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Donepezil for vascular cognitive impairment (Review)

Malouf R, Birks J

Malouf R, Birks J.
Donepezil for vascular cognitive impairment.
Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD004395.
DOI: 10.1002/14651858.CD004395.pub2.

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[Intervention Review]

Donepezil for vascular cognitive impairment

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Editorial group: Cochrane Dementia and Cognitive Improvement Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.
Review content assessed as up-to-date: 6 June 2005.

Citation: Malouf R, Birks J. Donepezil for vascular cognitive impairment. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD004395. DOI: 10.1002/14651858.CD004395.pub2.

ABSTRACT

Background

Vascular disease is the second commonest cause of dementia after Alzheimer's disease. There are difficulties in classifying patients with this type of cognitive impairment owing to varied clinical presentation and different types of arterial disease. There is some degree of overlap in the neuropathology of Alzheimer's and vascular dementia. Deficient cholinergic neurotransmission, a characteristic of Alzheimer's disease, has been postulated to contribute to the cognitive impairment of vascular disease of the brain. Cholinesterase inhibitors, such as donepezil, may therefore be a rational treatment.

Objectives

To assess the clinical efficacy and tolerability of donepezil on cognitive function, clinical global impression, activities of daily living and social functioning of people with vascular cognitive impairment.

Search methods

Relevant randomized controlled trials were identified from a search of the Cochrane Dementia and Cognitive Improvement Group Specialized Register on 7 June 2005 using the terms donepezil, E2020 and Aricept. This Register consists of records from all major healthcare databases and many ongoing trials databases. Unpublished trials were requested from the drug company Eisai Inc and they provided us with the required data.

Selection criteria

All unconfounded randomized double-blind trials comparing donepezil with placebo were eligible for inclusion. Trials using combinations of donepezil with other pharmacological interventions were excluded.

Data collection and analysis

Both reviewers assessed studies against the criteria for inclusion and extracted data. Data were pooled where appropriate, and weighted mean differences or Peto odds ratios with 95% confidence intervals calculated. Intention-to-treat analysis was undertaken when possible.

Main results

Two large-scale, randomized, double-blind, parallel-group controlled trials were identified for inclusion. A total of 1219 people with mild to moderate cognitive decline due to probable or possible vascular dementia (according to the NINCDS/AIREN criteria and the Hachinski Ischemia Scale) were recruited. Donepezil, at doses of 5 or 10 mg a day was compared with placebo for 24 weeks. For each outcome measure, mean change from baseline at weeks 12 and 24, using a last observation carried forward analysis, was calculated.

Cognitive function:

The donepezil groups showed statistically significantly better performance than the placebo groups on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) at 12 and 24 weeks.

The donepezil groups produced statistically significantly better scores than the placebo groups on the Mini-Mental State Examination (MMSE) at 12 and 24 weeks.

Global function:

The sum of the boxes of the Clinical Dementia Rating (CDR-SB) showed at 24 weeks a statistically significant benefit of 10 mg donepezil daily over both placebo and a 5 mg daily dosage.

The Clinician's Interview-Based Impression of Change-plus version (CIBIC-plus) showed improved global function of participants taking 5 mg of donepezil daily compared with the placebo group but this was not seen in the higher dose group.

A**ctivities of daily living and social behaviour:**

On the Instrumental Activity of Daily Living (IADL) scale, there was no statistically significant difference between the groups taking donepezil 5 mg per day donepezil and placebo, but the group taking 10 mg of donepezil a day showed benefit compared with placebo

There were statistically significant benefit for donepezil at either dosage compared with placebo on the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS).

Tolerability and adverse effects:

Broad range of adverse events were reported in the studies and data confirmed that donepezil was well tolerated, and most of the side effects were transient and were resolved by stopping the medication. Some of these events, especially nausea, diarrhoea, anorexia and cramp appeared more frequently on the 10 mg dose where there was a statistically significant difference compared with placebo.

Drop-out:

The drop-out rate was similar between the groups, 84.2% (330) patients completed the studies. The withdrawal rate was low and due mainly to side effects.

Authors' conclusions

Evidence from the available studies support the benefit of donepezil in improving cognition function, clinical global impression and activities of daily living in patients with probable or possible mild to moderate vascular cognitive impairment after 6 months treatment. Extending studies for longer periods would be desirable to establish the efficacy of donepezil in patients with advanced stages of cognitive impairment. Moreover, there is an urgent need for establishing specific clinical diagnostic criteria and rating scales for vascular cognitive impairment.

PLAIN LANGUAGE SUMMARY

Evidence of efficacy of donepezil for people with mild or moderate vascular cognitive impairment

Acetylcholine is a neurotransmitter involved in memory function. Acetylcholinesterase inhibitors, such as donepezil, inhibit the breakdown of acetylcholine and have been shown to be of benefit for people with mild to moderate Alzheimer's disease. Deficits in acetylcholine mediated neurotransmission have been postulated in cognitive impairment due to vascular disease of the brain. Two large-scales randomized trials provide evidence of beneficial effects from donepezil at doses of 5 or 10 mg per day over 24 weeks. The drug was well tolerated and drop-out rate was low.

BACKGROUND

Vascular cognitive impairment (VCI) is a clinical syndrome comprising a wide spectrum of cognitive dysfunctions resulting from brain damage due to vascular disease. The traditional concept of vascular dementia, reflected in the earlier term multi-infarct dementia, has been expanded to include a wide range of syndromes including subcortical vascular dementia (Binswanger's disease). Although it is now suspected that there may be a vascular element in their aetiology, degenerative dementias such as Alzheimer's disease, fronto-temporal dementias, and dementia with Lewy bodies are still held to be distinct entities (O'Brien 2003). The definition of vascular dementia has proved problematic in terms of determining criteria both for dementia and vascular pathogenesis (Hachinski 1992). A lack of validated and agreed criteria has been a barrier to epidemiological studies on this topic (APA 1994; Chui 1992). Some publications claim that vascular dementia is over diagnosed (Brust 1988); and others consider its frequency to be underestimated (Joynt 1988).

Vascular disease is the second most common cause of dementia and cognitive impairment after Alzheimer's disease (Jorm 1991). The prevalence of all forms of dementia and of vascular dementia rises with age (Hofman 1991; Zhang 1990). Between 1% and 4% of people aged over 65 years suffer from vascular dementia (Hebert 1995) and the prevalence of the disease appears to double every 5 or 10 years after the age of 65 years (Hofman 1991).

Vascular cognitive impairment (VCI) has recently been proposed as a term to include vascular dementia and all forms of mild to severe cognitive impairment due to cerebrovascular disease (O'Brien 2003). This term comprises three conditions: vascular cognitive impairment without dementia, vascular dementia, and Alzheimer's disease with a vascular component (mixed dementia). Vascular cognitive impairment without dementia (vascular CIND) Ebly 1995; Graham 1997 is the most prevalent subgroup of vascular cognitive impairment below the age of 85 years (Rockwood 2000). Vascular dementia (VaD) comprises dementias resulting from all types of vascular pathology. The current classification of VaD includes cortical vascular dementia, subcortical ischaemic vascular dementia, strategic-infarct dementia, hypoperfusion dementia, haemorraghic dementia, and dementias resulting from specific arteriopathies (O'Brien 2003).

The aetiology of Alzheimer's disease with a vascular component dementia (mixed dementia) is linked to both vascular and degenerative processes. Neuropathological studies have confirmed that cerebrovascular disease and Alzheimer's disease frequently coexist in the elderly population (MRC CFAS 2001; Heyman 1998; Snowdon 1997). Half of patients with vascular disease who became demented also have Alzheimer's disease (O'Brien 1994), and one third of pathologically confirmed Alzheimer's disease patients have evidence of vascular lesions (Gearing 1995). The link is partly due to the coexistence of Alzheimer type neuronal degeneration with congophilic angiopathy (Table 1), both processes associated with amyloid deposition (Table 1)(MRC CFAS 2001).

In vascular cognitive impairment there is typically an abrupt onset of cognitive difficulties, with widely varied clinical manifestations influenced by the causative pathology and the brain structures involved. Memory loss is not necessarily as prominent in VCI as in Alzheimer's disease (Stewart 1999). This reflects the particular susceptibility for involvement of the temporal lobe in Alzheimer's disease, while vascular lesions show no similar anatomical predilection (Rockwood 2000). Although concept of dementia usually implies progressive irreversible disease, vascular impairment more typically follows a stepwise course and stabilization or even partial recovery may occur (Meyer 1995). No significant difference in survival time has been found between VCI and probable Alzheimer's disease (Rockwood 2000).

Myocardial infarction, hypertension, atrial fibrillation (Table 1), peripheral vascular disease, diabetes mellitus, blood-brain barrier dysfunction, white matter lesions, smoking and hyperlipidaemia are modifiable risk factors for VCI (Desmond 1993; Meyer 1995; Rockwood 1997). Age, geographical origin, Asian ethnicity - vascular dementia represents over 50% of dementias in Japan (Ueda 1992) - genetic predisposition, and a history of prior stroke are non-modifiable risk factors. There is a history of prior stroke in 76% of patients with vascular dementia and in 57% of those with vascular cognitive impairment , as compared with only 5-7% of people with Alzheimer's disease (Rockwood 1997).

Advances in stroke management, and the recognition of the co-existence of vascular dementia and Alzheimer's disease have opened new prospects for the prevention and treatment of vascular dementia. Several approaches have focused on extending the cholinergic hypothesis to dementias other than Alzheimer's disease. Acetylcholine is a non-proteinaceous small-molecule involved in neurotransmission (Table 1) in the brain tracts subserving memory. Administration of the cholinergic antagonist scopolamine impairs learning in humans (Crow 1973). Acetylcholine acts on two types of receptors, nicotinic and muscarinic, and both types are also involved in modulation of cerebral blood flow (Schwarz 1999; Zhang 1998).

One of the earliest neurochemical changes documented in Alzheimer's disease is reduction in choline acetyltransferase (ChAT) activity in the cerebral cortex and hippocampus (Bowen 1976; Davis 1976). This would be expected to reduce the synthesis of acetylcholine. Some studies have found that ChAT activity is more than 40% lower in brains affected by vascular dementia than in controls (Mann 1986; Perry 1977). The temporal cortex, hippocampus and basal ganglia have been reported to be the most consistently affected (Gottfries 1994). Decreased acetylcholine concentrations have been found in the cerebrospinal fluid of people with Binswanger's disease and dementia with multiple small infarcts (Tohgi 1996). These observations raise the possibil-

ity that drugs enhancing cholinergic neurotransmission may be beneficial in vascular cognitive impairment and dementia.

Cholinesterase inhibitors delay the breakdown of acetylcholine and so increase synaptic transmission between neurons. Four cholinesterase inhibitors, tacrine, donepezil, rivastigmine, and galantamine, have been approved by the United State Food and Drug Administration for the treatment of people with Alzheimer's disease. Donepezil (Aricept), a second generation cholinesterase inhibitor, is a piperidine-based agent. It is a non -competitive, reversible antagonist of cholinesterase and is highly selective for acetyl- as opposed to butyryl-cholinesterase (Dawbarn 2001). Donepezil has been licensed in the United Kingdom since 1997 for treatment of mild to moderate Alzheimer's disease. The drug is well absorbed after oral administration and peak plasma concentration is reached in 3 to 4 hours. The drug has a long half-life of approximately 70 hours so allowing once-daily dosage.

There is preliminary evidence that these cholinesterase inhibitors may have value for dementias other than Alzheimer's disease (O'Brien 2001). The clinical trials that consider treatment of VaD with cholinergic agents are few; in contrast the trials of the therapeutic interventions for controlling the risk factors for VaD are widely performed. This review evaluates the impact of donepezil on cognitive function, global outcomes and activities of daily living of patients with cognitive vascular impairment, as revealed by randomized controlled trials.

OBJECTIVES

To assess the effects of donepezil in treatment and/or modifying the disease process of people with vascular cognitive impairment, vascular dementia, and mixed dementia.

METHODS

Criteria for considering studies for this review

Types of studies

All unconfounded, randomized trials involving participants with vascular dementia in which treatment with donepezil was compared with placebo were eligible for inclusion.

Types of participants

Patients diagnosed as having vascular cognitive impairment or dementia or mixed dementia on a basis of standardized diagnostic criteria such as the ADDTC (California State Alzheimer's Disease Diagnostic and Treatment Center) (Chui 1992), NINCDS/AIREN (National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l' Enseignement en Neurosciences) (Roman 1993), and ICD-10 (International Classification of Diseases of World Health Organization) (WHO 1992).
Diagnosis of the vascular cognitive impairment without dementia were based on scores on cognitive impairment scales.

Types of interventions

Donepezil at any dose with parallel placebo control.

Types of outcome measures

The review assessed the following outcomes:

- global impression
- functional performance
- behavioural disturbance
- quality of life
- cognitive function
- effect on carer
- death
- safety and adverse effects
- brain image changes

Search methods for identification of studies

The trials were identified from a last updated search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 7 June 2005 using the search terms: donepezil, aricept and E2020 and limiting the search to cortical, subcortical, multi-infarct, Binswanger, vascular, post-stroke and mixed dementia.
The Specialized Register at that time contained records from the following databases:

- CENTRAL: January 2005 (issue 1);
- MEDLINE: 1966 to 2005/02;
- EMBASE: 1980 to 2005/01;
- PsycINFO: 1887 to 2005/01;
- CINAHL: 1982 to 2004/12;
- SIGLE (Grey Literature in Europe): 1980 to 2004/06;
- ISTP (Index to Scientific and Technical Proceedings): to May 2000;
- INSIDE (BL database of Conference Proceedings and Journals): to June 2000;
- Aslib Index to Theses (UK and Ireland theses): 1970 to March 2003;
- Dissertation Abstract (USA): 1861 to March 2003;
- ADEAR (Alzheimer's Disease Clinical Trials Database): to 25 March 2005;
- National Research Register: issue 1/2005;
- Current Controlled trials (last searched April 2005) which includes:

Alzheimer Society
GlaxoSmithKline
HongKong Health Services Research Fund
Medical Research Council (MRC)
NHS R&D Health Technology Assessment Programme
Schering Health Care Ltd
South Australian Network for Research on Ageing
US Dept of Veterans Affairs Cooperative Studies
National Institutes of Health (NIH)

- ClinicalTrials.gov: last searched March 2005;

LILACS (Latin American and Caribbean Health Science Literature): last searched April 2003.

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module.

Unpublished trials were requested from the drug company Eisai Inc and they provided us with the required data. The MRC group provided us with information about ongoing open-label trial 309, which is an extension to 307 and 308.

Data collection and analysis

The reviewers independently discarded publications deemed as irrelevant on the basis of title and abstract.

QUALITY ASSESSMENT

The methodological quality of each selected trial was assessed using the Cochrane Collaboration guidelines (Mulrow 1997):

- In category A (adequate), the report describes allocation of treatment by: (i) some forms of centralized randomized scheme, such as having to provide details of an enrolled participant to an office by telephone to receive the treatment group allocation; (ii) some form of randomization scheme controlled by a pharmacy; (iii) numbered or coded containers, as in a pharmaceutical trial in which capsules from identical-looking numbered bottles are administrated sequentially to enrolled participants; (iv) an on-site or coded computer system, provided that the allocations were in a locked, unreadable file that could be accessed only after inputting the characteristics of an enrolled participants; or (v) if assignment envelopes were used, the report should at least specify that they were sequentially numbered, sealed, and opaque; (vi) other combinations of described elements of the process that provide assurance of adequate concealment.
- Category B (intermediate) is where the report describes allocation of treatment by: (i) use of a "list" of "table" to allocate assignments; (ii) use of "envelopes" or "sealed envelopes"; (iii) stating the study as "randomized" without further detail.
- Category C (inadequate) is where the report describes allocation of treatment by: (i) alternation; (ii) reference to case record numbers, dates of birth, day of week, or any such approach; (iii) any allocation procedure that is transparent before assignment, such as an open list of random numbers or assignments. Empirical research has shown that lack of adequate allocation concealment is associated with bias. Trials with unclear concealment measures have been shown liable to yield more pronounced estimates of treatment effects than trials that have adequate measure to conceal allocation schedules, but the effect is less pronounced than inadequately concealed trials.

Trials falling in categories A or B were included in the review. Randomized controlled trials where the combination of donepezil with other anticholinesterase inhibitors were applied, were excluded.

DATA EXTRACTION

Data were extracted from the published reports. The summary statistics required for each trial and each outcome for continuous data are the mean change from baseline, the standard error of the mean change, and the number of patients for each treatment group at each assessment. Where changes from baseline are not reported, the mean, standard deviation and the number of patients for each treatment group at each time point were extracted if available.

For binary data the numbers in each treatment group and the numbers experiencing the outcome of interest were sought.

The baseline assessment is defined as the latest available assessment prior to randomization, but no longer than two months prior.

For each outcome measure, data were sought on every patient assessed. To allow an intention-to-treat analysis, the data were sought irrespective of compliance, whether or not the patient was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. If intention-to-treat data were not available in the publications, "on-treatment" or the data of those who complete the trial were sought and indicated as such.

Data from titration phases prior to the randomised phase were not used to assess safety or efficacy because patients were usually not randomised, nor were treatments concealed.

DATA ANALYSIS

The outcomes measured in clinical trials of dementia and cognitive impairment often arise from ordinal rating scales. Where the rating scales used in the trials have a reasonably large number of categories (more than 10) the data were treated as continuous outcomes arising from a normal distribution.

Summary statistics (n, mean and standard deviation) were required for each rating scale at each assessment time for each treatment group in each trial for change from baseline. When change from baseline results were not reported, the required summary statistics were calculated from the baseline and assessment time treatment group means and standard deviations. In this case a zero correlation between the measurements at baseline and assessment time was assumed. This method overestimates the standard deviation of the change from baseline, but this conservative approach is considered to be preferable in a meta-analysis.

The meta-analysis requires the combination of data from the trials that may not use the same rating scale to assess an outcome. The measure of the treatment difference for any outcome was the weighted mean difference (WMD) when the pooled trials use the same rating scale or test, and the standardised mean difference,

which is the absolute mean difference divided by the pooled standard deviation when they used different rating scales or tests.
The duration of the trials was either 12 or 24 weeks. A separate meta-analysis was conducted for each period. Some trials may contribute data to more than one time period if multiple assessments have been done.
For binary outcomes, such as clinical improvement or no clinical improvement, the odds ratio was used to measure treatment effect. A weighted estimate of the typical treatment effect across trials was calculated.
Overall estimates of treatment differences are presented. In all cases the overall estimate from a fixed effects model is presented and a test for heterogeneity using a standard chi-square statistic or I^2 performed. If, however, there is evidence of heterogeneity of the treatment effect between trials then either only homogeneous results are pooled, or a random-effects model used (in which case the confidence intervals are broader than those of a fixed-effects model).

Subgroup analysis
Where relevant, and data are available, subgroups investigated were: age, sex, severity of impairment, duration of treatment.

RESULTS

Description of studies

Two 24 week international, double blind, randomized, parallel-group, controlled trials fulfilled the criteria for inclusion in this review. Three open-label setting studies were found in the search (Meyer 2002; Shua-Haim 2000, 309) for drug efficacy, safety and tolerability, but these were excluded, and further clinical studies (Lendon 2002) are underway to establish the efficacy of donepezil in vascular cognitive impairment.
PARTICIPANTS:
1219 patients from United states, Europe, Canada and Australia were eligible for enrolment. The trials were carried out by the Donepezil Study Group and supported by Eisai Inc. They had identical protocols. The protocol was reviewed and approved by the designated Human Subjects Review Board at each participant's site. The (NINDS-AIREN) criteria were applied for diagnosing probable or possible VaD patients, 73% had probable VaD and 27% had possible VaD. The inclusion criteria limited the trial to patients with mild to moderate dementia with cognitive decline based on baseline Mini-Mental State Examination (MMSE) scores of 10 to 26. The mean Hachinski score was 9.7. The capability of performance was an additional essential entry criterion. More than half of the patients were aged over 75 years, and there was a greater proportion of men (57.6%). The majority of the patients had an abrupt onset of symptoms with stepwise deterioration. A high percentage (99%) of the patients reported concomitant diseases (Table 2), 70% with hypertensin, 39% with hypercholesterolaemia, 60%of the patients had suffered from a stroke and 17.5% had a history of transient ischemics attack (TIA)(Table 1). Consequently, 99% of patients were on concomitant medications (Table 3). Aspirin was the most prevalent medication (63% were taking aspirin). During the intervention period other cholinesterase inhibitors and anticholinergics were not allowed.
The majority of the patients had experienced a stroke (60%) or TIA (20%) before their dementia became apparent. MRI and CT scans showed cerebrovascular abnormalities in 99% of patients. The most commonly observed abnormality was subcortical stroke (33%). White matter changes in the absence of other types of lesion were rare. More than 25% of patients showed mixed pathologies.

Patients were excluded if there was evidence of cognitive decline as a consequence of stroke based on brain images, or any cerebrovascular disease, or of Alzheimer's disease and other forms of dementia, of psychiatric disorders, of stroke and myocardial infarction within the previous three months, of any life-threatening illnesses and of drug and alcohol abuse, with additional exclusion criteria comprising hypersensitivity to cholinesterase inhibitors.

Patients were assigned randomly into three groups: placebo, 5 mg/day donepezil and 10 mg/day donepezil. The three group were homogenous according to baseline psychometric scores (Table 4; Table 5). Neurological examination and psychometric assessment were assessed at baseline and at weeks 6,12, 18 and 24.
INTERVENTION:
Two doses of donepezil (5 and 10 mg per day) were compared with placebo. An evening single dose of donepezil was used. 406 patients received donepezil 5 mg/day, 421 were randomized to 5 mg/day for 28 days followed by an increase in dose to 10 mg/day for 24 weeks. Patients taking the 10 mg/day dose who could not tolerate the medication were discontinued from the study (the dose was not modified).
DROP-OUT:
Low withdrawal rates due to adverse events were reported.
ADVERSE EVENTS:
The safety of donepezil was assessed by monitoring the changes in the laboratory values, vital signs, electrocardiogram abnormalities followed by clinical assessment.
Baseline assessment:

- Hachinski Ischaemic Scale (HIS) (Hachinski 1975): A means of distinguishing between multi-infarct and primary degenerative dementia. Scores of 4 and below are labeled primary degenerative dementia and scores of 7 and above are multi-infarct dementia. Features such as abrupt onset, fluctuating course, history of strokes, focal neurological signs and symptoms scored 2. Features such as nocturnal confusion, relative preservation of personality, depression, somatic complaints, emotional incontinence, hypertension and evidence

of atherosclerosis scored one. The higher the score the greater is the possibility of ischaemic dementia.

National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l' Enseignement en Neurosciences criteria (Roman 1993) (NINCDS/AIREN): A current valid and reliable criterion for the diagnosis of vascular cognitive impairment. This criterion assesses the following:

- The heterogeneity of vascular dementia and pathologic subtypes such as Ischaemic and haemorraghic stroke, cerebral hypoxic events.
- Varied clinical course, that may be stabilized, remitting, or progressive.
- Early neurological findings such as gait disorders and personality changes.
- Finding the link between the stroke events and the onset of the cognitive decline.
- Supporting the clinical findings with brain image changes.
- The value of the neuropsychological tests to document impairment in multiple cognitive domains.
- A protocol for neuropathological evaluation and correlative studies of clinical, radiological and neuropsychological features. The level of diagnostic certainty is defined as probable, or possible.
- Computerized tomography CT and magnetic resonance imaging (MRI): computerized tomography (CT) and MRI rating scans were performed prior to the enrolment and showed that more than 99% of the patients had abnormalities on the brain image, 33% emerged subcortical infarcts and 25% with mixed pathology (cortical and subcortical) and rarely with white matter lesions.
- Laboratory tests
- Physical and neurological examination

Primary assessment:

- Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) (Rosen 1984): A standard cognitive scale used in drug trials. It assess a set of cognitive functions including memory, language, and praxis. The battery comprises 11 individual tests, spoken language ability (0-5), comprehension of spoken language (0-5), recall of test instructions (O-5), word finding difficulty (0-5), following orders (0-5), naming object (0-5), construction drawing (0-5), ideational praxis (0-5), orientation (0-8), word recall (0-10) and word recognition (0-2). The score ranges from 0 to 70, the high score indicates greater impairment.

