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Rivastigmine for Alzheimer's disease (Review)

Birks JS, Chong LY, Grimley Evans J

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TABLE OF CONTENTS

[Intervention Review]

Rivastigmine for Alzheimer's disease

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ABSTRACT

Background

Alzheimer's disease is the commonest cause of dementia affecting older people. One of the therapeutic strategies aimed at ameliorating the clinical manifestations of Alzheimer's disease is to enhance cholinergic neurotransmission in the brain by the use of cholinesterase inhibitors to delay the breakdown of acetylcholine released into synaptic clefts. Tacrine, the first of the cholinesterase inhibitors to undergo extensive trials for this purpose, was associated with significant adverse effects including hepatotoxicity. Other cholinesterase inhibitors, including rivastigmine, with superior properties in terms of specificity of action and lower risk of adverse effects have since been introduced. Rivastigmine has received approval for use in 60 countries including all member states of the European Union and the USA.

Objectives

To determine the clinical efficacy and safety of rivastigmine for patients with dementia of Alzheimer's type.

Search methods

We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group Specialized Register, on 2 March 2015 using the terms: Rivastigmine OR exelon OR ENA OR "SDZ ENA 713". ALOIS contains records of clinical trials identified from monthly searches of a number of major healthcare databases (Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS), numerous trial registries and grey literature sources.

Selection criteria

We included all unconfounded, double-blind, randomised, controlled trials in which treatment with rivastigmine was administered to patients with dementia of the Alzheimer's type for 12 weeks or more and its effects compared with those of placebo in a parallel group of patients, or where two formulations of rivastigmine were compared.

Data collection and analysis

One review author (JSB) applied the study selection criteria, assessed the quality of studies and extracted data.

Main results

A total of 13 trials met the inclusion criteria of the review. The trials had a duration of between 12 and 52 weeks. The older trials tested a capsule form with a dose of up to 12 mg/day. Trials reported since 2007 have tested continuous dose transdermal patch formulations delivering 4.6, 9.5 and 17.7 mg/day.

Our main analysis compared the safety and efficacy of rivastigmine 6 to 12 mg/day orally or 9.5 mg/day transdermally with placebo.

Seven trials contributed data from 3450 patients to this analysis. Data from another two studies were not included because of a lack of information and methodological concerns. All the included trials were multicentre trials and recruited patients with mild to moderate Alzheimer's disease with a mean age of about 75 years. All had low risk of bias for randomisation and allocation but the risk of bias due to attrition was unclear in four studies, low in one study and high in two studies.

After 26 weeks of treatment rivastigmine compared to placebo was associated with better outcomes for cognitive function measured with the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score (mean difference (MD) -1.79; 95% confidence interval (CI) -2.21 to -1.37, n = 3232, 6 studies) and the Mini-Mental State Examination (MMSE) score (MD 0.74; 95% CI 0.52 to 0.97, n = 3205, 6 studies), activities of daily living (SMD 0.20; 95% CI 0.13 to 0.27, n = 3230, 6 studies) and clinician rated global impression of changes, with a smaller proportion of patients treated with rivastigmine experiencing no change or a deterioration (OR 0.68; 95% CI 0.58 to 0.80, n = 3338, 7 studies).

Three studies reported behavioural change, and there were no differences compared to placebo (standardised mean difference (SMD) -0.04; 95% CI -0.14 to 0.06, n = 1529, 3 studies). Only one study measured the impact on caregivers using the Neuropsychiatric Inventory-Caregiver Distress (NPI-D) scale and this found no difference between the groups (MD 0.10; 95% CI -0.91 to 1.11, n = 529, 1 study). Overall, participants who received rivastigmine were about twice as likely to withdraw from the trials (odds ratio (OR) 2.01, 95% CI 1.71 to 2.37, n = 3569, 7 studies) or to experience an adverse event during the trials (OR 2.16, 95% CI 1.82 to 2.57, n = 3587, 7 studies).

Authors' conclusions

Rivastigmine (6 to 12 mg daily orally or 9.5 mg daily transdermally) appears to be beneficial for people with mild to moderate Alzheimer's disease. In comparisons with placebo, better outcomes were observed for rate of decline of cognitive function and activities of daily living, although the effects were small and of uncertain clinical importance. There was also a benefit from rivastigmine on the outcome of clinician's global assessment. There were no differences between the rivastigmine group and placebo group in behavioural change or impact on carers. At these doses the transdermal patch may have fewer side effects than the capsules but has comparable efficacy. The quality of evidence is only moderate for all of the outcomes reviewed because of a risk of bias due to dropouts. All the studies with usable data were industry funded or sponsored. This review has not examined economic data.

PLAIN LANGUAGE SUMMARY

Rivastigmine for people with Alzheimer's disease

Review question

We reviewed evidence comparing the effectiveness and safety of rivastigmine with placebo in people with Alzheimer's disease.

Background

Alzheimer's disease is the commonest cause of dementia affecting older people. As the disease progresses, people lose the ability to remember, communicate, think clearly and perform the usual daily activities. Their behaviour or personality may also change. In severe Alzheimer's disease, the patients lose the ability to care for themselves and require full time care.

Currently, there is no cure available for Alzheimer's disease, but a few pharmacological interventions are available to alleviate symptoms.

The symptoms are caused by the loss of a type of nerve cell in the brain called cholinergic neurons. Rivastigmine, an acetylcholinesterase inhibitor, works by increasing the levels of a brain chemical called acetylcholine which allows the nerve cells to communicate. This may improve the symptoms of dementia. Rivastigmine can be taken orally, either as capsules or a liquid, or by applying a patch on the skin. Its effectiveness in improving the symptoms of Alzheimer's disease and safety were evaluated in this review.

Study characteristics

This review included double-blinded randomised controlled trials, and the evidence was searched for up to March 2015 using the standard Cochrane methods. The review included studies conducted for at least 12 weeks that compared the safety and effectiveness of rivastigmine compared with placebo. Thirteen studies that met these criteria were found. Most of these studies involved people with mild to moderate Alzheimer's disease with an average age of around 75 years.

Key results

Results from seven trials showed that patients on rivastigmine (6 to 12 mg/day by mouth, or 9.5 mg/day by skin patch) were better for three outcomes than those on placebo, after six months of treatment. The differences were quite small for cognitive function (2 points, using the ADAS-Cog which has a range of 70 points) and activities of daily living (standardised mean difference (SMD) of 0.20, which is considered a small effect). Patients on rivastigmine were more likely to show overall improvement compared with those on placebo (odds ratio of 1.47, 95% confidence interval (CI) of 1.25 to 1.72) . However, there was no difference for behavioural changes (reported by three trials) or impact on carers (reported by one trial). Patients on rivastigmine were also about twice as likely to experience adverse events, although this risk

might have been slightly less for patients using patches compared with capsules. It was possible that certain types of adverse events were less in people using patches than taking capsules (nausea, vomiting, weight loss, dizziness).

In summary, rivastigmine may be of benefit to people with Alzheimer's disease. It is possible that the using a patch is associated with reduced side effects compared to using oral capsules.

Quality of evidence

The quality of the evidence for most of the outcomes reviewed was moderate. The main factors affecting our confidence in the results included relatively high number of patients dropping out in some of the trials (the rates of dropout in the rivastigmine arms were higher). There were also concerns about the applicability of the evidence for the long term treatment of Alzheimer's disease since data from double-blinded randomised controlled trials were only available for up to 12 months. All the data included in the main analysis of this review came from studies either sponsored or funded by the drug manufacturer (Novartis Pharma).

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Rivastigmine compared to placebo for Alzheimer's disease

Rivastigmine (capsules 6 to 12 mg/day in two divided doses or 10 cm^2 (9.8 mg/day) patch) compared to placebo for Alzheimer's disease

Patient or population: patients with Alzheimer's disease, mild to moderate
Settings: multicentre, mostly in Europe or United States
Intervention: rivastigmine (capsules 6 to 12 mg/day in 2 divided doses or 10 cm^2 patch) for 24 to 26 weeks
Comparison: placebo for 24 to 26 weeks

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Rivastigmine (capsules 6 to 12 mg/day b.i.d. or 10 cm^2 patch)				
Cognitive function (change from baseline at 26 weeks using ADAS-Cog)		The mean score in the rivastigmine group was **1.79 lower** (2.21 to 1.37 lower)		3232 (6 studies)	⊕⊕⊕⊖ **moderate**[1,2,]	ADAS-Cog score has a maximum of 70 points, the lower score of the rivastigmine group indicates greater improvement
Cognitive function (change from baseline at 26 weeks using MMSE)		The mean score in the rivastigmine group was **0.74 higher** (0.52 to 0.97 higher)		3205 (6 studies)	⊕⊕⊕⊖ **moderate**[1,2]	MMSE has a maximum score of 30 points, a lower score indicates greater impairment. treatment effect was in favour of rivastigmine

Activities of daily living (change from baseline at 26 weeks measured using various scales)		The mean score in the rivastigmine group was **0.2 standard deviations higher** (0.13 to 0.27 higher)		3230 (6 studies)	⊕⊕⊕⊖ **moderate**[1]	SMD 0.2 (0.13 to 0.27) A SMD of 0.2 is considered a small effect size. Treatment effect in favour of rivastigmine
Physician rated global impression tests (no change or worse compared with baseline, measured using Global Impression of Change at 26 weeks)	**810 per 1000**	**744 per 1000** (712 to 773)	**OR 0.68** (0.58 to 0.8)	3338 (7 studies)	⊕⊕⊕⊖ **moderate**[1]	Treatment effect was in favour of rivastigmine
Behavioural symptoms (change from baseline at 26 weeks measured using various scales)		The mean score in the rivastigmine group was **0.04 standard deviations lower** (0.14 lower to 0.06 higher)		1529 (3 studies)	⊕⊕⊕⊖ **moderate**[1,3]	SMD -0.04 (-0.14 to 0.06) A SMD of 0.2 is considered a small effect size. The size of this SMD and its small confidence interval suggests that there is no difference between the two groups
Acceptability of treatment (as measured by withdrawals from trials before end of treatment at 26 weeks)	**149 per 1000**	**260 per 1000** (230 to 293)	**OR 2.01** (1.71, 2.37)	3569 (7 studies)	⊕⊕⊕⊖ **moderate**[1]	Withdrawals significantly more frequent in rivastigmine group compared with

						placebo group
Incidence of adverse events (at least one adverse event by 26 weeks)	**761 per 1000**	**870 per 1000** (850 to 888)	**OR 2.14** (1.80 to 2.53)	3587 (7 studies)	⊕⊕⊕⊖ **moderate**[1]	Adverse events significantly more frequent in rivastigmine group compared with placebo group
Quality of life of patients or carers (measured using NPI-D carer distress scale (change from baseline at 24 weeks)		The mean score in the rivastigmine group was **0.1 higher** (0.91 lower to 1.11 higher)		529 (1 study)	⊕⊕⊕⊖ **moderate**[1]	The size of this MD and its small confidence interval suggests that there is no difference between the two groups

*The **assumed risk** used the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

[1] Confidence in estimate of effect lowered due to relatively high dropout rates across studies, which are higher in the treatment group. The ITT analysis in these studies used LOCF (last observed carried forward) imputations. In addition, results are available up to only 26 weeks, longer term data would be more applicable.
[2] There was high heterogeneity the ADAS-Cog outcome due to B352, which had high dropout rates and showed a difference of 3.8 points, compared to 1.2 to 1.6 points for the other studies. However, evidence not further downgraded; removal of this study from the analysis will only result in a small change of estimate by about 0.35 points.
[3] Three studies (IDEAL; Lopez-Pousa 2005; Nakamura 2011) reported a scale measuring behavioural disturbance.
[4] The protocol for most studies had some measures related to quality of life or impact on carers, but only one study reported this (IDEAL).

BACKGROUND

Description of the condition

Alzheimer's disease (AD), alone or in combination with other brain conditions, is the commonest cause of dementia affecting older people. It is associated with the loss of cholinergic neurons in parts of the brain subserving aspects of memory. As the disease progresses, people lose the ability to remember, communicate, think clearly and perform their usual daily activities. Their behaviour or personality may also change. In severe AD, people lose the ability to care for themselves and require full time care.

Currently there is no cure available for AD, but a few pharmacological interventions are available to alleviate symptoms.

Description of the intervention

Acetylcholinesterase inhibitors, such as rivastigmine, delay the breakdown of acetylcholine released into synaptic clefts and may enhance cholinergic neurotransmission.

Tacrine, the first of the acetylcholinesterase inhibitors to undergo extensive trials for this purpose, was associated with significant disadvantages, including low oral bioavailability and metabolism involving hepatic microsomal enzymes with a consequent risk of interactions with other drugs. Tacrine was also associated with adverse effects including hepatotoxicity. Several other acetylcholinesterase inhibitors, including rivastigmine, galantamine, and donepezil, have now been introduced. They are believed to have superior properties in terms of specificity of action and low incidence of adverse effects.

Rivastigmine is a 'pseudo-irreversible' inhibitor of acetyl and butyrylcholinesterases with a phenylcarbamate structure, the metabolism of which is almost totally independent of the hepatic cytochrome P450 system. After binding to cholinesterase, the carbamate portion of rivastigmine is slowly hydrolysed, cleaved, conjugated to a sulphate and excreted. Rivastigmine has an oral bioavailability of 0.355 and low (40%) binding to plasma proteins. Its elimination half-life is around two hours. Its disposition is essentially unaltered in patients with renal or hepatic impairment (Jann 2000) and the risk of interactions with other drugs is low (Grossberg 2000). This is of particular relevance for elderly patients with AD, some of whom may also need medications for other conditions. The drug is selective both to the central nervous system (CNS) and within it. In studies in human volunteers the inhibition of central acetylcholinesterase was substantially greater than the inhibition of peripheral acetylcholinesterase or butyrylcholinesterase (Kennedy 1999). Evidence from animal studies suggests that rivastigmine is a more potent inhibitor of acetylcholinesterase in the cortex and hippocampus, the brain regions most affected by AD (Polinsky 1998). Rivastigmine also preferentially inhibits the G1 enzymatic form of acetylcholinesterase, which predominates in the brains of patients with AD (Polinsky 1998). Rivastigmine is long-acting and readily penetrates the CNS after parenteral or oral administration. The duration of cholinesterase inhibition by rivastigmine is approximately 10 hours.

Rivastigmine can be administered orally as capsules or liquid or from a transdermal patch, which has been developed more recently. Based on pharmacokinetic principles, the transdermal patch form was postulated to have advantages over the oral form. Adherence was expected to be improved by once daily dosing. Tolerance was also expected to be improved as the patch delivers a more steady concentration of rivastigmine to the body and has a lower equivalent dose to the oral form (9.5 mg as a transdermal patch is equivalent to 12 mg daily in the oral form).

Why it is important to do this review

Large multicentre trials have been completed in the USA, Canada, Europe, Australia and South Africa. Rivastigmine has received approval for use in 60 countries including all the member states of the European Union and in the USA, where it received approval from the Food and Drugs Administration (FDA) in April 2000. It is important to assess the safety and efficacy of this intervention in a systematic review.

OBJECTIVES

1. To determine the clinical efficacy and safety of rivastigmine for patients with dementia of Alzheimer's type
2. To compare the efficacy and safety of the oral and transdermal formulations of rivastigmine

METHODS

Criteria for considering studies for this review

Types of studies

We included double-blind, randomised controlled trials in which rivastigmine was administered for 12 weeks or longer and compared with placebo; or rivastigmine patches were compared with rivastigmine capsules. Trials in which the allocation to treatment was not randomised, or in which treatment allocation was not concealed, were excluded. This was because prior knowledge of treatment allocation may lead to biased allocation of patients (Schulz 1995).

Types of participants

The patients in trials to be included were diagnosed with probable AD according to internationally accepted criteria such as the Diagnostic and Statistical Manual of Mental Disorders DSM-IV (DSM IV) and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann 1984).

Types of interventions

Objective 1

Intervention: rivastigmine given at any dose, using any method of administration

Comparison: placebo

Objective 2

Intervention: rivastigmine patches at the manufacturer's recommended dose

Comparison: rivastigmine capsules at the manufacturer's recommended dose

Types of outcome measures

In the original protocol and during the review, we looked for all the following outcomes:

1. cognitive function (as measured by psychometric tests);
2. functional performance;
3. global impression;
4. behavioural disturbance;
5. acceptability of treatment as measured by withdrawal from trials;
6. incidence of adverse effects;
7. effect on carers;
8. death;
9. institutionalisation rates;
10. quality of life;
11. dependency.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group Specialized Register, on 2 March 2015. The search terms used were: Rivastigmine OR exelon OR ENA OR "SDZ ENA 713".

ALOIS is maintained by the Trials Search Co-ordinator of the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy people. The studies are identified from:

1. monthly searches of a number of the major healthcare databases, MEDLINE, EMBASE, CINAHL, PsycINFO and LILACS;
2. monthly searches of a number of the trial registers, ISRCTN, UMIN (Japan's Trial Register), the World Health Organization (WHO) Clinical Trials Registry Platform portal (which covers ClinicalTrials.gov, ISRCTN, the Chinese Clinical Trials Register, the German Clinical Trials Register, the Iranian Registry of Clinical Trials, and the Netherlands National Trials Register, plus others);
3. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
4. six-monthly searches of a number of grey literature sources, ISI Web of Knowledge Conference Proceedings, Index to Theses, Australasian Digital Theses.

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.

Additional searches were performed in many of the sources listed above to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used can be seen in Appendix 1.

The latest search for this review (March 2015) retrieved a total of 17 results for consideration.

Searching other resources

In addition, the search engines Copernic and Google were used to find evidence of unreported or unpublished trials using the word rivastigmine and its synonyms. Novartis websites, the Food and Drug Administration (FDA), European Medicines Agency (EMEA) and National Institute for Health and Care Excellence (NICE) websites were searched for data and evidence of trials.

1. Reference searching
The references of all identified studies were inspected for more studies.

2. Pharmaceutical companies
Novartis, the developer of rivastigmine, was contacted for information about any unpublished and published trials.

Data collection and analysis

Selection of studies

Irrelevant citations were discarded by a review of the title of the publication and its abstract. In the presence of any suggestion that the article could possibly be relevant, it was retrieved in full for further assessment. In the later versions of the review, one review author (JSB) selected the trials for inclusion in the review from the culled citation list.

There were multiple publications for most of the industry sponsored trials, often reporting different aspects (outcomes) of the studies or different lengths of follow up.

Data extraction and management

Data were extracted from the published reports in journals and unpublished company reports using data collection forms. One review author (JSB) extracted information from the reports of each study.

In addition to extracting pre-specified information about study characteristics and aspects of methodology relevant to risk of bias, the following summary statistics, required for each trial and each outcome, were extracted.

- For continuous data, mean change from baseline, the standard deviation, and the number of patients for each treatment group at each assessment. Where changes from baseline were not reported, the mean, standard deviation and 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.
- For ordinal variables which can be approximated to continuous variables, the main outcomes of interest were the assessment score at the time point being considered and the change from baseline (i.e. pre-randomisation or at randomisation) at this time point. For some binary and ordinal outcomes the endpoint category relative to the baseline category was the outcome of interest. For other categorical outcomes, such as the Clinical Global Impression of Change (CIBIC-Plus), the endpoint itself was of clinical relevance as all patients had begun, by definition, at the same baseline score.

The baseline assessment score was the latest available score, no longer than two months prior to the randomisation. Studies may have included a titration period prior to the randomisation phase of the study. Data from any open follow-on phase, after the randomised phase, were not used to assess safety or efficacy.

For each outcome measure, data were sought on every patient assessed. To allow an intention-to-treat analysis (ITT), the data were sought irrespective of compliance and whether or not the patient was subsequently deemed ineligible or otherwise excluded from treatment or follow up. If ITT data were not available, an analysis of patients who completed treatment was conducted.

Assessment of risk of bias in included studies

The risk of bias assessment was conducted using the standard recommended approach for assessing the risk of bias in studies included in Cochrane reviews. The Cochrane Collaboration risk of bias tool is available in RevMan 5.2 and assesses the following domains:

- sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcomes assessment;
- incomplete outcome data;
- selective outcome reporting;
- 'other bias'.

We made a judgement about the risk of bias in each domain, assigning it to one of three categories: 'high', 'low' or 'unclear' risk of bias. These assessments were based on the criteria for making judgements that are listed in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions*. The criteria focus on whether the risk is of importance (that is whether the presence of the risk could have an important impact on the results or the outcomes of the trial) rather than whether a risk of bias is present or not (Higgins 2011). The levels of risk may be different for different outcomes and this was considered during the assessment.

If insufficient detail was reported to make a judgement, this was usually considered as an ‘unclear' risk of bias. An ‘unclear’ judgement was also used in situations where it was clear what happened in the study but its likely impact on the study results was not known.

Measures of treatment effect

For dichotomous outcomes (where the outcome of interest was either present or absent), the estimate of treatment effect of the intervention was expressed as the Peto odds ratio (OR) together with the 95% confidence interval (CI).

For continuous data the measure of treatment effect was the mean difference (MD) or the standardised mean difference (SMD).

Unit of analysis issues

The review only included parallel-group, double-blinded randomised controlled trials (RCTs), with individual patients randomised. No unit of analysis issues were expected or encountered.

Dealing with missing data

Where data were missing from the published report of a trial, the authors or the study sponsors were contacted to obtain the data and to clarify any uncertainty.

We made no attempts at data imputation, except for the estimation of standard deviations for continuous data using the methods detailed in section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Where possible we reported ITT analyses. We conducted sensitivity analyses to compare methods of dealing with missing data.

Assessment of heterogeneity

Potential differences between the included studies in the types of participants, interventions or control used were assessed before pooling data. No subgroup analyses were planned.

We assessed heterogeneity between studies using the Chi^2 test (with a significance level set at $P < 0.10$) and the I^2 statistic, which calculates the percentage of variability due to heterogeneity rather than to chance, with I^2 values over 50% suggesting substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

Outcomes reported in a trial were compared with the protocol, whenever possible, to examine whether all of the study's pre-specified outcomes that were of interest to the review had been reported.

Data synthesis

For ordinal variables, such as psychometric test scores, functional and quality of life scales, where there are a large number of possible scores, the measure was treated as continuous and the mean difference or the SMD was calculated.

For ordinal variables with only a small number of possible values, such as the Clinical Global Impression of Change, the data were reduced to a binary variable. The two classes were improvement compared with no change or worse. For all binary variables the Peto method of the typical OR was used.

The duration of the trials varied between 12 weeks and 1 year. Separate meta-analyses were conducted for endpoints of 12 weeks, 24 to 26 weeks and 52 weeks. Some trials contributed data to more than one meta-analysis if multiple assessments had been done.

A weighted estimate of the typical treatment effect across trials was calculated. Overall estimates of the treatment difference are presented. In all cases the overall estimate from a fixed-effect model was presented.

Subgroup analysis and investigation of heterogeneity

Heterogeneity were examined both visually and using the I^2 statistic. Where there was evidence of heterogeneity of the treatment effect between trials then sensitivity analyses were conducted, where only homogeneous results were pooled.

There were no pre-identified subgroups for subgroup analysis.

Sensitivity analysis

This review sought to analyse data using ITT data whenever possible. Some studies reported both an ITT analysis that included all patients randomised and a per protocol analysis. The ITT analysis results reported in studies often involved data imputation techniques such as the last observation carried forward (LOCF) for patients who did not complete the study. The impact of different ways of dealing with missing data were investigated using a sensitivity analysis of as observed, ITT and per protocol analyses. These results were tabulated and any important discrepancies discussed.

Summary of findings table

We summarised the data on the efficacy and safety of the currently recommended dose of rivastigmine (6 to 12 mg/day orally or 9.5 mg/day transdermally) in the summary of findings table using GRADE methods (Guyatt 2008) to assess the overall quality of the evidence.

RESULTS

Description of studies

Results of the search

The updated searches performed in 2011, 2013, 2014 and 2015 retrieved a total of 112 references. The full texts of 42 references were read and, of these, 10 were of studies that could be included or additional reports of studies already included, and 32 were of studies that were excluded.

Included studies

The characteristics of the 13 included trials are summarised in Characteristics of included studies.

Design, participants, samples sizes and setting

Important details of study design (number of participants, duration of follow up, mean Mini-Mental State Examination (MMSE) of participants at baseline and description of interventions) are summarised in Table 1 and the objectives of the trials in Table 2.

Only randomised, double-blinded placebo controlled trials or studies comparing different formulations were included in this review. Thirteen studies met the inclusion criteria of the review.

Six trials, phase II and III, were all supported by Novartis Pharmaceuticals Corporation and were completed by 1996. They are identified by their Novartis or ADENA code (ADENA was the name given by Novartis to the Exelon Phase III clinical trials programme). The two phase II trials were designed to assess the tolerability, efficacy and safety of rivastigmine over three to four months. The four phase III trials were designed to assess the efficacy and safety of rivastigmine in patients with mild to moderately severe AD over six months. The trials had many features in common. They were all multicentre, randomised, double-blind, parallel-group trials. All trials compared rivastigmine with placebo, with at least two treatment groups of different rivastigmine regimens.

Of the seven later trials, three were also sponsored by Novartis (IDEAL; Lopez-Pousa 2005; Nakamura 2011). The key information about these seven trials is summarised as follows.

- There is limited information available about Tai 2000, which has been published only as an abstract. This trial appeared to be an independent trial carried out in Taiwan. Eighty participants with mild to moderate AD were treated with rivastigmine or placebo for 26 weeks. No data were available to include in the meta-analyses.
- Ballard 2005 was a small 26 week trial (n = 93) with three treatment arms, rivastigmine, quetiapine and placebo, of equal size. The objective was to compare the efficacy of rivastigmine and quetiapine for agitation in people with possible or probable AD who were living in institutions. We did not include any data from this trial in the meta-analyses because of concerns about a high risk of attrition bias and exclusion of the most severely impaired patients from the analyses.

Karaman 2005 and Lopez-Pousa 2005 aimed to investigate the efficacy of rivastigmine for patients with more advanced disease than those previously tested.

- Karaman 2005 was a small 12 month trial (n = 44, mean baseline MMSE = 12.2). We did not include data from this trial in our meta-analyses due to concern about a high risk of bias.
- Lopez-Pousa 2005 was a 6 month trial (n = 218, mean baseline MMSE = 8.8). In addition to the outcomes of cognitive function, activities of daily living and global clinical change, Lopez-Pousa 2005 was the earliest included trial to assess behavioural symptoms.
- Mowla 2007 was a 12 week trial in mild to moderate AD with three treatment groups, rivastigmine, rivastigmine plus fluoxetine and placebo. The rivastigmine plus fluoxetine group was not included in this review. There were 82 participants in total in the rivastigmine and placebo groups. We were not able to include any data from this trial in the meta-analyses due to incomplete reporting of results.

IDEAL and Nakamura 2011 were the only trials to include transdermal rivastigmine.

- IDEAL was a 6 month study (n = 1195) in mild to moderate AD, with 4 treatments arms, rivastigmine capsules, 2 doses of transdermal rivastigmine and placebo.
- Nakamura 2011 was a 24 week dose finding trial in mild to moderate AD (n = 859) with 3 treatment arms, 2 doses of transdermal rivastigmine and placebo..

All studies used current diagnostic criteria for dementia (DSM-IV) and probable AD (NINCDS-ADRDA) (McKhann 1984) except Tai 2000, which did not give its diagnostic criteria. The severity of disease was mostly assessed by the MMSE rating scale, and patients that were included had MMSE scores of 10 to 26 inclusive apart from 2 studies (Karaman 2005; Lopez-Pousa 2005), which randomised patients with MMSE scores of 3 to 12. The list of exclusions was not extensive. Patients with severe and unstable illnesses (cardiovascular or pulmonary disease, unstable diabetes mellitus, peptic ulceration within the preceding five years, evidence of alcohol or substance abuse) were excluded, as were individuals taking medications such as anticholinergic drugs, acetylcholine precursor health food supplements, memory enhancers, insulin and psychotropic drugs. The procedures followed were in accordance with the ethical standards of the relevant institutional committees on human experimentation and with the Declaration of Helsinki (Helsinki declaration).

Interventions

Information about treatment groups and actual doses achieved are tabulated in Table 1 and Table 3 respectively.

Twelve studies investigated the oral form of rivastigmine, and one of these studies also included an arm randomised to a rivastigmine patch (IDEAL).

Earlier industry sponsored trials investigated a range of doses, from 2 mg/day to 12 mg/day in two or three divided doses. In later trials (Ballard 2005; Karaman 2005; Lopez-Pousa 2005; Mowla 2007; IDEAL) only the dose range of 6 to 12 mg/day was used to compare against placebo. Tai 2000 investigated doses of 3 to 6 mg/day in two divided doses. All studies with high oral doses achieved a mean daily dose of between 9.3 to 10.7 mg/day, except for Karaman 2005 (8.3 mg/day) and B351 (8.5 mg/day). The mean daily doses achieved for medium doses were between 5.7 and 6 mg/day. Further information on the doses achieved was not available for four trials (B103; Ballard 2005; Mowla 2007; Tai 2000).

Two studies evaluated the safety and efficacy of patches. IDEAL investigated 6 to 12 mg/day capsules in 2 doses and the other 2 arms tested rivastigmine patches, a 10 cm^2 patch which delivered 9.5 mg/day and a 20 cm^2 patch which delivered 17.4 mg/day. Patients were titrated to their target dose in four week steps. Patients in the patch groups started with a 5 cm^2 patch until the target dose was achieved; in the capsule group they began with 3 mg/day, increased by steps of 3 mg/day. All patients had a rivastigmine or placebo patch once a day and a rivastigmine or placebo capsule twice a day. Nakamura 2011 investigateda 10 cm^2 patch which delivered 9.5 mg/day, a 5 cm^2 patch which delivered 4.6 mg/day and a placebo arm. Patients were titrated to their target patch dose over four week intervals, followed by an eight week maintenance period.

Outcomes

The trials examined cognitive, functional and global effects, behavioural symptoms, as well as the safety and tolerability of rivastigmine.

Apart from the outcome measures related to safety or adverse effects, all the outcomes for the effectiveness of rivastigmine were measured by questionnaires or psychometric tests. Different types of instruments were utilised to measure each outcome. The details of the outcomes measured and reported in each trial are summarised in Table 4.

1. Cognitive function

- Alzheimer's Disease Assessment Scale (ADAS-Cog) (Rosen 1984). ADAS-Cog comprises 11 individual tests: spoken language ability (0 to 5), comprehension of spoken language (0 to 5), recall of test instructions (0 to 5), word finding difficulty (0 to 5), following commands (0 to 5), naming object (0 to 5), construction drawing (0 to 5), ideational praxis (0 to 5), orientation (0 to 8), word recall (0 to 10) and word recognition (0 to 12). The total score ranges from 0 to 70, the higher the score indicating greater impairment.
- The ADAS-CogA total score is the ADAS-Cog plus the attention item from the ADAS-Noncog.
- The Mini-Mental State Examination (MMSE) (Folstein 1975) evaluates cognition in five areas: orientation, immediate recall, attention and calculation, delayed recall and language. The test takes only 15 minutes to administer and the scores range from 0 (severe impairment) to 30 (normal).
- The Severe Impairment Battery (SIB) (Panisset 1994; Saxton 1990) is a 40-item questionnaire designed to assess the severity of cognitive dysfunction in advanced AD and is divided into 9 domains: memory, language, orientation, attention, praxis, vasospastically, construction, orientation to name and social interaction. The score ranges from 0 (greatest impairment) to 100 (no impairment).
- The Revised Wechsler Memory Scale (WMS-R) (Wechsler 1987) comprises a series of brief subtests, some taken from the WMS and each measuring a different facet of memory, which are summarised into five composite scores and finally two major scores using weights prescribed by Wechsler. Some of the tests were used in B103.
- The Fuld Object-Memory Test (OME) (Fuld 1981) evaluates short term memory and learning by measuring the recall of 10 previously viewed objects.
- The Benton Visual Retention Test (VRT) (Benton 1974) evaluates visual memory by assessing the accuracy of reproduction of each of 10 designs shown briefly to the individual.
- The Trail Making Test (TMT) (Reitan 1958) assesses the time taken to connect a series of 25 numbered dots.
- The Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) (Schneider 1997) provides a single global rating of change from baseline, rated by an independent observer who has no access to the other efficacy or safety data.
- The Ten-Point Clock Drawing Test (Watson 1993) assesses visuospatial and executive functions.
- The Mental Function Impairment (MENFIS) (Homma 1991) evaluates core symptoms of dementia including cognitive, motivational and emotional aspects based on an interview with the patient and carer. The score ranges from 0 to 78 (greater functional deficit).
- Digital substitution test (DSST).

2. Activities of daily living

- The Progressive Deterioration Scale (PDS) (DeJong 1989) is an instrument with 29 items assessing the activities of daily living as rated by a carer. Each item is scored on a visual analogue scale of 0 to 100, and the total score is the mean item score. The score of 0 to 100 decreases with severity of dementia.
- The Alzheimer's Disease Cooperative Study activities of daily living inventory for severe Alzheimer's disease (ADCS-ADL) (Galasko 1997). This is a 19-item scale for basic and complex abilities validated in patients with moderate to severe dementia. The total score ranges from 0 to 54 (no impairment). Items include basic activities of daily living (eating, bathing) and complex activities (operating taps, switching lights).
- The Caregiver Activity Survey (CAS) is completed by the caregiver and includes six items for which the caregiver estimates the amount of time spent in the previous 24 hours helping the patient with activities of daily living.
- The Nurses' Observation Scale for Geriatric Patients (NOSGER) (Brunner 1990) is designed to assess various cognitive functions and behaviour as related to activities of daily living and as assessed by a caregiver who sees the patient frequently. The NOSGER contains 6 x 5 = 30 items which were selected to

assess the following dimensions: (a) memory, (b) self-care, (c) instrumental activities of daily life, (d) mood, (e) disturbing behaviour, (f) social behaviour.The Disability Assessment for Dementia (DAD) is a 46-item structured interview for the carer, scored 0 to 100 (least impairment), to evaluate activities of daily living (Gelinas 1999).

3. Behavioural symptoms

- The Neuropsychiatric Instrument (NPI) (Cummings 1994) is a 12-item, carer rated instrument to evaluate behavioural and neuropsychiatric symptoms, including delusions, hallucinations, agitation and aggression, depression or dysphoria, anxiety, elation or euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night-time behaviour and appetite or eating disorder. The frequency is rated from 1 (occasional, less than once a week) to 4 (very frequent) and severity from 1 (mild) to 3 (severe). The product of frequency and severity ranges from 1 to 12, with a total score ranging from 12 to 120 for the 10 domains summed. A lower score indicates improvement.
- The Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield 1995) scale, range from 29 to 203, is widely used in nursing homes to assess agitation. The scale examines 29 types of agitated behaviour, including pacing, verbal or physical aggression, performing repetitious mannerisms, screaming, and general restlessness. The frequency of these behaviours is measured on a 7-point scale, ranging from 1 (never occurs) to 7 (occurs several times an hour, and includes cluster scores for physical and verbal aggression, and total aggression.
- The Behavioural Pathology in AD (BEHAVE-AD) assesses potentially remediable behavioural problems (agitation, aggression, affect, psychosis) in patients with AD. It consists of 22 symptoms grouped into 7 categories, each scored by a carer on a 4-point scale (Reisberg 1989).

4. Physician rated global impression tests

- A Clinician's Interview-Based Impression of Change scale (CIBIC-Plus) (Reisberg 1994) includes information supplied by the caregiver and patient. It provides a global rating of patient function in four areas: general, cognitive, behaviour and activities of daily living. All patients are scored as 4 at baseline; subsequent assessment on a scale of 1 to 7 is relative to baseline, with 1 showing marked improvement and 7 marked worsening.
- The Global Deterioration Scale (GDS) (Reisberg 1982) is reported as a score from 1 to 7, 1 indicating normality to 7 indicating very severe dementia, and is a global assessment carried out by a clinician who has access to all information about a patient.
- The Clinical Global Impression of Change (CGIC) (Guy 1976) is a global rating of all domains of a patient's current condition in comparison with baseline. It is a 7-point scale ranging from 1 (very much improved) to 7 (very much worse), with 4 indicating no change. The assessment is conducted by the same clinician at both time points with input from relatives or carers.

5. Acceptability of treatment, as measured by withdrawal from trial

In anticipation of the typical gastrointestinal adverse events associated with cholinesterase inhibitors, which can be dose-dependent, the various arms of the older trials compared both different doses and twice or thrice daily dosage schedules. Three fixed doses were tested in B351, but the other trials aimed for a maximum tolerated dose within a prescribed range. The period of titration was longer for larger doses and varied between 3 and 12 weeks. The later trials tested a transdermal patch formulation which provided continuous delivery of the drug with the objective of improving tolerability. The mean daily doses of rivastigmine at different time points are presented in Table 3. Safety and tolerability were evaluated by recording adverse events and serious adverse events. In addition, routine physical examinations with blood and urine analyses were performed and vital signs and electrocardiograms were checked at all clinic visits. Seven trials reported the withdrawal rate at 26 weeks (B303/B305; B304; B351; B352; IDEAL; Lopez-Pousa 2005; Nakamura 2011).

6. Incidence of adverse events

The studies reported the types of adverse events reported by patients, and the number of patients experiencing these events, usually focusing on the most commonly experienced adverse events. A wide range of adverse events which were consistent with the anticholinergic properties of rivastigmine were reported, including gastrointestinal adverse events such as nausea, vomiting, abdominal pain or discomfort, and diarrhoea. Other adverse events reported included falls, insomnia, agitation, weight loss, headache, dizziness, and cutaneous adverse events where patches were used.

The same seven studies which reported on withdrawal from the trial before completion of the study also reported the number of patients who experienced at least one adverse event. Most of these studies had defined a safety population which is the basis for the adverse events analyses.

7. Quality of life of patients and carers

Only one study reported changes in the NPI-D carer distress scale. This study reported the change from baseline at 24 weeks (IDEAL).

Excluded studies

Please see Characteristics of excluded studies.

Risk of bias in included studies

(Figure 1 and Figure 2)

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

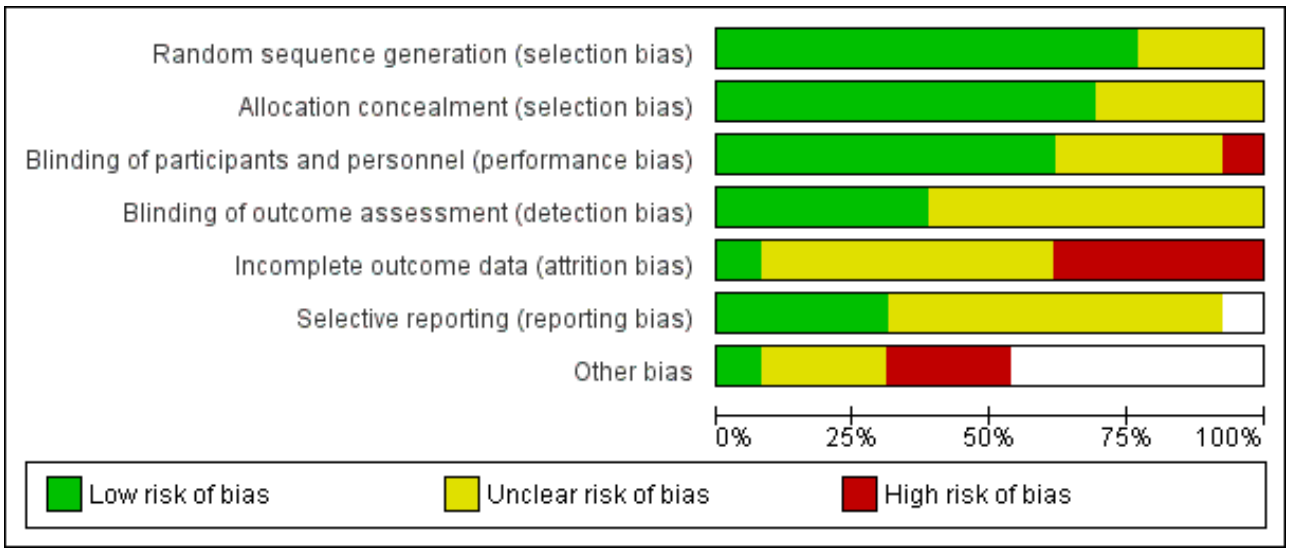
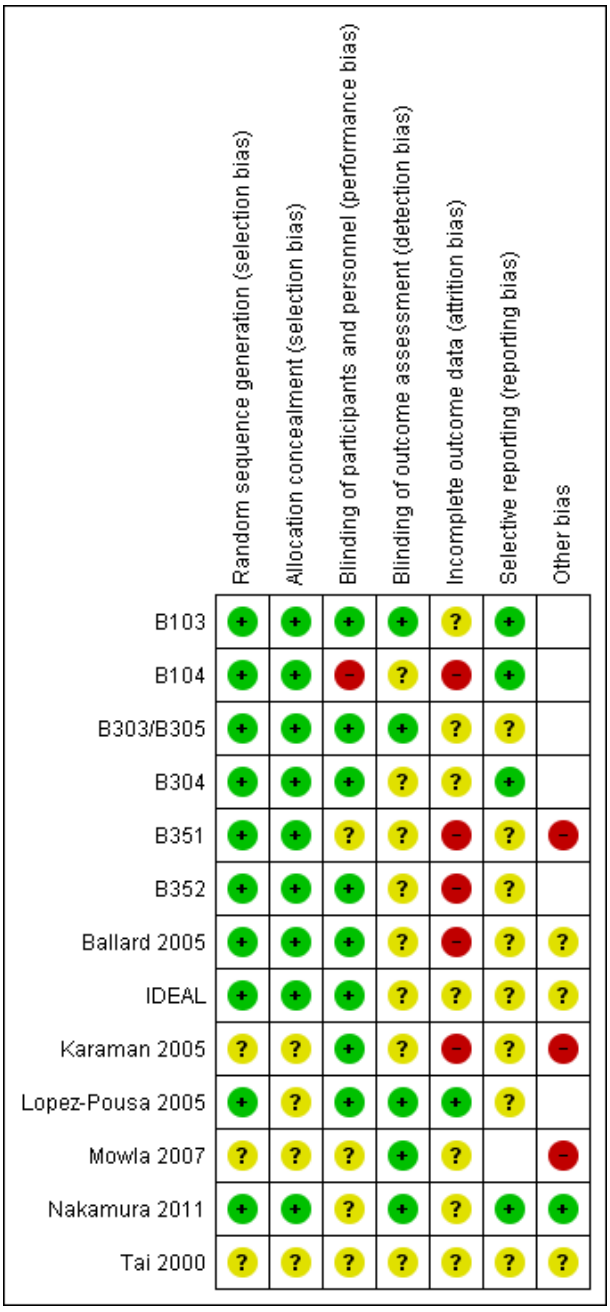


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All the trials sponsored by Novartis were considered to be at low risk of bias for randomisation and allocation concealment, other than Lopez-Pousa 2005 where it was difficult to be sure whether allocation was concealed effectively.

Of the independent trials, Ballard 2005 had a low risk of allocation bias, with clearly described procedures. However, the risk of bias in this domain was unclear for Tai 2000 (an abstract), Karaman 2005 and Mowla 2007 because there were no descriptions of methods. Karaman 2005 was of particular concern as only "participants who tolerated the drug well and perceived benefit were invited to continue rivastigmine treatment" after eight weeks.

Blinding

All trials were double-blinded and placebo controlled, with precautions taken to maintain the blinding such as ensuring the placebo was identical in appearance to the active treatment. However, in B104 the placebo group received the treatment twice daily whereas one of the treatment arms received the intervention three times daily. There were no descriptions of additional steps taken to mask this. The difference in the number of times the capsules were taken could have unmasked the three times per day group. The effectiveness of double-blinding in Mowla 2007 was also unclear because all patients in this study had received the placebo during the six week pre-randomisation run-in period.

Of the two studies testing patches, IDEAL was considered to be at low risk of bias for blinding as a double dummy was used. Nakamura 2011 stated that "patients, investigator staff, persons performing the assessments and data analysts are all blinded", but it was unclear how this was achieved since the study had used different patch sizes (2.5, 5, 7.5 and 10 cm^2) to achieve the target dose.

Incomplete outcome data

Attrition bias was a major concern. There were substantial losses from Ballard 2005 where 19% (6/31) of those randomised to rivastigmine did not start treatment compared with 6% of those randomised to placebo. Only 18/31 in the rivastigmine group completed the trial compared with 27/31 in the placebo group. Those with a low baseline score on the Severe Impairment Battery (SIB) were not included in the analyses. These concerns led us to exclude data from Ballard 2005 from the meta-analyses.

Karaman 2005, although the longest duration included trial (52 weeks), lost very few patients: only 3 of 24 in the rivastigmine group and none from the placebo group. This was a much lower rate of loss than for any other trial.

For the other 11 studies missing assessments caused major problems in the analysis and interpretation of the results. Approximately 17% of patients from the 1 to 4 mg daily and placebo groups and 35% of patients from the 6 to 12 mg daily groups left the trial before completing treatment. If patients dropped out at random from each group, that is the dropout was not associated with the treatment, the comparisons between groups are not biased but estimates of differences are reduced in precision. However, the dropout rates were not random and were related to treatment. Various methods were used in the trials for dealing with missing data.

The older trials (B303/B305; B304; B351; B352) reported in detail the methods using for dealing with missing data. Approximately a third of the patients who dropped out contributed endpoint data (retrieved drop out (RDO)). The ITT analyses included the completers (observed cases (OC)) data and the RDO data, and for the remainder of the patients the last available assessment (last observation carried forward (LOCF)). This remainder comprised approximately 6% of the patients in the placebo and 1 to 4 mg daily groups, and 24% for the 6 to 12 mg daily group at 26 weeks. An overestimate of the outcome effect would be expected.

In order to compare the different methods of dealing with missing assessments, for two outcomes (ADAS-Cog and CIBIC-Plus) we conducted meta-analyses on three different groups of patients: OC only, RDO + OC, and ITT (OC + RDO + LOCF). The results are presented in Table 5. These analyses showed that compared with OC or RDO + OC, the ITT analyses did not produce results favouring rivastigmine, indeed the opposite was true but the differences between results were small. Therefore, the ITT analyses were considered satisfactory and were reported for all other outcomes. Further analysis of the data from the ITT, the OC and RDO + OC analyses to investigate the size and direction of the bias due to differential dropouts from the arms of the rivastigmine trials (Birks 2008) led to the conclusion that the absolute size of the bias was small and the direction could not be ascertained.

Selective reporting

For most of the studies the risk of reporting bias across all outcomes was difficult to judge. A few of the studies had listed the Caregiver Activities Survey (CAS) as an outcome in their protocols but these were not reported in the study results. In addition B304 and B351, two large randomised trials, were not published. Our data were obtained from information provided by Novartis Ltd.

For three of the studies (B104; B304; Nakamura 2011) sufficient information was available from the study protocols and we considered these as low risk of bias. However, there was insufficient information to assess the risk of reporting bias in the other studies.

Other potential sources of bias

Out of these 13 studies included in the review, only four (Ballard 2005; Karaman 2005; Mowla 2007; Tai 2000) were conducted without direct sponsorship or funding from the manufacturer, Novartis Pharma, but none provided data that could be included in the review.

Karaman 2005 reported standard deviations for the outcome measures that were an order of magnitude smaller than those seen in any other trial. We have asked the authors for clarification of these unusual findings but have not received a reply.

Effects of interventions

See: **Summary of findings for the main comparison** Rivastigmine compared to placebo for Alzheimer's disease

There are 13 included trials but 4 (Ballard 2005; Karaman 2005; Mowla 2007; Tai 2000) did not contribute to the analyses. Data from Ballard 2005 was excluded because of the high attrition rate from the rivastigmine group and concern over the elimination from the analyses of patients with a low baseline score. Data from Mowla 2007 could not be included due to incomplete reporting. No data could be used from Tai 2000 as the trial report provided insufficient information. The data from Karaman 2005 were of concern because of the potential for biased results and were omitted from the analyses. Although the longest duration trial, 52 weeks, only 3 of 24 in the rivastigmine group and none from the placebo group were lost. This was a much lower rate of loss than for any other trial. The numbers randomised were not reported but it was stated that patients were excluded at eight weeks if they did not appear to benefit.

In order to meet the objectives of the review we conducted analyses comparing various doses and formulations of rivastigmine with placebo or comparing different formulations of rivastigmine.

The rating scales and cognitive tests used differ in the direction representing improvement. A decrease in score indicates clinical improvement with the ADAS-Cog, the CIBIC-Plus and the GDS, while an increase shows improvement for the PDS and MMSE.

Comparison of rivastigmine (6 to 12 mg/day twice daily capsules or 10 cm^2 (9.5 mg/day) patch) with placebo

Cognitive function

The meta-analysis, using weighted mean differences (WMDs), revealed a benefit on cognitive function as measured by the ADAS-Cog test scores for rivastigmine compared with placebo at 26 weeks

(ITT analysis, WMD -1.79; 95% CI -2.21 to -1.37, P < 0.00001, 6 studies).

The MMSE showed similar results in favour of rivastigmine at 26 weeks compared with placebo (ITT analysis, WMD 0.74; 95% CI 0.52 to 0.97, P < 0.00001, 6 studies).

Activities of daily living

The meta-analysis, using standardised mean differences (SMDs), showed an improvement associated with rivastigmine compared with placebo at 26 weeks (ITT analysis, WMD 0.20; 95% CI 0.13 to 0.27, P < 0.00001, 6 studies).

Global assessment

The seven-point CIBIC-Plus scale, or the ADCS-CGIC scale, measuring global clinical state was dichotomized by counting those showing no change or decline against those showing improvement. There were benefits associated with rivastigmine compared with placebo at 26 weeks (ITT analysis, 1339/1848 rivastigmine, 1197/1490 placebo) (OR 0.68; 95%CI 0.58 to 0.80, P < 0.00001, 7 studies).

Behavioural symptoms

Three studies (IDEAL; Lopez-Pousa 2005; Nakamura 2011) assessed behavioural symptoms using the Neuropsychiatric Instrument (NPI-10 and NPI-12). There was no difference between rivastigmine and placebo at 26 weeks.

Withdrawals before the end of treatment

The meta-analysis of withdrawals before the end of treatment showed a significant difference in favour of placebo compared with rivastigmine 26 weeks (571/2038 rivastigmine, 240/1531 placebo) (OR 2.06; 95%CI 1.74 to 2.45, P < 0.00001, 7 studies).

Adverse events

The meta-analysis of numbers of patients with at least one adverse event showed that at 26 weeks there was a significant difference between the rivastigmine and placebo groups in favour of placebo (1637/2025 rivastigmine, 1123/1562 placebo) (OR 2.16; 95%CI 1.82 to 2.57, P < 0.00001, 7 studies).

Quality of life of carers

One study reported the changes in NPI-D carer distress scale from baseline and this was reported at 24 weeks (IDEAL). No significant difference was detected (MD 0.10; 95% CI -0.91 to 1.11, 1 study).

Comparison of rivastigmine (1 to 4 mg/day and 6 to 12 mg/day twice daily capsules) with placebo

Cognitive function

The meta-analysis, using WMDs, revealed a benefit on cognitive function as measured by ADAS-Cog test scores for the lower dose rivastigmine compared with placebo at 26 weeks, but not at 12 weeks; and for the higher dose at 12 and 26 weeks:

- rivastigmine 1 to 4 mg/day at 12 weeks (ITT analysis, WMD -0.31; 95% CI -0.87 to 0.25, P = 0.01, 3 studies);
- rivastigmine 6 to 12 mg/day at 12 weeks (ITT analysis, WMD -1.49; 95% CI -1.96 to -1.01, P < 0.00001, 4 studies);
- rivastigmine 1 to 4 mg/day at 26 weeks (ITT analysis, WMD -0.84; 95% CI -1.48 to -0.19, P = 0.01, 3 studies);
- rivastigmine 6 to 12 mg/day at 26 weeks (ITT analysis, WMD -1.99; 95% CI -2.49 to -1.50, P < 0.00001, 5 studies).

The MMSE showed similar results in favour of lower dose rivastigmine at 26 weeks and higher dose rivastigmine at 26 weeks, compared with placebo:

- rivastigmine 1 to 4 mg/day at 26 weeks (ITT analysis, WMD 0.43; 95% CI 0.08 to 0.78, P = 0.02, 3 studies);
- rivastigmine 6 to 12 mg/day at 26 weeks (ITT analysis, WMD 0.82; 95% CI 0.56 to 1.08, P < 0.00001, 5 studies).

One study (Lopez-Pousa 2005) used the Severe Impairment Battery (SIB), which showed benefit associated with higher dose rivastigmine compared with placebo at 26 weeks (MD 4.53; 95% CI 0.47 to 8.59, P = 0.03).

