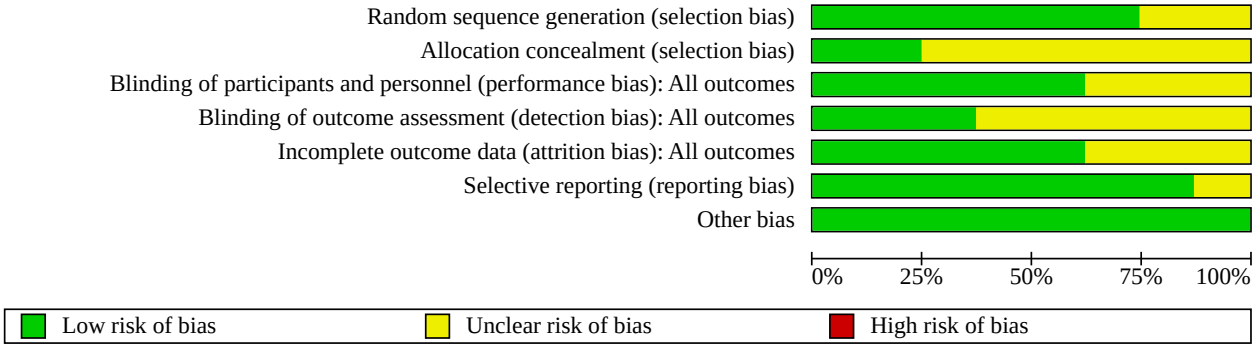
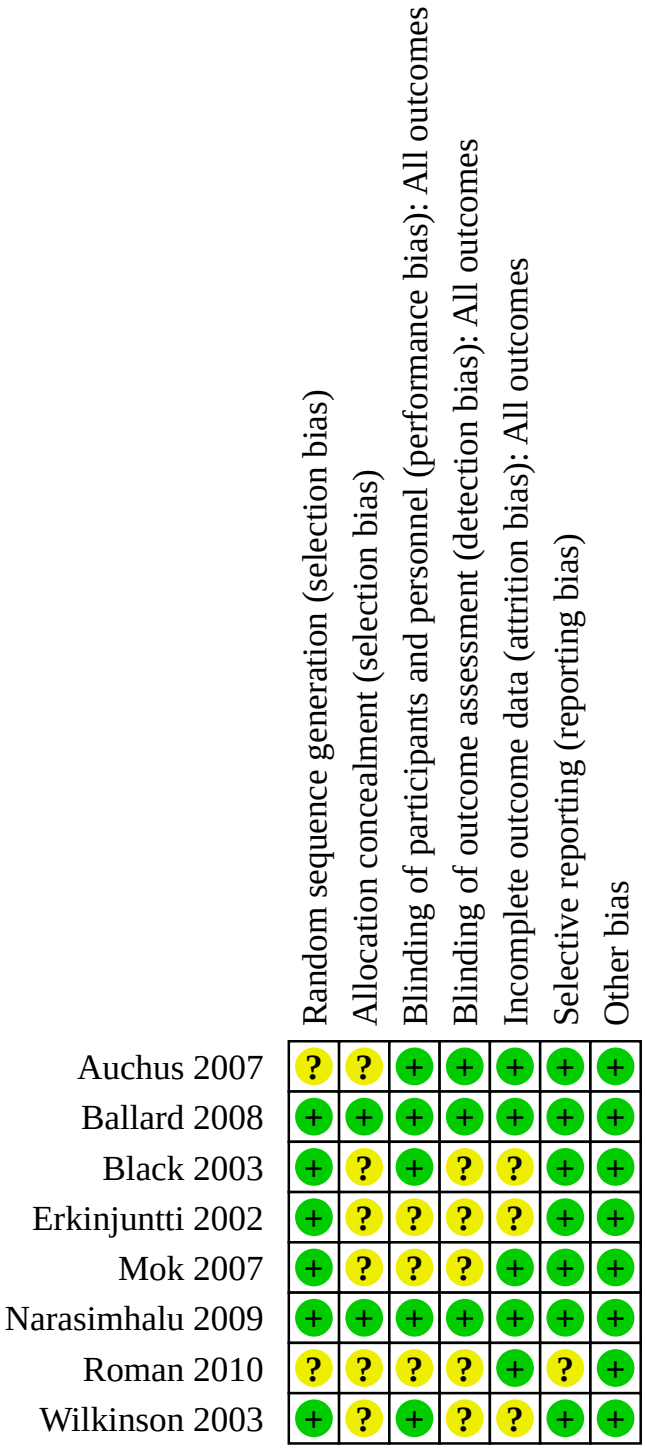


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Donepezil

One trial that evaluated donepezil 5 mg did not provide sufficient information to assess sequence generation (unclear risk) (Roman 2010). The other two trials, which evaluated donepezil 5 mg and 10 mg (Black 2003; Wilkinson 2003), reported adequate methods for sequence generation (low risk).

No trial provided sufficient information to enable assessment on allocation concealment (unclear risk).

Rivastigmine

All trials that evaluated rivastigmine reported adequate methods for random sequence generation (low risk) (Mok 2007; Ballard 2008; Narasimhalu 2009).

One trial did not provide sufficient information to enable assessment on allocation concealment (unclear bias) (Mok 2007), whilst allocation concealment for the other two trials was well-described (low risk).

Galantamine

We assessed one trial that evaluated galantamine as at unclear risk of bias for random sequence generation and allocation concealment (Auchus 2007), whilst the other study had an unclear risk of bias for allocation concealment (Erkinjuntti 2002).

Blinding

Donepezil

All three trials that evaluated donepezil were described as double-blinded. Two trials reported adequate blinding of participants and personnel (performance bias) (low risk) (Black 2003; Wilkinson 2003). The two trials also provided information regarding blinding of some (but not all) of the outcome measures, therefore we judged the risk of detection bias to be unclear.

We considered one trial to have an unclear risk of performance bias (Roman 2010); the same trial also provided no details of blinding on any of the trial outcome measures and was therefore judged as at unclear risk of detection bias.

Rivastigmine

All three trials that evaluated rivastigmine were reported as double-blinded. Two trials reported adequate blinding of participants, personnel, and outcome assessment, and were thus assessed as at low risk of performance and detection bias (Ballard 2008; Narasimhalu 2009).

We judged one trial to be at unclear risk of performance and detection bias due to limited information on blinding of trial personnel and no description of blinding of outcome assessors (Mok 2007).

Galantamine

Both trials that evaluated galantamine were reported as double-blinded. One trial described adequate blinding of study participants, personnel, and outcome assessments, and was thus assessed as at low risk of performance and detection bias (Auchus 2007). However, the other trial provided insufficient information regarding blinding of the study team and outcome measures, and was therefore judged as at unclear risk of performance and detection bias (Erkinjuntti 2002).

Incomplete outcome data

Across the included studies, the percentage of participants who completed the trials ranged from 75.3% to 98%.

Donepezil

Only one of the three trials that evaluated donepezil was at low risk of attrition bias (Roman 2010). The other two studies reported a higher rate of discontinuation in the treatment arms and were thus considered as at unclear risk of attrition bias (Black 2003; Wilkinson 2003).

Rivastigmine

All three trials that evaluated rivastigmine met the criteria for low risk of attrition bias due to balanced numbers across intervention groups with similar reasons for loss to follow-up.

Galantamine

One trial that evaluated galantamine met the criteria for low risk of attrition bias due to balanced numbers across intervention groups with similar reasons for loss to follow-up (Auchus 2007). The other study reported a higher rate of discontinuation in the treatment arms and was thus considered as at unclear risk of attrition bias (Erkinjuntti 2002).

Selective reporting

Donepezil

One of the three trials that evaluated donepezil did not report final data for one of the primary outcome measures and was judged as at unclear risk of reporting bias (Roman 2010).

Rivastigmine

All three trials that evaluated rivastigmine reported the benefits and harms of the interventions in the manner specified in the methods section of the trial publications. We judged all three trials as at low risk of reporting bias.

Galantamine

Both trials that evaluated galantamine reported the benefits and harms of the interventions in the manner specified in the methods section of the trial publications. We judged both trials as at low risk of reporting bias.

Other potential sources of bias

We identified no other sources of bias in the included studies, which we judged to be at low risk of bias for this domain.

Effects of interventions

See: **Summary of findings 1** Donepezil 5 mg compared to placebo for vascular dementia and other vascular cognitive impairments; **Summary of findings 2** Donepezil 10 mg compared to placebo for vascular dementia and other vascular cognitive impairments; **Summary of findings 3** Rivastigmine compared to placebo for vascular dementia and other vascular cognitive impairments;

Summary of findings 4 Galantamine compared to placebo for vascular dementia and other vascular cognitive impairments

See Summary of findings 1 for donepezil 5 mg results; Summary of findings 2 for donepezil 10 mg results; Summary of findings 3 for rivastigmine results; and Summary of findings 4 for galantamine results. The 'Summary of findings' tables display estimates of treatment effects for the primary and secondary outcome measures, for each of the four interventions versus placebo, after 24 or 26 weeks of treatment.

No data were available for secondary outcomes: incidence of development of new dementia, carer burden, institutionalisation and quality of life.

Donepezil 5 mg and 10 mg

Primary outcomes

Cognition

The ADAS-Cog (range 0 to 70) was used to assess changes in cognition from baseline to 24 weeks. Donepezil 5 mg improved cognition slightly, although the size of the change is unlikely to be clinically important (3 trials, 1601 participants: mean difference (MD) −0.92, 95% confidence interval (CI) −1.44 to −0.40; using observed case (OC) or last observation carried forward (LOCF); high-certainty evidence) (Analysis 1.1). Donepezil 10 mg probably improved cognition slightly more, although the size of the change may still not reach clinical importance (2 trials, 608 participants: MD −2.21, 95% CI −3.07 to −1.35; OC data only; moderate-certainty evidence) (Analysis 1.2). Heterogeneity was low (I^2 = 0%) in both analyses.

Clinical global impression

The CIBIC-Plus (7-point Likert scale) was used to assess changes in clinical global impression from baseline to 24 or 26 weeks. Participants were categorised as improved or stable/worse. Donepezil 5 mg improved clinical global impression slightly (2 trials, 712 participants: odds ratio (OR) 1.58, 95% CI 1.10 to 2.27; using OC or LOCF; high-certainty evidence) (Analysis 2.1). Donepezil 10 mg probably had little of no effect on clinical global impression (2 trials, 699 participants: OR 1.15, 95% CI 0.78 to 1.70; using OC or LOCF; moderate-certainty evidence) (Analysis 2.2). Heterogeneity was moderate for donepezil 5 mg and 10 mg (I^2 =24% and 30%, respectively).

Functional performance in activities of daily living

The Alzheimer's Disease Functional Assessment and Change Scale (ADFACS; range 0 to 54) was used to assess changes in functional performance in activities of daily living, from baseline to 24 or 26 weeks. Donepezil 5 mg probably had little to no effect on functional performance (2 trials, 798 participants; MD −0.73, 95% CI −1.52 to 0.06; using LOCF; moderate-certainty evidence) (Analysis 3.1). Donepezil 10 mg probably resulted in a slight improvement in functional performance, although the size of the change is unlikely to be clinically important (2 trials, 813 participants: MD −0.95, 95% CI −1.73 to −0.17; using LOCF; moderate-certainty evidence) (Analysis 3.2). Heterogeneity was low (I^2 = 0%) in both analyses.

Adverse events

Adverse events reported in the studies included nausea and vomiting, diarrhoea, dizziness, headache, and hypertension. There was probably little to no difference in the number of adverse events between donepezil 5 mg and placebo (3 trials, 1772 participants: OR 1.22, 95% CI 0.94 to 1.58; using LOCF; moderate-certainty evidence) (Analysis 4.1). Donepezil 10 mg resulted in a slight excess of adverse events compared with placebo (2 trials, 813 participants: OR 1.95, 95% CI 1.20 to 3.15; using LOCF; high-certainty evidence) (Analysis 4.2). Heterogeneity was low (I^2 = 0%) in both analyses.

Secondary outcomes

Serious adverse events

There was probably little to no difference in the number of serious adverse events reported between donepezil 5 mg and placebo (3 trials, 1772 participants: OR 0.94, 95% CI 0.72 to 1.22; using LOCF; moderate-certainty evidence) (Analysis 5.1) or between donepezil 10 mg and placebo (2 trials, 813 participants: OR 1.15, 95% CI 0.81 to 1.64; using LOCF; moderate-certainty evidence) (Analysis 5.2). Heterogeneity was low for donepezil 5 mg (I^2 = 0%) and moderate for donepezil 10 mg (I^2 = 46%).

Behavioural disturbance

The included trials did not assess this outcome.

Deaths

For donepezil 5 mg, there was between-trial heterogeneity (I^2 = 70%) as well as imprecision and risk of bias, so we were very uncertain of the result (3 trials, 1772 participants: OR 1.46, 95% CI 0.60 to 3.50; using LOCF; very low-certainty evidence) (Analysis 7.1). There was probably little to no difference in deaths that occurred during the trial between donepezil 10 mg and placebo (2 trials, 813 participants: OR 0.94, 95% CI 0.34 to 2.58; using LOCF; moderate-certainty evidence) (Analysis 7.2). Heterogeneity was low in this analysis (I^2 = 0%).

Rivastigmine 3 to 12 mg

Primary outcomes

Cognition

The ADAS-Cog (range 0 to 70) was used to assess changes in cognition from baseline to 24 or 26 weeks. The results suggest that rivastigmine may have little or no effect on cognition (2 trials, 748 participants: MD 0.03, 95% CI −3.04 to 3.10; using LOCF; low-certainty evidence) (Analysis 1.3). Heterogeneity was moderate for the pooled result (I^2 = 63%).

Clinical global impression

The included trials did not assess this outcome.

Functional performance in activities of daily living

The ADCS-ADL (range 0 to 54) and Instrumental Activities of Daily Living Scale (IADL) (range 0 to 8) were used to assess changes in functional performance in activities of daily living, from baseline to 24 or 26 weeks. The results showed that there may be little to no benefit in functional performance with rivastigmine (3 trials, 800 participants: standardised mean difference (SMD) 0.02, 95% CI −0.12 to 0.16; using LOCF; low-certainty evidence) (Analysis 3.3). Heterogeneity was low for the pooled result (I^2 = 0%).

Adverse events

The evidence is very uncertain regarding the effect of rivastigmine on adverse events (3 trials, 831 participants: OR 3.21, 95% CI 0.36 to 28.88; using LOCF; very low-certainty evidence) (Analysis 4.3). Heterogeneity was high for the pooled result (I^2 = 95%).