- The Clinician's Interview-Based Impression of Change-plus version (CIBIC-plus) (Knopman 1994): A global assessment instrument that provides an index of clinically important change for the assessment of dementia patients. The rating of patient function focuses on domains of concentration, orientation, memory, language, behaviour, initiative and activities of daily living. The global assessment CIBI is performed at the bedside by a skilled clinician who makes an unbiased assessment of whether an individual patient has changed or not in an important way. The scale rating is made on a 7- point scale with the following delineation:

1-Very much improved: A major activity in the patient's daily routine or in mental status has been regained in addition to regaining functional independence.
2-Improved: In this stage some measures of functional independence-social, instrumental, cognitive has been regained.
3-Minimally improved: A noticeable change in the patient's functioning, social interactions, or mental clarity.
4- Indicating no change since baseline.
5-Minimally worsened: A marked decline in patient's functioning, social interactions, or mental clarity in any aspects of performance.
6-Worsened: A functional dependence on some measure.
7-Very much worse: There is a lost of a major activity in patient's daily activity or mental status as well as the loss of functional independence.

Secondary assessment:

- Mini-Mental State Examination (MMSE) (Folstein 1975): A short administrated test takes from 10 to 15 minutes. The test evaluates cognition in five areas: orientation, immediate recall, attention and calculation, delayed recall and language, the scores ranges from 0-30, score 0 is severe impairment, score 30 is normal.

- The sum of the boxes of the Clinical Dementia Rating (CDR-SB) (Berg 1988): it is a useful rating of cognitive performance in six major categories. The global CDR is derived from the scores in each of the six categories (box scores). The degree of impairment is rated in six categories of cognitive function: Memory (M), Orientation (O), judgment and problem solving (JPS), community affairs (CA), home and hobbies (HH), and personal care (PC). Memory is the primary category and all others are secondary. The degree of impairment is defined as none(0), questionable (0.5), mild (1), moderate (2), or severe (3).

- The Alzheimer's Disease Functional Assessment and Change Scale (ADFACS) (Mohs 2001): Comprises a 16-item functional assessment based on basic Activity of Daily Living (ADL) (toileting, feeding, dressing, personal hygiene and grooming, bathing, walking) and Instrumental ADL (use of telephone, household tasks, using household appliances, managing money, shopping, preparing food, wandering outside and inside the house, hobbies and leisure activities, handling personal mail, grasp of situations or explanation). The total score of basic ADL ranges from 0 to 24. Each of the basic ADL is scored on a scale of 0 to 4, 0 (no impairment) to 4 (very severe impairment). The total score of the instrumental ADL ranges from 0 to 30, each of the instrumental ADL items is scored on a scale of 0 (no impairment) to 3 (severely impaired).

AUGUST 2005 UPDATE

The update search revealed 16 references. No further randomized-controlled trials were found which could be included. Two references reported the same extension trial for Study 307/309 and Study 308/309. In Study 307/309, 885 patients with VaD according to National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l' Enseignement en Neurosciences (NINDS-AIREN) diagnostic criteria who had completed one of the two identical double-blind, placebo-controlled, 24-week trials with donepezil (Study 307/309 and Study 308/309), were enrolled in a multicenter,open-label trial (OL). 5 mg/day of donepezil was administered for the first 6 weeks, increased optionally to 10 mg/day. Results were stated at week 30 and week 54. The continual donepezil therapy was applied for a total period of 12-18 months. 674 completed for 30 weeks and a small group of 192 patients continued for 54 weeks.

The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) was used to assess changes in cognitive function. The data were reported as mean±SD change from double-blind baseline score. The results outlined that patients who remained on donepezil for at least 12 months maintained their initial improvement on ADAS-cog score (Week 30 OL: 5 mg/d, -1.2±0.4 N = 244; 10 mg/d -0.6±0.4 N = 236). The ADAS-cog score remained close to baseline for patients who received donepezil for more than 18 months (Week 54 OL: 5 mg/d, 1.2±0.9 N = 59; 10 mg/d 0.4±0.7 N = 69). These results supported the conclusion that there are benefits from long-term donepezil consumption on cognitive function. However, the assessment had been made based on one cognitive function outcome. Therefore, there is a need to estimate the changes on other outcomes involving activities of daily living. There was also insufficient documentation of the drug's safety. These data did not contribute to the meta-analysis of this review.

Risk of bias in included studies

Two randomized double blind, parallel-group studies were eligible for inclusion. A computer-generated randomization protocol was used to assign the treatment allocation. Two varied doses of donepezil were applied (5 and 10 mg): for the first 28 days all participants received a dose of 5 mg donepezil, then patients in 10 mg group were allocated the 10 mg dose. There was no significant difference between the placebo and treatment groups for all baseline characteristics. Blindness was assured by using placebo and donepezil tablets of identical appearance.

Effects of interventions

There were two included studies and both provided data that were pooled in the meta-analyses. Analysis of the treatment effect was based on the completers population, defined as all subjects randomized to treatment who complied with treatment until the endpoint and on the ITT-LOCF population, who were randomized to treatment, received at least one dose of study medication and provided data at baseline and at least one post baseline assessment. The completers data of two treatment groups, 5 and 10 mg/day of donepezil were analysed separately at two different time points, 12 and 24 weeks.

Donepezil efficacy for cognitive functions measures:

The assessment of the effect of donepezil on the cognitive measures were determined according to the changes from baseline of two measures scores (MMSE and ADAS-cog).The meta-analyses showed benefits associated with donepezil (5 and 10 mg/day) compared with placebo on cognitive function as shown by improvement in the ADAS-cog and MMSE scores at 12 and 24 weeks.

(ADAS-cog)

donepezil (5 mg/day) at 12 weeks (WMD -1.47, 95% CI -2.22 to -0.72, P = 0.0001) (completers)

donepezil (5 mg/day) at 24 weeks (WMD -1.66, 95% CI -2.45 to -0.87, P < 0.0001) (completers)

donepezil (10 mg/day) at 12 weeks (WMD -2.27, 95%CI -3.05 to -1.49, P < 0.00001) (completers)

donepezil (10 mg/day) at 24 weeks (WMD -2.21, 95%CI -3.07 to -1.35, <0.00001) (completers)

donepezil (5 mg/day) at endpoint (WMD -1.66, 95% CI -2.40 to -0.92, P < 0.0001) (ITT-LOCF)

donepezil (10 mg/day) at endpoint (WMD -2.17, 95%CI -2.97 to -1.37, P < 0.00001) (ITT-LOCF)

MMSE

donepezil (5 mg/day) at 12 weeks (WMD 1.12, 95% CI 0.58 to 1.66, P < 0.0001) (completers)

donepezil (5 mg/day) at 24 weeks (WMD 0.83, 95% CI 0.38 to 1.29, P = 0.0004) (completers)

donepezil (10 mg/day) at 12 weeks (WMD 1.39, 95%CI 0.83 to 1.95, P < 0.00001) (completers)

donepezil (10 mg/day) at 24 weeks (WMD 1.08, 95%CI 0.62 to 1.55, P < 0.00001) (completers)

donepezil (5 mg/day) at endpoint (WMD 0.65, 95% CI 0.04 to 1.26, P = 0.04) (ITT-LOCF)

donepezil (10 mg/day) at endpoint (WMD 1.10, 95%CI 0.50 to 1.70, P = 0.0003) (ITT-LOCF)

Donepezil efficacy for global assessment:

- CIBIC-plus: the 7-point CIBIC-plus scale, assessing global clinical state, was dichotomized, counting those showing no change or decline compared with those showing improvement, and analyses using the odds ratio. There was benefit associated with donepezil (5 mg/day) compared with placebo at 24 weeks, but not for donepezil (10 mg/day).

donepezil (5 mg/day) at 24 weeks (OR 1.56, 95% CI 1.15 to 2.11, P = 0.004) (completers)

- CDR-SB: The CDR-SB measuring both cognitive function and aspects of everyday functioning in a single score, shows benefit associated with donepezil (10 mg/day) compared with placebo at 24 weeks, but not for the lower dose of donepezil.

The numbers of completers in study 308 were not reported for this outcome and were approximated by the numbers of completers reported for ADAS-cog assessment, similarly for the ITT-LOCF population.

donepezil (10 mg/day) at 24 weeks (WMD -0.46 95%CI -0.72 to -0.20, P = 0.0005) (completers)
donepezil (10 mg/day) at endpoint (WMD -0.36 95%CI -0.60 to -0.13, P = 0.002) (ITT-LOCF)

Donepezil efficacy for measures of activity of daily living:

- The assessment were based on the score changes from baseline of the IADAL,and ADFACS scales. The numbers of completers in study 308 were not reported for this outcome and were approximated by the numbers of completers reported for ADAS-cog assessment, similarly for the ITT-LOCF population:
- IADL: There was benefit associated with donepezil (5 and 10 mg/day) compare with placebo at 24 weeks for the completers population, but not for the ITT-LOCF population.

donepezil (5 mg/day) at 24 weeks (WMD -0.81, 95%CI -1.45 to -0.16, P = 0.01) (completers)
donepezil (10 mg/day) at 24 weeks (WMD -0.85, 95%CI -1.48 to -0.21, P = 0.009) (completers)

- ADFACS: There was benefit associated with donepezil (5 and 10 mg/day) compare with placebo at 24 weeks for the completers population, and with the higher dose donepezil only for the ITT_LOCF population:

donepezil (5 mg/day) at 24 weeks (WMD -0.97, 95%CI -1.80 to -0.14, P = 0.02) (completers)
donepezil (10 mg/day) at 24 weeks (WMD -0.95, 95%CI -1.79 to -0.11, P = 0.03) (completers)
donepezil (10 mg/day) at 24 weeks (WMD -0.95, 95%CI -1.73 to -0.17, P = 0.02) (endpoint)

Adverse events:

The meta-analysis of withdrawals before the end of treatment due to an adverse events shows a significant difference in favour of placebo compared with donepezil (10 mg/day) but no difference for the lower dose (donepezil (10 mg/day) at 24 weeks (OR 2.14, 95% CI 1.42 to 3.23, P = 0.0003)).
There were no significant differences for donepezil compared with placebo for the number who suffered serious adverse events.
The meta-analysis of numbers who suffered at least one adverse event shows a significant difference in favour of placebo compared with donepezil (10 mg/day) but no difference for the lower dose (donepezil (10 mg/day) at 24 weeks (OR 1.95, 95% CI 1.20 to 3.15, P = 0.007))
39 different adverse events were reported in the two trials. There were significant differences in favour of placebo compared with donepezil, usually the 10 mg/day dose, for several types of adverse events at 24 weeks.

- Digestive system side effects:

donepezil (10 mg/day) (OR 1.59, 95% CI 1.06 to 2.37, P = 0.02)

- Anorexia:

donepezil (5 mg/day) (OR 1.98, 95% CI 1.02 to 3.82, P = 0.04)
donepezil (10 mg/day) (OR 2.50, 95% CI 1.33 to 4.71, P = 0.005)

- Diarrhoea

donepezil (10 mg/day) (OR 1.75, 95% CI 1.15 to 2.65, P = 0.008)

- Nausea

donepezil (10 mg/day) (OR 2.45, 95% CI 1.55 to 3.87, P = 0.0001)

- Insomnia

donepezil (5 mg/day) (OR 2.16, 95% CI 1.00 to 4.70, P = 0.05)

- Skin carcinoma

donepezil (5 mg/day) (OR 0.11, 95% CI 0.01 to 0.90, P = 0.04)

- leg cramps and cramp

donepezil (5 mg/day) (OR 6.76, 95% CI 2.33 to 19.63, P = 0.0004)
donepezil (10 mg/day) (OR 10.84, 95% CI 3.83 to 30.70, P < 0.00001)

- abnormal dreams

donepezil (10 mg/day) (OR 4.75, 95% CI 1.79 to 12.63, P = 0.002)

- rhinitis
- donepezil (10 mg/day) (OR 3.54, 95% CI 1.51 to 8.33, P = 0.0042)

Non-completion:

The meta-analysis of total numbers of withdrawals before the end of treatment shows a significant difference in favour of placebo compared with donepezil (10 mg/day) but no difference for the lower dose.
donepezil (10 mg/day) at 24 weeks (OR 1.91 95% CI 1.35 to 2.70, P = 0.0003).

Interaction with other medication:

The allocated patients were on a varied spectrum of medications and the interaction between donepezil and other medication was not addressed during the trial.

Donepezil efficacy on brain image:

The treatment effect on the brain image findings was not monitored at the end of the intervention.

Donepezil efficacy on cost and institution rate:

There were no data for the efficacy of the intervention on the cost, caregivers' time and institutionalization.

Death-rate:

The death rate was low, and there were no significant differences between donepezil and placebo

DISCUSSION

Two large-scales randomized controlled studies (Study 307/309; Study 308/309) enrolled 1219 patients with probable or possible vascular cognitive impairment according NINDS-AIREN criteria, for 24 weeks donepezil intervention. The combined data provided the following results:

- The meta-analyses showed benefits associated with donepezil (10 mg/day) compared with placebo on cognitive function, global assessment and activities of daily living at 24 weeks.

- Donepezil was well tolerated and the incidence rate of adverse effects was low. Some of these side effects occurred more frequently in the active treatment groups, particularly in the 10 mg group.

To discuss and interpret the results, the following points should be highlighted:

- The patients:

Sufficient number of participants (1219 patients) were enrolled in the studies. The participants were frail older people with high levels of vascular risk factors, and were also on varied concomitant medications, which correspond to similar patients clinicians deal with in their clinical practice.

The patients were medically stabilized for the previous 6 months before enrolment into the trial. Therefore, there was tight medical control of their comorbid conditions. However, that does not reflect the status of the general population who are not included in medical trials. None the less, the sample was biased toward older people in the population, as most of the participants were aged over 75 years.

- The criteria:

Classification according to two diagnostic guidelines (NINDS-AIREN criteria and HIS scale) tend to enrol patients with different vascular cognitive impairment aetiology. Consequently, the studies probably contained patients with mixed dementia and the positive effect of donepezil might be due to the medication effect on the Alzheimer's disease component.

- The scale:

The rating scales that were used in these trials might be inappropriate to identify the changes seen in vascular dementia patients, as these scales are not specific for this type of dementia.

- The dose:

Two doses were administrated in these studies. The 10 mg dose had a greater effect than 5 mg dose on the cognition function.

- The trial period:

The two studies administered donepezil for 24 weeks. Results from longer intervention period were obtained from two open-label trials (Meyer 2002, 309) in patients with vascular dementia which showed that patients on titrated doses of donepezil for 12-18 months performed better on cognitive measures than their baseline assessment.

- Control group:

The placebo patients did not decline on the outcomes measures during the studies. This stability might be due to the tight control of the comorbid conditions in the conducted participants, and/or to virtual effect of vascular preventive therapy, as most of the patients were on aspirin and other medications.

- Tolerability:

The incidence of adverse events and the number of non-completers due to side effects were low, though some of the adverse effects appeared more frequently in the 10 mg group than in the placebo group.

The available results indicate that patients with mild to moderate vascular cognitive impairment benefit from donepezil as a symptomatic therapy.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence to date indicates that donepezil (5 or 10 mg per day) is well tolerated and can improve cognitive symptoms and functional ability in patients with vascular cognitive impairment. Long-term efficacy of donepezil in improving cognitive function of patients with VaD was described in a follow-up open-label trial for 12 to 18 months, but this trial does not provide an unbiased comparison with placebo.

Implications for research

Testing long-term treatment of donepezil is recommended to establish the drug safety and the drug efficacy in slowing the rate of cognitive deterioration in a large follow-up trial. There is a need to extend the treatment effect in patients with severe cognitive decline. Outcome measures used should include other measures as costs and caregiver burden. Other ethical requirements are to identify appropriate diagnosis, clinical criteria and rating scales for patients with VCI.

ACKNOWLEDGEMENTS

We gratefully acknowledge the contributions of the consumer editors: Clive Evers on the protocol and Mervyn Richardson on the review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study 307/309

Methods	A 24 week, multinational, double-blind, randomized, placebo-controlled, parallel-group trial
Participants	1- 603 with probable VaD(70%)and 30% with possible VaD according to NINDA-AIREN 2- mean age 73.9 3- 55.2% were males 4- MMSE score between 10 and 26 Exclusion Criteria: 1- Patients with any neurodegenerative disorders other than VaD 2- Patients with AD diagnosis 3- Patients with major depression or other psychiatric disorders 4- patients who had myocardial infarction within the previous 3 months 5- patients with life-threatening disease 6- patients with alcohol or drug abuse history 7- patients with hypersensitivity to donepezil
Interventions	1-placebo 2-5mg / day donepezil. 3-10 mg /day donepezil
Outcomes	Baseline assessment: 1- psychometric evaluations 2- neurological examination 3- laboratory assessment 4- vital signs 5- CT and MRI Primary outcome: 1- ADAS-cog 2- CIBIC-plus Secondary assessment: 1- MMSE 2- CDR-SB 3- ADFACS Safety assessment: 1- changing in laboratory values 2- changing in vital signs 3- electrocardiogram(ECG) changes 4- physical and neurological examination
Notes	Patients in the 10 mg donepezil group have received 5 mg /day of donepezil for the first 28 days

Risk of bias

Bias	Authors' judgement	Support for judgement

Study 307/309 (*Continued*)

Allocation concealment?	Low risk	A - Adequate

Study 308/309

Methods	A 24 week, multinational, double-blind, randomized, placebo-controlled, parallel-group trial
Participants	1-616 pateints from USA, Europe, Canada, and Australia, with probable VaD and 24% with possible VaD according to NINDS-AIREN criteria. 2-Mean age 75 3-40.1 were women 4-99.5 with abnormal brain image findings 5-Concomitant medication was permitted 6-Other anticholineasterase inhibitors were not allowed Exclusion criteria: 1-AD patients and other neurodegenerative disorders 2-patients with psychiatric disorders 3-MMSE below 10 or above 26 4-A history of new stroke within the prior 28 days. 5-A history of myocardial infarction within the last 3 months 6-Life-threatening disease 7-Ahistoruy of drug and alcohol abuse 8-hypersensitivity to donepezil
Interventions	1-placebo 2-5mg /day donepezil 3-10 mg /day donepezil
Outcomes	Primary outcome measures: 1-ADAS-cog 2-CIBIC-Plus Secondary outcomes: 1-MMSE 2-CDR-SB 3-ADFACS Safety assessment: 1-Changes in laboratory test value 2-Obseravation the changes in the vital signs 3-Electrogardiogram(ECG) changes 4-Physical and neurological examination
Notes	Patients in the 10 mg donepezil group they have received 5 mg /day donepezil for the first 28 days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

VaD: Vascular Dementia
NINDS-AIREN: National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l' Enseignement en Neurosciences
CVD: Cerebro- Vascular Disease
MMSE: Mini-Mental State Examination
ADAS-Cog: Alzheimer's Disease Assessment Scale-cogntive subscale
CIBIC-plus: the Clinician Interview Based Impression
MRI: Magnetic Resonance Imaging
CT: Computers-assisted tomography

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

Study	Reason for exclusion
Meyer 2002	Open-label trial
Rossor 2003	Open-label trial
Shua-Haim 2000	Open-label trial

DATA AND ANALYSES

Comparison 1. Donepezil vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-cog Completers	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Donepezil (5mg/day) at 12 weeks	2	695	Mean Difference (IV, Fixed, 95% CI)	-1.47 [-2.22, -0.72]
1.2 Donepezil (5mg/day) at 24 weeks	2	627	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-2.45, -0.87]
1.3 Donepezil (10mg/day) at 12 weeks	2	675	Mean Difference (IV, Fixed, 95% CI)	-2.27 [-3.05, -1.49]
1.4 Donepezil (10 mg/day) at 24 weeks	2	608	Mean Difference (IV, Fixed, 95% CI)	-2.21 [-3.07, -1.35]
2 ADAS-cog ITT-LOCF	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Donepezil (5mg/day) at endpoint	2	752	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-2.40, -0.92]
2.2 Donepezil (10 mg/day) at endpoint	2	748	Mean Difference (IV, Fixed, 95% CI)	-2.17 [-2.97, -1.37]
3 MMSE Completers	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Donepezil(5mg /day) at 12 weeks	1	359	Mean Difference (IV, Fixed, 95% CI)	1.12 [0.58, 1.66]
3.2 Donepezil (5mg /day) at 24 weeks	2	648	Mean Difference (IV, Fixed, 95% CI)	0.83 [0.38, 1.29]
3.3 Donepezil (10 mg/day) at 12 weeks	1	353	Mean Difference (IV, Fixed, 95% CI)	1.39 [0.83, 1.95]
3.4 Donepezil (10 mg/day) at 24 weeks	2	630	Mean Difference (IV, Fixed, 95% CI)	1.08 [0.62, 1.55]
4 MMSE ITT-LOCF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Donepezil (5mg /day) at endpoint	1	389	Mean Difference (IV, Fixed, 95% CI)	0.65 [0.04, 1.26]
4.2 Donepezil (10 mg/day) at endpoint	1	388	Mean Difference (IV, Fixed, 95% CI)	1.1 [0.50, 1.70]
5 CDR-SB completers	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Donepezil (5 mg/day) at 24 weeks	2	644	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.49, 0.04]
5.2 Donepezil (10 mg/day) at 24 weeks	2	622	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-0.72, -0.20]
6 CDR-SB ITT-LOCF	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Donepezil (5 mg/day) at endpoint	2	769	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.45, 0.03]
6.2 Donepezil (10 mg/day) at 24 weeks	2	763	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.60, -0.13]
7 IADL completers	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Donepezil (5 mg/day) at 24 weeks	2	644	Mean Difference (IV, Fixed, 95% CI)	-0.81 [-1.45, -0.16]

7.2 Donepezil (10 mg/ day) at 24 weeks	2	622	Mean Difference (IV, Fixed, 95% CI)	-0.85 [-1.48, -0.21]
8 IADL ITT-LOCF	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Donepezil (5 mg/day) at endpoint	2	783	Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.92, 0.25]
8.2 Donepezil (10 mg/ day) at endpoint	2	763	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.49, 0.64]
9 ADFACS Completers	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Donepezil (5mg/day) at 24 weeks	2	620	Mean Difference (IV, Fixed, 95% CI)	-0.97 [-1.80, -0.14]
9.2 Donepezil (10 mg/day) at 24 weeks	2	603	Mean Difference (IV, Fixed, 95% CI)	-0.95 [-1.79, -0.11]
10 ADFACS ITT-LOCF	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Donepezil (5mg/day) at endpoint	2	740	Mean Difference (IV, Fixed, 95% CI)	-0.73 [-1.52, 0.06]
10.2 Donepezil (10 mg/day) at endpoint	2	743	Mean Difference (IV, Fixed, 95% CI)	-0.95 [-1.73, -0.17]
11 CIBIC-plus (total number of patients who clinicaly improved)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Donepezil (5 mg/day) at 24 weeks	2	780	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [1.15, 2.11]
11.2 Donepezil (10 mg /day) at 24 weeks	2	779	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.83, 1.54]
12 CIBIC-plus (total number of pateints who clinically declined)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Donepezil (5mg/day) at 24 weeks	1	390	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.41, 1.02]
12.2 Donepezil (10 mg/day) at 24 weeks	1	389	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.57, 1.36]
13 Total number of patients who suffered from one side effect or more at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Donepezil (5mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.80, 1.92]
13.2 Donepezil (10mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	1.95 [1.20, 3.15]
14 Total number of patients who suffered from cardiovascular side effects at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Donepezil (5 mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.70, 1.40]
14.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.71, 1.41]
15 Total number of patients who suffered from hypertension at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Donepezil (5 mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.54, 1.89]
15.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.61, 2.06]
16 Total number of patients who suffered from syncope at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Donepezil (5 mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.25, 1.76]
16.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	1.79 [0.82, 3.90]