Activities of daily living

The PDS (carer assessment of the activities of daily living) showed an improvement associated with higher dose, but not lower dose, rivastigmine compared with placebo at 12 and 26 weeks:

- rivastigmine 1 to 4 mg/day at 12 weeks (WMD -0.77; 95% CI -1.84 to 0.30, 3 studies);
- rivastigmine 1 to 4 mg/day at 26 weeks (WMD -0.38; 95% CI -1.61 to 0.84) (3 studies);
- rivastigmine 6 to 12 mg/day at 12 weeks (WMD 1.08; 95% CI 0.19 to 1.98, P = 0.02, 4 studies);
- rivastigmine 6 to 12 mg/day at 26 weeks (WMD 2.15; 95% CI 1.13 to 3.16, P < 0.0001, 4 studies).

One study (IDEAL) assessing activities of daily living (ADL) using the ADCS-ADL scale showed benefit for 6 to 12 mg/day at 24 weeks (MD 1.80; 95% CI 0.20 to 3.40, P = 0.03).

Global assessment

The seven-point CIBIC-Plus scale, or the ADCS-CGIC scale, measuring global clinical state was dichotomized by counting those showing no change or decline against those showing improvement (as set out in the study protocols by Novartis) and analysed using the Peto OR. There were benefits associated with lower dose rivastigmine compared with placebo at 26 weeks, but not at 12 weeks; and benefits with the higher dose at both 12 and 26 weeks compared with placebo:

- rivastigmine 14 mg/day at 12 weeks (ITT analysis, 456/608 rivastigmine, 466/612 placebo) (OR 0.93; 95% CI 0.72 to 1.21, 3 studies);
- rivastigmine 6 to 12 mg/day at 12 weeks (ITT analysis, 688/950 rivastigmine, 645/825 placebo) (OR 0.74; 95% CI 0.60 to 0.92, P = 0.008, 4 studies);
- rivastigmine 1 to 4 mg/day at 26 weeks (ITT analysis, 457/614 rivastigmine, 500/623 placebo) (OR 0.71; 95% CI 0.55 to 0.93, P = 0.01, 3 studies);
- rivastigmine 6 to 12 mg/day at 26 weeks (ITT analysis, 957/1330 rivastigmine, 971/1223 placebo) (OR 0.66; 95% CI 0.55 to 0.79, P < 0.00001, 6 studies).

The GDS (global assessment) carried out at 26 weeks by a clinician who had access to all information about a patient was dichotomized by counting those showing moderately severe, severe or very severe dementia against those showing moderate or mild dementia. Using the Peto OR to compare with placebo, there were benefits associated with 6 to 12 mg daily rivastigmine (ITT analysis, 579/1056 on rivastigmine showed the worse condition compared to 511/868 on placebo) (OR 0.78; 95% CI 0.64 to 0.94, P = 0.01, 4 studies) but not with 1 to 4 mg daily rivastigmine.

Behavioural symptoms

Two studies (IDEAL; Lopez-Pousa 2005) assessed behavioural symptoms using the NPI (NPI-10 and NPI-12). There was no difference between rivastigmine and placebo:

- rivastigmine 6 to 12 mg/day at 26 weeks (ITT analysis, WMD -0.06; 95% CI -0.20 to 0.09, 2 studies).

Withdrawals before the end of treatment

The meta-analyses of withdrawals before the end of treatment showed no significant differences between withdrawals from the 1 to 4 mg daily rivastigmine group and from the placebo group at 12 and 26 weeks. There were significant differences for the higher dose group in favour of placebo at 12 and 26 weeks:

- rivastigmine 1 to 4 mg/day at 12 weeks (17/136 rivastigmine, 8/133 placebo) (OR 2.15; 95% Cl 0.95 to 4.89, 1 study);
- rivastigmine 1 to 4 mg/day at 26 weeks (113/644 rivastigmine, 113/646 placebo) (OR 1.01; 95% CI 0.75 to 1.34, 3 studies);
- rivastigmine 6 to 12 mg/day at 12 weeks (20/133 rivastigmine, 8/133 placebo) (OR 2.60; 95% CI 1.19 to 5.68, P = 0.02, 1 study);
- rivastigmine 6 to 12 mg/day at 26 weeks (448/1458 rivastigmine, 1194/1243 placebo) (OR 2.19; 95% CI 1.83 to 2.63, P < 0.00001, 6 studies).

Adverse events

Most adverse events occurred within the titration period. The meta-analyses of numbers of patients with at least one adverse event showed that by the end of the titration period and at 26 weeks there were no significant differences between the lower dose rivastigmine and placebo groups. There were, however, significant differences between the higher dose rivastigmine and placebo groups in favour of placebo by the end of the titration period and at 26 weeks:

- rivastigmine 1 to 4 mg/day at the end of the titration period (440/644 rivastigmine, 437/646 placebo) (OR 1.04; 95% Cl 0.82 to 1.31, 3 studies);
- rivastigmine 1 to 4 mg/day at 26 weeks (509/644 rivastigmine, 518/646 placebo) (OR 0.93; 95% CI 0.71 to 1.23, 3 studies);
- rivastigmine 6 to 12 mg/day at the end of the titration period (920/1072 rivastigmine, 584/878 placebo) (OR 2.96; 95% CI 2.39 to 3.68, P < 0.00001, 4 studies);
- rivastigmine 6 to 12 mg/day at 26 weeks (1242/1450 rivastigmine, 901/1276 placebo) (OR 2.49; 95% CI 2.05 to 3.02, P < 0.00001, 6 studies).

A similar pattern was seen for the number of patients with at least one severe adverse event. The rivastigmine 1 to 4 mg daily group did not differ significantly from the placebo group, but there were significant differences between the rivastigmine 6 to 12 mg daily and placebo groups in favour of the latter for the titration period:

- rivastigmine 1 to 4 mg/day at the end of the titration period (48/644 rivastigmine, 51/646 placebo) (OR 0.94; 95% CI 0.62 to 1.42, 3 studies);
- rivastigmine 6 to 12 mg/day at the end of the titration period (130/1052 rivastigmine versus 61/868 placebo) (OR 1.88; 95% CI 1.39 to 2.55, P < 0.0001, 4 studies).

There were many types of adverse events reported and only the significant results are reported here. There were significant differences in favour of placebo for the rivastigmine 6 to 12 mg daily group by the end of the titration period and by 26 weeks for the number of patients suffering nausea, vomiting, diarrhoea, anorexia, headache, syncope, abdominal pain and dizziness. There were significant differences in favour of placebo for the rivastigmine 1 to 4 mg daily group compared to placebo by the end of the titration period and by 26 weeks for the number of patients suffering nausea, vomiting, diarrhoea and anorexia.

Withdrawals before the end of treatment due to adverse events

The meta-analyses of withdrawals at 26 weeks due to adverse events showed no significant differences in withdrawals from the lower dose rivastigmine and placebo groups. There were, however, significant differences between the rivastigmine 6 to 12 mg daily and placebo groups in favour of placebo (291/1453 versus 94/1276) (OR 2.73, 95% CI 2.19 to 3.41, P < 0.00001, 6 studies).

Comparison of rivastigmine (20 cm^2 (17.4 mg/day) patch) with placebo

Cognitive function

The meta-analysis, using MDs, showed that rivastigmine had a benefit compared with placebo for cognitive function as measured by the ADAS-Cog at 24 weeks:

- rivastigmine (ITT analysis, MD -2.60; 95% CI -3.72 to -1.48, P < 0.00001, 1 study).

The MMSE showed similar results in favour of rivastigmine at 26 weeks, compared with placebo:

- rivastigmine (ITT analysis, MD 0.90; 95% CI 0.32 to 1.48, P = 0.002, 1 study).

The TMT-A showed similar results in favour of rivastigmine at 26 weeks, compared with placebo:

- rivastigmine (ITT analysis, MD -14.20; 95% CI -24.11 to -4.29, P = 0.005, 1 study).

There was no significant difference between rivastigmine and placebo for the clock drawing test.

Activities of daily living

The ADCS-ADL showed benefit in favour of rivastigmine compared with placebo at 24 weeks:

- rivastigmine (ITT analysis, MD 2.30; 95% CI 0.52 to 4.08, P = 0.01, 1 study).

Behavioural symptoms

One study assessed behavioural symptoms using the NPI (NPI-12). There was no difference between rivastigmine and placebo (ITT analysis, MD -0.60; 95% CI -2.88 to 1.68, 1 study).

Withdrawals before the end of treatment

There was a significant difference between rivastigmine and placebo in favour of placebo for total withdrawals before the end of treatment (62/303 rivastigmine compared with 36/302 placebo) (OR 1.90; 95% CI 1.22 to 2.97, P = 0.005).

Adverse events

There was a significant difference between rivastigmine and placebo in favour of placebo for the total number of patients that had at least one adverse event by 24 weeks (200/303 rivastigmine compared with 139/302 placebo) (OR 2.28; 95% CI 1.64 to 3.16, P < 0.00001).

There was a significant difference between rivastigmine and placebo in favour of placebo for the total number of patients that had at least one adverse event of dizziness (21/303 compared with 7/302) (ITT analysis, OR 3.14; 95% CI 1.31 to 7.50, P = 0.01), nausea (64/303 compared with 15/302) (OR 5.12; 95% CI 2.85 to 9.22, P < 0.00001), vomiting (57/303 compared with 10/302) (ITT analysis, OR 6.77; 95% CI 3.38 to 13.53, P < 0.00001), weight decrease (23/303 compared with 4/302) (ITT analysis, OR 6.12; 95% CI 2.09 to 17.92, P = 0.0009), and decreased appetite (15/303 compared with 3/302) (ITT analysis, OR 5.19; 95% CI 1.49 to 18.12, P = 0.01, 1 study).

Withdrawals before the end of treatment due to adverse events

The meta-analyses of withdrawals at 26 weeks due to adverse events showed no significant differences in withdrawals from the rivastigmine and placebo groups (26/303 rivastigmine compared with 15/302 placebo) (OR 1.80; 95% CI 0.93 to 3.46, 1 study).

Quality of life of carers

One study assessed the NPI-D carer distress scale at 24 weeks (IDEAL). No significant difference between rivastigmine and placebo was detected (ITT analysis, MD 0.00; 95% CI -1.07 to 1.07).

Comparison of rivastigmine (10 cm^2 (9.5 mg/day) patch) with placebo

Cognitive function

The meta-analysis, using WMDs and MDs, showed a benefit of the 10 cm^2 rivastigmine patch on cognitive function as measured by the ADAS-Cog, MMSE, TMT-A and MENFIS at 24 weeks:

- ADAS-cog (ITT analysis, WMD -1.34; 95% CI -2.02 to -0.66, P = 0.0001, 2 studies);
- MMSE (ITT analysis, WMD 0.64; 95% CI 0.26 to 1.02, P = 0.0009, 2 studies);
- TMT-A (ITT analysis, MD -20.0; 95% CI -29.8 to -10.2, P < 0.0001, 1 study);
- MENFIS (ITT analysis, MD -1.30; 95% CI -2.32 to -0.28, P = 0.01, 1 study).

Activities of daily living

The ADCS-ADL showed benefit in favour of rivastigmine at 24 weeks (ITT analysis, MD 2.20; 95% CI 0.62 to 3.78, P = 0.006, 1 study).

The DAD showed benefit in favour of rivastigmine at 24 weeks (ITT analysis, MD 2.3; 95% CI 0.34 to 4.26, P = 0.02, 1 study).

Global assessment

The seven-point CIBIC-Plus scale measuring global clinical state was dichotomized by counting those showing no change or decline against those showing improvement and analysed using the Peto OR. There was no difference between rivastigmine and placebo at 24 weeks (382/518 rivastigmine, 426/545 placebo) (ITT analysis, OR 0.77; 95% CI 0.58 to 1.02, P = 0.07, 2 studies).

Withdrawals before the end of treatment

There was a significant difference between rivastigmine and placebo in favour of placebo for total withdrawals before the end of treatment (123/580 rivastigmine compared with 82/590 placebo) (OR 1.67; 95% CI 1.23 to 2.26, P = 0.001, 2 studies).

Adverse events

There were significant differences between rivastigmine and placebo in favour of placebo for the total number of patients that had at least one adverse event by 24 weeks (395/578 rivastigmine compared with 361/588 placebo) (OR 1.39; 95% CI 1.08 to 1.80, P = 0.01, 2 studies) and withdrawals due to adverse events (62/580 rivastigmine compared with 36/590 placebo) (OR 1.84; 95% CI 1.20 to 2.82, P = 0.005, 2 studies).

There were significant differences between rivastigmine and placebo in favour of placebo for the total number of patients that had at least one adverse event at the application site: erythema (113/287 compared with 55/286) (OR 2.73; 95% CI 1.87 to 3.98, P < 0.00001, 1 study), application site pruritis (100/287 compared with 61/286) (OR 1.97; 95% CI 1.36 to 2.86, P = 0.0004, 1 study), application site oedema (31/287 compared with 7/286) (OR 4.83; 95% CI 2.09 to 11.15, P = 0.0002, 1 study), application site exfoliation (11/282 compared with 4/286) (OR 3.68; 95% CI 1.20 to 1.33, P = 0.02), contact dermatitis (68/287 compared with 40/286) (OR 1.91; 95% CI 1.24 to 2.94, P = 0.003, 1 study), nausea (41/578 compared with 24/588) (OR 1.80; 95% CI 1.07 to 3.02, P = 0.03, 2 studies) and vomiting (41/578 compared with 21/588) (OR 2.06; 95% CI 1.20 to 3.53, P = 0.009, 2 studies).

Withdrawals before the end of treatment due to adverse events

There was a significant difference between rivastigmine and placebo in favour of placebo for withdrawals due to adverse events (62/580 rivastigmine compared with 36/590 placebo) (OR 1.84; 95% CI 1.20 to 2.82, P = 0.005, 2 studies).

Comparison of rivastigmine (5 cm^2 (4.6 mg/day) patch) with placebo

This comparison was made in one study (Nakamura 2011).

Cognitive function

There was no difference between rivastigmine and placebo at 24 weeks for cognitive function measured using the ADAS-Cog scale (ITT analysis, MD 0.80; 95% CI -1.62 to 0.02), MMSE ITT analysis, MD

0.00; 95% CI -0.52 to 0.52) and MENFIS (ITT analysis, MD -0.70; 95% CI -0.70, 95% CI -1.72 to 0.32).

Activities of daily living

There was no difference between rivastigmine and placebo at 24 weeks for activities of daily living measured using the DAD scale (ITT analysis, MD 1.20; 95% CI -0.73 to 3.13).

Global assessment

There was no difference between rivastigmine and placebo at 24 weeks for global assessment measured using the CIBIC-plus J scale (212/269 rivastigmine, 226/267 placebo) (ITT analysis, OR 0.67; 95% CI 0.43 to 1.05).

Behavioural symptoms

There was no difference between rivastigmine and placebo at 24 weeks for behavioural symptoms measured using the BEHAVE-AD scale (ITT analysis, MD 0.00; 95% CI -0.67 to 0.67).

Withdrawals before the end of treatment

There was a significant difference between rivastigmine and placebo in favour of placebo for total withdrawals before the end of treatment (64/284 rivastigmine compared with 46/288 placebo) (OR 1.53; 95% CI 1.01 to 2.33, P = 0.05).

Adverse events

There was a significant difference between rivastigmine and placebo in favour of placebo for the total number of patients that had at least one adverse event at 24 weeks (243/282 rivastigmine compared with 222/286 placebo) (OR 1.80; 95% CI 1.16 to 2.78, P = 0.009), but no difference for deaths.

There were significant differences between rivastigmine and placebo in favour of placebo for the total number of patients that had at least one adverse event at the application site: erythema (106/282 compared with 55/286) (OR 2.53; 95% CI 1.73 to 3.70, P < 0.00001, 1 study), application site pruritis (92/282 compared with 61/286) (OR 1.79; 95% CI 1.23 to 2.60, P = 0.003, 1 study), application site oedema (35/282 compared with 7/286) (OR 5.65; 95% CI 2.46 to 12.94, P < 0.0001, 1 study), application site exfoliation (14/282 compared with 4/286) (OR 3.68; 95% CI 1.20 to 11.35, P = 0.02), contact dermatitis (69/282 compared with 40/286) (OR 1.99; 95% CI 1.30 to 3.06, P = 0.002, 1 study); but no difference between rivastigmine and placebo for adverse events of nasopharyngitis, nausea, vomiting and diarrhoea.

Withdrawals before the end of treatment due to adverse events

There was a significant difference between rivastigmine and placebo in favour of placebo for withdrawals due to adverse events (38/284 rivastigmine compared with 21/288 placebo) (OR 1.96; 95% CI 1.12 to 3.44, P = 0.02).

Comparison of rivastigmine (10 cm^2 (9.5 mg/day) patch) with rivastigmine (6 to 12 mg/day twice daily) capsules

Cognitive function

One study (IDEAL) showed no difference between the rivastigmine patch and rivastigmine capsules on cognitive function as measured by the ADAS-Cog, MMSE, TMT-A and MENFIS at 24 weeks:

- ADAS-cog (ITT analysis, MD 0.0; 95% CI -1.10 to 1.10, P = 1.0, 1 study);
- MMSE (ITT analysis, MD 0.30; 95% CI -0.27 to 0.87, P = 0.30, 1 study);
- TMT-A (ITT analysis, MD -2.6; 95% CI -13.5 to 8.3, P = 0.64, 1 study);
- clock drawing (ITT analysis, MD 0.1; 95% CI -0.5 to 0.7, P = 0.73, 1 study).

Activities of daily living

The ADCS-ADL showed no difference between the rivastigmine patch and rivastigmine capsules at 24 weeks (ITT analysis, MD 0.40; 95% CI -1.23 to 2.03, P = 0.63, 1 study).

Global assessment

The seven-point CIBIC-Plus scale measuring global clinical state was dichotomized by counting those showing no change or decline against those showing improvement and analysed using the Peto OR. There was no difference between the rivastigmine patch and rivastigmine capsules at 24 weeks (171/248 rivastigmine patch, 161/267253 rivastigmine capsules) (ITT analysis, OR 1.27; 95% CI 0.88 to 1.84, P = 0.21, 1 study).

Behavioural symptoms

One study assessed behavioural symptoms using the NPI (NPI-12). There was no difference between the rivastigmine patch and rivastigmine capsules (ITT analysis, MD 0.50; 95% CI -1.55 to 2.55, P = 0.63, 1 study).

Withdrawals before the end of treatment

There was no significant difference between rivastigmine and placebo for withdrawals before the end of treatment (64/293 compared with 63/297) (OR 1.09; 95% CI 0.70 to 154, P = 0.85, 1 study).

Adverse events

There was a significant difference between the rivastigmine patch and rivastigmine capsules in favour of the patch for the total number of patients that had at least one adverse event by 24 weeks (147/291 rivastigmine compared with 186/294 placebo) (OR 0.59; 95% CI 0.43 to 0.82, P = 0.002, 1 study).

There were significant differences between the rivastigmine patch and rivastigmine capsules in favour of the patch for the total number of patients that had at least one adverse event of decreased appetite (2/291 compared with 12/294) (OR 0.16; 95% CI 0.04 to 0.73, P = 0.02, 1 study), dizziness (7/291 compared with 22/294) (OR 0.30; 95% CI 0.13 to 0.72, P = 0.007, 1 study), asthenia (5/291 compared with 17/294) (OR 0.28; 95% CI 0.10 to 0.78, P = 0.01, 1 study), nausea (21/291 compared with 68/294) (OR 0.26; 95% CI 0.15 to 0.43, P < 0.001, 1 study) and vomiting (18/291 compared with 50/294) (OR 0.32; 95% CI 0.18 to 0.57, P < 0.001, 1 study).

Withdrawals before the end of treatment due to adverse events

There was no significant difference between rivastigmine and placebo for withdrawals due to adverse events (28/293 rivastigmine compared with 24/297 placebo) (OR 1.20; 95% CI 0.68 to 2.13, P = 0.53, 1 study).

DISCUSSION

Summary of main results

The results of the review showed the following main findings.

- The currently recommended doses of rivastigmine (6 to 12 mg/day in two divided doses for capsules and 9.5 mg/day for transdermal patches) have some benefits compared to placebo at 26 weeks for cognitive function, activities of daily living and the physician rated global impression scales. No difference was found for behavioural symptoms or the impact on carers. Patients on rivastigmine are about twice as likely (OR of about 2) to experience adverse events or to withdraw from the trial before the end of the study.
- Limited evidence from one trial suggests that the transdermal formulation (9.5 mg/day) is as effective as the oral formulation (6 to 12 mg/day) and is associated with a lower incidence of adverse events but does not affect the rate of withdrawals due to adverse events.

Outcomes

The two cognitive tests used, the MMSE and ADAS-Cog, assess similar domains and a high correlation between the results would be expected. The results from 5 studies show that 6 to 12 mg daily of oral rivastigmine improved the cognitive function of patients with mild to moderate probable Alzheimer's disease treated over a period of 26 weeks, by 0.8 points on the MMSE (range 0 to 30) and by 2.0 points on the ADAS-Cog (range 0 to 70), when compared with placebo. The results from 2 studies show that the 9.5 mg/day of rivastigmine in a transdermal patch improved cognitive function by 0.6 points on the MMSE and 1.4 points on the ADAS-cog when compared with placebo. Pooling the data showed a treatment effect of 0.7 points on the MMSE and 1.8 points on the ADAS-Cog. There was a smaller effect on cognitive function in the 1 to 4 mg daily oral treatment group.

Four studies assessed the effect of 6 to 12 mg daily oral rivastigmine on activities of daily living as reported by a carer using the PDS rating scale (range 0 to 100). Rivastigmine showed a benefit of 2.2 points compared with placebo, but the difference between placebo and 1 to 4 mg daily rivastigmine was not significant. The 10 cm^2 (9.5 mg/day) patch showed a benefit of 2.2 points on the ADCS-ADL scale (range 0 to 54) when compared with placebo.

The US Food and Drug Administration (FDA) requires an independent clinician to assess global clinical state after interviewing the patient and the carer at baseline and the endpoint. When the results of global impression measures were dichotomized to compare the number of patients who improved with the numbers who showed no change or whose condition had deteriorated, the 6 to 12 mg daily group was significantly better than the placebo group at 12 and 26 weeks, and there was a similar significant difference favouring the 1 to 4 mg daily group over placebo at 26 weeks. The 10 cm^2 (9.5 mg/day) patch was also significantly better than placebo at 24 weeks.The clinician and carer, whilst following the guidelines for the application of the CIBIC-Plus, are essentially making an assessment of whether the patient has improved or not based on criteria relevant to them. This is perhaps closest to what is commonly meant by the term 'meaningful improvement'.

Minimal clinically important differences (MCID), patient derived scores that represent changes in a score that have meaning for patients, have been suggested for the ADAS-cog (3 points in severe AD (Howard 2011)) and MMSE (1.4 points in mild AD (Schrag 2012)). Comparing our findings with these we might conclude that the treatment effects for cognitive function are unlikely to be clinically relevant.

Adverse effects

When taking capsules, a fairly lengthy titration period of up to 12 weeks is needed to develop tolerance and to minimize adverse effects such as nausea, vomiting, diarrhoea, abdominal pain, dizziness, headache and anorexia. The target was to treat patients with a maximum tolerated dose administered in two divided doses, the upper limit being 12 mg per day. There were significantly more total dropouts and dropouts due to adverse events from the 6 to 12 mg daily dose groups than from placebo groups and therefore adverse effects remain a clinical issue. There was no hepatotoxicity associated with rivastigmine and no statistically or clinically significant changes in vital signs.

The continuous dose patch was introduced to improve tolerability. One study (IDEAL) tested two sizes of rivastigmine patch, one delivering a higher dose than previously tested in a 20 cm^2 patch (17.4 mg/day) and one 10 cm^2 patch (9.5 mg/day), a dose similar to the usual oral dose. Another study (Nakamura 2011) tested 5 cm^2 (4.6 mg/day) and 10 cm^2 (9.5 mg/day) patches. The smallest patch showed no treatment effect when compared with placebo for cognition, global function and activities of daily living. The efficacy of the 9.5 mg/day patch was comparable to that of the capsules with a similar daily dose, but was associated with significantly fewer adverse events of nausea, vomiting, dizziness and asthenia. There was no difference in the number of withdrawals due to adverse events. Therefore, the 9.5 mg/day patch appears to have advantages compared with both the higher dose patches and the 6 to 12 mg/day capsules in terms of the overall incidence of adverse events, but it may not reduce the incidence of the more serious events that lead to cessation of treatment.

Overall completeness and applicability of evidence

We were able to include evidence from both published and unpublished trials in this systematic review. There were 3319 participants. Most participants were in industry sponsored trials. Data from two independent trials (n = 162) were not available and we excluded data from two other independent trials (n = 75) from our analyses because of concerns about risk of bias. The participants in the included trials had mainly mild to moderate dementia due to Alzheimer's disease. They were not highly selected with respect to their general health so that all but the seriously ill were included. Only two trials included patients with severe dementia, and we excluded the data from one of these leaving data on only 218 patients with severe dementia included in the analyses.

The main limitations in the completeness and applicability of the evidence were the lack of long term data beyond 26 weeks and the limited range of outcomes measured. Beyond 26 weeks, some trials continued as an open label, extension phase. There were very few data on outcomes important to patients and carers, such as quality of life.

Quality of the evidence

The quality of the evidence at 26 weeks is moderate for most outcomes. Our main concern for the evidence is that only seven studies have contributed data to the meta-analysis, and all of these studies were either industry sponsored or industry funded. In addition, withdrawals from these studies were of concern.

The results from B352 nearly always showed greater benefits for rivastigmine on each outcome than demonstrated in B303/B305, B304 and B351. B352 was responsible for the heterogeneity between trials that was reported for some of the measures of cognitive function. There are no obvious differences between B352 and the other phase III trials. It was conducted only in the US, but so was B351. The doses reached by patients in B352 were higher than those of B351, by 1.2 mg per day on average. Results from B352 have been more extensively reported than the other three phase III trials but there is no reason to suppose that this trial is of any more importance in the overall assessment of rivastigmine. We have not downgraded the evidence based on this heterogeneity concern since the impact on the overall pooled results is small and does not change the interpretation of any of the results.

Outcomes such as behavioural symptoms and quality of life are important to patients but these were only reported by three studies and one study, respectively. Hence, the quality of evidence for these was lower.

Potential biases in the review process

The initial protocol of the review, which was published in 1998, had aimed to include all double-blinded randomised controlled trials (RCTs) of rivastigmine with a minimum study period of two weeks, regardless of the doses or formulations used. However, this resulted in a large number of possible comparisons. In addition, studies often used multiple instruments to report the same outcome, for example cognitive function was measured using the MMSE, ADAS-Cog and other tests. For some of these outcomes we decided to use only the most commonly used tests in the main analysis.

In this update we decided to concentrate on the currently recommended doses (6 and 12 mg/day for oral doses, and 9.5 mg/day for transdermal patches), and a minimum treatment duration of six months for the main analysis. We considered the decision to focus on longer term data was clinically sensible since a titration period was required to reach the target doses.

Mowla 2007, Karaman 2005, Ballard 2005 and Tai 2000, all non-industry funded studies, did not provide data that could be included in the review.

Agreements and disagreements with other studies or reviews

Most patients from the four phase III trials continued in an open label phase for a further 26 weeks during which the maximum tolerated dose was administered. Results from these extension phases have been described as showing a possible beneficial effect of rivastigmine on disease progression (Product monograph, Novartis 1998). Reported results showed that patients who had received placebo or rivastigmine 1 to 4 mg daily in the randomised phase showed initial improvement on the ADAS-Cog before declining at the same rate as the 6 to 12 mg daily group, although remaining more impaired by approximately 1.5 points. These results must be interpreted with caution. The randomised, double-blind conditions no longer prevailed. There had been differential dropout from the groups and there was no placebo group for the comparison. An imputed rate of decline for placebo patients was obtained by extrapolating from the randomised phase and not from actual observations.

There is much interest in the identification of patient characteristics that might predict a response to a cholinesterase inhibitor. Burns 2004 reported that cholinesterase inhibitors may be effective in patients with more severe disease. Data were pooled from three studies (B303/B305; B351; B352) for those with a baseline MMSE of 10, 11 or 12 (n = 117), in the group treated with rivastigmine (6 to 12 mg/day) or placebo, and the analysis showed that rivastigmine benefited those with more severe disease. This result has not added anything substantial to what was known already. The analysis of the total dataset from these trials demonstrated that rivastigmine was of benefit to the population randomised.

Erkinjuntti 2002, funded by Novartis Pharmaceuticals, investigated the response to rivastigmine of those without hypertension compared to those with using the data from B303/B305. They reported that particular benefits may be observed in those with vascular risk factors. These results are based on retrospective analysis of the study data and there has been no study confirming this finding using prospective data.

Farlow 2003a retrieved dropouts from the studies B303/B305, B351 and B352. These patients stopped treatment before the end of the trials but were invited back for assessment at the endpoint. Farlow concluded that those who had been in the rivastigmine groups had deteriorated less than those from the placebo groups, and therefore rivastigmine had provided a beneficial delay in disease progression. The two groups cannot be compared. The participants belong to a highly selected group, those who stopped treatment and agreed to return. The placebo group was much smaller than the rivastigmine group (38 compared with 88). Those who left the trial from the placebo group may have done so because their illness was more severe. This may have applied to some of those in the rivastigmine group who left but, in addition, there were those who left because they suffered from adverse effects. It is not possible to compare these two groups in a meaningful way.

Grossberg 2000 was a Novartis funded extension study examining the data from the four phase III studies and the related open label extension studies. Those who had been taking rivastigmine continuously for two years were compared with historical controls and the study concluded that rivastigmine has a beneficial effect on cognitive performance for up to two years in patients with Alzheimer's disease. These results must be treated with caution as the two groups are not comparable.

Several reviews of rivastigmine have been published. Schneider 1998 and Spencer 1998 both limited analysis and interpretation to the three trials B352, B303/B305 and B351. Spencer reported that "individual and pooled results indicate that rivastigmine usually produces cognitive, global and functional changes that indicate significantly less deterioration than was observed with placebo". Schneider reported that "the pooled analyses confirm the efficacy of rivastigmine in the treatment of both the cognitive and functional deficits of mild to moderately severe AD". Clegg 2002 was the report from NICE (National Institute of Clinical Excellence, UK) of

the systematic review on which the decision was made that the cholinesterase inhibitors would be available on the National Health Service to treat those with Alzheimer's disease. Williams 2003 was a review of all aspects of rivastigmine, and summarised the clinical trials but without meta-analyses.

Hauber 2000 calculated the potential savings costs using rivastigmine compared with no treatment for Alzheimer's disease. Hauber used a disease stage model. Results from two phase III trials of rivastigmine, together with extrapolation beyond the six month duration of the trial, identified the stage of disease using the MMSE assessments. Costs of healthcare resource use was estimated as a function of MMSE, using data from Canadian sources. Rivastigmine was judged to be cost effective due to the delay in disease progression. The analysis was repeated in a UK and US setting. These results are not based on randomised evidence and rest on many assumptions. It would be unwise to base decisions on whether rivastigmine should be prescribed to patients on the basis of cost-effectiveness studies such as these. Fillit 2004 presents an excellent summary of the cost-effectiveness studies and of the assumptions on which they are based. Fillit concludes that the results from these studies are not reliable and that outcomes related to costs and healthcare resource use must be assessed in randomised clinical trials.

AUTHORS' CONCLUSIONS

Implications for practice

Use of rivastigmine in doses of 6 to 12 mg daily is associated with statistically significant benefits in terms of cognitive function. Benefits are also seen in the activities of daily living and clinician rated global impression scale ratings, which suggests that they may be of clinical as well as statistical significance. At lower doses (4 mg or less total daily dose) differences were in the same direction and were significant for cognitive function. Significant differences in the CIBIC-Plus were seen at 26 weeks but not earlier. The 10 cm^2 (9.5 mg/day) patch has been tested in two placebo controlled trials and shows similar benefits to the 6 to 12 mg oral dose. One double-blind placebo controlled study of longer than 26 weeks is included in this review, but the data were not included in the meta-analyses due to concerns about the study. This present review has not examined economic data.

Side effects observed were predictably related to the cholinergic actions of the drug. They may be related to the pharmacokinetics of the drug and merit further study. Three sizes of transdermal patch have been tested in two trials, and there is evidence that the 9.5 mg/day patch is associated with fewer side effects than the capsules or the higher dose larger patches and has comparable efficacy to all three.

Implications for research

Longer term studies with a focus on clinically significant endpoints need to be linked to economic analyses to generate information on cost-utility.

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CHARACTERISTICS OF STUDIES

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

B103

Methods	Double-blinded, 3 arm, parallel-group randomised controlled trial 13 week treatment followed by 2 weeks of washout with placebo with an optional double-masked extension
Participants	**Setting:** Europe and UK; 54 centres, between March 1991 and March 1992 **Sample size:** 402 participants (226 female, 176 male), 133 in the 6 mg/day group, 136 in the 4 mg/day group and 133 in the placebo group A**ge:** range 50 to 90 years, mean age 69.4 years **Inclusion criteria:** • Age 50 to 90 years • Had a diagnosis of DSM-III for mild to moderate dementia, NINCDS-ADRDA criteria for probable AD, MMSE score of at least 16 points and able to perform 3 out of 4 other tests of the psychometric battery • Medication for non-cognitive aspects of AD or concomitant conditions was allowed **Exclusion criteria:** • cognitive enhancing medications were discontinued for 3 weeks before entry
Interventions	1. Rivastigmine: 4 mg/day divided into 2 doses (titrated to target dose in 1 week)

B103 *(Continued)*

	2. Rivastigmine: 6 mg/day divided into 2 doses (titrated to target dose in 3 weeks) 3. Placebo (identical) taken twice daily Doses maintained for 10 weeks after titration period to week 13. All patients then had a 2 week washout period with placebo (single-blinded)
Outcomes	Outcomes measured at baseline and at 13 weeks 1. Cognitive function • Mini Mental State Examination (MMSE) • Fuld Object-Memory Test (OME) • Benton Visual Retention Test (VRT) • Trail Making Test (TMT) • Digitial symbol substitution test (DSST) • Nurses' Observation Scale for Geriatric Patients (NOSGER) 2. Activities of daily living • Nurses' Observation Scale for Geriatric Patients (NOSGER) • Performace of three individual activities of daily living 3. Behavioural symptoms • Nurses' Observation Scale for Geriatric Patients (NOSGER) 4. Physician rated global impression tests • Clinical Global Impression of Change (CGIC) 5. Incidence of adverse events • reported as incidence of most frequent events: nausea, vomiting, diarrhoea, abdominal pain, headache and dizziness 6. Discontinuation • total withdrawals • withdrawal due to adverse events
Source of funding	Novartis Pharma Ltd
Declaration of interest	Study sponsored by Novartis Pharma
Notes	Primary hypothesis:to assess short term (3 month) symptomatic efficacy of rivastigmine 4 and 6 mg/d compared with placebo in patients with AD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned a randomisation number by the investigator in chronological order according to a list generated by study sponsor (Novartis)
Allocation concealment (selection bias)	Low risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active medication and placebo capsules had the same physical appearance, and the number of capsules for each dose intake was the same in all three groups

B103 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A total of 346/402 (86%) patients completed study. Analyses done with ITT population with imputations for missing values and an observed case population
Selective reporting (reporting bias)	Low risk	Outcomes listed in protocol were reported

B104

Methods	Double-blinded, 3 arm parallel-group randomised controlled trial 18 week treatment
Participants	**Setting:** Europe and Canada; 11 centres, between January 1993 and September 1993 **Sample size:** 114 participants **Age:** range years, mean age years **Inclusion criteria:** • Age up to 90 years • Diagnosis of mild to moderate dementia according to DSM III-R, and probable AD according to NINCDS-ADRDA criteria • MMSE score between 12 and 26 points **Exclusion criteria:** concomitant conditions or medications that may confound assessment of dementia; current diagnosis or history of significant medical, neurological or psychiatric disorder
Interventions	1. Rivastigmine: 6 to 12 mg/day divided into 2 doses 2. Rivastigmine: 6 to 12 mg/day divided into 3 doses 3. Placebo (identical looking) twice daily Titration to a maximum dose of 12 mg/day or maximum tolerated dose during weeks 1 to 10, followed by 8 weeks maintenance of dose
Outcomes	Measured at 18 weeks 1. Cognitive function • Alzheimer's Disease Assessment Scale (ADAS-Cog) • Wechsler Memory Scale (WMS) (digit span, delayed recall, word fluency) 2. Activities of daily living • Nurses' Observation Scale for Geriatric Patients (NOSGER) 3.Global evaluation (physician rated) • CIBIC plus 4. Behavioural symptoms • Nurses' Observation Scale for Geriatric Patients (NOSGER) 5. Incidence of adverse events 6. Discontinuation

B104 *(Continued)*

	• withdrawal due to adverse events
Source of funding	Novartis Pharma Ltd
Declaration of interest	Sponsored by Novartis Pharma Ltd
Notes	Main hypothesis: to investigate tolerability of rivastigmine 10 week titration phase to a maximum of 12 mg daily or maximum tolerated dose, then 8 weeks maintenance phase

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not described "patients were randomly assigned to one of three treatment groups"
Allocation concealment (selection bias)	Low risk	Not described Comment: likely to be low risk since this is a large multicentre trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Identifical placebo used, taken twice daily Comment: this effectively unblinded the group assigned to three times daily regimen
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Clinician who rated the CIBIC did not have access to baseline results and psychometric tests and also did not ask questions; however, it was unclear how effective this was
Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 85/114 (75%) completed the study. Numbers of participants who completed the study were different between groups: 92% for placebo, 89% for three times daily group and 78% for twice daily group. The efficacy analysis was conducted only in "valid" patients, defined as all those patients who had completed the study according to protocol
Selective reporting (reporting bias)	Low risk	Outcomes listed in protocol reported

B303/B305

Methods	Double-blinded, placebo controlled 3 arm parallel-group randomised controlled trial 26 weeks of treatment
Participants	**Setting:** 45 centres, Europe and North America **Sample size:** 725 participants (428 female, 297 male) **Age:** 45 to 95 years, mean age 72 years **Inclusion criteria:** • DSM-IV, NINCDS-ADRDA criteria for probable AD • MMSE 10 to 26 inclusive • 50 to 85 years old (outside this range with approval of medical expert) • most concomitant diseases, most medications **Exclusion criteria:**

B303/B305 *(Continued)*

	• severe and unstable cardiac disease, severe obstructive pulmonary disease, other life threatening conditions (e.g. rapidly progressing malignancies) • anticholinergic drugs, acetylcholine precursor health food supplements, memory enhancers, insulin, psychotropic drugs (apart from occasional use of chloral hydrate for agitation or insomnia)
Interventions	1. Rivastigmine 1 to 4 mg/day divided into 2 doses 2. Rivastigmine 6 to 12 mg/day divided into 2 doses 3. Placebo Doses increased weekly in steps of 1.5 mg/day during weeks 1 to 12, but had to be within target range by week 7; thereafter, multiple single level dose increases or decreases were permitted provided patients remained within their assigned dose range (otherwise patients discontinued study, but were asked to return for scheduled efficacy evaluations)
Outcomes	Assessments made and reported at baseline, 12, 18, 26 weeks 1. Cognitive function • Alzheimer's Disease Assessment Scale (ADAS-Cog) • Mini-Mental State Examination (MMSE) • ADAS-CogA (total score is the ADAS-Cog plus the attention item from the ADAS-Noncog) 2. Activities of daily living • Progressive Deterioration Scale (PDS) • Caregiver Activity Survey (CAS) - listed in protocol but was not in study report 3. Physician rated global impression tests • Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus) • Global Deterioration Scale (GDS) 4. Adverse events
Source of funding	Novartis Pharma
Declaration of interest	Sponsored by Novartis Pharma
Notes	Main hypothesis: to assess the effects of rivastigmine on the core domains of AD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly allocated ... according to a computer generated randomisation code at Novartis Pharma"
Allocation concealment (selection bias)	Low risk	Not described Comment: likely to be low risk since this is a large multicentre trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo, and "the number taken were the same at each dose for all groups"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not described

B303/B305 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	An 80% completion (581/725). Proportion of participant completions was unbalanced across groups: 203/239 (87%) in placebo, 209/243 (86%) in low dose rivastigmine (1 to 4 mg/day) and 164/243 (67.5%) in higher dose (6 to 2 mg/day) group
Selective reporting (reporting bias)	Unclear risk	One of the outcomes listed in protocol, CAS, was not reported

B304

Methods	Double-blinded, placebo controlled, parallel-group randomised controlled trial 26 week treatment and follow up
Participants	**Setting:** 37 centres, Australia, Canada, Italy, South Africa, UK and Ireland **Sample size:** 678 participants out of 788 screened **Age:** mean age 71.4 years **Inclusion criteria:** • DSM-IV, NINCDS-ADRDA criteria for probable AD • MMSE range 10 to 26 inclusive **Exclusion criteria:** • significant illness, severe chronic pulmonary disease, psychiatric or neurological disorder, severe cardiovascular problems, clinically significant laboratory tests, including those indicative of impaired renal or liver function
Interventions	1. Rivastigmine 2 to 12 mg/day divided into 2 doses 2. Rivastigmine 2 to 12 mg/day divided into 3 doses 3. Placebo Started at 2 mg/day, and increased at weekly intervals in 1 mg/day steps until reaching the maximum tolerated dose. Titration lasted 10 days to 12 weeks. Patients who could not tolerate 2 mg/day by 10 days were withdrawn from study. Tolerability could be optimised by maintaining a dose level for periods of up to 2 weeks. During maintenance, dose variation allowed
Outcomes	1. Cognitive function • Alzheimer's Disease Assessment Scale (ADAS-Cog) • Mini-Mental State Examination (MMSE) 2. Activities of daily living • Progressive Deterioration Scale (PDS) • Caregiver Activity Survey (CAS) - listed in protocol but was not in study report 3. Physician rated global impression tests • Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus) • Global Deterioration Scale (GDS) 4. Adverse events
Source of funding	Funded by Novartis
Declaration of interest	Sponsored by Novartis Pharma

B304 *(Continued)*

Notes	Main hypothesis: to evaluate the efficacy and safety of individual highest well tolerated doses (range 2 to 12 mg/d) of rivastigmine twice or three times daily for 26 weeks compared to placebo, in the therapy of patients with probable AD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: not described, likely to be low risk; large multicentre trial
Allocation concealment (selection bias)	Low risk	Comment: not described, likely to be low risk, large multicentre trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Administration of each dose level was achieved by using a combination of active medication and placebo so that the appropriate daily dose was presented as 2 capsules t.i.d" Comment: used matching placebo, number of capsules taken were the same at each dose
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall 82% completion, 83% in three times daily group, 76% in two times daily group, 85% in placebo group. Comment: data were imputed using 'retrieved dropout' assessment, or last observed carried forward (LOCF) if retrieved dropout was not available
Selective reporting (reporting bias)	Low risk	Outcomes listed in protocol reported except for CAS (Caregiver Activity Survey)

B351

Methods	Double-blinded, placebo controlled, parallel-group randomised controlled trial 26 week treatment and follow up
Participants	**Setting:** USA, 14 centres between December 1994 to 22 March 1996 **Sample size:** 702 participants (393 female, 309 male) **Age:** range 45 to 89 years, mean 74.5 years **Inclusion criteria:** • 50 years or older • DSM-IV, NINCDS-ADRDA criteria for probable AD, MMSE range 10 to 26 inclusive • head computed tomography or magnetic resonance imaging scan consistent with AD within 12 months • most concomitant disease, most medications **Exclusion criteria:** • severe and unstable medical illnesses • anticholinergic drugs, acetylcholine precursor health food supplements, memory enhancers, insulin, psychotropic drugs (apart from occasional use of chloral hydrate for agitation or insomnia)
Interventions	1. Rivastigmine: 3 mg/day divided into 2 doses

B351 *(Continued)*

	2. Rivastigmine: 6 mg/day divided into 2 doses 3. Rivastigmine: 9 mg/day divided into 2 doses 4. Placebo Titration during weeks 1 to 12 to the fixed dose, fixed dose between week 13 and 26, no dose reductions allowed Patients who discontinued prematurely were asked to return at weeks 12, 18, and 26 for efficacy evaluation
Outcomes	1. Cognitive function • Alzheimer's Disease Assessment Scale (ADAS-Cog) • Mini-Mental State Examination (MMSE) • ADAS-Cog with the attention item from ADAS 2. Activities of daily living • Progressive Deterioration Scale (PDS) • Caregiver Activity Survey (CAS) - listed in protocol but was not in study report **3**. Physician rated global impression tests • Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus) • Global Deterioration Scale (GDS) 4. Adverse events
Source of funding	Novartis Pharma
Declaration of interest	Novartis Pharma
Notes	Main hypothesis: to evaluate the efficacy and safety of 3 fixed doses of rivastigmine (3, 6, 9 mg/day) and placebo for 26 weeks of treatment, and dose-efficacy and dose-safety relationships in patients with probable mild to moderate AD Assessments: baseline, 12,18, 26 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not described, likely low risk
Allocation concealment (selection bias)	Low risk	Not described, likely low risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available
Incomplete outcome data (attrition bias) All outcomes	High risk	A 66% completion rate overall. Higher percentage in the 9 mg group (49%) and 6 mg (37%) group discontinued compared to the placebo group (25%)

B351 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study data were not published, obtained from the company. Only data pooled with other studies were published by the pharmaceutical company (pooled with B303 and B352)
Other bias	High risk	

B352

Methods	Double-blinded, placebo controlled, parallel-group randomised controlled trial 26 week treatment and follow up
Participants	**Setting:** USA, 22 centres **Sample size:** 699 participants (426 female, 273 male) **Age:** range 45 to 89 years, mean 74.5 years **Inclusion criteria:** • DSM-IV, NINCDS-ADRDA criteria for probable AD, MMSE range 10 to 26 inclusive • head computed tomography or magnetic resonance imaging scan consistent with AD within 12 months • most concomitant disease, most medications **Exclusion:** • severe and unstable medical illnesses • anticholinergic drugs, acetylcholine precursor health food supplements, memory enhancers, insulin • psychotropic drugs (apart from occasional use of chloral hydrate for agitation or insomnia)
Interventions	1. Rivastigmine 1 to 4 mg/day divided into 2 doses 2. Rivastigmine 6 to 12 mg/day divided into 2 doses 3. Placebo Titration phase (fixed dose) weeks 0 to 7, flexible phase weeks 8 to 26, dose twice daily with food
Outcomes	1. Cognitive function • Alzheimer's Disease Assessment Scale (ADAS-Cog) • Mini-Mental State Examination (MMSE) 2. Activities of daily living • Progressive Deterioration Scale (PDS) • Caregiver Activity Survey (CAS) - listed in protocol but was not in study report 3. Physician rated global impression tests • Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus) • Global Deterioration Scale (GDS) Assessments: baseline, 12, 18, 26 weeks
Source of funding	Novartis Pharma
Declaration of interest	Investigator and author received payment or employed by Novartis
Notes	The study had an open label extension after 16 weeks
Risk of bias	

B352 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation procedures managed by Statistical Programming Group at Corning-Besselaar, independent of sponsor and investigating centres
Allocation concealment (selection bias)	Low risk	"At each study site, the research coordinator accessed an interactive voice response system that assigned the next available patient randomisation number, thus maintaining the blind in assigning medication to patients throughout the study and serving as a tracking system for all randomised patients."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Throughout the study all patients received two capsules twice daily Comment: identifical placebo appearance, dosing schedule and good allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Rate of completion differed between arms, 197/235 (84%) in placebo, 199/233 (85%) in low dose arm, and 149/231 (65%) in the high dose arm
Selective reporting (reporting bias)	Unclear risk	CAS scale listed in protocol but not reported in study

Ballard 2005

Methods	Double-blinded, placebo controlled 3 arm, randomised controlled trial 26 weeks
Participants	**Setting:** UK, participants lived in care facilities **Sample size:** 93 (74 female, 19 male), 31 in each group **Age:** mean 83.8 (SD 7.7) years **Inclusion criteria:** • lived in care facilities • probable or possible AD • clinically significant agitation and CMAI > 39 for at least 6 weeks • age > 60 years • NPI irritability or aberrant motor behaviour score ≥ 4 • no use of antipsychotic or cholinesterase inhibitors within 4 weeks of randomisation **Exclusion:** • severe, advanced, progressive or unstable disease • poorly controlled medical conditions, bradycardia, sick sinus syndrome, active uncontrolled peptic ulceration within past three months, clinically significant urinary condition
Interventions	1. Quetiapine (50 to 100 mg/day in two doses) 2. Rivastigmine (6 to 12 mg/day in two doses) 3. Placebo Investigators aimed to reach the target dose at week 12

Ballard 2005 *(Continued)*

Outcomes	1. Cogntive function • Severe impairment battery (SIB) measured at 6 weeks 2. Behavioral symptoms • Cohen-Mansfield Agitation Inventory (CMAI) Patients were evaluated at 6, 12 and 26 weeks
Source of funding	Alzheimer's Research Trust, general donation to the main investigator's (Clive Ballard) research programme and profits from previously completed commercial trials
Declaration of interest	Main investigator has received honoraria and research donations to support this research programme from Novartis and Astra Zeneca (manufacturers)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated with block randomisation (block sizes of three and six)" done by study statistician using Stata
Allocation concealment (selection bias)	Low risk	"The randomisation clinician faxed a form to the statistician, who communicated allocation to the pharmacy, ensuring concealment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy design used, placebo for both types of drugs used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	High risk	High number of participants not completing treatment. Outcomes were only available for about half of all patient randomised for the SIB (cognitive function) and CMAI (behavioural disturbance) at 26 weeks
Selective reporting (reporting bias)	Unclear risk	Unclear why report emphasised 6 week results (still within titration period), rather than 26 week data Comment - insufficient information to determine
Other bias	Unclear risk	Unclear. Some patients were excluded from trial

IDEAL

Methods	Double-blinded, placebo controlled, parallel-group randomised controlled trial 24 weeks
Participants	**Setting:** North, South and Central America, Asia and Europe, 21 countries, 100 centres **Sample size:** 1195 participants (796 female, 399 male) out of 1464 screened **Age:** range 50 to 85 years, mean 73.3 (SD 7.8) years

IDEAL *(Continued)*

	MMSE mean 16.5 (SD 3.0) **Inclusion criteria:** • DSM-IV for dementia of Alzheimer's type, NINCDS-ADRDA criteria for probable AD • MMSE range 10 to 20 • head computed tomography or magnetic resonance imaging scan consistent with AD within 12 months, most concomitant disease, most medications **Exclusion criteria:** • severe and unstable medical illnesses • the use of any investigational drugs, new psychotropic or dopaminergic drugs, cholinesterase inhibitors or anticholinergic agents during the 4 weeks prior to randomisation was prohibited
Interventions	1. Rivastigmine patch 10 cm^2 (9.5 mg/24h) 2. Rivastigmine patch 20 cm^2 (17.4 mg/24h) 3. Rivastigmine capsules 6 to 12mg/day divided into 2 doses 4. Placebo Titration phase weeks 0 to 7, flexible phase weeks 8 to 26, dose twice daily with food
Outcomes	1. Cognitive function • Alzheimer's Disease Assessment Scale (ADAS-Cog) • Mini-Mental State Examination (MMSE) • 10-point clock drawing • Trail making Test part A 2. Activities of daily living • Alzheimer's Disease Cooperative Study activities of daily living inventory (ADCS-ADL) 3. Physician rated global impression tests • Alzheimer's Disease Cooperative Study (ADCS-CGIC) 4. Behavioural disturbances • Neuropyschiatric Instrument (NPI)
Source of funding	"Study supported by Novartis Pharma AG, Basel, Switzerland. Data were collected by investigators and co-investigators, entered into a central database using electronic data capture software, and analysed by Novartis Pharma AG, which vouches for the data and the analysis"
Declaration of interest	Some of the investigators were employees of Novartis Pharma
Notes	There was a 4-week screening period prior to randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	" Patients were sequentially assigned the lowest available identification number at each centre, Automated random assignment of treatment using interactive voice-response system."
Allocation concealment (selection bias)	Low risk	automated random assignment of treatment using interactive voice-response system.Independent rater at 16 and 24 weeks who had no access to other data.

IDEAL *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	double dummy used, patients received placebo capsule and/or patch
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described - insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	About 79% completion in active treatment arms, and 88% in placebo arm at 26 weeks. Main ITT analysis used LOCF imputation.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to determine risk
Other bias	Unclear risk	None identified.