Secondary outcomes

Serious adverse events

There may be little to no difference in serious adverse events reported between rivastigmine and placebo (2 trials, 622 participants: OR 1.42, 95% CI 0.90 to 2.25; using LOCF; low-certainty evidence) (Analysis 5.3), (I^2 = 0%).

Behavioural disturbance

The NPI (range 0 to 144) was used to assess changes in behavioural disturbance from baseline to 24 or 26 weeks. There was probably little to no effect of rivastigmine on behavioural disturbance (3 trials, 796 participants: MD 0.21, 95% CI −1.25 to 1.66; using LOCF; moderate-certainty evidence) (Analysis 6.1). Heterogeneity was low for the pooled result (I^2 = 0%).

Deaths

The results showed no evidence of increased deaths with rivastigmine (3 trials, 800 participants: OR 1.45, 95% CI 0.51 to 4.15; using LOCF; low-certainty evidence) (Analysis 7.3). Heterogeneity was low for the pooled result (I^2 = 0%).

Galantamine 16 to 24 mg

Primary outcomes

Cognition

The ADAS-Cog (range 0 to 70) was used to assess changes in cognition from baseline to 26 weeks. The results showed that galantamine probably improves cognition slightly, although the size of the change may not reach clinical importance (2 trials, 1188 participants: MD −2.01, 95% CI −3.18 to −0.85; using OC or LOCF; moderate-certainty evidence) (Analysis 1.4). Heterogeneity was moderate for the pooled result (I^2 = 57%).

Clinical global impression

The CIBIC-Plus (7-point Likert scale) was used to assess changes in clinical global impression from baseline to 24 or 26 weeks. The results showed that galantamine improves clinical global impression although this may not be clinically important (2 trials, 1326 participants: OR 1.32, 95% CI 1.03 to 1.70; using LOCF; high-certainty evidence) (Analysis 2.3). Heterogeneity was low for the pooled result (I^2 = 0%).

Functional performance in activities of daily living

The ADCS-ADL (range 0 to 54) and Disability Assessment for Dementia Scale (DAD) (range 0 to 100) were used to assess changes in functional performance in ADL, from baseline to 24 or 26 weeks. The results showed that there may be little or no benefit in functional performance with galantamine (2 trials, 1174 participants: SMD 0.11, 95% CI −0.24 to 0.46; using OC or LOCF; low-certainty evidence) (Analysis 3.4). Heterogeneity was high for the pooled result (I^2 = 88%).

Adverse events

The results showed that galantamine probably leads to a slight increase in adverse events (2 trials, 1378 participants: OR 1.57, 95% CI 1.02 to 2.43; using LOCF; moderate-certainty evidence) (Analysis 4.4). Heterogeneity was moderate for the pooled result (I^2 = 67%).

Secondary outcomes

Serious adverse events

The results showed that galantamine probably has little or no effect on the occurrence of serious adverse events (1 trial, 786 participants: OR 1.12, 95% CI 0.78 to 1.59; using LOCF; moderate-certainty evidence) (Analysis 5.4).

Behavioural disturbance

The NPI (range 0 to 144) was used to assess changes in behavioural disturbance from baseline to 24 or 26 weeks. The results showed that galantamine may not improve behavioural disturbance (2 trials, 1151 participants: MD −0.13, 95% CI −4.05 to 3.79; using OC or LOCF; low-certainty evidence) (Analysis 6.2). Heterogeneity was high for the pooled result (I^2 = 84%).

Deaths

Galantamine probably does not lead to a difference in number of deaths compared with placebo (2 trials, 1378 participants: OR 0.53, 95% CI 0.26 to 1.10; using LOCF; moderate-certainty evidence) (Analysis 7.4). Heterogeneity was low for the pooled result (I^2 = 0%).

Sensitivity analyses

Two sets of analyses were compared for the primary cognitive outcome (measured using ADAS-Cog), one using OC data, and the other using intention-to-treat/LOCF data. Two trials investigating donepezil 5 mg and donepezil 10 mg, Black 2003; Wilkinson 2003, and one trial investigating galantamine, Erkinjuntti 2002, reported both OC and LOCF data for cognitive function. Within-trial comparisons are reported in Analysis 8.1; Analysis 8.2; Analysis 8.3. There is generally little difference between the results for OC and LOCF data, but the sensitivity analysis result for cognition with donepezil 5 mg is more uncertain when LOCF data are used, suggesting the result should be interpreted with caution.

Results of NMA for treatment effects

We conducted an NMA for the main metrics of benefit and harm (cognition and adverse events), for which results were available in the standard pairwise meta-analysis, for two or more of the following; donepezil 5 mg, donepezil 10 mg, rivastigmine, and galantamine. For each NMA, Bayesian models employing LOCF data were used (as LOCF data were available for all drugs), for each of the included outcome measures. Cognition (ADAS-Cog) was used to demonstrate benefit, and rate of adverse events to demonstrate harm. See Table 1 for Summary of findings: NMA results.

Benefit: effect on cognition

Overall cognition data (see network plot in Figure 4), using ADAS-Cog results, were available from seven RCTs (3537 participants). Seven indirect comparisons were possible. A Bayesian model was used. The between-study standard deviation was 0.95. The results of the NMA in Table 1 and the forest plot in Figure 5 show the superiority of donepezil 10 mg (MD −2.18, 95% CI −3.87 to −0.47) over the other drugs and placebo, followed in order of superiority

by galantamine (MD −1.84, 95% CI −3.63 to −0.14), donepezil 5 mg (MD −0.74, 95% CI −2.14 to 0.71), and rivastigmine (MD −0.53, 95% CI −2.35 to 1.94) (Figure 6). Estimates of benefits as calculated in the NMA are shown in Table 2.

Figure 4. Network plot: Cognition. The nodes represent an intervention. The solid lines connecting each pair of interventions represent a direct comparison, and the dotted lines an indirect comparison. The numbers on the lines represent the number of trials available for direct comparison.

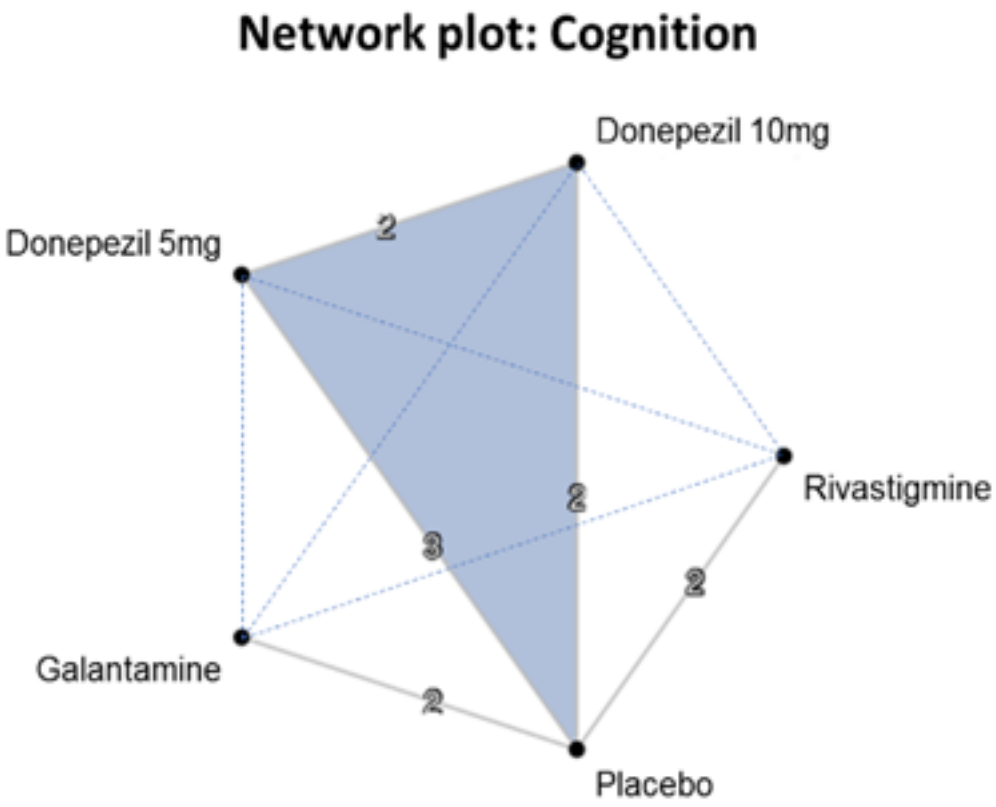


Figure 5. Forest plot (Bayesian model) network meta-analysis results: Cognition.

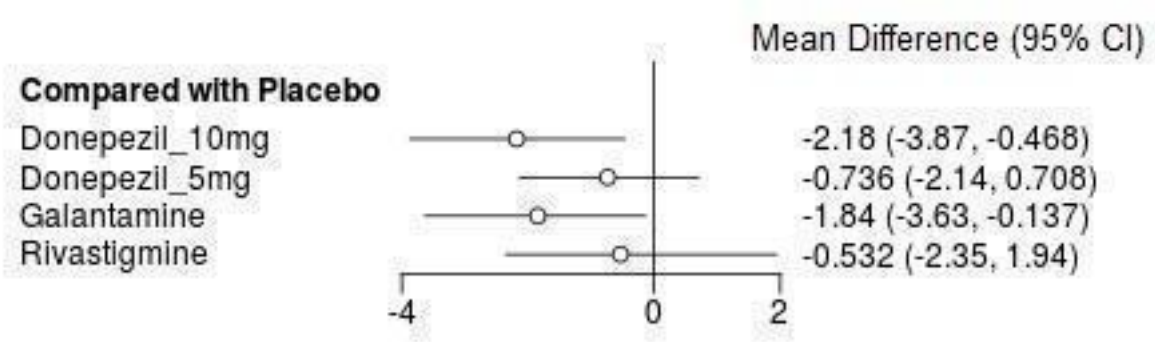
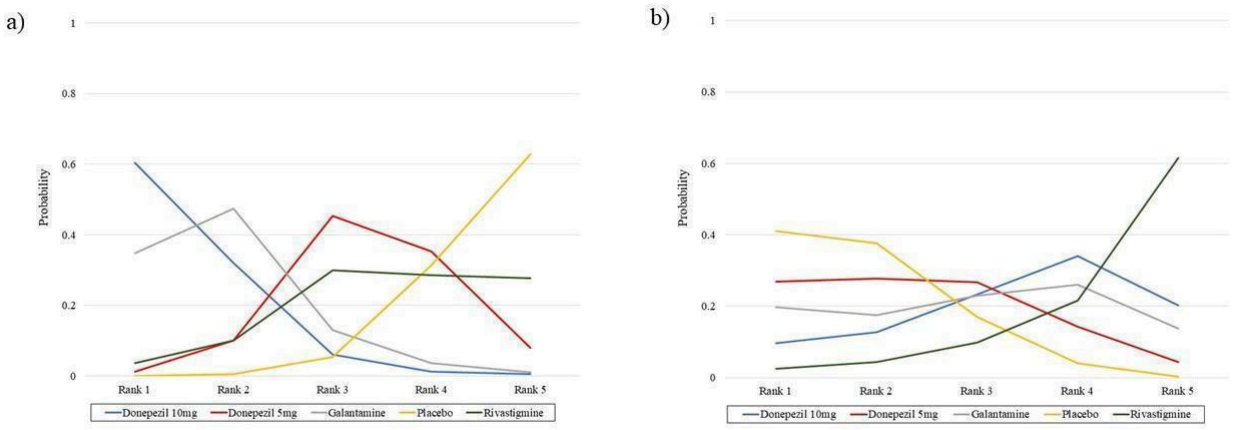


Figure 6. Ranking probabilities for (a) Outcome: cognition, (b) Outcome: adverse events. The horizontal axis shows the possible ranks, and the vertical axis the ranking probabilities. Each line connects the estimated probabilities of being at a particular rank for every intervention.



Harm: effect on adverse events

Overall adverse events (see network plot in Figure 7) were available from eight RCTs (3981 participants). Seven indirect comparisons were possible. A Bayesian model was used. The between-study standard deviation was 1.12. The results of the NMA in Table 1 and the forest plot in Figure 8 show the superiority of donepezil 5 mg (OR 1.23, 95% CI 0.29 to 5.28, but low-certainty evidence) over the other drugs (placebo showing best effect), followed in order of superiority by galantamine (OR 1.60, 95% CI 0.28 to 9.25), donepezil 10 mg (OR 2.00, 95% CI 0.36 to 11.50), and rivastigmine (OR 3.75, 95% CI 0.74 to 15.40, with very low-certainty evidence) (Figure 6). Estimates of harms as calculated in the NMA are shown in Table 3. The results apply to oral rivastigmine only, as the transdermal route of administration was not investigated in the included trials.

Figure 7. Network plot: Adverse events. The nodes represent an intervention. The solid lines connecting each pair of interventions represent a direct comparison, and the dotted lines an indirect comparison. The numbers on the lines represent the number of trials available for direct comparison.