17 Total number of patients who suffered from bradycardia at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Donepezil (5 mg/day)	1	397	Odds Ratio (M-H, Fixed, 95% CI)	2.39 [0.61, 9.40]
17.2 Donepezil (10 mg/day)	1	405	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.19, 4.84]
18 Total number of patients who had hypotension at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 Donepezil (5 mg/day)	1	397	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.22]
18.2 Donepezil (10 mg/day)	1	405	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.19, 4.84]
19 Total number of patients who suffered from digestive system side effects at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 donepezil (5mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.87, 1.97]
19.2 donepzeil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [1.06, 2.37]
20 Total number of patients who suffered from anorexia at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 Donepezil (5 mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	1.98 [1.02, 3.82]
20.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	2.50 [1.33, 4.71]
21 Total number of patients who suffered from constipation at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.46, 2.82]
21.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.16, 1.48]
22 Total number of patients who suffered from diarrhoea at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 Donepezil (5 mg /day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.98, 2.30]
22.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	1.75 [1.15, 2.65]
23 Total number of patients who suffered from nausea at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 Donepezil (5 mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.83, 2.25]
23.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	2.45 [1.55, 3.87]
24 Total number of patients who suffered from dyspepsia at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.32, 1.81]
24.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.23, 1.46]
25 Total number of patients who suffered from vomiting at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 Donepezil (5 mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.55, 1.83]
25.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.67, 2.11]
26 Total number of patients who suffered from neurological side effects at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 donepezil (5mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.72, 1.58]
26.2 donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.83, 1.82]
27 Total number of patients who suffered from back pain at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

27.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.91 [0.70, 5.19]
27.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.11, 1.79]
28 Total number of patients who suffered from headache at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.41, 1.79]
28.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.37, 1.62]
29 Total number of patients who suffered from agitation at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.42, 2.46]
29.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.46, 2.56]
30 Total number of patients who suffered from stroke at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 donepezil 5 mg /day	2	798	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.42, 1.71]
30.2 donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.57, 2.12]
31 Total number of patients who suffered from confusion at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
31.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.49, 2.42]
31.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.23, 1.46]
32 Total number of patients who suffered from depression at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
32.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.45, 2.26]
32.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.39, 2.03]
33 Total number of patients who suffered from dizziness at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
33.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.35, 1.35]
33.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.36, 1.38]
34 Total number of patients who suffered from insomnia at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
34.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	2.16 [1.00, 4.70]
34.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	1.98 [0.91, 4.32]
35 Total number of patients who suffered from at least one serious adverse event(SAE) at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
35.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.50, 1.45]
35.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.52, 1.49]
36 Total number of patients who suffered from skin carcinoma at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
36.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.90]
36.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.13, 1.48]
37 Total number of patients who suffered from pathologic fracture at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
37.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.23, 8.45]

37.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.22, 8.17]
38 Total number of patients who suffered from pneumonia at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
38.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.15, 3.13]
38.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.02, 1.99]
39 Total number of patients who suffered from TIA at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
39.1 Donepezil (5 mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.39, 2.10]
39.2 Donepezil (10 mg/ day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.13, 1.11]
40 Total number of patients who suffered from angina at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
40.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 5.13]
40.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.13, 6.43]
41 Total number of patients who suffered from a convulsion at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
41.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.03, 2.97]
41.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.03, 2.87]
42 Total number of patients who suffered from colitis at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
42.1 Donepezil (10 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.60]
42.2 Donepezil (10 mg /day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	2.72 [0.28, 26.34]
43 Total number of patients who suffered from asthenia at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
43.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.52, 2.12]
43.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [0.72, 2.70]
44 Total numbers of patients who suffered from cramps and leg cramps at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
44.1 Donepezil (5 mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	6.76 [2.33, 19.63]
44.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	10.84 [3.83, 30.70]
45 Total number of patients who suffered from skin abrasion at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
45.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.56, 3.91]
45.2 Donezpezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	1.57 [0.61, 4.07]
46 Total number of patients who suffered from peripheral oedema at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
46.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.52, 2.85]
46.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.23, 1.65]
47 Total number of patients who suffered from abnormal dreams at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
47.1 Donepezil (5 mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	2.20 [0.75, 6.42]
47.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	4.75 [1.79, 12.63]

48 Total number of patients who suffered from rhinitis at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
48.1 Donepezil (5 mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	2.14 [0.86, 5.32]
48.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	3.54 [1.51, 8.33]
49 Total number of patients who suffered from infection at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
49.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.78, 2.32]
49.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.59, 1.83]
50 Total number of patients who suffered from pain at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
50.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.38, 1.53]
50.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.28, 1.23]
51 Total number of patients who suffered from skin rash at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
51.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.51, 3.28]
51.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.23, 1.95]
52 Total number of patients who suffered from urinary incontinence at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
52.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.23, 2.02]
52.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	1.99 [0.84, 4.71]
53 Total number of patients who suffered from urinary tract infection at 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
53.1 Donepezil (5 mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.71, 2.79]
53.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.39, 1.76]
54 Total number of patients who withdrew before the end point of the intervention	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
54.1 donepezil(5 mg/day)	2	761	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.59, 1.24]
54.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	1.91 [1.35, 2.70]
55 Total number of patients who suffered from syncope at 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
55.1 Donepezil (5 mg/day)	2	798	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.25, 1.76]
55.2 Donepezil (10 mg/day)	2	813	Odds Ratio (M-H, Fixed, 95% CI)	1.79 [0.82, 3.90]
56 Total number of patients who died by endpoint	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
56.1 Donepezil (5mg/day)	1	401	Odds Ratio (M-H, Fixed, 95% CI)	2.81 [0.29, 27.24]
56.2 Donepezil (10 mg/day)	1	408	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [0.16, 20.04]

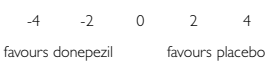
Analysis 1.1. Comparison 1 Donepezil vs placebo, Outcome 1 ADAS-cog Completers.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 1 ADAS-cog Completers

Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Donepezil (5mg/day) at 12 weeks							
Study 307/309	171	-1.38 (5.01)	174	-0.24 (5.05)		49.6 %	-1.14 [-2.20, -0.08]
Study 308/309	183	-2.7 (4.97)	167	-0.91 (5.07)		50.4 %	-1.79 [-2.84, -0.74]
Subtotal (95% CI)	**354**		**341**			**100.0 %**	**-1.47 [-2.22, -0.72]**
Heterogeneity: Chi^2 = 0.73, df = 1 (P = 0.39); I^2 =0.0%							
Test for overall effect: Z = 3.85 (P = 0.00012)							
2 Donepezil (5mg/day) at 24 weeks							
Study 307/309	153	-1.56 (5.32)	160	0.34 (5.06)		47.0 %	-1.90 [-3.05, -0.75]
Study 308/309	164	-2.02 (4.61)	150	-0.58 (5.14)		53.0 %	-1.44 [-2.52, -0.36]
Subtotal (95% CI)	**317**		**310**			**100.0 %**	**-1.66 [-2.45, -0.87]**
Heterogeneity: Chi^2 = 0.33, df = 1 (P = 0.57); I^2 =0.0%							
Test for overall effect: Z = 4.11 (P = 0.000039)							
3 Donepezil (10mg/day) at 12 weeks							
Study 307/309	162	-2.74 (5.35)	174	-0.24 (5.05)		49.3 %	-2.50 [-3.61, -1.39]
Study 308/309	172	-2.96 (5.25)	167	-0.91 (5.07)		50.7 %	-2.05 [-3.15, -0.95]
Subtotal (95% CI)	**334**		**341**			**100.0 %**	**-2.27 [-3.05, -1.49]**
Heterogeneity: Chi^2 = 0.32, df = 1 (P = 0.57); I^2 =0.0%							
Test for overall effect: Z = 5.69 (P < 0.00001)							
4 Donepezil (10 mg/day) at 24 weeks							
Study 307/309	143	-1.99 (5.38)	160	0.34 (5.06)		52.9 %	-2.33 [-3.51, -1.15]
Study 308/309	155	-2.65 (5.98)	150	-0.58 (5.14)		47.1 %	-2.07 [-3.32, -0.82]
Subtotal (95% CI)	**298**		**310**			**100.0 %**	**-2.21 [-3.07, -1.35]**
Heterogeneity: Chi^2 = 0.09, df = 1 (P = 0.77); I^2 =0.0%							
Test for overall effect: Z = 5.04 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.00, df = 3 (P = 0.39), I^2 =0%							

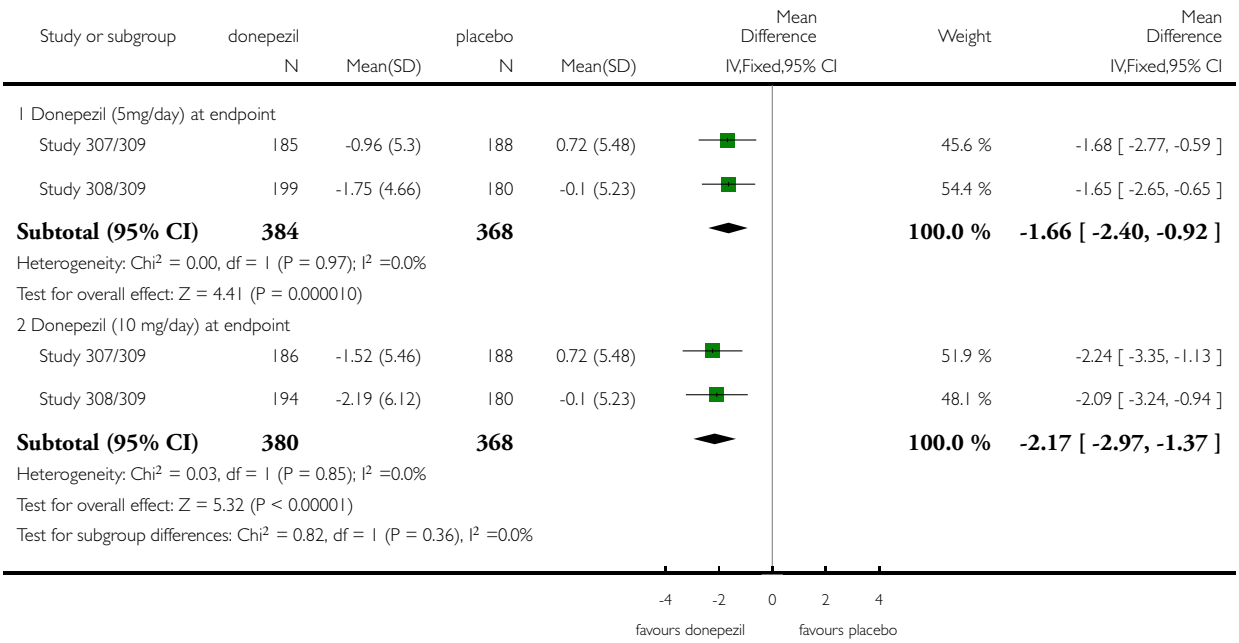


Analysis 1.2. Comparison 1 Donepezil vs placebo, Outcome 2 ADAS-cog ITT-LOCF.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 2 ADAS-cog ITT-LOCF



Analysis 1.3. Comparison 1 Donepezil vs placebo, Outcome 3 MMSE Completers.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 3 MMSE Completers

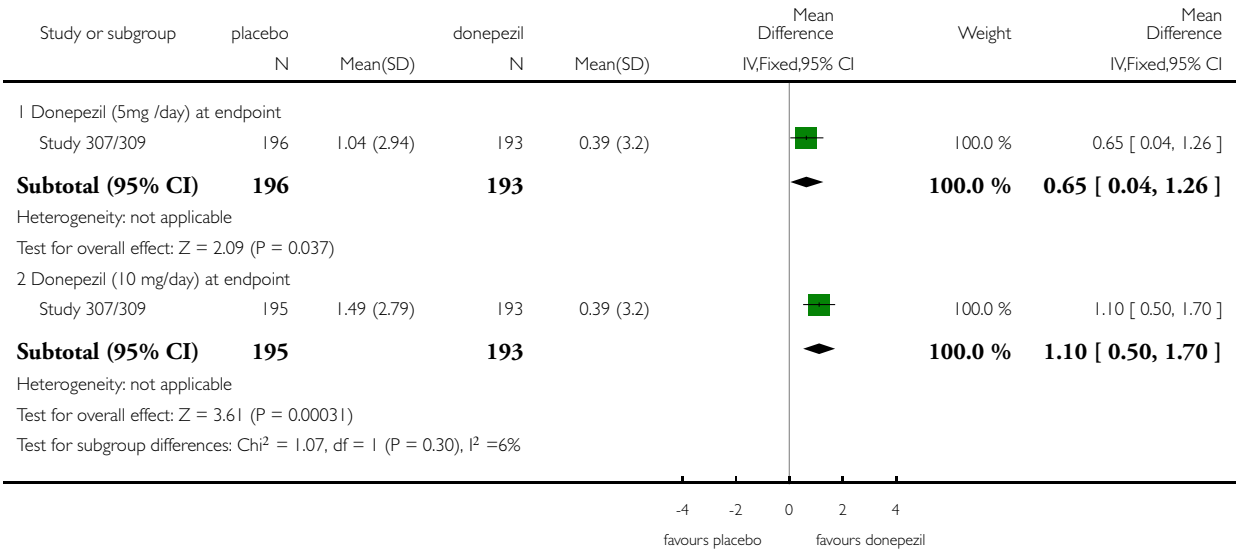
Study or subgroup	placebo N	Mean(SD)	donepezil N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Donepezil(5mg /day) at 12 weeks							
Study 308/309	185	1.38 (2.28)	174	0.26 (2.9)		100.0 %	1.12 [0.58, 1.66]
Subtotal (95% CI)	**185**		**174**			**100.0 %**	**1.12 [0.58, 1.66]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.05 (P = 0.000051)							
2 Donepezil (5mg /day) at 24 weeks							
Study 307/309	161	1.1 (3.05)	164	0.57 (3.12)		46.7 %	0.53 [-0.14, 1.20]
Study 308/309	166	1.51 (2.58)	157	0.41 (3.13)		53.3 %	1.10 [0.47, 1.73]
Subtotal (95% CI)	**327**		**321**			**100.0 %**	**0.83 [0.38, 1.29]**
Heterogeneity: Chi^2 = 1.48, df = 1 (P = 0.22); I^2 =32%							
Test for overall effect: Z = 3.57 (P = 0.00036)							
3 Donepezil (10 mg/day) at 12 weeks							
Study 308/309	179	1.65 (2.41)	174	0.26 (2.9)		100.0 %	1.39 [0.83, 1.95]
Subtotal (95% CI)	**179**		**174**			**100.0 %**	**1.39 [0.83, 1.95]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.89 (P < 0.00001)							
4 Donepezil (10 mg/day) at 24 weeks							
Study 307/309	148	1.53 (2.68)	164	0.57 (3.12)		52.6 %	0.96 [0.32, 1.60]
Study 308/309	161	1.63 (3.04)	157	0.41 (3.13)		47.4 %	1.22 [0.54, 1.90]
Subtotal (95% CI)	**309**		**321**			**100.0 %**	**1.08 [0.62, 1.55]**
Heterogeneity: Chi^2 = 0.30, df = 1 (P = 0.59); I^2 =0.0%							
Test for overall effect: Z = 4.55 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 2.32, df = 3 (P = 0.51), I^2 =0.0%							

Analysis 1.4. Comparison 1 Donepezil vs placebo, Outcome 4 MMSE ITT-LOCF.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 4 MMSE ITT-LOCF

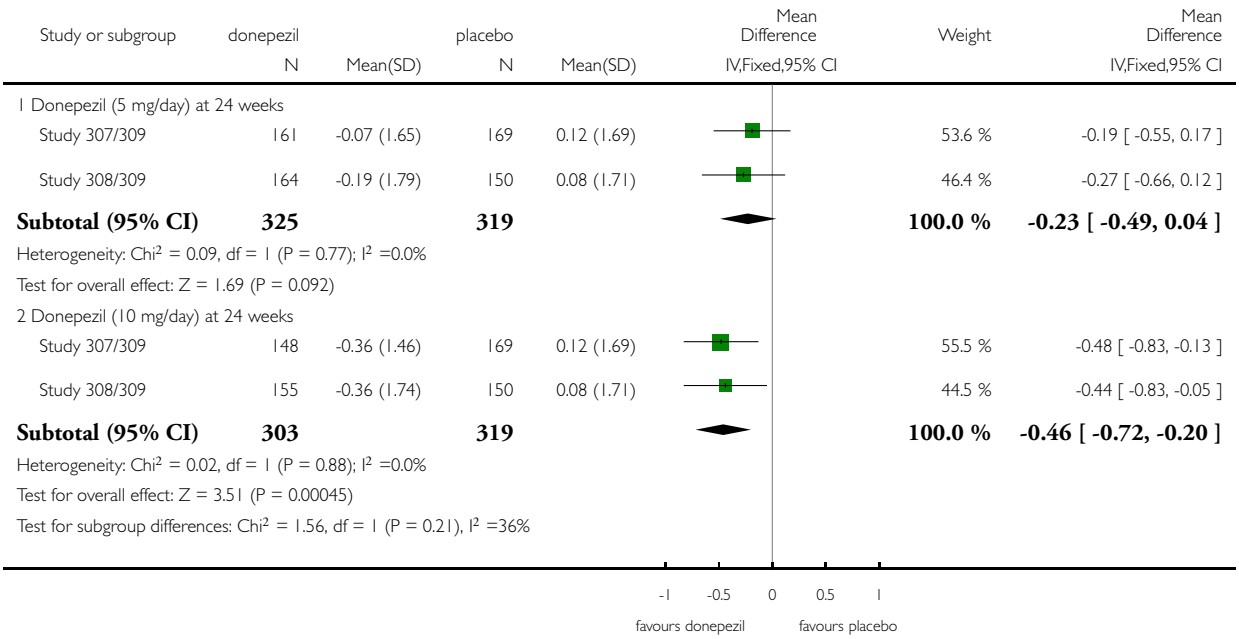


Analysis 1.5. Comparison 1 Donepezil vs placebo, Outcome 5 CDR-SB completers.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 5 CDR-SB completers

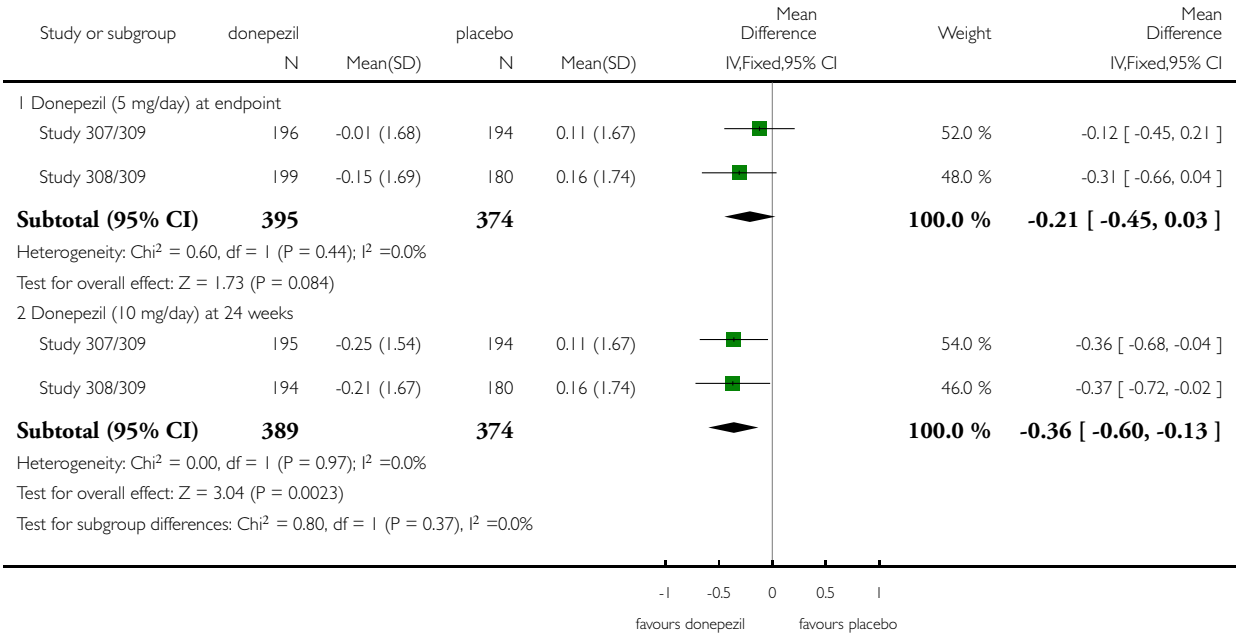


Analysis 1.6. Comparison 1 Donepezil vs placebo, Outcome 6 CDR-SB ITT-LOCF.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 6 CDR-SB ITT-LOCF

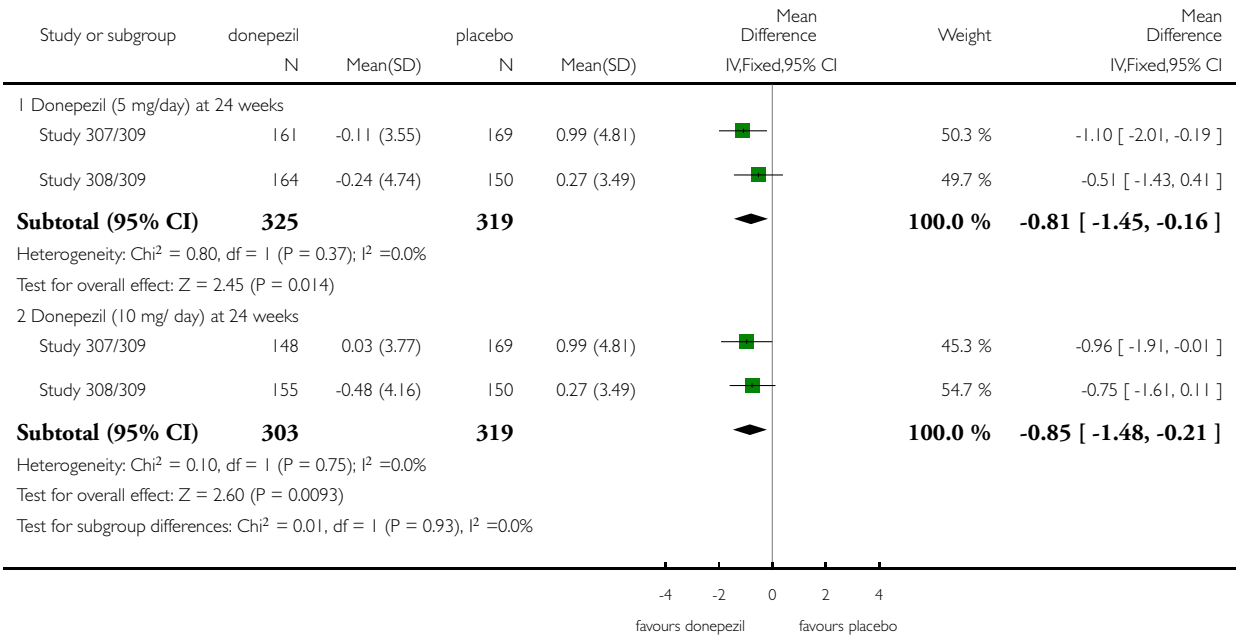


Analysis 1.7. Comparison 1 Donepezil vs placebo, Outcome 7 IADL completers.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 7 IADL completers