Karaman 2005

Methods	Double-blinded, placebo controlled, parallel-group randomised controlled trial 52 weeks
Participants	**Setting:** Turkey **Sample size:** 44 participants (24 female, 20 male), mean MMSE 12.2 **Age:** mean age 73.8 years **Inclusion criteria**: • dementia of the AD type, DSM-IV, NINCDS-ADRDA criteria for probable AD, supported by CT scan or MRI performed within 6 months before entry • age between 60 and 90 years • advanced, moderate AD: MMSE score < 14, ADAS-Cog score > 30 **Exclusion criteria:** • significant gastrointestinal illness; renal, hepatic, endocrine or cardiovascular disease; psychiatric or neurological disorder • cholinomimetic agent in preceding 60 days, other antidementia drugs
Interventions	1. Rivastigmine 12 mg/day divided into 2 doses 2. Placebo Titration phase weeks 0 to 2, 1.5 mg twice daily Week 3 to 4, 3.0 twice daily; week 5 to 6, 4.5 mg twice daily; week 7 to 8, 6 mg twice daily
Outcomes	1. Cognitive function • Alzheimer's Disease Assessment Scale (ADAS-Cog) • Mini-Mental State Examination (MMSE) 2. Activities of daily living • Alzheimer's Disease Cooperative Study activities of daily living inventory (ADCS-ADL) • Disability Assessment for Dementia (DAD) 3. Physician rated global impression tests • Global Deterioration Scale (GDS)

Karaman 2005 *(Continued)*

	• Clinician Interview-Based Impression of Change (CIBIC)
Source of funding	Not stated
Declaration of interest	Not stated
Notes	Baseline study characteristics reported were those of randomised patients who had received trial medication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to receive treatment with rivastigmine or placebo"
Allocation concealment (selection bias)	Unclear risk	Unclear - not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical tablets were given"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Rivastigmine and placebo were administered as identical tablets taken twice daily. In the rivastigmine group, patients received rivastigmine twice daily with food" There was no indication in paper how the investigators or outcomes assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Data from 21/24 patients in the rivastigmine group (and all the placebo patients) were available at 52 weeks. There was no information about loss to follow up, but the following was stated in the methods section: "At the conclusion of the 8-week study visit, participants who tolerated the drug well and perceived benefit were invited to continue rivastigmine treatment." It is unclear how many patients were excluded because they did not 'benefit' or 'tolerate' the drug well
Selective reporting (reporting bias)	Unclear risk	Insufficient information to determine
Other bias	High risk	As this study only extended the continuation to those who had perceived to benefit at the 8 week visit, this potentially introduced bias and broke the randomisation. It was not reported how many patients who were randomised initially continued to the 52 week study

Lopez-Pousa 2005

Methods	Double-blinded, placebo controlled, parallel-group randomised controlled trial 26 weeks
Participants	**Setting:** Spain, 21 centres **Sample size:** 218 participants, 77% female, mean MMSE 8.8 **Age:** mean age 77.6 years

Lopez-Pousa 2005 *(Continued)*

	Inclusion criteria: • age 55 years and above • dementia of AD type DSM-IV, NINCDS-ADRDA criteria for probable AD • severe AD, MMSE range 5 to 12 inclusive, GDS 5 to 6, Hachinski scale score of 4 **Exclusion criteria:** • sensitivity to cholinergic-like drugs • history of drug abuse, severe advanced disease, severe unstable cardiovascular disease, sinoatrial block, second or third degree atrioventricular block, institutionalisation, other cholinesterase inhibitors • other investigational drugs within 4 week entry to study
Interventions	1. Rivastigmine 12 mg/day divided into 2 doses 2. Placebo Titration phase weeks 0 to 4, 1.5 mg twice daily Weeks 5 to 8, 3.0 mg twice daily; weeks 9 to 12, 4.5 mg twice daily; weeks 13 to 16, 6 mg twice daily
Outcomes	1. Cognitive function • Mini-Mental State Examination (MMSE) • Severe Impairment Battery (SIB) 2. Activities of daily living • Alzheimer's Disease Cooperative Study activities of daily living (ADCS-ADL) 3. Behavioural symptoms • Neuropsychiatric Instrument (NPI): NPI-4 and NPI-10 4. Physician rated global impression tests • Alzheimer's Disease Cooperative Study (ADCS-CGIC) • Global Deterioration Scale (GDS) Other scales: Blessed Dementia Scale (Blessed 1968), a multidimensional performance scale
Source of funding	Not stated in study publication
Declaration of interest	Likely to be linked to pharmaceutical company, 2 of the 4 authors were employees of Novartis, randomisation scheme generated by a contract research organisation but was "reviewed" by Novartis
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated randomisation schedule", in blocks of 4
Allocation concealment (selection bias)	Unclear risk	"Eligible patients, identified at an initial screening visit were allocated randomisation number at second visit" Unclear whether this allocation was concealed

Lopez-Pousa 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Rivastigmine and placebo hard capsules were identical in appearance"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Medical monitors, centre personnel, patients and caregivers were blinded to treatment". Randomisation data were not available until after the study had been completed and the database locked
Incomplete outcome data (attrition bias) All outcomes	Low risk	An 83.5% completion in treatment arm, 88.1% completion in placebo ITT population was 104/109 in the treatment arm, 106/109 in the placebo arm Comment: early withdrawals were followed up. Documented, small percentage of missing data
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Mowla 2007

Methods	Double-blinded, 3 arm, placebo controlled, parallel-group randomised controlled trial 12 week study; 6 week single-blind placebo run-in period was included to exclude responders
Participants	**Setting:** Iran **Sample size:** 122 patients, 41 in rivastigmine group, 41 in placebo group **Age:** mean age 69.2 years, 53.5% female **Inclusion criteria:** • mild to moderate AD, diagnosed according to DSM-IV • MMSE 10 to 24, mean 16.1 (4.0) • Brief Cognitive Rating Scale 3 to 5 • Hachinski Ischemic Score < 4 • premorbid IQ > 80 **Exclusion criteria:** • dementia of other etiology, severe organic disease • other psychiatric disorder; Hamilton depression score < 10
Interventions	1. Rivastigmine 6 to 12 mg/day, twice daily 2. Rivastigmine 6 to 12 mg/day twice daily + fluoxetine 20 mg/day 2. Placebo No information was given as to whether there was any titration
Outcomes	1. Cognitive function • Mini-Mental State Examination (MMSE) • Wechsler Memory Scale (WMS-III) 2. Activities of daily living (ADL)

Mowla 2007 *(Continued)*

	• used a scale by Lawton and Brody 1969. This scale contains 8 items in Instrumental ADL and 6 items in Basic ADL, scored between 1 to 5 (1 = completely able, 5 = thoroughly unable) 3. Physician rated global impression tests • Clinical global impression (CGI)
Source of funding	Shiraz University of Medical Science Grant 83-421
Declaration of interest	None stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	“Same number of drugs were given to the patients of the 3 groups", “ there were no significant difference between the groups with respect to taking other medications” Comment: mentioned use of placebo, but unclear if these were identical to active treatments - all participants had received placebo during a 6 week run-in period
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Same number of drugs were given to the patients of the 3 groups"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rate was 7/41 (17%) in the rivastigmine group, and 8/40(20%) in the placebo group. Stated that “major cause of withdrawal was adverse events compared with loss of efficacy as the most common cause for group C”. Actual causes of loss to follow up not reported, relatively high numbers of loss to follow up for a short study of 12 weeks
Other bias	High risk	"a single blind placebo 6 week run in period was included to exclude placebo responders"

Nakamura 2011

Methods	Multicentre, randomised, double-blind, placebo controlled, 3 arm, parallel-group trial of 24 weeks A dose finding study (NCT00423085)
Participants	**Inclusion criteria:** • patients with dementia of Alzheimer's type according to DSM-IV and probable AD according to criteria of NINCDS-ADRDA, MMSE 10 to 20 • age 50 to 85 years **Exclusion criteria:**

Nakamura 2011 *(Continued)*

	• any other condition that can explain the patient's dementia • advanced, progressive disease that can prevent evaluation or put participants at risk • use of rivastigmine in the past • use of donepezil, other cholinesterase inhibitors, approved treatments for AD or other centrally acting anticholinergic drugs during the 4 weeks prior to efficacy assessments at baseline
Interventions	1. A 5 cm^2 patch (4.6 mg/day rivastigmine) 2. A 10 cm^2 patch (9.5 mg/day rivastigmine) 3. Placebo Participants were titrated to their target dose at 4 week intervals over 16 weeks, followed by an 8 week maintenance dose at weeks 17 to 24
Outcomes	1. Cognitive function • Japanese version ADAS-cog • Mental Function Impairment (MENFIS) 2. Activities of daily living • Disability Assessment for Dementia (DAD) 3. Physician rated global impression tests • Japanese version CIBIC-Plus 4. Behavioural symptoms • Behavioural Pathology in AD (BEHAVE-AD) Results were reported as intention-to-treat last observation carried forward at 24 weeks. Assessments were done during weeks 8, 16 and 24
Source of funding	A total of 4/9 authors had no interest to declare; the rest were employees of either Novartis or ONO Alpha-Plus Medical Communications Ltd (UK) provided medical writing and editorial support in the production of this manuscript; this service was sponsored by Novartis and ONO
Declaration of interest	Sponsored by Novartis and ONO Pharmaceutical Ltd (they jointly developed and marketed the transdermal patch in Japan)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The patient registration centre provided a randomisation number to the eligible participants and randomisation lists were generated by a Drug ALlocation Controller". A dynamic allocation was utilised, using body weight (< 45, 45 to < 55 and ≥ 55 kg) and MMSE score (≤ 15, > 15 points) as factors
Allocation concealment (selection bias)	Low risk	Likely to be low risk. Investigators had to offer enrolment to all eligible patients. Allocation number provided after eligibility criteria confirmed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Randomisation data kept strictly confidential by the Study Drug Allocation Controller until the time of unblinding" (only permitted during emergencies and at conclusion of study) However, 3 different patch sizes were used, 2.5 cm^2, 5 cm^2, 7.5 cm^2 and 10 cm^2

Nakamura 2011 *(Continued)*

		Since the higher dose group (10 cm^2) used bigger patches than the maximum for the 5 cm^2 group, unclear how blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"patients, investigator staff, persons performing the assessments and data analysts were all blinded"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	An 80.3% completion rate of study; 88% in placebo, about 80% in active treatment available as ITT-observed cases at week 24
Selective reporting (reporting bias)	Low risk	Outcomes listed in protocol were reported
Other bias	Low risk	None identified

Tai 2000

Methods	Double-blinded randomised controlled trial 26 weeks follow up
Participants	**Setting:** Taiwan **Sample size:** 80 **Inclusion criteria:** • mild to moderate AD
Interventions	1. Rivastigmine: 3 mg/day divided into 2 doses, escalating by 3 mg/day not faster than every two weeks until a dose that was not tolerated was reached 2. Placebo
Outcomes	1. Cognitive Function • MMSE • Neuropsychological Tests (NPT) 2.Activities of daily living - none stated 3. Physician rated global impression tests • CIBIC-Plus • Global Deterioration Scale 5. Frequency of adverse events 6. Withdrawal due to adverse events • study only reported overall withdrawals
Source of funding	Not stated
Declaration of interest	Not stated
Notes	

Tai 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information. Only abstract available
Allocation concealment (selection bias)	Unclear risk	No information. Only abstract available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information. Only abstract available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information. Only abstract available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to judge. Only abstract available
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge. Only abstract available
Other bias	Unclear risk	Insufficient information to judge. Only abstract available

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

Study	Reason for exclusion
ACTION	This trial compared two sizes of rivastigmine patches, but there was no placebo group
Almkvist 2004	This trial studied particular aspects of memory, but used historical controls as the untreated group
Auriacombe 2002	Open label, 6 month study of rivastigmine for patients who had failed to benefit from donepezil. Later extended to 12 months
B105	THis was a randomised, placebo controlled trial, but the duration was only 9 weeks
Bilikiewicz 2002	Open label study of rivastigmine in community setting
Blesa Gonzalez 2011	Trial investigating adverse events on changing to patches from tablets. There were 2 groups using patches, and one group continuing on tablets, but no placebo group. The trial was open label, and data were not reported for all groups, limiting usable comparisons
Brassen 2003	An unblinded study. Open controlled design of rivastigmine compared with donepezil, 35 AD patients
Caffarra 2007	There was no placebo group. Comparison of rivastigmine with donepezil, retrospective study
Cummings 2000	Open label study of nursing home patients

Study	Reason for exclusion
Cutler 1998	Open label non-randomised study
Cutler 2000	Open label study investigating the pharmacokinetics of oral and intravenous rivastigmine
Dantoine 2006	Comparison of rivastigmine with rivastigmine plus memantine in AD patients previously failing to respond on donepezil or galantamine, open label study
Doraiswamy 2000a	Open label extension to either B303 or B352
Edwards 2002	Open label study of nursing home patients, all on rivastigmine. Outcome was assessment of use of psychotropics
EXCEED	Donepezil compared with rivastigmine. A 24 month randomised controlled trial with no placebo group
Frankfort 2007	Study of effect of rivastigmine on specific cognitive domains. This is not an randomised controlled trial, treatment group compared with historical controls
Fuschillo 2001	Randomised study of donepezil compared with rivastigmine for AD. No placebo group
Holmes 2007	Randomised study of rivastigmine compared with risperidone, no placebo group
InDDEx	Randomised placebo controlled study of rivastigmine for patients with mild cognitive impairment but not dementia
Kim 2002	A 24 week open label study, all on rivastigmine
Malsch 2001	Open label 8 week study, patients randomised to two different titration schemes
McMillan 1999	Open label study of early non-responders
Novartis 2005	Open label extension study
OPTIMA	This trial compared two sizes of rivastigmine patches, but there was no placebo group
Potkin 1999a	Investigation of brain metabolism using positron emission tomography (PET) scans from 27 patients chosen non-randomly from study B351
Riepe 2005	This is not a randomised controlled trial; 12 week open label study of rivastigmine + memantine
Rozzini 2002	Randomised trial comparing rivastigmine with donepezil. No placebo group
Schmidt 2002	Open label study on the use of rivastigmine in routine clinical practice
Shanks 2001	Open label study, all on rivastigmine, assessing cerebral flow only
Shua-Haim 2002a	A 5 month study, comparing donepezil with rivastigmine with galantamine. No placebo group
Shua-Haim 2002b	Open label treatment of agitation in patients with AD
Shua-Haim 2002c	Donepezil, compared with rivastigmine, compared with galantamine
Small 2005	A pooled study of two open label extension studies of rivastigmine
Sobow 2002	Retrospective review of patients who had been prescribed rivastigmine or donepezil

Study	Reason for exclusion
Stefanova 2002	Rivastigmine compared with tacrine in matched groups
Thomas 2001	Open label trial
Tsolaki 2002	Retrospective study, comparing donepezil with rivastigmine
Venneri 2002	Non-randomised study of 4 patients. Rates of progression of disease in those treated with rivastigmine compared with untreated patients
Wang 2001	Open label, randomised study, comparing rivastigmine with donepezil
Wang 2003	Open label study of rivastigmine
Weiser 2002	Open label pilot study. Patients randomised to rivastigmine and risperidone, alone or in combination
Werber 2002	Non-randomised study of donepezil compared with tacrine, with rivastigmine. Outcome is cognition related brain evoked potential
Wilkinson 2002	Randomised, 12 week, open label study comparing donepezil with rivastigmine. No placebo group

DATA AND ANALYSES

Comparison 1. Rivastigmine (capsules 6 to 12 mg/day in two divided doses or 10 cm^2 (9.5 mg/day) patch) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-Cog (change from baseline at 24-26 weeks) ITT	6	3232	Mean Difference (IV, Fixed, 95% CI)	-1.79 [-2.21, -1.37]
2 MMSE (change from baseline at 24-26 weeks) ITT	6	3205	Mean Difference (IV, Fixed, 95% CI)	0.74 [0.52, 0.97]
3 Activities of daily living (change from baseline at 24-26 weeks) ITT	6	3230	Std. Mean Difference (IV, Fixed, 95% CI)	0.20 [0.13, 0.27]
4 Clinical Global Impression (no change or worse at 24-26 weeks) ITT	7	3338	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.58, 0.80]
5 Behavioural symptoms (change from baseline at 24-26 weeks) ITT	3	1529	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.14, 0.06]
6 Withdrawals before end of treatment at 24-26 weeks	7	3569	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [1.74, 2.45]
7 at least one adverse event by 24-26 weeks	7	3587	Odds Ratio (M-H, Fixed, 95% CI)	2.16 [1.82, 2.57]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8 NPI-D carer distress scale (change from baseline at 24-26 weeks) ITT	1	529	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.91, 1.11]

Analysis 1.1. Comparison 1 Rivastigmine (capsules 6 to 12 mg/day in two divided doses or 10 cm^2 (9.5 mg/day) patch) versus placebo, Outcome 1 ADAS-Cog (change from baseline at 24-26 weeks) ITT.

Study or subgroup	rivastigmine		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
B303/B305	242	-0.3 (6.8)	238	1.3 (7)		11.56%	-1.6[-2.83,-0.37]
B304	228	1.2 (7.2)	220	2.8 (7.2)		9.91%	-1.6[-2.93,-0.27]
B351	353	1 (5)	171	2.4 (5)		21.15%	-1.4[-2.31,-0.49]
B352	231	0.3 (6)	234	4.1 (6)		14.82%	-3.8[-4.89,-2.71]
IDEAL	501	-0.6 (6.4)	281	1 (6.8)		18.63%	-1.6[-2.57,-0.63]
Nakamura 2011	268	0.1 (5)	265	1.3 (5.1)		23.93%	-1.2[-2.06,-0.34]
Total ***	**1823**		**1409**			**100%**	**-1.79[-2.21,-1.37]**
Heterogeneity: Tau^2=0; Chi^2=15.88, df=5(P=0.01); I^2=68.51%							
Test for overall effect: Z=8.35(P<0.0001)							

Favours rivastigmine — Favours placebo

Analysis 1.2. Comparison 1 Rivastigmine (capsules 6 to 12 mg/day in two divided doses or 10 cm^2 (9.5 mg/day) patch) versus placebo, Outcome 2 MMSE (change from baseline at 24-26 weeks) ITT.

Study or subgroup	rivastigmine		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
B303/B305	242	0.2 (3.5)	239	-0.5 (3.6)		12.77%	0.72[0.09,1.35]
B304	227	-0.6 (3.6)	220	-1.4 (3.6)		11.54%	0.8[0.13,1.47]
B351	354	-0 (3)	173	-0.7 (3)		17.28%	0.65[0.1,1.2]
B352	231	0.2 (3)	235	-0.9 (3)		17.32%	1.1[0.56,1.64]
IDEAL	506	1 (3.3)	281	0 (3.5)		20.55%	0.95[0.45,1.45]
Nakamura 2011	246	0 (2.9)	251	-0.3 (2.8)		20.54%	0.3[-0.2,0.8]
Total ***	**1806**		**1399**			**100%**	**0.74[0.52,0.97]**
Heterogeneity: Tau^2=0; Chi^2=5.46, df=5(P=0.36); I^2=8.49%							
Test for overall effect: Z=6.43(P<0.0001)							

Favours placebo — Favours rivastigmine

Analysis 1.3. Comparison 1 Rivastigmine (capsules 6 to 12 mg/day in two divided doses or 10 cm² (9.5 mg/day) patch) versus placebo, Outcome 3 Activities of daily living (change from baseline at 24-26 weeks) ITT.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
B303/B305	241	0 (13.2)	237	-2.2 (13.4)		15.41%	0.17[-0.01,0.34]
B304	227	-2.7 (11.1)	221	-4.9 (11.2)		14.42%	0.2[0.01,0.38]
B351	349	-2.3 (10.4)	173	-3.1 (10.3)		14.95%	0.08[-0.11,0.26]
B352	231	-1.5 (10.3)	233	-4.9 (10.3)		14.8%	0.33[0.15,0.51]
IDEAL	501	-0.3 (9.5)	281	-2.3 (9.4)		23.17%	0.21[0.06,0.36]
Nakamura 2011	269	-1.9 (10.7)	267	-4.2 (12.4)		17.25%	0.2[0.03,0.37]
Total ***	**1818**		**1412**			**100%**	**0.2[0.13,0.27]**
Heterogeneity: Tau²=0; Chi²=3.83, df=5(P=0.57); I²=0%							
Test for overall effect: Z=5.49(P<0.0001)							

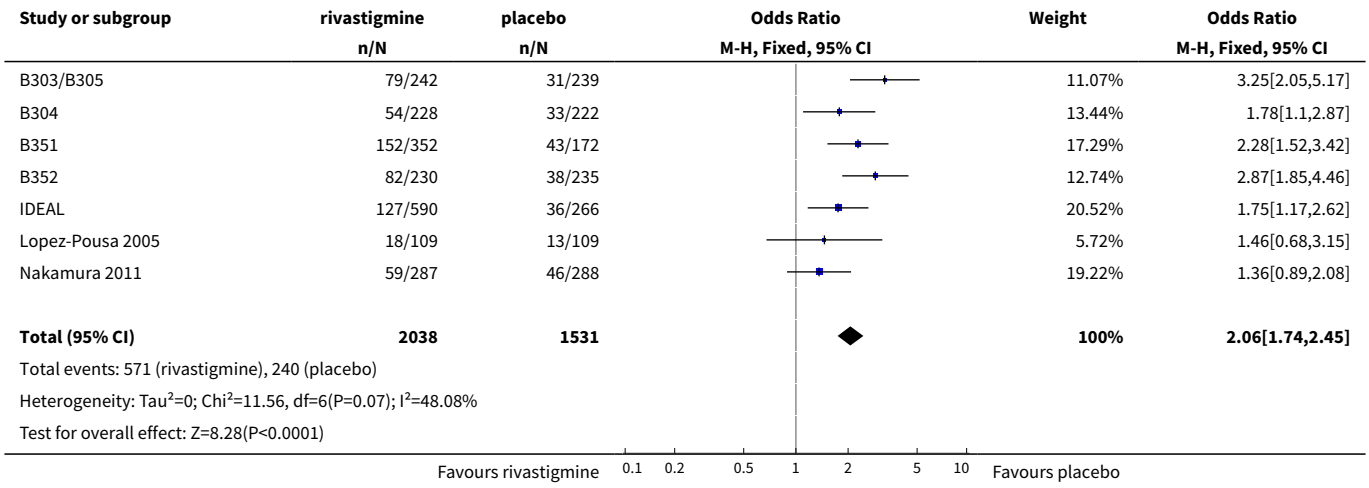
Analysis 1.4. Comparison 1 Rivastigmine (capsules 6 to 12 mg/day in two divided doses or 10 cm² (9.5 mg/day) patch) versus placebo, Outcome 4 Clinical Global Impression (no change or worse at 24-26 weeks) ITT.

Study or subgroup	rivastigmine n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
B303/B305	139/219	184/230		18.95%	0.43[0.28,0.66]
B304	171/222	175/216		11.78%	0.79[0.49,1.25]
B351	238/318	126/169		11.97%	1.02[0.66,1.56]
B352	167/214	190/224		11.79%	0.64[0.39,1.04]
IDEAL	332/501	200/278		25.08%	0.77[0.56,1.06]
Lopez-Pousa 2005	81/104	96/106		6.08%	0.37[0.16,0.82]
Nakamura 2011	211/270	226/267		14.35%	0.65[0.42,1.01]
Total (95% CI)	**1848**	**1490**		**100%**	**0.68[0.58,0.8]**
Total events: 1339 (rivastigmine), 1197 (placebo)					
Heterogeneity: Tau²=0; Chi²=10.96, df=6(P=0.09); I²=45.23%					
Test for overall effect: Z=4.59(P<0.0001)					

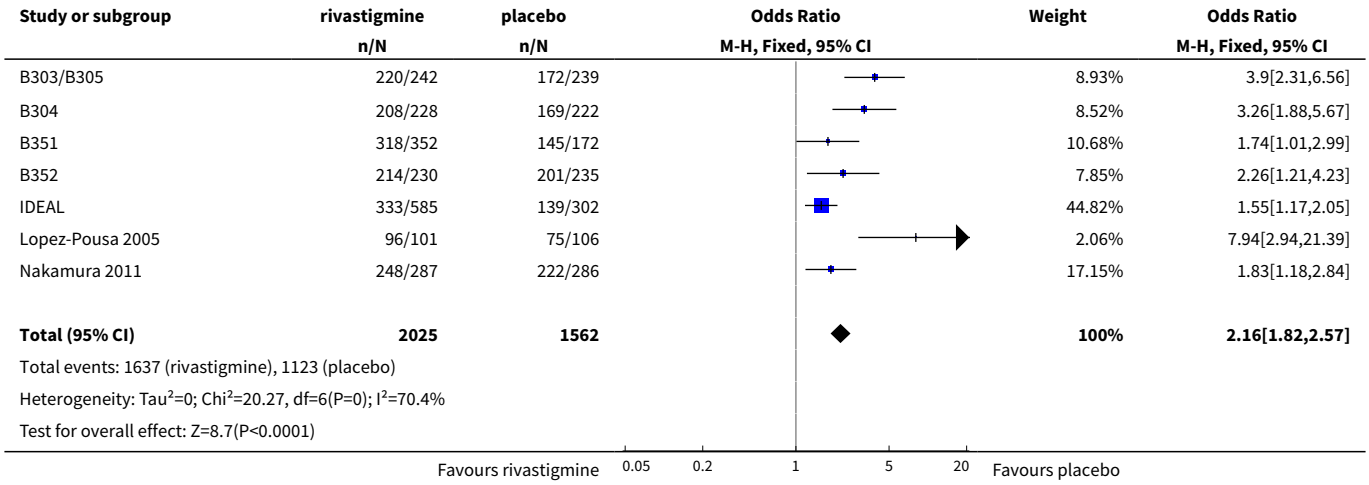
Analysis 1.5. Comparison 1 Rivastigmine (capsules 6 to 12 mg/day in two divided doses or 10 cm² (9.5 mg/day) patch) versus placebo, Outcome 5 Behavioural symptoms (change from baseline at 24-26 weeks) ITT.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
IDEAL	501	-1.9 (11.9)	281	-1.7 (13.8)		49.1%	-0.02[-0.17,0.13]
Lopez-Pousa 2005	104	-0.1 (15.2)	106	1.7 (17.5)		14.3%	-0.11[-0.38,0.16]
Nakamura 2011	270	-0.3 (4.7)	267	-0.1 (3.8)		36.6%	-0.05[-0.22,0.12]
Total ***	**875**		**654**			**100%**	**-0.04[-0.14,0.06]**
Heterogeneity: Tau²=0; Chi²=0.33, df=2(P=0.85); I²=0%							
Test for overall effect: Z=0.81(P=0.42)							

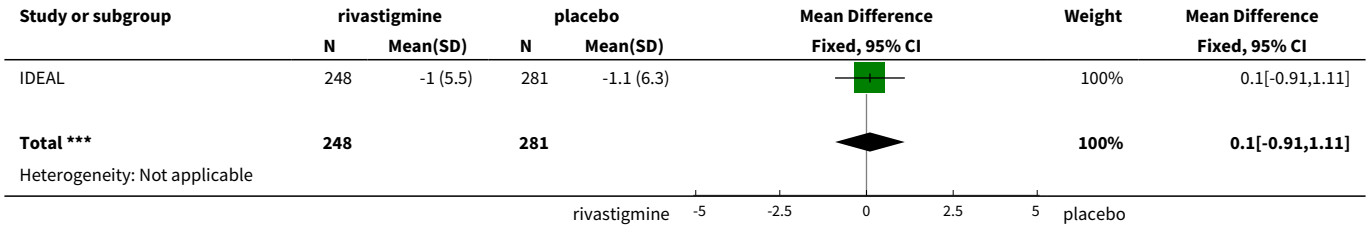
Analysis 1.6. Comparison 1 Rivastigmine (capsules 6 to 12 mg/day in two divided doses or 10 cm^2 (9.5 mg/day) patch) versus placebo, Outcome 6 Withdrawals before end of treatment at 24-26 weeks.

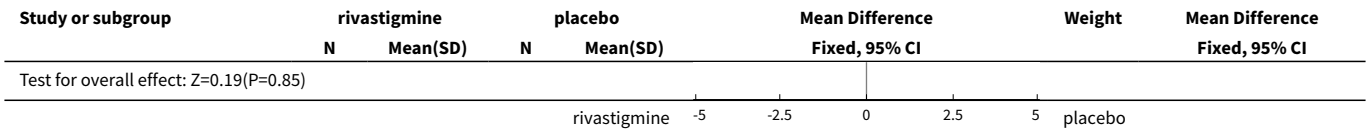


Analysis 1.7. Comparison 1 Rivastigmine (capsules 6 to 12 mg/day in two divided doses or 10 cm^2 (9.5 mg/day) patch) versus placebo, Outcome 7 at least one adverse event by 24-26 weeks.



Analysis 1.8. Comparison 1 Rivastigmine (capsules 6 to 12 mg/day in two divided doses or 10 cm^2 (9.5 mg/day) patch) versus placebo, Outcome 8 NPI-D carer distress scale (change from baseline at 24-26 weeks) ITT.





Comparison 2. Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 ADAS-Cog (change from baseline at 12 weeks) ITT	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 rivastigmine (1-4 mg/d) vs placebo	3	1293	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.87, 0.25]
1.2 rivastigmine (6-12 mg/d) vs placebo	4	1917	Mean Difference (IV, Fixed, 95% CI)	-1.49 [-1.96, -1.01]
2 ADAS-Cog (change from baseline at 26 weeks) ITT	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 rivastigmine (1-4 mg/d) vs placebo	3	1293	Mean Difference (IV, Fixed, 95% CI)	-0.84 [-1.48, -0.19]
2.2 rivastigmine (6-12 mg/d) vs placebo	5	2451	Mean Difference (IV, Fixed, 95% CI)	-1.99 [-2.49, -1.50]
3 MMSE (change from baseline at 26 weeks) ITT	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 rivastigmine (1-4 mg/d) vs placebo	3	1297	Mean Difference (IV, Fixed, 95% CI)	0.43 [0.08, 0.78]
3.2 rivastigmine (6-12 mg/d) vs placebo	5	2458	Mean Difference (IV, Fixed, 95% CI)	0.82 [0.56, 1.08]
4 SIB (change from baseline at 26 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Rivastigmine 6-12 mg/day	1	210	Mean Difference (IV, Fixed, 95% CI)	4.53 [0.47, 8.59]
5 ADCS-ADL (change from baseline at 26 weeks) ITT	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 rivastigmine (6-12 mg/d) vs placebo	1	535	Mean Difference (IV, Fixed, 95% CI)	1.80 [0.20, 3.40]
6 PDS (change from baseline at 12 weeks) ITT	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 rivastigmine (1-4 mg/d) vs placebo	3	1288	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-1.84, 0.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 rivastigmine (6-12 mg/d) vs placebo	4	1912	Mean Difference (IV, Fixed, 95% CI)	1.08 [0.19, 1.98]
7 PDS (change from baseline at 26 weeks) ITT	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 rivastigmine (1-4 mg/d) vs placebo	3	1288	Mean Difference (IV, Fixed, 95% CI)	-0.38 [-1.61, 0.84]
7.2 rivastigmine (6-12 mg/d) vs placebo	4	1912	Mean Difference (IV, Fixed, 95% CI)	2.15 [1.13, 3.16]
8 Clinical Global Impression (no change or worse at 12 weeks) ITT	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 rivastigmine (1-4 mg/d) vs placebo	3	1220	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.72, 1.21]
8.2 rivastigmine (6-12 mg/d) vs placebo	4	1775	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.60, 0.92]
9 Clinical Global Impression (no change or worse at 26 weeks) ITT	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 rivastigmine (1-4 mg/d) vs placebo	3	1237	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.55, 0.93]
9.2 rivastigmine (6-12 mg/d) vs placebo	6	2553	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.55, 0.79]
10 GDS(moderately severe, severe, or very severe dementia at 26 weeks) ITT	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 rivastigmine (1-4 mg/d) vs placebo	3	1296	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.71, 1.14]
10.2 rivastigmine (6-12 mg/d) vs placebo	4	1923	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.78 [0.64, 0.94]
11 CGIC (little or no improvement, or worse at 12 weeks) ITT	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
11.1 rivastigmine (1-4 mg/d) vs placebo	1	269	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.60, 1.77]
11.2 rivastigmine (6-12 mg/d) vs placebo	1	266	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.43, 1.22]
12 Behavioural disturbance NPI-10 or NPI-12 (change from baseline at 26 weeks) ITT	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Rivastigmine (6-12 mg/day) vs placebo	2	744	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.20, 0.09]
13 withdrawals before end of treatment at 12 weeks	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
13.1 rivastigmine (1-4 mg/d) vs placebo	1	269	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.15 [0.95, 4.89]
13.2 rivastigmine (6-12 mg/d) vs placebo	1	266	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.60 [1.19, 5.67]
14 withdrawals before end of treatment at 26 weeks	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
14.1 rivastigmine (1-4 mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.75, 1.34]
14.2 rivastigmine (6-12 mg/d) vs placebo	6	2701	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.19 [1.83, 2.63]
15 at least one adverse event by the end of titration period	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
15.1 rivastigmine (1-4 mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.82, 1.31]
15.2 rivastigmine (6-12 mg/d) vs placebo	4	1920	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.96 [2.39, 3.68]
16 at least one adverse event by 26 weeks	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
16.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.71, 1.23]
16.2 rivastigmine (6-12mg/d) vs placebo	6	2726	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.49 [2.05, 3.02]
17 dropouts due to adverse events by 12 weeks	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
17.1 rivastigmine (4mg/d) vs placebo	1	269	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.70 [1.06, 6.84]
17.2 rivastigmine (6mg/d) vs placebo	1	266	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.11 [1.28, 7.56]
18 dropouts due to adverse events by 26 weeks	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
18.1 rivastigmine (1-4 mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.69, 1.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.2 rivastigmine (6-12 mg/d) vs placebo	6	2729	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.73 [2.19, 3.41]
19 at least one adverse event of decreased appetite by 26 weeks	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
19.1 rivastigmine (6-12 mg/d) vs placebo	1	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.51 [1.26, 9.79]
20 at least one adverse event of weight decrease by 26 weeks	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
20.1 rivastigmine (6-12mg/d) vs placebo	1	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.55 [1.46, 8.66]
21 at least one adverse event of nausea by the end of titration period	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
21.1 rivastigmine (1-4mg/d) vs placebo	4	1559	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [1.36, 2.52]
21.2 rivastigmine (6-12 mg/d) vs placebo	5	2186	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.57 [4.59, 6.75]
22 at least one adverse event of nausea by 26 weeks	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
22.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [1.28, 2.36]
22.2 rivastigmine (6-12mg/d bid) vs placebo	6	2726	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.36 [4.50, 6.40]
23 at least one adverse event of vomiting by the end of titration period	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
23.1 rivastigmine (1-4mg/d) vs placebo	4	1559	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.97 [1.22, 3.16]
23.2 rivastigmine (6-12 mg/d) vs placebo	5	2187	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.72 [4.48, 7.29]
24 at least one adverse event of vomiting by 26 weeks	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
24.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [1.08, 2.52]
24.2 rivastigmine (6-12mg/d) vs placebo	6	2726	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.15 [4.20, 6.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25 at least one adverse event of diarrhoea by the end of titration period	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
25.1 rivastigmine (1-4mg/d) vs placebo	4	1559	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.68, 1.42]
25.2 rivastigmine (6-12 mg/d) vs placebo	5	2186	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.97 [1.51, 2.57]
26 at least one adverse event of diarrhoea by 26 weeks	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
26.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.67, 1.31]
26.2 rivastigmine (6-12mg/d) vs placebo	5	2516	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.76 [1.39, 2.24]
27 at least one adverse event of anorexia by the end of titration period	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
27.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.21 [1.24, 3.95]
27.2 rivastigmine (6-12 mg/d) vs placebo	4	1920	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.94 [3.56, 6.85]
28 at least one adverse event of anorexia by 26 weeks	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
28.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.13 [1.29, 3.52]
28.2 rivastigmine (6-12mg/d) vs placebo	5	2130	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.46 [3.34, 5.95]
29 at least one adverse event of headache by the end of titration period	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
29.1 rivastigmine (1-4mg/d) vs placebo	4	1559	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.69, 1.37]
29.2 rivastigmine (6-12 mg/d) vs placebo	5	2186	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.64 [1.26, 2.14]
30 at least one adverse event of headache by 26 weeks	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
30.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.84, 1.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30.2 rivastigmine (6-12mg/d) vs placebo	5	2516	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [1.34, 2.21]
31 at least one adverse event of insomnia by the end of titration period	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
31.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.64, 1.67]
31.2 rivastigmine (6-12 mg/d) vs placebo	4	1920	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.40 [0.94, 2.09]
32 at least one adverse event of insomnia by 26 weeks	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
32.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.70, 1.58]
32.2 rivastigmine (6-12mg/d) vs placebo	4	1920	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.95, 1.87]
33 at least one adverse event of syncope by the end of titration period	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
33.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [0.43, 5.20]
33.2 rivastigmine (6-12 mg/d) vs placebo	4	1920	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [0.99, 4.68]
34 at least one adverse event of syncope by 26 weeks	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
34.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.37, 2.69]
34.2 rivastigmine (6-12mg/d bid) vs placebo	4	1920	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [0.96, 3.11]
35 at least one adverse event of abdominal pain by the end of titration period	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
35.1 rivastigmine (1-4mg/d) vs placebo	4	1559	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.72, 1.88]
35.2 rivastigmine (6-12mg/d) vs placebo	5	2186	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.50 [1.80, 3.48]
36 at least one adverse event of abdominal pain by 26 weeks	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.77, 1.87]
36.2 rivastigmine (6-12mg/d) vs placebo	4	1920	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.24 [1.65, 3.05]
37 at least one adverse event of dizziness by the end of titration period	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
37.1 rivastigmine (1-4mg/d) vs placebo	4	1559	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.70, 1.39]
37.2 rivastigmine (6-12 mg/d) vs placebo	5	2186	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.86, 3.04]
38 at least one adverse event of dizziness by 26 weeks	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
38.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.91, 1.72]
38.2 rivastigmine (6-12mg/d) vs placebo	5	2516	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.24 [1.78, 2.82]
39 at least one adverse event of bone fracture by the end of titration period	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
39.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.25, 2.72]
39.2 rivastigmine (6-12 mg/d) vs placebo	4	1920	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.37, 2.46]
40 at least one adverse event of bone fracture by 26 weeks	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
40.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.27, 1.34]
40.2 rivastigmine (6-12mg/d) vs placebo	4	1920	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.34, 1.42]
41 at least one adverse event of asthenia by 26 weeks	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
41.1 rivastigmine (6-12mg/d) vs placebo	1	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.37 [1.79, 10.65]
42 at least one severe adverse event by the end of titration period	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

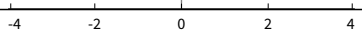
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
42.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.62, 1.42]
42.2 rivastigmine (6-12 mg/d) vs placebo	4	1920	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.88 [1.39, 2.55]
43 at least one serious adverse event by 26 weeks	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
43.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.70, 1.36]
43.2 rivastigmine (6-12mg/d) vs placebo	6	2726	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.93, 1.47]
44 deaths before end of treatment at 12 weeks	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
44.1 rivastigmine (1-4mg/d) vs placebo	1	269	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.34 [0.76, 71.14]
44.2 rivastigmine (6-12 mg/d) vs placebo	1	266	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.45 [0.46, 119.66]
45 deaths before end of treatment at 26 weeks	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
45.1 rivastigmine (1-4mg/d) vs placebo	3	1290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.98 [0.20, 19.15]
45.2 rivastigmine (6-12mg/d) vs placebo	6	2737	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.40, 3.37]
46 CIBIC-Plus (no change or worse at 12 weeks) OC	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
46.1 rivastigmine (1-4mg/d) vs placebo	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.72, 1.23]
46.2 rivastigmine (6-12mg/d) vs placebo	4	1630	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.58, 0.91]
47 CIBIC-Plus (no change or worse at 26 weeks) OC	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
47.1 rivastigmine (1-4mg/d) vs placebo	3	1036	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.50, 0.89]
47.2 rivastigmine (6-12mg/d) vs placebo	4	1353	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.49, 0.81]
48 CIBIC-Plus (no change or worse at 12 weeks) OC+RDO	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
48.1 rivastigmine (1-4mg/d) vs placebo	3	1221	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.72, 1.22]
48.2 rivastigmine (6-12mg/d) vs placebo	4	1777	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.60, 0.93]
49 CIBIC-Plus (no change or worse at 26 weeks)OC+RDO	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
49.1 rivastigmine (1-4mg/d) vs placebo	3	1093	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.52, 0.91]
49.2 rivastigmine (6-12mg/d) vs placebo	4	1542	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.51, 0.82]
50 CIBIC-Plus (no change or worse at 12 weeks) ALL+OC	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
50.1 rivastigmine (1-4mg/d) vs placebo	3	1293	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.77, 1.30]
50.2 rivastigmine (6-12mg/d) vs placebo	4	1917	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.72, 1.13]
51 CIBIC-Plus (no change or worse at 26 weeks) ALL+OC	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
51.1 rivastigmine (1-4mg/d) vs placebo	3	1297	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.55, 0.96]
51.2 rivastigmine (6-12mg/d) vs placebo	4	1921	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.69, 1.12]
52 ADAS-Cog (change from baseline at 12 weeks) OC	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
52.1 rivastigmine (1-4mg/d) vs placebo	3	1187	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-1.08, 0.15]
52.2 rivastigmine (6-12mg/d) vs placebo	4	1646	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-2.33, -1.27]
53 ADAS-Cog (change from baseline at 26 weeks) OC	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
53.1 rivastigmine (1-4mg/d) vs placebo	3	1045	Mean Difference (IV, Fixed, 95% CI)	-0.97 [-1.72, -0.21]
53.2 rivastigmine (6-12mg/d) vs placebo	4	1379	Mean Difference (IV, Fixed, 95% CI)	-2.62 [-3.29, -1.94]
54 ADAS-Cog (change from baseline at 12 weeks) OC+RDO	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
54.1 rivastigmine (1-4mg/d) vs placebo	3	1231	Mean Difference (IV, Fixed, 95% CI)	-0.37 [-0.96, 0.23]
54.2 rivastigmine (6-12mg/d) vs placebo	4	1795	Mean Difference (IV, Fixed, 95% CI)	-1.38 [-1.89, -0.88]
55 ADAS-Cog (change from baseline at 26 weeks) OC+RDO	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
55.1 rivastigmine (1-4mg/d) vs placebo	3	1123	Mean Difference (IV, Fixed, 95% CI)	-1.07 [-1.80, -0.34]
55.2 rivastigmine (6-12mg/d) vs placebo	4	1547	Mean Difference (IV, Fixed, 95% CI)	-2.39 [-3.03, -1.74]

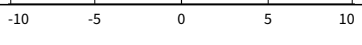
Analysis 2.1. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 1 ADAS-Cog (change from baseline at 12 weeks) ITT.

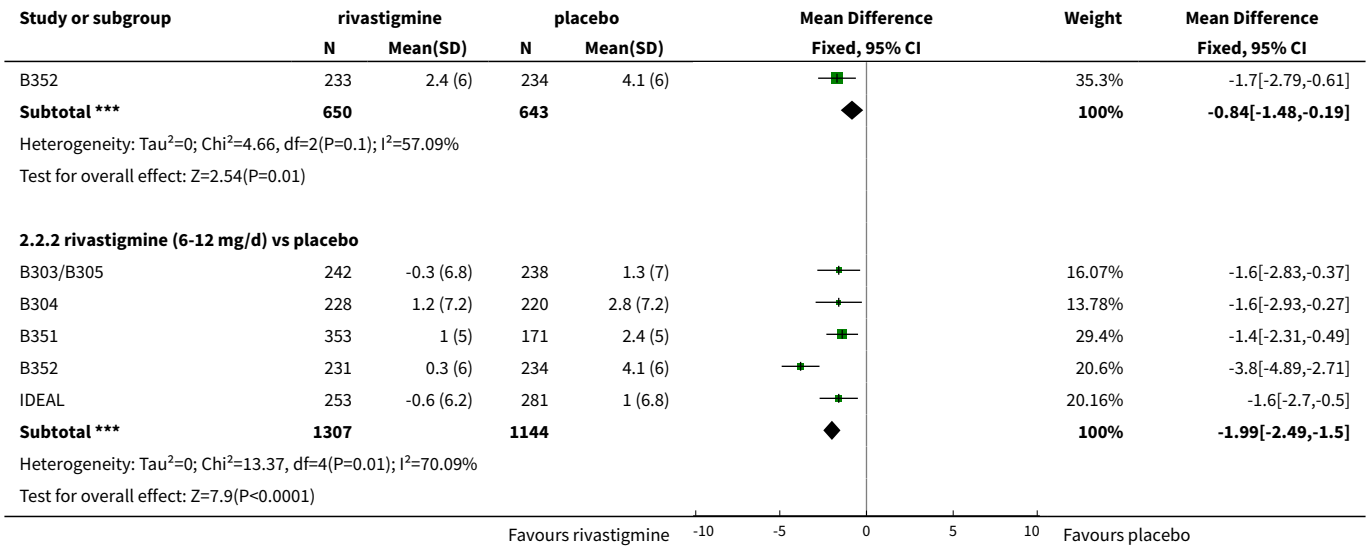
Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 rivastigmine (1-4 mg/d) vs placebo							
B303/B305	242	0.1 (5.6)	238	-0.1 (5.7)		30.69%	0.23[-0.78,1.24]
B351	175	0.3 (4.6)	171	0.8 (4.6)		33.38%	-0.5[-1.47,0.47]
B352	233	1.5 (5.2)	234	2.1 (5.1)		35.94%	-0.6[-1.53,0.33]
Subtotal ***	**650**		**643**			**100%**	**-0.31[-0.87,0.25]**
Heterogeneity: Tau^2=0; Chi^2=1.61, df=2(P=0.45); I^2=0%							
Test for overall effect: Z=1.09(P=0.28)							
2.1.2 rivastigmine (6-12 mg/d) vs placebo							
B303/B305	242	-1.5 (5.6)	238	-0.1 (5.7)		22.03%	-1.35[-2.36,-0.34]
B304	228	-0.8 (5.7)	220	0.9 (5.8)		19.85%	-1.7[-2.77,-0.63]
B351	353	0.4 (4.6)	171	0.8 (4.6)		31.92%	-0.45[-1.29,0.39]
B352	231	-0.6 (5.1)	234	2.1 (5.1)		26.2%	-2.7[-3.63,-1.77]
Subtotal ***	**1054**		**863**			**100%**	**-1.49[-1.96,-1.01]**
Heterogeneity: Tau^2=0; Chi^2=12.65, df=3(P=0.01); I^2=76.29%							
Test for overall effect: Z=6.14(P<0.0001)							



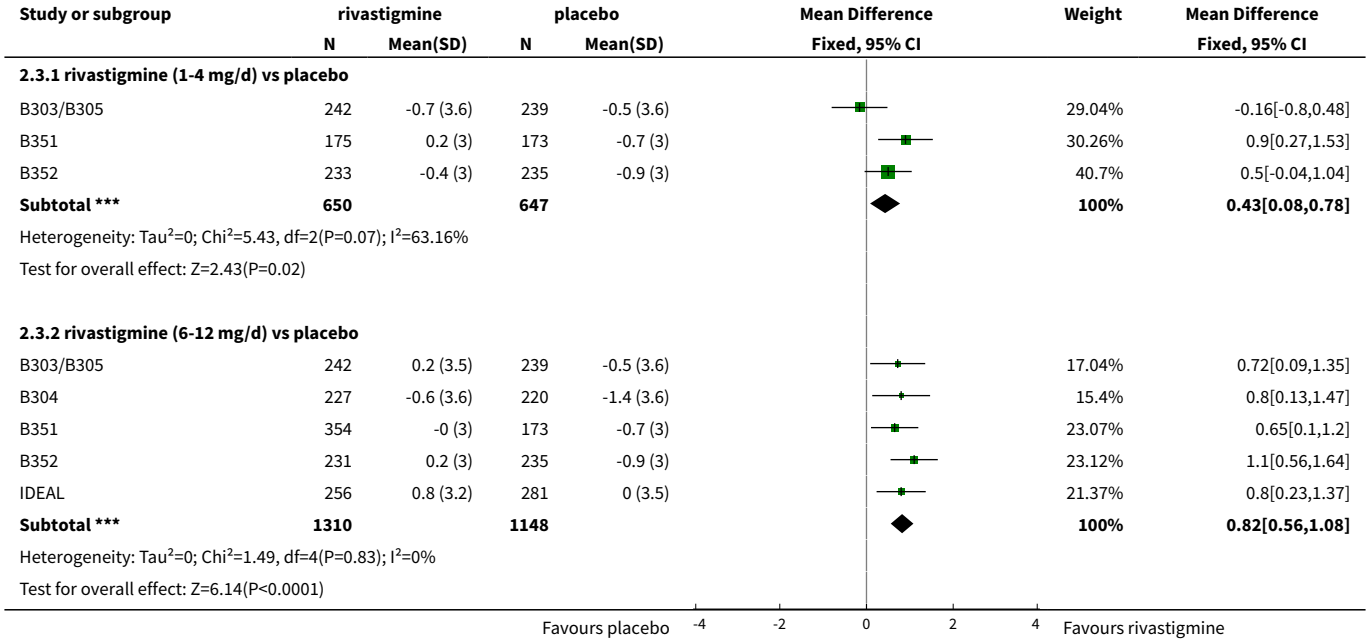
Analysis 2.2. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 2 ADAS-Cog (change from baseline at 26 weeks) ITT.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.2.1 rivastigmine (1-4 mg/d) vs placebo							
B303/B305	242	1.4 (6.9)	238	1.3 (7)		27.04%	0.1[-1.14,1.34]
B351	175	1.7 (5)	171	2.4 (5)		37.66%	-0.7[-1.75,0.35]

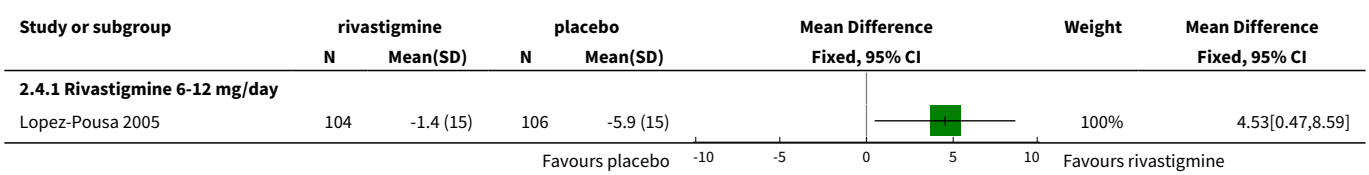


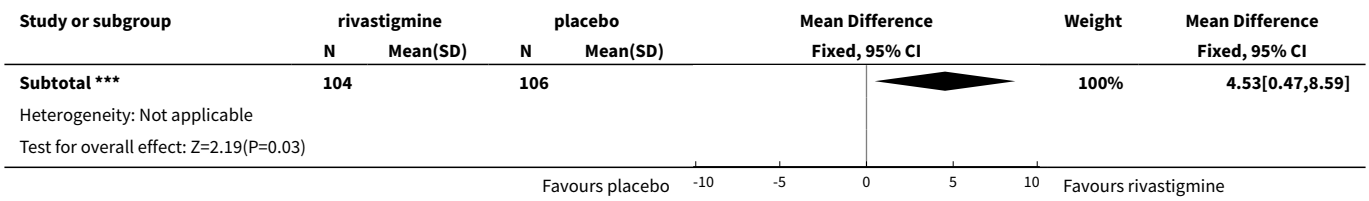


Analysis 2.3. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 3 MMSE (change from baseline at 26 weeks) ITT.

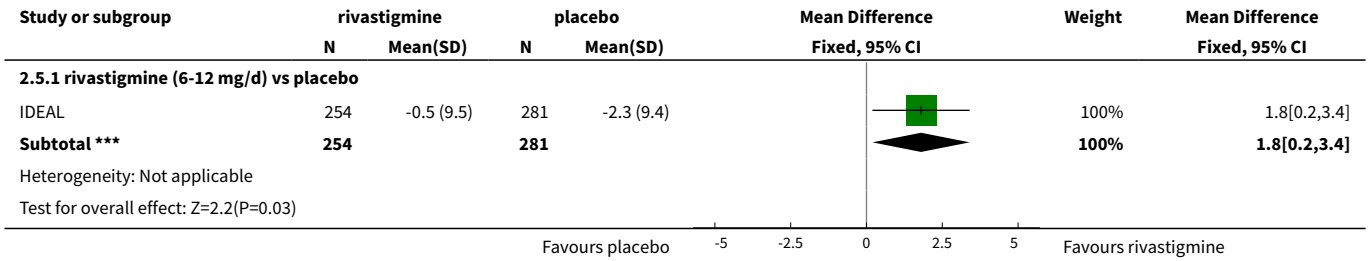


Analysis 2.4. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 4 SIB (change from baseline at 26 weeks).