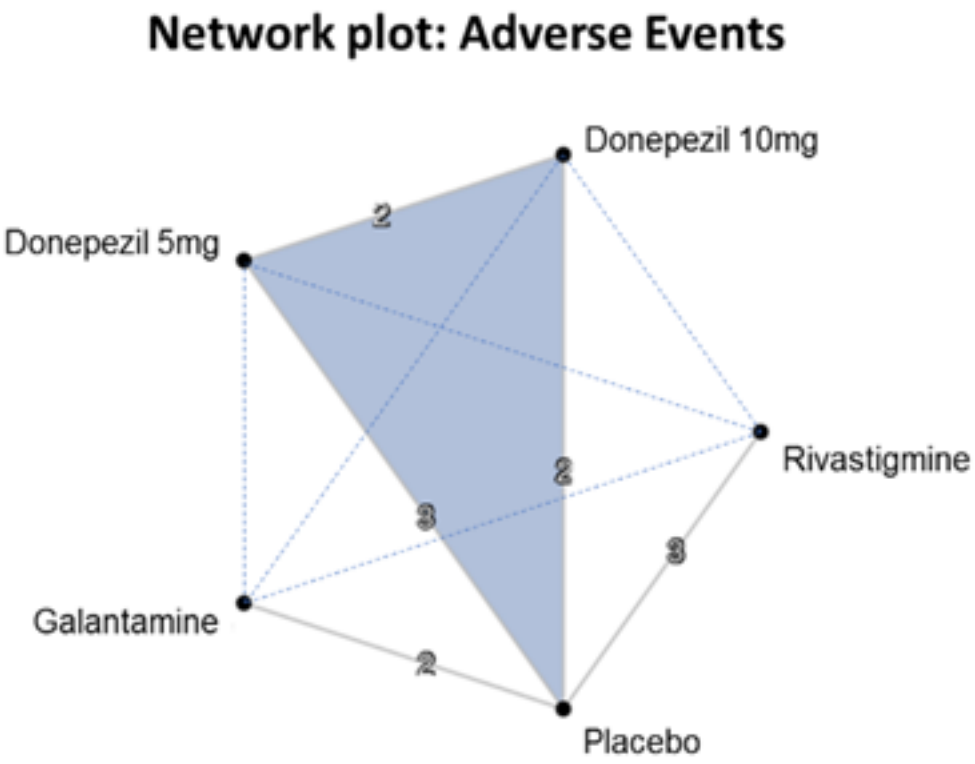
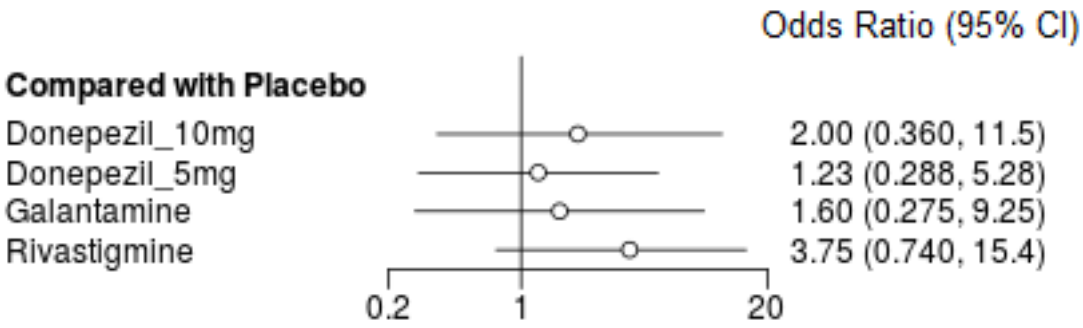


Figure 8. Forest plot (Bayesian model) network meta-analysis results: Adverse events.



DISCUSSION

By combining and updating three previous Cochrane Reviews, Malouf 2004; Birks 2006; Birks 2013, and adding a network meta-analysis, we aimed to assess the benefits and harms of cholinesterase inhibitors for vascular dementia and other VCI using contemporary systematic review methods. Through a comprehensive search, we identified eight eligible RCTs with a total of 4373 participants, of which three studied donepezil, three oral rivastigmine, and two galantamine.

It is important to note that the mean clinical important difference (MCID) is not known for any of the outcome measures in the populations studied in this review. Interpretation of effect estimates is therefore challenging. An MCID for cognition of a change of three ADAS-Cog points over six months in mild

Alzheimer's disease has been suggested (Schrag 2012). Manero 2013 proposed an MCID for functional performance of two points on the ADFACS, based on a two-point difference between cognitively normal people and those with mild cognitive impairment in Alzheimer's disease.

Summary of main results

In the pairwise comparisons, we reported small potential beneficial effects over placebo for: cognition (donepezil 5 mg or 10 mg daily and galantamine 16 to 24 mg daily); clinical global impression (donepezil 5 mg and galantamine); and functional performance (donepezil 10 mg), although the certainty of the evidence varied, and the size of the cognitive and functional effects probably did not reach clinical importance. We found no evidence of effects on behavioural disturbance.

With regard to harms, we found evidence of an increase in the rate of adverse events with donepezil 10 mg and galantamine, but not donepezil 5 mg. We found no evidence of increases in the numbers of serious adverse events or deaths with any of the cholinesterase inhibitors.

For oral rivastigmine, we found no evidence of benefits and were unable to draw any conclusions regarding harmful effects. However, inadequate dosage may have been an issue, as all the trials included participants who achieved a maximum daily dosage of less than 6 mg.

In the NMA of cholinesterase inhibitors, cognition represented benefit and adverse events harm. All drugs ranked above placebo for cognition and below placebo for adverse events. Donepezil 10 mg ranked first in terms of benefit, but third in terms of harms, when considering the network estimates and certainty of the evidence. Galantamine ranked second in terms of both benefit and harm. Rivastigmine had the lowest ranking of the cholinesterase inhibitors in both benefit and harm NMA estimates, but this may reflect possible inadequate doses received by some participants and small sample sizes. No trial investigated transdermal rivastigmine, which may have led to different conclusions.

Overall completeness and applicability of evidence

Despite conducting a comprehensive search for new trials, we found only one additional trial that met our review inclusion criteria since the completion of the previous reviews. The trials appeared to have included a representative population of patients with vascular dementia and VCI seen in clinical practice, where the trials were conducted. We did not include participants with CADASIL, so our results do not apply to this patient group. We selected seven commonly investigated outcome measures used in dementia research; however, not all of the included trials investigated all of the selected outcomes.

No trial investigated transdermal rivastigmine, which is reportedly better tolerated than any of the oral cholinesterase inhibitors when considering gastrointestinal adverse events. Possible underdosing of rivastigmine was also evident, as all trials included participants who received a maximum dose of less than 6 mg/day.

Quality of the evidence

Overall, the certainty of the evidence across the included trials in the pairwise comparisons varied from low to high. A major limitation of this review was the paucity of trials and data. Reliability and quality of data were poor for rivastigmine. Many of the pooled analyses were underpowered. Few trials were included for each cholinesterase inhibitor, and for some comparisons only one trial was included. This makes it difficult to accurately assess whether the effect estimates are reproducible. The certainty of evidence for many of the outcomes was downgraded for imprecision in the GRADE assessment.

A lack of consensus on what is a minimal clinically important difference for the included outcomes for this population renders interpretation difficult and reduces confidence in the conclusions.

In the NMA, we judged the overall certainty of the evidence to be moderate to high for the benefits estimates, but very low to moderate for the harms estimates.

Potential biases in the review process

We did not find any methodological issues in the preparation of this review that could put it at risk of potential biases. We selected a range of databases to search, without any language restrictions. We conducted the NMA according to applicable Cochrane guidance and sought advice from the NIHR-CRSU when required.

In the NMA, one of the underpinning assumptions is that the participants in the different trials are similar. We found no evidence of systematic differences across the included trials from either clinical or methodological points of view. However, we cannot rule out violation of the transitivity assumption because of the paucity of data.

Agreements and disagreements with other studies or reviews

Despite the inclusion of an additional trial (Roman 2010), we agree with the findings of the previous Cochrane Review (Malouf 2004), that donepezil 5 mg has a potential small benefit that probably does not reach clinical importance in cognition and clinical global impression at 24 weeks' follow-up. Donepezil 10 mg has a small potential benefit that probably does not reach clinical importance in cognition and functional performance on activities of daily living at 24 weeks' follow-up. We also agree that donepezil 10 mg leads to a higher rate of adverse events than placebo.

The original rivastigmine review did not pool the results due to differences in study populations (Birks 2013), therefore we cannot directly compare it with our review results. In our review we pooled the results and acknowledged potential heterogeneity in the interpretation of results. The authors of Birks 2013 suggested some evidence of benefit with rivastigmine, which was not supported by the results of our review. They also reported a significant number of withdrawals due to side effects, which is supported by the results of our NMA, which demonstrated oral rivastigmine to be the most inferior of all cholinesterase inhibitors investigated with regard to adverse events.

We agree with the findings of the original galantamine review (Birks 2006), that the data from two trials suggest some advantage over placebo in cognition and clinical global impression measures (but

probably not reaching clinical importance), but with a concomitant significant increase in the number of adverse events reported compared with placebo. We agree that no differences were reported between galantamine and placebo for any of the other outcome measures investigated.

Our NMA results also found potential beneficial effects on cognition (but not reaching clinical importance) with donepezil 5 mg, donepezil 10 mg, and galantamine, when compared with placebo. The results also agree that donepezil 10 mg, galantamine, and oral rivastigmine lead to a significantly higher rate of adverse events. These results were to be expected, as only one new trial was included in this update. Our update consolidates the results of the previous reviews through the inclusion of robust 'Risk of bias' assessments and GRADE ratings (Puhan 2014).

Donepezil 5 mg and 10 mg, galantamine, and rivastigmine were also reported to have a potential beneficial effect on cognition in another previous meta-analysis investigating cholinesterase inhibitors for vascular dementia (Kavirajan 2007). There was also a higher number of reported adverse events with cholinesterase inhibitors, compared with placebo. In comparison with Kavirajan 2007, our update included three additional trials: Roman 2010, Ballard 2008, and Narasimhalu 2009. These results are also supported in a more recent meta-analysis in vascular dementia patients that demonstrated an improvement in cognition with donepezil 5 mg and 10 mg and galantamine (Chen 2016), but as found in our study, no significant beneficial effect with rivastigmine. They also reported an increase in adverse events with cholinesterase inhibitor use. The review by Chen 2016 included two trials not included in this update, as we excluded trials investigating a primary population of patients with CADASIL and Alzheimer's disease. In a Cochrane Review investigating the efficacy of cholinesterase inhibitors in rarer dementias associated with neurological conditions, no clear benefit on cognition was reported in participants with CADASIL (Li 2015). As in our review, cholinesterase inhibitors were associated with more gastrointestinal side effects compared with placebo (Li 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Based on moderate- to high-certainty evidence, we found donepezil 5 mg, donepezil 10 mg, and galantamine 16 to 24 mg to have small beneficial effects on cognition (probably not reaching clinical importance) in participants with vascular dementia and other forms of vascular cognitive impairment, at 24 or 26 weeks' follow-up. Rates of adverse events were probably higher when compared with placebo for donepezil 10 mg and galantamine, but not for donepezil 5 mg. We could not draw any conclusions regarding adverse events for rivastigmine. We also found that donepezil 5 mg and galantamine had a small potentially beneficial effect that probably did not reach clinical importance on clinical global impression. Donepezil 10 mg had a small beneficial effect that probably did not reach clinical importance on performance of activities of daily living.

Our network meta-analysis results suggest that donepezil 10 mg ranks highest amongst the cholinesterase inhibitors in terms of cognition, followed by galantamine. In terms of adverse events, the network meta-analysis results and certainty of the evidence suggest that donepezil 5 mg ranks highest, followed by galantamine. Rivastigmine was not shown to have a beneficial effect on any of the outcomes investigated, but this may reflect underdosing, the poor quality of the evidence, and the high level of heterogeneity between the trials. Conclusions regarding rivastigmine should therefore be interpreted with caution. The results for rivastigmine only apply to the oral preparation, as the transdermal mode of delivery was not investigated in any of the included trials.

Implications for research

The signal of small benefits found in this review is sufficient to justify further research into donepezil 5 mg, donepezil 10 mg, and galantamine 16 to 24 mg for vascular dementia and other vascular cognitive impairments. For rivastigmine, further trials into the benefits and harms are needed for this patient population, as the results of this review are inconclusive due to poor reliability of data in the included trials. Furthermore, large, good-quality rivastigmine trials would be beneficial due to the potential underdosing reported in previous trials. The transdermal route of delivery of rivastigmine is a potential area for future research, as there is a need for evidence as to whether this could provide beneficial effects without the known deleterious side effects seen with the oral route. This is particularly important to clinicians, as rivastigmine patches are increasingly being used in some countries as a first-line treatment option for patients with vascular dementia and other vascular cognitive impairments.

Mixed dementias with a vascular component are common, especially in dementia syndromes seen in older age. It is uncertain whether the results described for the populations in the trials included in this review (who were felt to have predominant vascular pathology) would apply to those with more mixed neurodegeneration. Based on the results of this review, we also consider further research into the benefits of cholinesterase inhibitors for mixed vascular dementia and Alzheimer's disease to be justified.

The included studies all pre-date 2011, perhaps supporting the suggestion that further trials are required. A longer follow-up period should be investigated in future trials, as there may be longer-term effects of cholinesterase inhibitors that are not demonstrated in the trials. Our review has also highlighted that a core outcome set may be needed for research into outcomes in vascular dementia and other vascular cognitive impairments, due to the fact that some important outcomes were infrequently assessed. This would ensure that direct comparisons are possible between trials.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Auchus 2007

Study characteristics	
Methods	Randomised, placebo-controlled, multicentre, double-blind trial of 6 months duration
Participants	788 participants with probable vascular dementia (NINDS-AIREN criteria, clinical confirmation on MRI scan); mean age 72.3 years, 64% male participants
Interventions	Galantamine (8 or 12 mg twice a day) versus placebo for 6 months
Outcomes	ADAS-Cog/11, ADCS-ADL, CIBIC-Plus, ADAS-Cog/13, ADAS-Cog/10, NPI, EXIT25, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...subjects were randomly assigned (1:1) to either increasing doses of galantamine or placebo." Comment: unclear random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "After placebo run-in, all patients were randomly assigned to either increasing doses of galantamine, or placebo." Comment: methods used to randomise unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To ensure blinding, placebo tablets were administered using the same escalation schedule.