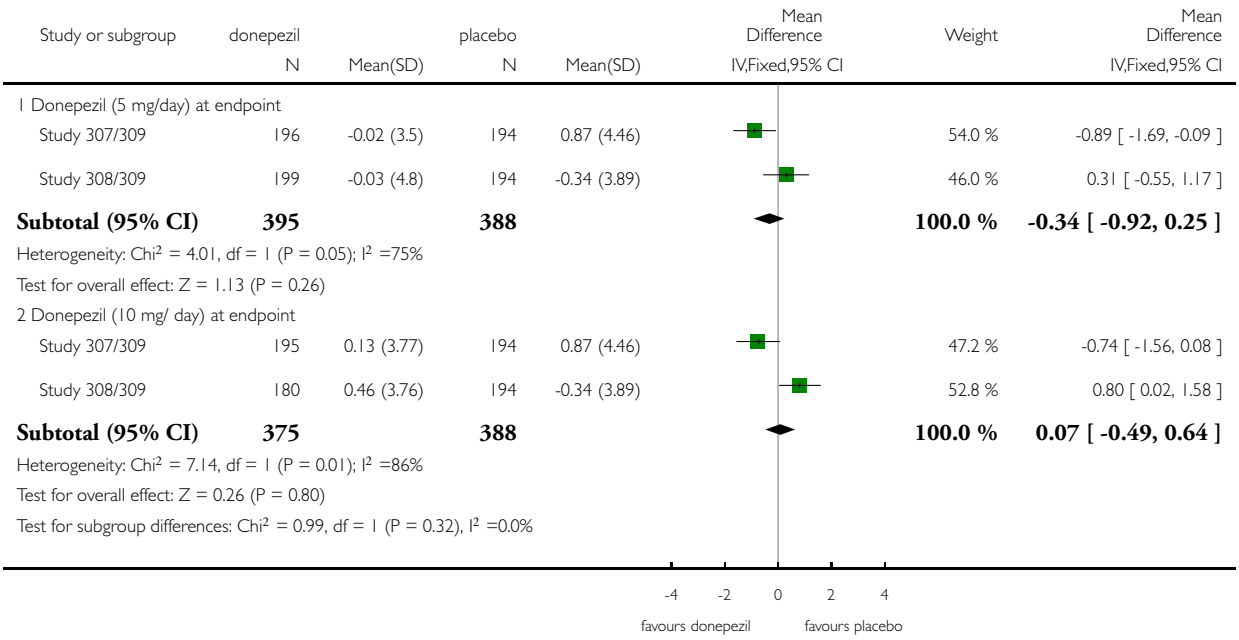


Analysis 1.8. Comparison 1 Donepezil vs placebo, Outcome 8 IADL ITT-LOCF.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 8 IADL ITT-LOCF



Analysis 1.9. Comparison 1 Donepezil vs placebo, Outcome 9 ADFACS Completers.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 9 ADFACS Completers

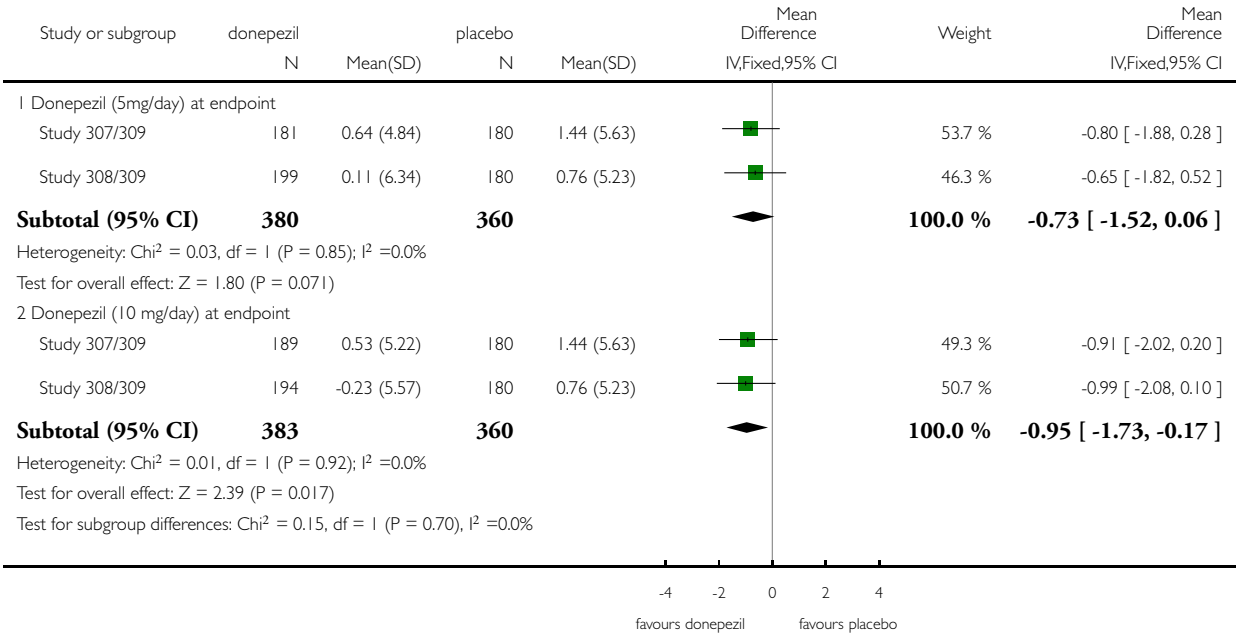
Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Donepezil (5mg/day) at 24 weeks							
Study 307/309	151	0.37 (4.67)	155	1.68 (5.73)		50.7 %	-1.31 [-2.48, -0.14]
Study 308/309	164	-0.35 (6.14)	150	0.27 (4.53)		49.3 %	-0.62 [-1.81, 0.57]
Subtotal (95% CI)	**315**		**305**			**100.0 %**	**-0.97 [-1.80, -0.14]**
Heterogeneity: Chi² = 0.66, df = 1 (P = 0.42); I² =0.0%							
Test for overall effect: Z = 2.28 (P = 0.022)							
2 Donepezil (10 mg/day) at 24 weeks							
Study 307/309	143	0.37 (5.26)	155	1.68 (5.73)		45.6 %	-1.31 [-2.56, -0.06]
Study 308/309	155	-0.38 (5.6)	150	0.27 (4.53)		54.4 %	-0.65 [-1.79, 0.49]
Subtotal (95% CI)	**298**		**305**			**100.0 %**	**-0.95 [-1.79, -0.11]**
Heterogeneity: Chi² = 0.59, df = 1 (P = 0.44); I² =0.0%							
Test for overall effect: Z = 2.21 (P = 0.027)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² =0.0%							

Analysis 1.10. Comparison 1 Donepezil vs placebo, Outcome 10 ADFACS ITT-LOCF.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 10 ADFACS ITT-LOCF

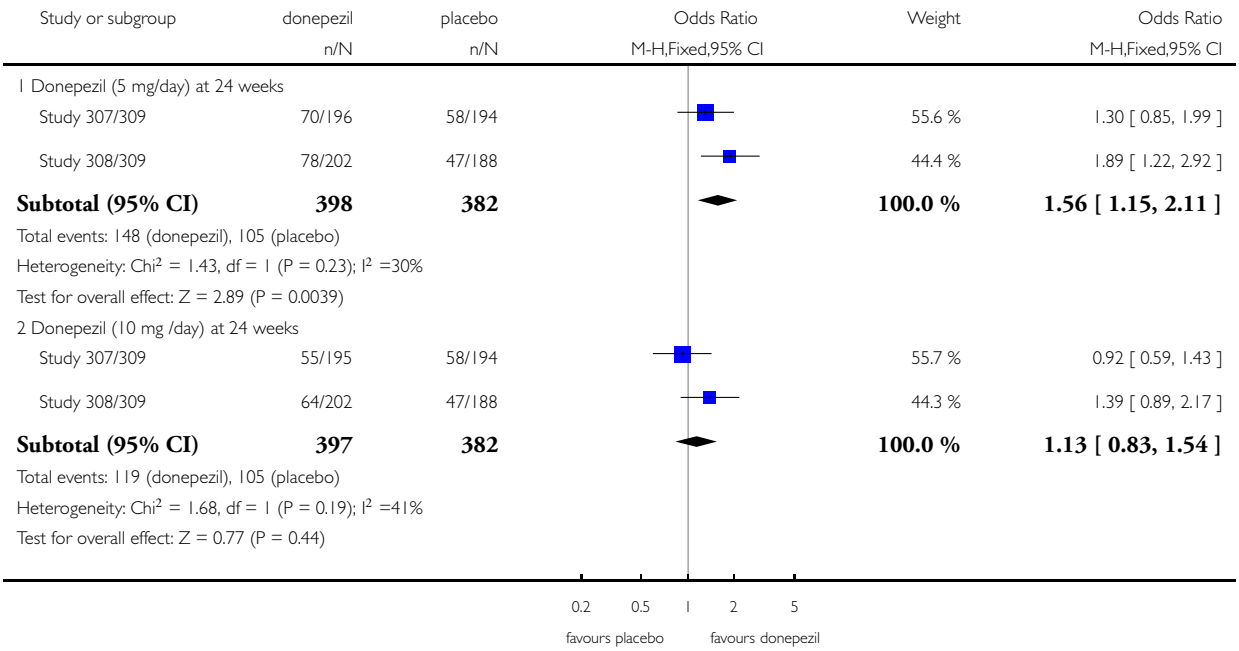


Analysis 1.11. Comparison 1 Donepezil vs placebo, Outcome 11 CIBIC-plus (total number of patients who clinicaly improved).

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 11 CIBIC-plus (total number of patients who clinicaly improved)

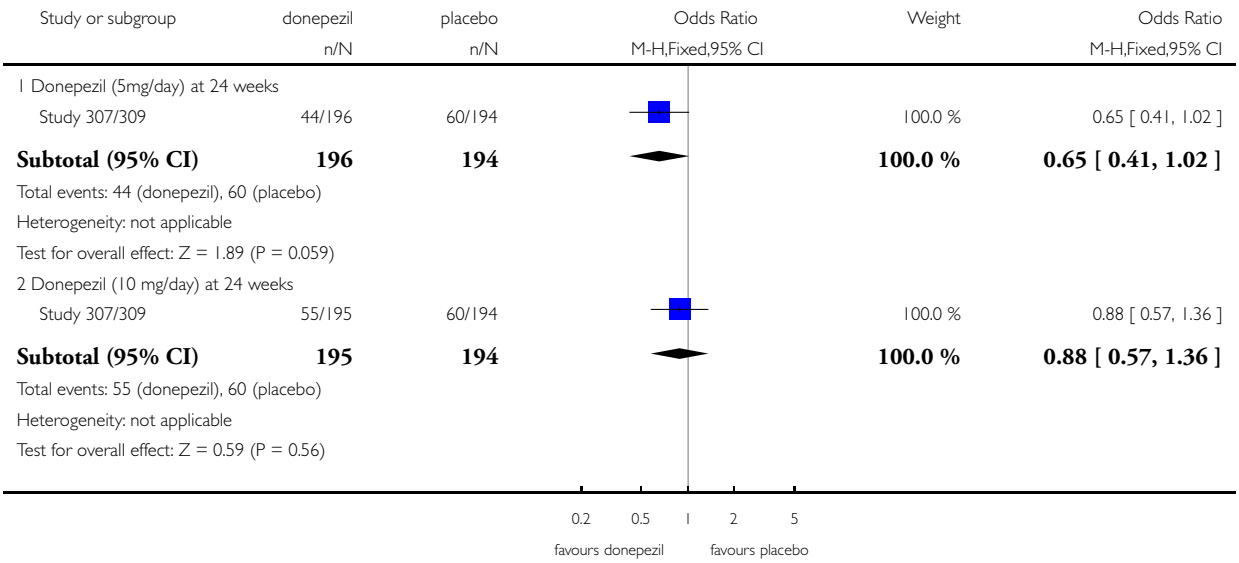


Analysis 1.12. Comparison 1 Donepezil vs placebo, Outcome 12 CIBIC-plus (total number of pateints who clinically declined).

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 12 CIBIC-plus (total number of pateints who clinically declined)

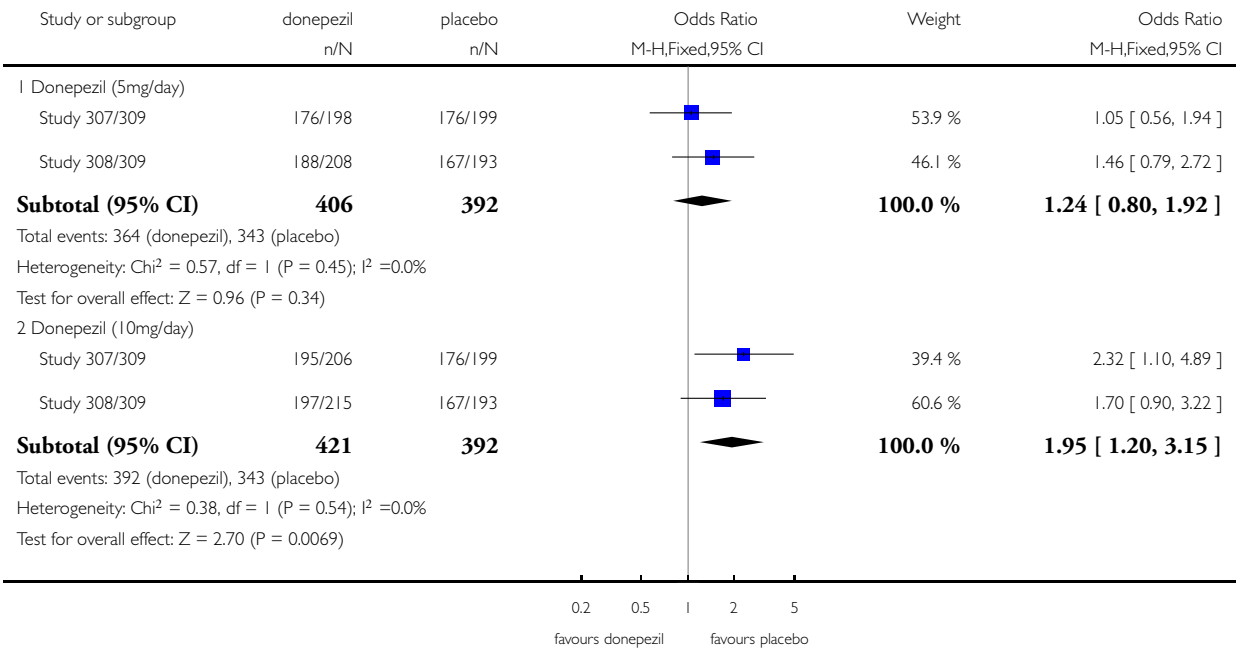


Analysis 1.13. Comparison 1 Donepezil vs placebo, Outcome 13 Total number of patients who suffered from one side effect or more at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 13 Total number of patients who suffered from one side effect or more at 24 weeks

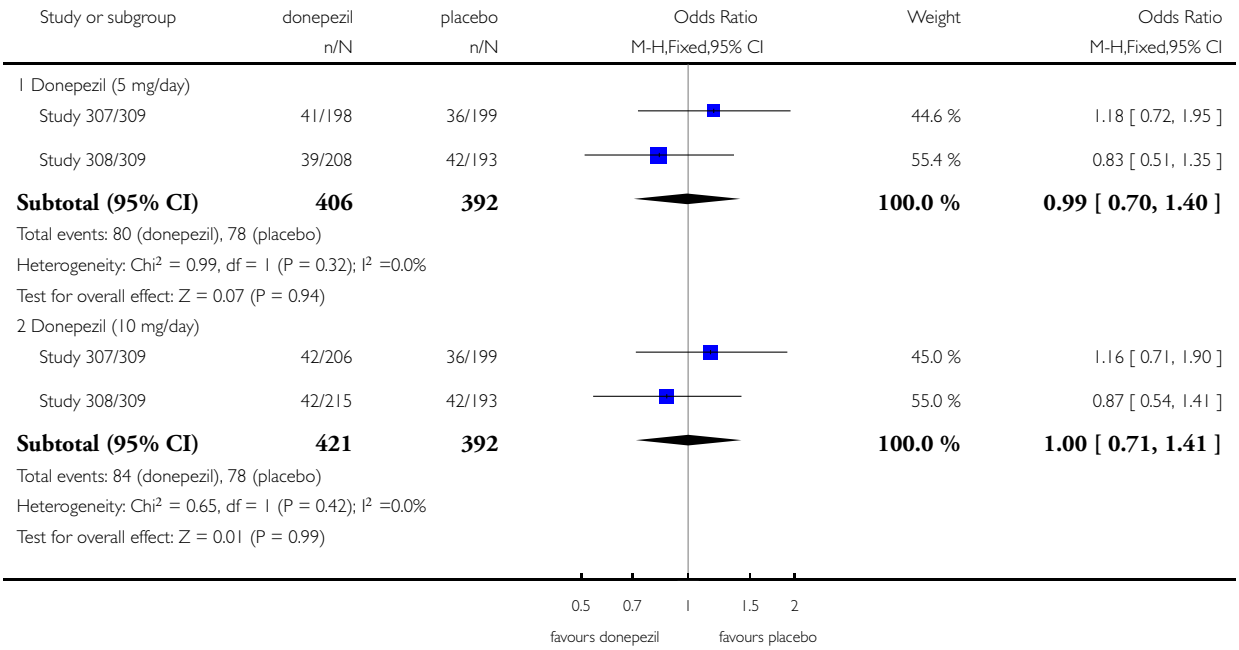


Analysis 1.14. Comparison 1 Donepezil vs placebo, Outcome 14 Total number of patients who suffered from cardiovascular side effects at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 14 Total number of patients who suffered from cardiovascular side effects at 24 weeks

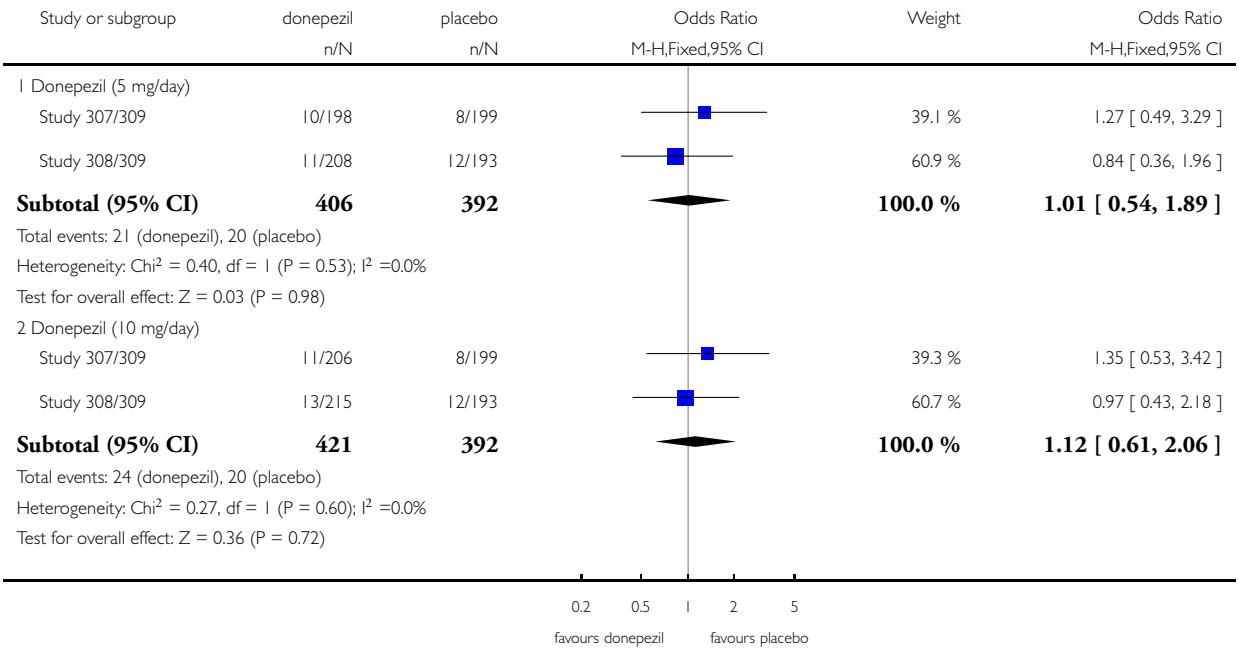


Analysis 1.15. Comparison 1 Donepezil vs placebo, Outcome 15 Total number of patients who suffered from hypertension at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 15 Total number of patients who suffered from hypertension at 24 weeks

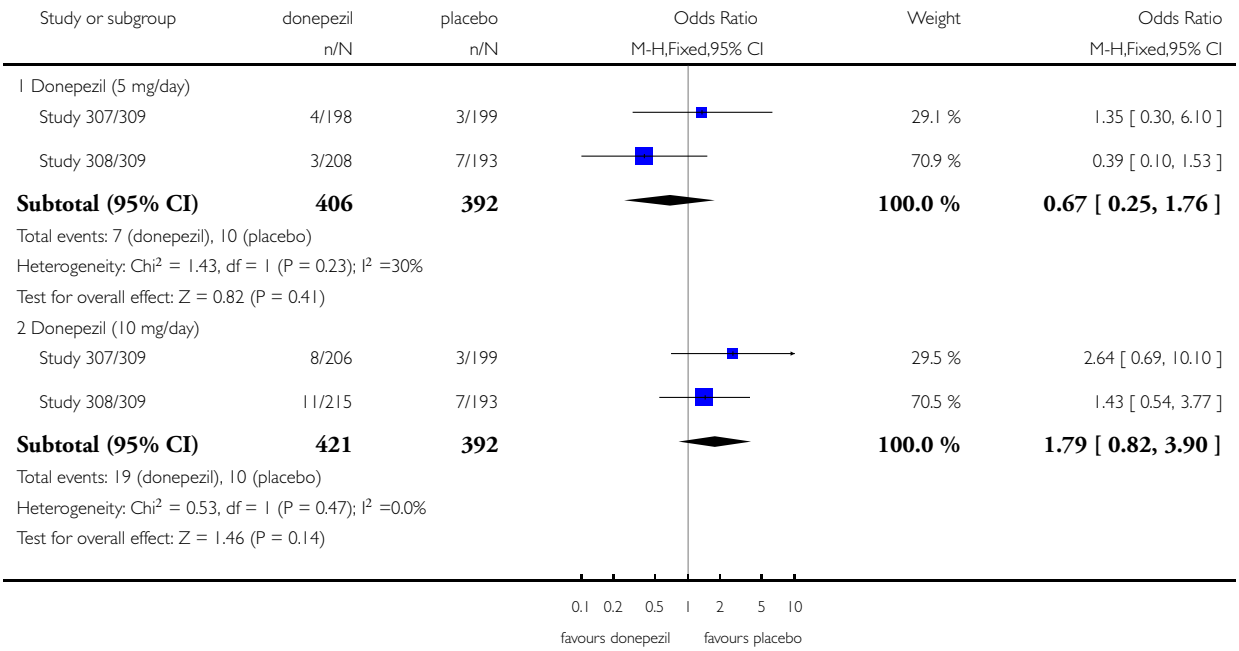


Analysis 1.16. Comparison 1 Donepezil vs placebo, Outcome 16 Total number of patients who suffered from syncope at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 16 Total number of patients who suffered from syncope at 24 weeks

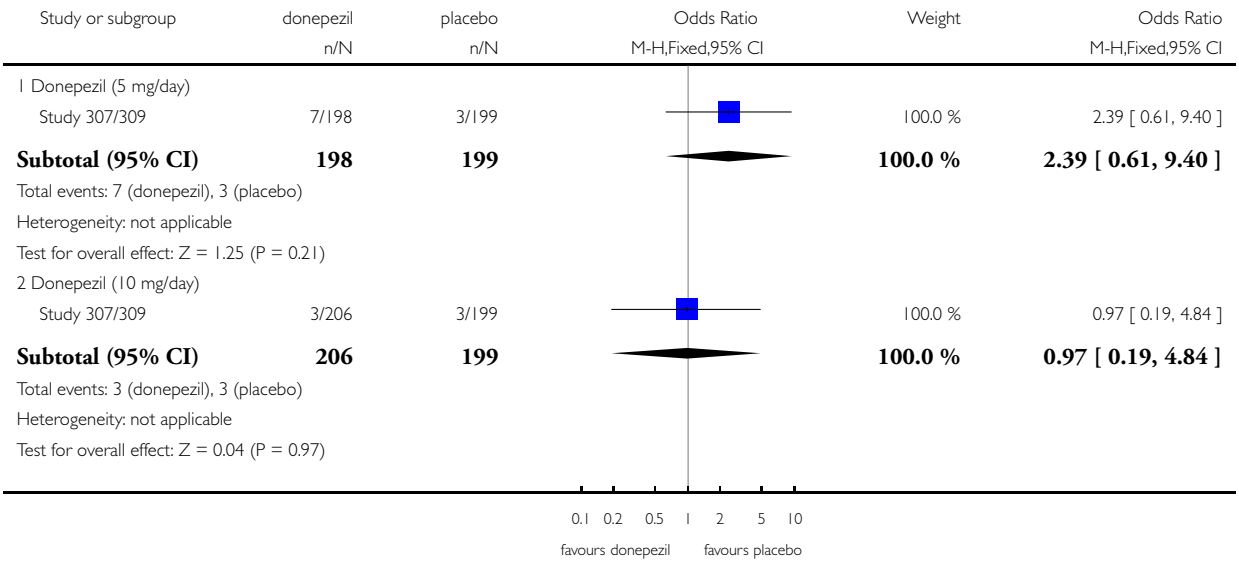


Analysis 1.17. Comparison 1 Donepezil vs placebo, Outcome 17 Total number of patients who suffered from bradycardia at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 17 Total number of patients who suffered from bradycardia at 24 weeks