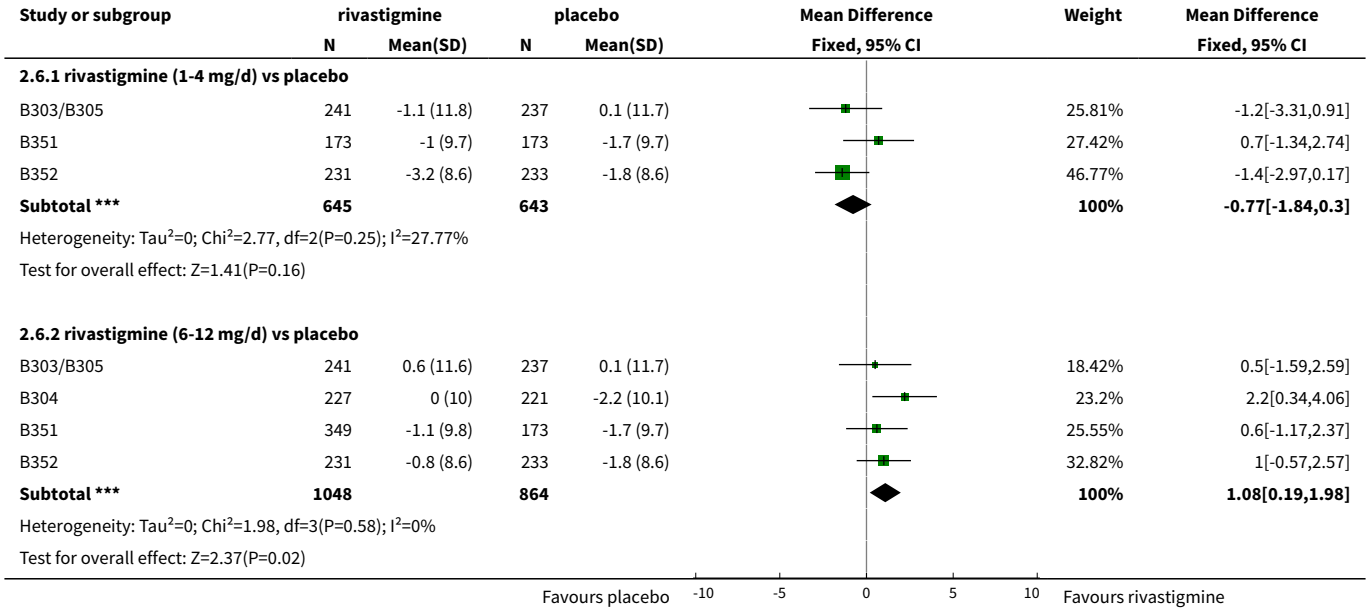




Analysis 2.5. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 5 ADCS-ADL (change from baseline at 26 weeks) ITT.

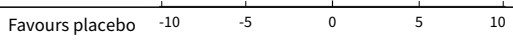


Analysis 2.6. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 6 PDS (change from baseline at 12 weeks) ITT.



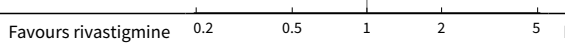
Analysis 2.7. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 7 PDS (change from baseline at 26 weeks) ITT.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.7.1 rivastigmine (1-4 mg/d) vs placebo							
B303/B305	241	-3.4 (13.4)	237	-2.2 (13.4)		25.85%	-1.24[-3.64,1.16]
B351	173	-2.9 (10.3)	173	-3.1 (10.3)		31.67%	0.2[-1.97,2.37]
B352	231	-5.2 (10.3)	233	-4.9 (10.3)		42.47%	-0.3[-2.17,1.57]
Subtotal ***	**645**		**643**			**100%**	**-0.38[-1.61,0.84]**
Heterogeneity: Tau²=0; Chi²=0.77, df=2(P=0.68); I²=0%							
Test for overall effect: Z=0.62(P=0.54)							
2.7.2 rivastigmine (6-12 mg/d) vs placebo							
B303/B305	241	0 (13.2)	237	-2.2 (13.4)		18%	2.2[-0.18,4.58]
B304	227	-2.7 (11.1)	221	-4.9 (11.2)		24%	2.2[0.13,4.27]
B351	349	-2.3 (10.4)	173	-3.1 (10.3)		28.87%	0.8[-1.08,2.68]
B352	231	-1.5 (10.3)	233	-4.9 (10.3)		29.14%	3.4[1.53,5.27]
Subtotal ***	**1048**		**864**			**100%**	**2.15[1.13,3.16]**
Heterogeneity: Tau²=0; Chi²=3.69, df=3(P=0.3); I²=18.62%							
Test for overall effect: Z=4.16(P<0.0001)							



Analysis 2.8. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 8 Clinical Global Impression (no change or worse at 12 weeks) ITT.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.8.1 rivastigmine (1-4 mg/d) vs placebo					
B303/B305	159/228	169/224		40.5%	0.75[0.5,1.13]
B351	111/157	120/169		30.29%	0.99[0.61,1.59]
B352	186/223	177/219		29.21%	1.19[0.73,1.94]
Subtotal (95% CI)	**608**	**612**		**100%**	**0.93[0.72,1.21]**
Total events: 456 (rivastigmine), 466 (placebo)					
Heterogeneity: Tau²=0; Chi²=2.09, df=2(P=0.35); I²=4.16%					
Test for overall effect: Z=0.52(P=0.61)					
2.8.2 rivastigmine (6-12 mg/d) vs placebo					
B303/B305	140/211	169/224		27.84%	0.64[0.43,0.97]
B304	153/215	179/213		23.19%	0.48[0.3,0.75]
B351	233/315	120/169		27.03%	1.16[0.76,1.77]
B352	162/209	177/219		21.94%	0.82[0.51,1.3]
Subtotal (95% CI)	**950**	**825**		**100%**	**0.74[0.6,0.92]**
Total events: 688 (rivastigmine), 645 (placebo)					
Heterogeneity: Tau²=0; Chi²=8.6, df=3(P=0.04); I²=65.14%					
Test for overall effect: Z=2.67(P=0.01)					



Analysis 2.9. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 9 Clinical Global Impression (no change or worse at 26 weeks) ITT.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.9.1 rivastigmine (1-4 mg/d) vs placebo					
B303/B305	160/229	184/230		39.99%	0.58[0.38,0.89]
B351	122/160	126/169		28.33%	1.1[0.66,1.81]
B352	175/225	190/224		31.68%	0.63[0.39,1.01]
Subtotal (95% CI)	**614**	**623**		**100%**	**0.71[0.55,0.93]**
Total events: 457 (rivastigmine), 500 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.95, df=2(P=0.14); I^2=49.31%					
Test for overall effect: Z=2.47(P=0.01)					
2.9.2 rivastigmine (6-12 mg/d) vs placebo					
B303/B305	139/219	184/230		19.88%	0.44[0.29,0.67]
B304	171/222	175/216		15.95%	0.79[0.5,1.25]
B351	238/318	126/169		18.28%	1.02[0.66,1.56]
B352	167/214	190/224		14.48%	0.64[0.39,1.03]
IDEAL	161/253	200/278		25.3%	0.68[0.47,0.98]
Lopez-Pousa 2005	81/104	96/106		6.12%	0.39[0.18,0.81]
Subtotal (95% CI)	**1330**	**1223**		**100%**	**0.66[0.55,0.79]**
Total events: 957 (rivastigmine), 971 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=10.16, df=5(P=0.07); I^2=50.79%					
Test for overall effect: Z=4.46(P<0.0001)					

Analysis 2.10. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 10 GDS(moderately severe, severe, or very severe dementia at 26 weeks) ITT.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.10.1 rivastigmine (1-4 mg/d) vs placebo					
B303/B305	109/242	102/238		42.07%	1.09[0.76,1.57]
B351	113/175	127/173		26.52%	0.66[0.42,1.04]
B352	172/233	178/235		31.4%	0.9[0.6,1.37]
Subtotal (95% CI)	**650**	**646**		**100%**	**0.9[0.71,1.14]**
Total events: 394 (rivastigmine), 407 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.87, df=2(P=0.24); I^2=30.23%					
Test for overall effect: Z=0.87(P=0.38)					
2.10.2 rivastigmine (6-12 mg/d) vs placebo					
B303/B305	87/241	102/238		27.51%	0.75[0.52,1.09]
B304	97/229	104/222		26.78%	0.83[0.58,1.21]
B351	220/354	127/173		25.13%	0.61[0.41,0.89]
B352	175/231	178/235		20.58%	1[0.66,1.53]
Subtotal (95% CI)	**1055**	**868**		**100%**	**0.78[0.64,0.94]**
Total events: 579 (rivastigmine), 511 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.14, df=3(P=0.37); I^2=4.58%					
Test for overall effect: Z=2.57(P=0.01)					

Analysis 2.11. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 11 CGIC (little or no improvement, or worse at 12 weeks) ITT.

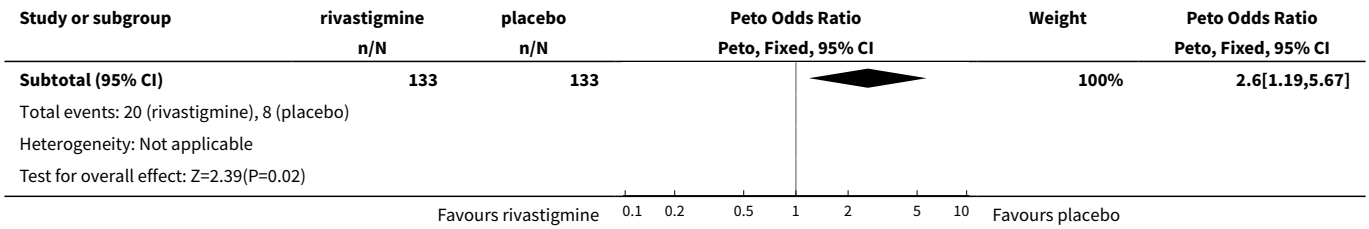
Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.11.1 rivastigmine (1-4 mg/d) vs placebo					
B103	101/136	98/133		100%	1.03[0.6,1.77]
Subtotal (95% CI)	**136**	**133**		**100%**	**1.03[0.6,1.77]**
Total events: 101 (rivastigmine), 98 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.11(P=0.91)					
2.11.2 rivastigmine (6-12 mg/d) vs placebo					
B103	89/133	98/133		100%	0.72[0.43,1.22]
Subtotal (95% CI)	**133**	**133**		**100%**	**0.72[0.43,1.22]**
Total events: 89 (rivastigmine), 98 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.21(P=0.23)					

Analysis 2.12. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 12 Behavioural disturbance NPI-10 or NPI-12 (change from baseline at 26 weeks) ITT.

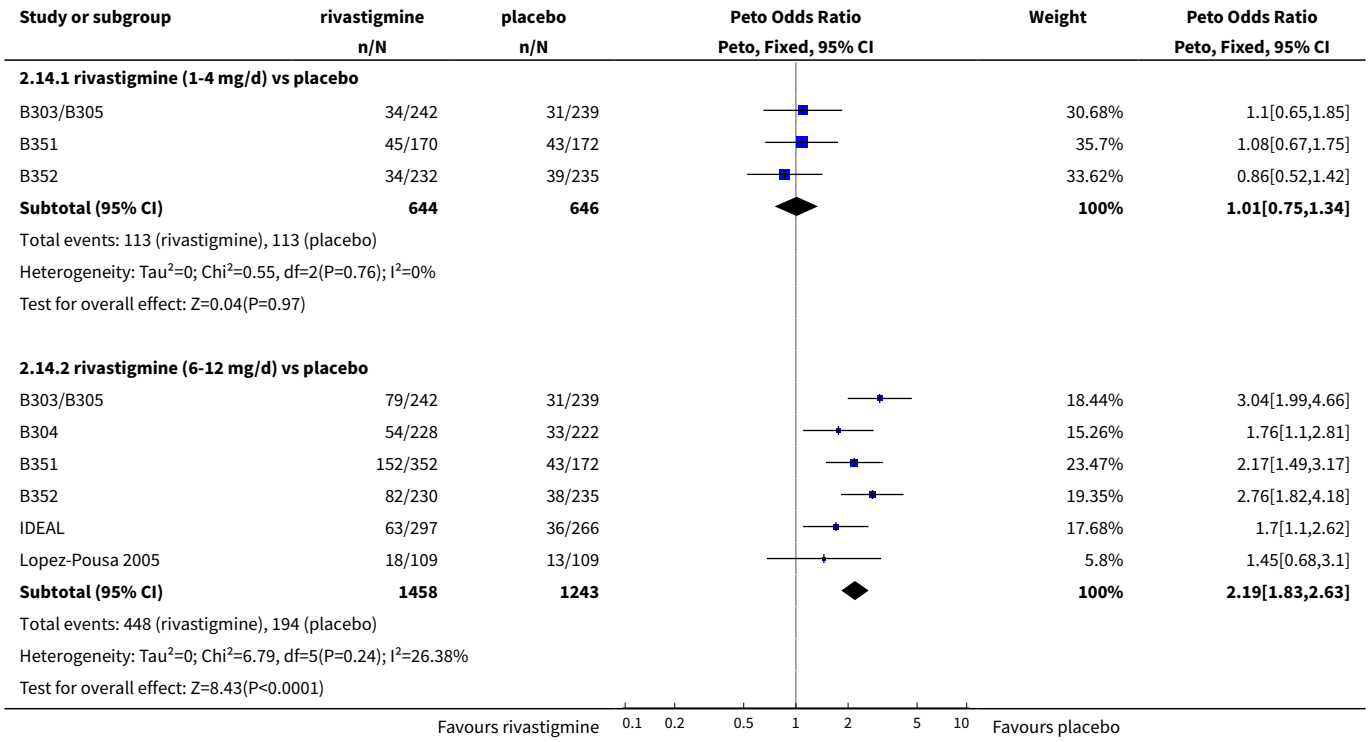
Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.12.1 Rivastigmine (6-12 mg/day) vs placebo							
IDEAL	253	-2.2 (11.9)	281	-1.7 (13.8)		71.75%	-0.04[-0.21,0.13]
Lopez-Pousa 2005	104	-0.1 (15.2)	106	1.7 (17.5)		28.25%	-0.11[-0.38,0.16]
Subtotal ***	**357**		**387**			**100%**	**-0.06[-0.2,0.09]**
Heterogeneity: $Tau^2=0$; $Chi^2=0.19$, df=1(P=0.66); $I^2=0\%$							
Test for overall effect: Z=0.8(P=0.42)							

Analysis 2.13. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 13 withdrawals before end of treatment at 12 weeks.

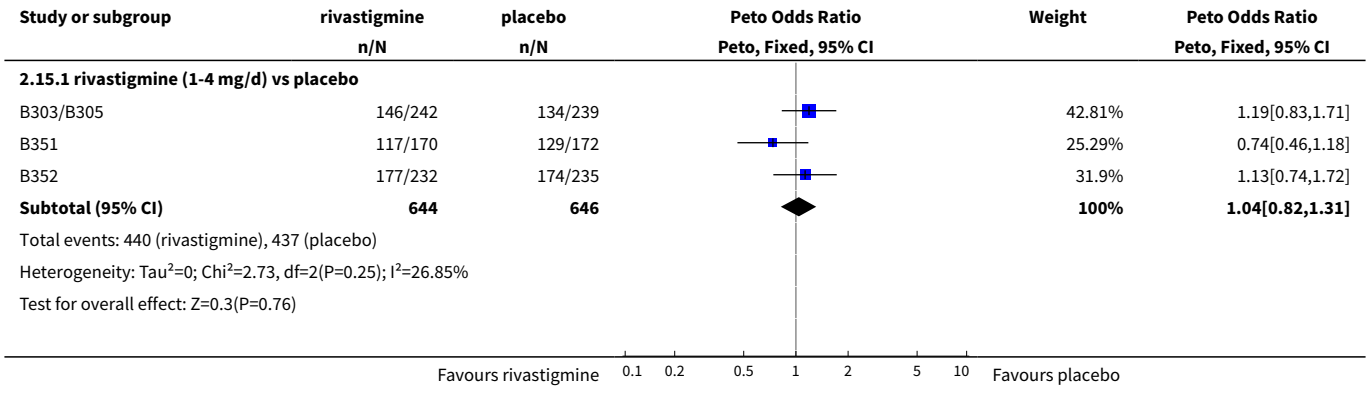
Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.13.1 rivastigmine (1-4 mg/d) vs placebo					
B103	17/136	8/133		100%	2.15[0.95,4.89]
Subtotal (95% CI)	**136**	**133**		**100%**	**2.15[0.95,4.89]**
Total events: 17 (rivastigmine), 8 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.83(P=0.07)					
2.13.2 rivastigmine (6-12 mg/d) vs placebo					
B103	20/133	8/133		100%	2.6[1.19,5.67]

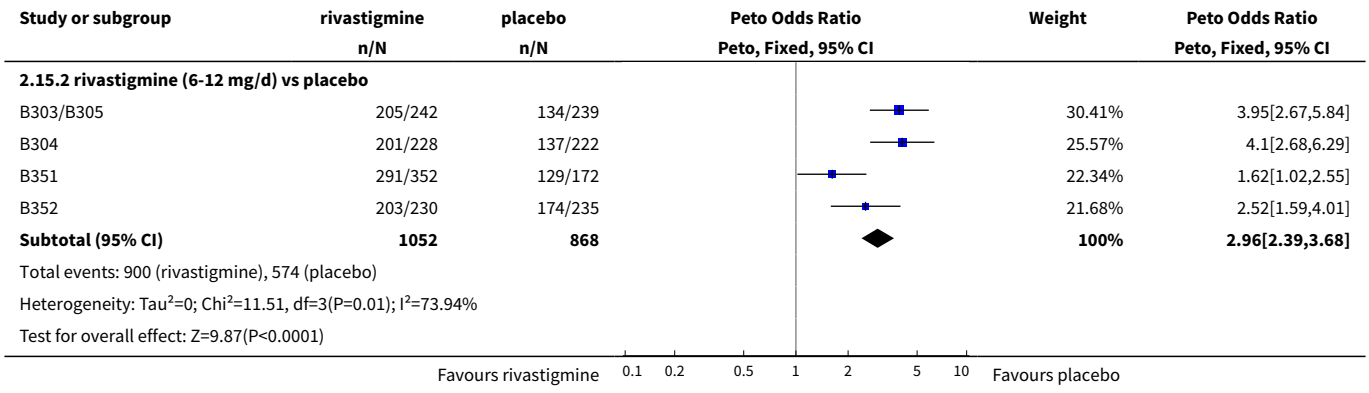


Analysis 2.14. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 14 withdrawals before end of treatment at 26 weeks.

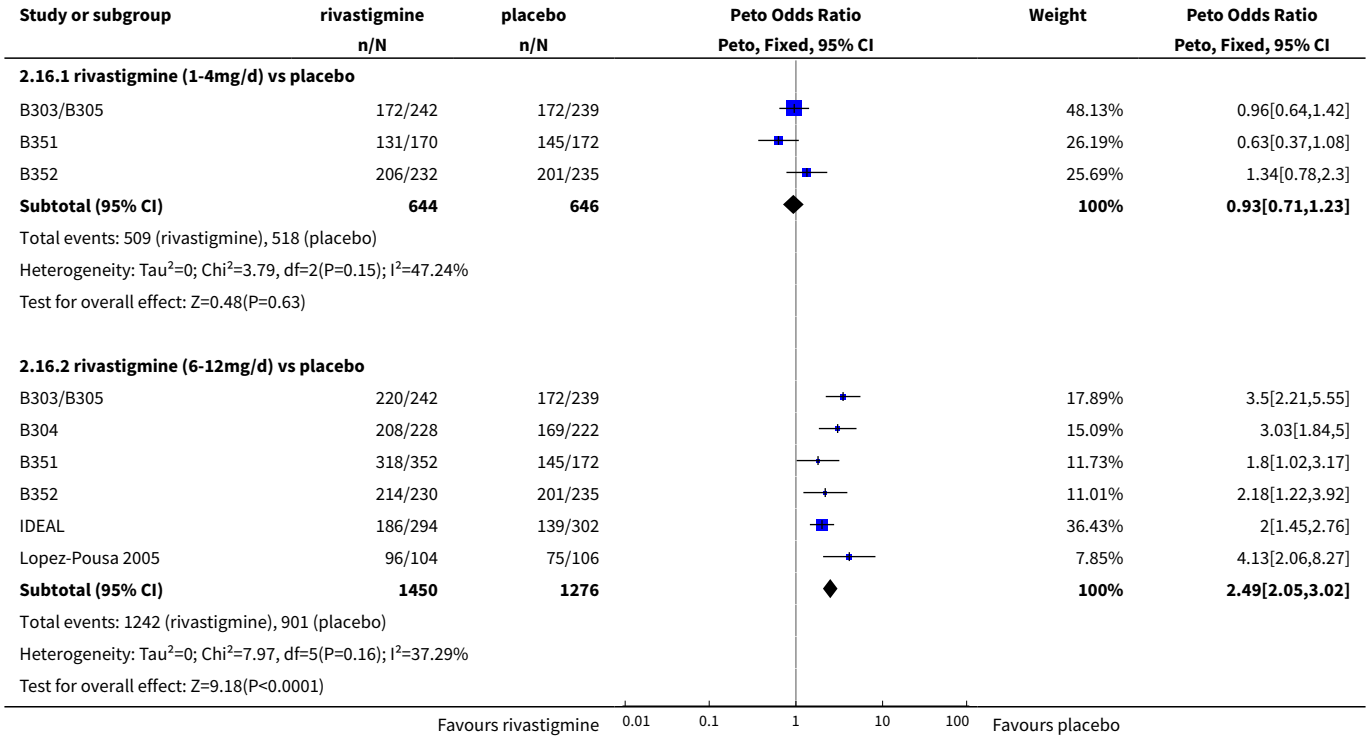


Analysis 2.15. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 15 at least one adverse event by the end of titration period.

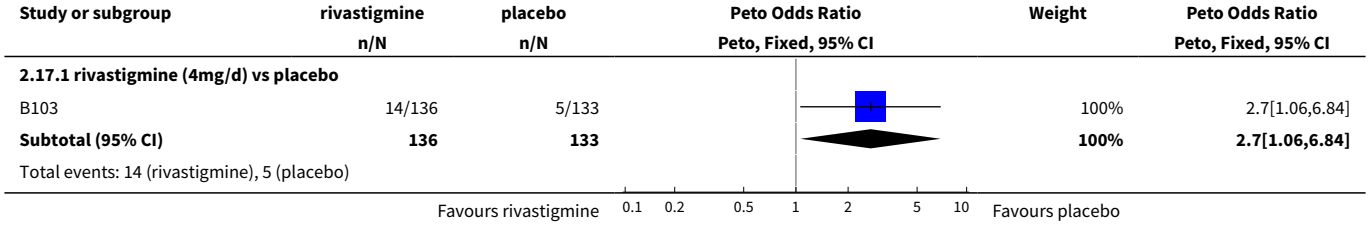


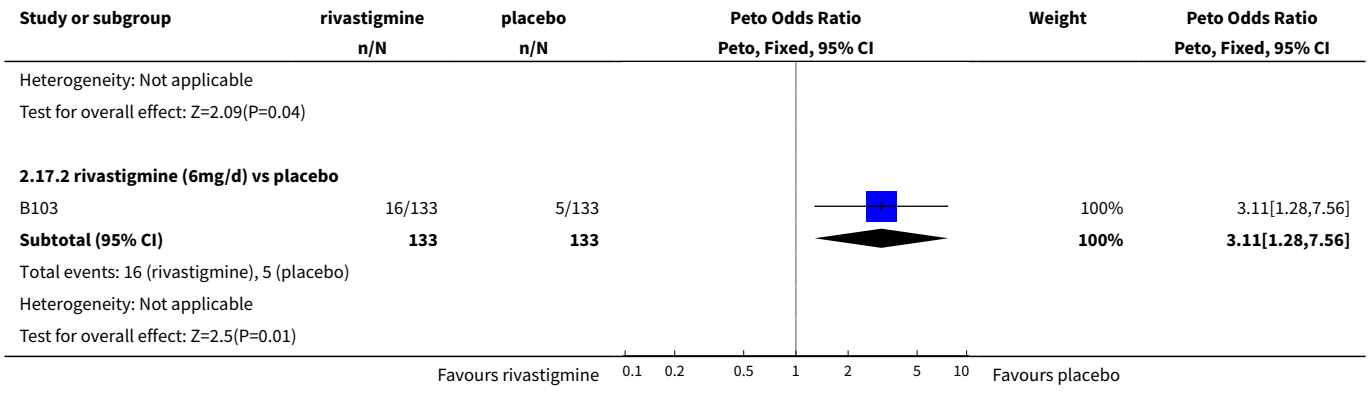


Analysis 2.16. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 16 at least one adverse event by 26 weeks.

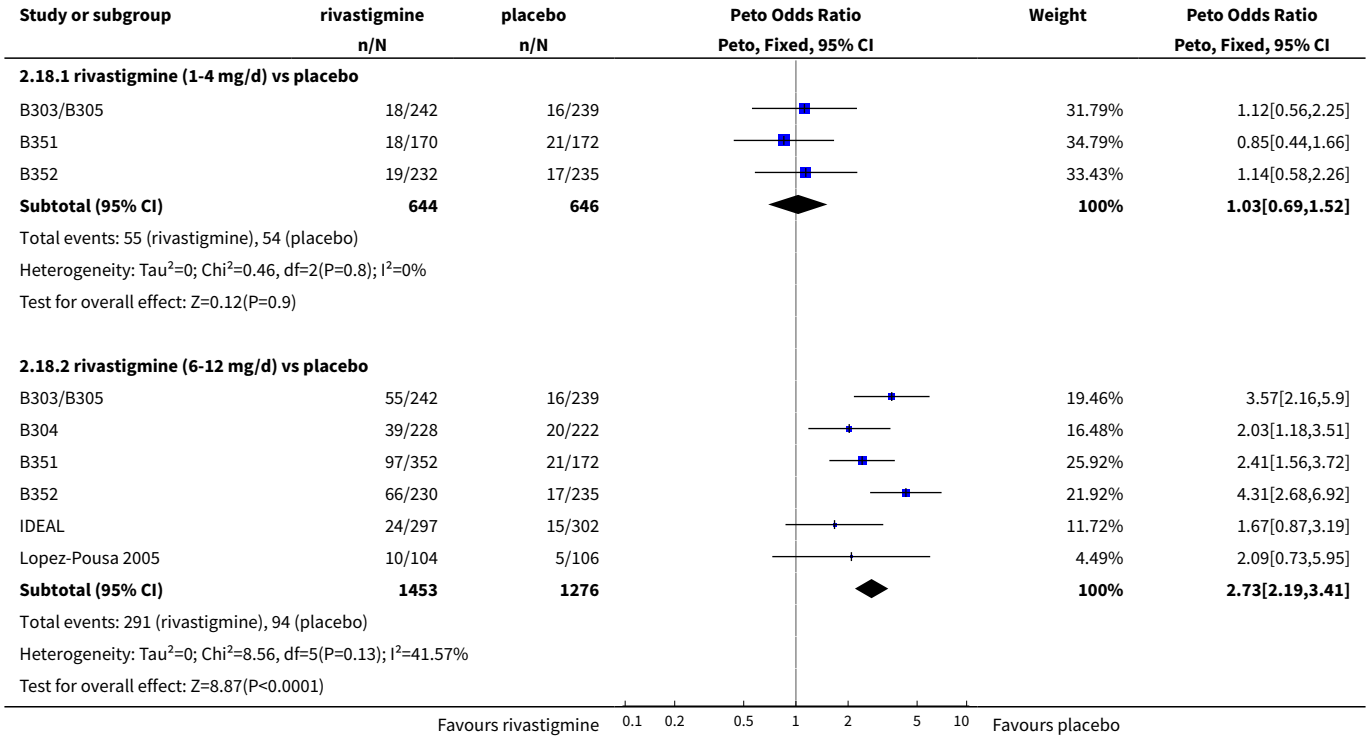


Analysis 2.17. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 17 dropouts due to adverse events by 12 weeks.

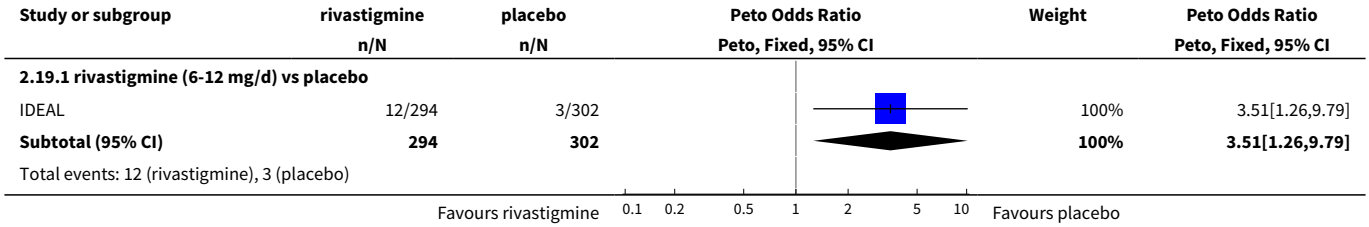


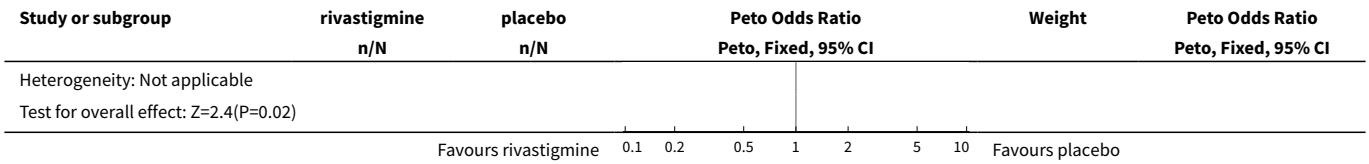


Analysis 2.18. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 18 dropouts due to adverse events by 26 weeks.

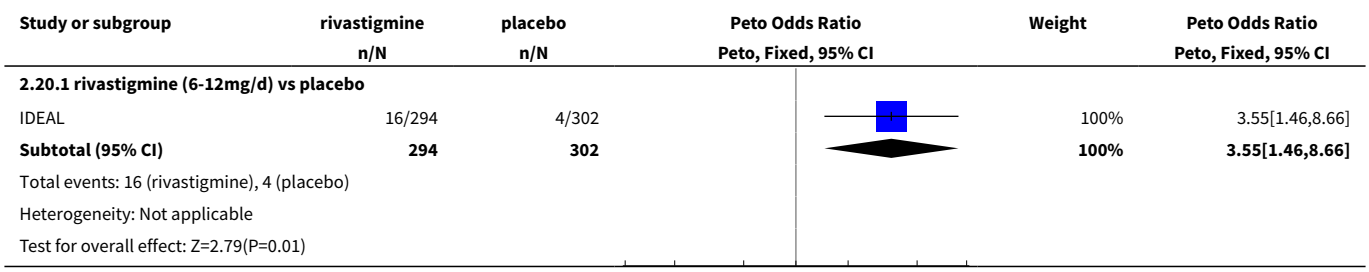


Analysis 2.19. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 19 at least one adverse event of decreased appetite by 26 weeks.

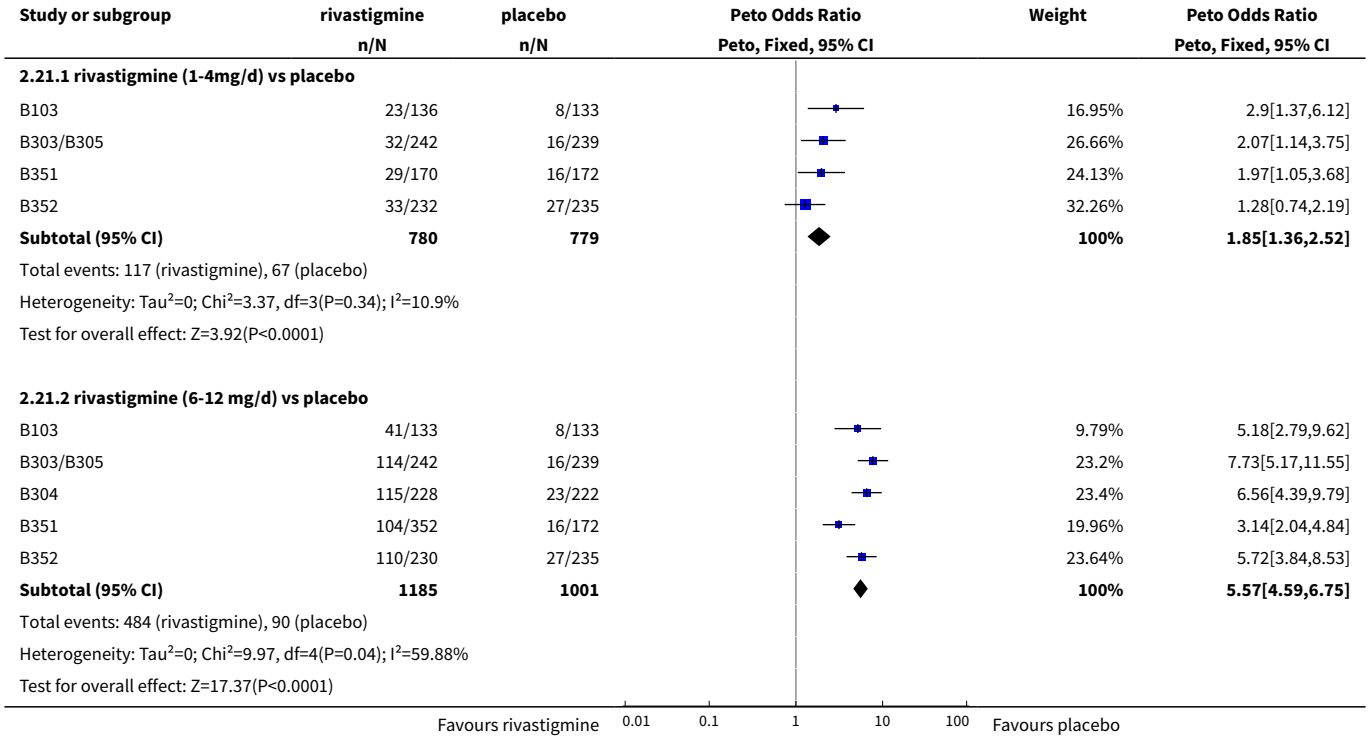




Analysis 2.20. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 20 at least one adverse event of weight decrease by 26 weeks.



Analysis 2.21. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 21 at least one adverse event of nausea by the end of titration period.



Analysis 2.22. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 22 at least one adverse event of nausea by 26 weeks.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.22.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	41/242	23/239		33.85%	1.88[1.11,3.19]
B351	38/170	20/172		29.41%	2.14[1.22,3.76]
B352	40/232	31/235		36.74%	1.37[0.83,2.27]
Subtotal (95% CI)	**644**	**646**		**100%**	**1.74[1.28,2.36]**
Total events: 119 (rivastigmine), 74 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.47, df=2(P=0.48); I^2=0%					
Test for overall effect: Z=3.54(P=0)					
2.22.2 rivastigmine (6-12mg/d bid) vs placebo					
B303/B305	121/242	23/239		20.43%	6.83[4.62,10.08]
B304	123/228	31/222		20.51%	5.88[3.99,8.68]
B351	121/352	20/172		18.4%	3.17[2.1,4.78]
B352	125/230	31/235		20.99%	6.31[4.3,9.27]
IDEAL	68/294	15/302		14.46%	4.54[2.86,7.21]
Lopez-Pousa 2005	28/104	2/106		5.22%	7.65[3.54,16.55]
Subtotal (95% CI)	**1450**	**1276**		**100%**	**5.36[4.5,6.4]**
Total events: 586 (rivastigmine), 122 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.97, df=5(P=0.08); I^2=49.86%					
Test for overall effect: Z=18.69(P<0.0001)					

Analysis 2.23. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 23 at least one adverse event of vomiting by the end of titration period.

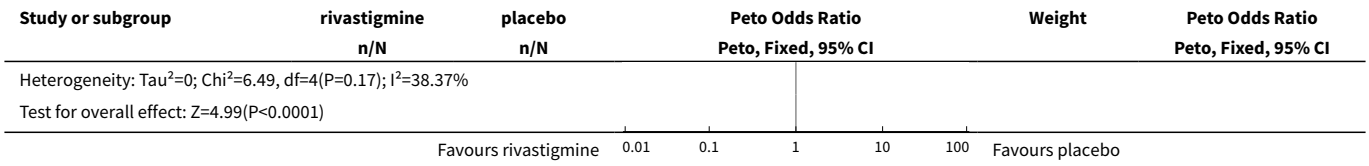
Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.23.1 rivastigmine (1-4mg/d) vs placebo					
B103	13/136	4/133		23.58%	3.01[1.13,8.03]
B303/B305	12/242	7/239		26.97%	1.71[0.68,4.27]
B351	6/170	6/172		17.13%	1.01[0.32,3.2]
B352	16/232	7/235		32.32%	2.3[1,5.32]
Subtotal (95% CI)	**780**	**779**		**100%**	**1.97[1.22,3.16]**
Total events: 47 (rivastigmine), 24 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.24, df=3(P=0.52); I^2=0%					
Test for overall effect: Z=2.78(P=0.01)					
2.23.2 rivastigmine (6-12 mg/d) vs placebo					
B103	24/133	4/133		9.68%	4.91[2.25,10.72]
B303/B305	70/242	7/239		24.95%	6.89[4.23,11.21]
B304	67/229	7/222		23.86%	6.68[4.06,10.99]
B351	57/352	6/172		18.85%	3.32[1.89,5.81]
B352	62/230	7/235		22.66%	6.64[3.98,11.07]
Subtotal (95% CI)	**1186**	**1001**		**100%**	**5.72[4.48,7.29]**
Total events: 280 (rivastigmine), 31 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.05, df=4(P=0.28); I^2=20.71%					
Test for overall effect: Z=14.05(P<0.0001)					

Analysis 2.24. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 24 at least one adverse event of vomiting by 26 weeks.

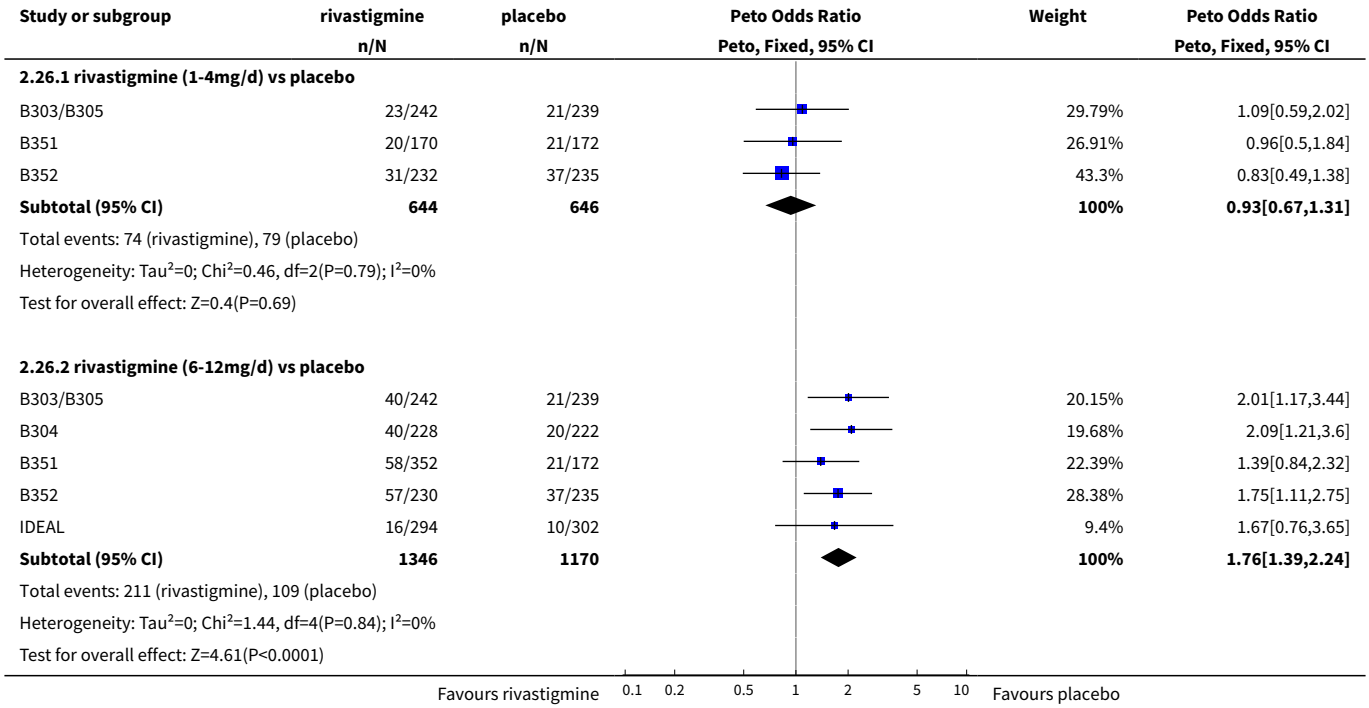
Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.24.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	19/242	14/239		36.33%	1.37[0.67,2.77]
B351	13/170	11/172		26.4%	1.21[0.53,2.77]
B352	24/232	10/235		37.27%	2.46[1.22,4.94]
Subtotal (95% CI)	**644**	**646**		**100%**	**1.65[1.08,2.52]**
Total events: 56 (rivastigmine), 35 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.07, df=2(P=0.35); I^2=3.48%					
Test for overall effect: Z=2.3(P=0.02)					
2.24.2 rivastigmine (6-12mg/d) vs placebo					
B303/B305	82/242	14/239		20.96%	5.76[3.68,9]
B304	88/228	14/222		21.51%	6.28[4.04,9.77]
B351	76/352	11/172		17.45%	2.99[1.83,4.88]
B352	75/230	10/235		18.94%	6.65[4.15,10.63]
IDEAL	50/294	10/302		14.71%	4.53[2.66,7.72]
Lopez-Pousa 2005	23/104	4/106		6.43%	5.1[2.28,11.42]
Subtotal (95% CI)	**1450**	**1276**		**100%**	**5.15[4.2,6.32]**
Total events: 394 (rivastigmine), 63 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.12, df=5(P=0.21); I^2=29.74%					
Test for overall effect: Z=15.71(P<0.0001)					

Analysis 2.25. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 25 at least one adverse event of diarrhoea by the end of titration period.

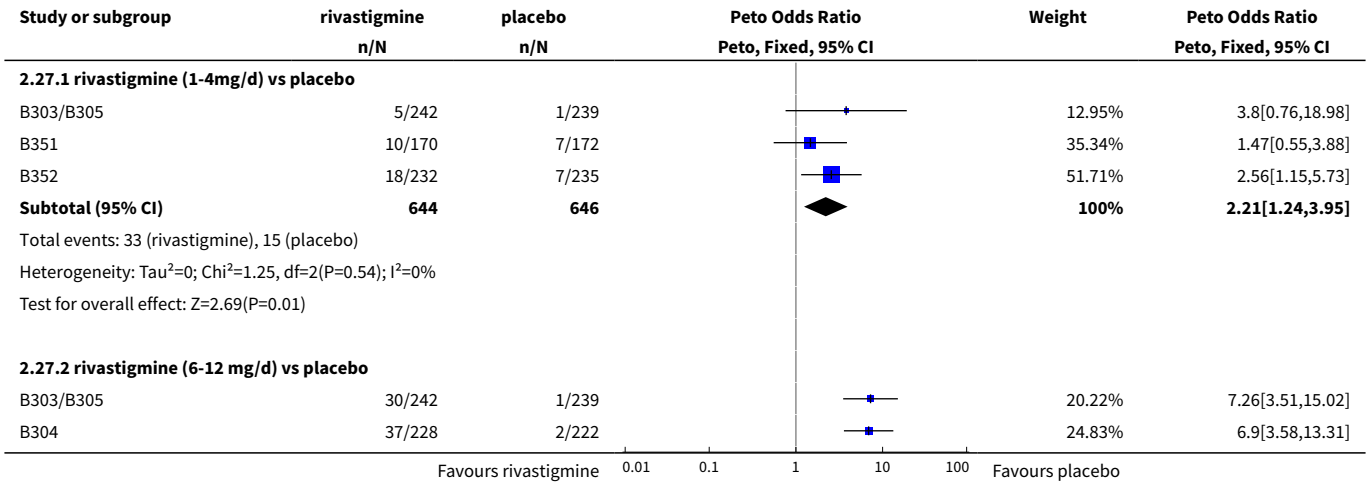
Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.25.1 rivastigmine (1-4mg/d) vs placebo					
B103	9/136	2/133		9.24%	3.67[1.1,12.23]
B303/B305	19/242	16/239		28.39%	1.19[0.6,2.36]
B351	13/170	19/172		25.39%	0.67[0.32,1.39]
B352	21/232	26/235		36.98%	0.8[0.44,1.46]
Subtotal (95% CI)	**780**	**779**		**100%**	**0.99[0.68,1.42]**
Total events: 62 (rivastigmine), 63 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.38, df=3(P=0.09); I^2=52.99%					
Test for overall effect: Z=0.08(P=0.94)					
2.25.2 rivastigmine (6-12 mg/d) vs placebo					
B103	16/133	2/133		7.76%	5.27[2.03,13.7]
B303/B305	31/242	16/239		19.59%	2[1.1,3.65]
B304	32/228	16/222		19.81%	2.04[1.12,3.72]
B351	49/352	19/172		24.1%	1.29[0.75,2.22]
B352	48/230	26/235		28.74%	2.08[1.26,3.41]
Subtotal (95% CI)	**1185**	**1001**		**100%**	**1.97[1.51,2.57]**
Total events: 176 (rivastigmine), 79 (placebo)					

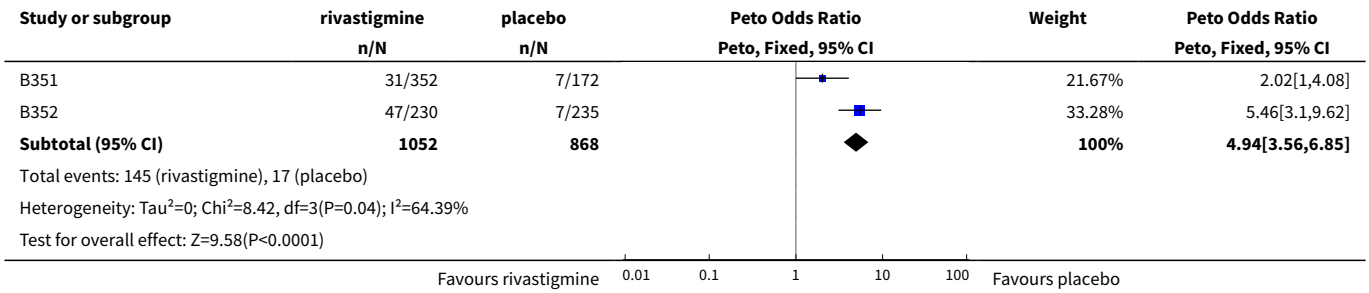


Analysis 2.26. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 26 at least one adverse event of diarrhoea by 26 weeks.

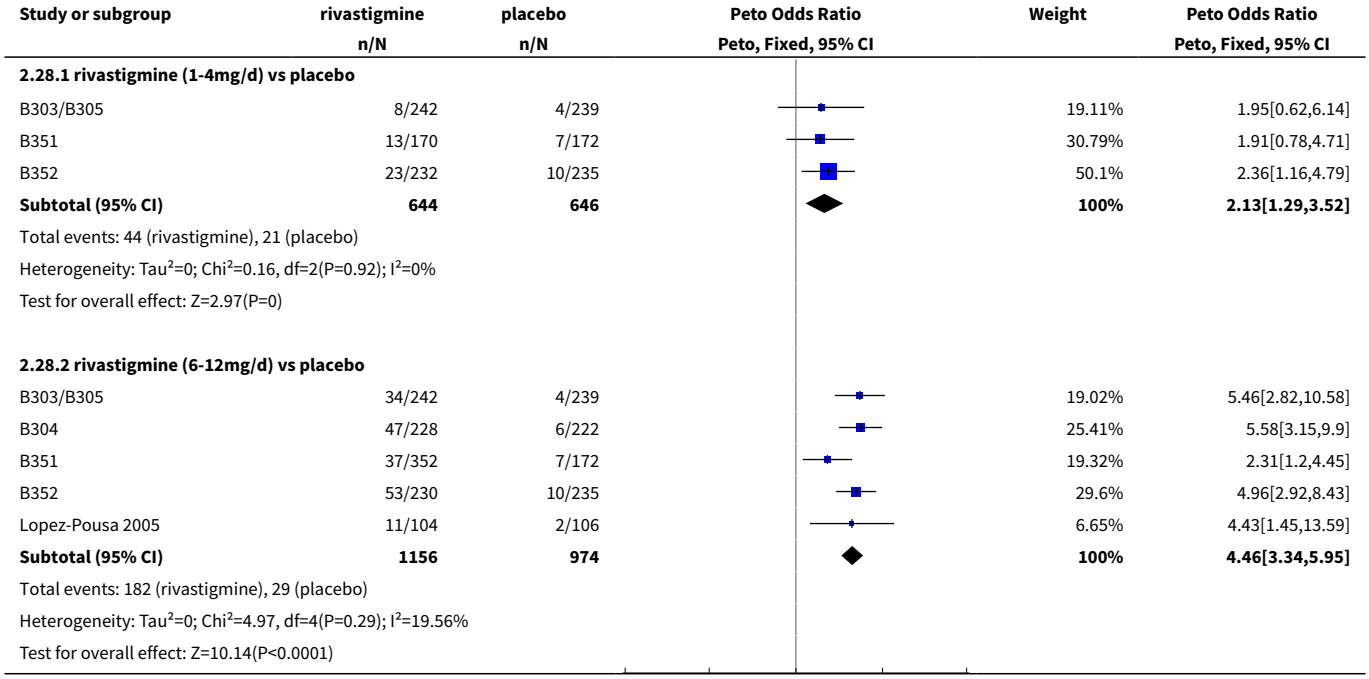


Analysis 2.27. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 27 at least one adverse event of anorexia by the end of titration period.

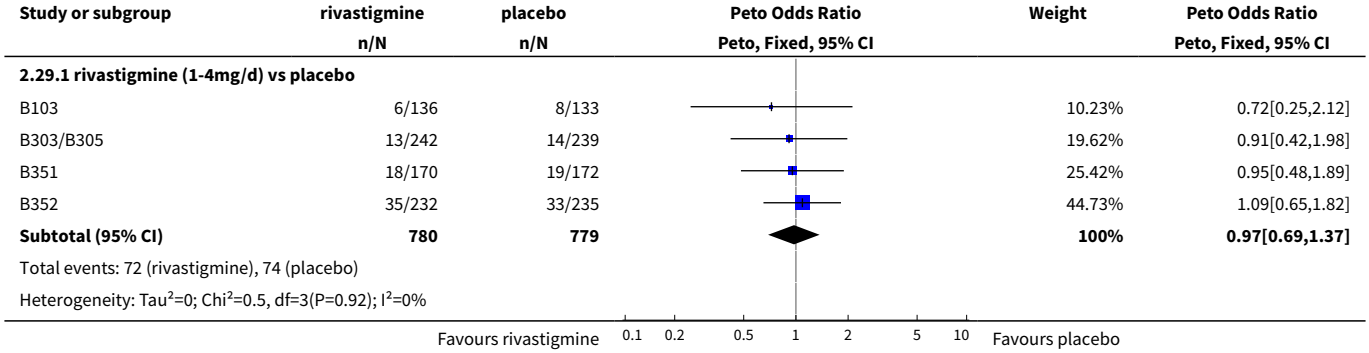


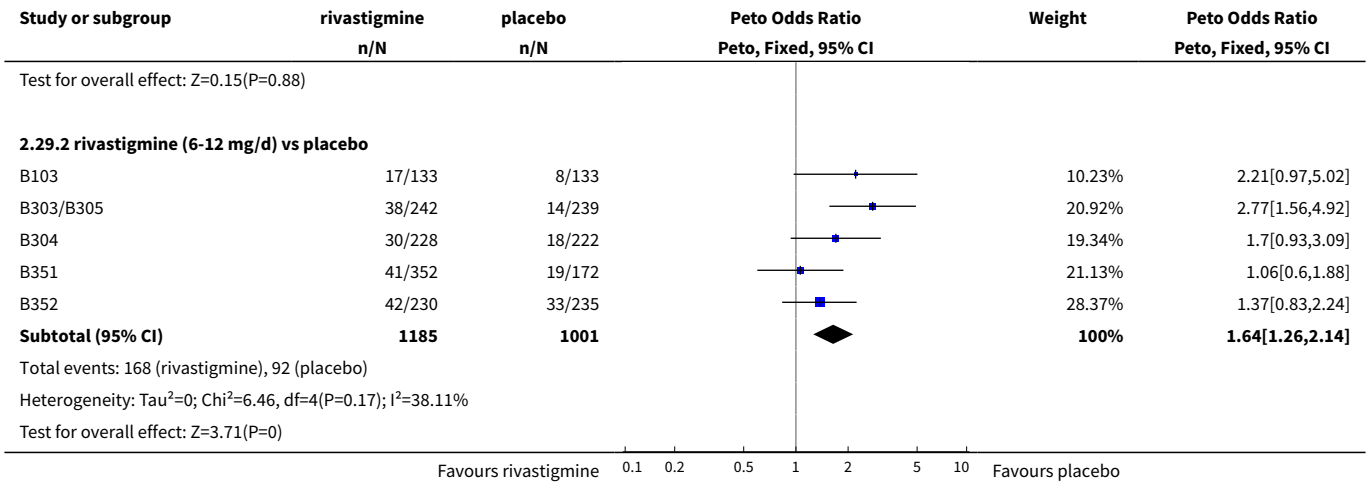


Analysis 2.28. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 28 at least one adverse event of anorexia by 26 weeks.