Auchus 2007 *(Continued)*

		Quote: "To ensure blinding, the examiner who measured the drug's efficacy in a particular subject was not the same person who treated that subject and recorded adverse events (AEs)." Comment: adequate blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To ensure blinding, the examiner who measured the drug's efficacy in a particular subject was not the same person who treated that subject and recorded adverse events (AEs)." Comment: adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	n = 303 (77%) participants in the treatment arm completed the trial, compared to n = 331 (85%) in the placebo arm. Comment: adequate comparable outcome data available
Selective reporting (reporting bias)	Low risk	All prespecified participant outcome data presented.
Other bias	Low risk	No other sources of bias

Ballard 2008

Study characteristics	
Methods	Randomised, placebo-controlled, multicentre, double-blind trial of 6 months duration
Participants	710 participants with vascular dementia (DSM-IV) and probable vascular dementia (NINDS-AIREN criteria); mean age 72.8 years, 62.3% male participants
Interventions	Rivastigmine (3 to 12 mg/day) versus placebo for 6 months
Outcomes	VaDAS, ADCS-CGIC, ADAS-Cog, ADCS-ADL, NPI, MMSE, GDS, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "All patients were assigned an identification number. Randomization of drug treatment was performed using a validated system that automated the random assignment of treatment groups." Comment: adequate
Allocation concealment (selection bias)	Low risk	Quote: "Randomization of drug treatment was performed using a validated system that automated the random assignment of treatment groups. Patients, caregivers, study site personnel, or any other personnel involved in the conduct of the study remained unaware of treatment groups until all patients had completed the study..." Comment: well-described concealment

Ballard 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients, caregivers, study site personnel, or any other personnel involved in the conduct of the study remained unaware of the treatment groups until all patients had completed the study and all data had been retrieved and finalised for analysis." Comment: well-described blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, caregivers, study site personnel, or any other personnel involved in the conduct of the study remained unaware of the treatment groups until all patients had completed the study and all data had been retrieved and finalised for analysis." Comment: clear blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	n = 275 (75.3%) participants in the treatment arm completed the trial, compared to n = 297 (81.6%) in the placebo arm. Comment: adequate comparable outcome data available
Selective reporting (reporting bias)	Low risk	All prespecified participant outcome data presented.
Other bias	Low risk	No other sources of bias

Black 2003

Study characteristics	
Methods	Randomised, placebo-controlled, multicentre, double-blind trial of 6 months duration
Participants	603 participants with probable or possible vascular dementia (NINDS-AIREN criteria); mean age 73.9 years, 55.2% male participants
Interventions	Donepezil (5 and 10 mg/day) versus placebo for 6 months
Outcomes	ADAS-Cog, CIBIC-Plus, MMSE, CDR-SB, ADFACS, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer generated randomisation protocol." Comment: adequate
Allocation concealment (selection bias)	Unclear risk	Quote "Patients were assigned to 1 of 3 treatment groups by a computer generated randomisation protocol" Comment: unclear concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: all the key groups of people were successfully blinded

Black 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The clinician rating the CIBIC-plus was blind to the patient's psychometric test scores and adverse events." Comment: blinding of other outcome measures was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	n = 161 (81.3%) participants in the donepezil 5 mg arm and n = 148 (71.8%) in the donepezil 10 mg arm completed the trial, compared to n = 169 (84.9%) in the placebo arm. Comment: greater attrition in the donepezil 10 mg treatment arm
Selective reporting (reporting bias)	Low risk	All prespecified participant outcome data presented.
Other bias	Low risk	No other sources of bias

Erkinjuntti 2002

Study characteristics	
Methods	Randomised, placebo-controlled, multicentre, double-blind trial of 6 months duration
Participants	592 participants with probable vascular dementia or Alzheimer's disease combined with CVD (NINDS-AIREN or NINCDS-ADRDA criteria plus significant radiological evidence of CVD on CT or MRI); mean age 75.1 years, 53% male participants
Interventions	Galantamine (24 mg/day) versus placebo for 6 months
Outcomes	ADAS-Cog/11, CIBIC-Plus, ADAS-Cog/13, DAD, NPI, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...patients were randomly assigned placebo or galantamine 24 mg/day for 6 months according to a randomisation code generated by the Janssen Research Foundation." Quote: "The randomisation ratio was two to one for galantamine versus placebo." Comment: adequate
Allocation concealment (selection bias)	Unclear risk	Quote: "...patients were randomly assigned... according to a randomisation code generated by Janssen Research Foundation" Comment: unclear concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Galantamine and placebo were administered as identical single tablets taken orally twice daily." Comment: adequate blinding of the participants, but limited information on blinding of the study team

Erkinjuntti 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "To avoid any potential unmasking of treatment allocation, an independent (masked to other components of the study), experienced, trained clinician undertook the CIBIC-plus assessments to provide an overall impression over the course of the trial." Comment: blinding of other outcome measures was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "More Galantamine patients than placebo patients discontinued the trial, mostly as a result of adverse events (19.7% vs 8.2%)" Comment: greater attrition in the galantamine treatment arm
Selective reporting (reporting bias)	Low risk	All prespecified participant outcome data reported.
Other bias	Low risk	No other sources of bias

Mok 2007

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled trial of 26 weeks duration
Participants	40 participants with subcortical vascular dementia (diagnosis included CT or MRI evidence); mean age 74.9 years, MMSE 3 to 24, mean 13.2
Interventions	Rivastigmine (mean 6 mg/day) versus placebo
Outcomes	MMSE (Chinese version), FAB, NPI (Chinese version), IADL, CDR, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Forty eligible patients were assigned randomly to either placebo (n = 20) or rivastigmine (n = 20) via a computer program generated code." Comment: adequate
Allocation concealment (selection bias)	Unclear risk	Quote: "Eligible patients were assigned randomly... via a computer generated code" Comment: unclear concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The study was a 26-week, double-blind, placebo-controlled, single-centre study in which treatment with 6 mg daily of rivastigmine or placebo was evaluated." Comment: no further description on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The study was a 26-week, double-blind, placebo-controlled, single-centre study in which treatment with 6 mg daily of rivastigmine or placebo was evaluated."

Mok 2007 *(Continued)*

		Comment: outcome vulnerable to bias as no blinding of the assessors is described
Incomplete outcome data (attrition bias) All outcomes	Low risk	This is a small study with 20 participants in each arm and only 1 dropout (due to death).
Selective reporting (reporting bias)	Low risk	All prespecified participant outcome data reported.
Other bias	Low risk	No other sources of bias

Narasimhalu 2009

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled trial of 6 months duration
Participants	50 participants with poststroke cognitive impairment (DSM-IV and MRI evidence), MMSE 16 to 29, mean 23.8; mean age 68.7 years, 44% male participants, 70% Chinese
Interventions	Rivastigmine (up to 9 mg/day) versus placebo
Outcomes	MMSE, Clock Test, Color Trails Test, ADAS-Cog, cognitive battery, FAB, ADCS-ADL, MCI, NPI, GDS, adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed in blocks of 4 using a randomisation list that was produced by the pharmaceutical company's supply management using a validated system that automates the random assignment of treatment groups to randomisation numbers in the specified ratio. The randomisation scheme was reviewed by a Biostatistics Quality Assurance Group and locked by them after approval." Comment: adequate
Allocation concealment (selection bias)	Low risk	Quote: "A trial coordinator blind to the treatment allocation randomised each patient. The patient, psychologist, trial coordinator, clinicians and investigators were blinded to the treatment allocation." Comment: well-described concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A trial coordinator blind to the treatment allocation randomised each patient. The patient, psychologist, trial coordinator, clinicians and investigators were blinded to the treatment allocation." Comment: well-described blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A trial coordinator blind to the treatment allocation randomised each patient. The patient, psychologist, trial coordinator, clinicians and investigators were blinded to the treatment allocation."

Narasimhalu 2009 *(Continued)*

		Comment: well-described blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 50 randomised, information on study outcomes was available for 49 patients (98%) as one patient in the placebo group died before a follow-up cognitive evaluation carried out at week 12." Comment: proportionally similar patients in treatment and placebo groups. Comparable numbers of death and discontinuation of study medication.
Selective reporting (reporting bias)	Low risk	All prespecified participant outcome data reported.
Other bias	Low risk	No other sources of bias

Roman 2010

Study characteristics		
Methods	Randomised, placebo-controlled, multicentre, double-blind trial of 6 months duration	
Participants	974 participants with possible or probable vascular dementia (NINDS-AIREN); mean age 73.0 years, 59% male participants	
Interventions	Donepezil (5 mg/day) versus placebo for 6 months	
Outcomes	ADAS-Cog, CIBIC-Plus, MMSE, CLOX 1/2, EXIT25, DAD, CDR-SB	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No method of sequence generation described.
Allocation concealment (selection bias)	Unclear risk	Quote: "Participants were randomly assigned 2:1 to donepezil 5mg or placebo" Comment: method used to randomly assign participants not described. Unclear concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Proportionally similar completion rates: placebo (86.8%) vs treatment (82.6%)

Roman 2010 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	All expected outcomes included; however, CIBIC-Plus was reported on a graph only.
Other bias	Low risk	No other sources of bias

Wilkinson 2003

Study characteristics	
Methods	Randomised, placebo-controlled, multicentre, double-blind trial of 6 months duration
Participants	616 participants with possible or probable vascular dementia (NINDS-AIREN) with clinical and radiologic evidence of CVD; mean age 75.0, 60% male participants
Interventions	Donepezil (5 or 10 mg/day) versus placebo
Outcomes	ADAS-Cog, CIBIC-Plus, MMSE, CDR-SB, ADFACS, adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to treatment groups by a computer-generated randomisation protocol." Comment: adequate
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were assigned to treatment groups by a computer generated randomisation protocol" Comment: unclear concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding was ensured by the use of identical-appearing placebo and donepezil tablets." Comment: adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "ADAS-cog assessment was performed by a trained clinician. An independent clinician, who was blinded to the patient's psycho- metric test scores and AE information, performed the CIBIC-plus." Comment: blinding of other outcome measures was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	n = 168 (80.8%) participants in the donepezil 5 mg arm and n = 162 (75.3%) in the donepezil 10 mg arm completed the trial, compared to n = 161 (83.4%) in the placebo arm. Comment: greater attrition in the donepezil 10 mg treatment arm
Selective reporting (reporting bias)	Low risk	All prespecified participant outcome data presented.
Other bias	Low risk	No other sources of bias

ADAS-Cog/10: Alzheimer's Disease Assessment Scale - Cognitive subscale / 10 questions; ADAS-Cog/11: Alzheimer's Disease Assessment Scale - Cognitive subscale / 11 questions; ADAS-Cog/13: Alzheimer's Disease Assessment Scale - Cognitive subscale / 13 questions; ADCS-ADL: Alzheimer's Disease Cooperative Study - Activities of Daily Living; ADCS-CGIC: Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change; ADFACS: Alzheimer's Disease Functional Assessment of Change Scale; CAB: Community Advisory Board; CDR: Clinical Dementia Rating; CDR-SB: Clinical Dementia Rating - Sum of Boxes; CIBIC-Plus: Clinician Interview Based Impression of Change - Plus Carergiver Interview; CLOX1/2: Executive Clock Drawing Task; CVD; Cardiovascular Disease; CT: Computerised Tomography; DAD: Disability Assessment for Dementia; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; EXIT25: Executive Interview 25 item; FAB: Frontal Assessment Battery; GDS: Global Deterioration Scale; IADL; Instrumental Activities of Daily Living; MCI: Mild Cognitive Impairment; MMSE: Mini Mental State Examination; MRI: Magnetic Resonance Imaging; NINCDS-ADRA: National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease Related Disorders Association; NINDS-AIREN: National Institute of Neurological Disorders and Stroke Association - Internationale Pour La Recherche et l'Enseignement en Neurosciences; NPI: Neuropsychiatric Inventory; VaDAS; Vascular Dementia Assessment.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Dichgans 2008	Study population cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

DATA AND ANALYSES

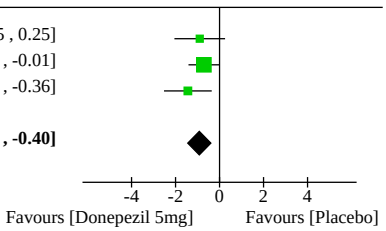
Comparison 1. Cognition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Donepezil 5 mg ADAS-Cog (OC or LOCF)	3	1601	Mean Difference (IV, Random, 95% CI)	-0.92 [-1.44, -0.40]
1.2 Donepezil 10 mg ADAS-Cog (OC)	2	608	Mean Difference (IV, Random, 95% CI)	-2.21 [-3.07, -1.35]
1.3 Rivastigmine ADAS-Cog (LOCF)	2	748	Mean Difference (IV, Random, 95% CI)	0.03 [-3.04, 3.10]
1.4 Galantamine ADAS-Cog (OC or LOCF)	2	1188	Mean Difference (IV, Random, 95% CI)	-2.01 [-3.18, -0.85]
1.5 Donepezil 5 mg ADAS-Cog (LOCF)	3	1772	Mean Difference (IV, Random, 95% CI)	-0.73 [-1.67, 0.22]
1.6 Donepezil 10 mg ADAS-Cog (LOCF)	2	813	Mean Difference (IV, Random, 95% CI)	-2.17 [-2.97, -1.37]
1.7 Galantamine ADAS-Cog (LOCF)	2	1279	Mean Difference (IV, Random, 95% CI)	-1.80 [-2.55, -1.05]

Analysis 1.1. Comparison 1: Cognition, Outcome 1: Donepezil 5 mg ADAS-Cog (OC or LOCF)

Study or Subgroup	Donepezil 5mg Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Black 2003	-0.56	5.3188	153	0.34	5.0596	160	20.8%	-0.90 [-2.05 , 0.25]
Roman 2010	-1.04	5.3457	648	-0.33	5.2361	326	55.8%	-0.71 [-1.41 , -0.01]
Wilkinson 2003	-2.02	4.6102	164	-0.58	5.1439	150	23.4%	-1.44 [-2.52 , -0.36]
Total (95% CI)			**965**			**636**	**100.0%**	**-0.92 [-1.44 , -0.40]**

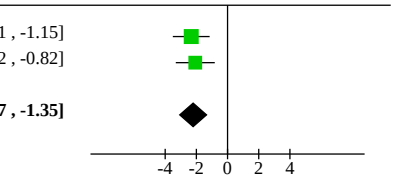
Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 3.44 (P = 0.0006)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Cognition, Outcome 2: Donepezil 10 mg ADAS-Cog (OC)

Study or Subgroup	Donepezil 10mg Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Black 2003	-1.99	5.3812	143	0.34	5.0596	160	52.9%	-2.33 [-3.51 , -1.15]
Wilkinson 2003	-2.65	5.976	155	-0.58	5.1439	150	47.1%	-2.07 [-3.32 , -0.82]
Total (95% CI)			**298**			**310**	**100.0%**	**-2.21 [-3.07 , -1.35]**

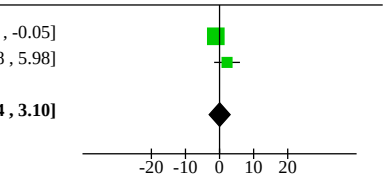
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 5.04 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Cognition, Outcome 3: Rivastigmine ADAS-Cog (LOCF)

Study or Subgroup	Rivastigmine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ballard 2008	-0.7	7.21	360	0.4	6.9862	338	65.8%	-1.10 [-2.15 , -0.05]
Narasimhalu 2009	-0.6	6.0565	25	-2.8	7.5101	25	34.2%	2.20 [-1.58 , 5.98]
Total (95% CI)			**385**			**363**	**100.0%**	**0.03 [-3.04 , 3.10]**

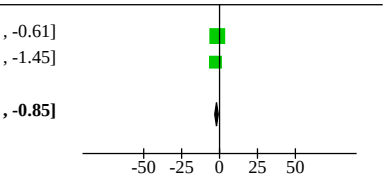
Heterogeneity: Tau² = 3.44; Chi² = 2.71, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Cognition, Outcome 4: Galantamine ADAS-Cog (OC or LOCF)