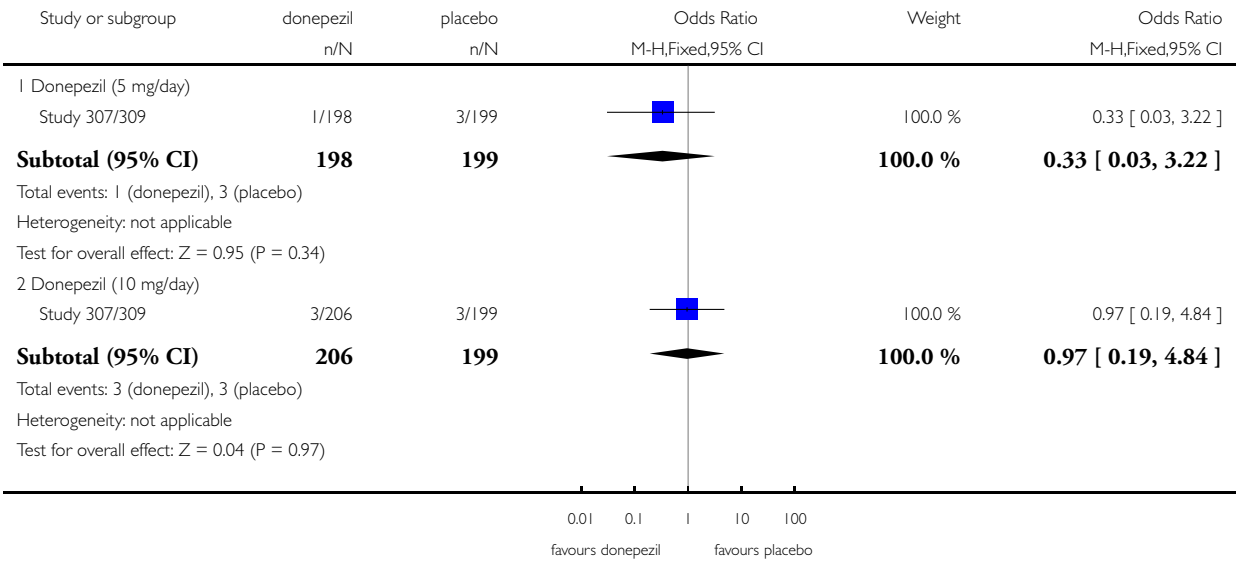


Analysis 1.18. Comparison 1 Donepezil vs placebo, Outcome 18 Total number of patients who had hypotension at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 18 Total number of patients who had hypotension at 24 weeks

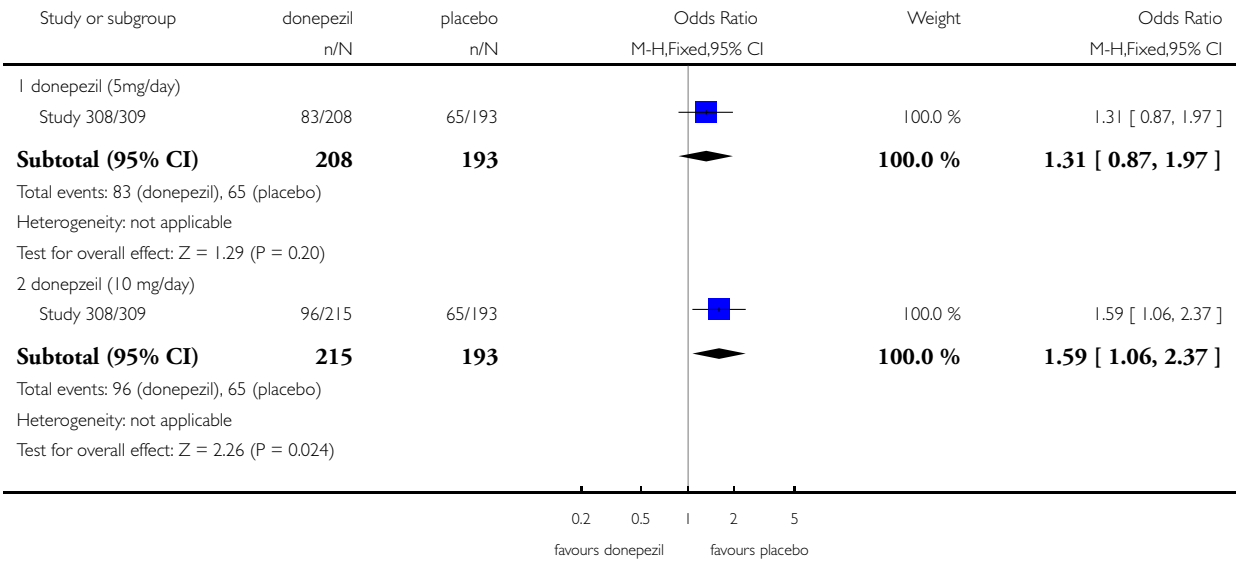


Analysis 1.19. Comparison 1 Donepezil vs placebo, Outcome 19 Total number of patients who suffered from digestive system side effects at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 19 Total number of patients who suffered from digestive system side effects at 24 weeks



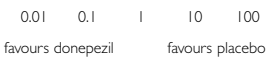
Analysis 1.20. Comparison 1 Donepezil vs placebo, Outcome 20 Total number of patients who suffered from anorexia at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 20 Total number of patients who suffered from anorexia at 24 weeks

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Donepezil (5 mg/day)					
Study 307/309	11/198	3/199		21.2 %	3.84 [1.06, 13.99]
Study 308/309	17/208	11/193		78.8 %	1.47 [0.67, 3.23]
Subtotal (95% CI)	**406**	**392**		**100.0 %**	**1.98 [1.02, 3.82]**
Total events: 28 (donepezil), 14 (placebo)					
Heterogeneity: Chi^2 = 1.56, df = 1 (P = 0.21); I^2 =36%					
Test for overall effect: Z = 2.03 (P = 0.043)					
2 Donepezil (10 mg/day)					
Study 307/309	17/206	3/199		20.9 %	5.88 [1.69, 20.38]
Study 308/309	19/215	11/193		79.1 %	1.60 [0.74, 3.46]
Subtotal (95% CI)	**421**	**392**		**100.0 %**	**2.50 [1.33, 4.71]**
Total events: 36 (donepezil), 14 (placebo)					
Heterogeneity: Chi^2 = 3.09, df = 1 (P = 0.08); I^2 =68%					
Test for overall effect: Z = 2.84 (P = 0.0046)					

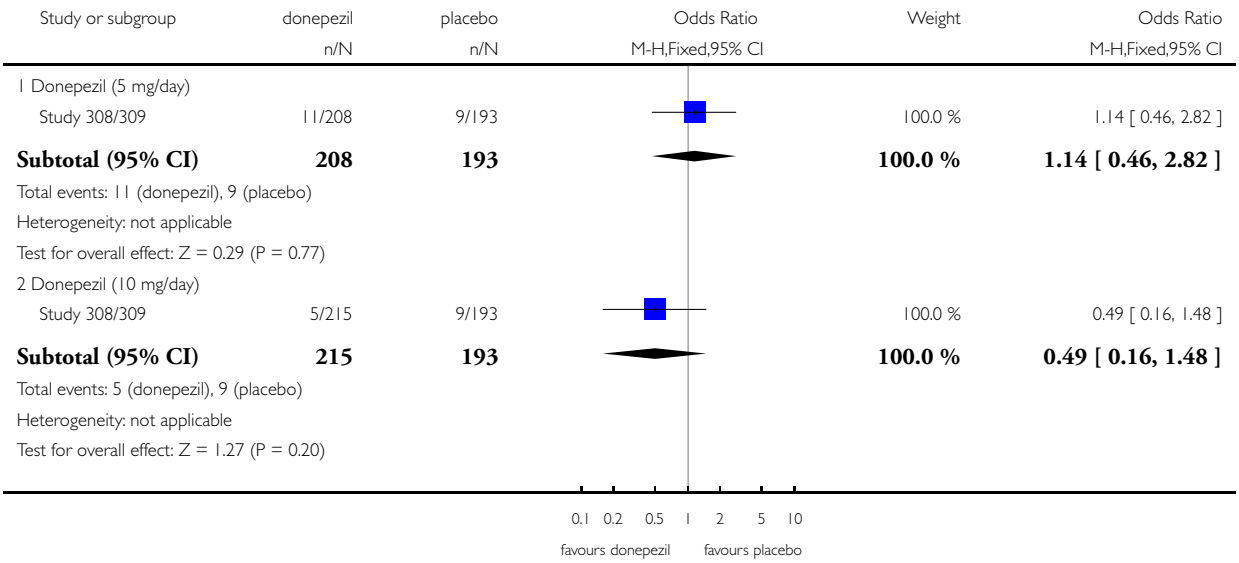


Analysis 1.21. Comparison 1 Donepezil vs placebo, Outcome 21 Total number of patients who suffered from constipation at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 21 Total number of patients who suffered from constipation at 24 weeks

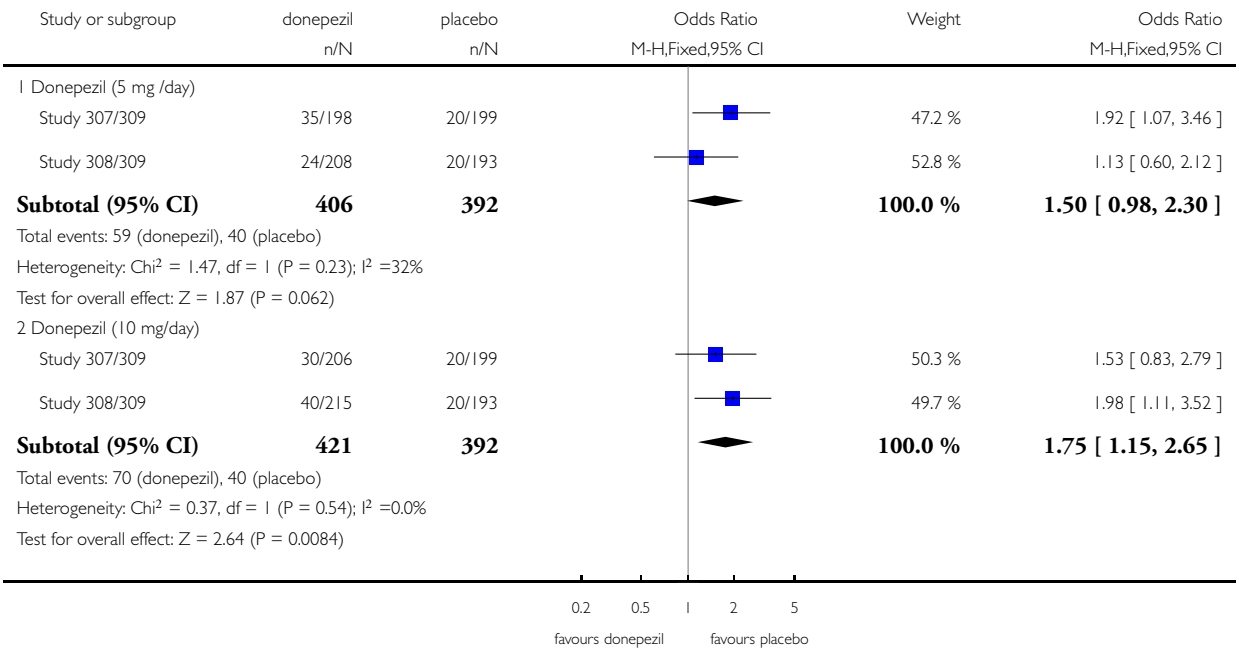


Analysis 1.22. Comparison 1 Donepezil vs placebo, Outcome 22 Total number of patients who suffered from diarrhoea at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 22 Total number of patients who suffered from diarrhoea at 24 weeks

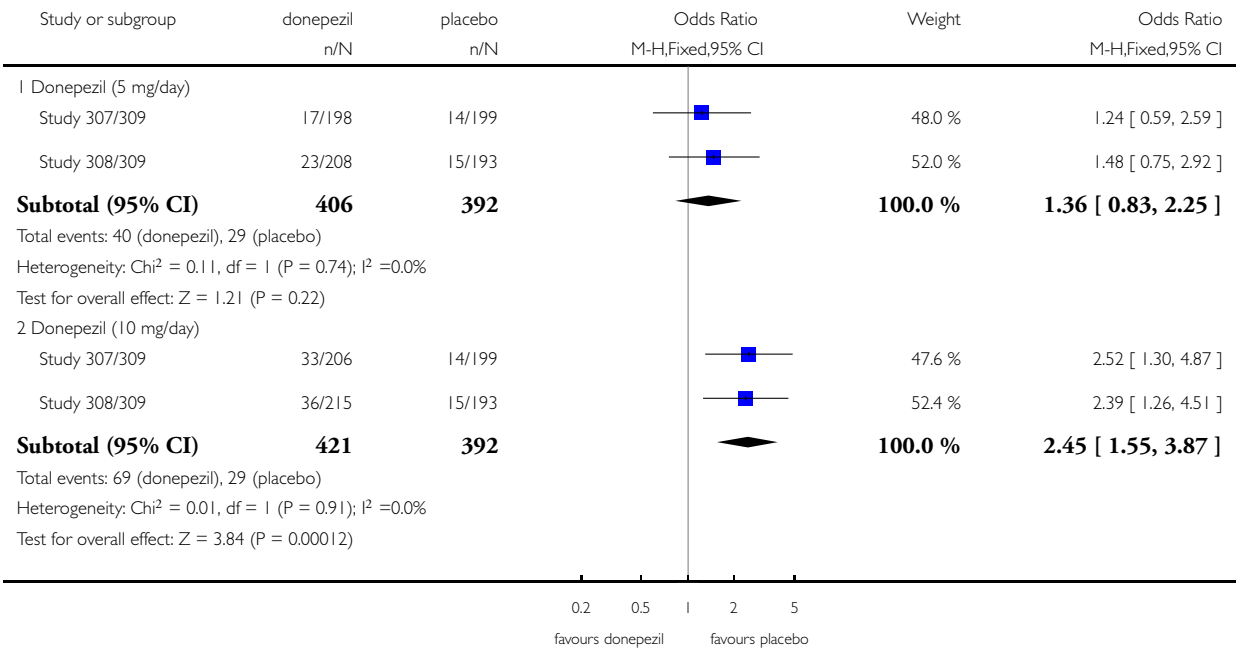


Analysis 1.23. Comparison 1 Donepezil vs placebo, Outcome 23 Total number of patients who suffered from nausea at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 23 Total number of patients who suffered from nausea at 24 weeks

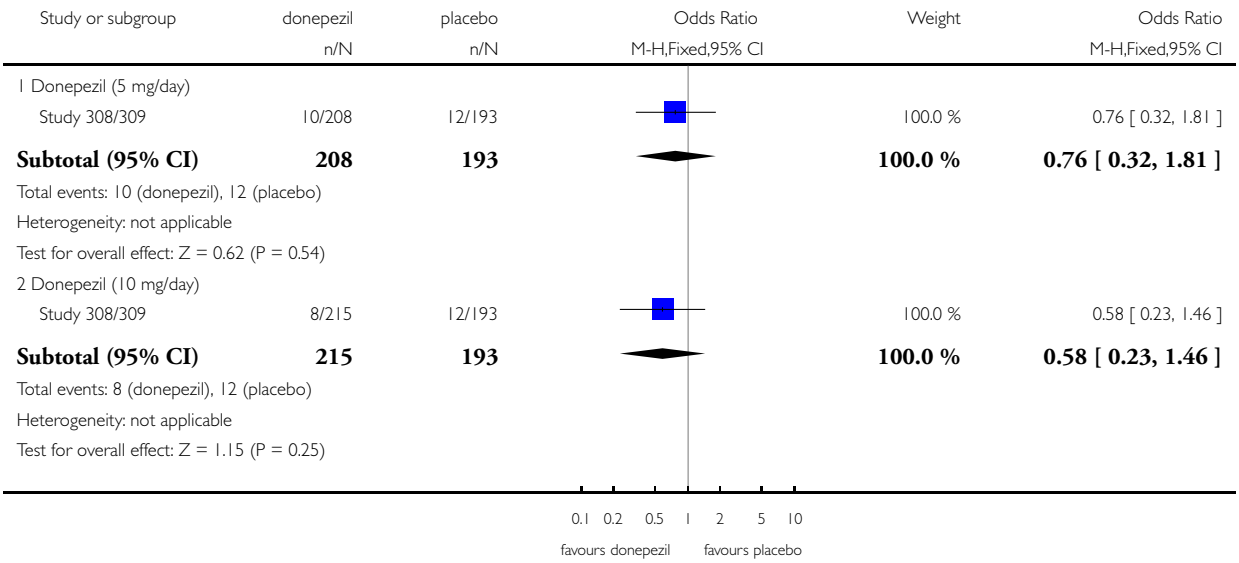


Analysis 1.24. Comparison 1 Donepezil vs placebo, Outcome 24 Total number of patients who suffered from dyspepsia at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 24 Total number of patients who suffered from dyspepsia at 24 weeks

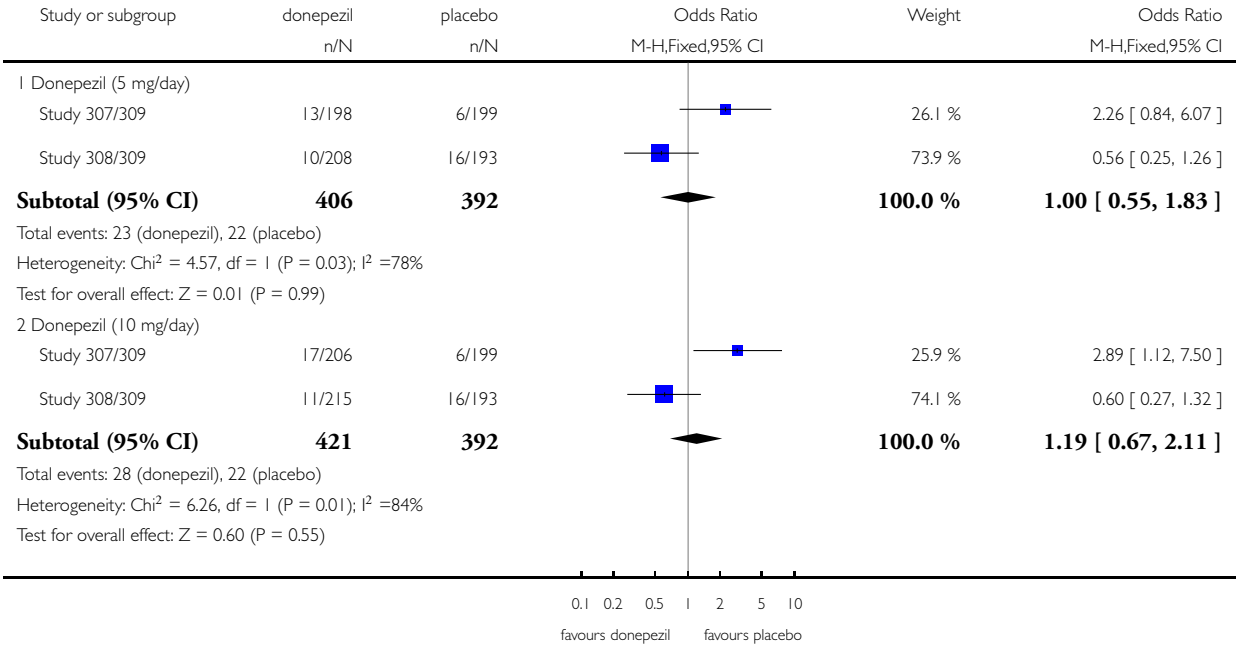


Analysis 1.25. Comparison 1 Donepezil vs placebo, Outcome 25 Total number of patients who suffered from vomiting at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 25 Total number of patients who suffered from vomiting at 24 weeks

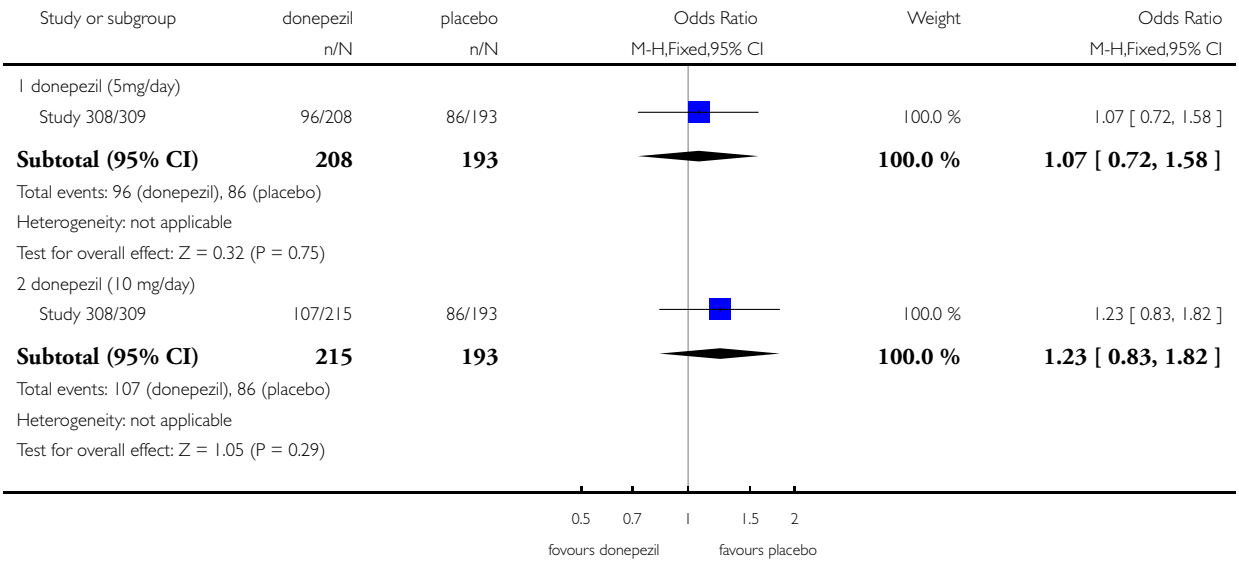


Analysis 1.26. Comparison 1 Donepezil vs placebo, Outcome 26 Total number of patients who suffered from neurological side effects at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 26 Total number of patients who suffered from neurological side effects at 24 weeks