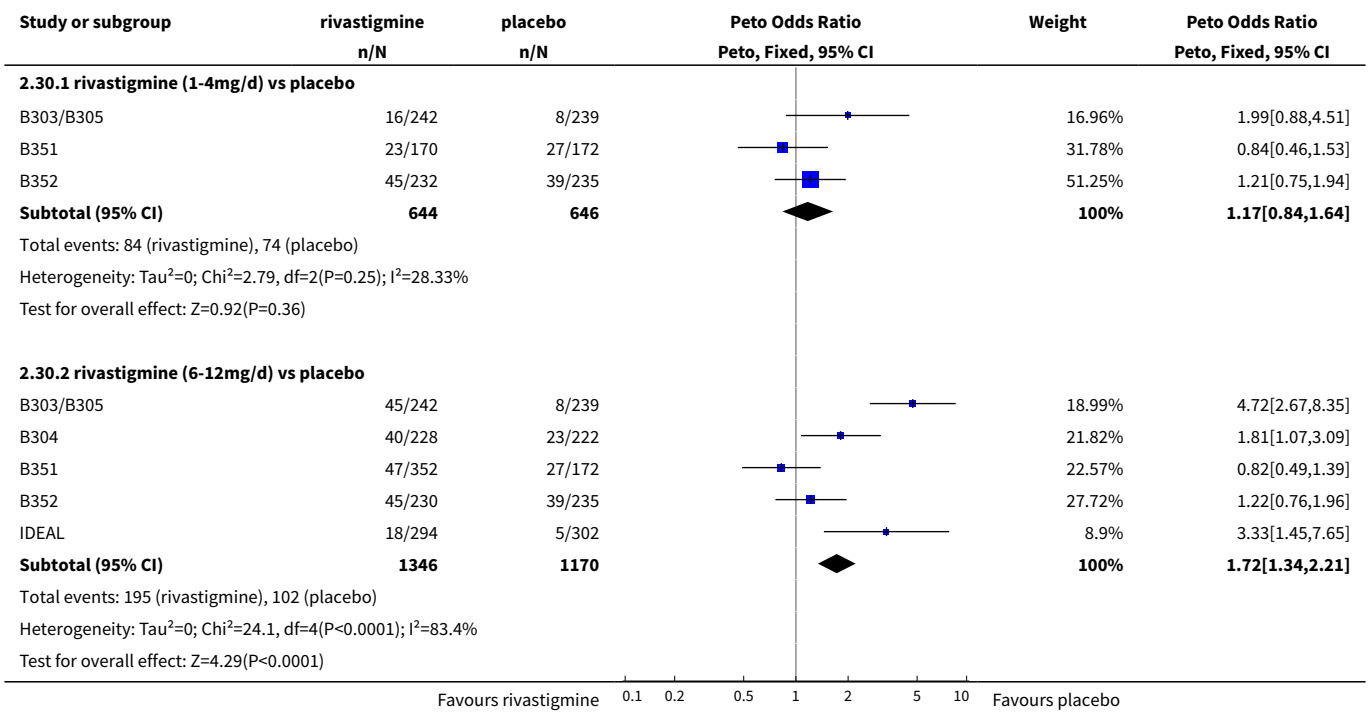


Analysis 2.29. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 29 at least one adverse event of headache by the end of titration period.

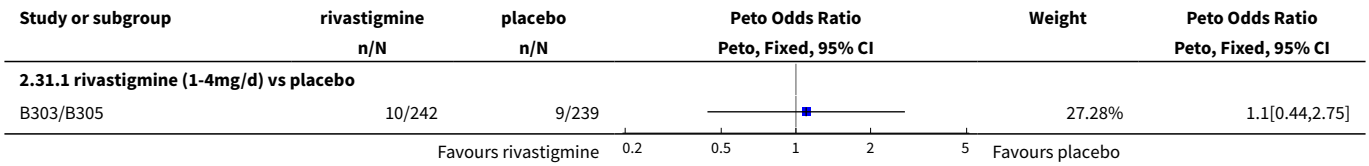


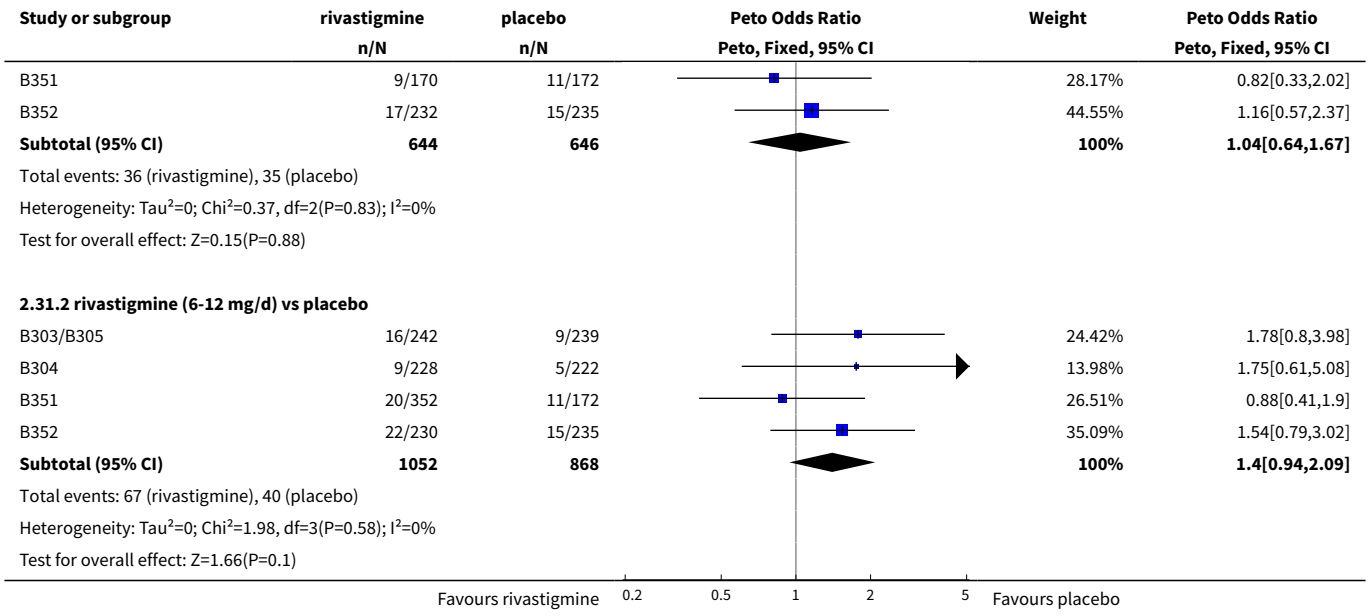


Analysis 2.30. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 30 at least one adverse event of headache by 26 weeks.

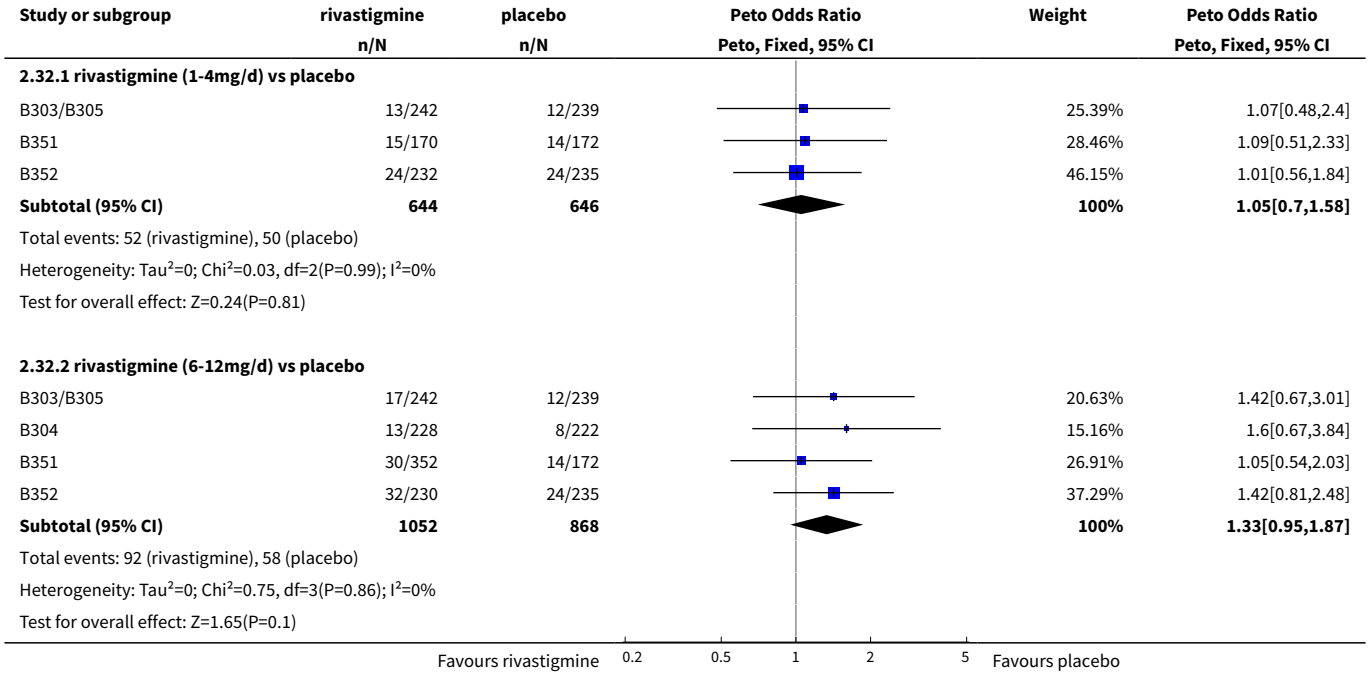


Analysis 2.31. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 31 at least one adverse event of insomnia by the end of titration period.



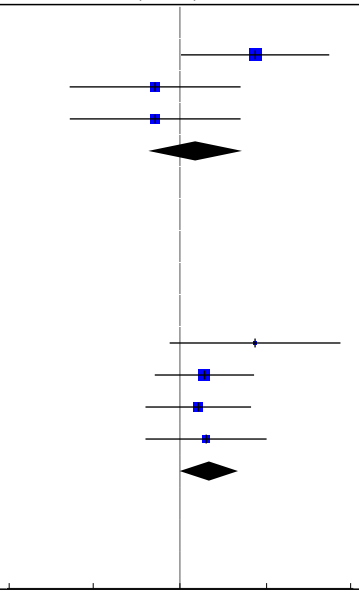


Analysis 2.32. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 32 at least one adverse event of insomnia by 26 weeks.



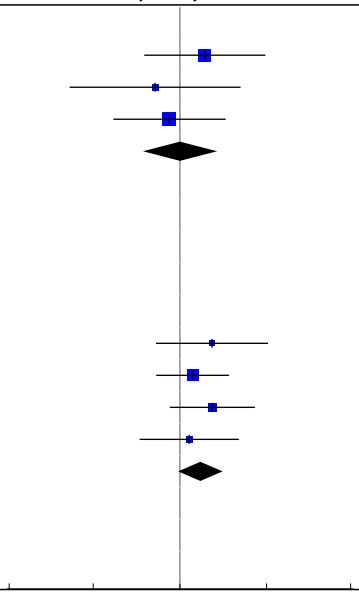
Analysis 2.33. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 33 at least one adverse event of syncope by the end of titration period.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.33.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	4/242	0/239		39.97%	7.39[1.03,52.79]
B351	1/170	2/172		29.99%	0.52[0.05,5.01]
B352	1/232	2/235		30.04%	0.52[0.05,5.01]
Subtotal (95% CI)	**644**	**646**		**100%**	**1.5[0.43,5.2]**
Total events: 6 (rivastigmine), 4 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.21, df=2(P=0.12); I^2=52.54%					
Test for overall effect: Z=0.64(P=0.52)					
2.33.2 rivastigmine (6-12 mg/d) vs placebo					
B303/B305	3/242	0/239		11.68%	7.36[0.76,71.08]
B304	6/228	3/222		34.56%	1.92[0.51,7.17]
B351	7/352	2/172		30.56%	1.63[0.4,6.62]
B352	4/230	2/235		23.2%	2.01[0.4,10.02]
Subtotal (95% CI)	**1052**	**868**		**100%**	**2.16[0.99,4.68]**
Total events: 20 (rivastigmine), 7 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.32, df=3(P=0.73); I^2=0%					
Test for overall effect: Z=1.94(P=0.05)					



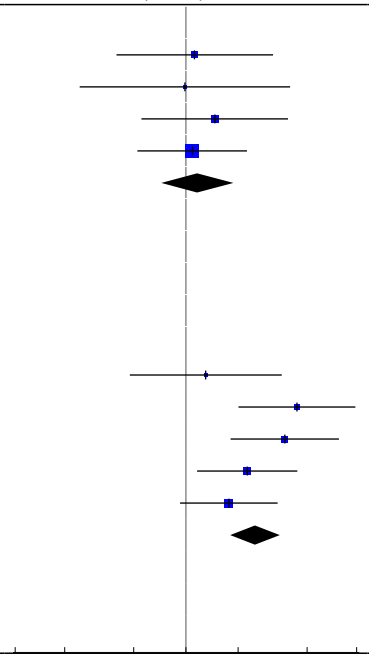
Analysis 2.34. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 34 at least one adverse event of syncope by 26 weeks.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.34.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	4/242	2/239		37.51%	1.94[0.39,9.68]
B351	1/170	2/172		18.84%	0.52[0.05,5.01]
B352	3/232	4/235		43.65%	0.76[0.17,3.37]
Subtotal (95% CI)	**644**	**646**		**100%**	**1[0.37,2.69]**
Total events: 8 (rivastigmine), 8 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.1, df=2(P=0.58); I^2=0%					
Test for overall effect: Z=0.01(P=0.99)					
2.34.2 rivastigmine (6-12mg/d bid) vs placebo					
B303/B305	5/242	2/239		15.64%	2.35[0.53,10.45]
B304	10/228	7/222		37.09%	1.4[0.53,3.69]
B351	12/352	2/172		27.25%	2.37[0.77,7.33]
B352	5/230	4/235		20.01%	1.28[0.34,4.79]
Subtotal (95% CI)	**1052**	**868**		**100%**	**1.72[0.96,3.11]**
Total events: 32 (rivastigmine), 15 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.84, df=3(P=0.84); I^2=0%					
Test for overall effect: Z=1.81(P=0.07)					



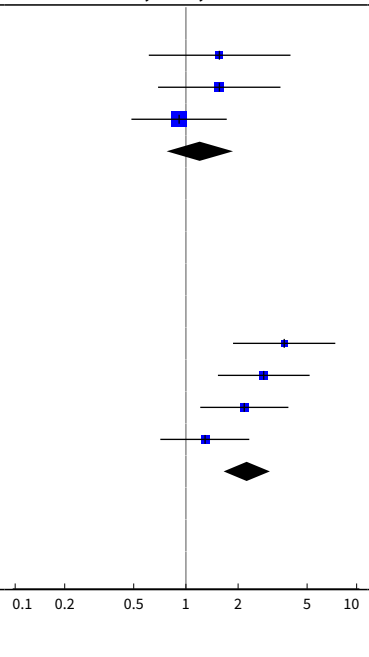
Analysis 2.35. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 35 at least one adverse event of abdominal pain by the end of titration period.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.35.1 rivastigmine (1-4mg/d) vs placebo					
B103	8/136	7/133		21.12%	1.12[0.4,3.18]
B303/B305	4/242	4/239		11.71%	0.99[0.24,3.99]
B351	10/170	7/172		24.07%	1.47[0.55,3.88]
B352	16/232	15/235		43.09%	1.09[0.52,2.25]
Subtotal (95% CI)	**780**	**779**		**100%**	**1.16[0.72,1.88]**
Total events: 38 (rivastigmine), 33 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.31, df=3(P=0.96); I^2=0%					
Test for overall effect: Z=0.62(P=0.54)					
2.35.2 rivastigmine (6-12mg/d) vs placebo					
B103	9/133	7/133		10.64%	1.3[0.48,3.57]
B303/B305	23/242	4/239		17.99%	4.37[2.01,9.49]
B304	26/228	6/222		20.99%	3.72[1.81,7.63]
B351	36/352	7/172		24.58%	2.26[1.16,4.39]
B352	25/230	15/235		25.81%	1.77[0.92,3.38]
Subtotal (95% CI)	**1185**	**1001**		**100%**	**2.5[1.8,3.48]**
Total events: 119 (rivastigmine), 39 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.96, df=4(P=0.2); I^2=32.91%					
Test for overall effect: Z=5.46(P<0.0001)					

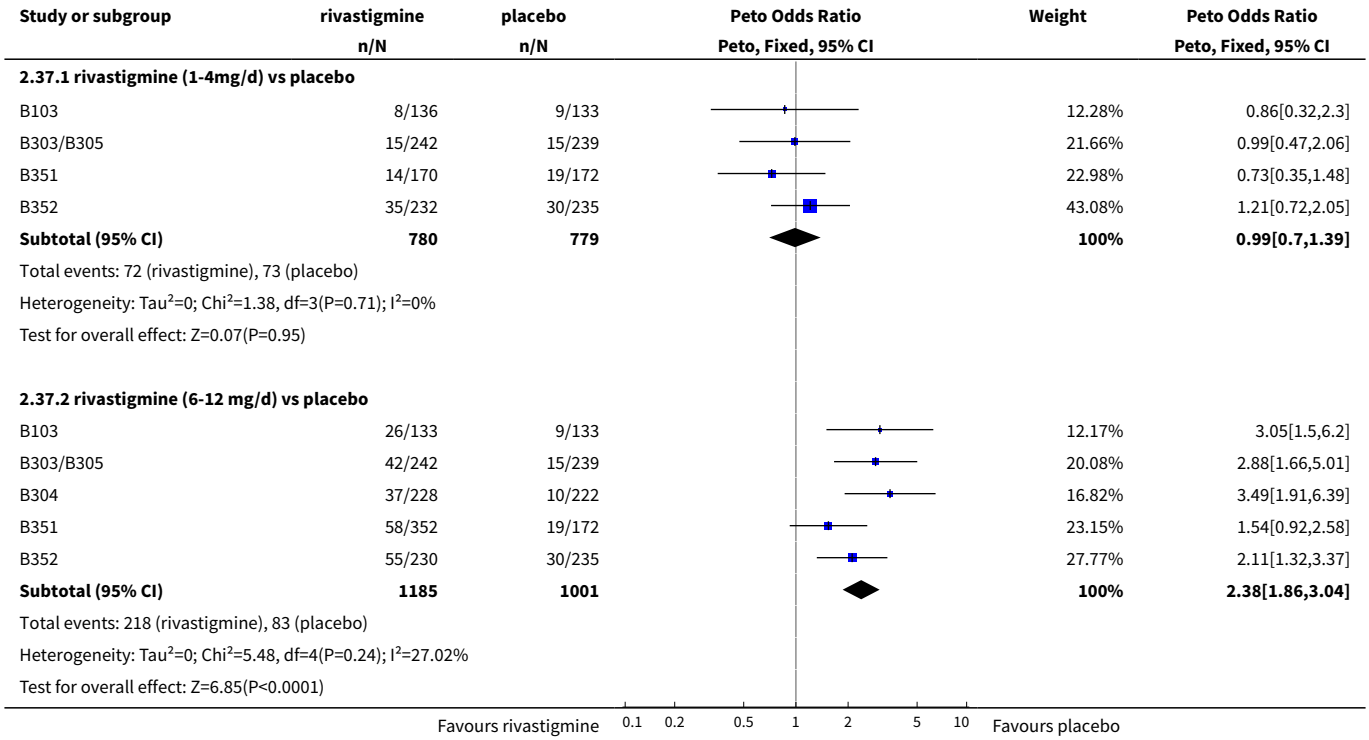


Analysis 2.36. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 36 at least one adverse event of abdominal pain by 26 weeks.

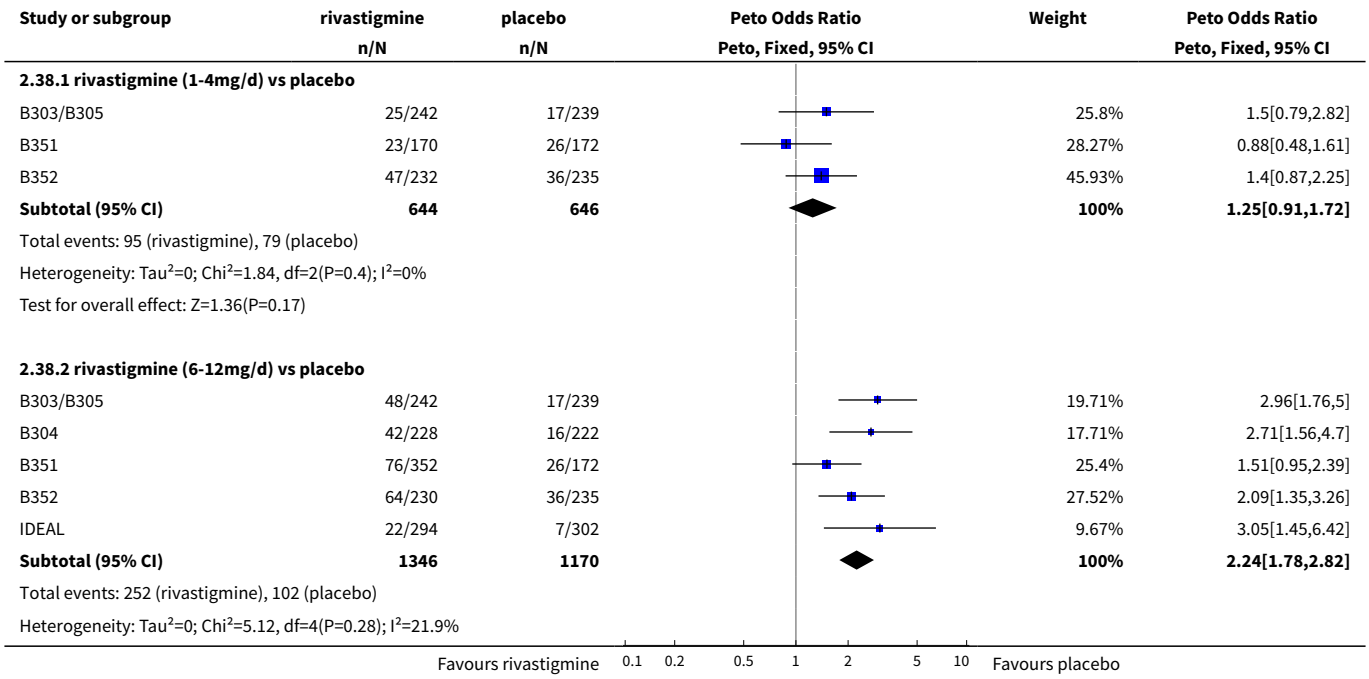
Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.36.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	11/242	7/239		22%	1.56[0.61,4.01]
B351	15/170	10/172		29.45%	1.56[0.69,3.51]
B352	20/232	22/235		48.54%	0.91[0.48,1.72]
Subtotal (95% CI)	**644**	**646**		**100%**	**1.2[0.77,1.87]**
Total events: 46 (rivastigmine), 39 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.41, df=2(P=0.49); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					
2.36.2 rivastigmine (6-12mg/d) vs placebo					
B303/B305	29/242	7/239		20.4%	3.69[1.87,7.27]
B304	34/228	12/222		25.3%	2.81[1.53,5.17]
B351	47/352	10/172		27.44%	2.17[1.21,3.9]
B352	27/230	22/235		26.85%	1.29[0.71,2.32]
Subtotal (95% CI)	**1052**	**868**		**100%**	**2.24[1.65,3.05]**
Total events: 137 (rivastigmine), 51 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=6, df=3(P=0.11); I^2=49.98%					
Test for overall effect: Z=5.17(P<0.0001)					

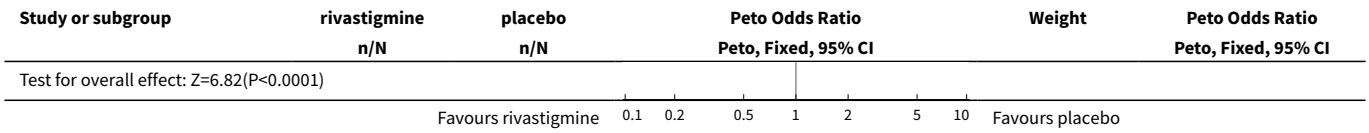


Analysis 2.37. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 37 at least one adverse event of dizziness by the end of titration period.

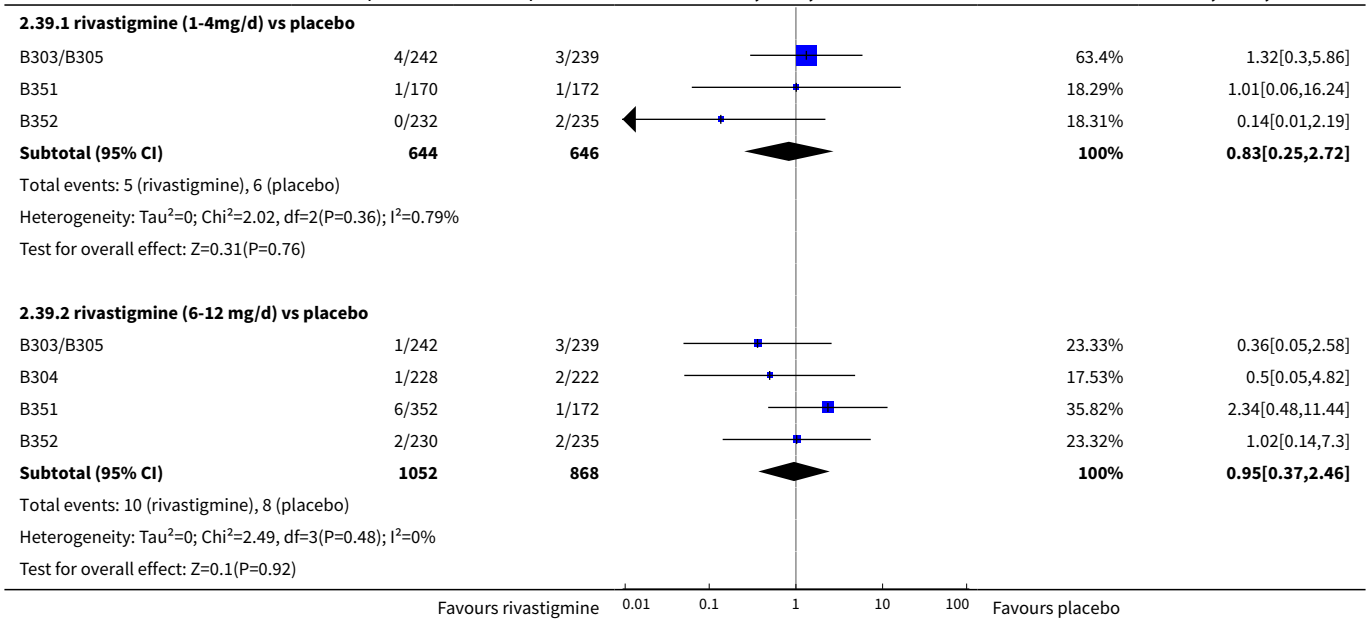


Analysis 2.38. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 38 at least one adverse event of dizziness by 26 weeks.

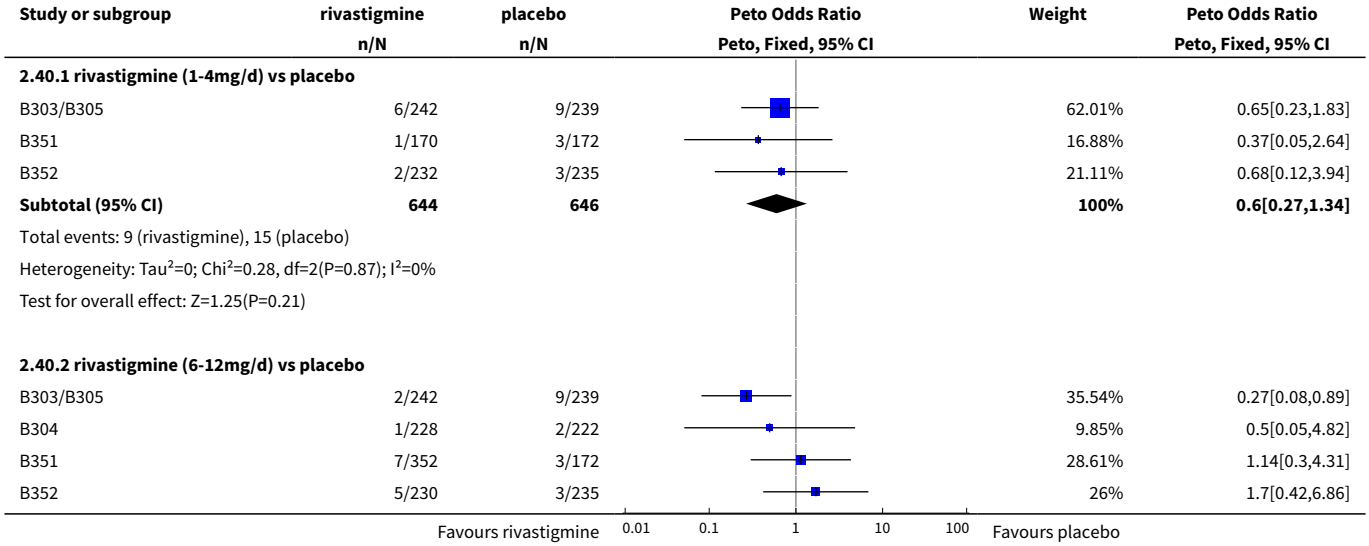


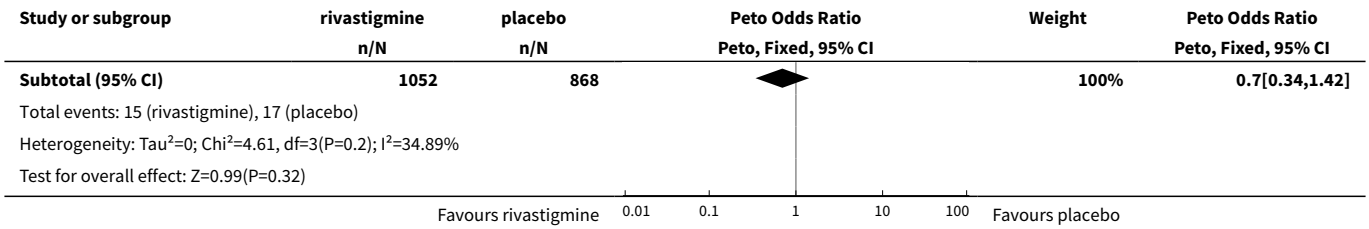


Analysis 2.39. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 39 at least one adverse event of bone fracture by the end of titration period.

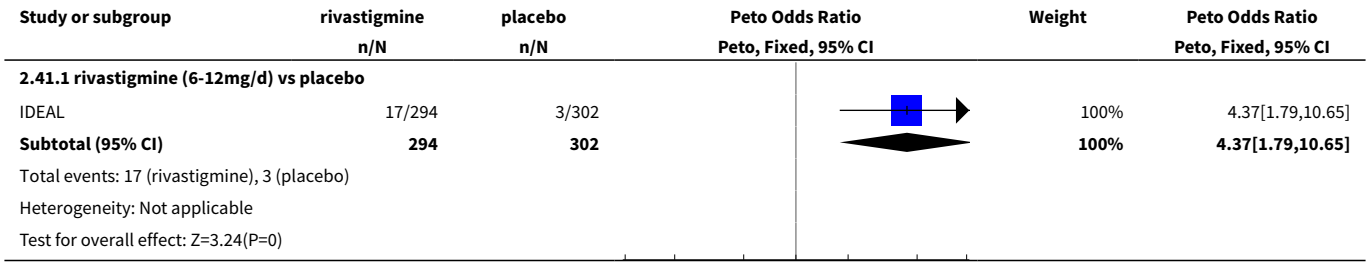


Analysis 2.40. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 40 at least one adverse event of bone fracture by 26 weeks.

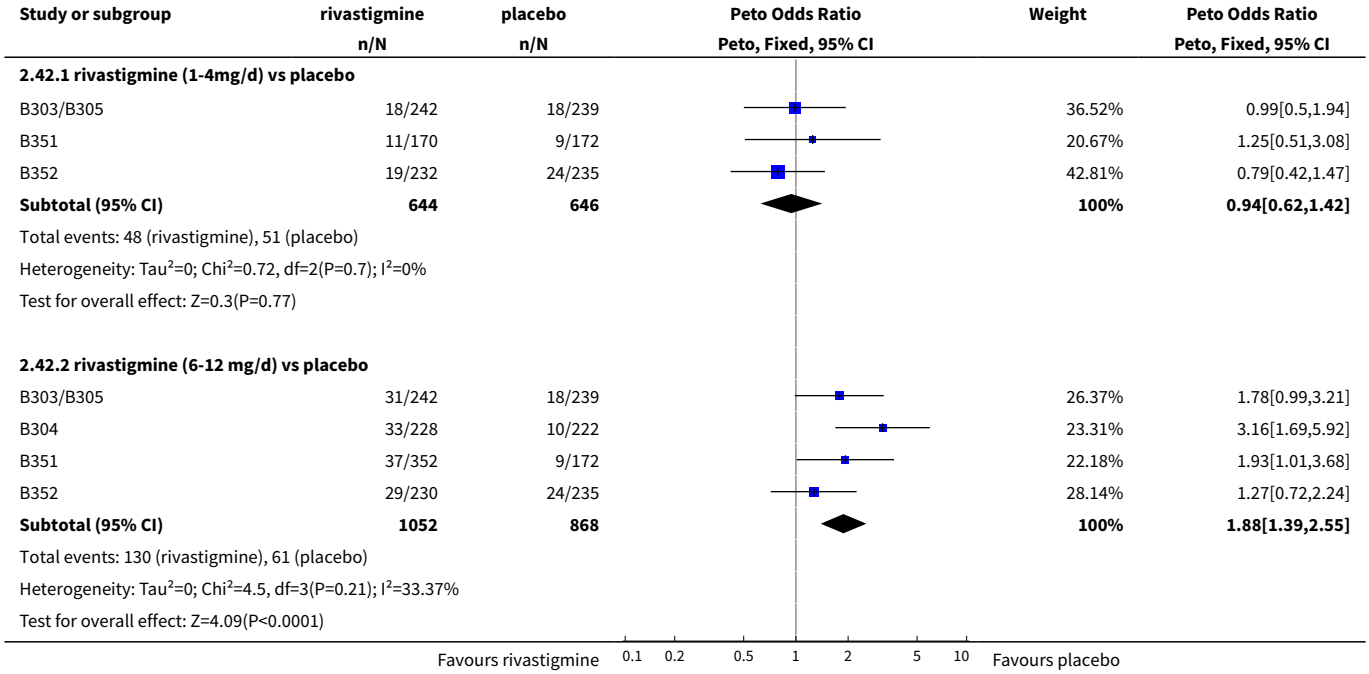




Analysis 2.41. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 41 at least one adverse event of asthenia by 26 weeks.

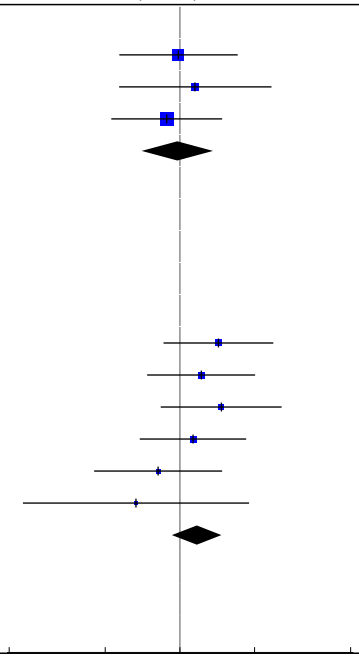


Analysis 2.42. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 42 at least one severe adverse event by the end of titration period.



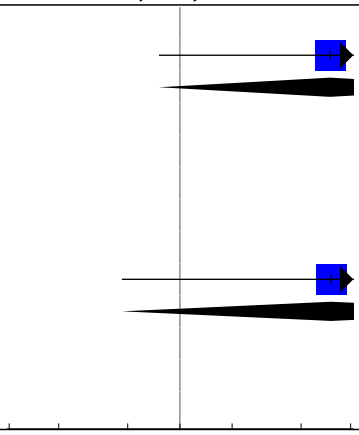
Analysis 2.43. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 43 at least one serious adverse event by 26 weeks.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.43.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	29/242	29/239		36.5%	0.99[0.57,1.71]
B351	18/170	16/172		21.93%	1.15[0.57,2.34]
B352	32/232	36/235		41.57%	0.88[0.53,1.48]
Subtotal (95% CI)	**644**	**646**		**100%**	**0.98[0.7,1.36]**
Total events: 79 (rivastigmine), 81 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.36, df=2(P=0.84); I^2=0%					
Test for overall effect: Z=0.15(P=0.88)					
2.43.2 rivastigmine (6-12mg/d) vs placebo					
B303/B305	40/242	29/239		20.43%	1.43[0.86,2.38]
B304	40/228	33/222		21.14%	1.22[0.74,2.01]
B351	47/352	16/172		16.9%	1.47[0.84,2.57]
B352	39/230	36/235		21.74%	1.13[0.69,1.85]
IDEAL	21/294	26/302		14.96%	0.82[0.45,1.48]
Lopez-Pousa 2005	6/104	9/106		4.83%	0.66[0.23,1.9]
Subtotal (95% CI)	**1450**	**1276**		**100%**	**1.17[0.93,1.47]**
Total events: 193 (rivastigmine), 149 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.77, df=5(P=0.58); I^2=0%					
Test for overall effect: Z=1.32(P=0.19)					



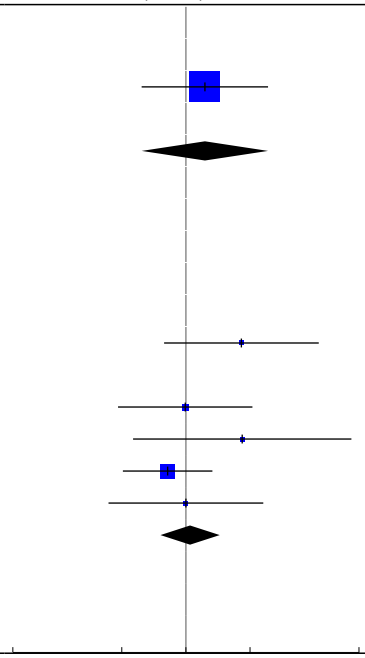
Analysis 2.44. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 44 deaths before end of treatment at 12 weeks.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.44.1 rivastigmine (1-4mg/d) vs placebo					
B103	3/136	0/133		100%	7.34[0.76,71.14]
Subtotal (95% CI)	**136**	**133**		**100%**	**7.34[0.76,71.14]**
Total events: 3 (rivastigmine), 0 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.72(P=0.09)					
2.44.2 rivastigmine (6-12 mg/d) vs placebo					
B103	2/133	0/133		100%	7.45[0.46,119.66]
Subtotal (95% CI)	**133**	**133**		**100%**	**7.45[0.46,119.66]**
Total events: 2 (rivastigmine), 0 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.42(P=0.16)					



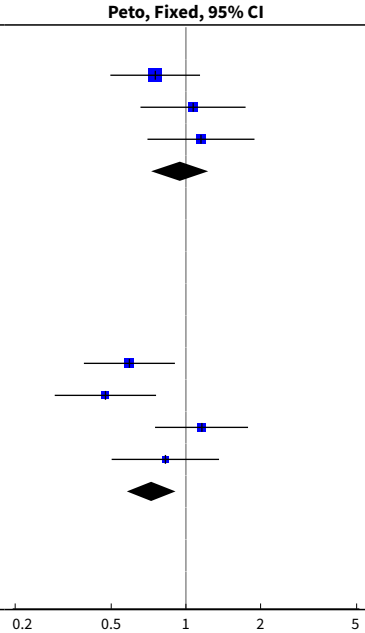
Analysis 2.45. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 45 deaths before end of treatment at 26 weeks.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.45.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	0/242	0/239			Not estimable
B351	2/170	1/172		100%	1.98[0.2,19.15]
B352	0/232	0/235			Not estimable
Subtotal (95% CI)	**644**	**646**		**100%**	**1.98[0.2,19.15]**
Total events: 2 (rivastigmine), 1 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
2.45.2 rivastigmine (6-12mg/d) vs placebo					
B303/B305	2/242	0/239		14.71%	7.33[0.46,117.51]
B304	0/228	0/222			Not estimable
B351	2/352	1/172		19.42%	0.98[0.09,10.93]
B352	1/230	0/235		7.37%	7.55[0.15,380.66]
IDEAL	2/297	4/302		43.84%	0.52[0.1,2.59]
Lopez-Pousa 2005	1/109	1/109		14.67%	1[0.06,16.09]
Subtotal (95% CI)	**1458**	**1279**		**100%**	**1.16[0.4,3.37]**
Total events: 8 (rivastigmine), 6 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.56, df=4(P=0.47); I^2=0%					
Test for overall effect: Z=0.28(P=0.78)					



Analysis 2.46. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 46 CIBIC-Plus (no change or worse at 12 weeks) OC.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.46.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	153/220	167/222		41.01%	0.75[0.5,1.14]
B351	105/148	112/161		29.97%	1.07[0.66,1.74]
B352	179/215	173/213		29.02%	1.15[0.7,1.89]
Subtotal (95% CI)	**583**	**596**		**100%**	**0.95[0.72,1.23]**
Total events: 437 (rivastigmine), 452 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.98, df=2(P=0.37); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					
2.46.2 rivastigmine (6-12mg/d) vs placebo					
B303/B305	122/190	167/222		28.62%	0.59[0.39,0.9]
B304	137/194	170/203		23.22%	0.47[0.3,0.76]
B351	198/273	112/161		27.59%	1.16[0.75,1.78]
B352	136/174	173/213		20.58%	0.83[0.5,1.36]
Subtotal (95% CI)	**831**	**799**		**100%**	**0.72[0.58,0.91]**
Total events: 593 (rivastigmine), 622 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.81, df=3(P=0.03); I^2=65.96%					
Test for overall effect: Z=2.8(P=0.01)					



Analysis 2.47. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 47 CIBIC-Plus (no change or worse at 26 weeks) OC.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.47.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	136/198	153/197		41.43%	0.63[0.41,0.99]
B351	89/120	98/129		24.88%	0.91[0.51,1.61]
B352	147/195	166/197		33.7%	0.58[0.35,0.94]
Subtotal (95% CI)	**513**	**523**		**100%**	**0.67[0.5,0.89]**
Total events: 372 (rivastigmine), 417 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.5, df=2(P=0.47); I^2=0%					
Test for overall effect: Z=2.73(P=0.01)					
2.47.2 rivastigmine (6-12mg/d) vs placebo					
B303/B305	92/155	153/197		30.18%	0.42[0.27,0.67]
B304	127/167	143/179		24.35%	0.8[0.48,1.33]
B351	139/193	89/120		24.08%	0.9[0.54,1.5]
B352	110/145	166/197		21.39%	0.58[0.34,1]
Subtotal (95% CI)	**660**	**693**		**100%**	**0.63[0.49,0.81]**
Total events: 468 (rivastigmine), 551 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.72, df=3(P=0.13); I^2=47.52%					
Test for overall effect: Z=3.56(P=0)					

Favours rivastigmine — Favours placebo

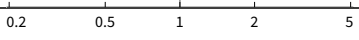
Analysis 2.48. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 48 CIBIC-Plus (no change or worse at 12 weeks) OC+RDO.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.48.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	160/229	169/224		40.52%	0.76[0.5,1.14]
B351	111/157	120/169		30.28%	0.99[0.61,1.59]
B352	186/223	177/219		29.2%	1.19[0.73,1.94]
Subtotal (95% CI)	**609**	**612**		**100%**	**0.94[0.72,1.22]**
Total events: 457 (rivastigmine), 466 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.03, df=2(P=0.36); I^2=1.34%					
Test for overall effect: Z=0.5(P=0.62)					
2.48.2 rivastigmine (6-12mg/d) vs placebo					
B303/B305	141/213	169/224		28.08%	0.64[0.42,0.97]
B304	155/215	179/213		22.88%	0.5[0.32,0.79]
B351	233/315	120/169		27.08%	1.16[0.76,1.77]
B352	162/209	177/219		21.97%	0.82[0.51,1.3]
Subtotal (95% CI)	**952**	**825**		**100%**	**0.75[0.6,0.93]**
Total events: 691 (rivastigmine), 645 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.93, df=3(P=0.05); I^2=62.16%					
Test for overall effect: Z=2.58(P=0.01)					

Favours rivastigmine — Favours placebo

Analysis 2.49. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 49 CIBIC-Plus (no change or worse at 26 weeks)OC+RDO.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.49.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	150/214	165/210		41.44%	0.64[0.42,0.99]
B351	101/135	108/142		26.27%	0.94[0.54,1.62]
B352	147/195	166/197		32.29%	0.58[0.35,0.94]
Subtotal (95% CI)	**544**	**549**		**100%**	**0.68[0.52,0.91]**
Total events: 398 (rivastigmine), 439 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.8, df=2(P=0.41); I^2=0%					
Test for overall effect: Z=2.65(P=0.01)					
2.49.2 rivastigmine (6-12mg/d) vs placebo					
B303/B305	115/186	165/210		29.86%	0.45[0.29,0.69]
B304	156/203	157/196		24.64%	0.83[0.51,1.33]
B351	158/218	108/142		24.25%	0.83[0.51,1.34]
B352	137/177	178/210		21.26%	0.62[0.37,1.03]
Subtotal (95% CI)	**784**	**758**		**100%**	**0.65[0.51,0.82]**
Total events: 566 (rivastigmine), 608 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.9, df=3(P=0.18); I^2=38.75%					
Test for overall effect: Z=3.61(P=0)					

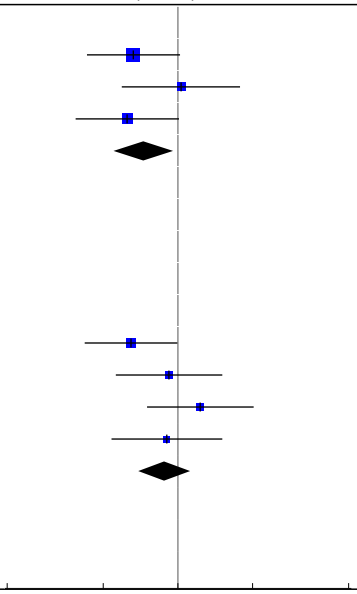


Analysis 2.50. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 50 CIBIC-Plus (no change or worse at 12 weeks) ALL+OC.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.50.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	175/242	183/238		40.95%	0.79[0.52,1.18]
B351	132/175	122/171		30.41%	1.23[0.77,1.98]
B352	197/233	194/234		28.64%	1.13[0.69,1.84]
Subtotal (95% CI)	**650**	**643**		**100%**	**1[0.77,1.3]**
Total events: 504 (rivastigmine), 499 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.29, df=2(P=0.32); I^2=12.69%					
Test for overall effect: Z=0.01(P=1)					
2.50.2 rivastigmine (6-12mg/d) vs placebo					
B303/B305	174/242	183/238		29.36%	0.77[0.51,1.16]
B304	171/228	187/220		23.08%	0.54[0.34,0.85]
B351	278/353	122/171		26.71%	1.51[0.98,2.31]
B352	193/231	194/234		20.84%	1.05[0.64,1.7]
Subtotal (95% CI)	**1054**	**863**		**100%**	**0.9[0.72,1.13]**
Total events: 816 (rivastigmine), 686 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=11.25, df=3(P=0.01); I^2=73.34%					
Test for overall effect: Z=0.89(P=0.37)					

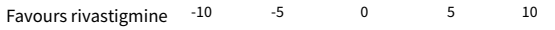
Analysis 2.51. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 51 CIBIC-Plus (no change or worse at 26 weeks) ALL+OC.

Study or subgroup	rivastigmine n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.51.1 rivastigmine (1-4mg/d) vs placebo					
B303/B305	180/242	194/238		41.17%	0.66[0.43,1.02]
B351	144/175	140/171		25.39%	1.03[0.59,1.78]
B352	185/233	205/238		33.44%	0.62[0.39,1.01]
Subtotal (95% CI)	**650**	**647**		**100%**	**0.73[0.55,0.96]**
Total events: 509 (rivastigmine), 539 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.12, df=2(P=0.35); I^2=5.45%					
Test for overall effect: Z=2.28(P=0.02)					
2.51.2 rivastigmine (6-12mg/d) vs placebo					
B303/B305	179/242	194/238		31.14%	0.65[0.42,0.99]
B304	188/228	184/220		23.63%	0.92[0.56,1.51]
B351	299/353	140/171		23.45%	1.23[0.75,2.02]
B352	196/231	205/238		21.77%	0.9[0.54,1.51]
Subtotal (95% CI)	**1054**	**867**		**100%**	**0.88[0.69,1.12]**
Total events: 862 (rivastigmine), 723 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.77, df=3(P=0.29); I^2=20.41%					
Test for overall effect: Z=1.05(P=0.29)					



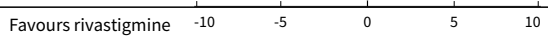
Analysis 2.52. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 52 ADAS-Cog (change from baseline at 12 weeks) OC.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.52.1 rivastigmine (1-4mg/d) vs placebo							
B303/B305	223	0.2 (6)	224	-0.1 (5.9)		30.73%	0.3[-0.8,1.4]
B351	150	0.2 (4.7)	158	0.9 (4.8)		33.22%	-0.7[-1.76,0.36]
B352	216	1.4 (5.4)	216	2.3 (5.4)		36.06%	-0.9[-1.92,0.12]
Subtotal ***	**589**		**598**			**100%**	**-0.46[-1.08,0.15]**
Heterogeneity: Tau^2=0; Chi^2=2.74, df=2(P=0.25); I^2=26.91%							
Test for overall effect: Z=1.49(P=0.14)							
2.52.2 rivastigmine (6-12mg/d) vs placebo							
B303/B305	198	-1.8 (5.9)	224	-0.1 (5.9)		22.01%	-1.7[-2.83,-0.57]
B304	196	-0.8 (5.8)	205	0.9 (5.7)		22.08%	-1.7[-2.83,-0.57]
B351	273	0.1 (4.8)	158	0.9 (4.8)		31.66%	-0.8[-1.74,0.14]
B352	176	-1 (5.4)	216	2.3 (5.4)		24.24%	-3.3[-4.37,-2.23]
Subtotal ***	**843**		**803**			**100%**	**-1.8[-2.33,-1.27]**
Heterogeneity: Tau^2=0; Chi^2=11.89, df=3(P=0.01); I^2=74.76%							
Test for overall effect: Z=6.68(P<0.0001)							



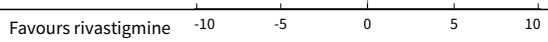
Analysis 2.53. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 53 ADAS-Cog (change from baseline at 26 weeks) OC.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.53.1 rivastigmine (1-4mg/d) vs placebo							
B303/B305	202	1.2 (7.3)	205	1.4 (7.5)		27.58%	-0.2[-1.64,1.24]
B351	123	2.1 (5.3)	129	2.6 (5.3)		33.28%	-0.5[-1.81,0.81]
B352	194	2.3 (6.1)	192	4.2 (6)		39.14%	-1.9[-3.11,-0.69]
Subtotal ***	**519**		**526**			**100%**	**-0.97[-1.72,-0.21]**
Heterogeneity: Tau^2=0; Chi^2=3.88, df=2(P=0.14); I^2=48.41%							
Test for overall effect: Z=2.51(P=0.01)							
2.53.2 rivastigmine (6-12mg/d) vs placebo							
B303/B305	157	-1.2 (7.5)	205	1.4 (7.5)		18.74%	-2.6[-4.16,-1.04]
B304	173	0.9 (6.8)	183	2.1 (6.8)		22.8%	-1.2[-2.61,0.21]
B351	195	0.9 (5.4)	129	2.6 (5.3)		32.27%	-1.7[-2.89,-0.51]
B352	145	-0.8 (6.2)	192	4.2 (6)		26.19%	-5[-6.32,-3.68]
Subtotal ***	**670**		**709**			**100%**	**-2.62[-3.29,-1.94]**
Heterogeneity: Tau^2=0; Chi^2=18.7, df=3(P=0); I^2=83.96%							
Test for overall effect: Z=7.61(P<0.0001)							



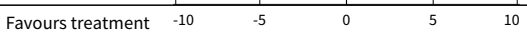
Analysis 2.54. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 54 ADAS-Cog (change from baseline at 12 weeks) OC+RDO.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.54.1 rivastigmine (1-4mg/d) vs placebo							
B303/B305	233	0.2 (6)	226	-0.1 (5.9)		29.96%	0.3[-0.79,1.39]
B351	158	0.3 (4.8)	167	0.9 (4.8)		32.57%	-0.6[-1.64,0.44]
B352	225	1.5 (5.3)	222	2.2 (5.2)		37.47%	-0.7[-1.67,0.27]
Subtotal ***	**616**		**615**			**100%**	**-0.37[-0.96,0.23]**
Heterogeneity: Tau^2=0; Chi^2=2.08, df=2(P=0.35); I^2=3.98%							
Test for overall effect: Z=1.21(P=0.23)							
2.54.2 rivastigmine (6-12mg/d) vs placebo							
B303/B305	227	-0.5 (5.9)	226	-0.1 (5.9)		21.56%	-0.41[-1.5,0.68]
B304	215	-0.9 (5.8)	213	0.9 (5.8)		21.08%	-1.8[-2.9,-0.7]
B351	314	0.3 (4.8)	167	0.9 (4.8)		31.36%	-0.6[-1.5,0.3]
B352	211	-0.6 (5.3)	222	2.2 (5.2)		26%	-2.8[-3.79,-1.81]
Subtotal ***	**967**		**828**			**100%**	**-1.38[-1.89,-0.88]**
Heterogeneity: Tau^2=0; Chi^2=14.41, df=3(P=0); I^2=79.18%							
Test for overall effect: Z=5.38(P<0.0001)							



Analysis 2.55. Comparison 2 Rivastigmine oral capsules (1 to 4 mg/day or 6 to 12 mg/day in two divided doses) versus placebo, Outcome 55 ADAS-Cog (change from baseline at 26 weeks) OC+RDO.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.55.1 rivastigmine (1-4mg/d) vs placebo							
B303/B305	217	1.5 (7.3)	213	1.4 (7.5)		27.09%	0.1[-1.3,1.5]
B351	138	2 (5.1)	142	2.8 (5.2)		36.44%	-0.8[-2.01,0.41]
B352	204	2.3 (6.3)	209	4.5 (6.2)		36.48%	-2.2[-3.41,-0.99]
Subtotal ***	**559**		**564**			**100%**	**-1.07[-1.8,-0.34]**
Heterogeneity: Tau^2=0; Chi^2=6.25, df=2(P=0.04); I^2=68.01%							
Test for overall effect: Z=2.87(P=0)							
2.55.2 rivastigmine (6-12mg/d) vs placebo							
B303/B305	186	-0.6 (7.5)	213	1.4 (7.5)		19.05%	-2[-3.48,-0.52]
B304	204	1.2 (7.2)	195	2.5 (7.1)		21.05%	-1.3[-2.7,0.1]
B351	221	1.1 (5.4)	142	2.8 (5.2)		33.47%	-1.7[-2.81,-0.59]
B352	177	0.1 (6.3)	209	4.5 (6.2)		26.44%	-4.4[-5.65,-3.15]
Subtotal ***	**788**		**759**			**100%**	**-2.39[-3.03,-1.74]**
Heterogeneity: Tau^2=0; Chi^2=13.96, df=3(P=0); I^2=78.51%							
Test for overall effect: Z=7.27(P<0.0001)							

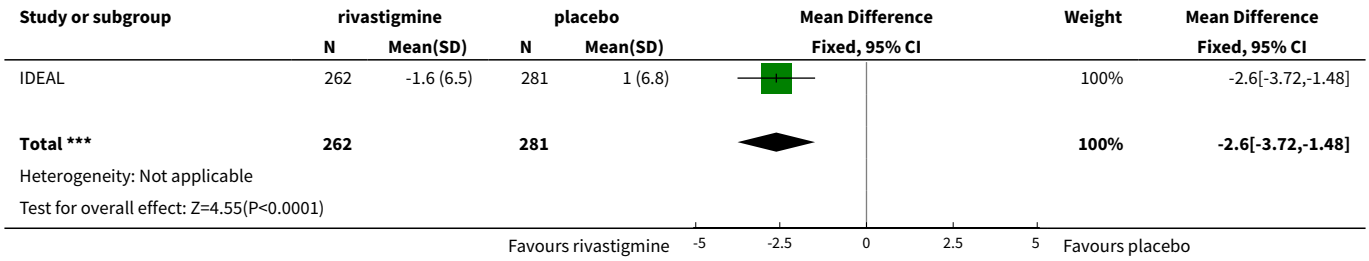


Comparison 3. Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo

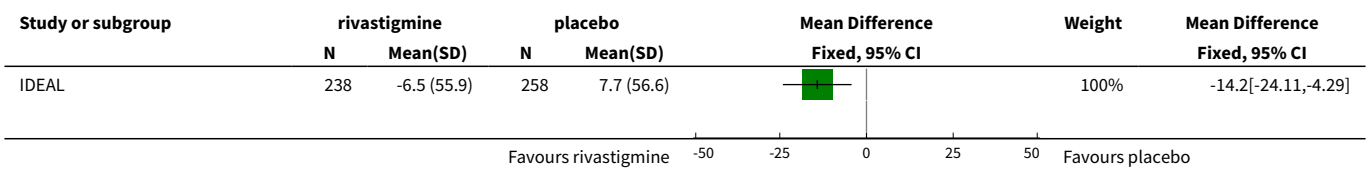
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-Cog (change from baseline at 24 weeks) ITT	1	543	Mean Difference (IV, Fixed, 95% CI)	-2.6 [-3.72, -1.48]
2 TMT-A (change from baseline at 24 weeks) ITT	1	496	Mean Difference (IV, Fixed, 95% CI)	-14.2 [-24.11, -4.29]
3 clock drawing (change from baseline at 24 weeks) ITT	1	520	Mean Difference (IV, Fixed, 95% CI)	0.2 [-0.34, 0.74]
4 MMSE (change from baseline at 24 weeks) ITT	1	543	Mean Difference (IV, Fixed, 95% CI)	0.90 [0.32, 1.48]
5 ADCS-ADL (change from baseline at 24 weeks) ITT	1	544	Mean Difference (IV, Fixed, 95% CI)	2.3 [0.52, 4.08]
6 NPI-12 (change from baseline at 24 weeks) ITT	1	544	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.88, 1.68]
7 withdrawals before end of treatment at 24 weeks	1	605	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.22, 2.97]
8 at least one adverse event by 24 weeks	1	605	Odds Ratio (M-H, Fixed, 95% CI)	2.28 [1.64, 3.16]
9 withdrawals due to an adverse event before end of treatment at 24 weeks	1	605	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [0.93, 3.46]

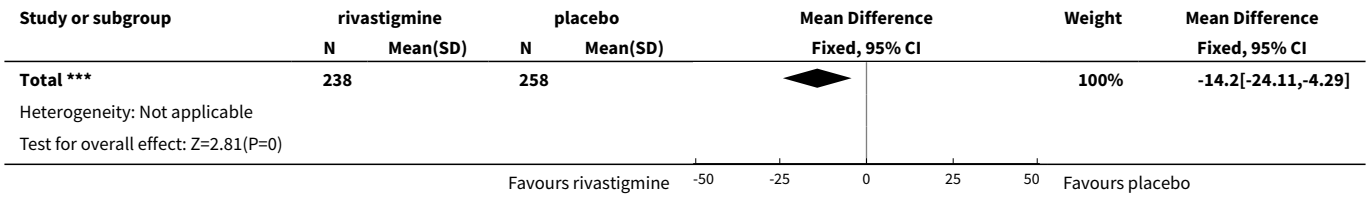
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 at least one adverse event of dizziness by 24 weeks	1	605	Odds Ratio (M-H, Fixed, 95% CI)	3.14 [1.31, 7.50]
11 at least one adverse event of nausea by 24 weeks	1	605	Odds Ratio (M-H, Fixed, 95% CI)	5.12 [2.85, 9.22]
12 at least one adverse event of vomiting by 24 weeks	1	605	Odds Ratio (M-H, Fixed, 95% CI)	6.77 [3.38, 13.53]
13 at least one adverse event of weight decrease by 24 weeks	1	605	Odds Ratio (M-H, Fixed, 95% CI)	6.12 [2.09, 17.92]
14 at least one adverse event of decreased appetite by 24 weeks	1	605	Odds Ratio (M-H, Fixed, 95% CI)	5.19 [1.49, 18.12]
15 at least one adverse event of headache by 24 weeks	1	605	Odds Ratio (M-H, Fixed, 95% CI)	2.66 [0.94, 7.56]
16 at least one adverse event of asthenia by 24 weeks	1	605	Odds Ratio (M-H, Fixed, 95% CI)	3.05 [0.82, 11.38]
17 deaths before end of treatment at 24 weeks	1	605	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [0.40, 7.06]
18 NPI-D carer distress scale (change from baseline at 24 weeks) ITT	1	544	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.07, 1.07]

Analysis 3.1. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 1 ADAS-Cog (change from baseline at 24 weeks) ITT.

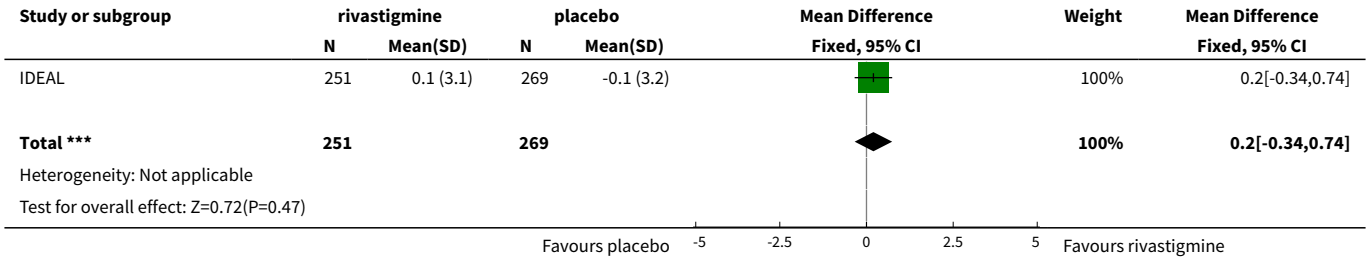


Analysis 3.2. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 2 TMT-A (change from baseline at 24 weeks) ITT.

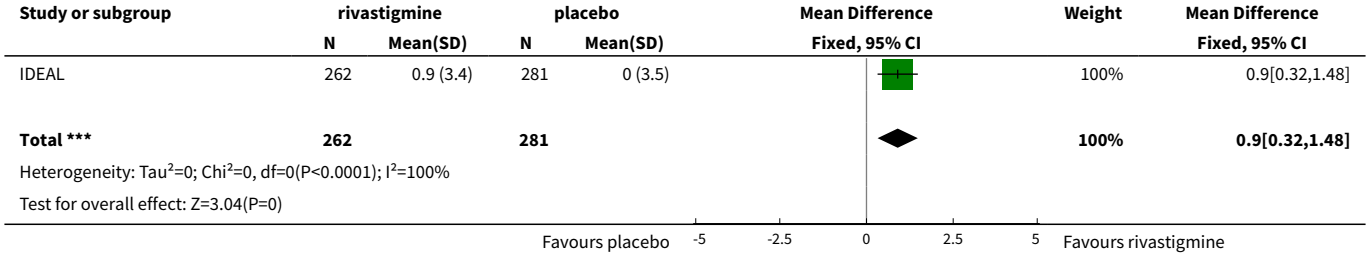




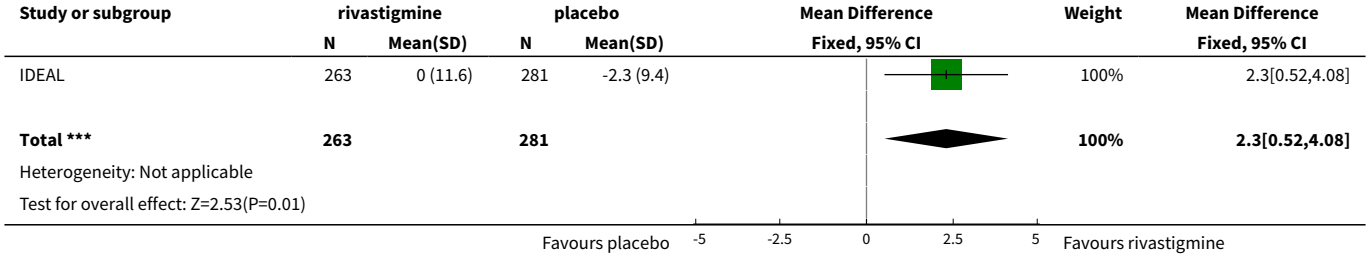
Analysis 3.3. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 3 clock drawing (change from baseline at 24 weeks) ITT.



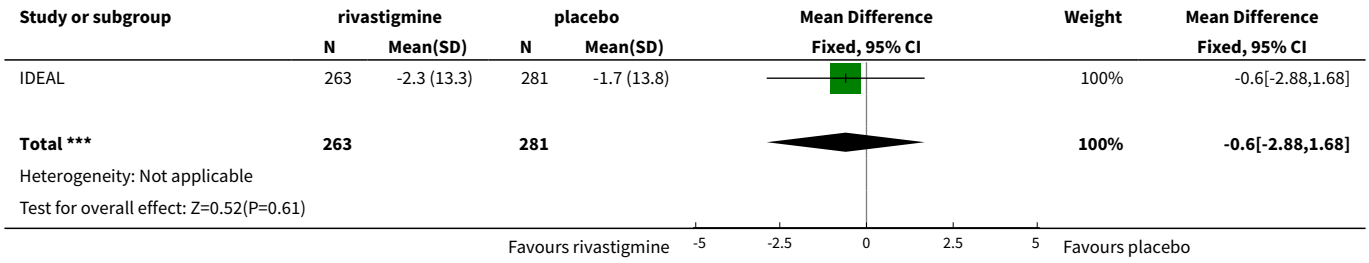
Analysis 3.4. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 4 MMSE (change from baseline at 24 weeks) ITT.



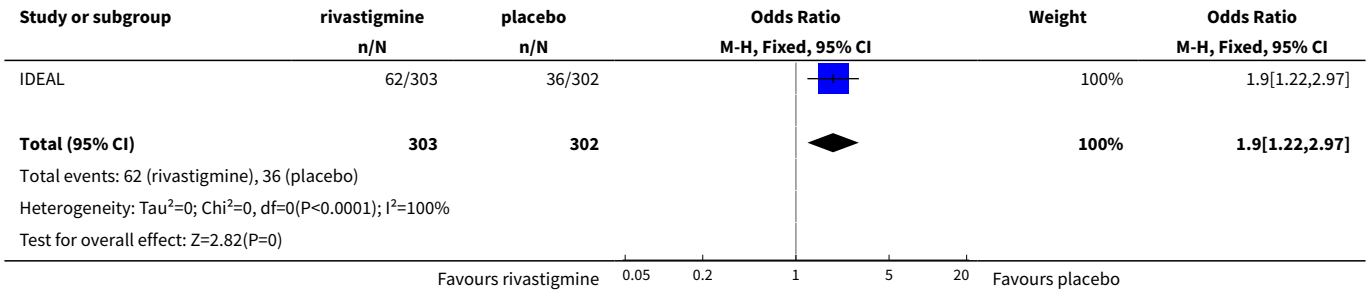
Analysis 3.5. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 5 ADCS-ADL (change from baseline at 24 weeks) ITT.



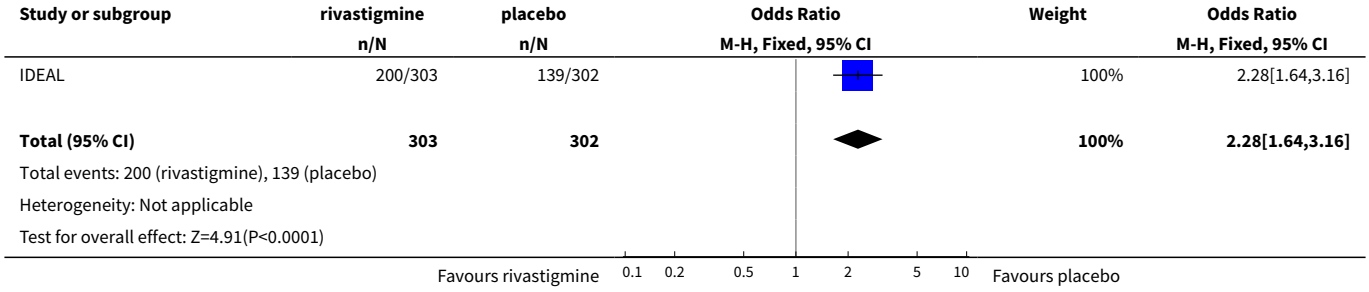
Analysis 3.6. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 6 NPI-12 (change from baseline at 24 weeks) ITT.



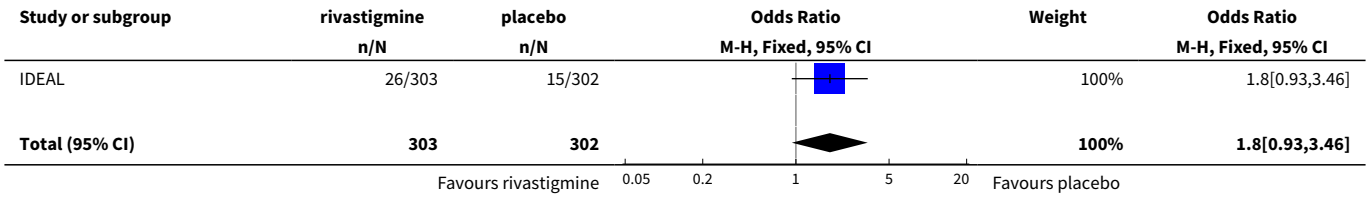
Analysis 3.7. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 7 withdrawals before end of treatment at 24 weeks.

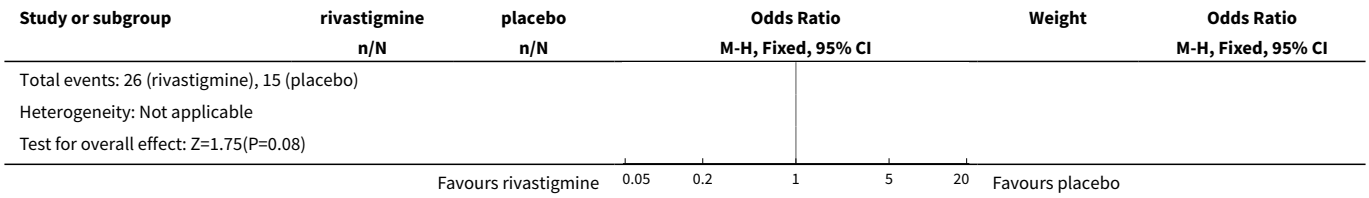


Analysis 3.8. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 8 at least one adverse event by 24 weeks.

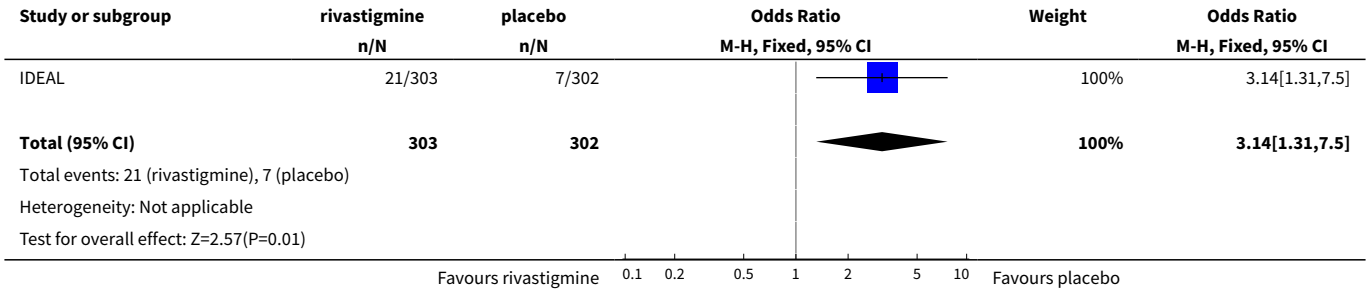


Analysis 3.9. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 9 withdrawals due to an adverse event before end of treatment at 24 weeks.

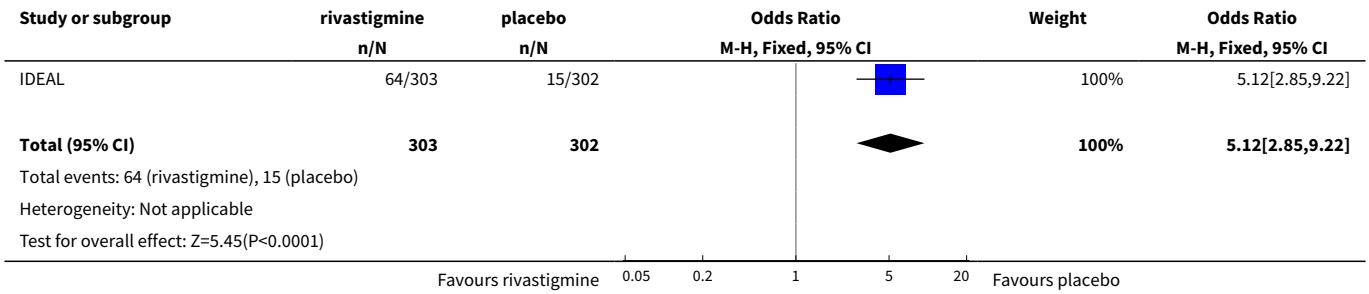




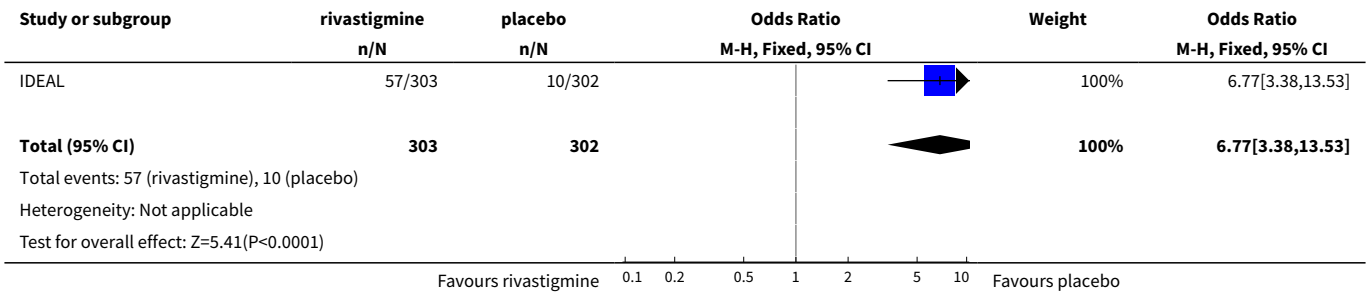
Analysis 3.10. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 10 at least one adverse event of dizziness by 24 weeks.



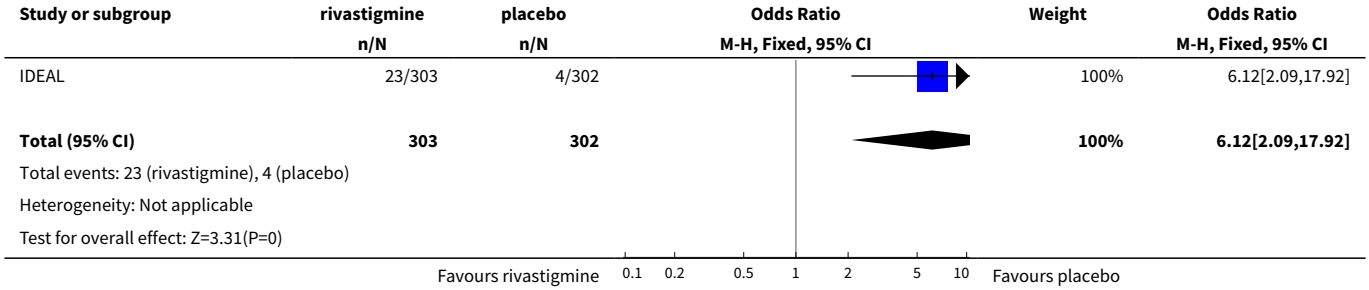
Analysis 3.11. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 11 at least one adverse event of nausea by 24 weeks.



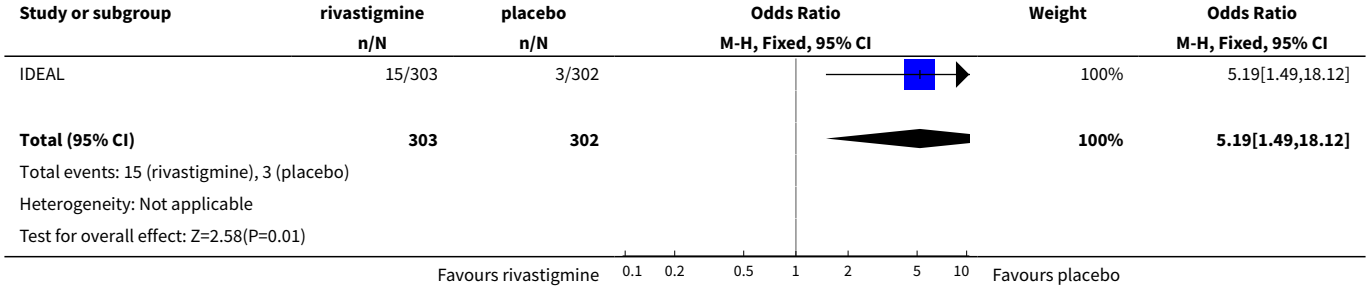
Analysis 3.12. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 12 at least one adverse event of vomiting by 24 weeks.



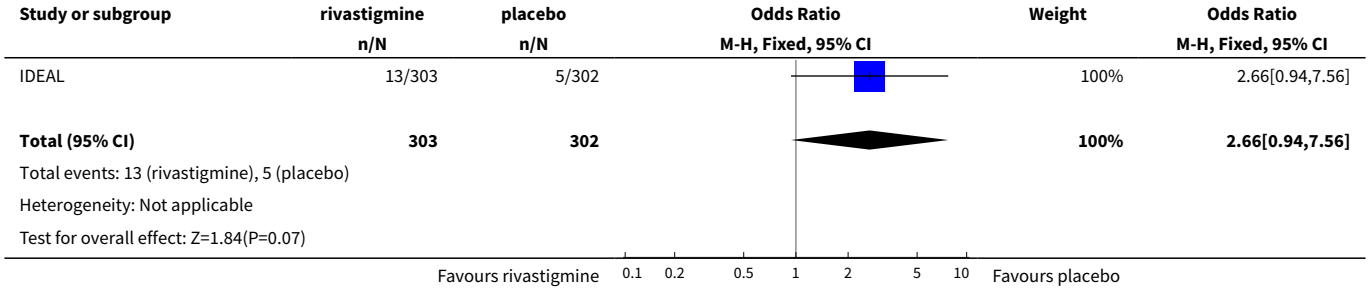
Analysis 3.13. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 13 at least one adverse event of weight decrease by 24 weeks.



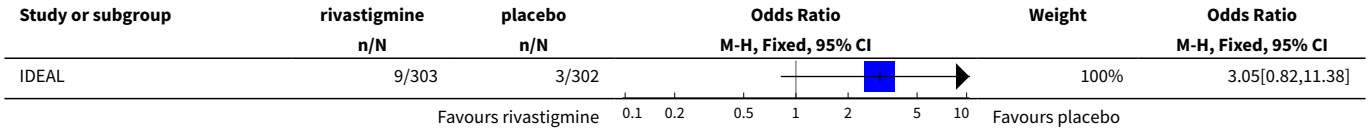
Analysis 3.14. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 14 at least one adverse event of decreased appetite by 24 weeks.

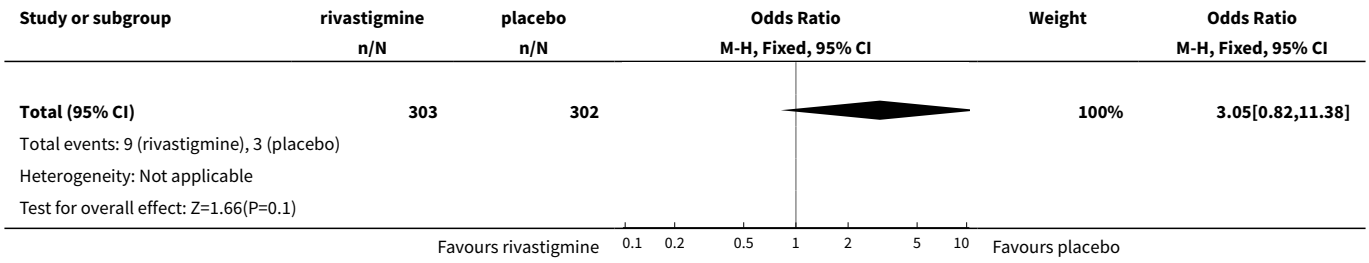


Analysis 3.15. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 15 at least one adverse event of headache by 24 weeks.

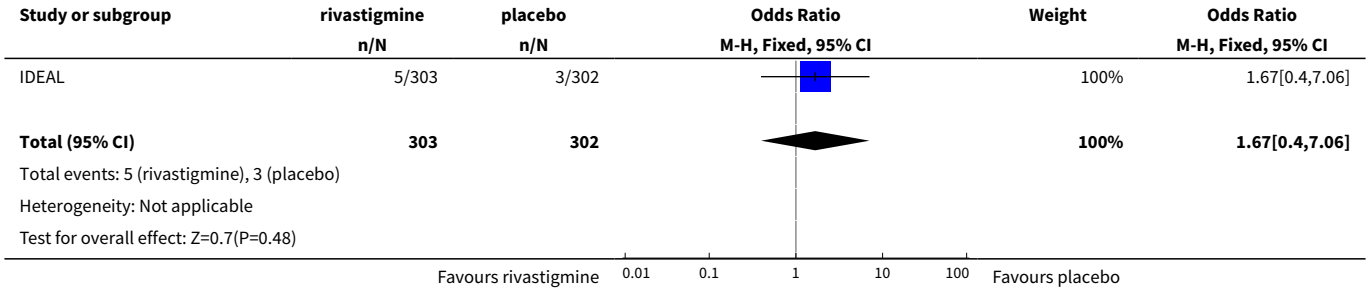


Analysis 3.16. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 16 at least one adverse event of asthenia by 24 weeks.

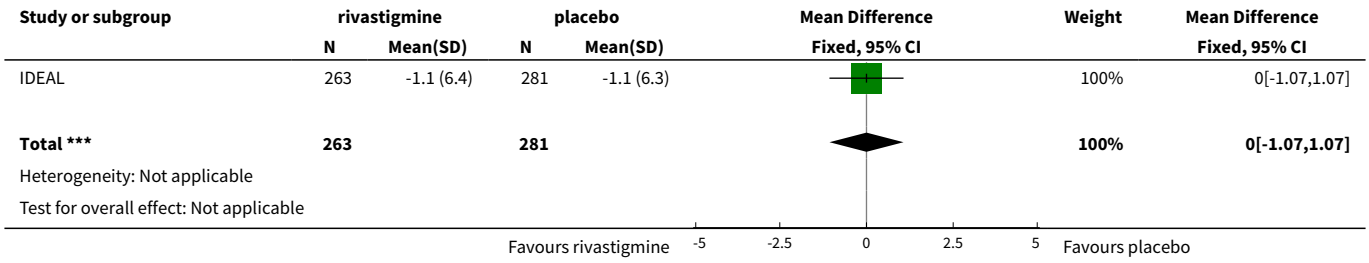




Analysis 3.17. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 17 deaths before end of treatment at 24 weeks.



Analysis 3.18. Comparison 3 Rivastigmine 20 cm^2 patch (17.4 mg/day) versus placebo, Outcome 18 NPI-D carer distress scale (change from baseline at 24 weeks) ITT.



Comparison 4. Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo

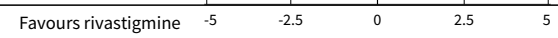
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 ADAS-Cog (change from baseline at 24 weeks) ITT	2	1062	Mean Difference (IV, Fixed, 95% CI)	-1.35 [-2.03, -0.66]
2 MMSE (change from baseline at 24 weeks) ITT	2	1028	Mean Difference (IV, Fixed, 95% CI)	0.64 [0.26, 1.02]
3 clock drawing (change from baseline at 24 weeks) ITT	1	514	Mean Difference (IV, Fixed, 95% CI)	0.4 [-0.17, 0.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 TMT-A (change from baseline at 24 weeks) ITT	1	499	Mean Difference (IV, Fixed, 95% CI)	-20.0 [-29.80, -10.20]
5 Mental Function Impairment MENFIS (change from baseline at 24 weeks) ITT	1	537	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-2.32, -0.28]
6 ADCS-ADL (change from baseline at 24 weeks) ITT	1	528	Mean Difference (IV, Fixed, 95% CI)	2.20 [0.62, 3.78]
7 Disability Assessment for Dementia (DAD) (change from baseline at 24 weeks) ITT	1	536	Mean Difference (IV, Fixed, 95% CI)	2.30 [0.34, 4.26]
8 BEHAVE-AD (change from baseline at 24 weeks) ITT	1	537	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.92, 0.52]
9 NPI-12 (change from baseline at 24 weeks) ITT	1	529	Mean Difference (IV, Fixed, 95% CI)	0.0 [-2.16, 2.16]
10 Clinical Global Impression (no change or worse at 24 weeks)	2	1063	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.58, 1.02]
11 withdrawals before end of treatment at 24 weeks	2	1170	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [1.23, 2.26]
12 at least one adverse event by 24 weeks	2	1460	Odds Ratio (M-H, Fixed, 95% CI)	1.63 [1.29, 2.06]
13 withdrawals due to an adverse event before end of treatment at 24 weeks	2	1170	Odds Ratio (M-H, Fixed, 95% CI)	1.84 [1.20, 2.82]
14 at least one adverse event of application site erythema by 24 weeks	1	573	Odds Ratio (M-H, Fixed, 95% CI)	2.73 [1.87, 3.98]
15 at least one adverse event of application site pruritis by 24 weeks	1	573	Odds Ratio (M-H, Fixed, 95% CI)	1.97 [1.36, 2.86]
16 at least one adverse event of application site edema by 24 weeks	1	573	Odds Ratio (M-H, Fixed, 95% CI)	4.83 [2.09, 11.15]
17 at least one adverse event application site exfoliation by 24 weeks	1	573	Odds Ratio (M-H, Fixed, 95% CI)	2.81 [0.88, 8.93]
18 at least one adverse event of dermatitis contact by 24 weeks	1	573	Odds Ratio (M-H, Fixed, 95% CI)	1.91 [1.24, 2.94]
19 at least one adverse event of nasopharyngitis by 24 weeks	1	573	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.62, 1.73]
20 at least one adverse event of nausea by 24 weeks	2	1166	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [1.07, 3.02]
21 at least one adverse event of vomiting by 24 weeks	2	1166	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [1.20, 3.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22 at least one adverse event of diarrhoea by 24 weeks	1	593	Odds Ratio (M-H, Fixed, 95% CI)	1.93 [0.87, 4.24]
23 at least one adverse event of weight decrease by 24 weeks	1	593	Odds Ratio (M-H, Fixed, 95% CI)	2.11 [0.63, 7.07]
24 at least one adverse event of dizziness by 24 weeks	1	593	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.36, 3.00]
25 at least one adverse event of decreased appetite by 24 weeks	1	593	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.11, 4.16]
26 at least one adverse event of headache by 24 weeks	1	593	Odds Ratio (M-H, Fixed, 95% CI)	2.11 [0.71, 6.26]
27 at least one adverse event of asthenia by 24 weeks	1	593	Odds Ratio (M-H, Fixed, 95% CI)	1.74 [0.41, 7.36]
28 deaths before end of treatment at 24 weeks	2	1170	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.28, 3.81]
29 NPI-D carer distress scale (change from baseline at 24 weeks) ITT	1	529	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.91, 1.11]

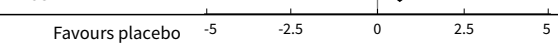
Analysis 4.1. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 1 ADAS-Cog (change from baseline at 24 weeks) ITT.

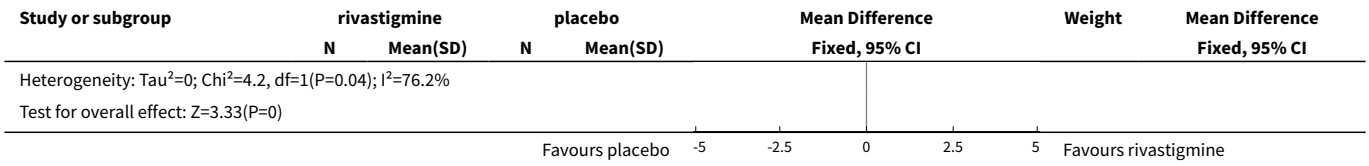
Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
IDEAL	248	-0.6 (6.4)	281	1 (6.8)		36.78%	-1.6[-2.73,-0.47]
Nakamura 2011	268	0.1 (5)	265	1.3 (5.1)		63.22%	-1.2[-2.06,-0.34]
Total ***	**516**		**546**			**100%**	**-1.35[-2.03,-0.66]**
Heterogeneity: Tau^2=0; Chi^2=0.31, df=1(P=0.58); I^2=0%							
Test for overall effect: Z=3.87(P=0)							



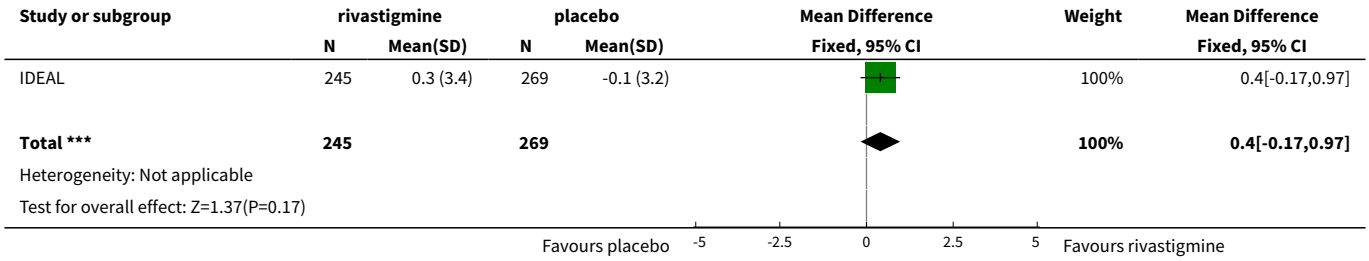
Analysis 4.2. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 2 MMSE (change from baseline at 24 weeks) ITT.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
IDEAL	250	1.1 (3.3)	281	0 (3.5)		42.78%	1.1[0.52,1.68]
Nakamura 2011	246	0 (2.9)	251	-0.3 (2.8)		57.22%	0.3[-0.2,0.8]
Total ***	**496**		**532**			**100%**	**0.64[0.26,1.02]**

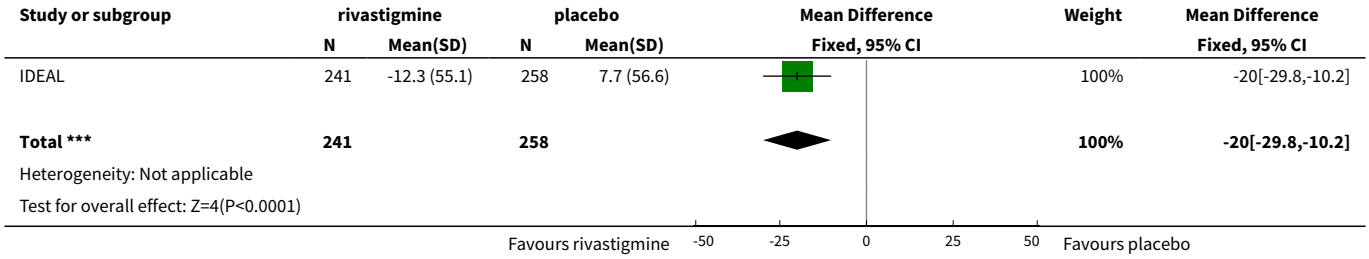




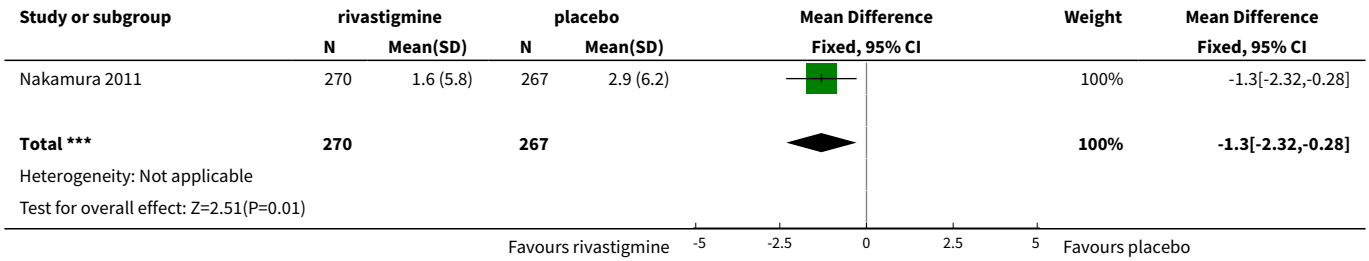
Analysis 4.3. Comparison 4 Rivastigmine 10 cm² patch (9.5 mg/day) versus placebo, Outcome 3 clock drawing (change from baseline at 24 weeks) ITT.



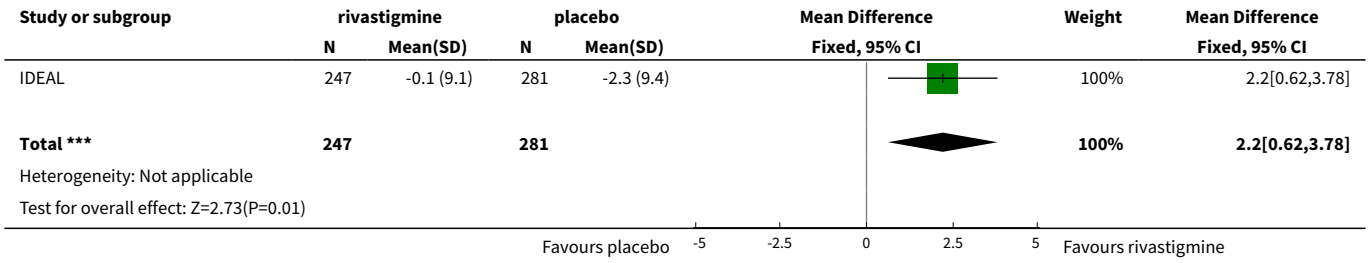
Analysis 4.4. Comparison 4 Rivastigmine 10 cm² patch (9.5 mg/day) versus placebo, Outcome 4 TMT-A (change from baseline at 24 weeks) ITT.



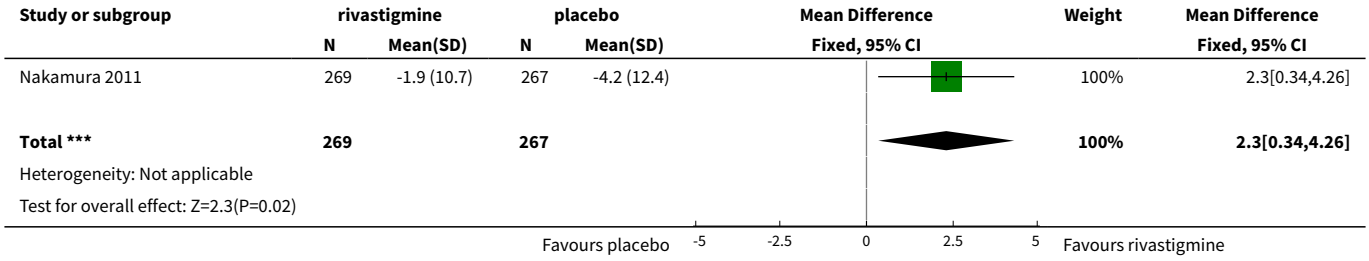
Analysis 4.5. Comparison 4 Rivastigmine 10 cm² patch (9.5 mg/day) versus placebo, Outcome 5 Mental Function Impairment MENFIS (change from baseline at 24 weeks) ITT.



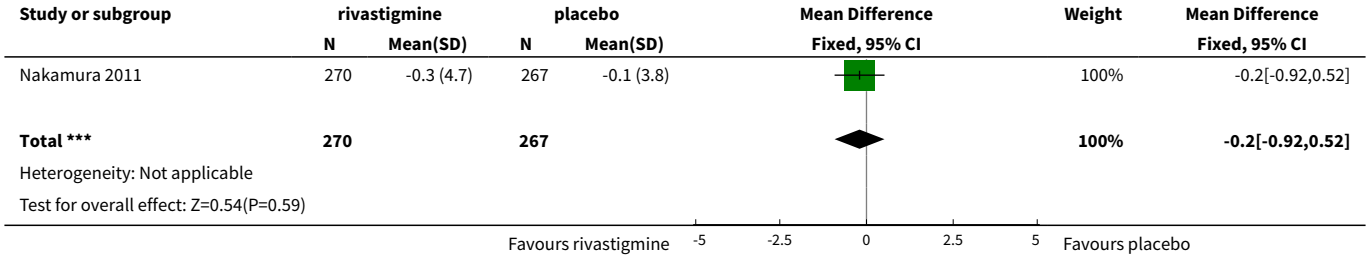
Analysis 4.6. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 6 ADCS-ADL (change from baseline at 24 weeks) ITT.



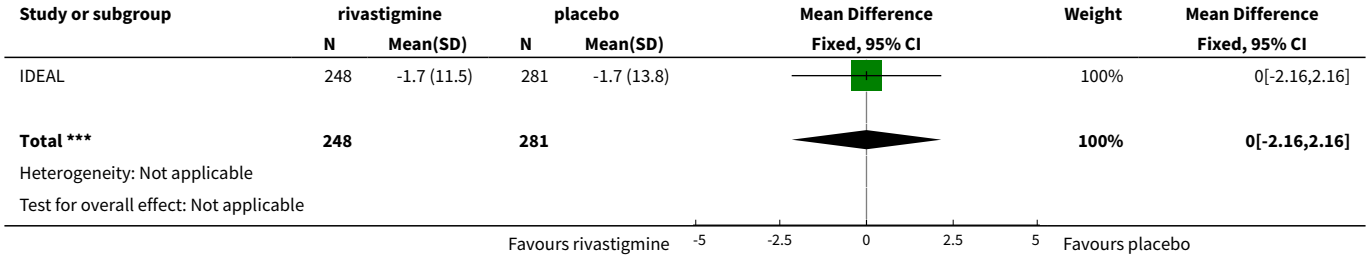
Analysis 4.7. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 7 Disability Assessment for Dementia (DAD) (change from baseline at 24 weeks) ITT.



Analysis 4.8. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 8 BEHAVE-AD (change from baseline at 24 weeks) ITT.

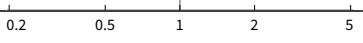


Analysis 4.9. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 9 NPI-12 (change from baseline at 24 weeks) ITT.



Analysis 4.10. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 10 Clinical Global Impression (no change or worse at 24 weeks).

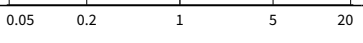
Study or subgroup	rivastigmine n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
IDEAL	171/248	200/278		54.11%	0.87[0.6,1.26]
Nakamura 2011	211/270	226/267		45.89%	0.65[0.42,1.01]
Total (95% CI)	**518**	**545**		**100%**	**0.77[0.58,1.02]**
Total events: 382 (rivastigmine), 426 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.96, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=1.83(P=0.07)					



Favours rivastigmine — Favours placebo

Analysis 4.11. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 11 withdrawals before end of treatment at 24 weeks.

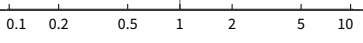
Study or subgroup	rivastigmine n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
IDEAL	64/293	36/302		43.17%	2.07[1.32,3.22]
Nakamura 2011	59/287	46/288		56.83%	1.36[0.89,2.08]
Total (95% CI)	**580**	**590**		**100%**	**1.67[1.23,2.26]**
Total events: 123 (rivastigmine), 82 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.76, df=1(P=0.18); I^2=43.13%					
Test for overall effect: Z=3.26(P=0)					



Favours rivastigmine — Favours placebo

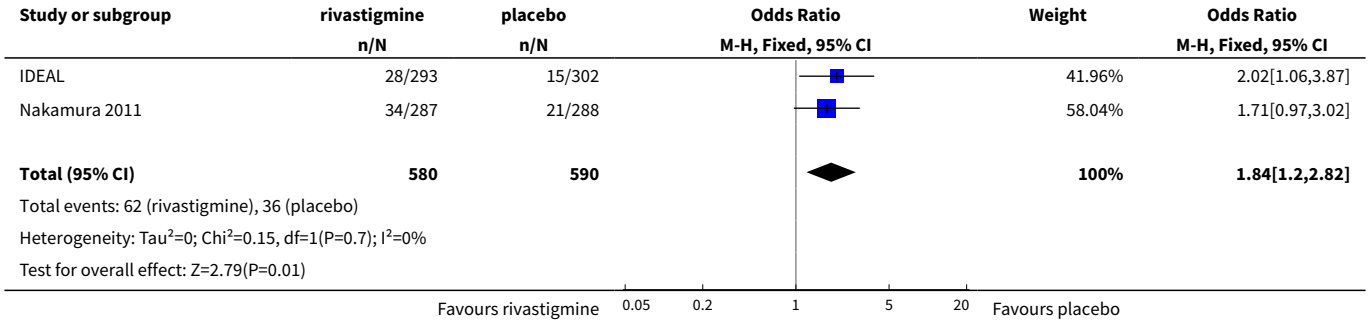
Analysis 4.12. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 12 at least one adverse event by 24 weeks.

Study or subgroup	rivastigmine n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
IDEAL	333/585	139/302		72.33%	1.55[1.17,2.05]
Nakamura 2011	248/287	222/286		27.67%	1.83[1.18,2.84]
Total (95% CI)	**872**	**588**		**100%**	**1.63[1.29,2.06]**
Total events: 581 (rivastigmine), 361 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.4, df=1(P=0.53); I^2=0%					
Test for overall effect: Z=4.06(P<0.0001)					

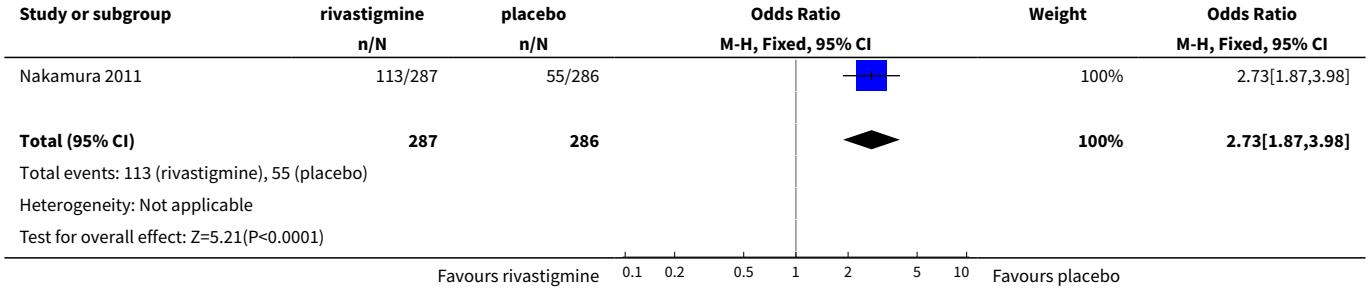


Favours rivastigmine — Favours placebo

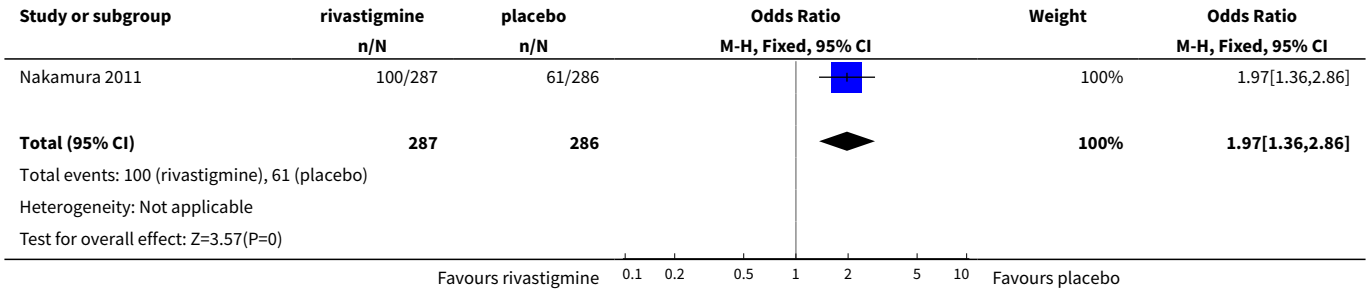
Analysis 4.13. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 13 withdrawals due to an adverse event before end of treatment at 24 weeks.