Study or Subgroup	Galantamine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Auchus 2007	-1.8	5.94	364	-0.3	6.32	372	57.1%	-1.50 [-2.39 , -0.61]
Erkinjuntti 2002	-1.7	6.8118	290	1	6.364	162	42.9%	-2.70 [-3.95 , -1.45]
Total (95% CI)			**654**			**534**	**100.0%**	**-2.01 [-3.18 , -0.85]**

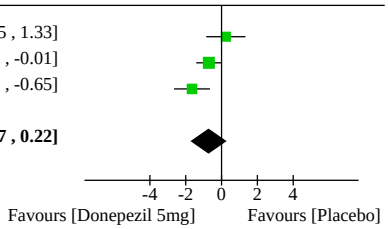
Heterogeneity: Tau² = 0.41; Chi² = 2.34, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 3.39 (P = 0.0007)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Cognition, Outcome 5: Donepezil 5 mg ADAS-Cog (LOCF)

Study or Subgroup	Donepezil 5mg Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Black 2003	0.96	5.4878	198	0.72	5.6427	199	29.6%	0.24 [-0.85 , 1.33]
Roman 2010	-1.04	5.3457	648	-0.33	5.2361	326	38.7%	-0.71 [-1.41 , -0.01]
Wilkinson 2003	-1.75	4.7593	208	-0.1	5.4181	193	31.7%	-1.65 [-2.65 , -0.65]
Total (95% CI)			**1054**			**718**	**100.0%**	**-0.73 [-1.67 , 0.22]**

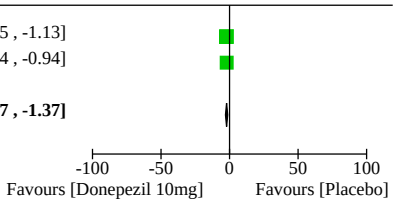
Heterogeneity: Tau² = 0.47; Chi² = 6.26, df = 2 (P = 0.04); I² = 68%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Cognition, Outcome 6: Donepezil 10 mg ADAS-Cog (LOCF)

Study or Subgroup	Donepezil 10mg Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Black 2003	-1.52	5.7411	206	0.72	5.6427	199	51.9%	-2.24 [-3.35 , -1.13]
Wilkinson 2003	-2.19	6.4517	215	-0.1	5.4181	193	48.1%	-2.09 [-3.24 , -0.94]
Total (95% CI)			**421**			**392**	**100.0%**	**-2.17 [-2.97 , -1.37]**

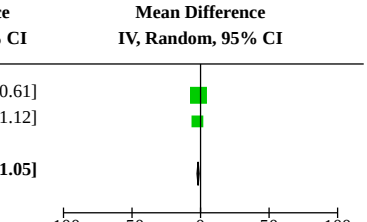
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 5.32 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Cognition, Outcome 7: Galantamine ADAS-Cog (LOCF)

Study or Subgroup	Galantamine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Auchus 2007	-1.8	5.94	364	-0.3	6.32	372	62.3%	-1.50 [-2.39 , -0.61]
Erkinjuntti 2002	-1.13	7.8	357	1.16	5.9	186	37.7%	-2.29 [-3.46 , -1.12]
Total (95% CI)			**721**			**558**	**100.0%**	**-1.80 [-2.55 , -1.05]**

Heterogeneity: Tau² = 0.03; Chi² = 1.11, df = 1 (P = 0.29); I² = 10%
Test for overall effect: Z = 4.70 (P < 0.00001)
Test for subgroup differences: Not applicable



Comparison 2. Clinical global impression

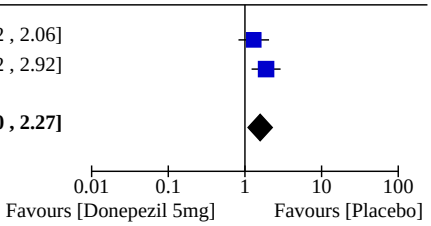
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 Donepezil 5 mg CIBIC-Plus (Improvement) (OC or LOCF)	2	712	Odds Ratio (M-H, Random, 95% CI)	1.58 [1.10, 2.27]
2.2 Donepezil 10 mg CIBIC-Plus (Improvement) (OC or LOCF)	2	699	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.78, 1.70]
2.3 Galantamine CIBIC-Plus (Improvement) (LOCF)	2	1326	Odds Ratio (M-H, Random, 95% CI)	1.32 [1.03, 1.70]
2.4 Donepezil 5 mg CIBIC-Plus (Improvement) (LOCF)	2	792	Odds Ratio (M-H, Random, 95% CI)	1.55 [1.14, 2.10]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.5 Donepezil 10 mg CIBIC-Plus (Improvement) (LOCF)	2	795	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.71, 1.72]

Analysis 2.1. Comparison 2: Clinical global impression, Outcome 1: Donepezil 5 mg CIBIC-Plus (Improvement) (OC or LOCF)

Study or Subgroup	Donepezil 5mg Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Black 2003	61	160	52	162	48.0%	1.30 [0.82 , 2.06]
Wilkinson 2003	78	202	47	188	52.0%	1.89 [1.22 , 2.92]
Total (95% CI)		**362**		**350**	**100.0%**	**1.58 [1.10 , 2.27]**
Total events:	139		99			

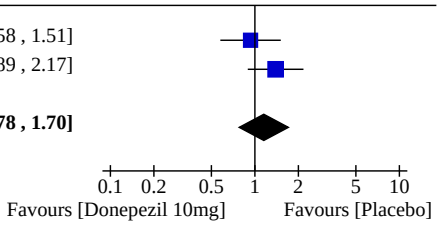
Heterogeneity: Tau² = 0.02; Chi² = 1.32, df = 1 (P = 0.25); I² = 24%
Test for overall effect: Z = 2.47 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Clinical global impression, Outcome 2: Donepezil 10 mg CIBIC-Plus (Improvement) (OC or LOCF)

Study or Subgroup	Donepezil 10mg Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Black 2003	45	147	52	162	47.1%	0.93 [0.58 , 1.51]
Wilkinson 2003	64	202	47	188	52.9%	1.39 [0.89 , 2.17]
Total (95% CI)		**349**		**350**	**100.0%**	**1.15 [0.78 , 1.70]**
Total events:	109		99			

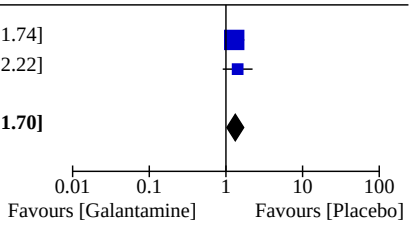
Heterogeneity: Tau² = 0.02; Chi² = 1.43, df = 1 (P = 0.23); I² = 30%
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Clinical global impression, Outcome 3: Galantamine CIBIC-Plus (Improvement) (LOCF)

Study or Subgroup	Galantamine Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Auchus 2007	139	363	121	371	68.6%	1.28 [0.95 , 1.74]
Erkinjuntti 2002	86	396	32	196	31.4%	1.42 [0.91 , 2.22]
Total (95% CI)		**759**		**567**	**100.0%**	**1.32 [1.03 , 1.70]**
Total events:	225		153			

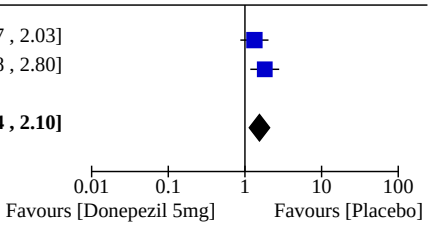
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.19 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Clinical global impression, Outcome 4: Donepezil 5 mg CIBIC-Plus (Improvement) (LOCF)

Study or Subgroup	Donepezil 5mg Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Black 2003	70	198	58	199	51.3%	1.33 [0.87 , 2.03]
Wilkinson 2003	78	207	47	188	48.7%	1.81 [1.18 , 2.80]
Total (95% CI)		**405**		**387**	**100.0%**	**1.55 [1.14 , 2.10]**
Total events:	148		105			

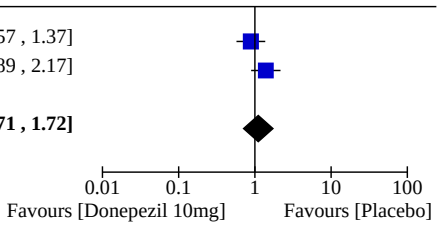
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.31); I² = 1%
Test for overall effect: Z = 2.81 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Clinical global impression, Outcome 5: Donepezil 10 mg CIBIC-Plus (Improvement) (LOCF)

Study or Subgroup	Donepezil 10mg Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Black 2003	55	206	58	199	50.5%	0.89 [0.57 , 1.37]
Wilkinson 2003	64	202	47	188	49.5%	1.39 [0.89 , 2.17]
Total (95% CI)		**408**		**387**	**100.0%**	**1.11 [0.71 , 1.72]**
Total events:	119		105			

Heterogeneity: Tau² = 0.05; Chi² = 2.03, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



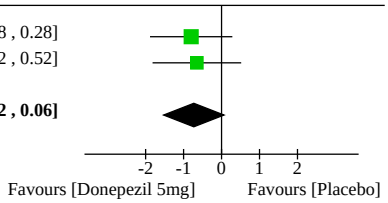
Comparison 3. Functional performance in activities of daily living

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Donepezil 5 mg ADFACS (LOCF)	2	798	Mean Difference (IV, Random, 95% CI)	-0.73 [-1.52, 0.06]
3.2 Donepezil 10 mg ADFACS (LOCF)	2	813	Mean Difference (IV, Random, 95% CI)	-0.95 [-1.73, -0.17]
3.3 Rivastigmine ADCS-ADL & IADL (LOCF)	3	800	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.12, 0.16]
3.4 Galantamine ADCS-ADL & DAD (OC or LOCF)	2	1174	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.24, 0.46]
3.5 Galantamine ADCS-ADL & DAD (LOCF)	2	1228	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.23, 0.42]

Analysis 3.1. Comparison 3: Functional performance in activities of daily living, Outcome 1: Donepezil 5 mg ADFACS (LOCF)

Study or Subgroup	Donepezil 5mg Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Black 2003	0.64	5.0656	198	1.44	5.9248	199	53.7%	-0.80 [-1.88 , 0.28]
Wilkinson 2003	0.11	6.49	208	0.76	5.4181	193	46.3%	-0.65 [-1.82 , 0.52]
Total (95% CI)			**406**			**392**	**100.0%**	**-0.73 [-1.52 , 0.06]**

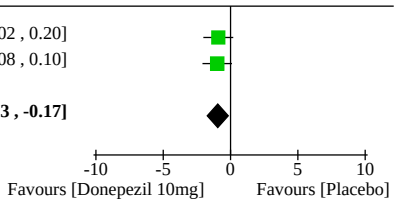
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.80 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Functional performance in activities of daily living, Outcome 2: Donepezil 10 mg ADFACS (LOCF)

Study or Subgroup	Donepezil 10mg Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Black 2003	0.53	5.454	206	1.44	5.9248	199	49.3%	-0.91 [-2.02 , 0.20]
Wilkinson 2003	-0.23	5.8652	215	0.76	5.4181	193	50.7%	-0.99 [-2.08 , 0.10]
Total (95% CI)			**421**			**392**	**100.0%**	**-0.95 [-1.73 , -0.17]**

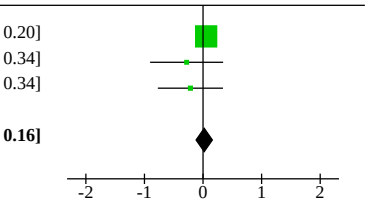
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.39 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Functional performance in activities of daily living, Outcome 3: Rivastigmine ADCS-ADL & IADL (LOCF)

Study or Subgroup	Rivastigmine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ballard 2008	-0.1	11.2719	365	-0.7	11.1445	345	88.8%	0.05 [-0.09 , 0.20]
Mok 2007	0	0.35	20	0.1	0.35	20	5.0%	-0.28 [-0.90 , 0.34]
Narasimhalu 2009	3.2	6.541	25	5.2	11.144	25	6.2%	-0.22 [-0.77 , 0.34]
Total (95% CI)			**410**			**390**	**100.0%**	**0.02 [-0.12 , 0.16]**

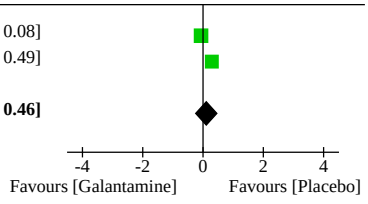
Heterogeneity: Tau² = 0.00; Chi² = 1.78, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.78)
Test for subgroup differences: Not applicable



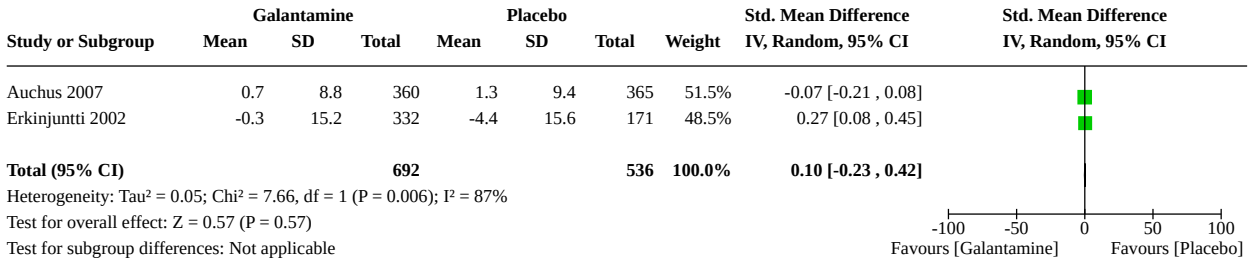
Analysis 3.4. Comparison 3: Functional performance in activities of daily living, Outcome 4: Galantamine ADCS-ADL & DAD (OC or LOCF)

Study or Subgroup	Galantamine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Auchus 2007	0.7	8.8	360	1.3	9.4	365	51.7%	-0.07 [-0.21 , 0.08]
Erkinjuntti 2002	0.2	15.2735	288	-4.4	16.4952	161	48.3%	0.29 [0.10 , 0.49]
Total (95% CI)			**648**			**526**	**100.0%**	**0.11 [-0.24 , 0.46]**

Heterogeneity: Tau² = 0.06; Chi² = 8.37, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