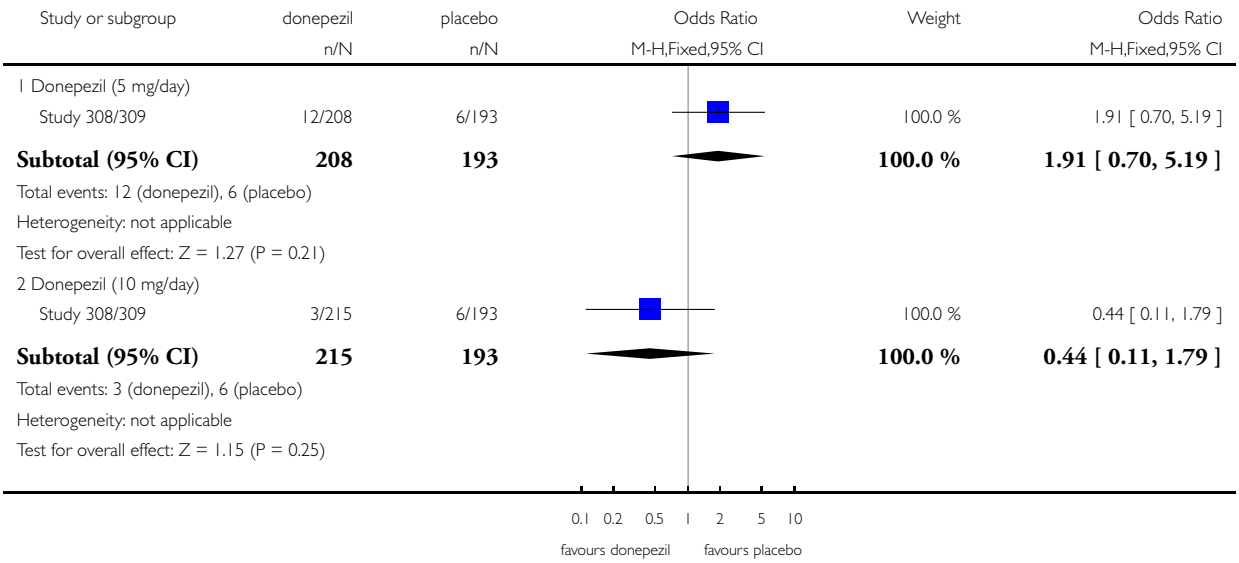


Analysis 1.27. Comparison 1 Donepezil vs placebo, Outcome 27 Total number of patients who suffered from back pain at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 27 Total number of patients who suffered from back pain at 24 weeks

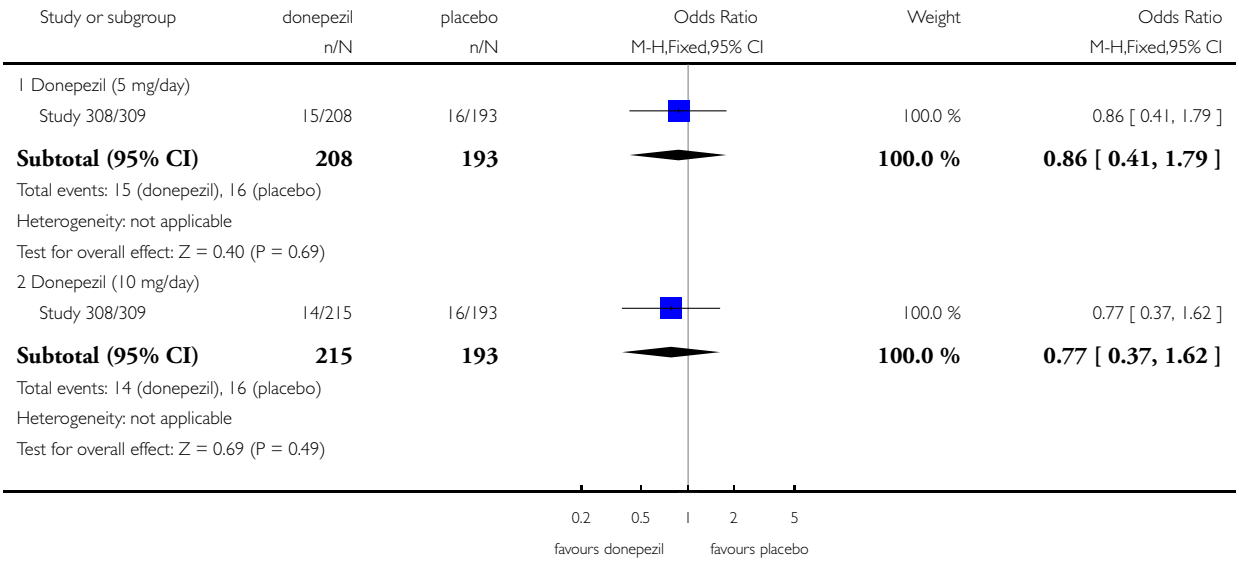


Analysis 1.28. Comparison 1 Donepezil vs placebo, Outcome 28 Total number of patients who suffered from headache at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 28 Total number of patients who suffered from headache at 24 weeks

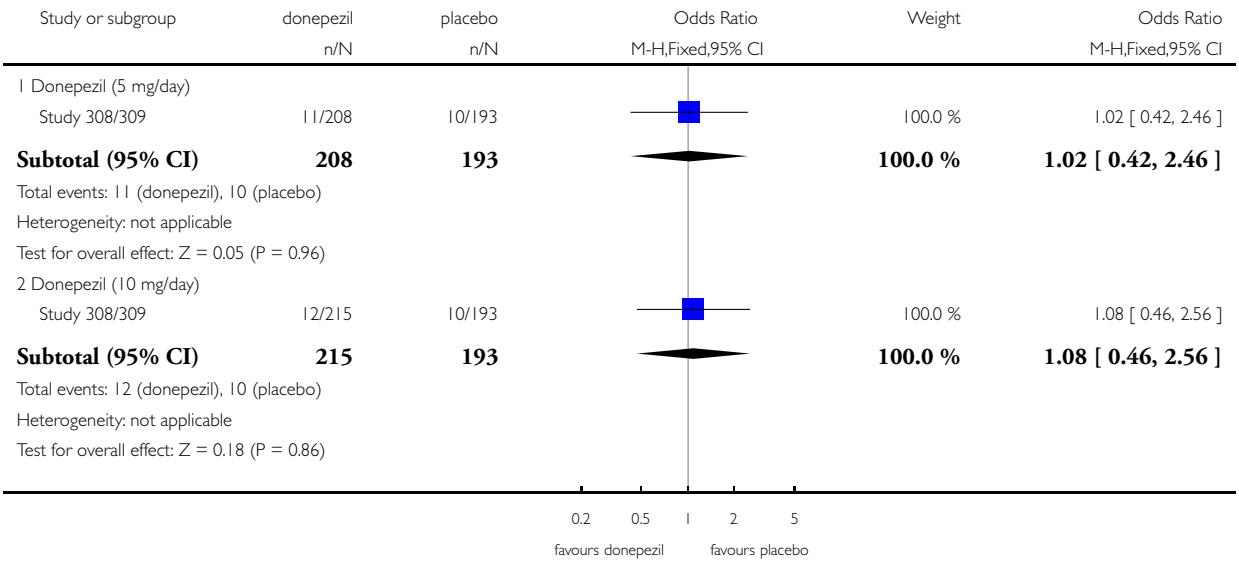


Analysis 1.29. Comparison 1 Donepezil vs placebo, Outcome 29 Total number of patients who suffered from agitation at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 29 Total number of patients who suffered from agitation at 24 weeks

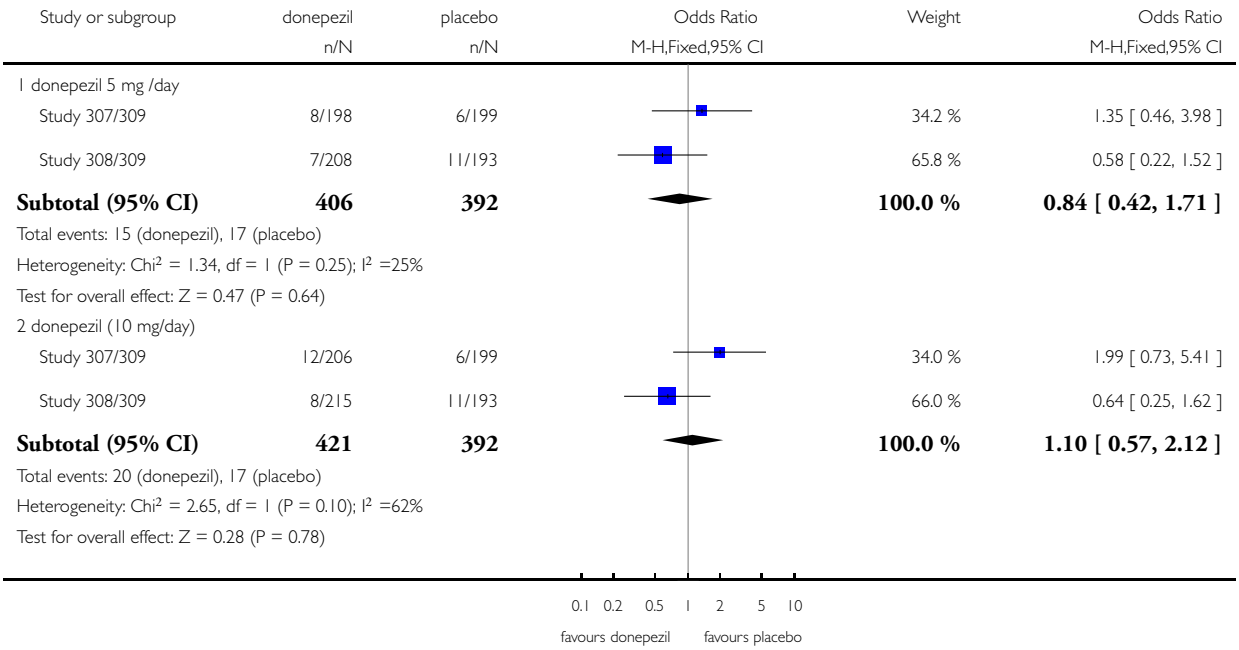


Analysis 1.30. Comparison 1 Donepezil vs placebo, Outcome 30 Total number of patients who suffered from stroke at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 30 Total number of patients who suffered from stroke at 24 weeks

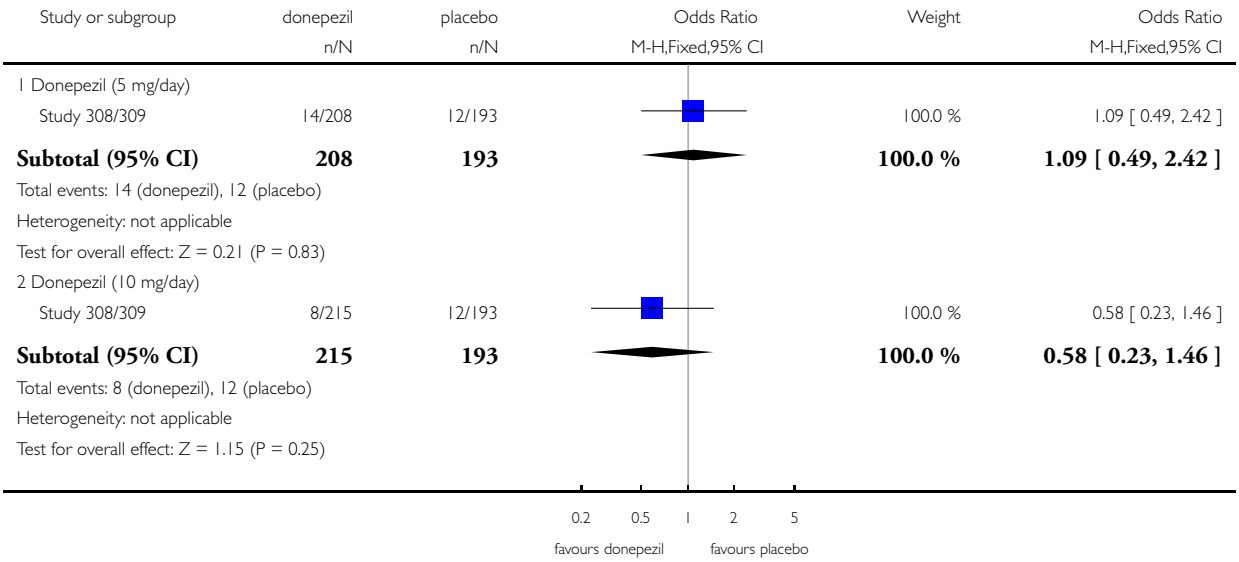


Analysis 1.31. Comparison 1 Donepezil vs placebo, Outcome 31 Total number of patients who suffered from confusion at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 31 Total number of patients who suffered from confusion at 24 weeks



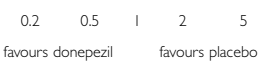
Analysis 1.32. Comparison 1 Donepezil vs placebo, Outcome 32 Total number of patients who suffered from depression at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 32 Total number of patients who suffered from depression at 24 weeks

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Donepezil (5 mg/day)					
Study 308/309	13/208	12/193		100.0 %	1.01 [0.45, 2.26]
Subtotal (95% CI)	**208**	**193**		**100.0 %**	**1.01 [0.45, 2.26]**
Total events: 13 (donepezil), 12 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					
2 Donepezil (10 mg/day)					
Study 308/309	12/215	12/193		100.0 %	0.89 [0.39, 2.03]
Subtotal (95% CI)	**215**	**193**		**100.0 %**	**0.89 [0.39, 2.03]**
Total events: 12 (donepezil), 12 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.27 (P = 0.79)					

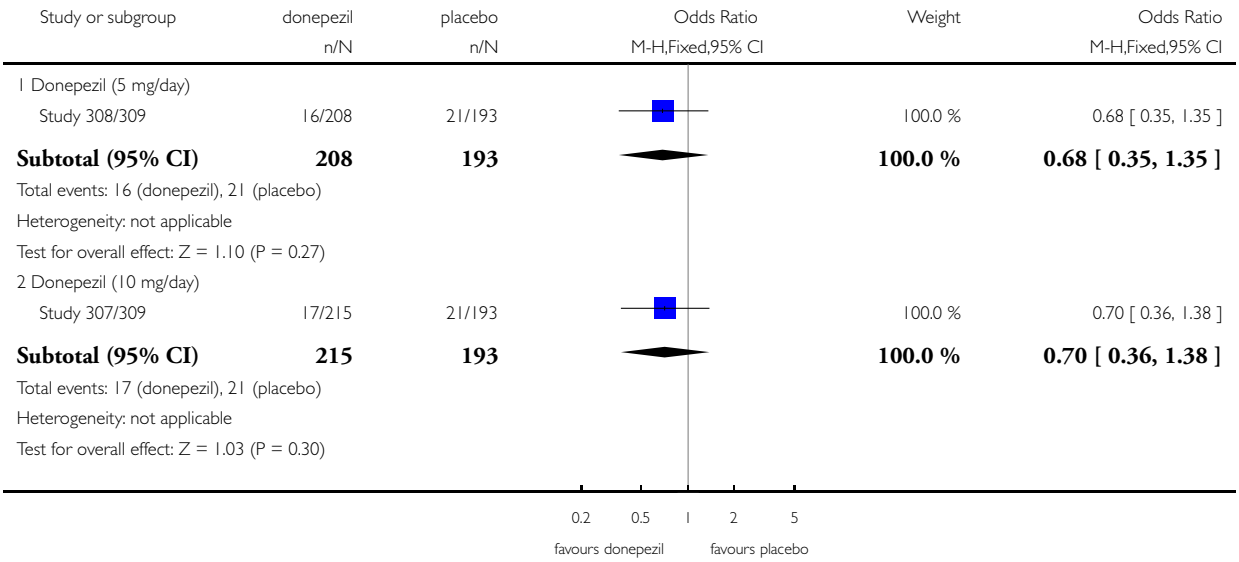


Analysis 1.33. Comparison 1 Donepezil vs placebo, Outcome 33 Total number of patients who suffered from dizziness at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 33 Total number of patients who suffered from dizziness at 24 weeks

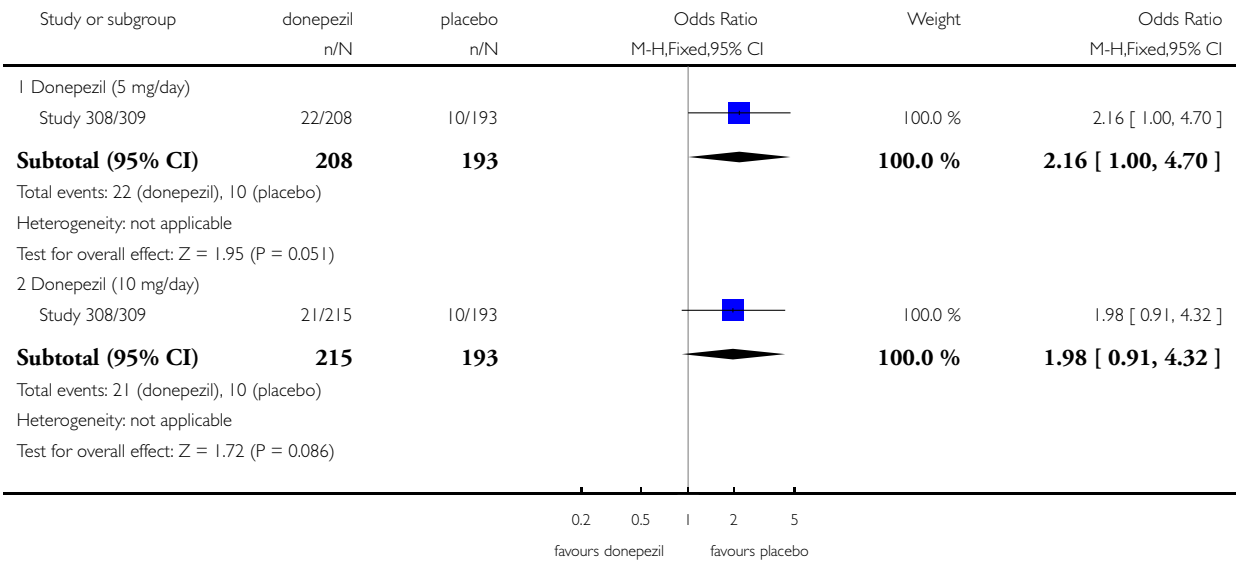


Analysis 1.34. Comparison 1 Donepezil vs placebo, Outcome 34 Total number of patients who suffered from insomnia at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 34 Total number of patients who suffered from insomnia at 24 weeks

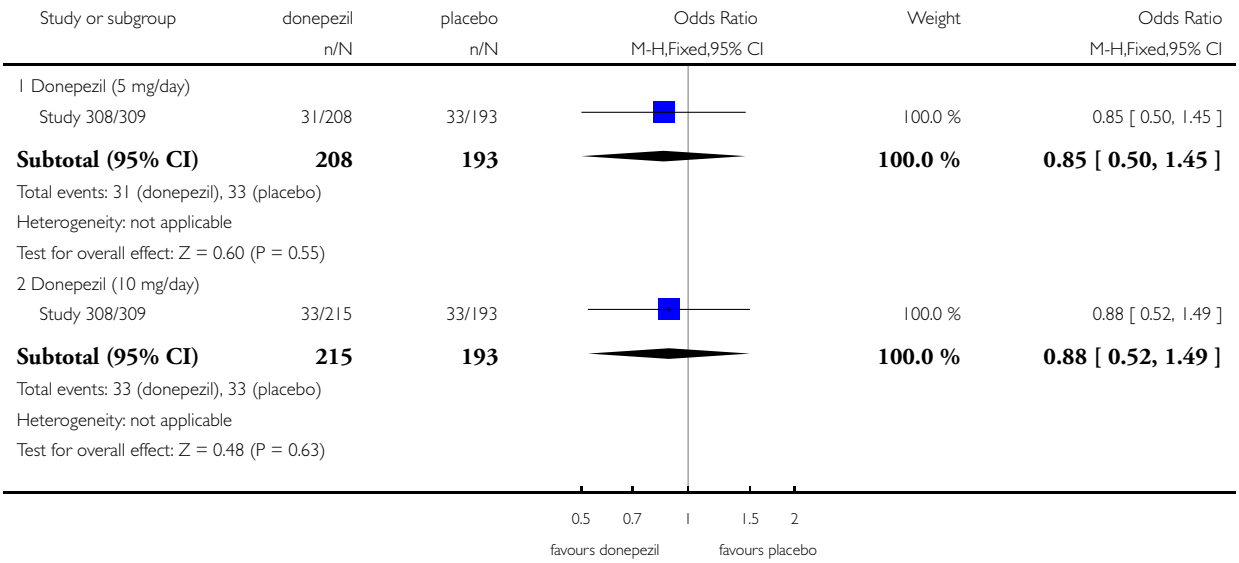


Analysis 1.35. Comparison 1 Donepezil vs placebo, Outcome 35 Total number of patients who suffered from at least one serious adverse event(SAE) at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 35 Total number of patients who suffered from at least one serious adverse event(SAE) at 24 weeks

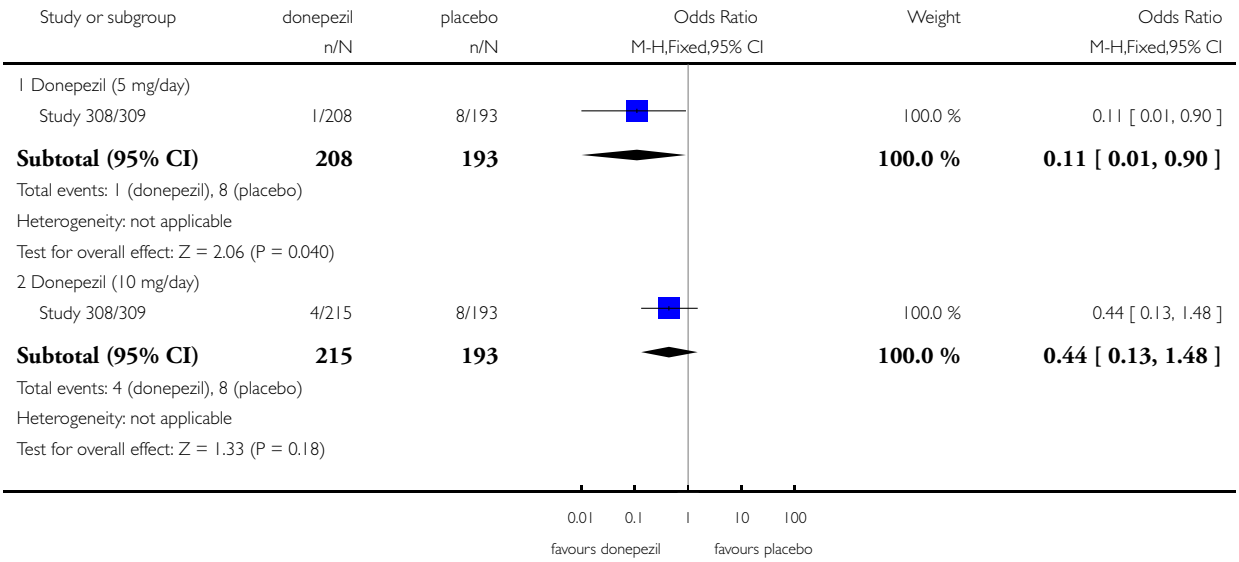


Analysis 1.36. Comparison 1 Donepezil vs placebo, Outcome 36 Total number of patients who suffered from skin carcinoma at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 36 Total number of patients who suffered from skin carcinoma at 24 weeks



Analysis 1.37. Comparison 1 Donepezil vs placebo, Outcome 37 Total number of patients who suffered from pathologic fracture at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 37 Total number of patients who suffered from pathologic fracture at 24 weeks