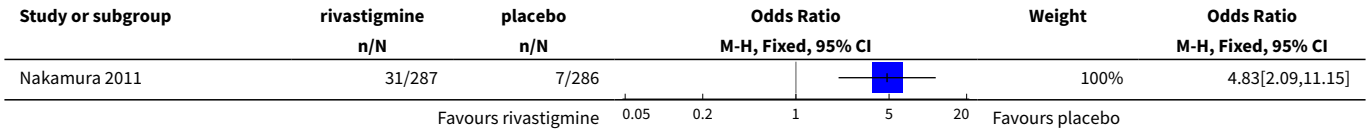
Analysis 4.14. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 14 at least one adverse event of application site erythema by 24 weeks.

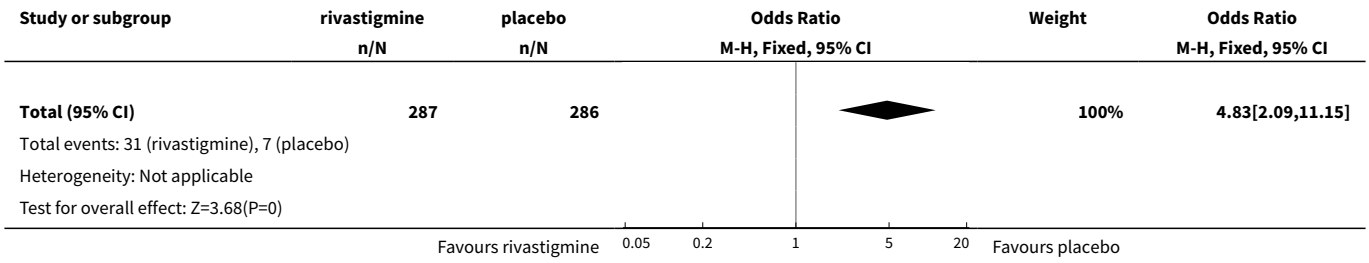


Analysis 4.15. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 15 at least one adverse event of application site pruritis by 24 weeks.

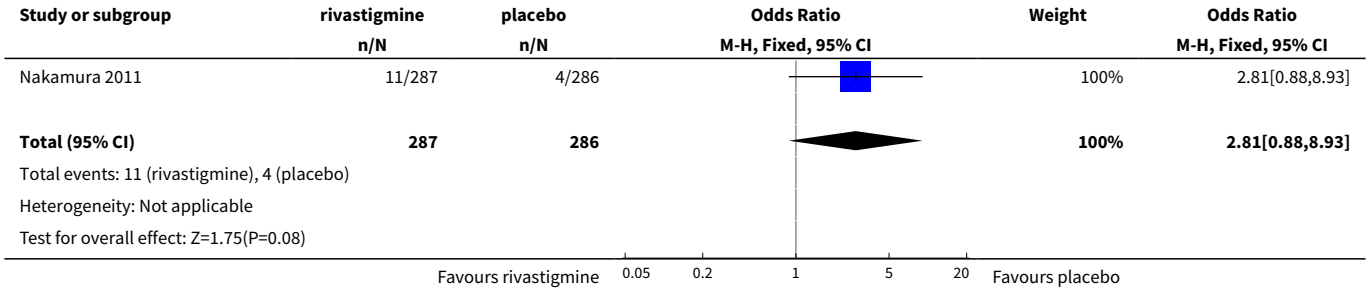


Analysis 4.16. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 16 at least one adverse event of application site edema by 24 weeks.

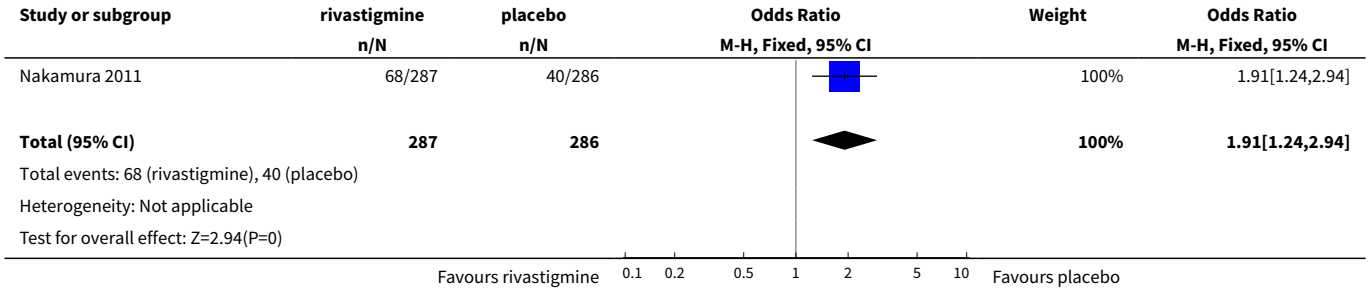




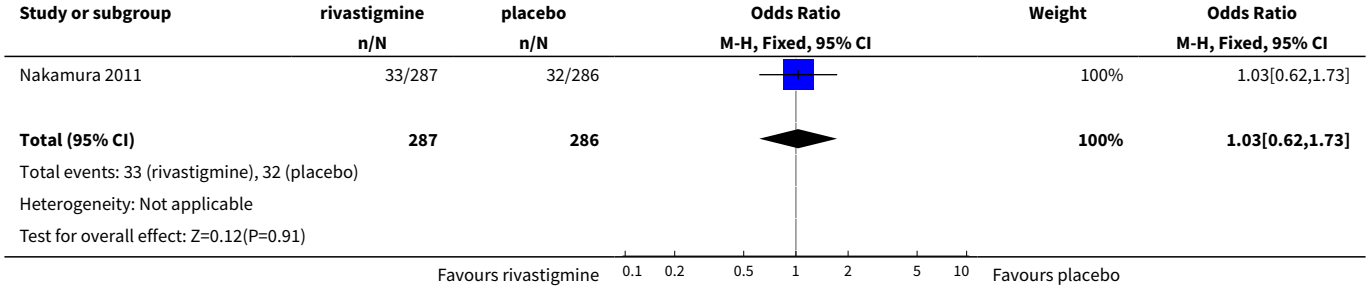
Analysis 4.17. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 17 at least one adverse event application site exfoliation by 24 weeks.



Analysis 4.18. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 18 at least one adverse event of dermatitis contact by 24 weeks.

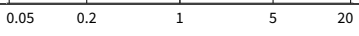


Analysis 4.19. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 19 at least one adverse event of nasopharyngitis by 24 weeks.



Analysis 4.20. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 20 at least one adverse event of nausea by 24 weeks.

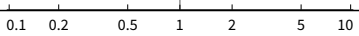
Study or subgroup	rivastigmine n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
IDEAL	21/291	15/302		61.96%	1.49[0.75,2.95]
Nakamura 2011	20/287	9/286		38.04%	2.31[1.03,5.15]
Total (95% CI)	**578**	**588**		**100%**	**1.8[1.07,3.02]**
Total events: 41 (rivastigmine), 24 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.66, df=1(P=0.42); I^2=0%					
Test for overall effect: Z=2.22(P=0.03)					



Favours rivastigmine — Favours placebo

Analysis 4.21. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 21 at least one adverse event of vomiting by 24 weeks.

Study or subgroup	rivastigmine n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
IDEAL	18/291	10/302		47.6%	1.93[0.87,4.24]
Nakamura 2011	23/287	11/286		52.4%	2.18[1.04,4.56]
Total (95% CI)	**578**	**588**		**100%**	**2.06[1.2,3.53]**
Total events: 41 (rivastigmine), 21 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%					
Test for overall effect: Z=2.62(P=0.01)					



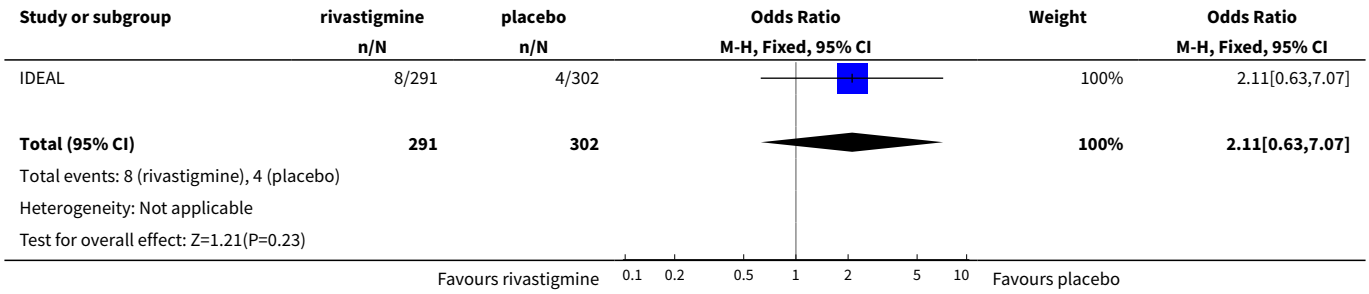
Favours rivastigmine — Favours placebo

Analysis 4.22. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 22 at least one adverse event of diarrhoea by 24 weeks.

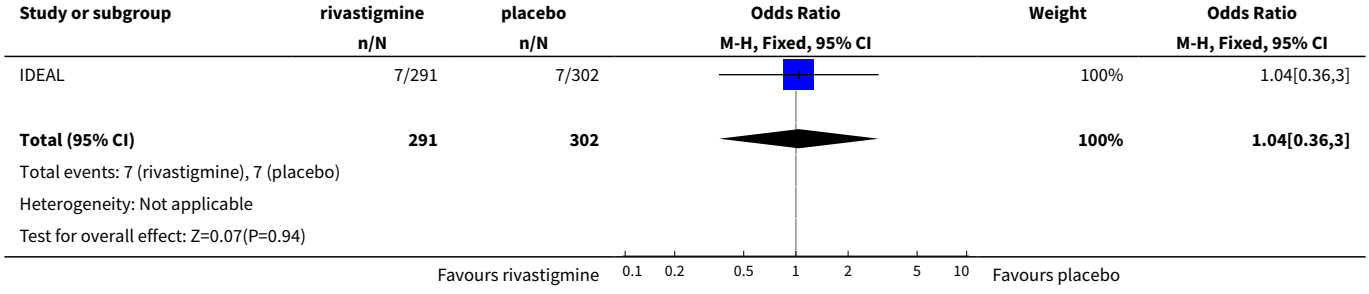
Study or subgroup	rivastigmine n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
IDEAL	18/291	10/302		100%	1.93[0.87,4.24]
Total (95% CI)	**291**	**302**		**100%**	**1.93[0.87,4.24]**
Total events: 18 (rivastigmine), 10 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.62(P=0.1)					

Favours rivastigmine — Favours placebo

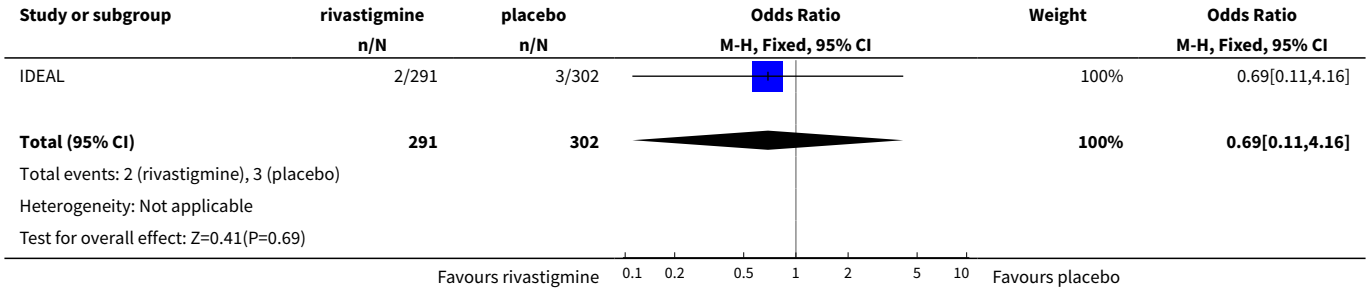
Analysis 4.23. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 23 at least one adverse event of weight decrease by 24 weeks.



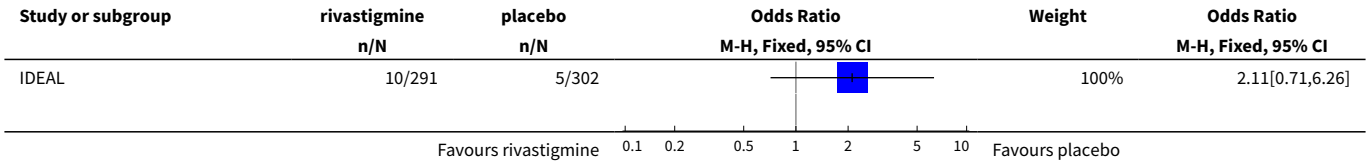
Analysis 4.24. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 24 at least one adverse event of dizziness by 24 weeks.

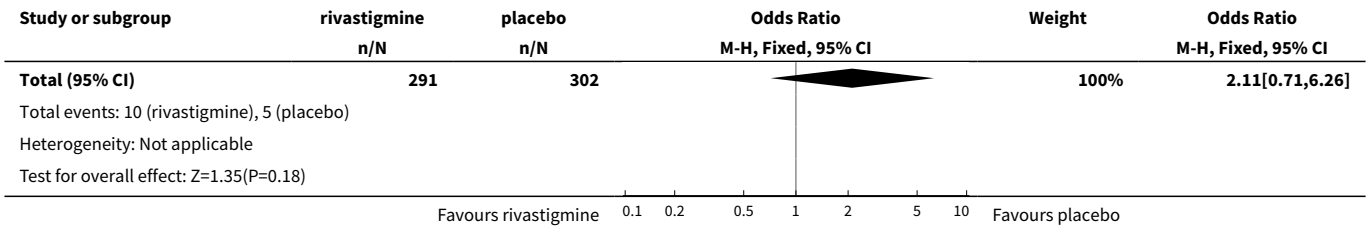


Analysis 4.25. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 25 at least one adverse event of decreased appetite by 24 weeks.

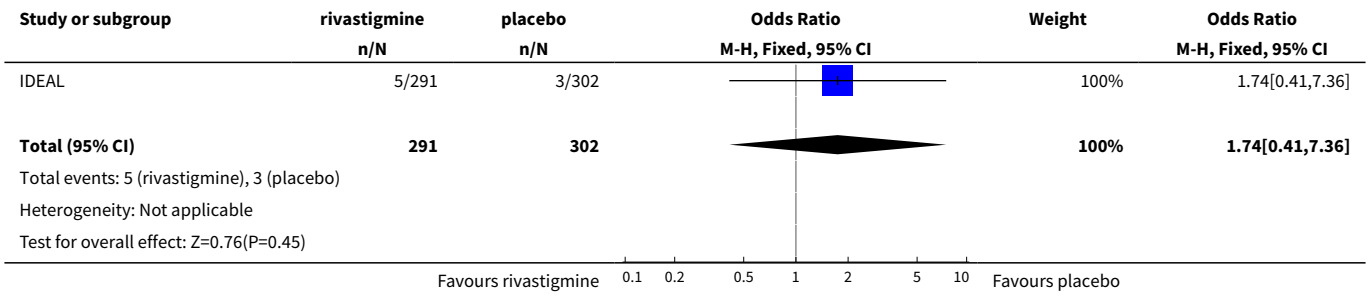


Analysis 4.26. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 26 at least one adverse event of headache by 24 weeks.

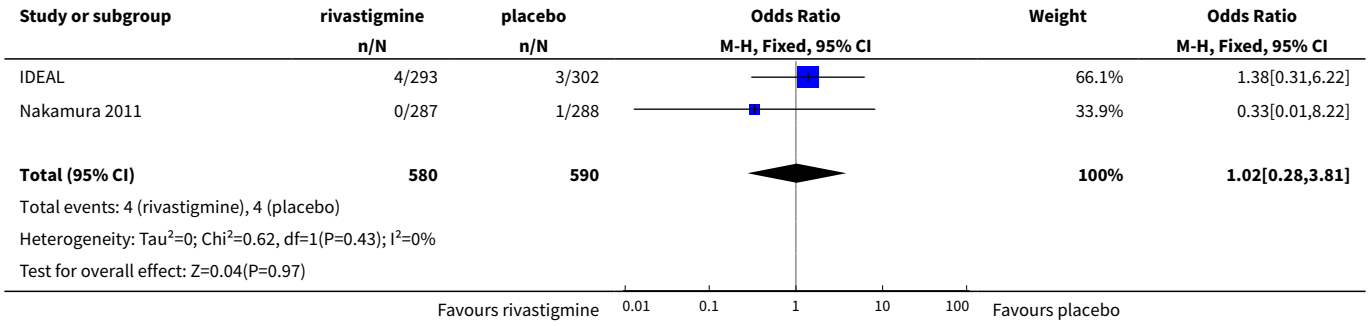




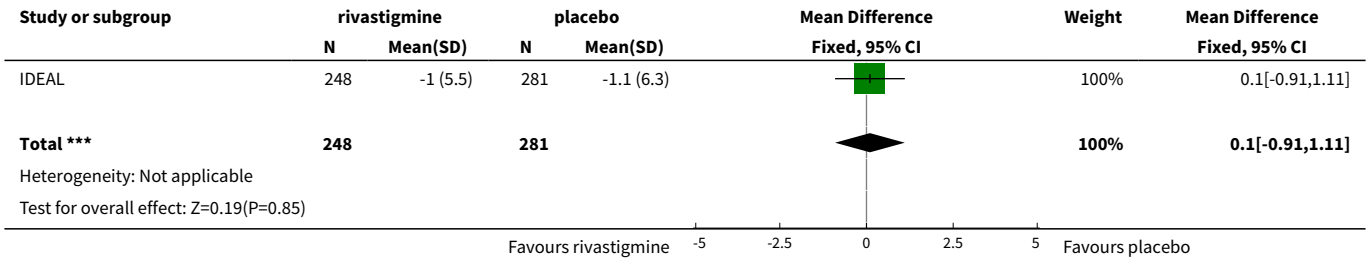
Analysis 4.27. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 27 at least one adverse event of asthenia by 24 weeks.



Analysis 4.28. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 28 deaths before end of treatment at 24 weeks.



Analysis 4.29. Comparison 4 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus placebo, Outcome 29 NPI-D carer distress scale (change from baseline at 24 weeks) ITT.

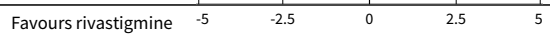


Comparison 5. Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-J Cog (change from baseline at 24 weeks) ITT	1	531	Mean Difference (IV, Fixed, 95% CI)	-0.8 [-1.62, 0.02]
2 MMSE (change from baseline at 24 weeks) ITT	1	487	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.52, 0.52]
3 Mental Function Impairment MENFIS (change from baseline at 24 weeks) ITT	1	536	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.72, 0.32]
4 Disability Assessment for Dementia (DAD) (change from baseline at 24 weeks) ITT	1	536	Mean Difference (IV, Fixed, 95% CI)	1.20 [-0.73, 3.13]
5 CIBIC-Plus J (no change or worse at 24 weeks) ITT	1	536	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.43, 1.05]
6 BEHAVE-AD (change from baseline at 24 weeks) ITT	1	536	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.67, 0.67]
7 withdrawals before end of treatment at 24 weeks	1	572	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [1.01, 2.33]
8 at least one adverse event by 24 weeks	1	568	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [1.16, 2.78]
9 withdrawals due to an adverse event before end of treatment at 24 weeks	1	572	Odds Ratio (M-H, Fixed, 95% CI)	1.96 [1.12, 3.44]
10 at least one adverse event of application site erythema by 24 weeks	1	568	Odds Ratio (M-H, Fixed, 95% CI)	2.53 [1.73, 3.70]
11 at least one adverse event of application site pruritis by 24 weeks	1	568	Odds Ratio (M-H, Fixed, 95% CI)	1.79 [1.23, 2.60]
12 at least one adverse event of application site edema by 24 weeks	1	568	Odds Ratio (M-H, Fixed, 95% CI)	5.65 [2.46, 12.94]
13 at least one adverse event application site exfoliation by 24 weeks	1	568	Odds Ratio (M-H, Fixed, 95% CI)	3.68 [1.20, 11.33]
14 at least one adverse event of dermatitis contact by 24 weeks	1	568	Odds Ratio (M-H, Fixed, 95% CI)	1.99 [1.30, 3.06]
15 at least one adverse event of nasopharyngitis by 24 weeks	1	568	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.38, 1.19]
16 at least one adverse event of nausea by 24 weeks	1	568	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.09, 1.24]
17 at least one adverse event of vomiting by 24 weeks	1	568	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.43, 2.38]
18 deaths before end of treatment at 24 weeks	1	572	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 16.29]

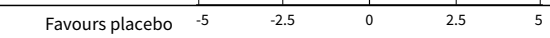
Analysis 5.1. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 1 ADAS-J Cog (change from baseline at 24 weeks) ITT.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nakamura 2011	266	0.5 (4.6)	265	1.3 (5.1)		100%	-0.8[-1.62,0.02]
Total ***	**266**		**265**			**100%**	**-0.8[-1.62,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.91(P=0.06)							



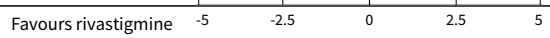
Analysis 5.2. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 2 MMSE (change from baseline at 24 weeks) ITT.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nakamura 2011	236	-0.3 (3.1)	251	-0.3 (2.8)		100%	0[-0.52,0.52]
Total ***	**236**		**251**			**100%**	**0[-0.52,0.52]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



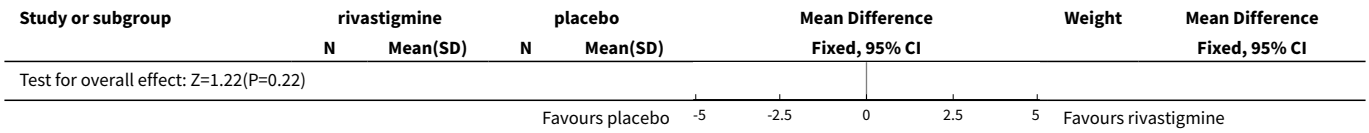
Analysis 5.3. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 3 Mental Function Impairment MENFIS (change from baseline at 24 weeks) ITT.

Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nakamura 2011	269	2.2 (5.9)	267	2.9 (6.2)		100%	-0.7[-1.72,0.32]
Total ***	**269**		**267**			**100%**	**-0.7[-1.72,0.32]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.35(P=0.18)							

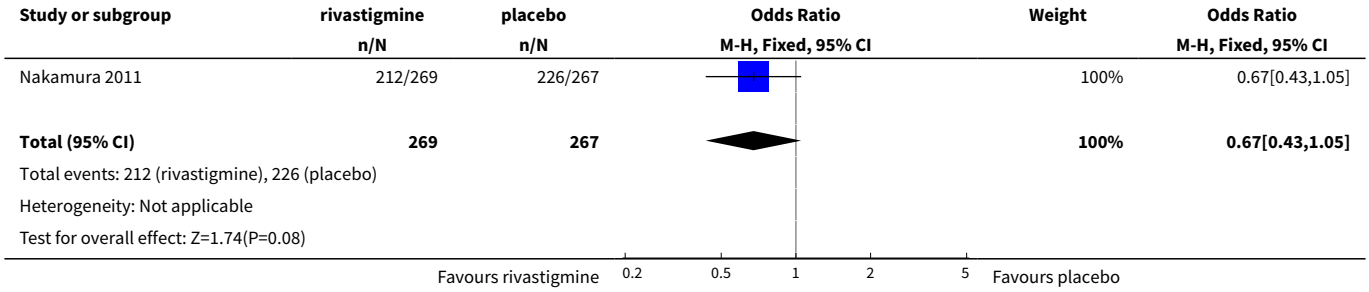


Analysis 5.4. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 4 Disability Assessment for Dementia (DAD) (change from baseline at 24 weeks) ITT.

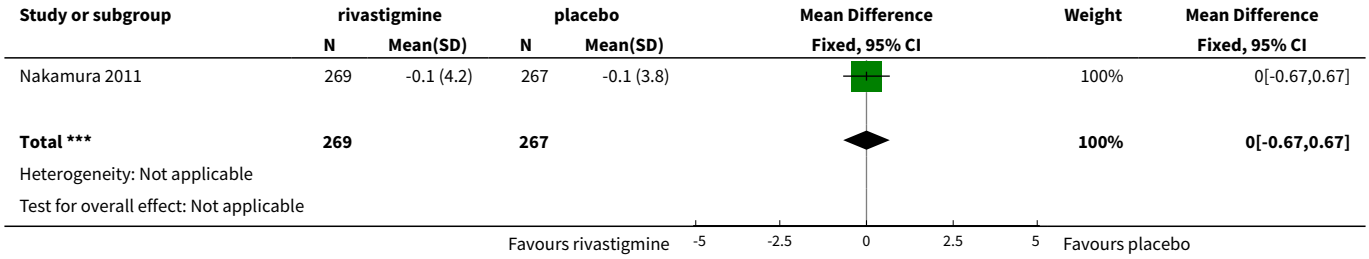
Study or subgroup	rivastigmine N	rivastigmine Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nakamura 2011	269	-3 (10.3)	267	-4.2 (12.4)		100%	1.2[-0.73,3.13]
Total ***	**269**		**267**			**100%**	**1.2[-0.73,3.13]**
Heterogeneity: Not applicable							



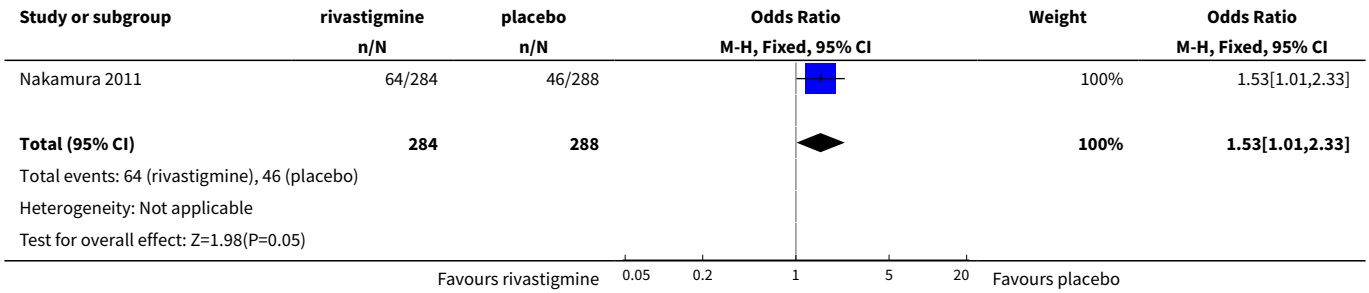
Analysis 5.5. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 5 CIBIC-Plus J (no change or worse at 24 weeks) ITT.



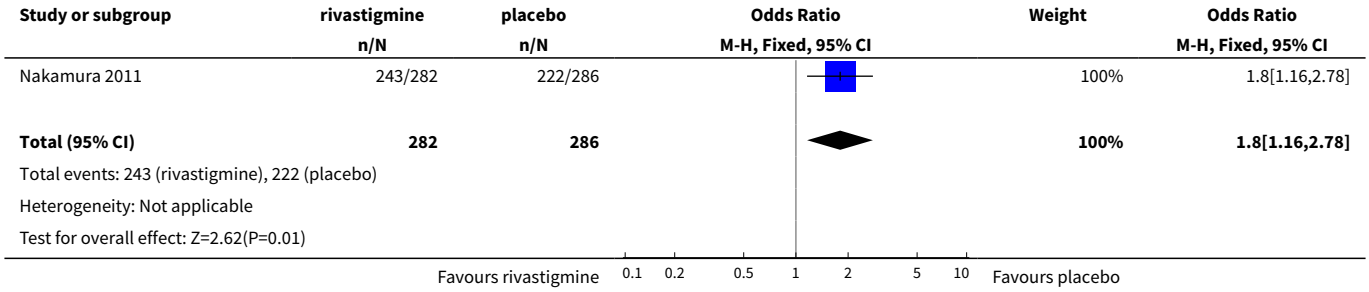
Analysis 5.6. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 6 BEHAVE-AD (change from baseline at 24 weeks) ITT.



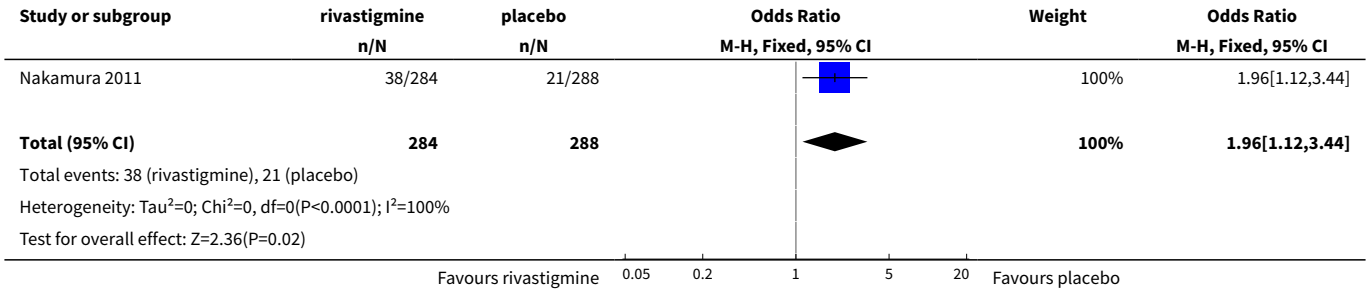
Analysis 5.7. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 7 withdrawals before end of treatment at 24 weeks.



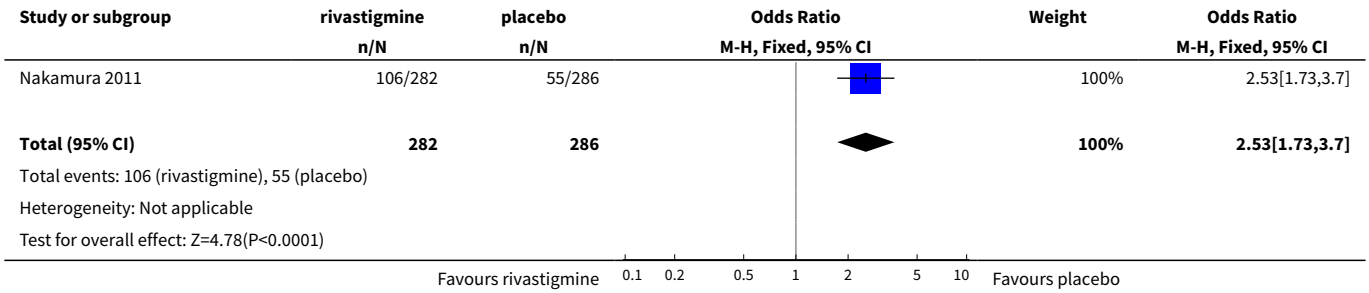
Analysis 5.8. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 8 at least one adverse event by 24 weeks.



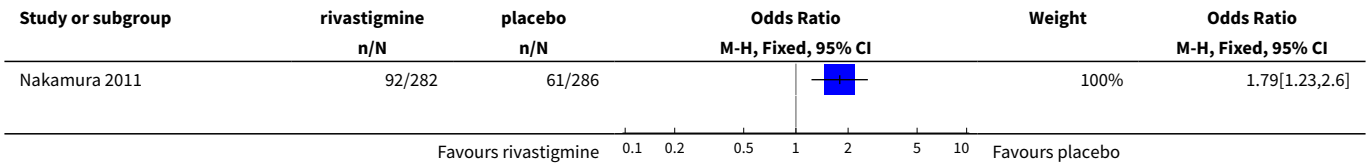
Analysis 5.9. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 9 withdrawals due to an adverse event before end of treatment at 24 weeks.

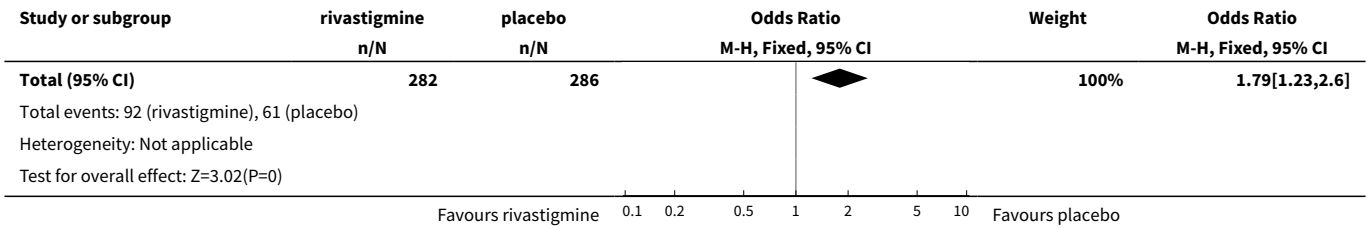


Analysis 5.10. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 10 at least one adverse event of application site erythema by 24 weeks.

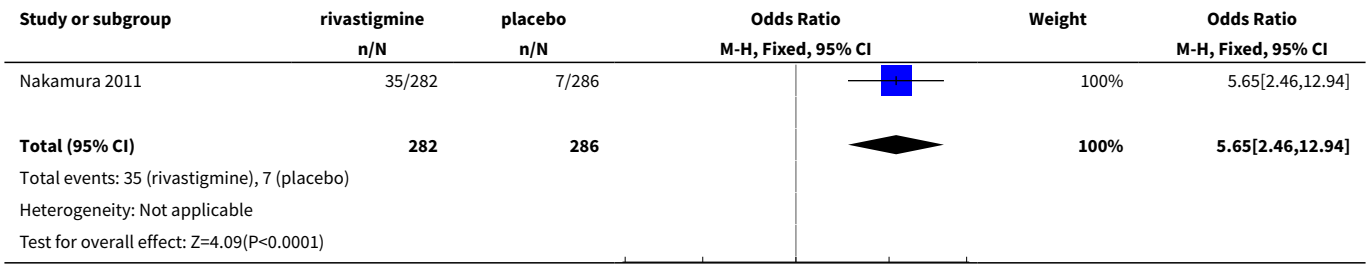


Analysis 5.11. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 11 at least one adverse event of application site pruritis by 24 weeks.

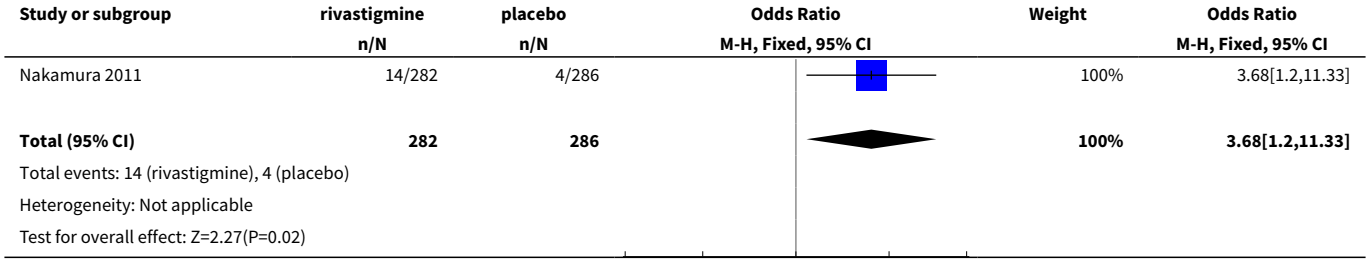




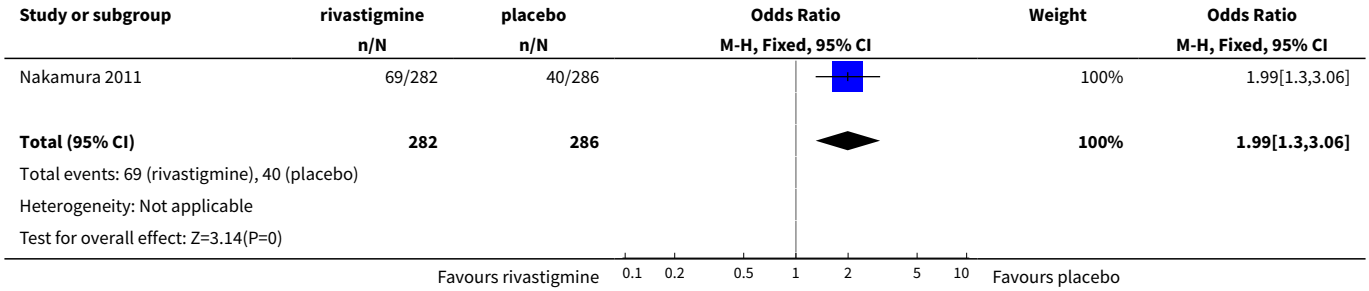
Analysis 5.12. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 12 at least one adverse event of application site edema by 24 weeks.



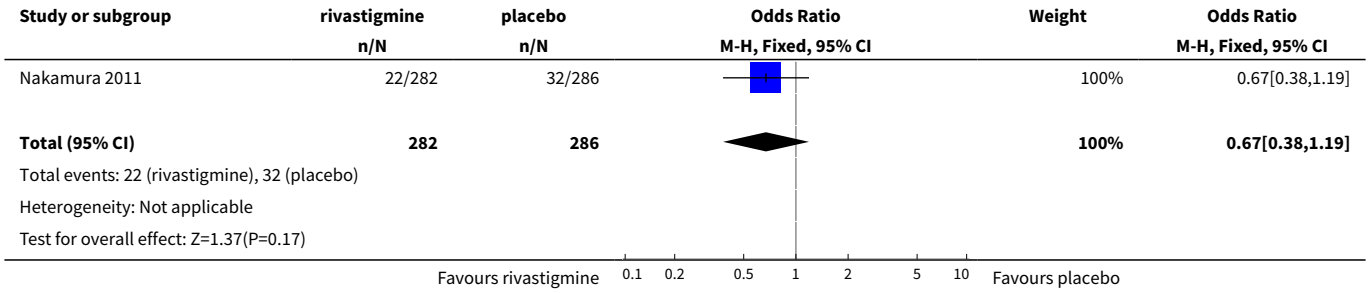
Analysis 5.13. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 13 at least one adverse event application site exfoliation by 24 weeks.



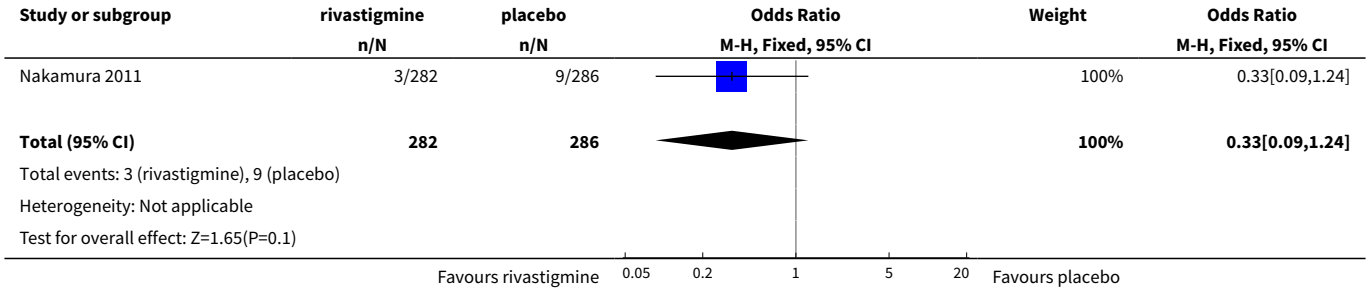
Analysis 5.14. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 14 at least one adverse event of dermatitis contact by 24 weeks.



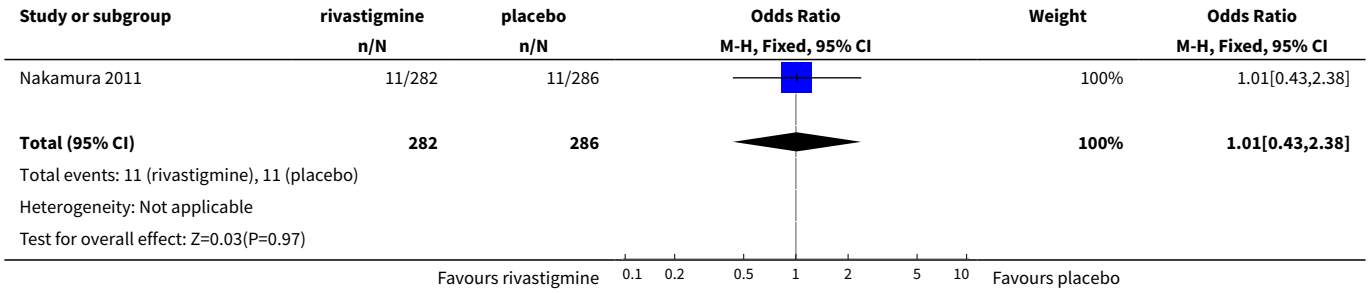
Analysis 5.15. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 15 at least one adverse event of nasopharyngitis by 24 weeks.



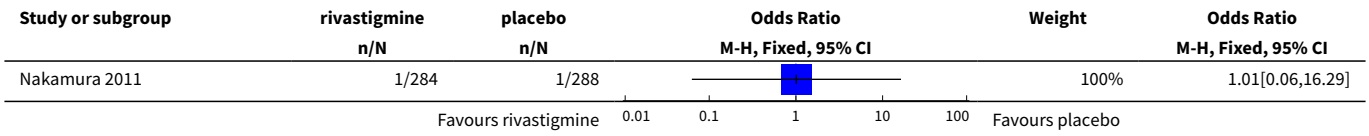
Analysis 5.16. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 16 at least one adverse event of nausea by 24 weeks.

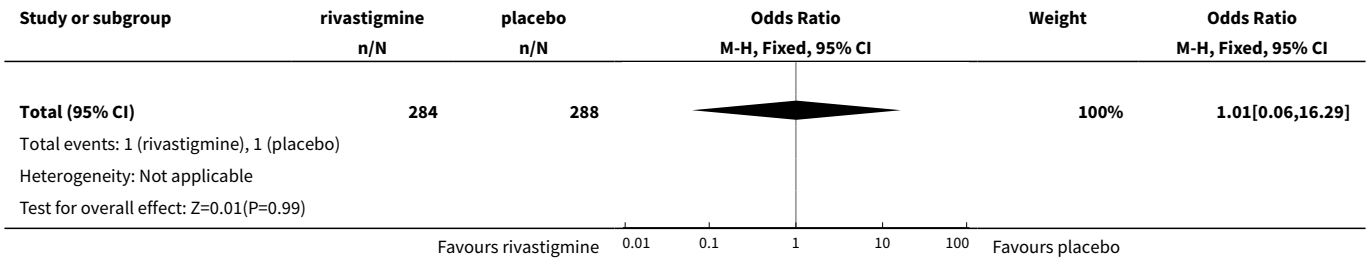


Analysis 5.17. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 17 at least one adverse event of vomiting by 24 weeks.



Analysis 5.18. Comparison 5 Rivastigmine 5 cm^2 patch (4.6 mg/day) versus placebo, Outcome 18 deaths before end of treatment at 24 weeks.





Comparison 6. Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 ADAS-Cog (change from baseline at 24 weeks) ITT	1	501	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.10, 1.10]
2 MMSE (change from baseline at 24 weeks) ITT	1	506	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.27, 0.87]
3 clock drawing (change from baseline at 24 weeks) ITT	1	491	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.46, 0.66]
4 TMT-A (change from baseline at 24 weeks) ITT	1	481	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-13.48, 8.28]
5 ADCS-ADL (change from baseline at 24 weeks) ITT	1	501	Mean Difference (IV, Fixed, 95% CI)	0.40 [-1.23, 2.03]
6 Clinical Global Impression (no change or worse at 24 weeks)	1	501	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.88, 1.84]
7 NPI-12 (change from baseline at 24 weeks) ITT	1	501	Mean Difference (IV, Fixed, 95% CI)	0.50 [-1.55, 2.55]
8 withdrawals before end of treatment at 24 weeks	1	590	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.70, 1.54]
9 at least one adverse event by 24 weeks	1	585	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.43, 0.82]
10 withdrawals due to an adverse event before end of treatment at 24 weeks	1	590	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.68, 2.13]
11 at least one adverse event of nausea by 24 weeks	1	585	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.15, 0.43]
12 at least one adverse event of vomiting by 24 weeks	1	585	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.18, 0.57]
13 at least one adverse event of diarrhoea by 24 weeks	1	585	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.57, 2.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 at least one adverse event of weight decrease by 24 weeks	1	585	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.21, 1.17]
15 at least one adverse event of dizziness by 24 weeks	1	585	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.13, 0.72]
16 at least one adverse event of decreased appetite by 24 weeks	1	585	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.04, 0.73]
17 at least one adverse event of headache by 24 weeks	1	585	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.25, 1.20]
18 at least one adverse event of asthenia by 24 weeks	1	585	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.10, 0.78]
19 deaths before end of treatment at 24 weeks + 30 days	1	590	Odds Ratio (M-H, Fixed, 95% CI)	2.56 [0.49, 13.31]
20 NPI-D carer distress scale (change from baseline at 24 weeks) ITT	1	501	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.96, 1.16]

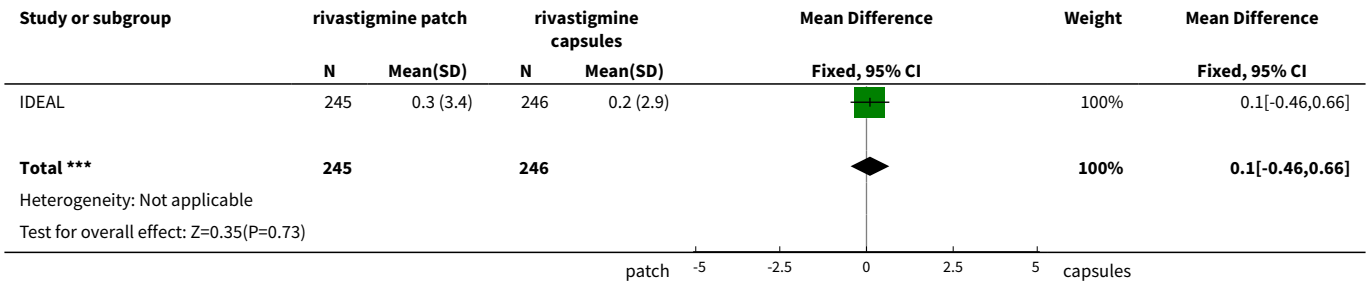
Analysis 6.1. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 1 ADAS-Cog (change from baseline at 24 weeks) ITT.

Study or subgroup	rivastigmine patch		rivastigmine capsules		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
IDEAL	248	-0.6 (6.4)	253	-0.6 (6.2)		100%	0[-1.1,1.1]
Total ***	**248**		**253**			**100%**	**0[-1.1,1.1]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

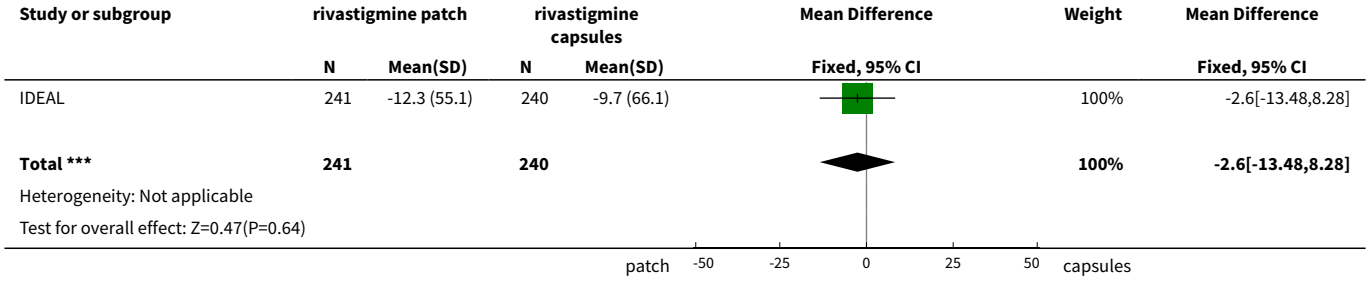
Analysis 6.2. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 2 MMSE (change from baseline at 24 weeks) ITT.

Study or subgroup	rivastigmine patch		rivastigmine capsules		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
IDEAL	250	1.1 (3.3)	256	0.8 (3.2)		100%	0.3[-0.27,0.87]
Total ***	**250**		**256**			**100%**	**0.3[-0.27,0.87]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.04(P=0.3)							

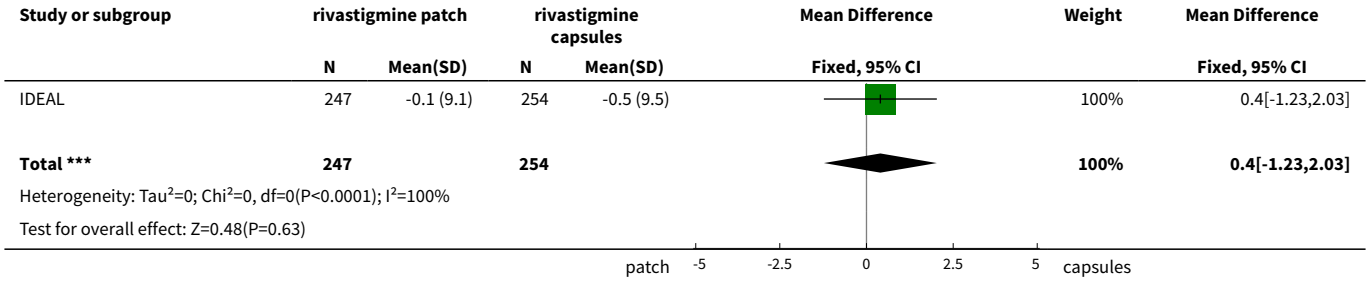
Analysis 6.3. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 3 clock drawing (change from baseline at 24 weeks) ITT.



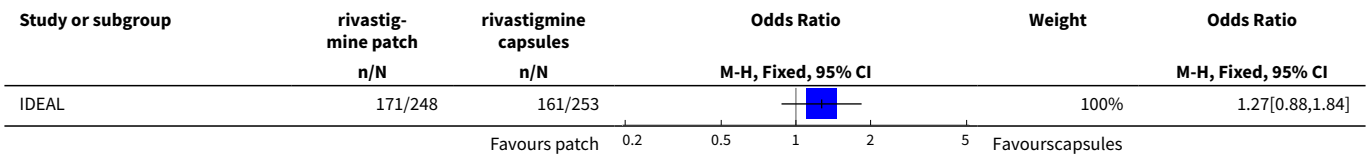
Analysis 6.4. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 4 TMT-A (change from baseline at 24 weeks) ITT.

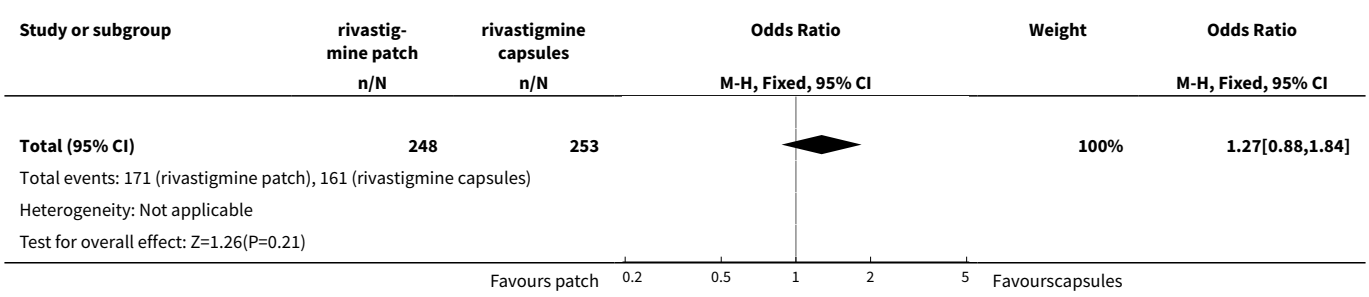


Analysis 6.5. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 5 ADCS-ADL (change from baseline at 24 weeks) ITT.

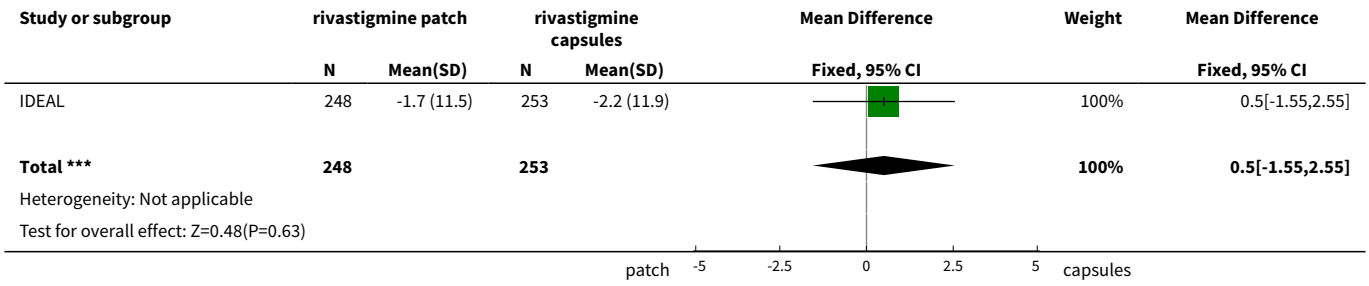


Analysis 6.6. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 6 Clinical Global Impression (no change or worse at 24 weeks).

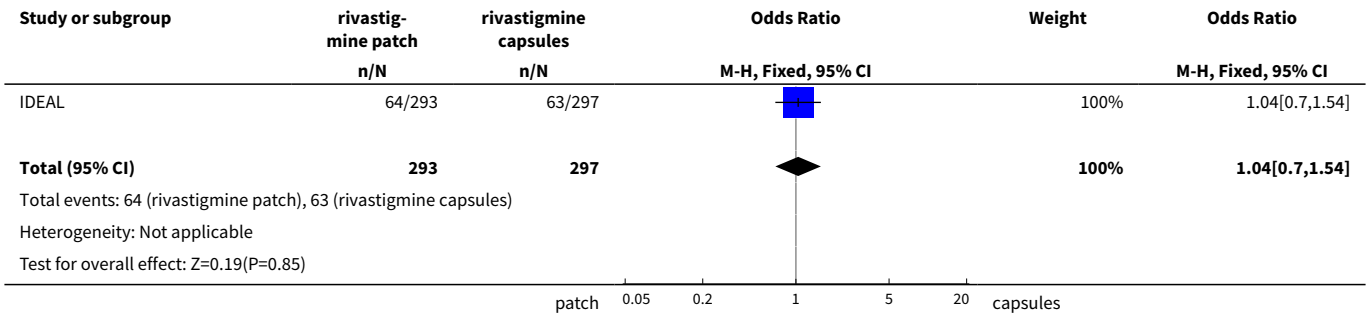




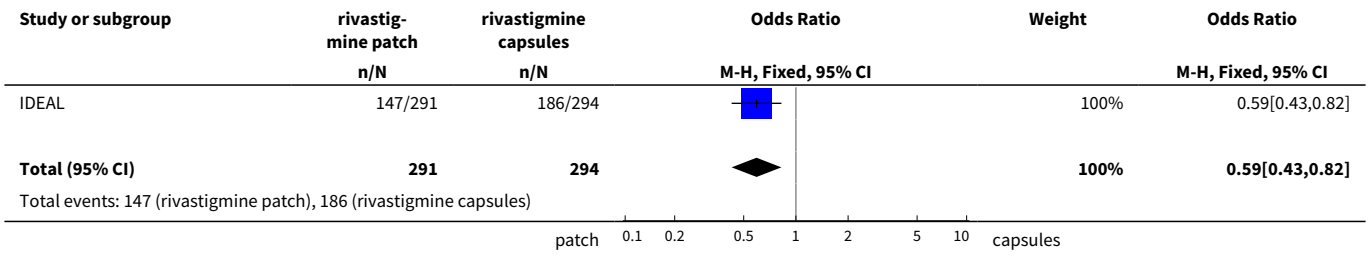
Analysis 6.7. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 7 NPI-12 (change from baseline at 24 weeks) ITT.

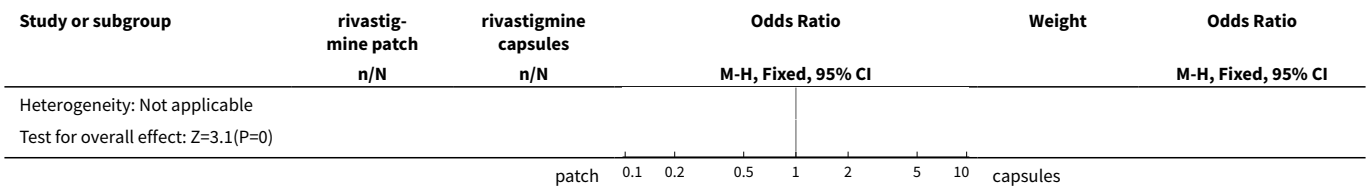


Analysis 6.8. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 8 withdrawals before end of treatment at 24 weeks.

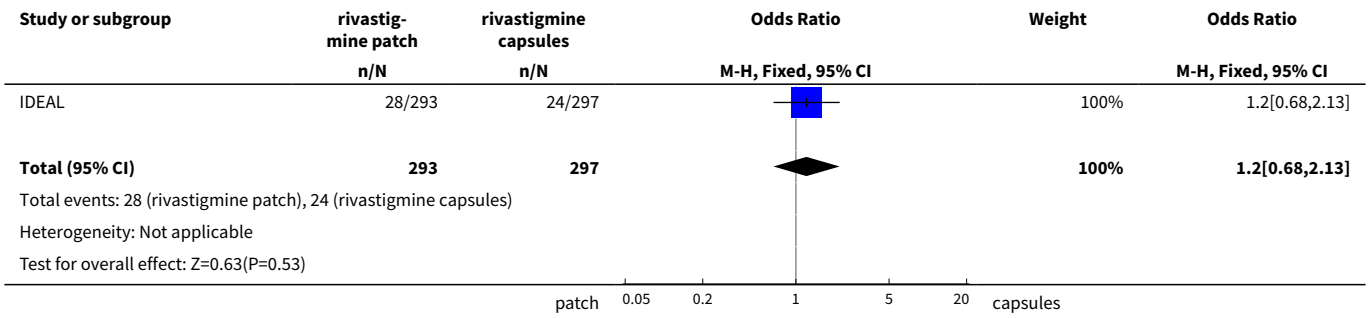


Analysis 6.9. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 9 at least one adverse event by 24 weeks.

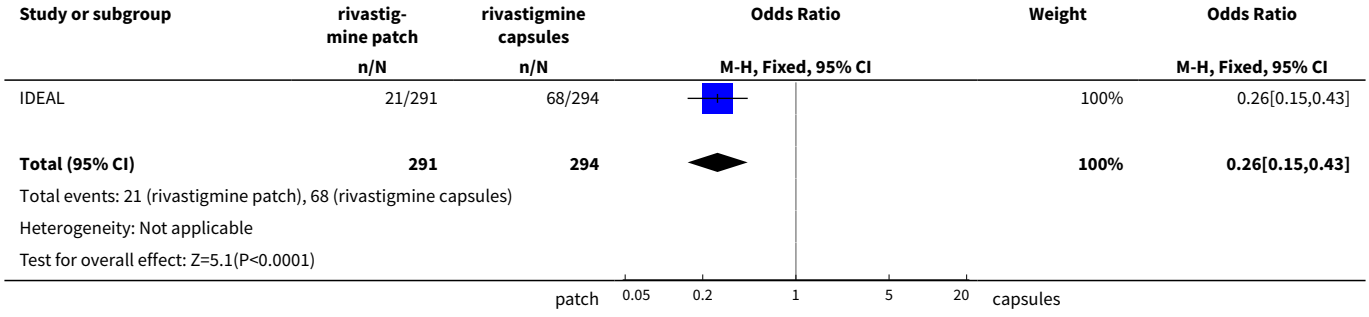




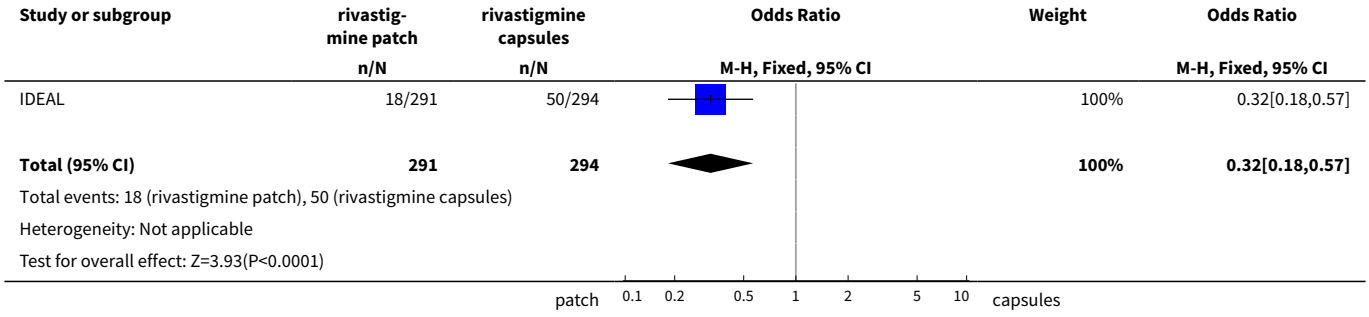
Analysis 6.10. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 10 withdrawals due to an adverse event before end of treatment at 24 weeks.



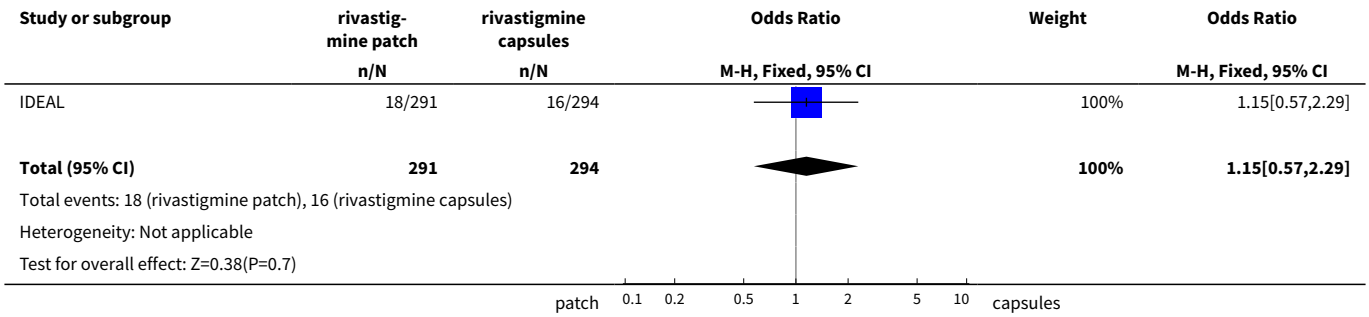
Analysis 6.11. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 11 at least one adverse event of nausea by 24 weeks.



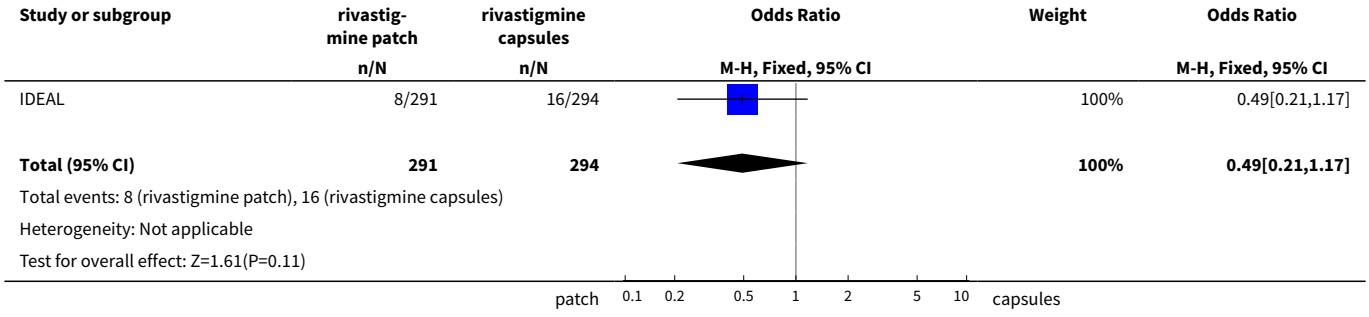
Analysis 6.12. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 12 at least one adverse event of vomiting by 24 weeks.



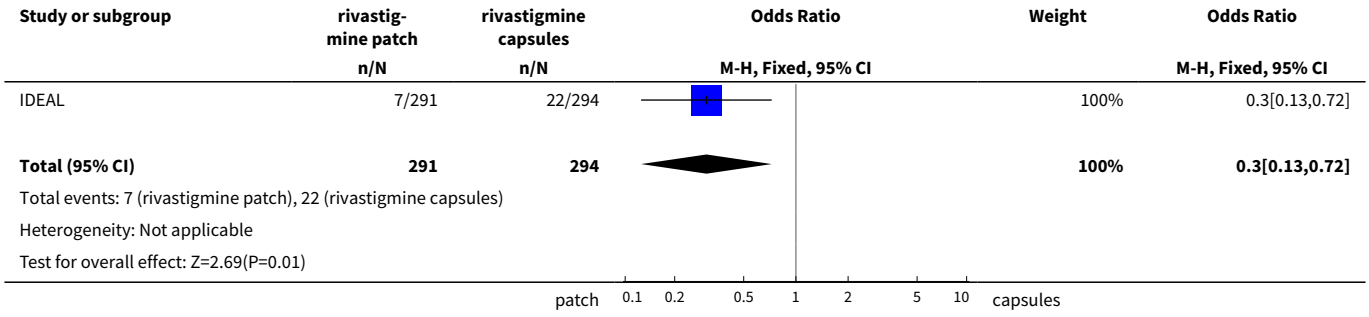
Analysis 6.13. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 13 at least one adverse event of diarrhoea by 24 weeks.



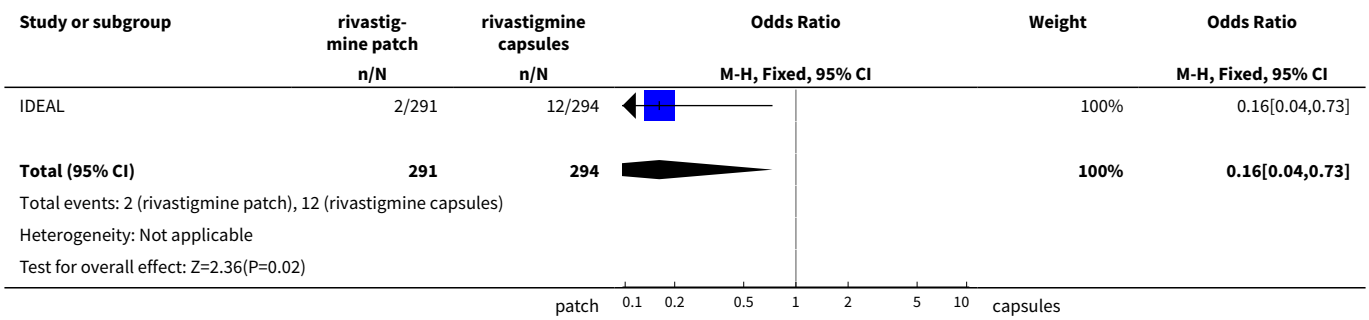
Analysis 6.14. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 14 at least one adverse event of weight decrease by 24 weeks.



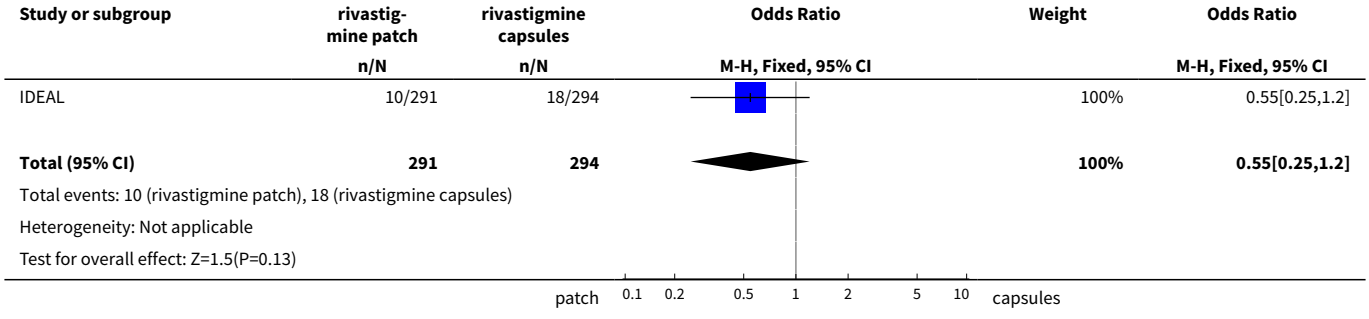
Analysis 6.15. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 15 at least one adverse event of dizziness by 24 weeks.



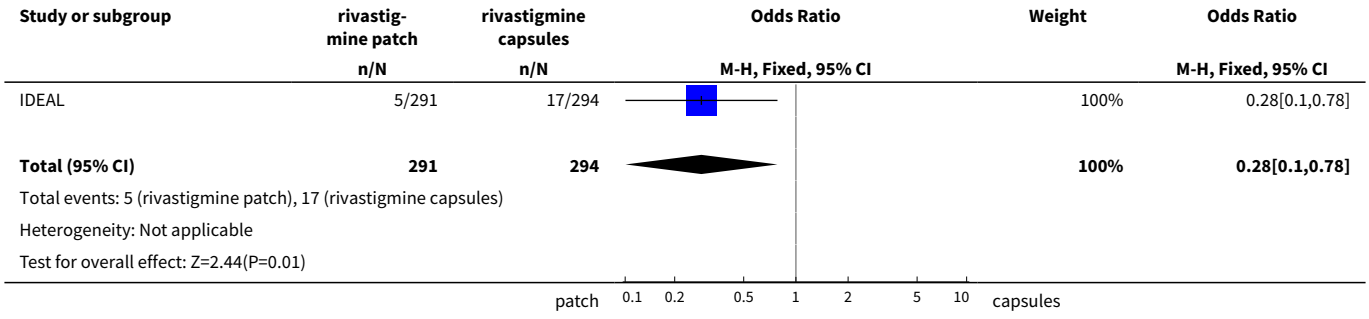
Analysis 6.16. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 16 at least one adverse event of decreased appetite by 24 weeks.



Analysis 6.17. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 17 at least one adverse event of headache by 24 weeks.



Analysis 6.18. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 18 at least one adverse event of asthenia by 24 weeks.

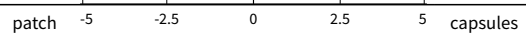


Analysis 6.19. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 19 deaths before end of treatment at 24 weeks + 30 days.

Study or subgroup	rivastigmine patch n/N	rivastigmine capsules n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
IDEAL	5/293	2/297		100%	2.56[0.49,13.31]
Total (95% CI)	**293**	**297**		**100%**	**2.56[0.49,13.31]**
Total events: 5 (rivastigmine patch), 2 (rivastigmine capsules)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.12(P=0.26)					

Analysis 6.20. Comparison 6 Rivastigmine 10 cm^2 patch (9.5 mg/day) versus rivastigmine capsules (6 to 12 mg/day in two divided doses), Outcome 20 NPI-D carer distress scale (change from baseline at 24 weeks) ITT.

Study or subgroup	rivastigmine patch N	Mean(SD)	rivastigmine capsules N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
IDEAL	248	-1 (5.5)	253	-1.1 (6.6)		100%	0.1[-0.96,1.16]
Total ***	**248**		**253**			**100%**	**0.1[-0.96,1.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.18(P=0.85)							



ADDITIONAL TABLES

Table 1. Description of the included studies at baseline

Study	Duration (weeks)	Partici-pants	Mean age (SD)	% males	Mean MMSE (SD)	country	Number of centres	Treatment groups
Oral (different doses versus placebo)								
B103 (Phase II)	13	402	69.4	44	-	Europe	54	1. 4 mg/day b.i.d 2. 6 mg/day b.i.d 3. placebo
B104 (Phase II)	18	114	71.2 (7.5)	39	19.5 (3.7)	Belgium, France, UK, Norway, Canada	11	1. 6 to 12 mg/day b.i.d. 2. 6 to 12 mg/day t.i.d 3. placebo
B303/B305* (Phase III)	26	725	72.0 (8.1)	41	20.0 (4.5)	France, Germany, Aus-tria, Switzerland, Cana-da, USA	44	1. 1 to 4 mg b.i.d 2. 6 to 12 mg/day b.i.d., placebo
B304* (Phase III)	26	677	71.4 (8.2)	41	18.5 (4.5)	UK, Ireland, Australia, Canada, RSA, Italy	37	1. 2 to 12 mg/day b.i.d. 2. 2 to 12 mg/day t.i.d. 3. placebo
B351* (Phase III)	26	702	74.1 (8.3)	44	20.0 (4.4)	USA	14	1. 3 mg/day t.i.d 2. 6 mg/day t.i.d 3. 9 mg/day b.i.d 4. placebo
B352* (Phase III)	26	699	74.5 (7.4)	39	19.7 (4.5)	USA	22	1. 1 to 4 mg per day b.i.d 2. 6 to 12 mg/day b.i.d. 3. placebo
Ballard 2005	26	93	83.8 (7.7)	20	-	UK	-	1. 6 to 12 mg/day b.i.d 2. placebo
Karaman 2005*	52	44	73.8	45	12.2	Turkey	1	1. 6 to 12 mg/day b.i.d. 2. placebo
Lopez-Pousa 2005*	26	218	77.6	23	8.8	Spain	21	1. 6 to 12 mg/day b.i.d. 2. placebo
Mowla 2007	12	122	69.2	46	16.1 (4.0)	Iran	-	1. 6 to 12 mg/day b.i.d.

Table 1. Description of the included studies at baseline *(Continued)*

								2. placebo
Tai 2000	26	80	-	-	-	Taiwan	-	1. 3 to 6 mg/day b.i.d. 2. placebo
Oral and patches								
IDEAL* (Phase III)	24	1195	73.3 (7.8)	33	16.5 (3.0)	North, Central and South America, Asia, Europe	100	1. patch 9.5 mg/day 2. patch 17.4 mg/day 3. capsules 6 to 12 mg/day b.i.d. 4. placebo
Patches								
Nakamura 2011	24	859	74.6 (7.2)	31.7	16.6 (3.0)	Japan	multicentre	1. patch 4.6 mg/day 2. patch 9.5 mg/day 3. placebo

* These studies met the inclusion criteria of the main analysis comparing rivastigmine at the therapeutic doses versus placebo.
b.i.d = bis in die in Latin, this means that a medication is taken two times a day, dividing the total daily dose into two doses.
t.i.d = ter in die in Latin, this means that a medication is taken three times a day, dividing the total daily dose into three doses.
MMSE = Mini-Mental Health State Examination. The score range from 0 (severe impairment) to 30 (normal).

Table 2. Objectives of included studies

Study	Objective
B103	To assess the short term (3 months) symptomatic efficacy and tolerability of rivastigmine 4 and 6 mg/day compared with placebo in patients with AD
B104	Primary: to determine the maximum tolerated dose (MTD) of rivastigmine in patients with mild to moderate dementia of the Alzheimer type (DAT)
	Secondary: to determine - a) whether tolerability is different when the drug is administered twice daily (b.i.d.) or three times daily (t.i.d.) - b) if nausea and vomiting, associated with cholinesterase inhibition, can be controlled with antiemetics thereby increasing the MTD, and - c) to assess the efficacy of rivastigmine at its MTD in comparison with that of placebo in the treatment of DAT
B303/B305	Primary 1: to evaluate the efficacy of two non-overlapping dose ranges of rivastigmine (1 to 4mg daily and 6 to 12 mg daily) versus placebo over a 26 week treatment period as assessed by two primary measures of outcome; change from baseline in ADAS-Cog score and the CIBIC-Plus score at week 26
	Primary 2: to evaluate the safety of the study medication as assessed by incidence of adverse events, clinical laboratory evaluations , vital signs, ECG recordings, and the results of physical examination made at baseline and throughout the study
	Secondary: to assess dose-efficacy and dose-safety relationships for rivastigmine
B304	Primary: to evaluate the efficacy and safety of individual highest well-tolerated doses (range 6 to 12 mg daily) of rivastigmine given b.i.d. or t.i.d. for 26 weeks compared with placebo in the therapy of patients with probable Alzheimer's disease
	Secondary: to compare the twice daily and three times daily dosing regimens with respect to efficacy and safety to evaluate changes in activities of daily living (ADL)
B351	Primary: to evaluate the efficacy and safety of three fixed doses of rivastigmine (3, 6 and 9 mg/day) and placebo for 26 weeks of treatment
	Secondary: to assess the dose-efficacy and dose-safety relationships for rivastigmine
	Tertiary: to explore the pharmacokinetics of rivastigmine at doses of 3, 6 and 9 mg daily
B352	Primary: to evaluate the efficacy and safety of two non-overlapping dose ranges of rivastigmine (1 to 4 mg daily and 6 to 12 mg daily) and placebo for 26 weeks of treatment
	Secondary: to assess the dose-efficacy and dose-safety relationships of rivastigmine. To investigate the relationship between plasma concentrations of rivastigmine and efficacy and safety
	Tertiary: to explore the pharmacokinetics of rivastigmine at doses of 1 to 4 and 6 to 12 mg daily
IDEAL	To compare the efficacy,safety and tolerability of a novel rivastigmine transdermal patch with conventional rivastigmine capsules and placebo in patients with AD
Karaman 2005	To evaluate the efficacy of rivastigmine for a period of 12 months in patients with advanced moderate AD
Lopez-Pousa 2005	To evaluate the safety and efficacy of rivastigmine in patients with more advanced AD
Mowla 2007	To assess the effect of serotonin augmentation on cognition and ADL of patients with AD

Table 2. Objectives of included studies *(Continued)*

Ballard 2005	To determine whether rivastigmine was better than placebo for agitation and cognition
Tai 2000	To evaluate the safety and efficacy of Exelon compared with placebo in patients with probable Alzheimer's disease who had dementia ranging from mild to moderate degree
Nakamura 2011	To evaluate the efficacy, safety, and tolerability of the 5 cm^2 (9 mg loading dose, 4.6 mg/24 h delivery rate) and 10 cm^2 (18 mg loading dose, 9.5 mg/day delivery rate) rivastigmine patch in Japanese patients with AD

Table 3. Mean daily dose (mg/day) of rivastigmine achieved in the studies at different time points

Time (weeks)	treatment group	B103	B104	B303/ B305	B304	B351	B352	IDEAL	Kara-man 2005	Lopez-Pousa 2005	Naka-mura 2011
10 to 12	low b.i.d.	4	-	3.8	-	2.9	3.6				
	medium b.i.d.	6	-	-	-	5.7	-				
	high b.i.d.	-	9.6	10.4	9.5	8.8	10.1		6.1		
	high t.i.d.	-	10.2	-	9.7	-	-				
26	low b.i.d.	-	-	3.7	-	2.8	3.5				
	medium b.i.d.	-	-	-	-	5.7	-				
	high b.i.d.	-	-	10.4	9.3	8.5	9.7	9.7	8.3	9.8	
	high t.i.d.	-	-	-	9.6	-	-				
	low patch										4.6
	medium patch							9.5			9.5
	high patch							16.5			
48	medium patch										
	high patch										
52	high b.i.d.								10.7		

Exact doses not available for B103, Ballard 2005, Tai 2000, Mowla 2007.

Table 4. Measured outcomes

Outcomes assessed	Cognitive function			Activities of daily living		Behav-ioural symp-toms	Physician rated global im-pression of change		Other domains
Study	ADAS-Cog	MMSE	Others	PDS	Others		CIBIC-Plus	Others	

Table 4. Measured outcomes *(Continued)*

B103		X	OE, TMT, NOSGER, DSST, VRT					CGIC	
B104	X		Wechsler psychometric tests, NOSGER				X		
B303/B305	X	X	ADAS-CogA	X	CAS		X	GDS	
B304	X	X	ADAS-CogA	X	CAS		X	GDS	
B351	X	X	ADAS-CogA	X	CAS		X	GDS	
B352	X	X	ADAS-CogA	X	CAS		X	GDS	
Ballard 2005			SIB			CMAI			
Karaman 2005	X	X		X	ACDS-ADL, DAD		X	GDS	
IDEAL	X	X	CLOCK DRAWING, TMT		ACDS-ADL	NPI-12		ADCS-CGIC	
Lopez-Pousa 2005		X	SIB, BLESSED DEMENTIA SCALE		ACDS-ADL	NPI-10, NPI-4		GDS ADCS-CGIC	
Mowla 2007			WMS-III,		ADL			CGI	Hamilton score
Tai 2000		X	NPT				X	GDS	
Nakamura 2011	X	X	MENFIS		DAD	BEHAVE-AD	X		

x indicated that the study measured this outcome.
The full names of these scales and their properties are described in Types of outcome measures.

Table 5. Comparison of different methods of dealing with missing values

Time point	population	rivastigmine n	placebo n	result	probability level	95% confidence limits
1 to 4 mg daily versus placebo, ADAS-Cog measured as change from baseline						
12 weeks	ITT	650	643	favours rivastigmine WMD -0.31	0.30	-0.87, 0.25
	OC	589	598	favours rivastigmine WMD -0.46	0.14	-1.08, 0.15
	RDO + OC	616	615	favours rivastigmine WMD -0.37	0.20	-0.96, 0.23
18 weeks	ITT	650	643	favours rivastigmine WMD -1.07	0.0004	-1.66, -0.48
	OC	558	552	favours rivastigmine WMD -1.19	0.0005	-1.86, -0.52
	RDO + OC	573	572	favours rivastigmine WMD -1.33	0.00008	-1.99, -0.67
26 weeks	ITT	650	644	favours rivastigmine WMD -0.84	0.01	-1.48, -0.19
	OC	519	526	favours rivastigmine WMD -0.96	0.01	-1.72, -0.21
	RDO + OC	559	564	favours rivastigmine WMD -1.07	0.004	-1.80, -0.34
6 to 12 mg daily versus placebo, ADAS-Cog measured as change from baseline						
12 weeks	ITT	1054	863	favours rivastigmine WMD -1.49	<0.00001	-1.96, -1.01
	OC	843	803	favours rivastigmine WMD -1.80	<0.00001	-2.33, -1.27
	RDO + OC	967	828	favours rivastigmine WMD -1.38	<0.00001	-1.89, -0.88
6 to 12 mg daily versus placebo, ADAS-Cog measured as change from baseline						
18 weeks	ITT	1054	863	favours rivastigmine WMD -1.79	<0.00001	-2.30,- 1.29
	OC	732	742	favours rivastigmine WMD -2.36	<0.00001	-2.96, -1.76
	RDO + OC	837	772	favours rivastigmine WMD -2.12	<0.00001	-2.69, -1.55
26 weeks	ITT	1054	863	favours rivastigmine WMD -2.09	<0.00001	-2.65, -1.54
	OC	670	709	favours rivastigmine WMD -2.62	<0.00001	-3.29, -1.94
	RDO + OC	788	759	favours rivastigmine WMD -2.39	<0.00001	-3.03, -1.74
1 to 4 mg daily versus placebo, CIBIC-Plus measured as no change or worse						
12 weeks	ITT	608	612	favours rivastigmine Peto OR 0.93	0.60	0.72, 1.21
	OC	583	596	favours rivastigmine Peto OR 0.95	0.70	0.72, 1.23
	RDO + OC	609	612	favours rivastigmine	0.60	0.72, 1.22

Table 5. Comparison of different methods of dealing with missing values *(Continued)*

				Peto OR 0.94		
18 weeks	ITT	614	620	favours rivastigmine	0.90	0.75, 1.26
				Peto OR 0.98		
	OC	556	554	favours placebo	0.80	0.80, 1.37
				Peto OR 1.04		
	RDO + OC	570	576	favours placebo	0.90	0.78, 1.34
				Peto OR 1.02		
26 weeks	ITT	614	623	favours rivastigmine	0.01	0.55, 0.93
				Peto OR 0.71		
	OC	513	523	favours rivastigmine	0.006	0.50, 0.89
				Peto OR 0.67		
	RDO + OC	544	549	favours rivastigmine	0.008	0.52, 0.91
				Peto OR 0.68		
1 to 4 mg daily versus placebo, CIBIC-Plus measured as no change or worse						
12 weeks	ITT	950	825	favours rivastigmine	0.008	0.60, 0.92
				Peto OR 0.74		
	OC	831	799	favours rivastigmine	0.005	0.58, 0.91
				Peto OR 0.72		
	RDO + OC	952	825	favours rivastigmine	0.01	0.60, 0.93
				Peto OR 0.75		
18 weeks	ITT	970	835	favours rivastigmine	0.06	0.65, 1.01
				Peto OR 0.81		
	OC	720	741	favours rivastigmine	0.005	0.57, 0.91
				Peto OR 0.72		
	RDO + OC	820	772	favours rivastigmine	0.02	0.62, 0.97
				Peto OR 0.77		
26 weeks	ITT	973	839	favours rivastigmine	0.0007	0.55, 0.85
				Peto OR 0.68		
	OC	660	693	favours rivastigmine	0.0004	0.49, 0.81
				Peto OR 0.63		
	RDO + OC	784	758	favours rivastigmine	0.0003	0.51, 0.82

Table 5. Comparison of different methods of dealing with missing values *(Continued)*

Peto OR 0.65

The results for two outcomes, ADAS-Cog and CBIC at 12, 18 and 26 weeks, have been pooled for 3 studies, B303/B305, B351. B352. These studies reported results for 3 populations, intention-to-treat (ITT), completers (OC), and completers + retrieved dropout (RDO + OC). The table reports the results of the meta-analyses for 2 comparisons (1 to 4 mg daily versus placebo and 6 to 12 mg/day versus placebo) for the 3 populations at the 3 time points.

APPENDICES

Appendix 1. Searches: February 2013, January 2014, March 2015

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois) [Searched on 02 March 2015; up-to-date: 01 March 2015]	rivastigmine OR "SDZ ENA 713" OR exelon	Feb 2013: Jan 2014: 5 March 2015: 17
2. MEDLINE In-process and other non-indexed citations and MEDLINE Feb 2013: 1950-present (OvidSP) Jan 2014: 1950-present [24 January 2014] (OvidSP)	1. exp Dementia/ 2. Delirium, Dementia, Amnestic, Cognitive Disorders/ 3. dement*.mp. 4. alzheimer*.mp. 5. ("organic brain disease" or "organic brain syndrome").mp. 6. "benign senescent forgetfulness".mp. 7. (cerebr* adj2 deteriorat*).mp. 8. (cerebral* adj2 insufficient*).mp. 9. or/1-8 10. Rivastigmin*.ti,ab. 11. exelon*.ti,ab. 12. (ENA or "SDZ ENA 713").ti,ab. 13. *Cholinesterase Inhibitors/ 14. or/10-13 15. 9 and 14 16. controlled trial.pt. 17. controlled clinical trial.pt. 18. .ab. 19. placebo.ab.	Feb 2013: 299 Jan 2014: 144

(Continued)

	20. drug therapy.fs. 21. randomly.ab. 22. trial.ab. 23. groups.ab. 24. or/16-23 25. (animals not (humans and animals)).sh. 26. 24 not 25 27. 15 and 26 28. (2011* or 2012* or 2013*).ed. 29. 27 and 28	
3. EMBASE Feb 2013: 1974-2013 Feb 14 (OvidSP) Jan 2014: 1974-2014 January 23 (OvidSP)	1. cognitive defect/ 2. dement*.mp. 3. alzheimer*.mp. 4. ("organic brain disease" or "organic brain syndrome").mp. 5. (cerebr* adj2 deteriorat*).mp. 6. (cerebral* adj2 insufficient*).mp. 7. Alzheimer disease/ 8. AD.ab. 9. or/1-8 10. RIVASTIGMINE/ 11. rivastigmin*.ti,ab. 12. exelon*.ti,ab. 13. (ENA or "SDZ ENA 713").ti,ab. 14. or/10-13 15. 9 and 14 16. controlled trial/ 17. controlled clinical trial/ 18. placebo.ab. 19. randomly.ab. 20. trial.ab. 21. ("double-blind*" or "double-mask*").ti,ab. 22. or/16-21 23. 15 and 22	Feb 2013: 135 Jan 2014: 79

(Continued)

	24. (2011* or 2012* or 2013*).em. 25. 23 and 24	
4. PsycINFO Feb 2013: 1806-February week 2 2013 (OvidSP) Jan 2014: 1806-January week 3 2014 (OvidSP)	1. alzheimer*.mp. 2. ("organic brain disease" or "organic brain syndrome").mp. 3. (cerebr* adj2 deteriorat*).mp. 4. (cerebral* adj2 insufficient*).mp. 5. Alzheimer's Disease/ 6. AD.ab. 7. or/1-6 8. rivastigmin*.ti,ab. 9. exelon*.ti,ab. 10. (ENA or "SDZ ENA 713").ti,ab. 11. or/8-10 12. 7 and 11 13. (2011* or 2012* or 2013*).up. 14. 12 and 13	Feb 2013: 56 Jan 2014: 28
5. CINAHL (EBSCOhost) Feb 2013: all dates to February week 1 2013	S1 (MH "Dementia+") S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S3 (MH "Wernicke's Encephalopathy") S4 TX dement* S5 TX alzheimer* S6 TX lewy* N2 bod* S7 TX deliri* S8 TX chronic N2 cerebrovascular S9 TX "organic brain disease" or "organic brain syndrome" S10 TX "normal pressure hydrocephalus" and "shunt*" S11 TX "benign senescent forgetfulness" S12 TX cerebr* N2 deteriorat* S13 TX cerebral* N2 insufficient* S14 TX pick* N2 disease S15 TX creutzfeldt or jcd or cjd	Feb 2013: 50

(Continued)

S16 TX huntington*

S17 TX binswanger*

S18 TX korsako*

S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18

S20 TX "cognit* impair*"

S21 TX "cognit* defect*"

S22 (MH "Cognition Disorders+")

S23 TX MCI

S24 TX ACMI

S25 TX ARCD

S26 TX SMC

S27 TX CIND

S28 TX BSF

S29 TX AAMI

S30 AB MD

S31 AB LCD

S32 AB QD OR "questionable dementia"

S33 TX AACD

S34 TX MNCD

S35 TX "N-MCI" or "A-MCI" or "M-MCI"

S36 TX "preclinical AD"

S37 TX "pre-clinical AD"

S38 TX "preclinical alzheimer*" or "pre-clinical alzheimer*"

S39 TX aMCI OR MCIa

S40 TX "CDR 0.5" or "clinical dementia rating scale 0.5"

S41 TX "GDS 3" OR "stage 3 GDS"

S42 TX "global deterioration scale" AND "stage 3"

S43 TX "Benign senescent forgetfulness"

S44 TX "mild neurocognit* disorder*"

S45 TX prodrom* N2 dement*

S46 TX "age-related symptom*"

S47 TX cognit* N2 deficit*

S48 TX cognit* N2 deteriorat*

S49 TX cognit* N2 declin*

(Continued)

	S50 TX cognit* N2 degenerat* S51 TX cognit* N2 complain* S52 TX cognit* N2 disturb* S53 TX cognit* N2 disorder* S54 TX memory N2 episod* or TX memory N2 los* or TX memory N2 impair* or TX memory N2 complain* S55 TX memory N2 disturb* or TX memory N2 disorder* or TX cerebr* N2 impair* or TX cerebr* N2 los* S56 TX cerebr* N2 complain* or TX cerebr* N2 deteriorat* or TX cerebr* N2 disorder* or TX cerebr* N2 disturb* S57 TX mental* N2 declin* or TX mental* N2 los* or TX mental* N2 impair* or TX mental* N2 deteriorat* S58 TX "pre-clinical dementia" or TX "preclinical dementia" S59 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 S60 S19 or S59	
6. Web of Science and conference proceedings Feb 2013: 1950 to Feb 14 2013 Jan 2014: 1950 to Jan 24 2014	Topic=(dement* OR alzheimer* OR "lewy bod*" OR DLB OR "vascular cognitive impairment*" OR FTD OF FTLD OR "cerebrovascular insufficienc*") AND Topic=(rivastigmin* OR exelon OR "SDZ ENA 713") AND Topic=(random* OR placebo OR "double-blind*" OR trial OR RCT OR CCT) AND Year Published=(2011-2013) Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.	Feb 2013: 102 Jan 2014: 54
7. LILACS (BIREME) Feb 2013: all dates to 14 February 2013 Jan 2014: all dates to 24 January 2014	rivastigmine OR rivastigmine OR "SDZ ENA 713" OR exelon [Words]	Feb 2013: 9 Jan 2014: 3
8. CENTRAL (*The Cochrane Library*) Feb 2013: Issue 4 of 12, 2013 Jan 2014: Issue 1 of 12, 2014	#1 MeSH descriptor: [Dementia] explode all trees #2 MeSH descriptor: [Delirium] this term only #3 MeSH descriptor: [Wernicke Encephalopathy] this term only #4 MeSH descriptor: [Delirium, Dementia, Amnestic, Cognitive Disorders] this term only #5 dement* #6 alzheimer* #7 "lewy* bod*" #8 deliri* #9 "chronic cerebrovascular"	Feb 2013: 7 Jan 2014: 12

(Continued)

	#10 "organic brain disease" or "organic brain syndrome" #11 "normal pressure hydrocephalus" and "shunt*" #12 "benign senescent forgetfulness" #13 "cerebr* deteriorat*" #14 "cerebral* insufficient*" #15 "pick* disease" #16 creutzfeldt or jcd or cjd #17 huntington* #18 binswanger* #19 korsako* #20 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 #21 rivastigmin* or exelon* or "SDZ ENA 713" #22 #20 and #21 from 2011 to 2013, in Trials	
9. Clinicaltrials.gov (www.clinicaltrials.gov) - all dates	rivastigmine OR exelon OR "SDZ ENA 713" | Interventional Studies | dementia OR alzheimer OR alzheimers OR lewy OR vascular cognitive impairment | Adult, Senior | received from 01/01/2011 to 02/15/2013	Feb 2013: 16 Jan 2014: 0
10. ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry – India; Clinical Research Information Service – Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register] - all dates	Advanced search: (rivastigmine OR exelon OR "SDZ ENA 713" | Interventional Studies) AND (received from 01/01/2011 to 02/15/2013)	Feb 2013: 136 Jan 2014: 2
TOTAL before de-duplication		Feb 2013: 922 Jan 2014: 327

(Continued)

TOTAL after de-dupe and first assess	Feb 2013: 36 Jan 2014: 24 March 2015: 17

Appendix 2. Update search: February 2011

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	Advanced search: Study design: RCT AND Health status: Alzheimer AND Intervention: rivastigmine	45
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (OvidSP)	1. exp Dementia/ 2. Delirium, Dementia, Amnestic, Cognitive Disorders/ 3. dement*.mp. 4. alzheimer*.mp. 5. ("organic brain disease" or "organic brain syndrome").mp. 6. "benign senescent forgetfulness".mp. 7. (cerebr* adj2 deteriorat*).mp. 8. (cerebral* adj2 insufficient*).mp. 9. or/1-8 10. Rivastigmin*.ti,ab. 11. exelon*.ti,ab. 12. (ENA or "SDZ ENA 713").ti,ab. 13. *Cholinesterase Inhibitors/ 14. or/10-13 15. 9 and 14 16. controlled trial.pt. 17. controlled clinical trial.pt. 18. .ab. 19. placebo.ab. 20. drug therapy.fs. 21. randomly.ab. 22. trial.ab. 23. groups.ab.	445

(Continued)

	24. or/16-23 25. (animals not (humans and animals)).sh. 26. 24 not 25 27. 15 and 26 28. (2008* or 2009* or 2010* or 2011*).ed. 29. 27 and 28	
3. EMBASE 1980-2011 week 6 (OvidSP)	1. cognitive defect/ 2. dement*.mp. 3. alzheimer*.mp. 4. ("organic brain disease" or "organic brain syndrome").mp. 5. (cerebr* adj2 deteriorat*).mp. 6. (cerebral* adj2 insufficient*).mp. 7. Alzheimer disease/ 8. AD.ab. 9. or/1-8 10. RIVASTIGMINE/ 11. rivastigmin*.ti,ab. 12. exelon*.ti,ab. 13. (ENA or "SDZ ENA 713").ti,ab. 14. or/10-13 15. 9 and 14 16. randomised controlled trial/ 17. controlled clinical trial/ 18. placebo.ab. 19. randomly.ab. 20. trial.ab. 21. ("double-blind*" or "double-mask*").ti,ab. 22. or/16-21 23. 15 and 22 24. (2008* or 2009* or 2010* or 2011*).em. 25. 23 and 24	226
4. PsycINFO	1. alzheimer*.mp.	98

(Continued)

1806-February week 2 2011 (OvidSP)	2. ("organic brain disease" or "organic brain syndrome").mp. 3. (cerebr* adj2 deteriorat*).mp. 4. (cerebral* adj2 insufficient*).mp. 5. Alzheimer's Disease/ 6. AD.ab. 7. or/1-6 8. rivastigmin*.ti,ab. 9. exelon*.ti,ab. 10. (ENA or "SDZ ENA 713").ti,ab. 11. or/8-10 12. 7 and 11 13. (2008* or 2009* or 2010* or 2011*).up. 14. 12 and 13	
5. CINAHL (EBSCO-host)	S1 (MH "Dementia+") S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S3 (MH "Wernicke's Encephalopathy") S4 TX dement* S5 TX alzheimer* S6 TX lewy* N2 bod* S7 TX deliri* S8 TX chronic N2 cerebrovascular S9 TX "organic brain disease" or "organic brain syndrome" S10 TX "normal pressure hydrocephalus" and "shunt*" S11 TX "benign senescent forgetfulness" S12 TX cerebr* N2 deteriorat* S13 TX cerebral* N2 insufficient* S14 TX pick* N2 disease S15 TX creutzfeldt or jcd or cjd S16 TX huntington* S17 TX binswanger* S18 TX korsako* S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18	120

(Continued)

S20 TX "cognit* impair*"

S21 TX "cognit* defect*"

S22 (MH "Cognition Disorders+")

S23 TX MCI

S24 TX ACMI

S25 TX ARCD

S26 TX SMC

S27 TX CIND

S28 TX BSF

S29 TX AAMI

S30 AB MD

S31 AB LCD

S32 AB QD OR "questionable dementia"

S33 TX AACD

S34 TX MNCD

S35 TX "N-MCI" or "A-MCI" or "M-MCI"

S36 TX "preclinical AD"

S37 TX "pre-clinical AD"

S38 TX "preclinical alzheimer*" or "pre-clinical alzheimer*"

S39 TX aMCI OR MCIa

S40 TX "CDR 0.5" or "clinical dementia rating scale 0.5"

S41 TX "GDS 3" OR "stage 3 GDS"

S42 TX "global deterioration scale" AND "stage 3"

S43 TX "Benign senescent forgetfulness"

S44 TX "mild neurocognit* disorder*"

S45 TX prodrom* N2 dement*

S46 TX "age-related symptom*"

S47 TX cognit* N2 deficit*

S48 TX cognit* N2 deteriorat*

S49 TX cognit* N2 declin*

S50 TX cognit* N2 degenerat*

S51 TX cognit* N2 complain*

S52 TX cognit* N2 disturb*

S53 TX cognit* N2 disorder*

(Continued)

	S54 TX memory N2 episod* or TX memory N2 los* or TX memory N2 impair* or TX memory N2 complain* S55 TX memory N2 disturb* or TX memory N2 disorder* or TX cerebr* N2 impair* or TX cerebr* N2 los* S56 TX cerebr* N2 complain* or TX cerebr* N2 deteriorat* or TX cerebr* N2 disorder* or TX cerebr* N2 disturb* S57 TX mental* N2 declin* or TX mental* N2 los* or TX mental* N2 impair* or TX mental* N2 deteriorat* S58 TX "pre-clinical dementia" or TX "preclinical dementia" S59 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 S60 S19 or S59	
6. ISI Web of Knowledge – all databases [includes: Web of Science (1945-present); BIOSIS Previews (1926-present); MEDLINE (1950-present); Journal Citation Reports]	Topic=(rivastigmine OR exelon OR ena OR "SDZ ENA 713") AND Topic=(alzheimer* OR AD OR "ADD") AND Topic=(random* OR placebo OR trial OR "double-blind*") AND Year Published=(2008-2011)	191
7. LILACS (BIREME)	rivastigmine OR exelon	7
8. CENTRAL (*The Cochrane Library*) (Issue 4 of 4, Oct 2010)	#1 MeSH descriptor Dementia explode all trees #2 MeSH descriptor Delirium, this term only #3 MeSH descriptor Wernicke Encephalopathy, this term only #4 MeSH descriptor Delirium, Dementia, Amnestic, Cognitive Disorders, this term only #5 dement* #6 alzheimer* #7 "lewy* bod*" #8 deliri* #9 "chronic cerebrovascular" #10 "organic brain disease" or "organic brain syndrome" #11 "normal pressure hydrocephalus" and "shunt*" #12 "benign senescent forgetfulness" #13 "cerebr* deteriorat*" #14 "cerebral* insufficient*" #15 "pick* disease"	40

(Continued)

	#16 creutzfeldt or jcd or cjd #17 huntington* #18 binswanger* #19 korsako* #20 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19) #21 rivastigmin* OR Exelon* OR "SDZ ENA 713" #22 #21 AND #20	
9. Clinicaltrials.gov (www.clinicaltrials.gov)	Advanced search: Intervention: rivastigmine OR Exelon OR "SDZ ENA 713" AND Condition: Alzheimer OR Alzheimer's OR ad OR dementia OR alzheimers	18
10. ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry – India; Clinical Research Information Service – Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]	(Alzheimer OR Alzheimer's OR ad OR dementia OR alzheimers) AND (rivastigmine OR Exelon) AND (2008-2011)	5
TOTAL before de-duplication		1195
TOTAL after de-dupe and first-assess		45

WHAT'S NEW

Date	Event	Description
2 March 2020	Amended	One word changed/corrected in PLS

HISTORY

Protocol first published: Issue 3, 1998
Review first published: Issue 3, 1998

Date	Event	Description
10 September 2015	Amended	Third author added (previously omitted in error); Implications for research section edited to remove incorrect text.
10 September 2015	New citation required but conclusions have not changed	Third author added (previously omitted in error); Implications for research section edited to remove incorrect text.
2 March 2015	New search has been performed	A pre-publication search was run for this review on 2 March 2015. All results were assessed and no new studies were identified
2 March 2015	New citation required but conclusions have not changed	Conclusions unchanged
24 January 2014	New search has been performed	An update search was performed for this review on 24 January 2014.
15 February 2013	New search has been performed	A pre-publication search was performed for this review on 15 February 2013
10 May 2011	New search has been performed	An update search was performed for this review on 16 February 2011
24 March 2009	Amended	Table 1 and Discussion have been amended
18 December 2008	New search has been performed	Update searches were run in March 2008
4 September 2008	New citation required and conclusions have changed	An update search was performed on 27 March 2008. Two new studies have been included, IDEAL and Mowla 2007.
15 June 2006	New search has been performed	Update 2006. Two new trials in more severe dementia, Karaman 2005 and Lopez-Pousa 2005, were included. We have contacted the authors of Karaman 2005 for clarification of their unusual drop out rates and unusually small standard deviations of outcome measures before drawing firm conclusions from the data, but have not received a reply.
30 August 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

This updated review was prepared by J Birks and J Grimley Evans. V Iakovidou and M Tsolaki made contributions to the original review.

Contact editor: Frans Verhey.

Consumer editor: Mervyn Richardson.

The review has been peer reviewed anonymously.

The 2014 update was undertaken by J Birks.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2014 update of the review, the results were reorganised to focus on currently recommended doses. The main analysis was done for the 26 week period and seven outcomes were prioritised for meta-analysis. The other analyses done in earlier versions are retained in the appendix.

The risk of bias assessment of individual studies was also expanded for this update, with additional assessments on blinding, selective reporting and other biases carried out.

NOTES

Update 2014

Additional studies were included: Mowla 2007, Nakamura 2011

Update 2005

One new trial, Ballard 2005, met the inclusion criteria for the review but its results could not be included in the analyses. There were substantial losses from the trial, and of concern was the elimination of those participants with low baseline scores from the analyses.

November 2003: following an update search, one additional trial, Tai 2000, was added. There is only limited information available about this trial. It appears to be an independent trial carried out in Taiwan. No results could be used from Tai 2000.

The review authors dealt with the consumer editor and peer reviewer comments.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*drug therapy]; Caregivers [psychology]; Cholinesterase Inhibitors [*administration & dosage] [adverse effects]; Cognition Disorders [drug therapy]; Drug Administration Schedule; Phenylcarbamates [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Rivastigmine; Severity of Illness Index

MeSH check words

Humans