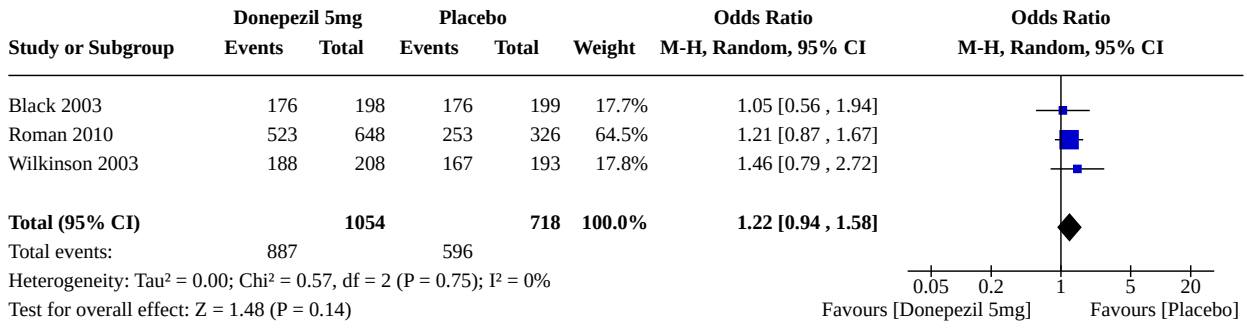
Analysis 3.5. Comparison 3: Functional performance in activities of daily living, Outcome 5: Galantamine ADCS-ADL & DAD (LOCF)



Comparison 4. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Donepezil 5 mg (LOCF)	3	1772	Odds Ratio (M-H, Random, 95% CI)	1.22 [0.94, 1.58]
4.2 Donepezil 10 mg (LOCF)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	1.95 [1.20, 3.15]
4.3 Rivastigmine (LOCF)	3	831	Odds Ratio (M-H, Random, 95% CI)	3.21 [0.36, 28.88]
4.4 Galantamine (LOCF)	2	1378	Odds Ratio (M-H, Random, 95% CI)	1.57 [1.02, 2.43]

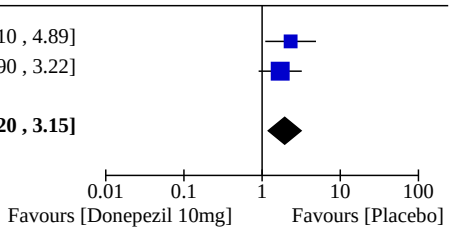
Analysis 4.1. Comparison 4: Adverse events, Outcome 1: Donepezil 5 mg (LOCF)



Analysis 4.2. Comparison 4: Adverse events, Outcome 2: Donepezil 10 mg (LOCF)

Study or Subgroup	Donepezil 10mg Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Black 2003	195	206	176	199	39.4%	2.32 [1.10 , 4.89]
Wilkinson 2003	197	215	167	193	60.6%	1.70 [0.90 , 3.22]
Total (95% CI)		**421**		**392**	**100.0%**	**1.95 [1.20 , 3.15]**
Total events:	392		343			

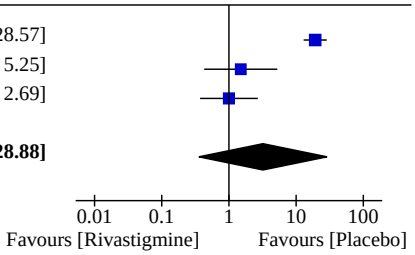
Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Adverse events, Outcome 3: Rivastigmine (LOCF)

Study or Subgroup	Rivastigmine Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ballard 2008	320	363	96	344	35.1%	19.22 [12.94 , 28.57]
Mok 2007	12	20	10	20	31.8%	1.50 [0.43 , 5.25]
Narasimhalu 2009	10	40	11	44	33.1%	1.00 [0.37 , 2.69]
Total (95% CI)		**423**		**408**	**100.0%**	**3.21 [0.36 , 28.88]**
Total events:	342		117			

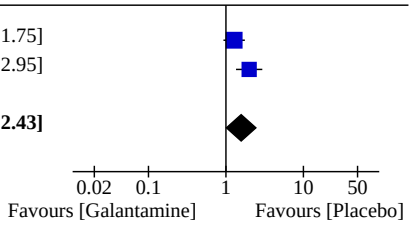
Heterogeneity: Tau² = 3.54; Chi² = 40.05, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Adverse events, Outcome 4: Galantamine (LOCF)

Study or Subgroup	Galantamine Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Auchus 2007	301	396	278	390	53.3%	1.28 [0.93 , 1.75]
Erkinjuntti 2002	320	396	133	196	46.7%	1.99 [1.35 , 2.95]
Total (95% CI)		**792**		**586**	**100.0%**	**1.57 [1.02 , 2.43]**
Total events:	621		411			

Heterogeneity: Tau² = 0.07; Chi² = 3.02, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 2.03 (P = 0.04)
Test for subgroup differences: Not applicable



Comparison 5. Serious adverse events

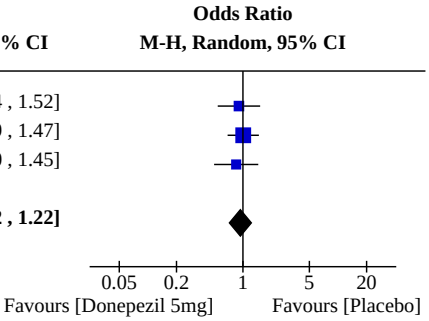
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 Donepezil 5 mg (LOCF)	3	1772	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.72, 1.22]
5.2 Donepezil 10 mg (LOCF)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.81, 1.64]
5.3 Rivastigmine (LOCF)	2	622	Odds Ratio (M-H, Random, 95% CI)	1.42 [0.90, 2.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4 Galantamine (LOCF)	1	786	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.78, 1.59]

Analysis 5.1. Comparison 5: Serious adverse events, Outcome 1: Donepezil 5 mg (LOCF)

Study or Subgroup	Donepezil 5mg Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Black 2003	34	198	37	199	26.6%	0.91 [0.54 , 1.52]
Roman 2010	94	648	47	326	48.9%	1.01 [0.69 , 1.47]
Wilkinson 2003	31	208	33	193	24.5%	0.85 [0.50 , 1.45]
Total (95% CI)		**1054**		**718**	**100.0%**	**0.94 [0.72 , 1.22]**
Total events:	159		117			

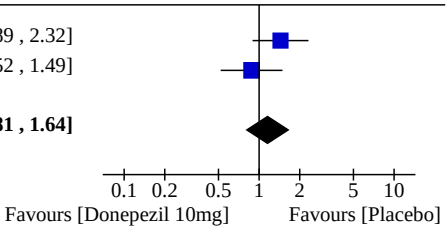
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 2 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Serious adverse events, Outcome 2: Donepezil 10 mg (LOCF)

Study or Subgroup	Donepezil 10mg Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Black 2003	51	206	37	199	49.0%	1.44 [0.89 , 2.32]
Wilkinson 2003	33	215	33	193	51.0%	0.88 [0.52 , 1.49]
Total (95% CI)		**421**		**392**	**100.0%**	**1.15 [0.81 , 1.64]**
Total events:	84		70			

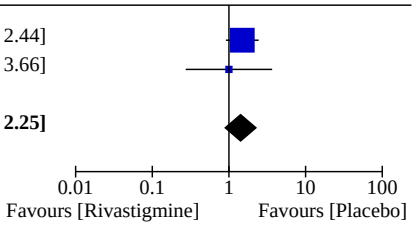
Heterogeneity: Chi² = 1.85, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Serious adverse events, Outcome 3: Rivastigmine (LOCF)

Study or Subgroup	Rivastigmine Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ballard 2008	42	275	32	297	87.4%	1.49 [0.91 , 2.44]
Narasimhalu 2009	6	25	6	25	12.6%	1.00 [0.27 , 3.66]
Total (95% CI)		**300**		**322**	**100.0%**	**1.42 [0.90 , 2.25]**
Total events:	48		38			

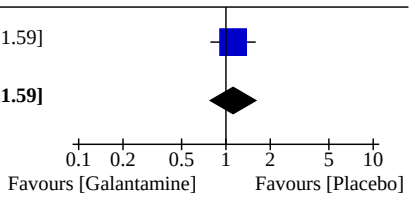
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Serious adverse events, Outcome 4: Galantamine (LOCF)

Study or Subgroup	Galantamine Events	Galantamine Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Auchus 2007	80	396	72	390	100.0%	1.12 [0.78 , 1.59]
Total (95% CI)		**396**		**390**	**100.0%**	**1.12 [0.78 , 1.59]**
Total events:	80		72			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.54)
Test for subgroup differences: Not applicable



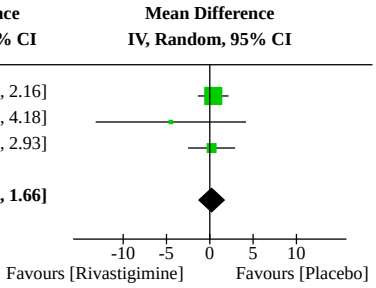
Comparison 6. Behavioural disturbance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Rivastigmine NPI (LOCF)	3	796	Mean Difference (IV, Random, 95% CI)	0.21 [-1.25, 1.66]
6.2 Galantamine NPI (OC or LOCF)	2	1151	Mean Difference (IV, Random, 95% CI)	-0.13 [-4.05, 3.79]
6.3 Galantamine NPI (LOCF)	2	1205	Mean Difference (IV, Random, 95% CI)	0.26 [-2.90, 3.42]

Analysis 6.1. Comparison 6: Behavioural disturbance, Outcome 1: Rivastigmine NPI (LOCF)

Study or Subgroup	Rivastigimine Mean	Rivastigimine SD	Rivastigimine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Ballard 2008	-1.4	12.0196	364	-1.8	11.8357	342	68.5%	0.40 [-1.36 , 2.16]
Mok 2007	-3.6	14	20	0.9	14	20	2.8%	-4.50 [-13.18 , 4.18]
Narasimhalu 2009	0.31	1.4293	25	0.1	6.7833	25	28.7%	0.21 [-2.51 , 2.93]
Total (95% CI)			**409**			**387**	**100.0%**	**0.21 [-1.25 , 1.66]**

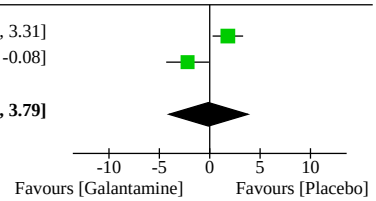
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Behavioural disturbance, Outcome 2: Galantamine NPI (OC or LOCF)

Study or Subgroup	Galantamine Mean	Galantamine SD	Galantamine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Auchus 2007	0.6	10.6	356	-1.2	10.1	362	51.8%	1.80 [0.29 , 3.31]
Erkinjuntti 2002	-1.2	10.022	279	1	11.1687	154	48.2%	-2.20 [-4.32 , -0.08]
Total (95% CI)			**635**			**516**	**100.0%**	**-0.13 [-4.05 , 3.79]**

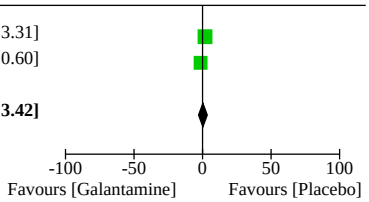
Heterogeneity: Tau² = 7.12; Chi² = 9.05, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6: Behavioural disturbance, Outcome 3: Galantamine NPI (LOCF)

Study or Subgroup	Galantamine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Auchus 2007	0.6	10.6	356	-1.2	10.1	362	52.3%	1.80 [0.29 , 3.31]
Erkinjuntti 2002	-0.3	10.3	322	1.13	11.1	165	47.7%	-1.43 [-3.46 , 0.60]
Total (95% CI)			**678**			**527**	**100.0%**	**0.26 [-2.90 , 3.42]**

Heterogeneity: Tau² = 4.38; Chi² = 6.23, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable



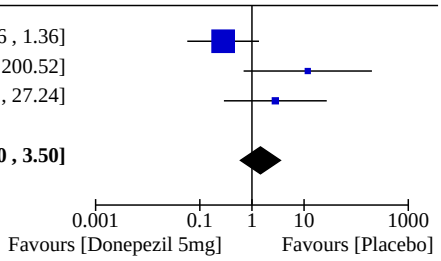
Comparison 7. Death (LOCF)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Donepezil 5 mg	3	1772	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.60, 3.50]
7.2 Donepezil 10 mg	2	813	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.34, 2.58]
7.3 Rivastigmine	3	800	Odds Ratio (M-H, Random, 95% CI)	1.45 [0.51, 4.15]
7.4 Galantamine	2	1378	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.26, 1.10]

Analysis 7.1. Comparison 7: Death (LOCF), Outcome 1: Donepezil 5 mg

Study or Subgroup	Donepezil 5mg Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Black 2003	2	198	7	199	80.5%	0.28 [0.06 , 1.36]
Roman 2010	11	648	0	326	7.6%	11.78 [0.69 , 200.52]
Wilkinson 2003	3	208	1	193	11.9%	2.81 [0.29 , 27.24]
Total (95% CI)		**1054**		**718**	**100.0%**	**1.46 [0.60 , 3.50]**
Total events:	16		8			

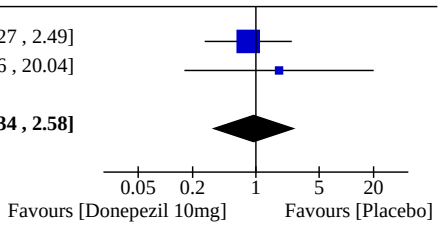
Heterogeneity: Chi² = 6.57, df = 2 (P = 0.04); I² = 70%
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Death (LOCF), Outcome 2: Donepezil 10 mg

Study or Subgroup	Donepezil 10mg Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Black 2003	6	206	7	199	82.5%	0.82 [0.27 , 2.49]
Wilkinson 2003	2	215	1	193	17.5%	1.80 [0.16 , 20.04]
Total (95% CI)		**421**		**392**	**100.0%**	**0.94 [0.34 , 2.58]**
Total events:	8		8			

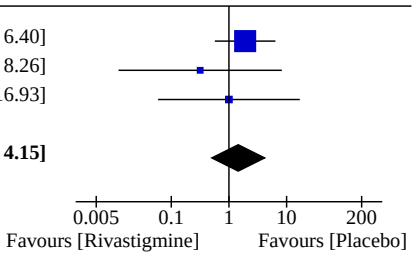
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable



Analysis 7.3. Comparison 7: Death (LOCF), Outcome 3: Rivastigmine

Study or Subgroup	Rivastigmine Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ballard 2008	8	365	4	345	75.7%	1.91 [0.57 , 6.40]
Mok 2007	0	20	1	20	10.4%	0.32 [0.01 , 8.26]
Narasimhalu 2009	1	25	1	25	13.8%	1.00 [0.06 , 16.93]
Total (95% CI)		**410**		**390**	**100.0%**	**1.45 [0.51 , 4.15]**
Total events:	9		6			