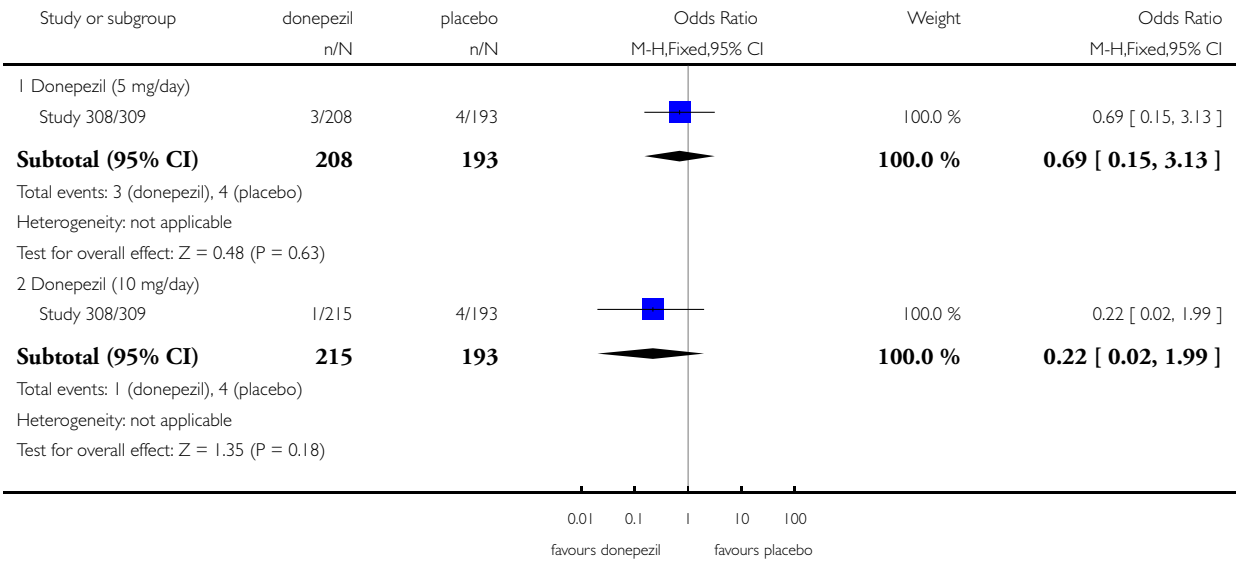
Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Donepezil (5 mg/day)					
Study 308/309	3/208	2/193		100.0 %	1.40 [0.23, 8.45]
Subtotal (95% CI)	**208**	**193**		**100.0 %**	**1.40 [0.23, 8.45]**
Total events: 3 (donepezil), 2 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
2 Donepezil (10 mg/day)					
Study 308/309	3/215	2/193		100.0 %	1.35 [0.22, 8.17]
Subtotal (95% CI)	**215**	**193**		**100.0 %**	**1.35 [0.22, 8.17]**
Total events: 3 (donepezil), 2 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					

Analysis 1.38. Comparison 1 Donepezil vs placebo, Outcome 38 Total number of patients who suffered from pneumonia at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 38 Total number of patients who suffered from pneumonia at 24 weeks

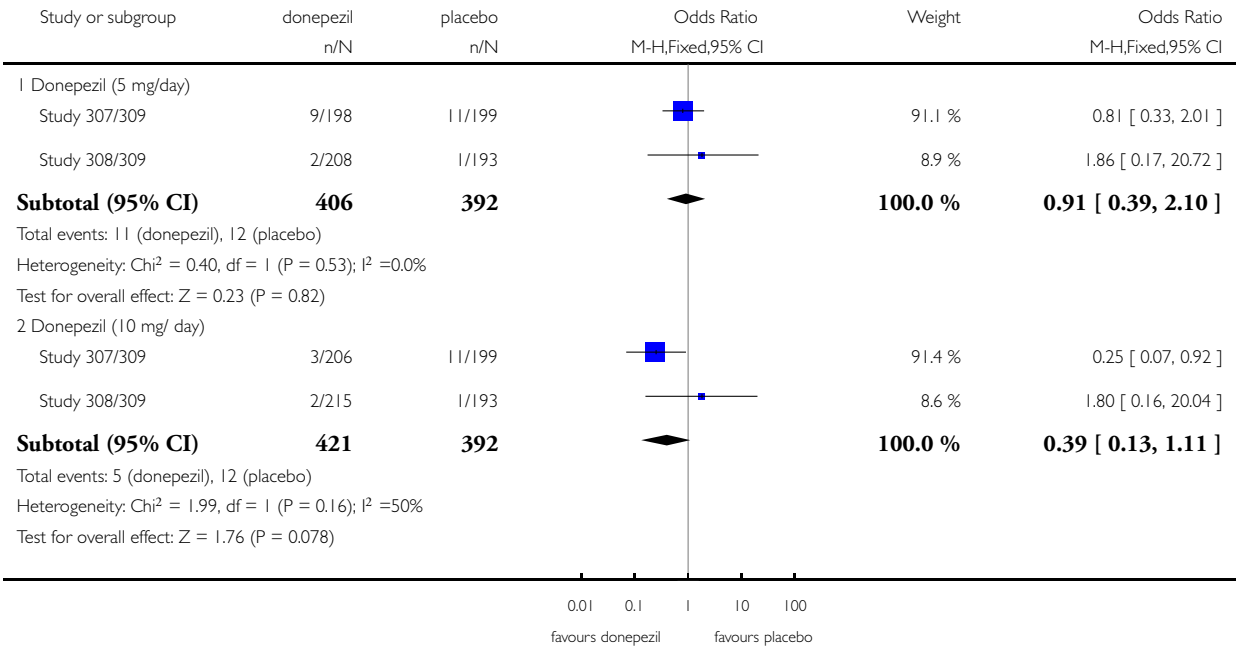


Analysis 1.39. Comparison 1 Donepezil vs placebo, Outcome 39 Total number of patients who suffered from TIA at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 39 Total number of patients who suffered from TIA at 24 weeks

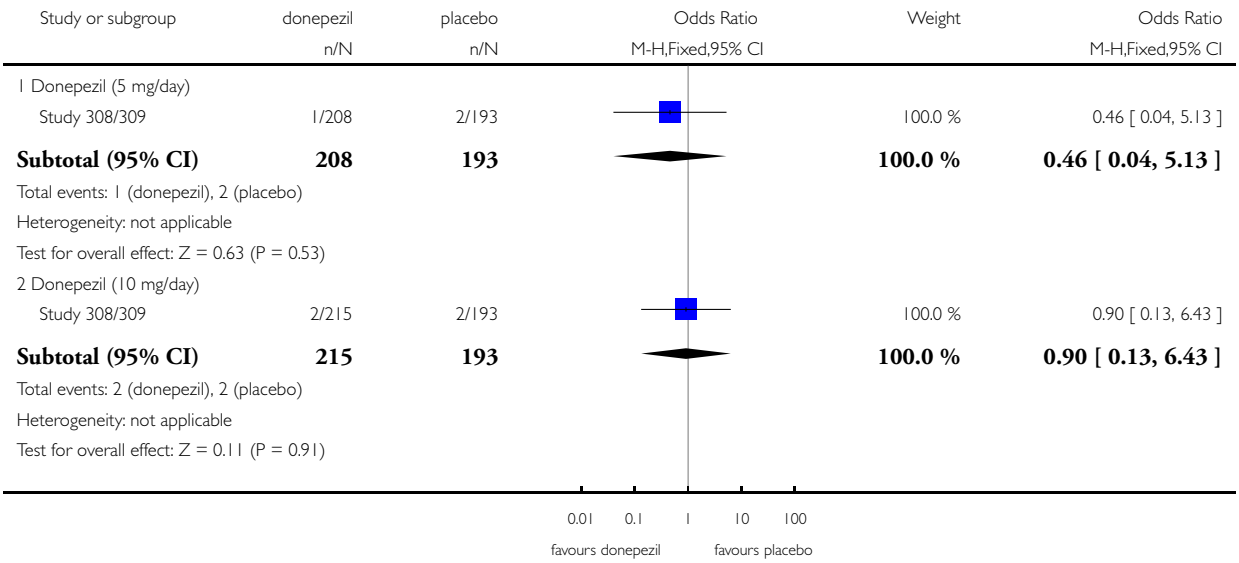


Analysis 1.40. Comparison 1 Donepezil vs placebo, Outcome 40 Total number of patients who suffered from angina at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 40 Total number of patients who suffered from angina at 24 weeks

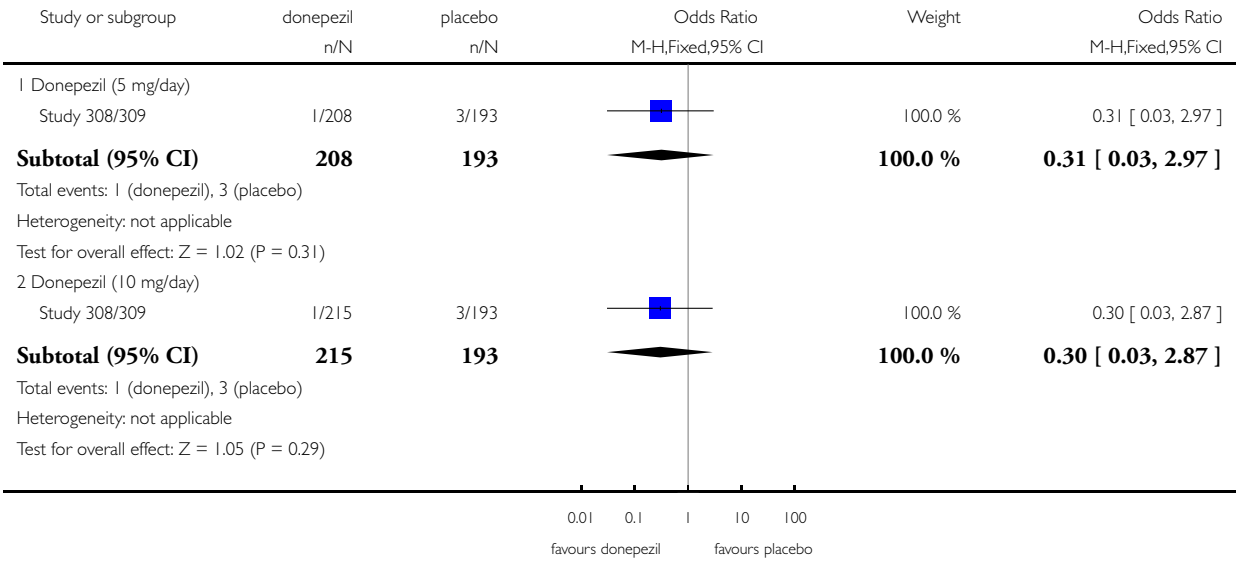


Analysis 1.41. Comparison 1 Donepezil vs placebo, Outcome 41 Total number of patients who suffered from a convulsion at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 41 Total number of patients who suffered from a convulsion at 24 weeks

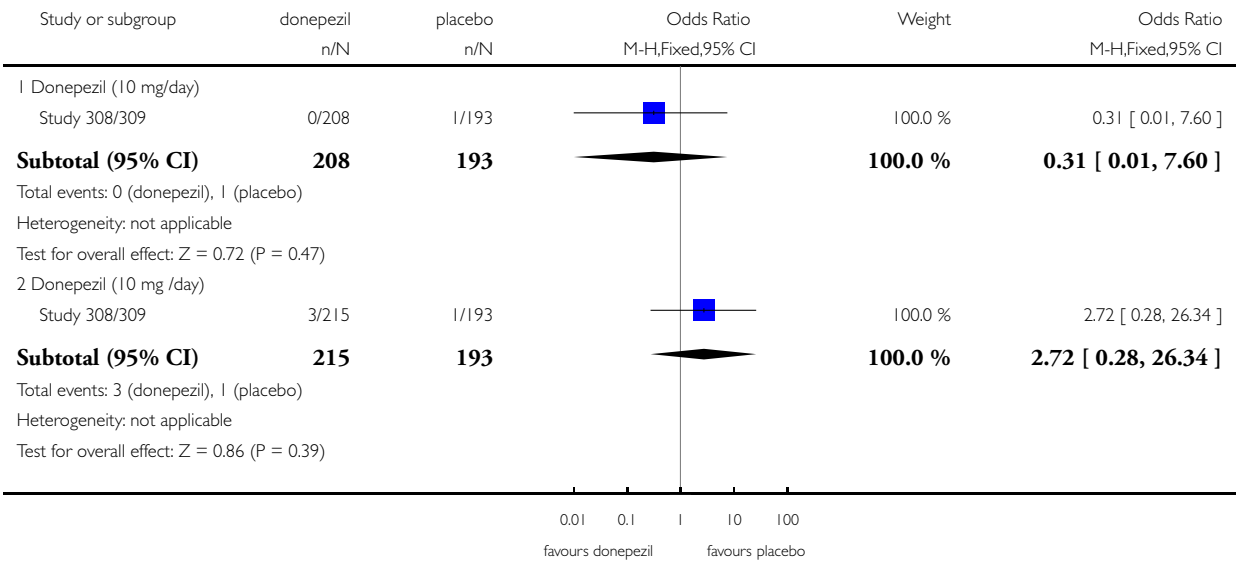


Analysis 1.42. Comparison 1 Donepezil vs placebo, Outcome 42 Total number of patients who suffered from colitis at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 42 Total number of patients who suffered from colitis at 24 weeks

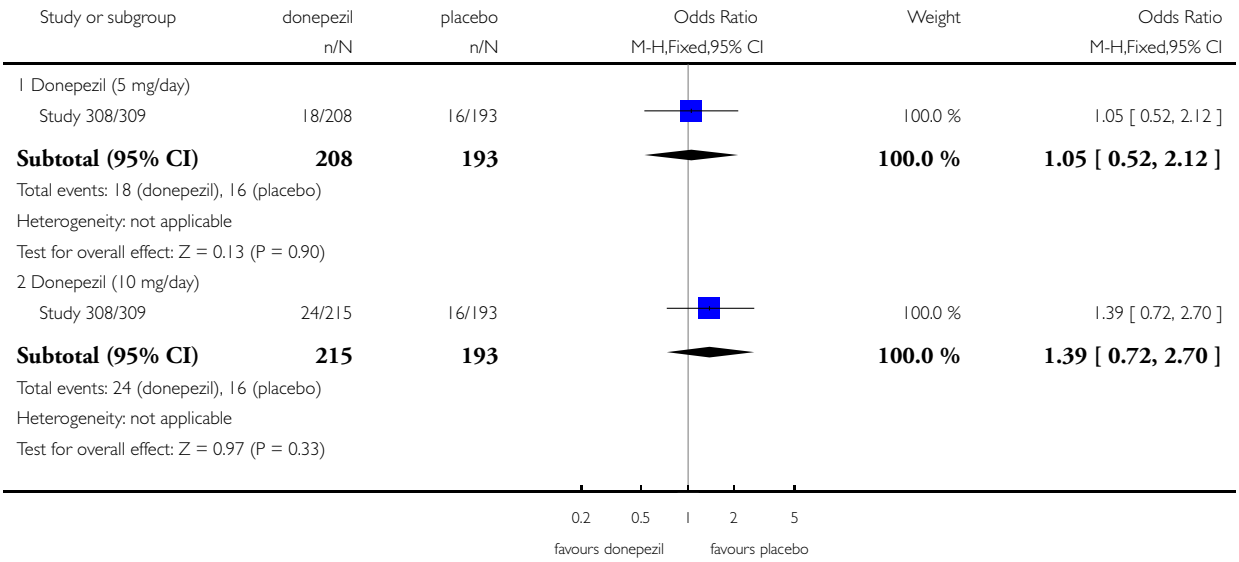


Analysis 1.43. Comparison 1 Donepezil vs placebo, Outcome 43 Total number of patients who suffered from asthenia at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 43 Total number of patients who suffered from asthenia at 24 weeks



Analysis 1.44. Comparison 1 Donepezil vs placebo, Outcome 44 Total numbers of patients who suffered from cramps and leg cramps at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 44 Total numbers of patients who suffered from cramps and leg cramps at 24 weeks

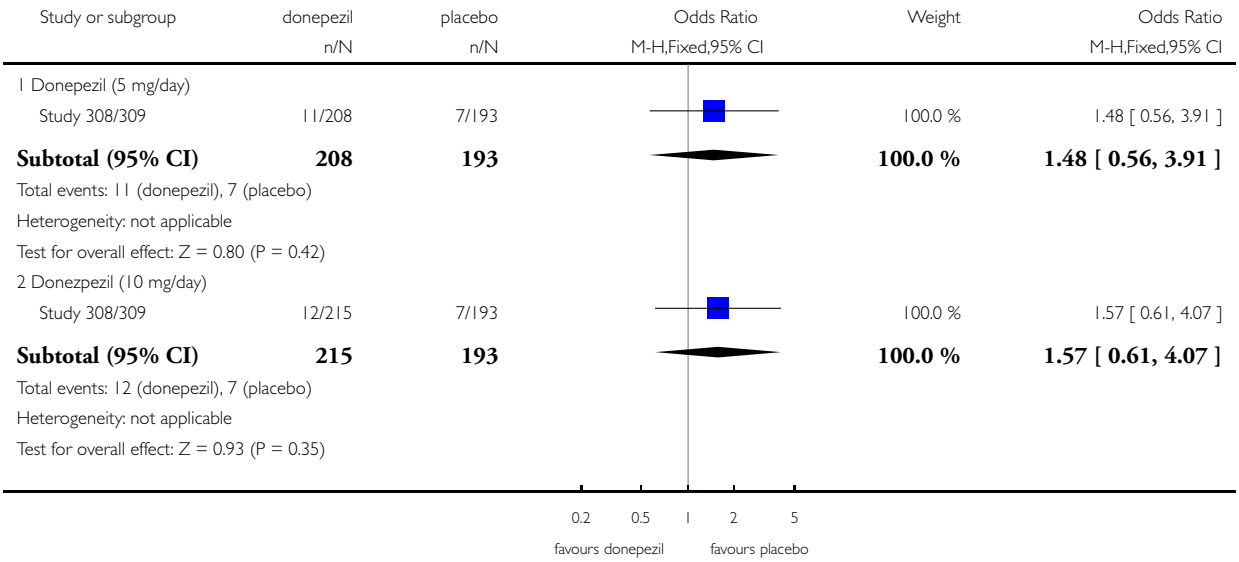
Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Donepezil (5 mg/day)					
Study 307/309	15/198	3/199		73.8 %	5.36 [1.53, 18.80]
Study 308/309	11/208	1/193		26.2 %	10.72 [1.37, 83.84]
Subtotal (95% CI)	**406**	**392**		**100.0 %**	**6.76 [2.33, 19.63]**
Total events: 26 (donepezil), 4 (placebo)					
Heterogeneity: Chi^2 = 0.33, df = 1 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 3.51 (P = 0.00044)					
2 Donepezil (10 mg/day)					
Study 307/309	28/206	3/199		72.7 %	10.28 [3.07, 34.39]
Study 308/309	13/215	1/193		27.3 %	12.36 [1.60, 95.36]
Subtotal (95% CI)	**421**	**392**		**100.0 %**	**10.84 [3.83, 30.70]**
Total events: 41 (donepezil), 4 (placebo)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 4.49 (P < 0.00001)					

Analysis 1.45. Comparison 1 Donepezil vs placebo, Outcome 45 Total number of patients who suffered from skin abrasion at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 45 Total number of patients who suffered from skin abrasion at 24 weeks

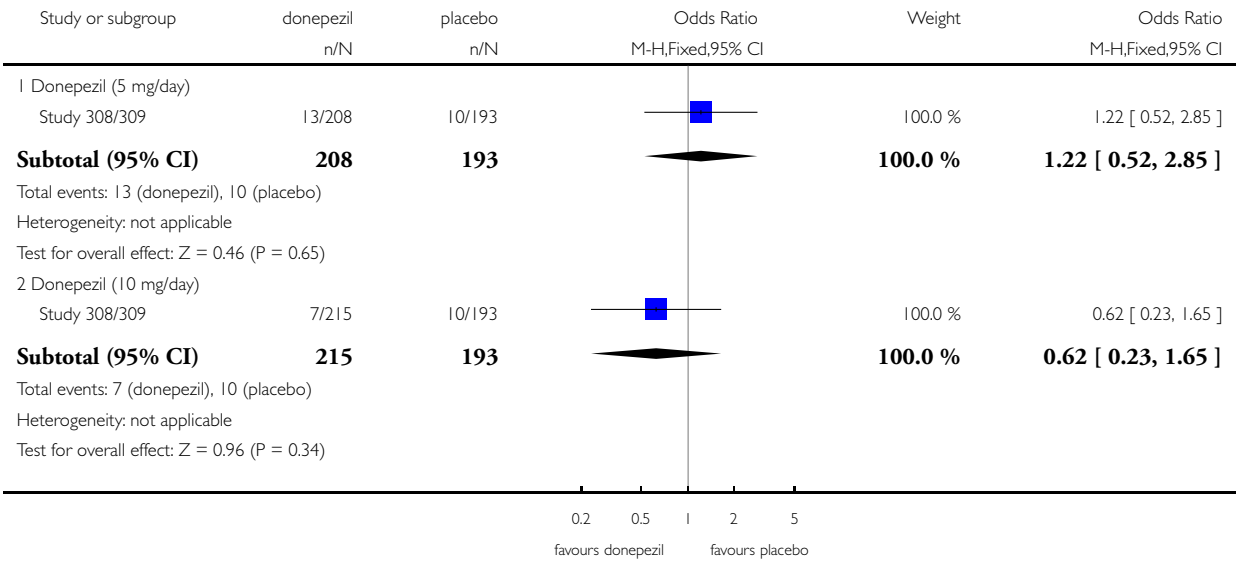


Analysis 1.46. Comparison 1 Donepezil vs placebo, Outcome 46 Total number of patients who suffered from peripheral oedema at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 46 Total number of patients who suffered from peripheral oedema at 24 weeks

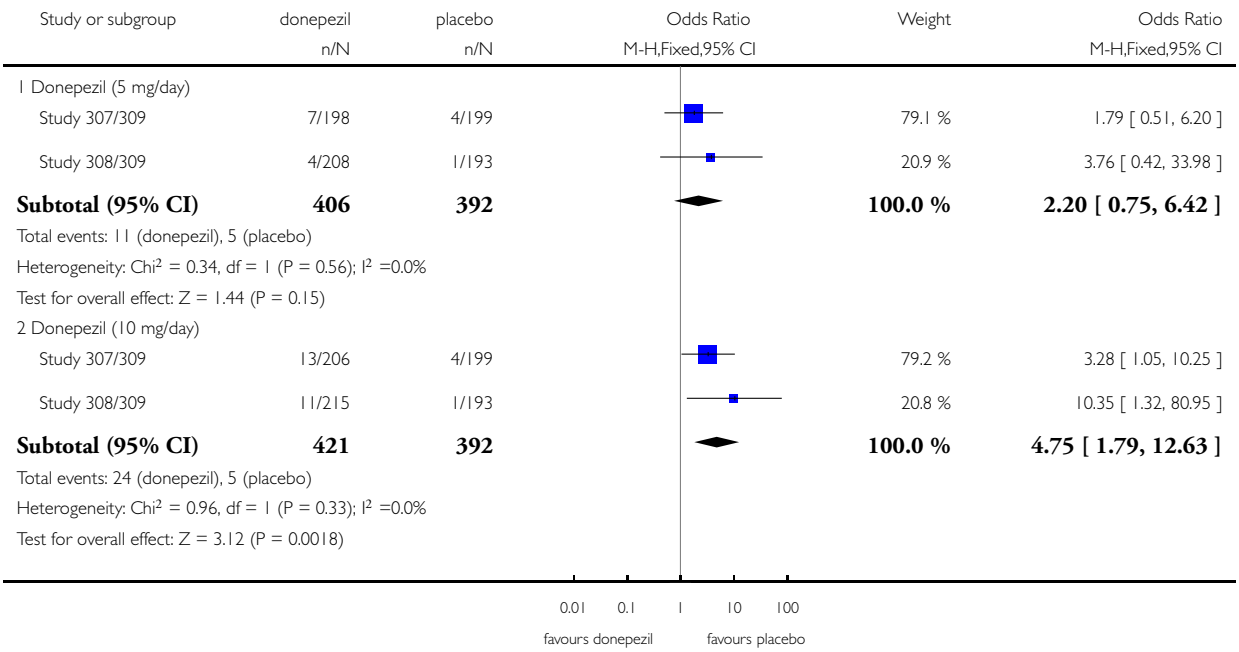


Analysis 1.47. Comparison 1 Donepezil vs placebo, Outcome 47 Total number of patients who suffered from abnormal dreams at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 47 Total number of patients who suffered from abnormal dreams at 24 weeks



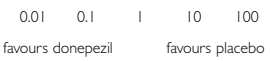
Analysis 1.48. Comparison 1 Donepezil vs placebo, Outcome 48 Total number of patients who suffered from rhinitis at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 48 Total number of patients who suffered from rhinitis at 24 weeks