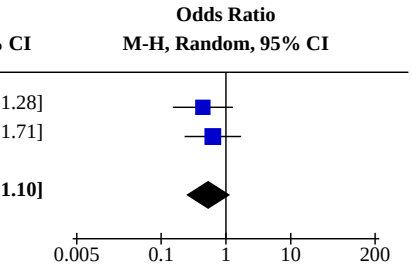
Heterogeneity: Tau² = 0.00; Chi² = 1.10, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 7.4. Comparison 7: Death (LOCF), Outcome 4: Galantamine

Study or Subgroup	Galantamine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Auchus 2007	5	396	11	390	46.9%	0.44 [0.15 , 1.28]
Erkinjuntti 2002	9	396	7	196	53.1%	0.63 [0.23 , 1.71]
Total (95% CI)		**792**		**586**	**100.0%**	**0.53 [0.26 , 1.10]**
Total events:	14		18			

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.69 (P = 0.09)
Test for subgroup differences: Not applicable



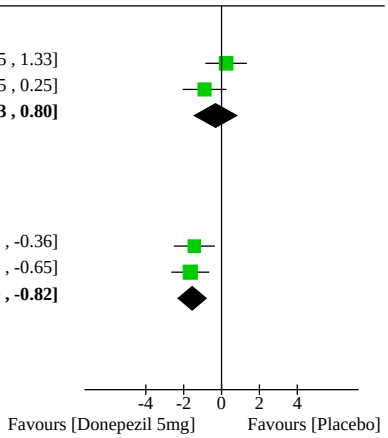
Comparison 8. Sensitivity analyses: comparison of OC and LOCF analyses

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.1 Donepezil 5 mg. Outcome: Cognition (ADAS-Cog)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1.1 OC then LOCF	1	710	Mean Difference (IV, Random, 95% CI)	-0.32 [-1.43, 0.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1.2 OC then LOCF	1	715	Mean Difference (IV, Random, 95% CI)	-1.55 [-2.29, -0.82]
8.2 Donepezil 10 mg. Outcome: Cognition (ADAS-Cog)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.2.1 OC then LOCF	1	708	Mean Difference (IV, Random, 95% CI)	-2.28 [-3.09, -1.47]
8.2.2 OC then LOCF	1	723	Mean Difference (IV, Random, 95% CI)	-2.52 [-3.40, -1.63]
8.3 Galantamine. Outcome: Cognition (ADAS-Cog)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.3.1 OC then LOCF	1	995	Mean Difference (IV, Random, 95% CI)	-2.48 [-3.34, -1.62]

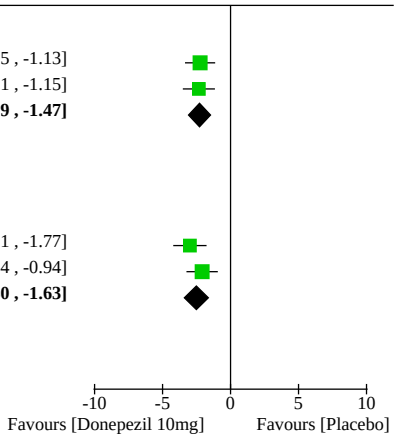
Analysis 8.1. Comparison 8: Sensitivity analyses: comparison of OC and LOCF analyses, Outcome 1: Donepezil 5 mg. Outcome: Cognition (ADAS-Cog)

Study or Subgroup	Donepezil 5mg Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
8.1.1 OC then LOCF								
Black 2003	0.96	5.4878	198	0.72	5.6427	199	51.3%	0.24 [-0.85 , 1.33]
Black 2003	-0.56	5.3188	153	0.34	5.0596	160	48.7%	-0.90 [-2.05 , 0.25]
Subtotal (95% CI)			**351**			**359**	**100.0%**	**-0.32 [-1.43 , 0.80]**
Heterogeneity: Tau² = 0.32; Chi² = 1.98, df = 1 (P = 0.16); I² = 49%								
Test for overall effect: Z = 0.55 (P = 0.58)								
8.1.2 OC then LOCF								
Wilkinson 2003	-2.02	4.6102	164	-0.58	5.1439	150	46.0%	-1.44 [-2.52 , -0.36]
Wilkinson 2003	-1.75	4.7593	208	-0.1	5.4181	193	54.0%	-1.65 [-2.65 , -0.65]
Subtotal (95% CI)			**372**			**343**	**100.0%**	**-1.55 [-2.29 , -0.82]**
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%								
Test for overall effect: Z = 4.14 (P < 0.0001)								



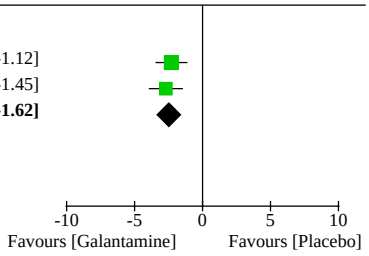
Analysis 8.2. Comparison 8: Sensitivity analyses: comparison of OC and LOCF analyses, Outcome 2: Donepezil 10 mg. Outcome: Cognition (ADAS-Cog)

Study or Subgroup	Donepezil 10mg Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
8.2.1 OC then LOCF								
Black 2003	-1.52	5.7411	206	0.72	5.6427	199	53.1%	-2.24 [-3.35 , -1.13]
Black 2003	-1.99	5.3812	143	0.34	5.0596	160	46.9%	-2.33 [-3.51 , -1.15]
Subtotal (95% CI)			**349**			**359**	**100.0%**	**-2.28 [-3.09 , -1.47]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%								
Test for overall effect: Z = 5.54 (P < 0.00001)								
8.2.2 OC then LOCF								
Wilkinson 2003	-2.65	5.976	155	0.34	5.0596	160	47.2%	-2.99 [-4.21 , -1.77]
Wilkinson 2003	-2.19	6.4517	215	-0.1	5.4181	193	52.8%	-2.09 [-3.24 , -0.94]
Subtotal (95% CI)			**370**			**353**	**100.0%**	**-2.52 [-3.40 , -1.63]**
Heterogeneity: Tau² = 0.04; Chi² = 1.10, df = 1 (P = 0.29); I² = 9%								
Test for overall effect: Z = 5.60 (P < 0.00001)								



Analysis 8.3. Comparison 8: Sensitivity analyses: comparison of OC and LOCF analyses, Outcome 3: Galantamine. Outcome: Cognition (ADAS-Cog)

Study or Subgroup	Galantamine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
8.3.1 OC then LOCF								
Erkinjuntti 2002	-1.13	7.8	357	1.16	5.9	186	53.4%	-2.29 [-3.46 , -1.12]
Erkinjuntti 2002	-1.7	6.8118	290	1	6.364	162	46.6%	-2.70 [-3.95 , -1.45]
Subtotal (95% CI)			**647**			**348**	**100.0%**	**-2.48 [-3.34 , -1.62]**
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%								
Test for overall effect: Z = 5.68 (P < 0.00001)								



ADDITIONAL TABLES

Table 1. Network meta-analysis results: 'Summary of findings' table

Bayesian network meta-analysis: 'Summary of findings' table							
BENEFITS							
Patients: vascular dementia and other vascular cognitive impairments **Interventions:** cholinesterase inhibitors **Comparator:** placebo **Outcome:** cognition (using ADAS-Cog,* continuous) (follow-up at 24 or 26 weeks) **Setting:** outpatients							
Total RCTs: 7 **Total participants: 3537**	**Relative effect (95% CI)**	**Anticipated absolute effect**			**Certainty of evidence (GRADE)**	**Ranking**	**Interpretation of findings**
		With treatment	**Without treatment**	**Difference**			
Donepezil 10 mg 2 RCTs; 608 participants	-	MD −2.18 (−3.87 to −0.47) Network estimates	Mean change from baseline ranged across control groups from −0.58 to 0.34.	-	⊕⊕⊕⊕ HIGH	1	Definitely superior to placebo
Galantamine 2 RCTs; 1188 participants (Dose ranges: 16 to 24 mg/day)	-	MD −1.84 (−3.63 to −0.14) Network estimates	Mean change from baseline ranged across control groups from 0.3 to 1.	-	⊕⊕⊕⊕ HIGH	2	Definitely superior to placebo
Donepezil 5 mg 3 RCTs; 1601 participants	-	MD −0.74 (−2.14 to 0.71) Network estimates	Mean change from baseline ranged across control groups from −0.58 to 0.34.	-	⊕⊕⊕⊖ MODERATE[1]	3	Probably not superior to placebo
Rivastigmine 2 RCTs; 748 participants	-	MD −0.53 (−2.35 to 1.94) Network estimates	Mean change from baseline ranged across control groups from −2.8 to 0.4.	-	⊕⊕⊕⊖ MODERATE[2]	4	Probably not superior to placebo

Table 1. Network meta-analysis results: 'Summary of findings' table *(Continued)*
(Dose ranges: 3 to 12 mg/day)

HARMS

Patients: vascular dementia and other vascular cognitive impairments

Interventions: cholinesterase inhibitors

Comparator: placebo

Outcome: adverse events (follow-up at 24 or 26 weeks)

Setting: outpatients

Total RCTs: 8 **Total participants: 3981**	**Relative effect (95% CI)**	**Anticipated absolute effect**			**Certainty of evidence (GRADE)**	**Ranking**	**Interpretation of findings**
		With treatment	**Without treatment**	**Difference**			
Donepezil 10 mg 2 RCTs; 813 participants	OR 2.00 (0.36 to 11.50) Network estimates	933 per 1000	875 per 1000	58 per 1000 more (from 159 fewer to 113 more)	⊕⊕⊕⊖ MODERATE[1]	3	Probably inferior to placebo
Galantamine 2 RCTs; 1378 participants (Dose ranges: 16 to 24 mg/day)	OR 1.60 (0.28 to 9.25) Network estimates	790 per 1000	701 per 1000	89 per 1000 more (from 309 fewer to 255 more)	⊕⊕⊕⊖ MODERATE[1]	2	Probably inferior to placebo
Donepezil 5 mg 3 RCTs; 1772 participants	OR 1.23 (0.29 to 5.28) Network estimates	857 per 1000	830 per 1000	27 per 1000 more (from 244 fewer to 133 more)	⊕⊕⊖⊖ LOW[1,2]	1	May be inferior to placebo
Rivastigmine 3 RCTs;	OR 3.75 (0.74 to 15.40)	607 per 1000	287 per 1000	314 per 1000 more (from 58 fewer to 574 more)	⊕⊖⊖⊖ VERY LOW[1,3]	4	Uncertain evidence suggesting inferior to placebo

Table 1. Network meta-analysis results: 'Summary of findings' table *(Continued)*

831 participants (Dose ranges: 3 to 12 mg/day)	Network estimates	

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial

*Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) ranges from 0 to 70, with a higher score indicating greater impairment. A 4-point ADAS-Cog change at 6 months is considered clinically meaningful.

GRADE Working Group grades of evidence:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Some imprecision (wide 95% CI) (downgraded once).
[2]Downgraded for unclear risk of bias for more than 2 domains.
[3]Some inconsistency in point estimates (downgraded once).

Table 2. Network meta-analysis results: estimates of benefits*

	Donepezil 10 mg	Donepezil 5 mg	Galantamine	Placebo	Rivastigmine
Donepezil 10 mg	Donepezil 10 mg	1.44 (−0.26, 3.14)	0.32 (−2.17, 2.72)	2.18 (0.47, 3.87)	1.63 (−0.76, 4.72)
Donepezil 5 mg	−1.44 (−3.14, 0.26)	Donepezil 5 mg	−1.11 (−3.42, 1.1)	0.74 (−0.71, 2.14)	0.19 (−2.05, 3.09)
Galantamine	−0.32 (−2.72, 2.17)	1.11 (−1.1, 3.42)	Galantamine	1.84 (0.14, 3.63)	1.31 (−1.08, 4.46)
Placebo	−2.18 (−3.87, −0.47)	−0.74 (−2.14, 0.71)	−1.84 (−3.63, −0.14)	Placebo	−0.53 (−2.35, 1.94)
Rivastigmine	−1.63 (−4.72, 0.76)	−0.19 (−3.09, 2.05)	−1.31 (−4.46, 1.08)	0.53 (−1.94, 2.35)	Rivastigmine

*Estimates of benefit (cognition, as assessed using Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)) from the Bayesian network meta-analysis. The estimates are mean differences (95% confidence intervals) of cognition, for treatment columns compared to treatment rows.

Table 3. Network meta-analysis results: estimates of harms*

	Donepezil 10 mg	Donepezil 5 mg	Galantamine	Placebo	Rivastigmine
Donepezil 10 mg	Donepezil 10 mg	0.61 (0.11, 3.51)	0.8 (0.07, 9.32)	0.5 (0.09, 2.78)	1.88 (0.17, 16.82)
Donepezil 5 mg	1.63 (0.28, 9.18)	Donepezil 5 mg	1.3 (0.13, 12.77)	0.81 (0.19, 3.48)	3.04 (0.34, 22.08)
Galantamine	1.25 (0.11, 14.72)	0.77 (0.08, 7.48)	Galantamine	0.63 (0.11, 3.63)	2.35 (0.21, 21.19)
Placebo	2.00 (0.36, 11.50)	1.23 (0.29, 5.28)	1.60 (0.28, 9.25)	Placebo	3.75 (0.74, 15.40)
Rivastigmine	0.53 (0.06, 5.94)	0.33 (0.05, 2.98)	0.43 (0.05, 4.86)	0.27 (0.06, 1.35)	Rivastigmine

*Estimates of harm (adverse events) from the Bayesian network meta-analysis. The estimates are odd ratios (95% confidence intervals) of adverse events, for treatment columns compared to treatment rows.

APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
1. CENTRAL (The Cochrane Library) (issue 8 of 12, 2020) http://cr-so.cochrane.org/SearchSim-ple.php [Date of most recent search 19 August 2020]	#1 MESH DESCRIPTOR CADASIL EXPLODE ALL TREES 7 #2 MESH DESCRIPTOR Cerebrovascular Disorders EXPLODE ALL TREES 12799 #3 MESH DESCRIPTOR Dementia, Multi-Infarct EXPLODE ALL TREES 63 #4 MESH DESCRIPTOR Dementia, Vascular EXPLODE ALL TREES 308 #5 MESH DESCRIPTOR Neurocognitive Disorders EXPLODE ALL TREES 9256 #6 (subcortical ischemic vascular disease*):TI,AB,KY 3 #7 (vascular cognitive impairment*):TI,AB,KY 156 #8 (vascular dement*):TI,AB,KY 754 #9 dement*:TI,AB,KY 11281 #10 VaD:TI,AB,KY 423 #11 VCI:TI,AB,KY 67 #12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 29557 #13 MESH DESCRIPTOR Cholinesterase Inhibitors EXPLODE ALL TREES 1774 #14 MESH DESCRIPTOR TACRINE EXPLODE ALL TREES 106 #15 MESH DESCRIPTOR GALANTAMINE EXPLODE ALL TREES 201 #16 (acetylcholinesterase inhibitor*):TI,AB,KY 475 #17 (anti-alzheimer* ADJ2 drug*):TI,AB,KY 7 #18 anti-cholinesteras*:TI,AB,KY 18 #19 (anti-dementia drug*):TI,AB,KY 43 #20 (cholinesterase inhibitor*):TI,AB,KY 1496 #21 (memory drug):TI,AB,KY 1719 #22 (SDZ ENA 713):TI,AB,KY 7 #23 Anticholinesterase*:TI,AB,KY 133 #24 anti-cholinesterase:TI,AB,KY 15 #25 aricept:TI,AB,KY 142 #26 cognex:TI,AB,KY 11 #27 donezepil:TI,AB,KY 11 #28 E2020:TI,AB,KY 48 #29 exelon:TI,AB,KY 91 #30 galantamine:TI,AB,KY 583	April 2019 - 1652 August 2020 - 251

(Continued)

	#31 Nivalin:TI,AB,KY 3 #32 Razadyne:TI,AB,KY 5 #33 reminyl:TI,AB,KY 49 #34 rivastigmine:TI,AB,KY 647 #35 tacrine:TI,AB,KY 223 #36 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 5068 #37 #12 AND #36 1649	
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP) [Date of most recent search 19 August 2020]	1 exp CADASIL/ 2 exp Cerebrovascular Disorders/ 3 exp Dementia, Multi-Infarct/ 4 exp Dementia, Vascular/ 5 exp Neurocognitive Disorders/ 6 "subcortical ischemic vascular disease*".ti,ab. 7 "vascular cognitive impairment*".ti,ab. 8 "vascular dement*".ti,ab. 9 dement*.ti,ab. 10 VaD.ti,ab. 11 VCI.ti,ab. 12 or/1-11 13 exp Cholinesterase Inhibitors/ 14 exp Tacrine/ 15 exp Galantamine/ 16 exp Donepezil/ 17 "acetylcholinesterase inhibitor*".ti,ab. 18 "anti-alzheimer* ADJ2 drug*".ti,ab. 19 "anti-cholinesteras*".ti,ab. 20 "anti-dementia drug*".ti,ab. 21 "cholinesterase inhibitor*".ti,ab. 22 "memory drug".ti,ab. 23 "SDZ ENA 713".ti,ab. 24 Anticholinesterase*.ti,ab. 25 anti-cholinesterase.ti,ab. 26 aricept.ti,ab.	April 2019 - 5899 August 2020 - 584

(Continued)

	27 cognex.ti,ab.	
	28 donezepil.ti,ab.	
	29 E2020.ti,ab.	
	30 exelon.ti,ab.	
	31 galantamine.ti,ab.	
	32 galanthamine.ti,ab.	
	33 Nivalin.ti,ab.	
	34 Razadyne.ti,ab.	
	35 reminyl.ti,ab.	
	36 rivastigmine.ti,ab.	
	37 tacrine.ti,ab.	
	38 or/13-37	
	39 12 and 38	
	40 randomized controlled trial.pt.	
	41 controlled clinical trial.pt.	
	42 randomized.ab.	
	43 placebo.ab.	
	44 drug therapy.fs.	
	45 randomly.ab.	
	46 trial.ab.	
	47 groups.ab.	
	48 or/40-47	
	49 exp animals/ not humans.sh.	
	50 48 not 49	
	51 39 and 50	
3. EMBASE 1974 to 18 August 2020 [Date of most recent search 19 August 2020]	1 exp CADASIL/ 2 exp cerebrovascular disease/ 3 exp multiinfarct dementia/ 4 "subcortical ischemic vascular disease*".ti,ab. 5 "vascular cognitive impairment*".ti,ab. 6 "vascular dement*".ti,ab. 7 dement*.ti,ab. 8 VaD.ti,ab. 9 VCI.ti,ab.	April 2019 - 2406 August 2020 - 262

(Continued)

10 or/1-9

11 exp cholinesterase inhibitor/

12 exp tacrine/

13 exp galantamine/

14 exp donepezil/

15 "acetylcholinesterase inhibitor*".ti,ab.

16 "anti-alzheimer* ADJ2 drug*".ti,ab.

17 "anti-cholinesteras*".ti,ab.

18 "anti-dementia drug*".ti,ab.

19 "cholinesterase inhibitor*".ti,ab.

20 "memory drug".ti,ab.

21 "SDZ ENA 713".ti,ab.

22 Anticholinesterase*.ti,ab.

23 anti-cholinesterase.ti,ab.

24 aricept.ti,ab.

25 cognex.ti,ab.

26 donezepil.ti,ab.

27 E2020.ti,ab.

28 exelon.ti,ab.

29 galantamine.ti,ab.

30 galanthamine.ti,ab.

31 Nivalin.ti,ab.

32 Razadyne.ti,ab.

33 reminyl.ti,ab.

34 rivastigmine.ti,ab.

35 tacrine.ti,ab.

36 or/11-35

37 10 and 36

38 randomized controlled trial/

39 controlled clinical trial/

40 random$.ti,ab.

41 randomization/

42 intermethod comparison/

43 placebo.ti,ab.

(Continued)

	44 (compare or compared or comparison).ti. 45 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 46 (open adj label).ti,ab. 47 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 48 double blind procedure/ 49 parallel group$1.ti,ab. 50 (crossover or cross over).ti,ab. 51 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 52 (assigned or allocated).ti,ab. 53 (controlled adj7 (study or design or trial)).ti,ab. 54 (volunteer or volunteers).ti,ab. 55 trial.ti. 56 or/38-55 57 37 and 56	
4. PsycINFO (Ovid SP) (1806 to 18 August 2020) [Date of most recent search 19 August 2020]	1 exp Cerebrovascular Disorders/ 2 exp Vascular Dementia/ 3 CADASIL.ti,ab. 4 "subcortical ischemic vascular disease*".ti,ab. 5 "vascular cognitive impairment*".ti,ab. 6 "vascular dement*".ti,ab. 7 dement*.ti,ab. 8 VaD.ti,ab. 9 VCI.ti,ab. 10 or/1-9 11 exp Cholinesterase Inhibitors/ 12 exp Galanthamine/ 13 "acetylcholinesterase inhibitor*".ti,ab. 14 "anti-alzheimer* ADJ2 drug*".ti,ab. 15 "anti-cholinesteras*".ti,ab. 16 "anti-dementia drug*".ti,ab. 17 "cholinesterase inhibitor*".ti,ab. 18 "memory drug".ti,ab. 19 "SDZ ENA 713".ti,ab.	April 2019 - 496 August 2020 - 25

(Continued)

	20 Anticholinesterase*.ti,ab.	
	21 anti-cholinesterase.ti,ab.	
	22 aricept.ti,ab.	
	23 cognex.ti,ab.	
	24 donezepil.ti,ab.	
	25 E2020.ti,ab.	
	26 exelon.ti,ab.	
	27 galantamine.ti,ab.	
	28 galanthamine.ti,ab.	
	29 Nivalin.ti,ab.	
	30 Razadyne.ti,ab.	
	31 reminyl.ti,ab.	
	32 rivastigmine.ti,ab.	
	33 tacrine.ti,ab.	
	34 or/11-33	
	35 10 and 34	
	36 exp Clinical Trials/	
	37 randomly.ab.	
	38 randomi?ed.ti,ab.	
	39 placebo.ti,ab.	
	40 groups.ab.	
	41 "double-blind*".ti,ab.	
	42 "single-blind*".ti,ab.	
	43 RCT.ti,ab.	
	44 or/36-43	
	45 35 and 44	
	46 from 45 keep 1-496	
5. CINAHL (EBSCOhost)	S52 S38 AND S51	April 2019 - 670
[Date of most recent search 19 August 2020]	S51 S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50	August 2020 - 47
	S50 MH "Random Assignment"	
	S49 MH "Single-Blind Studies" or MH "Double-Blind Studies" or MH "Triple-Blind Studies"	
	S48 MH "Crossover Design"	
	S47 MH "Factorial Design"	

(Continued)

S46 MH "Placebos"

S45 MH "Clinical Trials"

S44 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study"

S43 TX crossover OR "cross-over"

S42 AB placebo*

S41 TX random*

S40 TX trial*

S39 TX "latin square"

S38 S11 AND S37

S37 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36

S36 TX tacrine

S35 TX rivastigmine

S34 TX reminyl

S33 TX Razadyne

S32 TX Nivalin

S31 TX galanthamine

S30 TX galantamine

S29 TX exelon

S28 TX E2020

S27 TX donezepil

S26 TX cognex

S25 TX aricept

S24 TX anti-cholinesterase

S23 TX Anticholinesterase*

S22 TX SDZ ENA 713

S21 TX memory drug

S20 TX cholinesterase inhibitor*

S19 TX anti-dementia drug*

S18 TX anti-cholinesteras*

S17 TX anti-alzheimer* N2 drug*

S16 TX acetylcholinesterase inhibitor*

S15 (MH "Donepezil")

S14 (MH "Galanthamine")

(Continued)

	S13 (MH "Tacrine") S12 (MH "Cholinesterase Inhibitors+") S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 S10 TX VCI S9 TX VaD S8 TX dement* S7 TX vascular dement* S6 TX vascular cognitive impairment* S5 TX subcortical ischemic vascular disease S4 (MH "Dementia, Vascular+") S3 (MH "Dementia, Multi-Infarct") S2 (MH "Cerebrovascular Disorders+") S1 (MH "CADASIL")	
6. ISI Web of Science – core collection (ISI Wed of Science) (from 1900) [Date of most recent search 19 August 2020]	TOPIC: (CADASIL OR Vascular Dementia OR vascular cognitive impairment OR VaD OR VCI OR vascular cognitive impairment)AND TOPIC: (Cholinesterase Inhibitors OR TACRINE OR GALANTAMINE OR Donepezil OR acetylcholinesterase inhibitors OR Anticholinesterase OR aricept OR cognex OR exelon) ANDTOPIC: (randomly OR randomised OR randomized OR "random allocat*" OR RCT OR CCT OR "double blind*" OR "single blind*" OR "double blind*" OR "single blind*" OR trial)	April 2019 - 450 August 2020 - 21
7. LILACS (BIREME) [Date of most recent search 19 August 2020]	dementia OR demencia OR demência OR CADASIL OR Vascular Dementia OR vascular cognitive impairment OR VaD OR VCI OR vascular cognitive impairment [Words] and Cholinesterase Inhibitors OR TACRINE OR GALANTAMINE OR Donepezil OR acetylcholinesterase inhibitors OR Anticholinesterase OR aricept OR cognex OR exelon [Words] and randomly OR randomised OR randomized OR trial OR ensaio clínico OR control OR controlled [Words]	April 2019 - 14 August 2020 - 1
8. ClinicalTrials.gov (www.clinicaltrials.gov) [Date of most recent search 17 April 2019. NB ICTRP databse not available 19 August 2020]	INTERVENTIONAL AND dementia OR CADASIL OR Vascular Dementia OR vascular cognitive impairment OR VaD OR VCI OR vascular cognitive impairment AND Cholinesterase Inhibitors OR TACRINE OR GALANTAMINE OR Donepezil OR acetylcholinesterase inhibitors OR Anticholinesterase OR aricept OR cognex OR exelon	April 2019 - 268 August 2020 - 10
9. ICTRP (http://apps.who.int/trialsearch) [Date of most recent search 19 August 2020]	dementia OR CADASIL OR Vascular Dementia OR vascular cognitive impairment OR VaD OR VCI OR vascular cognitive impairment AND Cholinesterase Inhibitors OR TACRINE OR GALANTAMINE OR Donepezil OR acetylcholinesterase inhibitors OR Anticholinesterase OR aricept OR cognex OR exelon	April 2019 - 269 August 2020 -
10. ALOIS (CRS web) [Date of most recent search 19	1 Cholinesterase Inhibitors OR TACRINE OR GALANTAMINE OR Donepezil OR acetylcholinesterase inhibitors OR Anticholinesterase OR aricept OR cognex OR exelon AND INREGISTER 2 (Vascular OR VAD OR CADASIL OR VCI):AB,TI AND INREGISTER 3 #1 AND #2	April 2019 - 90 August 2020 - 7

(Continued)

August 2020]

Total hits retrieved	April 2019 - 12214 August 2020 -1208
Total after deduplication	April 2019 - 7402 August 2020 - 1037

HISTORY

Protocol first published: Issue 4, 2019
Review first published: Issue 2, 2021

CONTRIBUTIONS OF AUTHORS

All authors have made a substantial contribution to the conception and design of the protocol; have drafted the work or revised it critically for intellectual content; have approved the final version to be published; and agree to be accountable for all aspects of the work.

DECLARATIONS OF INTEREST

Ceri E Battle: none known

Azmil H Abdul-Rahim: none known

Susan D Shenkin: none known

Jonathan Hewitt: none known

Terry J Quinn: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Due to clinical diversity between the studies, we opted to report all direct treatment comparisons using random-effects models. This was to ensure consistency in reporting (rather than reporting some fixed-effect and some random-effects models) and so that more conservative estimates were reported.

For rivastigmine, we were unable to separate participants who received the manufacturer's recommended final dose from participants receiving lower doses, as planned in our protocol. We pooled all doses of rivastigmine.

As fewer than 10 studies were included in the network meta-analysis, funnel plots were not used.

We were unable to complete a sensitivity analysis including only trials rated as at low risk of bias across all domains, and those trials reporting observed case (OC) and last observation carried forward (LOCF) results for all outcomes, due to an insufficient number of trials. However, we have completed a sensitivity analysis that compared the primary cognitive outcome (measured using ADAS-Cog scale), one using OC data, and the other using LOCF data.

We were unable to complete a sensitivity analysis including only participants with vascular dementia (excluding those with mild vascular cognitive impairment), due to an insufficient number of trials.

We were unable to complete a network meta-regression or subgroup analysis (or both) using any effect modifiers, due to an insufficient number of trials.