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Donepezil (5 mg/day)					
Study 307/309	7/198	6/199		85.3 %	1.18 [0.39, 3.57]
Study 308/309	8/208	1/193		14.7 %	7.68 [0.95, 61.98]
Subtotal (95% CI)	**406**	**392**		**100.0 %**	**2.14 [0.86, 5.32]**
Total events: 15 (donepezil), 7 (placebo)					
Heterogeneity: Chi^2 = 2.55, df = 1 (P = 0.11); I^2 =61%					
Test for overall effect: Z = 1.63 (P = 0.10)					
2 Donepezil (10 mg/day)					
Study 307/309	14/206	6/199		85.0 %	2.35 [0.88, 6.23]
Study 308/309	11/215	1/193		15.0 %	10.35 [1.32, 80.95]
Subtotal (95% CI)	**421**	**392**		**100.0 %**	**3.54 [1.51, 8.33]**
Total events: 25 (donepezil), 7 (placebo)					
Heterogeneity: Chi^2 = 1.73, df = 1 (P = 0.19); I^2 =42%					
Test for overall effect: Z = 2.90 (P = 0.0037)					

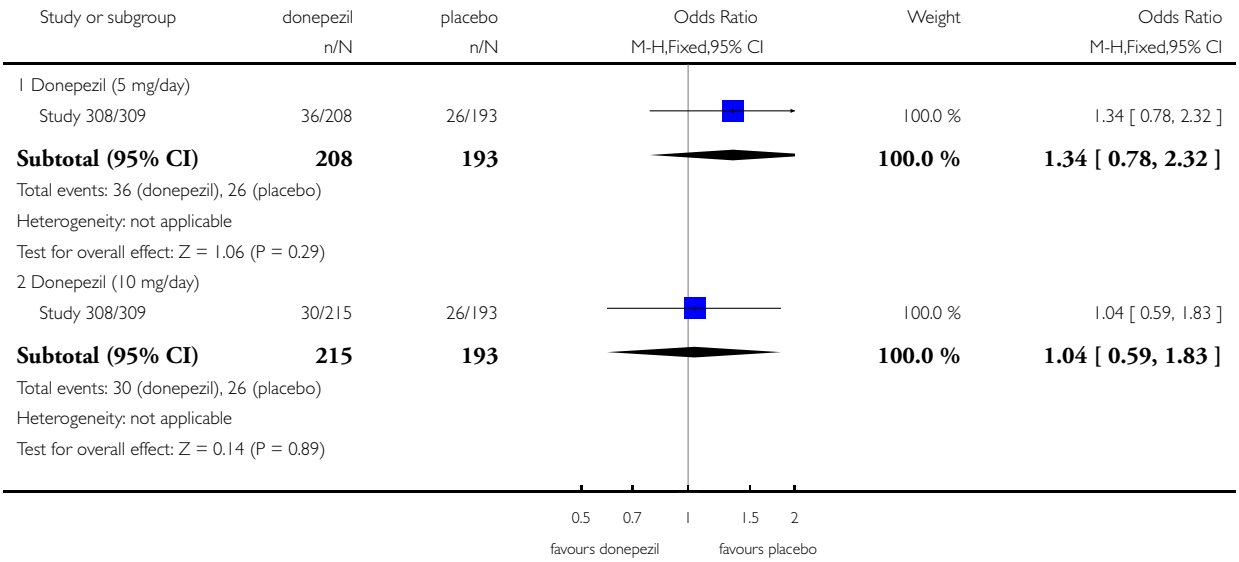


Analysis 1.49. Comparison 1 Donepezil vs placebo, Outcome 49 Total number of patients who suffered from infection at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 49 Total number of patients who suffered from infection at 24 weeks

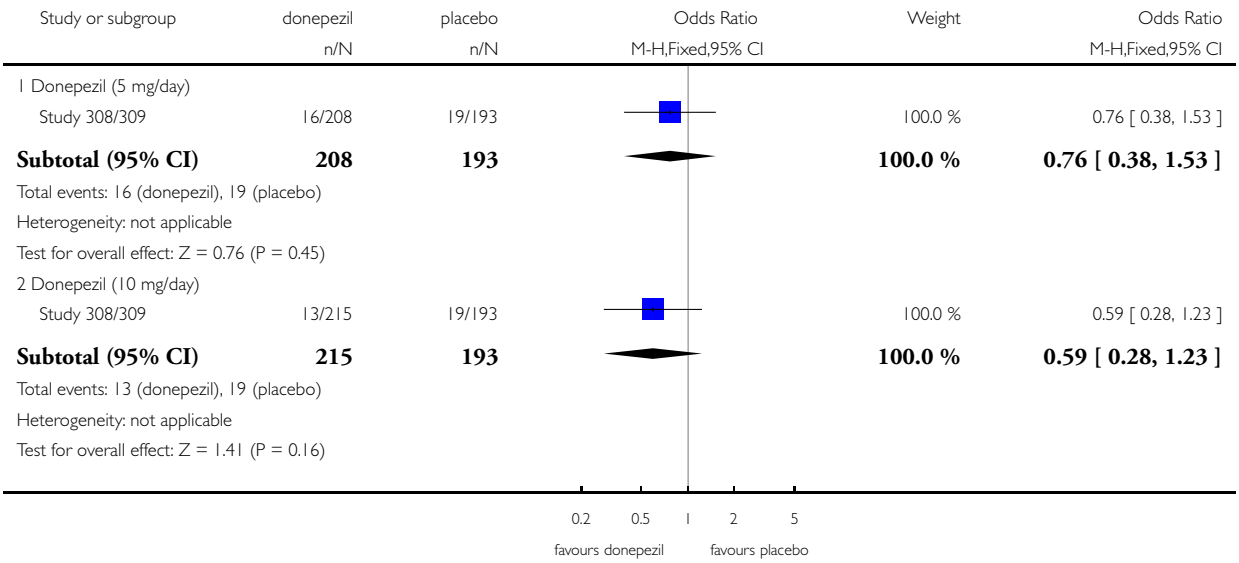


Analysis 1.50. Comparison 1 Donepezil vs placebo, Outcome 50 Total number of patients who suffered from pain at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 50 Total number of patients who suffered from pain at 24 weeks

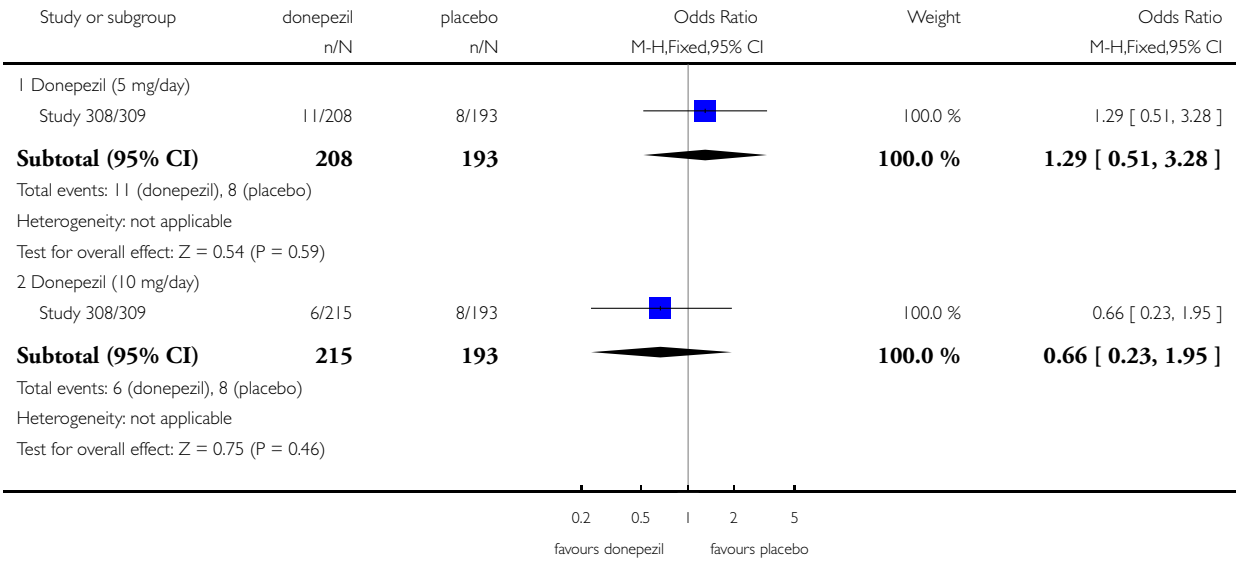


Analysis 1.51. Comparison 1 Donepezil vs placebo, Outcome 51 Total number of patients who suffered from skin rash at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 51 Total number of patients who suffered from skin rash at 24 weeks

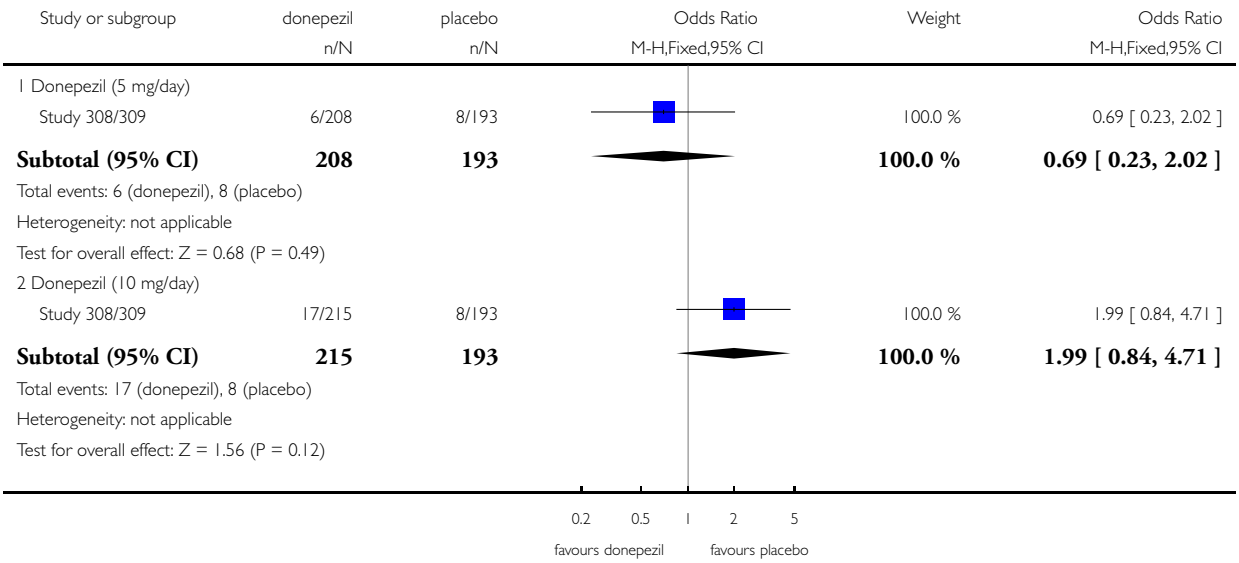


Analysis 1.52. Comparison 1 Donepezil vs placebo, Outcome 52 Total number of patients who suffered from urinary incontinence at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 52 Total number of patients who suffered from urinary incontinence at 24 weeks

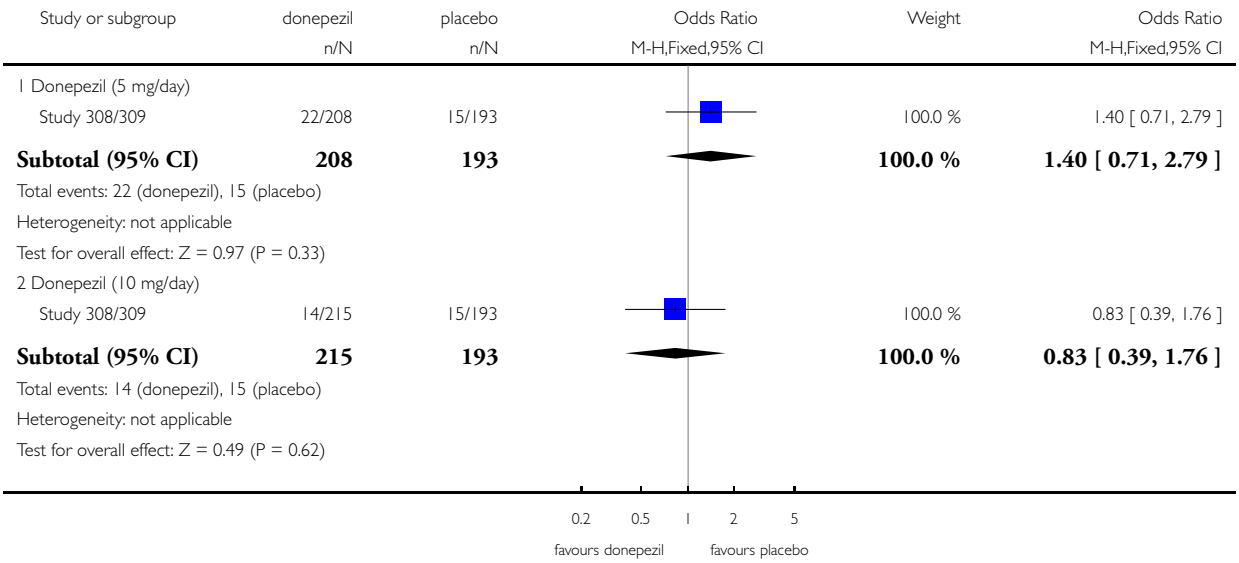


Analysis 1.53. Comparison 1 Donepezil vs placebo, Outcome 53 Total number of patients who suffered from urinary tract infection at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 53 Total number of patients who suffered from urinary tract infection at 24 weeks



Analysis 1.54. Comparison 1 Donepezil vs placebo, Outcome 54 Total number of patients who withdrew before the end point of the intervention.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 54 Total number of patients who withdrew before the end point of the intervention

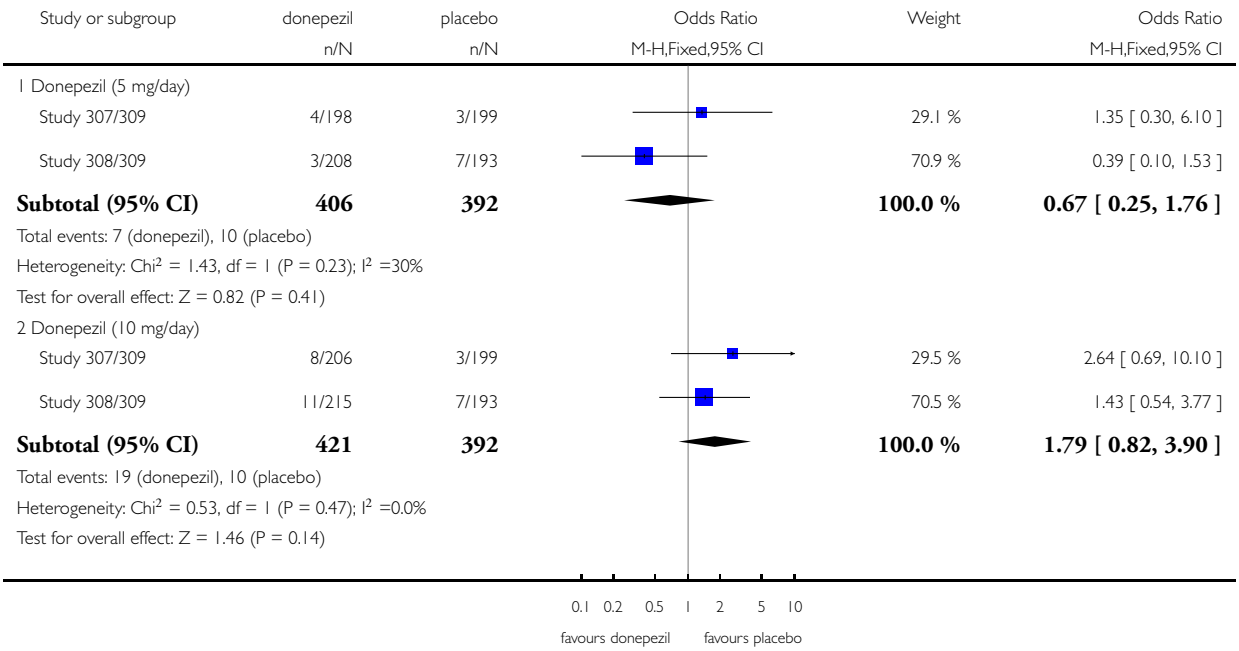
Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 donepezil(5 mg/day)					
Study 307/309	30/199	37/161		56.4 %	0.59 [0.35, 1.02]
Study 308/309	40/208	32/193		43.6 %	1.20 [0.72, 2.00]
Subtotal (95% CI)	**407**	**354**		**100.0 %**	**0.86 [0.59, 1.24]**
Total events: 70 (donepezil), 69 (placebo)					
Heterogeneity: Chi^2 = 3.43, df = 1 (P = 0.06); I^2 =71%					
Test for overall effect: Z = 0.82 (P = 0.41)					
2 Donepezil (10 mg/day)					
Study 307/309	58/206	30/199		46.3 %	2.21 [1.35, 3.61]
Study 308/309	53/215	32/193		53.7 %	1.65 [1.01, 2.69]
Subtotal (95% CI)	**421**	**392**		**100.0 %**	**1.91 [1.35, 2.70]**
Total events: 111 (donepezil), 62 (placebo)					
Heterogeneity: Chi^2 = 0.69, df = 1 (P = 0.41); I^2 =0.0%					
Test for overall effect: Z = 3.64 (P = 0.00027)					

Analysis 1.55. Comparison 1 Donepezil vs placebo, Outcome 55 Total number of patients who suffered from syncope at 24 weeks.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 55 Total number of patients who suffered from syncope at 24 weeks

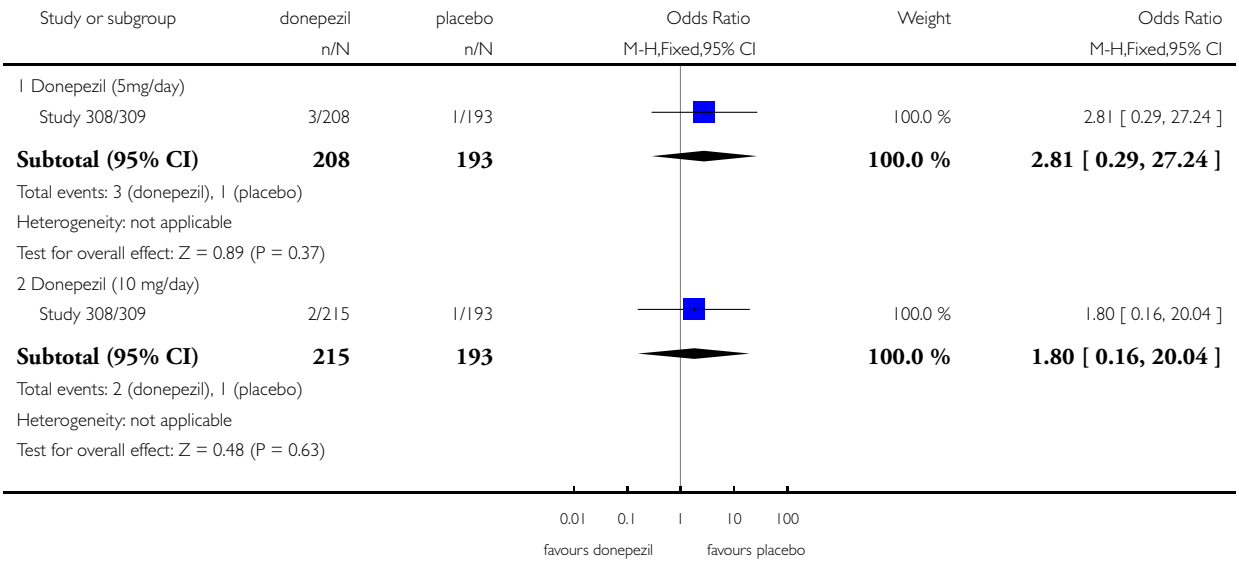


Analysis 1.56. Comparison 1 Donepezil vs placebo, Outcome 56 Total number of patients who died by endpoint.

Review: Donepezil for vascular cognitive impairment

Comparison: 1 Donepezil vs placebo

Outcome: 56 Total number of patients who died by endpoint



ADDITIONAL TABLES

Table 1. GLOSSARY

Expression	Defination
Cognitive dysfunction	A disturbance in the brain stages of processing information: input operation, storage, processing the data and output
Vascular cognitive impairment	The aetiology of cognitive dysfunction is due to vascular events such as stroke, embolism, bleeding, infarction
Atrial fibrillation	Abnormal heart rthym, common in advancing age, heart rate is between 350 to 600 per minute
Blood-brain barrier	A protective barrier formed by blood vessels and glio-cell, it prevents some substances from entering the brain
Amyloid	Glycoprotein deposites extracellulary in tissues in amyloidosis

Table 1. GLOSSARY (*Continued*)

Congophilic angiopathy	A condition of blood vessels characterised by deposition on the vessels wall of amyloid, that takes a Congo red stain
Arteriopathies	Any disease that affects the arteries
Neurotransmitters	Any substance that is released from the axon terminal of a presynaptic neuron and travels across the synaptic cleft to inhibit or excite the target cell
Transient Ischaemic Attack (TIA)	A temporary neurological symptom that starts suddenly and does not last more than 24 hours

Table 2. CONCOMITANT CARDIOVASCULAR RISK FACTORS

CARDIOVASCULAR RISKS	NUMBER OF PATIENTS %
Cardiovascular disease	1095 (89.8)
Hypertension	857 (70.3)
Smoking	752 (61.7)
Diabetes	219 (18.0)
Hypercholesterolemia	480 (39.4)
Angina and coronary artery disease	358 (29.4)
Peripheral vascular disease	271 (22.2)

Table 3. CONCOMITANT MEDICATIONS

MEDICATIONS	NUMBER OF PATIENTS %
Antithrombotic agents	1007 (82.6)
Aspirin	766 (62.8)
Agents acting on renin-angiotensin system	421 (34.5)
Diuretics	379 (31.1)
Antibacterials	379 (31.1)
Calcium channel blockers	375 (30.8)
Analgesics	362 (29.7)

Table 3. CONCOMITANT MEDICATIONS (*Continued*)

serum lipid reducing agents	340 (27.9)
Concomitant medications	1212 (99.4)

Table 4. BASELINE PSYCHOMETRIC SCORES OF STUDY 308

Psychometric Scale	Placebo	Donepezil 5 mg	Donepezil 10 mg
Hachinski score	9.6	9.4	9.5
ADAS-cog	18.8	20.8	20.6
MMSE	22.2	21.8	21.5
CDR-SB	5.6	6.0	6.1
ADFACS	15.1	15.7	16.1

Table 5. BASLINE PSYCHOMETRIC SCORES OF STUDY 307

Psychometric sale	Placebo	Donepezil 5 mg	Domepezil 10 mg
Hachinski score	10.0	9.8	10.0
ADAS-cog	20.1	21.2	20.9
MMSE	21.7	21.9	21.8
CDR-SB	6.1	6.4	6.1
ADAFACS	15.9	17.3	15.3

WHAT'S NEW

Last assessed as up-to-date: 6 June 2005.

Date	Event	Description
4 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 1, 2004

Date	Event	Description
17 August 2005	New search has been performed	August 2005 update: no further trials were eligible for inclusion in this review. The long term efficacy and safety of donepezil were investigated for 12-18 months in an-open label follow up trial (Study 309), whose results support the long-term efficacy of donepezil in vascular cognitive impairment patients
19 November 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

-RM: drafting review versions, all correspondence, in-excluding of studies, data-analysis, entering data in RevMan

-JB: commenting on drafts

-Contact editor: J Grimley Evans

-Consumer editor protocol: Clive Evers

-Consumer editor review: Mervyn Richardson

The review has been peer reviewed anonymously

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Division of Clinical Geratology, Nuffield Department of Clinical Medicine, University of Oxford, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Activities of Daily Living; Cognition Disorders [*drug therapy]; Dementia, Vascular [*drug therapy]; Indans [*therapeutic use]; Nootropic Agents [*therapeutic use]; Piperidines [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans