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[Intervention Review]

Galantamine for Alzheimer's disease and mild cognitive impairment

Clement Loy[1], Lon Schneider[2]

[1]Level 7, Garvan Institute of Medical Research, Darlinghurst, Australia. [2]University of Southern California Keck School of Medicine, Los Angeles, CA, USA

Contact: Clement Loy, Level 7, Garvan Institute of Medical Research, 384 Victoria St, Darlinghurst, NSW, 2010, Australia. clementloy@fastmail.fm.

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ABSTRACT

Background

Galantamine is a specific, competitive, and reversible acetylcholinesterase inhibitor.

Objectives

To assess the clinical effects of galantamine in patients with mild cognitive impairment (MCI), probable or possible Alzheimer's disease (AD), and potential moderators of effect.

Search methods

The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group, last updated on 25 April 2005 using the terms galanthamin*, galantamin* and Reminyl. Published reviews were inspected for further sources. Additional information was collected from unpublished clinical research reports for galantamine obtained from Janssen and from http://www.clinicalstudyresults.org/.

Selection criteria

Trials selected were randomised, double-blind, parallel-group comparisons of galantamine with placebo for a treatment duration of greater than 4 weeks in subjects with MCI or AD.

Data collection and analysis

Data were extracted independently by the reviewers and pooled where appropriate and possible. Outcomes of interest include the clinical global impression of change (CIBIC-plus or CGIC), Alzheimer's Disease Assessment Scale-cognitive sub scale (ADAS-cog), Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL), Disability Assessment for Dementia scale (DAD) and Neuropsychiatric Inventory (NPI). Potential moderating variables of treatment effect assessed included trial duration, dose, and diagnosis of possible versus probable Alzheimer's disease.

Main results

Ten trials with a total 6805 subjects were included in the analysis.
Treatment with galantamine led to a significantly greater proportion of subjects with improved or unchanged global rating scale rating (k = 8 studies), at all dosing levels except for 8 mg/d . Confidence intervals for the ORs overlapped across the dose range of 16 mg to 36 mg per day, with point estimates of 1.6 - 1.8 when analysed with the intention-to-treat sample.
Treatment with galantamine also led to significantly greater reduction in ADAS-cog score at all dosing levels (k = 8), with greater effect over six months compared to three months. Confidence intervals again overlapped. Point estimate of effect was lower for 8 mg/d but similar

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for 16 mg to 36 mg per day. For example, treatment effect for 24 mg/d over six months was 3.1 point reduction in ADAS-cog (95%CI 2.6-3.7, k = 4, ITT).
ADCS-ADL, DAD and NPI were reported only in a small proportion of trials: all showed significant treatment effect in some individual trials at least. Confidence interval of treatment effect for the one trial recruiting patients with possible AD overlapped with the other seven recruiting patients with probable AD. Galantamine's adverse effects appeared similar to those of other cholinesterase inhibitors and to be dose related.
Prolong release / once daily formulation of galantamine at 16 - 24mg/d was found to have similar efficacy and side-effect profile as the equivalent twice-daily regime.
Data from the two MCI trials suggest marginal clinical benefit, but a yet unexplained excess in death rate.

Authors' conclusions

Subjects in these trials were similar to those seen in earlier anti dementia AD trials, consisting primarily of mildly to moderately impaired outpatients. Galantamine's effect on more severely impaired subjects has not yet been assessed.
Nevertheless, this review shows consistent positive effects for galantamine for trials of three to six months' duration. Although there was not a statistically significant dose-response effect, doses above 8 mg/d were, for the most part, consistently statistically significant.
Galantamine's safety profile in AD is similar to that of other cholinesterase inhibitors with respect to cholinergically mediated gastrointestinal symptoms. It appears that doses of 16 mg/d were best tolerated in the single trial where medication was titrated over a four week period, and because this dose showed statistically indistinguishable efficacy with higher doses, it is probably most preferable initially. Longer term use of galantamine has not been assessed in a controlled fashion.
Galantamine use in MCI is not recommended due to its association with an excess death rate.

PLAIN LANGUAGE SUMMARY

Galantamine improves global and cognitive symptoms at doses of 16 mg/day or greater, in people with mild to moderate Alzheimer's disease, for at least 6 months

Alzheimer's disease is a progressive neurodegenerative illness, affecting thinking and memory. Galantamine is a reversible cholinesterase inhibitor that inhibits the degradation of the neurotransmitter acetylcholine, and may have other actions on nicotinic receptors as well. The review finds that galantamine was more effective than placebo in improving cognitive function. A greater proportion of people taking galantamine than of those taking placebo was rated as improved or not changed after three to six months. There was evidence of improvement on measures of activities of daily living and behavioral symptoms. Longer-term controlled studies have yet to be performed or published.

Data from the two MCI trials suggest marginal clinical benefit, but a yet unexplained excess in death rate.

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BACKGROUND

Galantamine (also called galanthamine, marketed as Reminyl by Janssen), an alkaloid extracted from Amaryllidaceae (Galanthus woronowi, the Caucasian snowdrop) and daffodil bulbs, but now synthesized, is a reversible, competitive inhibitor of acetylcholinesterase with very little butyrylcholinesterase inhibitory activity (Harvey 1995; Pacheco 1995). It has received regulatory approval in at least 29 counties, including Argentina, Australia, Canada, Czechia, the European Union (except for The Netherlands), Iceland, Korea, Mexico, Norway, Poland, Singapore, Sweden, South Africa, Switzerland, Thailand, and the United States.

Galantamine is 10 to 50-fold more selective for acetyl compared to butyryl cholinesterase (Thomsen 1990). Competitive inhibitors compete with acetylcholine at the acetylcholinesterase binding sites, while non-competitive inhibitors bind to the sites independent of acetylcholine concentration. Because competitive acetylcholinesterase inhibitors are dependent on acetylcholine concentration, they may be less likely to bind to the enzymatic site in areas that have high acetylcholine levels. While in brain areas where acetylcholine is low, there may be a greater amount of binding to acetylcholinesterase. Theoretically, competitive inhibitors will have more effect in areas with low levels of acetylcholine and less effect in areas with higher acetylcholine. This may provide a selective effect in the brain areas affected in AD that have lower acetylcholine levels. In addition, galantamine is an allosteric modulator at nicotinic cholinergic receptor sites, enhancing the effect of acetylcholine at these receptors, and thus may enhance cholinergic transmission (Sweeney 1988; Maelicke 1997).

Early open labeled uncontrolled studies have shown mild benefit for patients with Alzheimer's disease, but for the most part were not statistically significant (Kewitz 1994; Rainer 1993; Thomsen 1990a; Thomsen 1990b; Wilcock 1993). Since then, a number of large scale double-blind randomised controlled trials have been carried out, providing data needed for this review.

OBJECTIVES

The aim of this review is to assess the clinical effect of galantamine in patients with mild cognitive impairment (MCI), probable or possible Alzheimer's disease (AD) and to investigate potential moderators of effect. Additional reasons to undertake this review are to test for significant consensus among trials that may have contradictory findings; to gather potential information about efficacy which can be revealed only by assessing systematic variations in study design, data characteristics, and methodology; and to assess the development of a particular research domain.

METHODS

Criteria for considering studies for this review

Types of studies

Studies were selected for this review if they fulfilled the following criteria:
(1) it comprised of a clinical trial in MCI or AD
(2) the trial was double-blind, parallel-group, placebo-controlled, with randomised and unconfounded treatment assignment to placebo or galantamine
(3) sample selection criteria were specified
(4) outcome instruments were specified
(5) duration was specified

Types of participants

Patients who met criteria for clinical criteria for MCI, NINCDS-ADRDA 'probable AD' or 'possible AD' (McKhann 1984), for DSM-III-R criteria for primary degenerative dementia of the Alzheimer's type (APA 1987), or for DSM -IV, 'dementia of the Alzheimer's type'.

Types of interventions

1) Any oral dose of galantamine
2) Placebo

Types of outcome measures

1. Alzheimer's Disease Assessment Scale-Cognitive Subscale (Rosen 1984). This 70 point scale encompasses a broad range of cognitive function typically affected by AD. Higher scores indicate worsening. Positive change scores indicate worsening. The European ADAS and French ADAS (EURO-ADAS and Greco-ADAS, respectively) were also included.
2. Global Rating/ Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus). These were typically assessed using the process of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC; Schneider 1997). Scores range from 1 to 7, with 4 indicating no change, scores below 4 indicating improvement, and scores above 4 indicating worsening.
3. Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL; Galasko 1997). This ADL scale was specifically designed for Alzheimer's disease and the version used here was scored from 0 to 78; negative change scores normally indicate worsening, but were re coded to be consistent with MetaView.
4. Disability Assessment for Dementia scale (DAD; Gelinas 1999). This 46-item scale assesses both basic and instrumental ADLs, leisure activities, initiation, planning and organization, and effective performance. It is administered to an informant and has a total score ranging from 0 to 100.
5. Neuropsychiatric Inventory (NPI; Cummings 1994). This scale assesses the following ten items: delusions, hallucinations, agitation/aggression, depression, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/liability, aberrant motor behavior. The total score ranges from 0 to 120; positive change scores indicate worsening.

Search methods for identification of studies

The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 25 April 2005 using the terms galanthamin* galantamin* and reminyl.

The Specialized Register at that time contained records from the following databases:
CENTRAL: January 2005 (issue 1);
MEDLINE: 1966 to 2005/02;
EMBASE: 1980 to 2005/01;
PsycINFO: 1887 to 2005/01;
CINAHL: 1982 to 2004/12;
SIGLE (Grey Literature in Europe): 1980 to 2004/06;
ISTP (Index to Scientific and Technical Proceedings): to May 2000;
INSIDE (BL database of Conference Proceedings and Journals): to June 2000;
Aslib Index to Theses (UK and Ireland theses): 1970 to March 2003;

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Dissertation Abstract (USA): 1861 to March 2003;
ADEAR (Alzheimer's Disease Clinical Trials Database): to 25 March 2005;
National Research Register: issue 1/2005;
Current Controlled trials (last searched April 2005) which includes:
Alzheimer Society
GlaxoSmithKline
HongKong Health Services Research Fund
Medical Research Council (MRC)
NHS R&D Health Technology Assessment Programme
Schering Health Care Ltd
South Australian Network for Research on Ageing
US Dept of Veterans Affairs Cooperative Studies
National Institutes of Health (NIH)
ClinicalTrials.gov: last searched March 2005;
LILACS:Latin American and Caribbean Health Science Literature: last searched April 2003

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

Published reports were inspected for additional sources. Additional information was collected from unpublished "clinical research reports" obtained from Janssen and the website www.clinicalstudyresults.org.

Data collection and analysis

Selection of studies

A single reviewer (JO) discarded irrelevant citations, based on the title of the publication and its abstract. Any suggestion that an article could possibly be relevant, caused it to be retrieved for further assessment. This was repeated by another reviewer (CL) for the 2004 and 2005 updates

A single reviewer independently selected the trials for initial inclusion in the review from the culled citation list. These trials were reviewed by a second reviewer (LS).

Quality Assessment

The reviewers assessed the methodological quality of each trial using the Cochrane Collaboration guidelines (Mulrow 1997).

- Category A (adequate) is where the report describes allocation of treatment by: (i) some form of centralized randomised scheme, such as having to provide details of an enrolled participant to an office by phone to receive the treatment group allocation; (ii) some form of randomizations scheme controlled by a pharmacy; (iii) numbered or coded containers, such as in a pharmaceutical trial in which capsules from identical-looking numbered bottles are administrated sequentially to enrolled participants; (iv) an on-site or coded computer system, given that the allocations were in a locked, unreadable file that could be accessed only after inputting the characteristics of an enrolled participant; or (v) if assignment envelopes were used, the report should at least specify that they were sequentially numbered, sealed, opaque envelopes; (vi) other combinations of described elements of the process that provides assurance of adequate concealment.
- Category B (unclear) is where the report describes the study as 'randomised' but no further detail is available.
- Category C (inadequate) is where the report describes allocation of treatment by: (i) alternation; (ii) reference to case record numbers, dates of birth, day of week, or any other such approach; (iii) any allocation procedure that is entirely transparent before assignment, such as an open list of random numbers or assignments.
- Category D (not used) is where randomisation is not used.

Empirical research has shown that lack of adequate allocation concealment is associated with bias. Trials with unclear concealment measures have been shown to yield more pronounced estimates of treatment effects than trials that have taken adequate measures to conceal allocation schedules, but less pronounced than inadequately concealed trials (Chalmers 1983, Schulz 1995). Thus trials will be included if they conform to categories A or B, and those falling into category C were excluded.

Other aspects of trial quality were not assessed by a scoring system although details were noted of blinding, whether intention-to-treat analyses were extractable from the published data, and the number of patients lost to follow-up.

Data extraction

Data were independently extracted by JO, subsequently by the update reviewer (CL), and cross-checked by a second reviewer (LS). Any discrepancies were discussed.

Data were required to provide either: (a) means and standard deviations (or standard error) for pre- and post-tests, (b) means and standard deviations (or standard error) for change scores, (c) individual data for each patient in the trial. For categorical ratings, data were required to provide either: (a) the percentage of improvers for both drug and placebo groups, (b) frequencies of improvers for both drug and placebo groups, or (c) individual data for each patient in the trial.

Data analysis

For continuous or ordinal variables, the main outcome of interest is change in score from baseline (i.e. pre-randomisation or at randomisation) to the final assessment. If ordinal scale data appear to be approximately normally distributed or if the analysis that the investigators performed suggested parametric tests were appropriate, then the outcome measures were treated as continuous data.

For binary outcomes or ordinal data that could be treated dichotomously, such as global ratings under some instances, the endpoint itself is of interest and the Peto method of the 'typical odds ratio' was used.

A test for heterogeneity of treatment effect among trials was made using a standard chi-squared statistic or the I-squared statistic. If a test of heterogeneity is negative then a weighted estimate of the typical treatment effect across trials, the 'typical odds ratio' (e.g., the odds of an unfavourable outcome among treatment-allocated patients to the corresponding odds among controls) is calculated using Peto's log-rank test adapted for ordinal data (EBCTCG 1990). If, however, there was evidence of heterogeneity of the treatment effect between trials then either only homogeneous results are pooled, or a random effects model used (in which case the confidence intervals would be broader than a fixed effects model).

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Additional hypotheses tested were that galantamine has no differential effect when compared with placebo, based upon daily dose.

RESULTS

Description of studies

Eleven trials were identified that met inclusion criteria for the review (GAL-95-05; GAL-INT-10 Brodaty; GAL-INT-11 DeKosky; GAL-INT-6Erkinjuntti; Kewitz 1994b; GAL-USA-1 Raskind; GAL-INT-2 Rockwood; GAL-USA-10 Tariot; GAL-INT-1 Wilcock; GAL-93-01 Wilkinson; GAL-INT-18 Winblad). One of these did not provide sufficient outcome data for analysis (Kewitz 1994b). Of the remaining ten, seven were published in peer-reviewed journals (GAL-INT-10 Brodaty; GAL-INT-6Erkinjuntti; GAL-USA-1 Raskind; GAL-INT-2 Rockwood; GAL-USA-10 Tariot; GAL-INT-1 Wilcock; GAL-93-01 Wilkinson). Unpublished clinical research reports were obtained from Janssen and the website www.clinicalstudyresults.org for the remainder (GAL-95-05; GAL-INT-11 DeKosky; GAL-INT-18 Winblad), and for the breakdown of subgroup data in GAL-INT-6Erkinjuntti.

Methods

All eleven trials were parallel group designs. Treatment lasted from 12 weeks to 2 years with 26 weeks being most common. Trials of 5 months to 29 weeks were aggregated as '6 month' trials for the purposes of analyses.

Participants

The number of participants randomised in the trials ranged from 95 to 1062 (k=11). Those trials reporting the number excluded after randomizations (k=10) reported 204 to 1019 completers, with a completion rate ranging from 68.9-80.4%. Two trials enrolled subjects with MCI and mild impairment / Clinical Dementia Rating= 0.5 (GAL-INT-11 DeKosky; GAL-INT-18 Winblad). Most trials enrolled mildly to moderately impaired subjects with AD, using the MMSE to set high and low cutoff scores (GAL-95-05:12-24; GAL-INT-10 Brodaty: 10-24; GAL-INT-6Erkinjuntti: 10-25; GAL-USA-1 Raskind: 11-24; GAL-INT-2 Rockwood: 11-24; GAL-USA-10 Tariot: 10-22; GAL-INT-1 Wilcock: 11-24; GAL-93-01 Wilkinson: 13-24), so that the highest MMSE score allowed ranged from 22 to 25, and the lowest from 10 to 12.

Interventions

All eleven trials compared galantamine against placebo.

The exact dosing regime in Kewitz 1994b was unclear.

Four trials tested a single dosing regime against placebo. Two studied subjects with AD (GAL-95-05: 32mg/d; GAL-INT-6Erkinjuntti: 24mg/d), and two subjects with MCI (GAL-INT-11 DeKosky & GAL-INT-18 Winblad, both with flexible regimes of 16-24mg/d).

Three trials tested two different dosing regimes against placebo: 24mg/d or 32mg/d (GAL-USA-1 Raskind; GAL-INT-2 Rockwood; GAL-INT-1 Wilcock). GAL-INT-2 Rockwood permitted subjects to remain on either 24 or 32mg/d.

Two trials tested three different dosing regimes against placebo. GAL-USA-10 Tariot tested doses of 8mg/d, 16mg/d and 24mg/d, and GAL-93-01 Wilkinson tested doses of 18mg/d, 24mg/d and 36mg/d. It should be noted that the Wilkinson trial included an interim analysis that resulted in the remaining subjects being allocated solely to the placebo or 18mg/d. Although this was done in a blinded fashion, the integrity of the data may have been compromised.

One trial tested the prolonged release / once daily formulation and twice daily dosing (both with flexible regime of 16-24mg/d) against placebo (GAL-INT-10 Brodaty).

The most frequent doses tested were 24 mg/d (in nine trials) and 32 mg/d (in five trials). Six trials reported 4-week placebo run-ins prior to treatment randomisation.

All trials had patients begin at a lower dose and increase over time to the daily maximum. Exact dose escalation regime for Kewitz 1994b was unclear. One trial escalated daily dose by 4mg each week until maximum assigned dose (GAL-INT-6Erkinjuntti). Four trials escalated daily dose by 8mg each week until maximum assigned dose (GAL-95-05: GAL-USA-1 Raskind; GAL-INT-2 Rockwood; GAL-INT-1 Wilcock). One trial escalated daily dose by 8mg every 4 weeks (GAL-USA-10 Tariot). One trial used a variable escalation regime bringing the dose from 8mg/d to 18-36mg/d within 5-14 days(GAL-93-01 Wilkinson). Three trials escalated daily dose by 8mg every 4 weeks, with an option to reduce dosage from 24 mg/d back to 16 mg/d (GAL-INT-10 Brodaty; GAL-INT-11 DeKosky; GAL-INT-18 Winblad).

Outcome measures

The following range of outcome measures were used among trials:

1. Cognitive Tests
ADAS-cog or Euro-ADAS-cog (k=11, 1 of which did not provide sufficient data for analysis)
Expanded ADAS-cog (k=3)

2. Global rating scales
CIBIC-plus (k=4)
ADCS-CGIC (k=4)
Unspecified physician's global rating (k=1, which did not provide sufficient data for analysis)

3. Activities of Daily Living
ADCS-ADL (Galasko 1997; k=2)

4.Disability Assessment
Disability Assessment for Dementia (Gelinas 1999; k=4)

5. Behavioral measures
NPI (Cummings 1994; k=4)

Risk of bias in included studies

Most of the trials had sufficient methodological quality, having been designed as Phase II and III clinical trials. All trials had quality ratings of A except for three trials where the randomizations scheme was not reported. These were all given quality ratings of B, and include: Kewitz 1994b (abstract only); GAL-INT-11 DeKosky & GAL-INT-18 Winblad (both unpublished clinical research reports).

Effects of interventions

Global Rating scales

Out of the eight AD trials that provided sufficient outcome data for analysis, all provided global rating data using observed cases (OC) analyses and ITT. Rating scale data were dichotomized

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into those who had no change or improvement versus those who worsened. Analyses revealed statistically significant results in favour of treatment in OC and ITT analyses at both 3 months and 6 months.

- For trials of 3 months' duration, by OC analysis, dosing at 18 mg/d and 24 mg/d failed to show a statistically significant effect. Dosing at 24-32 mg/d (Odds Ratio (OR) 2.3; 95%CI 1.3 - 3.9) and 36 mg/d (OR 3.4; 95%CI 1.2 - 9.5) were both statistically significant in favour of treatment.
- For trials of 3 months' duration, by ITT analysis, dosing at 24 mg/d and 24-32 mg/d failed to show a statistically significant effect. Dosing at 18 mg/d (OR 2.4, 95%CI 1.2 -5.0) and 36 mg/d (OR 2.7; 95%CI 1.2 -6.2) were all statistically significant in favour of treatment.
- For trials of 6 months duration (5-months to 29 weeks), by OC analysis, dosing at 8 mg/d, 16-24 mg (bid or prolonged release) and 32mg/d (tds dosing) failed to show a statistically significant effect. Dosing at 16 mg (OR 2.3; 95% CI 1.6 - 3.3), 24 mg (OR 2.1; 95%CI 1.6 -2.6), 32 mg (bd dosing) (OR 1.9; 95%CI 1.4 - 2.7) were all statistically significant in favour of treatment.
- For trials of 6 months' duration, by ITT analyses, doses of 8 mg/d, 16-24 mg (bid or prolonged release) and 32 mg/d (tds dosing) failed to show a statistically significant effect. Dosing at 16 mg (OR 2.0; 95% CI 1.4 - 2.9), 24 mg (OR 1.9; 95%CI 1.6 -2.3), 32 mg (OR 1.8; 95%CI 1.3 - 2.4) were all statistically significant in favour of treatment.

When the global rating results (OC) were aggregated by dose, irrespective of duration, all dosages showed statistically significant effects with overlapping confidence intervals, except for 8mg/d.

- OR for 16-24 mg/d was 1.63 (95%CI 1.3-2.1, k=3)
- OR for 24 mg/d to 24-32 mg/d was 2.1 (95%CI 1.7-2.5, k=6)
- OR for 32-36 mg/d was 1.7 (95%CI 1.4-2.2, k=4)

For ITT analyses, the results were similar with significant and overlapping confidence intervals:

- OR for 16-24 mg/d was 1.7 (95%CI 1.3-2.1 k=3)
- OR for 24 mg/d to 24-32 mg/d was 1.8 (95%CI 1.5-2.2, k=6)
- OR for 32-36 mg/d was 1.6 (95%CI 1.3-2.0)

ADAS-cog Scores

Out of the eight AD trials that provided sufficient outcome data for analysis, all provided ADAS-cog change from baseline data using observed cases (OC) analyses and ITT. The analyses revealed statistically significant results in favour of treatment in OC and ITT analyses at both 3 months and 6 months.

- For trials of 3 months' duration, statistically significant effects were found at all dosing levels by both OC and ITT analysis. As expected, OC analysis yielded slightly more favourable estimates. There was only one trial at each dosing level. Weighted mean difference in ADAS-cog score by ITT for 18mg/d was 1.7 (95%CI 0.2-3.6), 24mg 3.0 (95%CI 0.8-5.2), 24-32mg 1.7 (95%CI 0.6-2.8), and 36mg 2.3 (95%CI 0.4-4.2).
- For trials of 6 months' duration, statistically significant effects were found at all dosing levels by both OC and ITT analysis. As expected, OC analysis yielded slightly more favourable estimates. Weighted mean difference in ADAS-cog score by ITT for 8 mg/d was 1.3 (95%CI 0.03-2.6), 16 mg 3.1 (95%CI 2.1-4.1), 16-24 mg bid 2.8 (95%CI 1.8-3.8), 16-24 mg prolonged release 2.5 (95%CI 1.6-3.4), 24 mg 3.1 (95%CI 2.6-3.7), 32 mg bd dosing 3.3 (95%CI 2.4-4.1) and 32 mg tds dosing 2.9 (95%CI 1.8-4.0).

Proportion of patients with 4 or more point improvement in ADAS-cog was reported at 3 months in 1 trial and 6 months in 3. The single trial reporting at 3 months showed a statistically significant result by OC but not ITT. Trials reporting at 6 months (all with OC data only) did not find a statistically significant effect for 8 mg/d. Statistically significant effect was found for 16 mg/d (OR 2.2, 95%CI 1.5-3.4), 24 mg (OR 2.4, 95%CI 1.8-3.2), and 32 mg (OR 2.7, 95%CI 1.9-4.0).

ADCS-ADL Scores

Treatment effect on ADCS-ADL scale was reported in one trial only for the dosing levels of 8 mg/d, 16 mg/d, 16-24 mg/d and 24mg/d. As expected, OC analysis yielded slightly more favourable estimates. Significantly smaller decrease in the ADCS-ADL score by ITT was reported for 16mg/d (3.1points, 95%CI 1.6-4.6) and 24mg/d (2.3points, 95%CI 0.6-4.0). Data was only available in OC form for 16-24 mg/d, finding a significantly smaller decrease in ADCS-ADL in the prolonged release group (2.4 points, 95%CI 0.8-4.0) but not the bid group.

DAD Scores

Treatment effect on DAD was reported at 3 months in 1 trial and at 6 months in 2. Statistically significant treatment effects were found at 3 months for 24-32 mg/d by OC and ITT. Change from baseline by ITT was 4.8 points (95%CI 2.1-7.6). Statistically significant treatment effects were also found at 6 months by OC and ITT. Change from baseline by ITT for 24 mg/d was 3.7 (95%CI 1.4-6.9), 32 mg/d 3.5 (95%CI 0.5-6.5).

NPI Scores

Treatment effect on NPI was reported at 3 months in 1 trial and at 6 months in 3. No statistically significant treatment effect was found at 3 months for 24-32 mg/d by OC and ITT. At six months, for 16 mg/d, treatment effect was statistically significant by OC and ITT, with a 2.1 point reduction by ITT (95%CI 0.2-4.0). For 16-24mg/d, no statistically significant treatment effect was found for the prolong release or bid group. For 24 mg/d, treatment effect was statistically significant by OC but not ITT.

Probable versus possible AD

One of the eight AD trials recruited patients with possible AD while the other seven recruited patients with probable AD. Treatment effects found in the former had overlapping confidence intervals with the rest of the trials.

Prolonged release/ once daily formulation vs. twice daily dosing

The 16-24mg/d prolonged release formation was found to have overlapping confidence intervals with the 16-24mg/d twice daily dosing (GAL-INT-10 Brodaty)- in terms of treatment effects, adverse effects and proportion of treatment withdrawal.

MCI trials

Neither of the MCI trials (GAL-INT-11 DeKosky, GAL-INT-18 Winblad) found significant treatment effect in terms of ADAS-cog at twelve months or twenty-four months. One of the trials GAL-INT-11 DeKosky) reached marginal significance in terms of dementia conversion rate to dementia (change of CDR score from 0.5 to >=1.0)

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at twenty-four months. Combining data from both trials, 12-24 mg/d bid galantamine confers an OR of 0.74 (95%CI 0.58-0.94) in dementia conversion at twenty-four months.

MRI brain atrophy rate

Dekosky et al. (GAL-INT-11 DeKosky) also used volumetric MRI brain imaging as an outcome measure. They found significantly lower whole brain but not hippocampal atrophy rate in MCI subjects treated with 12-24 mg/d galantamine (bid) compared to the placebo group. The clinical significance of this is unclear.

Other comments

The majority of ITT data reported in these trials were calculated using the Last Observation Carried Forward (LOCF) method. As a rule, the ITT treatment group size reported in these analyses were also smaller than the randomisation group size. Thus these ITT estimates are less conservative than traditional ITT.

Safety

In general, galantamine appeared well tolerated. As expected, gastrointestinal side effects were significantly more common in the treatment groups and in a dose-related fashion. As an example, the OR for nausea ranged from 2.9 (95%CI 1.7-5.3) for 16mg/d to 4.6 (95%CI 3.0-7.0) for 32mg/d.

Comparison of adverse effects between trials was limited by different methods of reporting. Adverse events appearing at least 5% more often in the treatment groups were reported in four published trials (GAL-INT-10 Brodaty; GAL-USA-10 Tariot; GAL-USA-1 Raskind; GAL-INT-1 Wilcock). The proportion of subjects with these adverse events was also analysed. The adverse events recorded include tremor; anorexia; vomiting; nausea; weight loss; headache; abdominal pain; diarrhea; dizziness; and agitation. For 8mg/d, none of the adverse events was statistically significantly more frequent than placebo. Nausea, vomiting and diarrhea were statistically significant at 16mg/d. Nausea, vomiting, dizziness, weight loss, anorexia, tremor and headache were statistically significant at 24mg/d. Nausea, vomiting, dizziness, weight loss, anorexia, abdominal pain, tremor and headache were statistically significant at 32mg/d.

The data for 3-month trials were similar to that of 6-month, with nausea, vomiting, headache, somnolence, and agitation being those of greatest magnitude.

Four trials reported more galantamine-treated subjects than placebo-treated subjects discontinuing (GAL-USA-1 Raskind; GAL-INT-1 Wilcock; GAL-95-05; GAL-93-01 Wilkinson). Overall, galantamine-treated subjects were more likely than placebo-treated subjects to discontinue for any reason from trials of 6 months in length at daily doses of 24 mg (OR 1.7; 95%CI 1.3-2.2), 32 mg-bd dosing (OR 2.6; 95%CI 1.9-3.5), and 32 mg-tds dosing (OR 2.4; 95%CI 1.6-3.5) . For 3-month trials, subjects were more likely to discontinue at doses of 24mg and higher.

Overall, galantamine-treated subjects were more likely to discontinue due to adverse events from trials of 6 months in length compared to placebo-treated subjects, for those subjects treated with daily doses of 16-24 mg (prolonged release: OR 1.9; 95%CI 1.0-3.6),24 mg (OR 2.1; 95%CI 1.5-2.9), 32 mg-bd dosing (OR 3.6; 95%CI 2.6 -5.2) and 32 mg-tds dosing (OR 2.8; 95%CI 1.8-4.3). Note that ORs for 8 mg/d and 16 mg/d doses were not significantly greater than placebo. For 3-month trials, subjects were more likely to discontinue at doses of 24mg and higher.

All but 3 (Kewitz 1994b; GAL-93-01 Wilkinson; GAL-INT-1 Wilcock) of the 9 AD trials reported proportion of subjects deceased during the trial period. None found excess death in the treatment groups compared to the placebo group. On the other hand, pooled data from the MCI trials found significantly higher death rate in the galantamine groups. Causes of death in the galantamine group was detailed in one of the clinical research reports (GAL-INT-11 DeKosky), which included: bronchial carcinoma/sudden death, cerebrovascular disorder/syncope, myocardial infarct and suicide. An interim study from the manufacturer (GAL-COG-3002 2005) reported a hazard ratio of 4.9 (95%CI 1.8-13.40) during the double blind phase, and an interim adjusted hazard ratio of 3.0 (95%CI 1.3-7.3) after taking into account of some of the retrieved dropout subjects. Further data collection from these two MCI trials and another open label MCI trial is in progress (GAL-COG-3002 2005).

DISCUSSION

A clear picture is forming regarding the use of galantamine in AD now that the database available for review consists of seven published peer-reviewed trials, one unpublished multicenter trial, and one meeting abstract. This review shows overall positive effects for galantamine for trials of 3 months, 5 months and 6 months duration. In addition, although there was not a statistically significant dose effect, doses above 8mg/d were, for the most part, consistently statistically significant. Thus, there is evidence demonstrating efficacy for galantamine on global ratings, cognitive tests, assessments of ADLs and behavior. The one trial recruiting patients with possible AD shows similar treatment effect to the other trials recruiting patients with probable AD. The prolong release / once daily formulation of galantamine was found to have similar efficacy and side-effect profile as the equivalent twice-daily regime. Magnitude of treatment effect also appears to be similar to other cholinesterase inhibitors including donepezil, rivastigmine, and tacrine.

A comparatively narrow range of cognitive impairment ratings were used as entry criteria to these trials, leading to inclusion of mostly mildly or moderately impaired patients. A post-hoc analysis (Wilkinson 2002) pooling subgroup data among patients with a MMSE score of 10-12 from four of these trials (GAL-INT-1 Wilcock, GAL-INT-2 Rockwood, GAL-USA-1 Raskind,GAL-USA-10 Tariot), found galantamine to have a statistically significant effect on cognitive, functional and behavioral measures. However a proper systematic review and analysis was not completed, and the resulting effect size and significance was not compared to the subgroup with MMSE scores above 12- so no conclusions can be drawn. Post-hoc analysis of data from GAL-USA-10 Tariot also found statistically significant drug efficacy among patients with previous exposure to acetylcholinesterase inhibitors (Mintzer 2003), but the same criticism applies.

Galantamine's adverse event profile is similar to other cholinesterase inhibitors with respect to cholinergically mediated gastrointestinal symptoms. No information is available on adverse events that occurred less than 5% more frequently in the treatment groups. There appears to be a dose response relationship for these adverse events with doses of 32mg/day associated with greater incidence of withdrawals. GAL-USA-5 randomised 6-

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week galantamine withdrawal versus continuing galantamine or placebo. Adverse event rates were similar across the groups though sample size for this trial was small (N=118).

It appears that doses of 16 mg/d were best tolerated in the single trial where medication was titrated over 4 week periods, and because this dose showed statistically indistinguishable efficacy with higher doses, it is probably most preferable initially.

Longer term use of galantamine has not been assessed in a controlled fashion. Data have been collected only from participants in open-label extensions to these published clinical trials, and some of this data has been compared against placebo data from an Alzheimer's Disease trial for another drug, i.e., historical controls (Blesa 2003). Comparisons to historical controls are bias-prone and a more valid study such as a randomised controlled trial is needed.

Economic assessments based on some of the trials included in this review, using Canadian (Getsios 2001) and US (Migliaccio-Walle2003) cost data have also been published.

Data from the two MCI trials suggests marginal clinical benefit, but a yet unexplained excess in death rate. Galantamine use in MCI is therefore not recommended.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review suggest that doses of 16 mg/d and above improve cognitive function and either improve or maintain global function for at least 6 months. These findings apply to subjects with mildly to moderately severe cognitive impairment. There is limited information on efficacy for improving activities of daily living or overall behavior. The duration of efficacy is unknown as is the length of time patients should be treated. Adverse event data is available for only 6 months as well.

Galantamine use in MCI is not recommended due to excess death rate in the treatment group.

Implications for research

Future trials are needed in more heterogeneous and typical clinical populations, involving people with more severely impaired cognitive functioning and with more mildly impaired cognitive functioning than the subjects included in these trials, and over durations longer than 6 months. Trials that contrast galantamine with other cholinesterase inhibitors or other medications such as memantine are desirable. Given that adverse events are dose related, an optimal dose is needed that provides sufficient improvement while minimizing adverse events. This dose may be 16 mg/d but further research is needed. It will be important to assess more accurately the effects of galantamine on ADLs, aspects of problematic behavior and caregiver burden, and the implications for health economics.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

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GAL-93-01 Wilkinson

Methods	Randomized Double-blind Parallel-group Placebo-controlled Duration: 12 weeks
Participants	Country: UK No. of Centers: 8 Diagnosis: Probable Alzheimer's disease defined by: NINCDS-ADRDA. Inclusion: MMSE 13-24, presence of a caregiver. Exclusion: Failure to provide informed consent; presence of any condition likely to interfere with the trial; use of antidepressants, antipsychotic drugs, antiparkinsonian drugs, insulin, anticonvulsants, sedatives, antihypertensive agents (except ACE inhibitors and diuretics), other centrally acting cholinergic or anticholinergic agents (except inhaled drugs for asthma). Total No. of patients: 285 Sex: 42.3% male Age: [placebo 74.2 (+/-0.9)] [galantamine 24mg 72.9 (+/-1.1)] [galantamine 24mg 72.9 (+/-1.1)] [galantamine 36mg 75.4 (+/-1.0)]
Interventions	Route: oral Treatment: galantamine 6mg t.i.d. galantamine 8mg t.i.d. galantamine 12mg t.i.d. Treatment commenced at 4mg b.i.d. and was progressively increased every several days and then weekly by to assigned maximum dose (5, 8, and 14 days respectively). Control: Placebo t.i.d.
Outcomes	ADAS-cog (Alzheimer's Disease Assessment Scale, Cognitive subscale/11 item) CIBIC-Plus (Clinician Interview Based Impression of Change) IADL (Instrumental Activities of Daily Living) PDS-1 (Progressive Deterioration Scale)
Notes	No. excluded after randomization: 81 No. not included in analysis: 81 excluded from completer analysis

Risk of bias

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

GAL-95-05

Methods	Randomized Double-blind Parallel-group Placebo-controlled Duration: 29 weeks
Participants	Country: UK, Finland, Denmark, France, Belgium, Germany, Netherlands No. of Centers:73 Diagnosis: Probable Alzheimer's Disease defined by: DSMIV and NINCDS-ADRDA. Inclusion: MMSE 12-24, age 45 or greater, Hachinski ischaemic score <4, consent, responsible caregiver Exclusion: other neurodegenerative disorders, secondary causes of dementia, co-exisiting medical conditions, concurrent medications including psychotropic , cognitive enhancers & others

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GAL-95-05 *(Continued)*

	Total No. of patients: 554 Sex: 38.3% male Age: 72.9+/-8.5
Interventions	Route: oral Treatment: galantamine HBr 40mg (glantamine 32mg/d) Treatment commenced at 8mg/d and was progressively increased weekly by 8mg/d for two weeks (16mg/d, 24mg/d), then raised by 4mg/d at week 4 (28mg/d) then to assigned maximum dose at week 5. Control: Placebo t.i.d.
Outcomes	EURO-ADAS-cog CIBIC-Plus NOSGER (Nurses' Observation Scale for Geriatric Patients)
Notes	No. excluded after randomization: 133 No. not included in analysis: Not stated

Risk of bias

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

GAL-INT-1 Wilcock

Methods	Randomized Double-blind Parallel-group Placebo-controlled, with 4-week placebo run-in Duration: 26 weeks
Participants	Country: 8 European No. of Centers: 86 Diagnosis: At least 6 month history of progressive cognitive decline, Senile Dementia Alzheimer's Type defined by: NINCDS-ADRDA. Inclusion: MMSE score of 11 to 24, ADAS-cog score > 11; CT or MRI < 12 months previously with no evidence of multi-infarct dementia or active cerebrovascular disease; responsible caregiver; discontinued from antidementia medications; discontinued where possible form anticholinergic or cholinomimetic agents. Exclusion: Past cholinesterase inhibitor use; uncontrolled hypertension, heart failure, type II diabetes mellitus, hypothyroidism; other neurodegenerative disorders; cardiovascular disease that would affect completion of the trial; clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, endocrine conditions; urinary outflow obstruction; active peptic ulcer; history of epilepsy, significant substance abuse. Total No. of patients: 653 Sex: Not stated. Age: [placebo 72.7 (7.6)] [galantamine 24mg 71.9 (8.3)] [galantamine 32mg 72,1 (8.6)]
Interventions	Route: oral Treatment: galantamine 12mg b.i.d. galantamine 16mg b.i.d. Treatment commenced at 4mg b.i.d. and was progressively increased weekly by 8mg/d to assigned maximum dose. Control: Placebo b.i.d.
Outcomes	ADAS-cog

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GAL-INT-1 Wilcock *(Continued)*

	ADCS-CGIC Expanded ADAS-cog DAD (Disability Assessment for Dementia)
Notes	No. excluded after randomization: 128 No. not included in analysis: 128

Risk of bias

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

GAL-INT-10 Brodaty

Methods	Randomized double-blind parallel, 3-group, active & placebo-controlled trial, with 4-week placebo run-in Duration: 7 months
Participants	Country: 5, international No. of Centres: 93 Diagnosis: At least 6 month history of progressive cognitive decline, mild to moderate probable Alzheimer's Disease defined by: NINCDS-ADRDA. Inclusion: MMSE 10-24 and ADAS-cog/11>=18, living with or regularly visited daily by respobsible caregiver >=5 days/week Exclusion: other neurodegenerative disorders or cognitive impairment due to other identifiable causes; vascular dementia or clinically active cerebrovascular disease; epilepsy or significant psychiatric disease or a range of other medical illnesses; use of any dementia treatment agents, recently commenced or dose-adjusted Vitamin E, chronic NSAID or COX-2 inhibitor use; or use of a range of other medications. Total No. of Patients: 971 Sex: Male 36% Age: [placebo 76.3 (SD8.0)] [galantamine 76.5 (7.8)] [galantamine prolonged-release 76.6 (7.6)]
Interventions	Route: oral Treatment groups: galantamine & prolonged- release galantamine groups were both titrated from an initial dose of 8mg/d for the first 4 weeks to a maximum daily dose of 16 or 24 mg/d, by week 12, depending of safety & tolerability. Galantamine was administered in a twice daily regime, and the controlled-release group was given placebo doses in the evening to maintain blinding. Placebo control: placebo b.i.d.
Outcomes	Primary outcomes: Change from baseline at 26 weeks in- ADAS-cog/11 (Alzheimer's Disease Assessment Scale, Cognitive subscale/11 item) CIBIC-Plus (Clinician Interview Based Impression of Change) Key secondary outcomes: Change from baseline at 26 weeks in: ADCS-ADL NPI
Notes	No. not receiving treatment: 1/320 prolonged release galantamine, 1/327 galantamine, 4/324 placebo No. withdrawn: 68/320 prolonged release galantamine, 75/327 galantamine, 54/324 placebo No. with outcome data at end of trial: ADAS-cog: 240/320 prolonged release galantamine, 227/327 galantamine, 248/324 placebo CIBIC-plus: 246/320 prolonged release galantamine, 240/327 galantamine, 259/324 placebo No. with safety data at end of trial:

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GAL-INT-10 Brodaty *(Continued)*

	319/320 prolonged release galantamine, 326/327 galantamine, 320/324 placebo

Risk of bias

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

GAL-INT-11 DeKosky

Methods	Randomised double-blind parallel group placebo-controlled trial Duration: 24 months
Participants	Country: 10, international No. of centres: not stated Diagnosis: men or women outpatient >= 50 years of age with gradual clinical decline of cognitive ability consistent with Mild Cognitive Impairment (CDR=0.5, memory score >=0.5), impairment of activities of daily living insufficient for diagnosis of dementia, and a New York University Paragarph Recall test with delayed recall score<=10. Exclusion: Not stated Total No. of patients: 995 randomized Sex: Not stated Age: >= 50 years of age
Interventions	Route: oral Treatment: galantamine was titrated from an initial dose of 8mg/d (4mg bd), to a final dose of 16-24mg/d, at month 3, as a twice-daily regime (8-12mg bd) Control: placebo bd
Outcomes	Primary efficacy outcome at 12 months: ADAS-cog/MCI CDR-SB Primary efficacy outcome at 24 months: Number and percentage of subjects converting from MCI to dementia (CDR>1.0) at 24 months Rate of brain/ hippocampal atrophy was also asssessed by MRI measurement
Notes	898/995 subjects analyzed for efficacy, 990/995 for safety A retreived dropout study (GAL-COG-3002) in progress

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

GAL-INT-18 Winblad

Methods	Randomised double-blind parallel group placebo-controlled trial Duration: 24 months
Participants	Country: 8, international No. of centres: not stated Diagnosis: men or women outpatient >= 50 years of age with gradual clinical decline of cognitive ability consistent with Mild Cognitive Impairment (CDR=0.5, memory score >=0.5), impairment of activities of

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GAL-INT-18 Winblad *(Continued)*

	daily living insufficient for diagnosis of dementia, and a New York University Paragarph Recall test with delayed recall score<=10. Exclusion: Not stated Total No. of patients: 1062 randomized Sex: Not stated Age: >= 50 years of age
Interventions	Route: oral Treatment: galantamine was titrated from an initial dose of 8mg/d (4mg bd), to a final dose of 16-24mg/d, at month 3, as a twice-daily regime (8-12mg bd) Control: placebo bd
Outcomes	Primary efficacy outcome at 12 months: ADAS-cog/MCI CDR-SB Primary efficacy outcome at 24 months: Number and percentage of subjects converting from MCI to dementia (CDR>1.0) at 24 months Rate of brain/ hippocampal atrophy was also asssessed by MRI measurement
Notes	1019/1062 subjects analyzed for efficacy, 1058/1062 for safety A retreived dropout study (GAL-COG-3002) in progress

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

GAL-INT-2 Rockwood

Methods	Randomized Double-blind Parallel-group, with 4-week placebo run-in Placebo-controlled Duration: 12 weeks
Participants	Country: International No. of Centers: 43 Diagnosis: At least 6 month history of progressive cognitive decline, Senile Dementia Alzheimer's Type defined by: NINCDS-ADRDA. Inclusion: MMSE score of 11 to 24, ADAS-cog score > 11; CT or MRI < 12 months previously with no evidence of multi-infarct dementia or active cerebrovascular disease; regular contact with responsible caregiver; discontinued from antidementia medications; discontinued where possible form anticholinergic or cholinomimetic agents. Exclusion: Past cholinesterase inhibitor use; uncontrolled hypertension, congestive heart failure, type II diabetes mellitus, hypothyroidism; other neurodegenerative disorders; cardiovascular disease that would affect completion of the trial; clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, endocrine conditions; urinary outflow obstruction; active peptic ulcer; history of epilepsy, significant substance abuse. Total No. of patients: 386 randomized Sex: [placebo 46.4% male] [galantamine 24-32mg 43.3% male] Age: [placebo 74.6 (0.7)] [galantamine 24-32mg 75.2 (0.45)]
Interventions	Route: oral Treatment: galantamine 12mg b.i.d. galantamine 16mg b.i.d.

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GAL-INT-2 Rockwood *(Continued)*

	Treatment commenced at 4mg b.i.d. and was progressively increased weekly by 8mg/d to 12 mg/ b.i.d. Investigator could increase dose to 16mg b.i.d. at end of week 3 or maintain at 12mg b.i.d. At week 4, dose could be kept at 16mg b.i.d. or reduced to 12mg b.i.d. Control: Placebo b.i.d.
Outcomes	ADAS-cog ADCS-CGIC Expanded ADAS-cog DAD (Disability Assessment for Dementia) Neuropsychiatric Inventory (NPI)
Notes	No. who failed to complete after randomization: 108 No. not included in OC analysis: 108

Risk of bias

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

GAL-INT-6Erkinjuntti

Methods	Randomized Double-blind Parallel-group Placebo-controlled, with 4-week placebo run-in Duration: 7 months
Participants	Country: Canada, Denmark, Finland, France, Germany, Ireland, Israel, Netherlands, Poland, UK; No. of centres: 66 Diagnosis: Probable vascular dementia according to NINDS-AIREN or possible Alzheimer's disease according to NINCDS-ADRDA with MMSE 10-25 and radiological evidence of significant cerebrovascular disease; Exclusion: other neurodegenerative disorders, secondary causes of dementia, co-exisiting medical conditions, significant cardiovascular disease, concurrent medications including dementia treatment, NSAID & others Total No. of patients: [592 randomized] [possible Alzheimer's disease with cerebrovascular disease-285 randomized] Sex: [placebo 54% male] [galantamine 24mg 52% male] Age: [placebo 75.2 (7.3)] [galantamine 24mg 75.0 (6.84)]; efficacy data used in analysis represents the possibly Alzheimer's Disease with cerebrovascular disease subgroup
Interventions	Route: oral Treatment: galantamine 12mg b.i.d. Treatment commenced at 4mg daily and was increased weekly by 4mg/d to 12mg b.i.d. Control: Placebo b.i.d.
Outcomes	ADAS-cog CIBIC-plus Response rate Expanded ADAS-cog DAD NPI
Notes	No. lost to follow-up (post randomization): 135

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GAL-INT-6Erkinjuntti *(Continued)*

Risk of bias

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

GAL-USA-1 Raskind

Methods	Randomized Double-blind Parallel-group Placebo-controlled, with 4-week placebo run-in Duration: 26 weeks/ 6 months
Participants	Country: USA No. of Centers: 33 Diagnosis: Senile Dementia Alzheimer's Type defined by: NINCDS-ADRDA. Inclusion: MMSE score of 11 to 24 inclusive, ADAS-cog score > 11; responsible caregiver; free for 30 days of medications indicated for dementia (3 months for cholinesterase inhibitors); written informed consent by patient or appropriate representative. Exclusion: Uncontrolled hypertension, heart failure, type II diabetes mellitus, hypothyroidism; other neurodegenerative disorders; cardiovascular disease that would affect completion of the trial; clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, endocrine conditions; urinary outflow obstruction; active peptic ulcer; history of epilepsy, significant substance abuse. Total No. of patients: 636 Sex: 242 males. Age: 70.3 +/- 1.6 to 71.1 +/- 1.5 (broken down by treatment group)
Interventions	Route: oral Treatment: galantamine 12mg b.i.d. galantamine 16mg b.i.d. Treatment commenced at 4mg b.i.d. and was increased weekly by 8mg/d to assigned maximum dose. Control: Placebo b.i.d.
Outcomes	ADAS-cog ADCS-CGIC DAD (Disability Assessment for Dementia)
Notes	No. excluded after randomization: 198 No. not included in observed case analysis: 198

Risk of bias

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

GAL-USA-10 Tariot

Methods	Randomized Double-blind Parallel-group Placebo-controlled, with 4-week placebo run in

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GAL-USA-10 Tariot *(Continued)*

	Duration: 5 months
Participants	Country: United States No. of Centers: Unstated Diagnosis: At least 6 month history of progressive cognitive decline, Senile Dementia Alzheimer's Type defined by: NINCDS-ADRDA. Inclusion: MMSE score of 10 to 22, ADAS-cog score > 17; CT or MRI < 12 months previously with no evidence of multi-infarct dementia or active cerebrovascular disease; responsible caregiver; free for 30 days of medications indicated for dementia; free for 60 days for cholinomimetic agents. Exclusion: Uncontrolled hypertension, heart failure, type II diabetes mellitus, hypothyroidism; other neurodegenerative disorders; cardiovascular disease that would affect completion of the trial; clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, endocrine conditions; urinary outflow obstruction; active peptic ulcer; history of epilepsy, significant substance abuse. Total No. of patients: 978 Sex: 353 males Age: 76.0 +/- 0.6 to 77.7 +/- 0.4
Interventions	Route: oral Treatment: galantamine 4mg b.i.d. galantamine 8mg b.i.d. galantamine 12mg b.i.d. Treatment commenced at 8mg/d and was increased 8mg/d every 4 weeks until the target dose had been reached. Control: Placebo b.i.d.
Outcomes	ADAS-cog ADCS-CGIC ADCS-ADL (Alzheimer's Disease Cooperative Study Activities of Daily Living), NPI (Neuropsychiatric Inventory)
Notes	No. excluded after randomization: 199 No. not included in observed cases analysis: 199

Risk of bias

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

Kewitz 1994b

Methods	Double-blind Parallel-group Placebo-controlled, with initial single-blind galantamine treatment (unstated duration) Duration: 13 weeks
Participants	Country: Unstated No. of Centers: Unstated Diagnosis: mild to moderately severe primary degenerative dementia Inclusion: Unstated Exclusion: Unstated Total No. of patients: 95 Sex: Unstated Age: Range = 60-87
Interventions	Route: oral Treatment: galantamine 10mg b.i.d. increased up to 50mg/d during first 3-weeks.

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Kewitz 1994b *(Continued)*

	Control: Placebo b.i.d.
Outcomes	ADAS-cog, CGIC
Notes	No. excluded after randomization: Not stated. No. not included in analysis: Not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

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

Study	Reason for exclusion
Anon 2001f	Commentary on GAL-INT6
Anon 2001g	Commentary on GAL-INT6
Bickel 1991	Pharmacokinetics study
Bores 1994	Pharmacokinetics study
Brashear 2003	GAL-INT-6
Brodaty 1996	Review article
Bullock 2001	Conference abstract- preliminary data from GAL-INT-6
Bullock 2004	Open label extension to GAL-INT-6
Burke 2002	Conference abstract describing NPI from GAL-USA-10 & GAL-INT-6
Caro 2002	Post hoc, subgroup, or selected combined exploratory analyses
Clegg 2001	HTA report covering all three cholinesterase inhibitors
Clegg 2002	Summary of HTA report (Clegg 2001)
Corey 2003	Review only
Coyle 2001	Review only
Cummings 2003	Review only
Cummings 2004	post hoc, subgroup, or selected combined exploratory analyses
Dal Bianco 1991	Not placebo-controlled
Dengiz 2004	Review only

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Study	Reason for exclusion
Doran 2003	Randomised different washout periods before switching from Donepezil to Galantamine; no results on register, not on Medline.
Erkinjuntti 2002a	Reply to Van Gool re GAL-INT-6
Erkinjuntti 2002b	Letter summarising GAL-INT-6
Erkinjuntti 2003	Open-labelled 6 month extension to GAL-INT-6
Fulton 1996	Review article
GAL-COG-3002 2005	Pooled MCI mortality data from different trials- referred to in Discussion/ Other references
GAL-MCI-301 2004	Open-label extension to MCI studies- stopped
Galasko 2004	post hoc, subgroup, or selected combined exploratory analyses
Gold 2004a	Superceded by Brodaty 05
Gold 2004b	Conference abstract only: GAL MCI trial baseline data
Hager 2004	Conference abstract only: open-label uncontrolled study
Haworth 2003b	Rater-blinded randomised trial of donepezil vs. galantamine. Likely to have been reported as Wilcock03 in Drugs Aging.
Janssen 2005	Prescription information only.
Jones 2004	GAL vs. Donepezil- RCT but open-labelled
Kertesz 2002	Comment on GAL-INT-6
Kewitz 1994	Not double-blind
Kewitz 1997	Pharmacokinetics study
Kurz 1998	GAL-INT-6
Kurz 2002	Non-cognitive outcome of GAL-INT-6
Kurz 2003	Open-label extension to GAL-INT-6
Kurz 2004	Conference abstract only, two Donepezil to GAL switching studies: randomizing washout period and galantamine dose
Lilienfeld 2001	Conference abstract on additional outcome (carer time requirement) from GAL-INT-1
Lyketsos 2002	Conference abstract reporting serial ADAS-cog up to 18.5 months from extension studies (from which 2 RCTs: unclear)
Lyketsos 2004	Open-label extension to Raskind and Tariot
MacGowan 1998	Not placebo-controlled
Marder 2002	Comment on GAL-INT-6

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Study	Reason for exclusion
Markowitz 2003	post hoc, subgroup, or selected combined exploratory analyses
Mintzer 2000	Preliminary conference abstract for Mintzer 2003 (see 'other references: additional references')
Mintzer 2001	Conference abstract comparing uncontrolled open label data at twelve months against historical controls
Moretti 2002	Comment on GAL-INT-6
Morris 2002	Conference abstract: 18.5 month open label extension study of GAAL-USA-10 and another unspecified trial
Mucke 1997	Review article. Preclinical studies
Nordberg 1998	Review article. Pharmacokinetics study
Novak 2004	Conference abstract only: effect of MCI clinical subtype on GAL efficacy- outcome not stated in abstract
Nye 2004	Conference abstract only: effect of ApoE genotype on GAL efficacy- outcome not stated in abstract
Orgogozo 2004	Superceded by subsequent paper in Current Medical Research & Opinion, which will be included under 'Other References'
Paskov 1974	Subjects did not have a diagnosis of dementia. Study was examining sexual function
Patterson 2002	Conference abstract: six month open label study (N=36)
Ping 2000	Randomised against Huperzine
Rabheru 2004	Conference abstract only, pooling behavioral outcome from 3 RCTs (details not stated)
Rainer 1993	Abstract with insufficient data
Rainer 1994	Single blind trial, not placebo controlled
Rainer 1997a	Review article
Rainer 1997b	Review article
Rainer 2001	Cross sectional study assessing cognition post drug cessation; only 5 patients on galantamine
Raskind 2000	Conference abstract reporting GAL-USA-1
Riemann 1994a	Subjects did not have a diagnosis of dementia. Outcome measure was sleep pattern.
Riemann 1994b	Review article on sleep and cholinergic function.
Sano 2003b	post hoc, subgroup, or selected combined exploratory analyses
Scheltens 2004	Conference abstract only: atrophy as outcome in MCI trial- methodology only: outcome not stated in abstract

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Study	Reason for exclusion
Schwalen 2004a	Conference abstract only: pooled efficacy data for patients with baseline ADAS-cog>30 pooled from 6 studies (details not in abstract), examining continuous vs. interrupted vs. delayed treatment.
Schwalen 2004b	Conference abstract only: post-hoc analysis of pooled data for patients with baseline MMSE <18 randomised to 24mg or 16mg/d
Scott 2000	Review only
Small 2003	Posthoc analysis of GAL-INT-6 plus open-label extension
Snorrason 1996	Subjects did not have a diagnosis of dementia. Not a clinical trial
Steiger-Baechler 200	Case description of cognition in 7 patients post cholinesterase inhibitor cessation- none on galantamine
Tariot 2000	Preliminary conference abstract for GAL-USA-10 Tariot
Thomsen 1990	Not a clinical trial
Thomsen 1990a	Not a randomized clinical trial
Thomsen 1990b	Not a clinical trial
Truyen 2000a	summary presentation of earlier galantamine findings
Truyen 2000b	summary presentation of earlier galantamine findings
Truyen 2001	specific data not included in abstract
van Gool 2002	Comment on GAL-INT-6
Vellas 2004	Conference abstract only: Pooled data on changes in DAD score/ADL from 6 RCTs
Wasielewski 1997	Review article
Wilcock 1993	Not placebo-controlled
Wilcock 2000i	Conference abstract on additional outcome (carer time requirement) from RCTs, referenced to Blesa 2000.
Wilcock 2000j	Conference abstract comparing uncontrolled open label data at twelve months against historical controls.
Wilkinson 2000	Conference abstract reporting GAL-INT-2
Zarotsky 2003	Review only

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

Galantamine CFIDS

Trial name or title	Not reported

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Galantamine CFIDS *(Continued)*

Methods	
Participants	Adults with Chronic Fatigue Syndrome
Interventions	Galantamine--dose not reportedPlaceboDuration: 4 monthsSites: 12Total N sought: 140
Outcomes	Not Reported
Starting date	Jan 29 1999
Contact information	
Notes	When completed, study will be excluded due to no AD subjects

Wilcock

Trial name or title	The safety and efficacy of Galanthamine in the treatment of vascular and mixed dementia
Methods	
Participants	Patients with vascular and mixed vascular/alzheimer's dementia
Interventions	Galanthamine--dosage not reportedPlacebo
Outcomes	Not reported
Starting date	1 Oct 1998
Contact information	Professor G WilcockDay HospitalFrenchay HospitalBeckspool RdFrenchayBristolBS16 1NDUKTel: 0117 970 1212
Notes	When completed, study will be excluded due to no AD patients enrolled.

DATA AND ANALYSES

Comparison 1. Global Rating OC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global Rating (no change or improvement at 3 months) OC	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 galantamine (18mg/d bid or tid) vs placebo	1	135	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [0.88, 4.37]
1.2 galantamine (24mg/d bid or tid) vs placebo	1	118	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.73 [0.73, 4.09]

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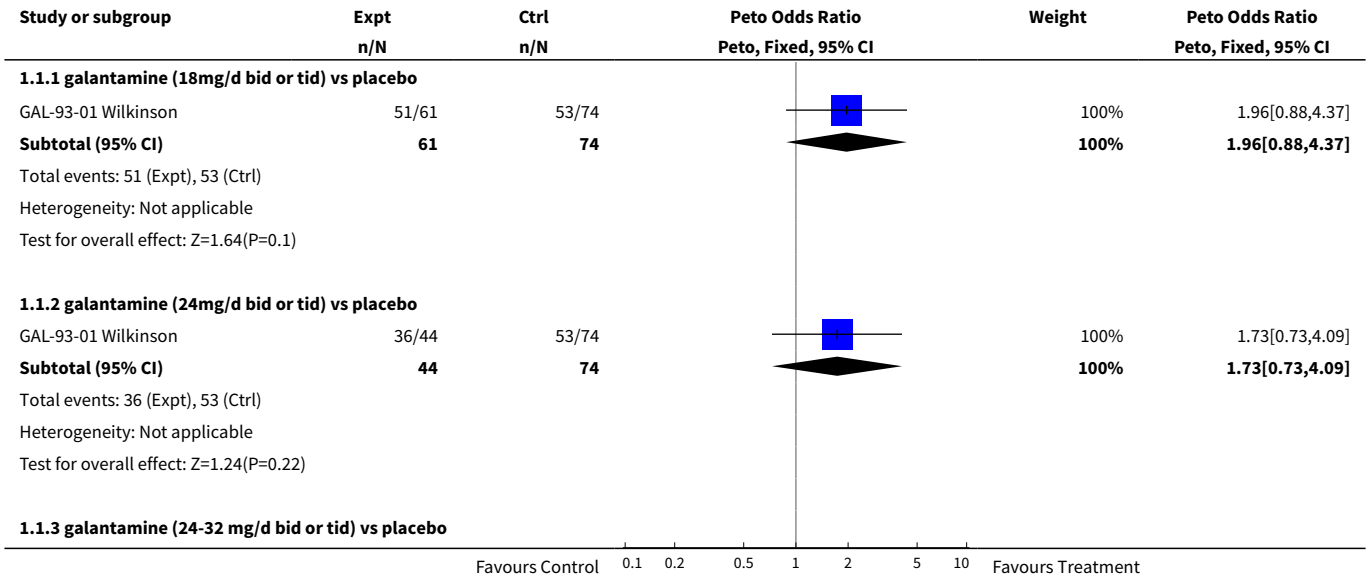
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 galantamine (24-32 mg/d bid or tid) vs placebo	1	281	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.28 [1.33, 3.91]
1.4 galantamine (36mg/d bid or tid) vs placebo	1	103	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.41 [1.22, 9.51]
2 Global Rating (no change or improvement at 6 months) OC	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 galantamine (8mg/d bid) vs placebo	1	340	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.71, 1.79]
2.2 galantamine (16mg/d bid) vs placebo	1	445	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.25 [1.55, 3.28]
2.3 galantamine (16-24mg/d bid) vs placebo	1	499	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.83, 1.69]
2.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	505	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.83, 1.70]
2.5 galantamine (24mg/d bid) vs placebo	4	1314	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.05 [1.64, 2.56]
2.6 galantamine (32mg/d bid) vs placebo	2	606	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [1.40, 2.69]
2.7 galantamine (32mg/d tds) vs placebo	1	414	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.87, 1.94]

Analysis 1.1. Comparison 1 Global Rating OC, Outcome 1 Global Rating (no change or improvement at 3 months) OC.



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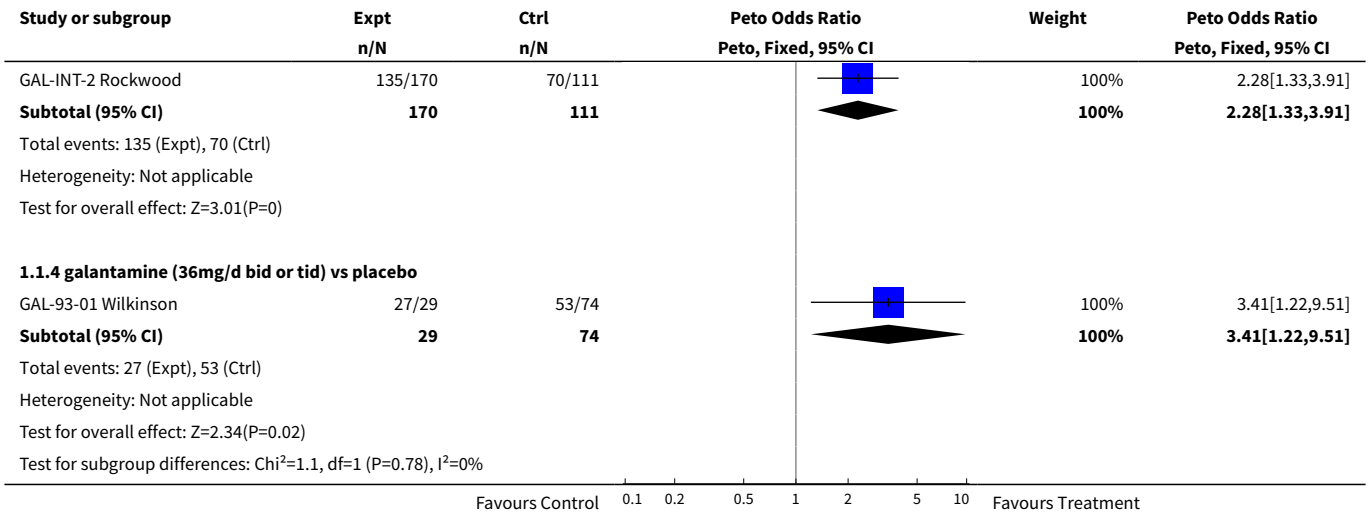
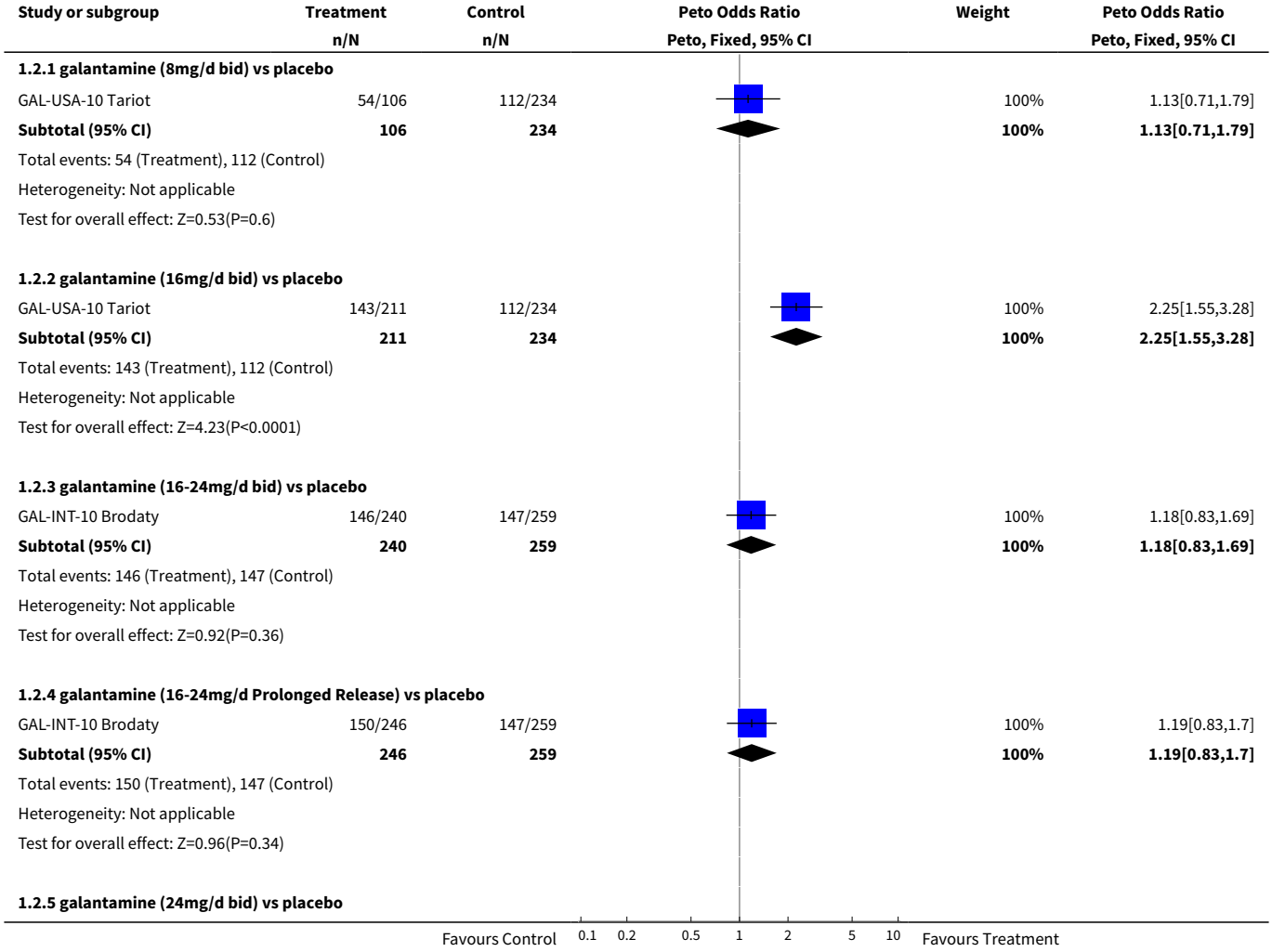


Analysis 1.2. Comparison 1 Global Rating OC, Outcome 2 Global Rating (no change or improvement at 6 months) OC.



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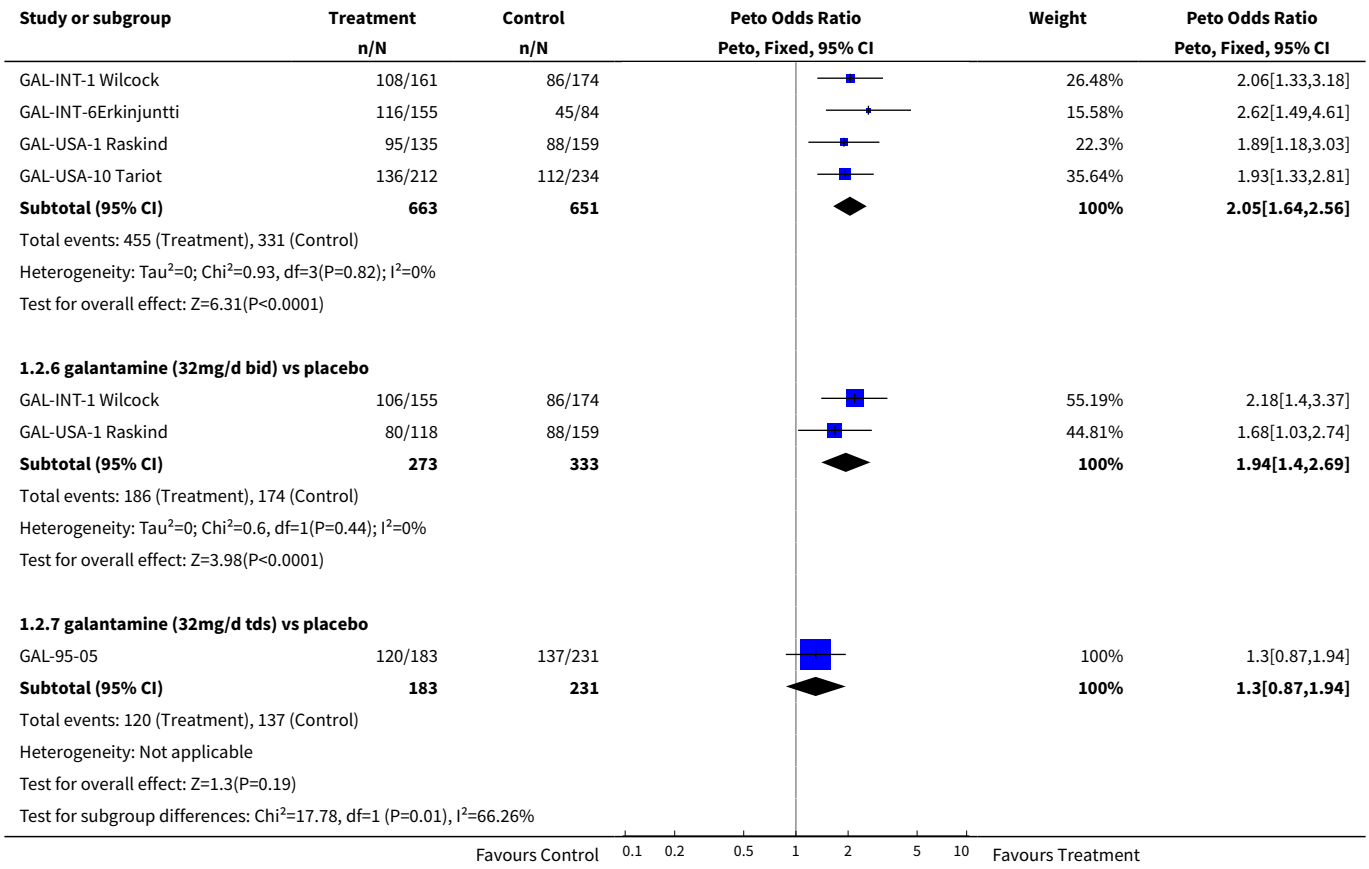

Comparison 2. ADAS-cog (Change from baseline) OC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-cog (Change from baseline at 3 months) OC	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 galantamine (18mg/d bid) vs placebo	1	115	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-5.45, -0.75]
1.2 galantamine (16-24mg/d bid) vs placebo	1	543	Mean Difference (IV, Fixed, 95% CI)	-2.6 [-3.47, -1.73]
1.3 galantamine (16-24mg/d Prolonged Release) vs placebo	1	544	Mean Difference (IV, Fixed, 95% CI)	-2.2 [-3.09, -1.31]
1.4 galantamine (24mg/d bid) vs placebo	1	97	Mean Difference (IV, Fixed, 95% CI)	-4.20 [-6.84, -1.56]
1.5 galantamine (24-32 mg/d bid) vs placebo	1	278	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-3.04, -0.76]
1.6 galantamine (32mg/d tds) vs placebo	1	398	Mean Difference (IV, Fixed, 95% CI)	-2.4 [-3.65, -1.15]

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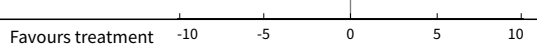
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7 galantamine (36mg/d bid) vs placebo	1	82	Mean Difference (IV, Fixed, 95% CI)	-4.1 [-6.60, -1.60]
2 ADAS-cog (Change from baseline at 6 months) OC	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 galantamine (8mg/d bid) vs placebo	1	351	Mean Difference (IV, Fixed, 95% CI)	-1.7 [-3.02, -0.38]
2.2 galantamine (16mg/d bid) vs placebo	1	433	Mean Difference (IV, Fixed, 95% CI)	-3.3 [-4.45, -2.15]
2.3 galantamine (16-24mg/d bid) vs placebo	1	475	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-4.18, -2.02]
2.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	488	Mean Difference (IV, Fixed, 95% CI)	-2.7 [-3.67, -1.73]
2.5 galantamine (24mg/d bid) vs placebo	4	1290	Mean Difference (IV, Fixed, 95% CI)	-3.38 [-4.04, -2.72]
2.6 galantamine (32mg/d bid or tds) vs placebo	2	599	Mean Difference (IV, Fixed, 95% CI)	-3.99 [-4.99, -2.99]
2.7 galantamine (32mg/d tds) vs placebo	1	394	Mean Difference (IV, Fixed, 95% CI)	-2.9 [-4.29, -1.51]

Analysis 2.1. Comparison 2 ADAS-cog (Change from baseline) OC, Outcome 1 ADAS-cog (Change from baseline at 3 months) OC.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 galantamine (18mg/d bid) vs placebo							
GAL-93-01 Wilkinson	62	-0.8 (6.2)	53	2.3 (6.6)		100%	-3.1[-5.45,-0.75]
Subtotal ***	**62**		**53**			**100%**	**-3.1[-5.45,-0.75]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=2.59(P=0.01)							
2.1.2 galantamine (16-24mg/d bid) vs placebo							
GAL-INT-10 Brodaty	268	-2.6 (5.1)	275	0 (5.3)		100%	-2.6[-3.47,-1.73]
Subtotal ***	**268**		**275**			**100%**	**-2.6[-3.47,-1.73]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.84(P<0.0001)							
2.1.3 galantamine (16-24mg/d Prolonged Release) vs placebo							
GAL-INT-10 Brodaty	269	-2.2 (5.3)	275	0 (5.3)		100%	-2.2[-3.09,-1.31]
Subtotal ***	**269**		**275**			**100%**	**-2.2[-3.09,-1.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.86(P<0.0001)							



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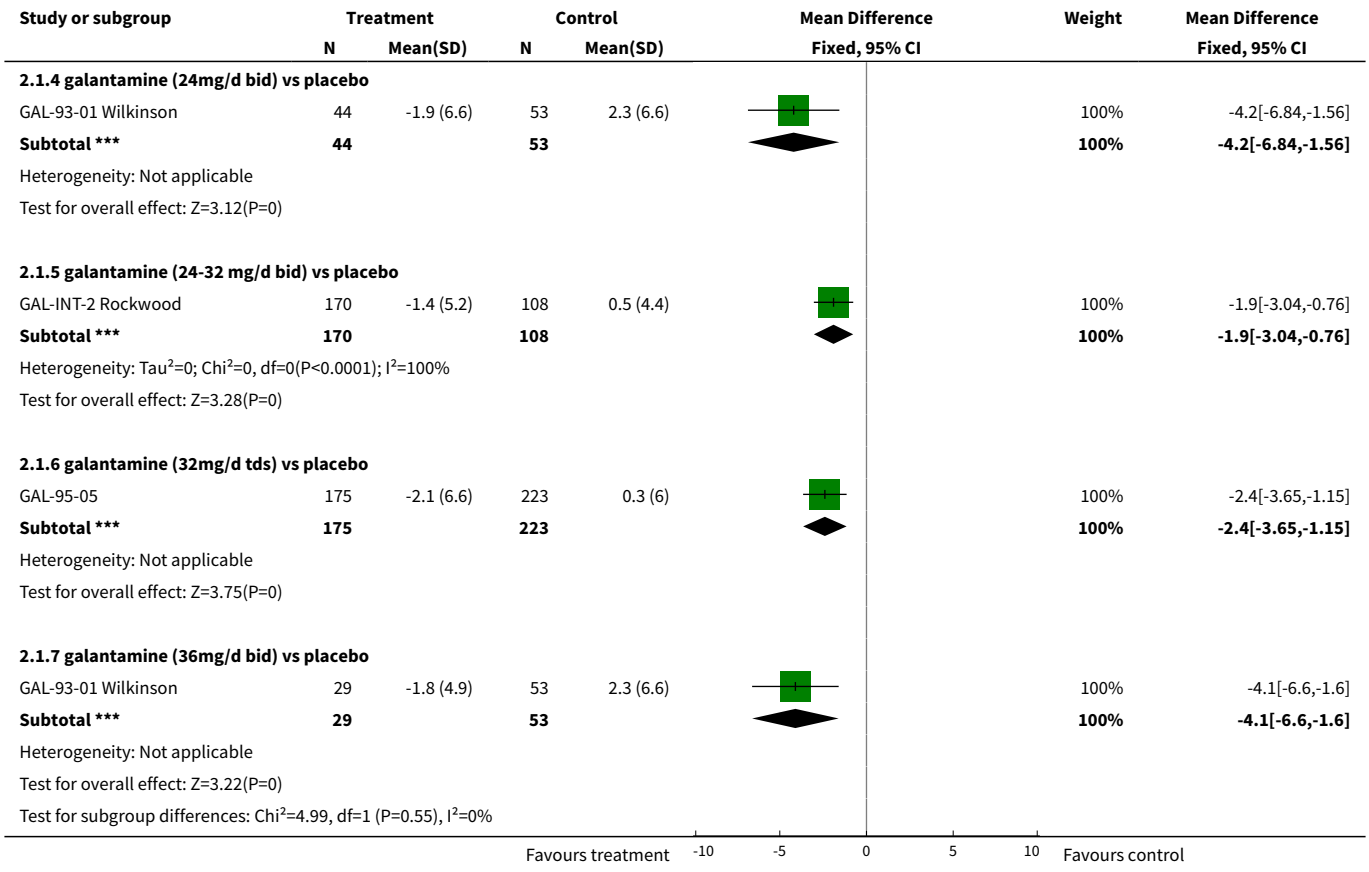
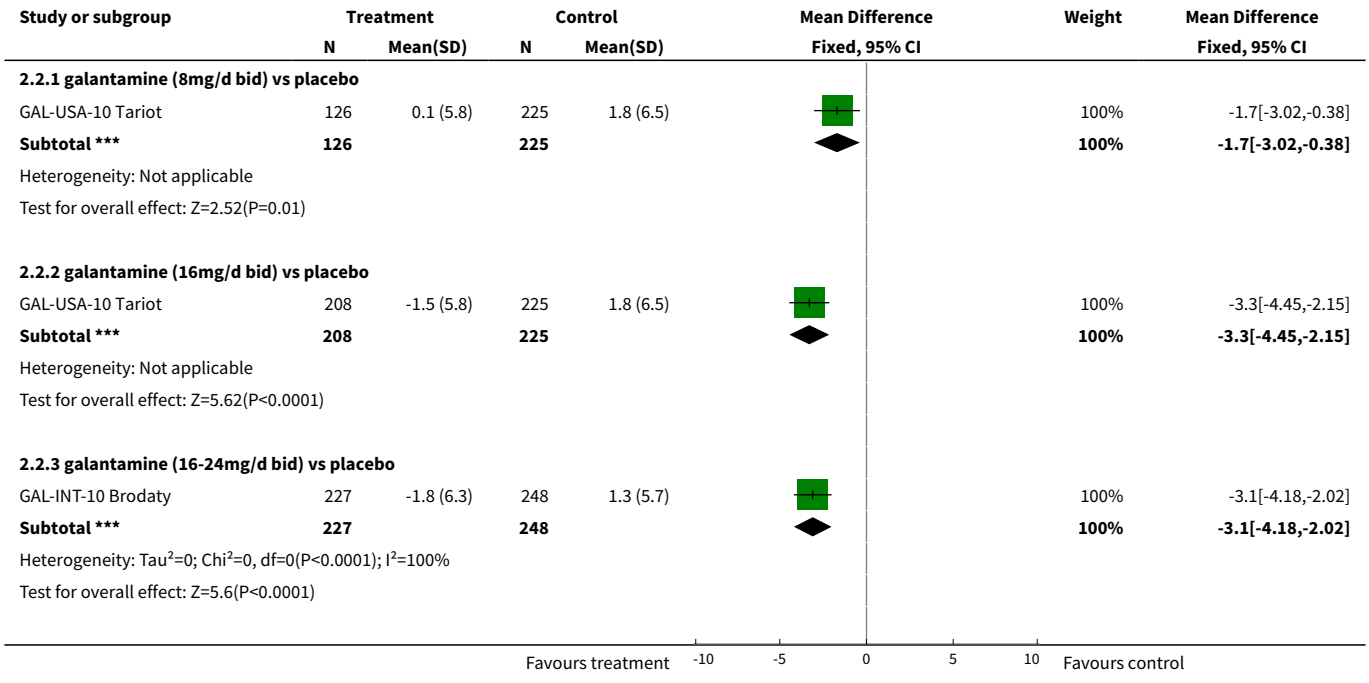


Analysis 2.2. Comparison 2 ADAS-cog (Change from baseline) OC, Outcome 2 ADAS-cog (Change from baseline at 6 months) OC.



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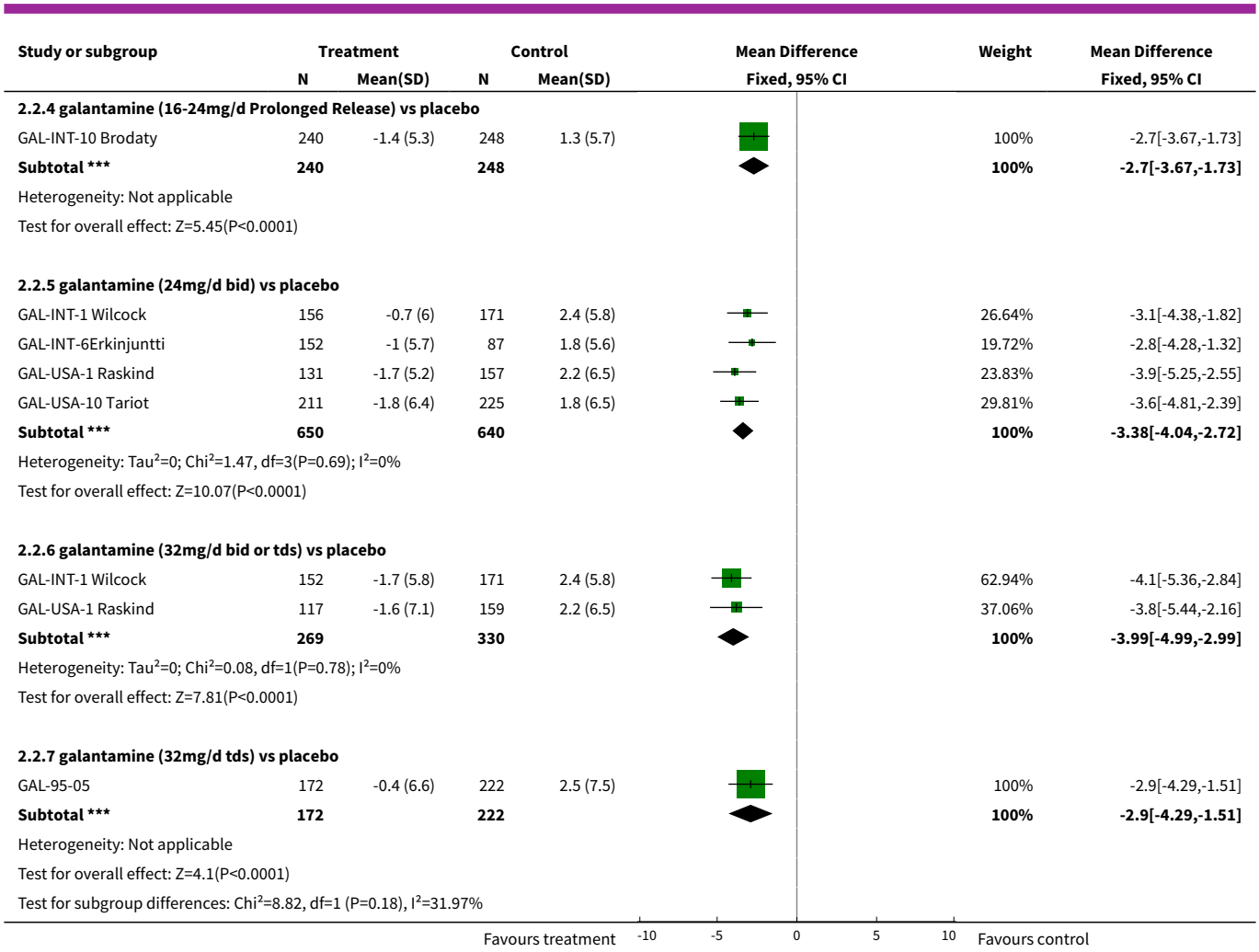

Comparison 3. ADAS-cog (4 points or more improvement) OC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-cog (4 points or more improvement at 3 months) OC	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.3 galantamine (24-32 mg/d bid or tid) vs placebo	1	270	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.79 [1.04, 3.09]
2 ADAS-cog (4 points or more improvement at 6 months) OC	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 galantamine (8mg/d bid) vs placebo	1	326	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.81, 2.55]
2.2 galantamine (16mg/d bid) vs placebo	1	433	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.24 [1.47, 3.42]

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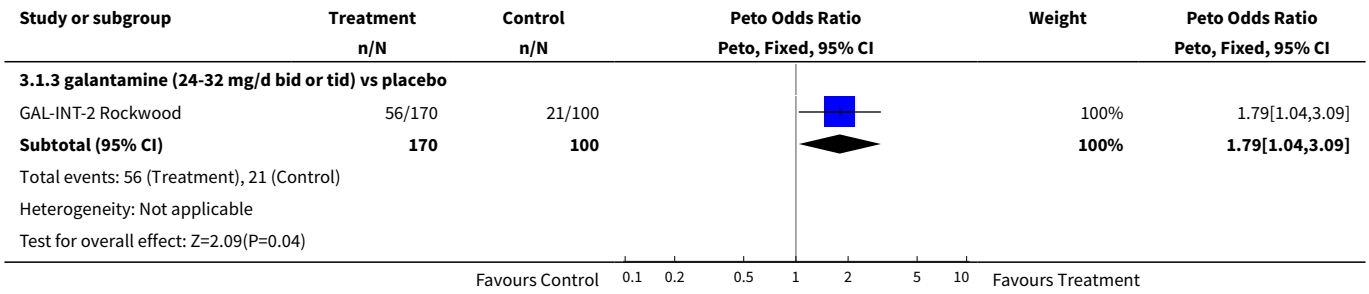
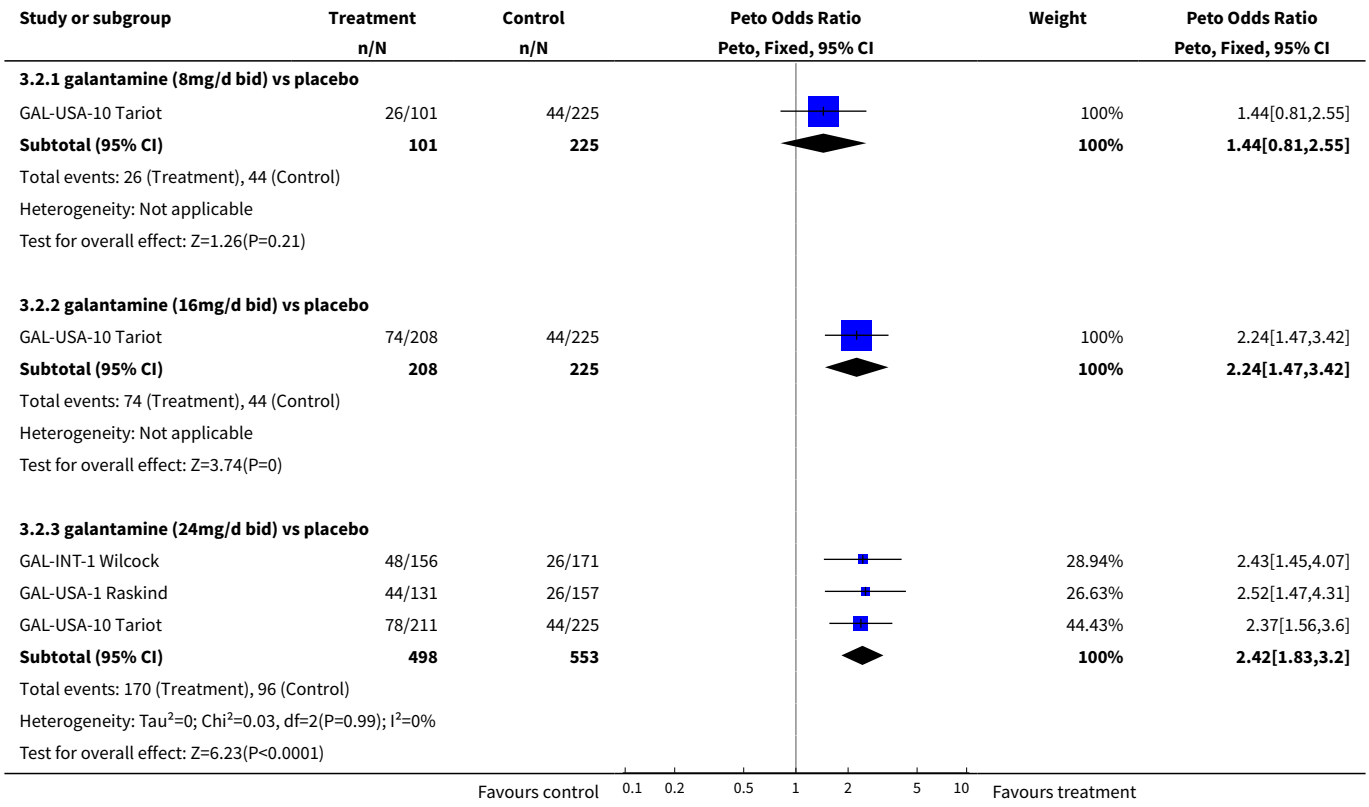
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 galantamine (24mg/d bid) vs placebo	3	1051	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.42 [1.83, 3.20]
2.4 galantamine (32mg/d bid) vs placebo	2	597	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.72 [1.86, 3.96]

Analysis 3.1. Comparison 3 ADAS-cog (4 points or more improvement) OC, Outcome 1 ADAS-cog (4 points or more improvement at 3 months) OC.



Analysis 3.2. Comparison 3 ADAS-cog (4 points or more improvement) OC, Outcome 2 ADAS-cog (4 points or more improvement at 6 months) OC.



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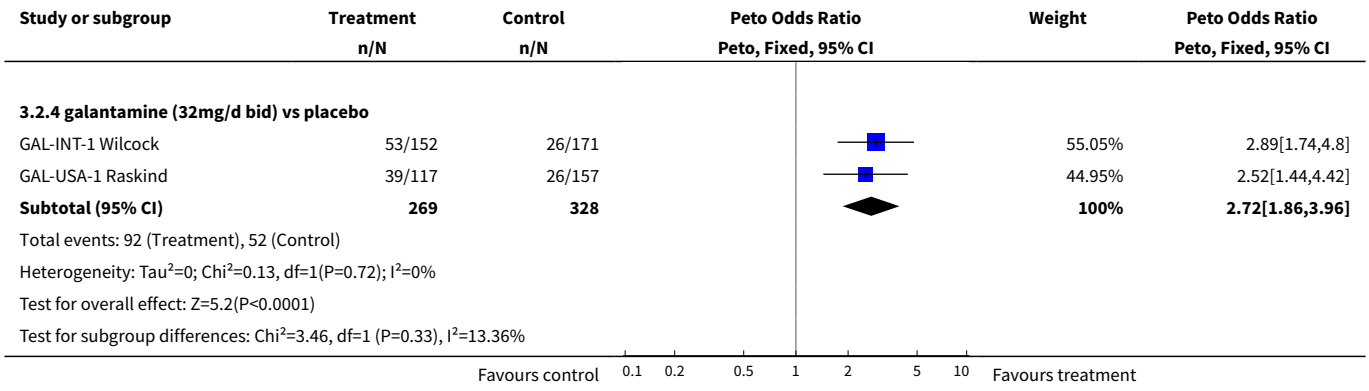
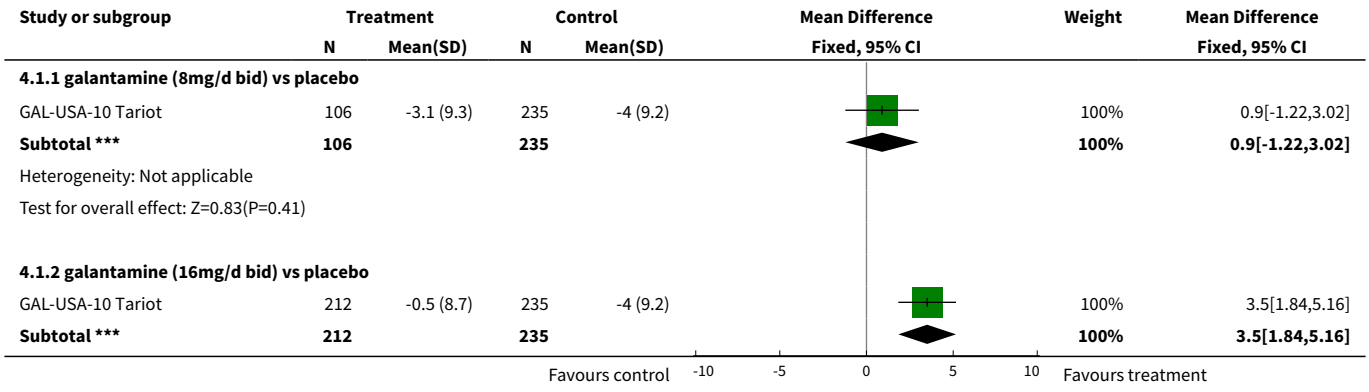


Comparison 4. ADCS-ADL (Change from baseline) OC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADCS/ADL (Change from baseline at 6 months) OC	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 galantamine (8mg/d bid) vs placebo	1	341	Mean Difference (IV, Fixed, 95% CI)	0.90 [-1.22, 3.02]
1.2 galantamine (16mg/d bid) vs placebo	1	447	Mean Difference (IV, Fixed, 95% CI)	3.50 [1.84, 5.16]
1.3 galantamine (16-24mg/d bid) vs placebo	1	500	Mean Difference (IV, Fixed, 95% CI)	1.4 [-1.09, 3.89]
1.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	503	Mean Difference (IV, Fixed, 95% CI)	2.4 [0.80, 4.00]
1.5 galantamine (24mg/d bid) vs placebo	1	447	Mean Difference (IV, Fixed, 95% CI)	2.4 [0.74, 4.06]

Analysis 4.1. Comparison 4 ADCS-ADL (Change from baseline) OC, Outcome 1 ADCS/ADL (Change from baseline at 6 months) OC.



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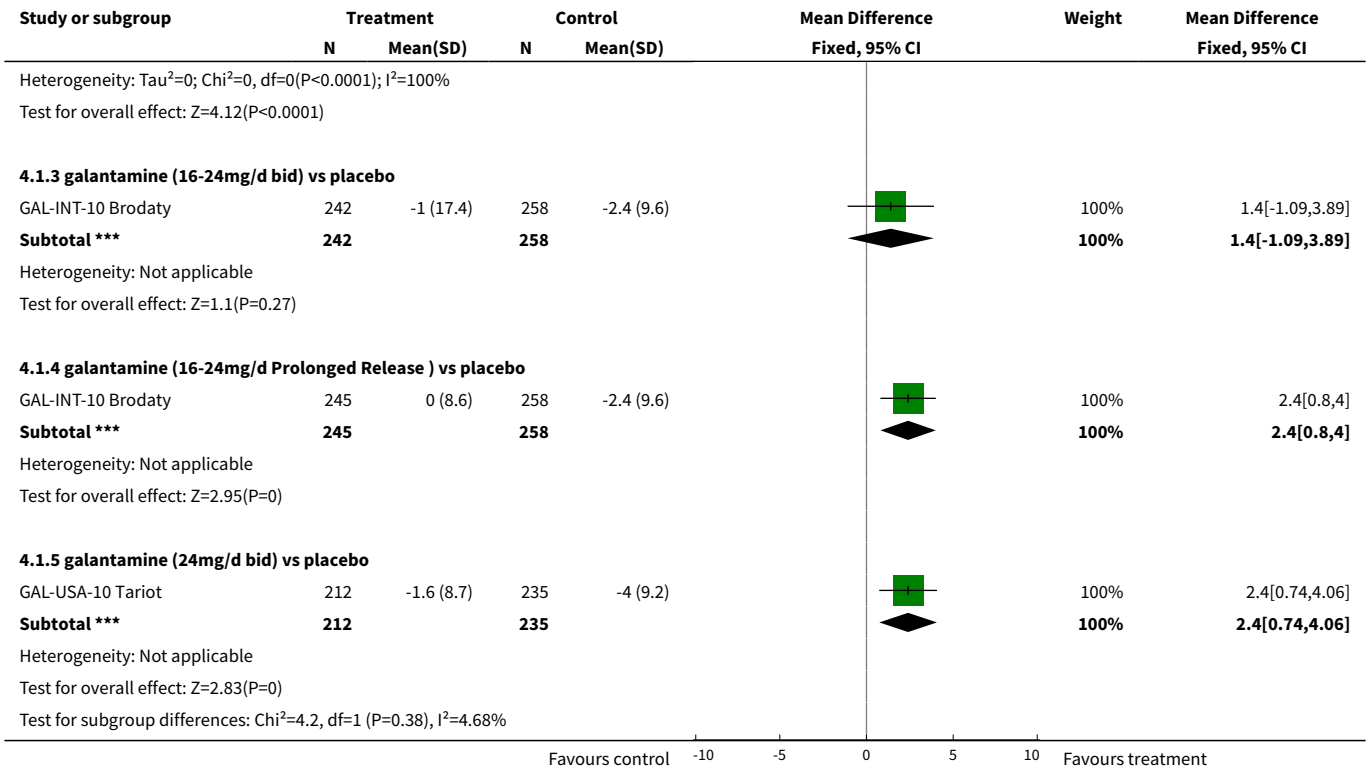

Comparison 5. NPI (Change from baseline) OC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NPI (Change from baseline at 3 months) OC	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 galantamine (24-32 mg/d bid or tid) vs placebo	1	282	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-4.07, 2.67]
2 NPI (Change from baseline at 6 months) OC	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 galantamine (8mg/d bid) vs placebo	1	340	Mean Difference (IV, Fixed, 95% CI)	0.0 [-2.55, 2.55]
2.2 galantamine (16mg/d bid) vs placebo	1	445	Mean Difference (IV, Fixed, 95% CI)	-2.4 [-4.48, -0.32]
2.3 galantamine (16-24mg/d bid) vs placebo	1	500	Mean Difference (IV, Fixed, 95% CI)	-1.3 [-3.59, 0.99]
2.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	503	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-2.80, 1.40]
2.5 galantamine (24mg/d bid) vs placebo	2	677	Mean Difference (IV, Fixed, 95% CI)	-2.09 [-3.84, -0.34]

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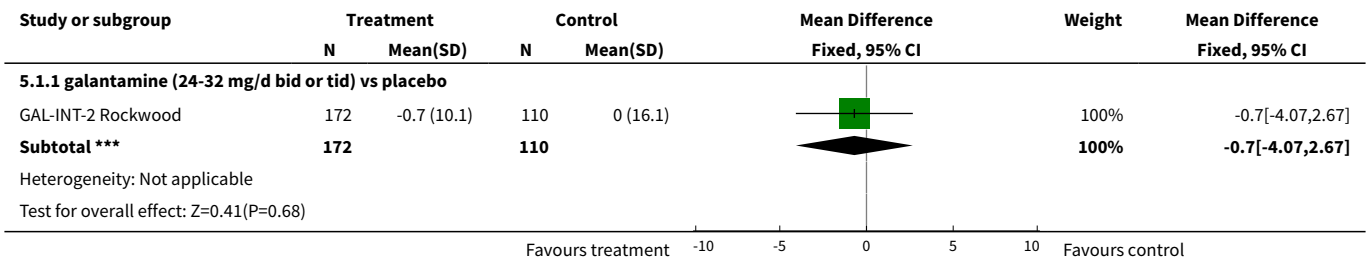
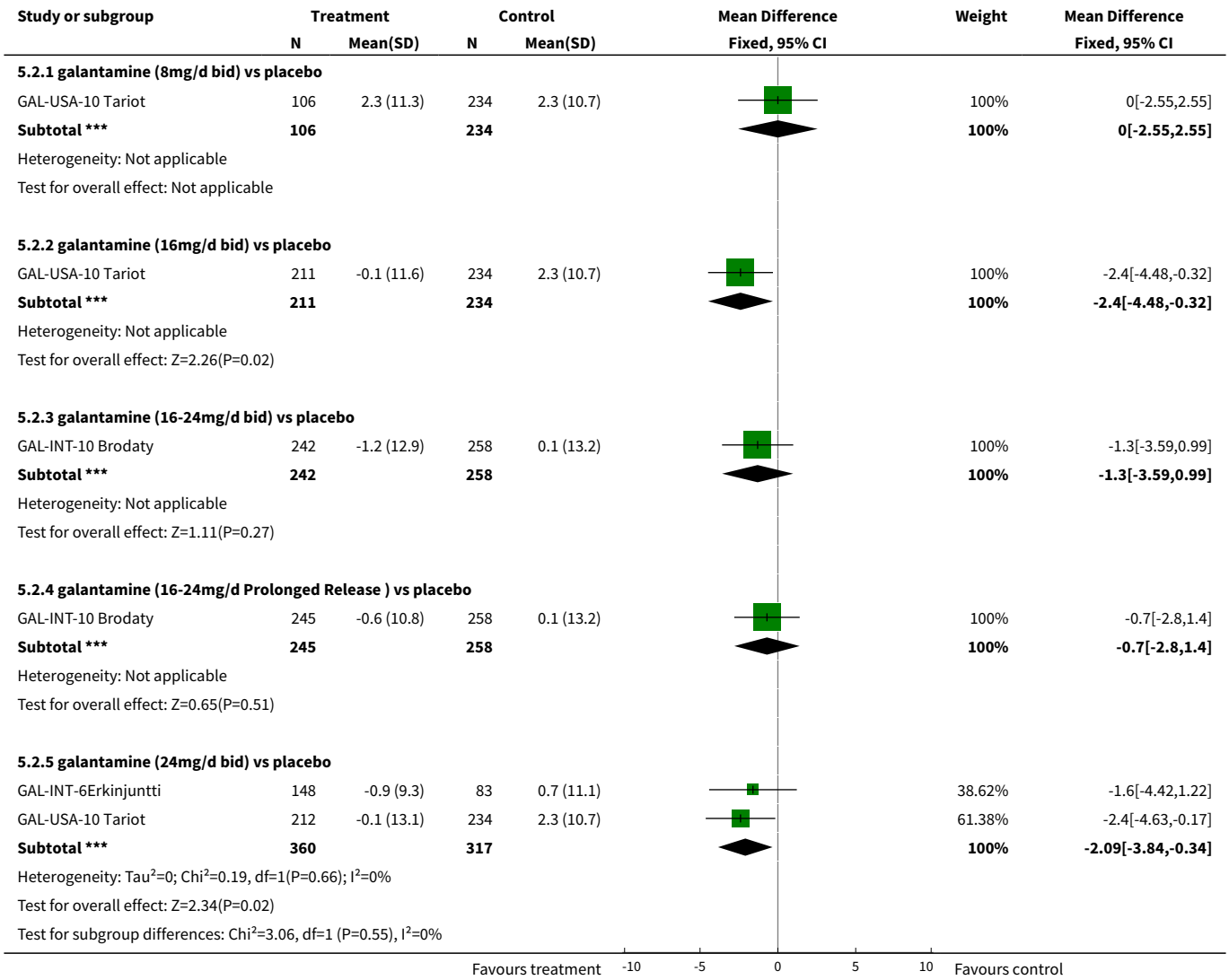
Analysis 5.1. Comparison 5 NPI (Change from baseline) OC, Outcome 1 NPI (Change from baseline at 3 months) OC.



Analysis 5.2. Comparison 5 NPI (Change from baseline) OC, Outcome 2 NPI (Change from baseline at 6 months) OC.



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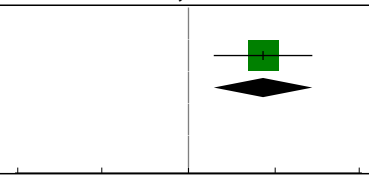
Comparison 6. DAD (Change from baseline) OC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAD (Change from baseline at 3 months) OC	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 galantamine (24-32 mg/d bid or tid) vs placebo	1	282	Mean Difference (IV, Fixed, 95% CI)	4.3 [1.46, 7.14]
2 DAD (Change from baseline at 6 months) OC	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 galantamine (24mg/d bid) vs placebo	2	575	Mean Difference (IV, Fixed, 95% CI)	3.87 [1.34, 6.39]
2.2 galantamine (32mg/d bid) vs placebo	1	334	Mean Difference (IV, Fixed, 95% CI)	3.80 [0.29, 7.31]

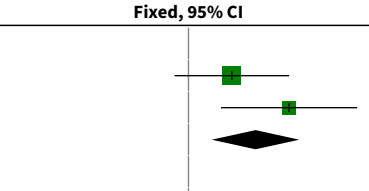
Analysis 6.1. Comparison 6 DAD (Change from baseline) OC, Outcome 1 DAD (Change from baseline at 3 months) OC.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.1.1 galantamine (24-32 mg/d bid or tid) vs placebo							
GAL-INT-2 Rockwood	172	0.1 (11.4)	110	-4.2 (12.2)		100%	4.3[1.46,7.14]
Subtotal ***	**172**		**110**			**100%**	**4.3[1.46,7.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.96(P=0)							



Analysis 6.2. Comparison 6 DAD (Change from baseline) OC, Outcome 2 DAD (Change from baseline at 6 months) OC.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.2.1 galantamine (24mg/d bid) vs placebo							
GAL-INT-1 Wilcock	159	-2.7 (14.8)	177	-5.2 (16.1)		58.59%	2.5[-0.8,5.8]
GAL-INT-6Erkinjuntti	153	-0.6 (15.2)	86	-6.4 (14.7)		41.41%	5.8[1.88,9.72]
Subtotal ***	**312**		**263**			**100%**	**3.87[1.34,6.39]**
Heterogeneity: Tau^2=0; Chi^2=1.59, df=1(P=0.21); I^2=37.19%							
Test for overall effect: Z=3(P=0)							
6.2.2 galantamine (32mg/d bid) vs placebo							
GAL-INT-1 Wilcock	157	-1.4 (16.5)	177	-5.2 (16.1)		100%	3.8[0.29,7.31]
Subtotal ***	**157**		**177**			**100%**	**3.8[0.29,7.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.12(P=0.03)							
Test for subgroup differences: Chi^2=0, df=1 (P=0.98), I^2=0%							



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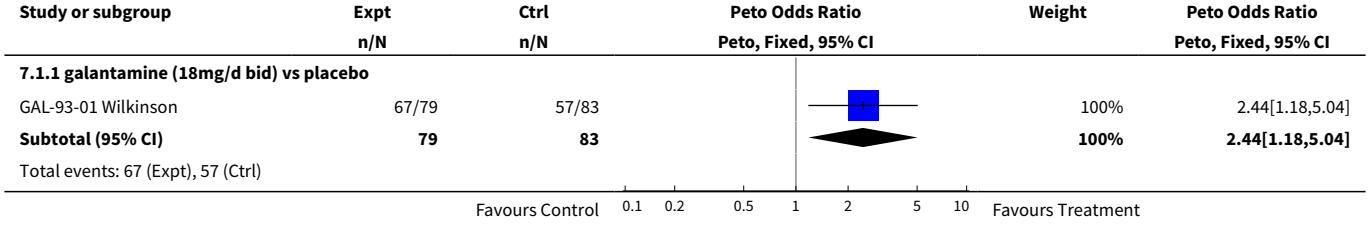
Comparison 7. Global Rating ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global Rating (no change or improvement at 3 months) ITT	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 galantamine (18mg/d bid) vs placebo	1	162	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.44 [1.18, 5.04]
1.2 galantamine (24mg/d bid) vs placebo	1	136	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.11 [0.96, 4.62]
1.3 galantamine (24-32 mg/d bid or tid) vs placebo	1	363	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.92, 2.37]
1.4 galantamine (36mg/d bid) vs placebo	1	130	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.70 [1.18, 6.17]
2 Global Rating (no change or improvement at 6 months) ITT	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 galantamine (8mg/d bid) vs placebo	1	391	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.77, 1.78]
2.2 galantamine (16mg/d bid) vs placebo	1	517	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.04 [1.44, 2.89]
2.3 galantamine (16-24mg/d bid) vs placebo	1	603	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.92, 1.76]
2.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	592	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.86, 1.66]
2.5 galantamine (24mg/d bid) vs placebo	4	1570	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.90 [1.55, 2.33]
2.6 galantamine (32mg/d bid) vs placebo	2	768	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.79 [1.34, 2.38]
2.7 galantamine (32mg/d tds) vs placebo	1	525	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.89, 1.83]

Analysis 7.1. Comparison 7 Global Rating ITT, Outcome 1 Global Rating (no change or improvement at 3 months) ITT.



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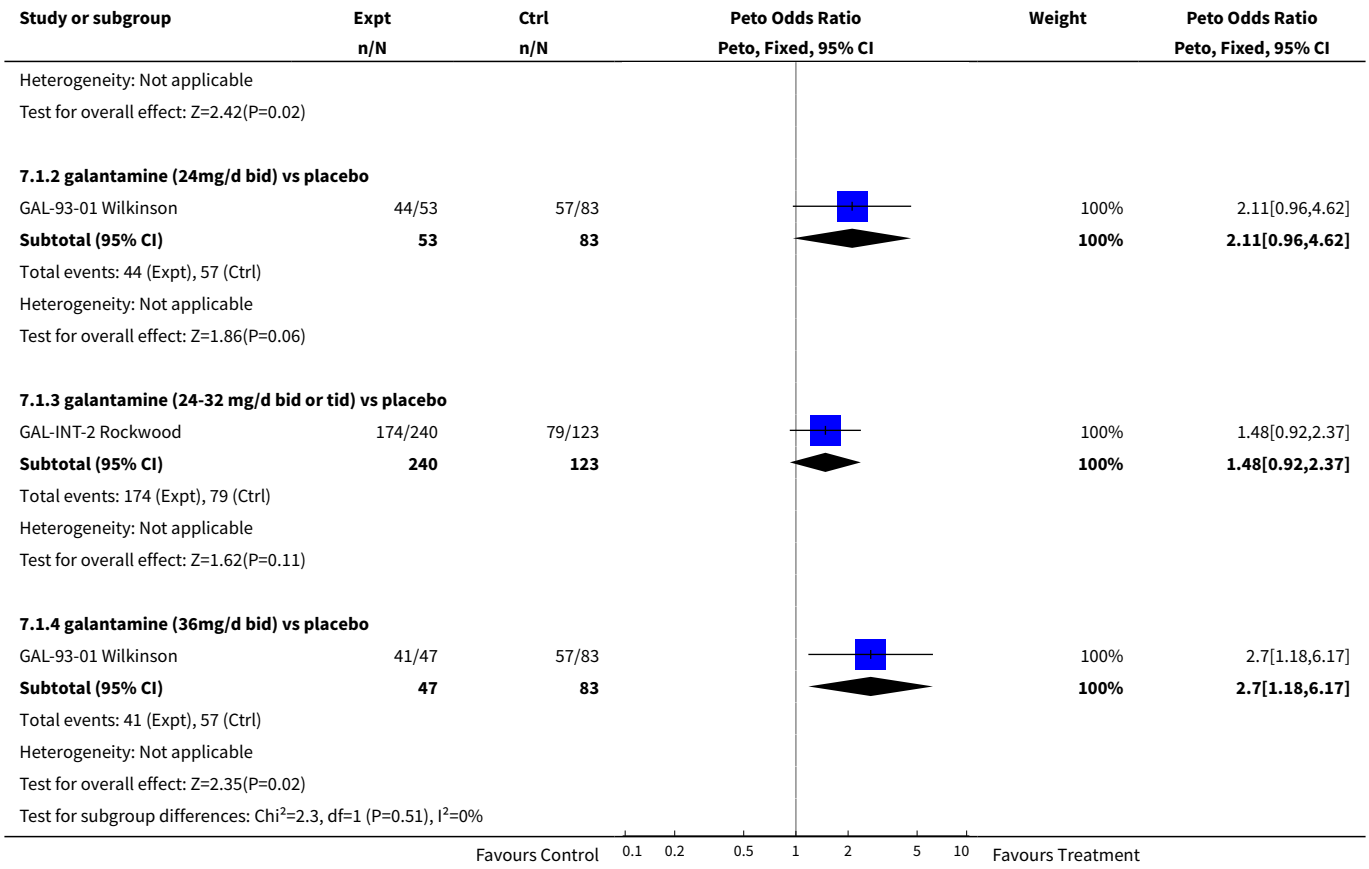
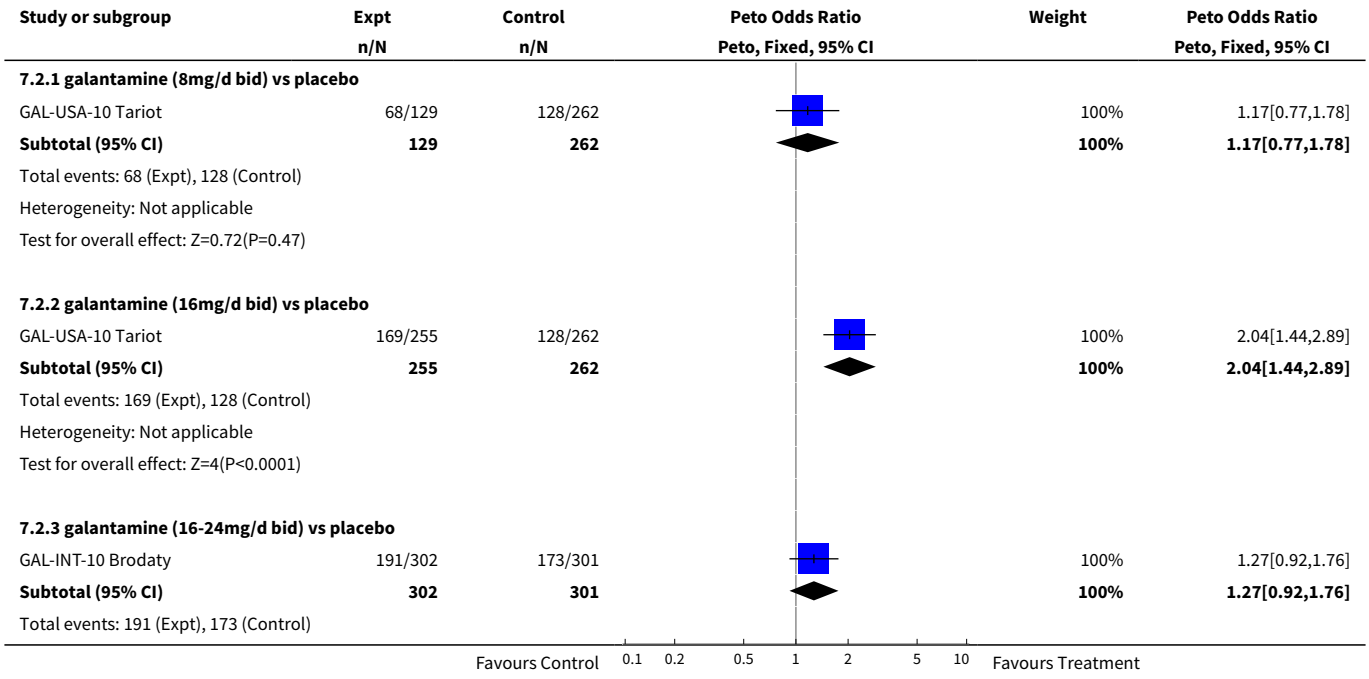


Analysis 7.2. Comparison 7 Global Rating ITT, Outcome 2 Global Rating (no change or improvement at 6 months) ITT.



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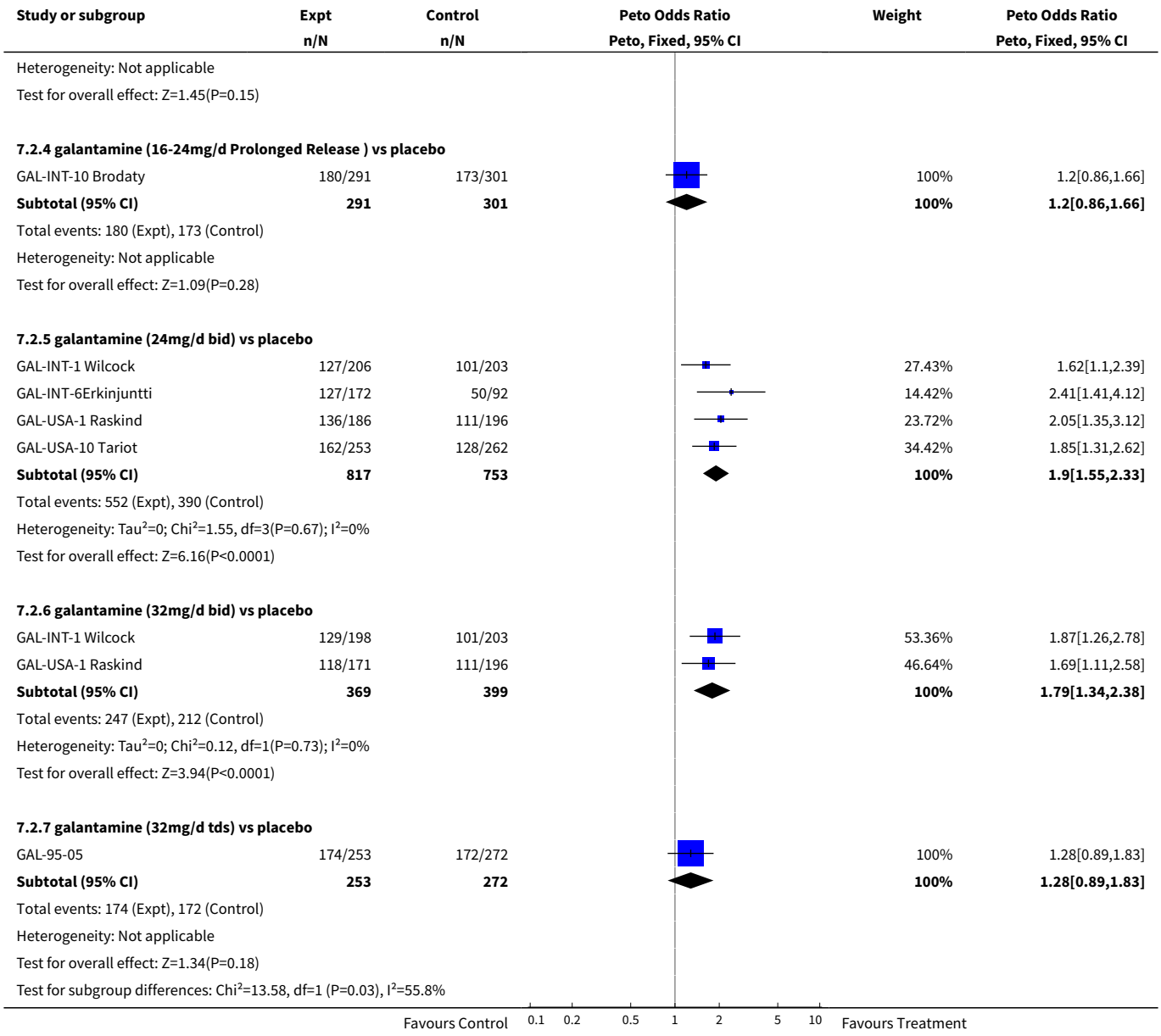

Comparison 8. ADAS-cog (Change from baseline) ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-cog (Change from baseline at 3 months) ITT	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 galantamine (18mg/d bid) vs placebo	1	163	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-3.64, 0.24]
1.2 galantamine (16-24mg/d bid) vs placebo	1	592	Mean Difference (IV, Fixed, 95% CI)	-2.7 [-3.55, -1.85]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 galantamine (16-24mg/d Prolonged Release) vs placebo	1	586	Mean Difference (IV, Fixed, 95% CI)	1.8 [0.94, 2.66]
1.4 galantamine (24mg/d bid) vs placebo	1	137	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-5.23, -0.77]
1.5 galantamine (24-32 mg/d bid or tid) vs placebo	1	359	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-2.79, -0.61]
1.6 galantamine (36mg/d bid) vs placebo	1	133	Mean Difference (IV, Fixed, 95% CI)	-2.3 [-4.24, -0.36]
2 ADAS-cog (Change from baseline at 6 months) ITT	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 galantamine (8mg/d bid) vs placebo	1	381	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-2.57, -0.03]
2.2 galantamine (16mg/d bid) vs placebo	1	508	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-4.13, -2.07]
2.3 galantamine (16-24mg/d bid) vs placebo	1	592	Mean Difference (IV, Fixed, 95% CI)	-2.8 [-3.76, -1.84]
2.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	587	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-3.39, -1.61]
2.5 galantamine (24mg/d bid) vs placebo	4	1630	Mean Difference (IV, Fixed, 95% CI)	-3.13 [-3.70, -2.55]
2.6 galantamine (32mg/d bid) vs placebo	2	825	Mean Difference (IV, Fixed, 95% CI)	-3.29 [-4.14, -2.44]
2.7 galantamine (32mg/d tds) vs placebo	1	553	Mean Difference (IV, Fixed, 95% CI)	-2.9 [-4.01, -1.79]
3 ADAS-cog (Change from baseline at 12 months in MCI) ITT	2	1903	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.62, 0.40]
3.1 galantamine (16-24mg/d bid) vs placebo in MCI	2	1903	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.62, 0.40]
4 ADAS-cog (Change from baseline at 24 months in MCI) ITT	2	1903	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.78, 0.37]
4.1 galantamine (16-24mg/d bid) vs placebo in MCI	2	1903	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.78, 0.37]

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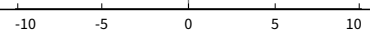
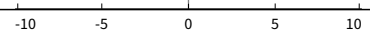
Analysis 8.1. Comparison 8 ADAS-cog (Change from baseline) ITT, Outcome 1 ADAS-cog (Change from baseline at 3 months) ITT.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.1.1 galantamine (18mg/d bid) vs placebo							
GAL-93-01 Wilkinson	81	-0.1 (6.3)	82	1.6 (6.3)		100%	-1.7[-3.64,0.24]
Subtotal ***	**81**		**82**			**100%**	**-1.7[-3.64,0.24]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.72(P=0.09)							
8.1.2 galantamine (16-24mg/d bid) vs placebo							
GAL-INT-10 Brodaty	296	-2.5 (5.2)	296	0.2 (5.3)		100%	-2.7[-3.55,-1.85]
Subtotal ***	**296**		**296**			**100%**	**-2.7[-3.55,-1.85]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6.26(P<0.0001)							
8.1.3 galantamine (16-24mg/d Prolonged Release) vs placebo							
GAL-INT-10 Brodaty	290	2 (5.3)	296	0.2 (5.3)		100%	1.8[0.94,2.66]
Subtotal ***	**290**		**296**			**100%**	**1.8[0.94,2.66]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.11(P<0.0001)							
8.1.4 galantamine (24mg/d bid) vs placebo							
GAL-93-01 Wilkinson	55	-1.4 (6.7)	82	1.6 (6.3)		100%	-3[-5.23,-0.77]
Subtotal ***	**55**		**82**			**100%**	**-3[-5.23,-0.77]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.63(P=0.01)							
8.1.5 galantamine (24-32 mg/d bid or tid) vs placebo							
GAL-INT-2 Rockwood	239	-1.1 (5.1)	120	0.6 (4.9)		100%	-1.7[-2.79,-0.61]
Subtotal ***	**239**		**120**			**100%**	**-1.7[-2.79,-0.61]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.05(P=0)							
8.1.6 galantamine (36mg/d bid) vs placebo							
GAL-93-01 Wilkinson	51	-0.7 (5)	82	1.6 (6.3)		100%	-2.3[-4.24,-0.36]
Subtotal ***	**51**		**82**			**100%**	**-2.3[-4.24,-0.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.32(P=0.02)							
Test for subgroup differences: Chi^2=63.22, df=1 (P<0.0001), I^2=92.09%							



Analysis 8.2. Comparison 8 ADAS-cog (Change from baseline) ITT, Outcome 2 ADAS-cog (Change from baseline at 6 months) ITT.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.2.1 galantamine (8mg/d bid) vs placebo							
GAL-USA-10 Tariot	126	0.4 (5.8)	255	1.7 (6.2)		100%	-1.3[-2.57,-0.03]
Subtotal ***	**126**		**255**			**100%**	**-1.3[-2.57,-0.03]**
Heterogeneity: Not applicable							



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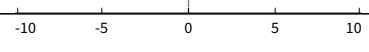
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=2(P=0.05)							
8.2.2 galantamine (16mg/d bid) vs placebo							
GAL-USA-10 Tariot	253	-1.4 (5.6)	255	1.7 (6.2)		100%	-3.1[-4.13,-2.07]
Subtotal ***	**253**		**255**			**100%**	**-3.1[-4.13,-2.07]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.91(P<0.0001)							
8.2.3 galantamine (16-24mg/d bid) vs placebo							
GAL-INT-10 Brodaty	296	-1.6 (6.2)	296	1.2 (5.7)		100%	-2.8[-3.76,-1.84]
Subtotal ***	**296**		**296**			**100%**	**-2.8[-3.76,-1.84]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.73(P<0.0001)							
8.2.4 galantamine (16-24mg/d Prolonged Release) vs placebo							
GAL-INT-10 Brodaty	291	-1.3 (5.3)	296	1.2 (5.7)		100%	-2.5[-3.39,-1.61]
Subtotal ***	**291**		**296**			**100%**	**-2.5[-3.39,-1.61]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.52(P<0.0001)							
8.2.5 galantamine (24mg/d bid) vs placebo							
GAL-INT-1 Wilcock	220	-0.5 (5.6)	215	2.4 (6)		27.61%	-2.9[-4,-1.8]
GAL-INT-6Erkinjuntti	182	-0.7 (5.7)	96	1.7 (5.4)		18.01%	-2.4[-3.76,-1.04]
GAL-USA-1 Raskind	202	-1.9 (5.1)	207	2 (6.5)		26%	-3.9[-5.03,-2.77]
GAL-USA-10 Tariot	253	-1.4 (6.2)	255	1.7 (6.2)		28.38%	-3.1[-4.18,-2.02]
Subtotal ***	**857**		**773**			**100%**	**-3.13[-3.7,-2.55]**
Heterogeneity: Tau^2=0; Chi^2=3.07, df=3(P=0.38); I^2=2.27%							
Test for overall effect: Z=10.64(P<0.0001)							
8.2.6 galantamine (32mg/d bid) vs placebo							
GAL-INT-1 Wilcock	217	-0.8 (6.3)	215	2.4 (6)		53.6%	-3.2[-4.36,-2.04]
GAL-USA-1 Raskind	197	-1.4 (6.2)	196	2 (6.5)		46.4%	-3.4[-4.65,-2.15]
Subtotal ***	**414**		**411**			**100%**	**-3.29[-4.14,-2.44]**
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%							
Test for overall effect: Z=7.57(P<0.0001)							
8.2.7 galantamine (32mg/d tds) vs placebo							
GAL-95-05	275	-0.3 (6.6)	278	2.6 (6.7)		100%	-2.9[-4.01,-1.79]
Subtotal ***	**275**		**278**			**100%**	**-2.9[-4.01,-1.79]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.13(P<0.0001)							
Test for subgroup differences: Chi^2=8.42, df=1 (P=0.21), I^2=28.72%							



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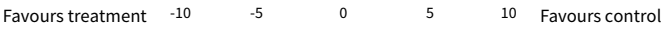
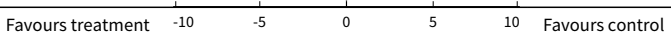
Analysis 8.3. Comparison 8 ADAS-cog (Change from baseline) ITT, Outcome 3 ADAS-cog (Change from baseline at 12 months in MCI) ITT.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.3.1 galantamine (16-24mg/d bid) vs placebo in MCI							
GAL-INT-11 DeKosky	442	-0.6 (5.6)	452	-0.3 (5.2)		52%	-0.3[-1.01,0.41]
GAL-INT-18 Winblad	498	-0.4 (5.9)	511	-0.5 (6.1)		48%	0.1[-0.64,0.84]
Subtotal ***	**940**		**963**			**100%**	**-0.11[-0.62,0.4]**
Heterogeneity: Tau^2=0; Chi^2=0.59, df=1(P=0.44); I^2=0%							
Test for overall effect: Z=0.42(P=0.68)							
Total ***	**940**		**963**			**100%**	**-0.11[-0.62,0.4]**
Heterogeneity: Tau^2=0; Chi^2=0.59, df=1(P=0.44); I^2=0%							
Test for overall effect: Z=0.42(P=0.68)							



Analysis 8.4. Comparison 8 ADAS-cog (Change from baseline) ITT, Outcome 4 ADAS-cog (Change from baseline at 24 months in MCI) ITT.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.4.1 galantamine (16-24mg/d bid) vs placebo in MCI							
GAL-INT-11 DeKosky	442	-1.2 (6.1)	452	-0.7 (6.2)		51.43%	-0.5[-1.3,0.3]
GAL-INT-18 Winblad	498	-0.6 (6.5)	511	-0.7 (6.9)		48.57%	0.1[-0.73,0.93]
Subtotal ***	**940**		**963**			**100%**	**-0.21[-0.78,0.37]**
Heterogeneity: Tau^2=0; Chi^2=1.04, df=1(P=0.31); I^2=4.01%							
Test for overall effect: Z=0.71(P=0.48)							
Total ***	**940**		**963**			**100%**	**-0.21[-0.78,0.37]**
Heterogeneity: Tau^2=0; Chi^2=1.04, df=1(P=0.31); I^2=4.01%							
Test for overall effect: Z=0.71(P=0.48)							



Comparison 9. ADAS-cog (4 point or more improvement) ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-cog (4 points or more improvement at 3 months) OC	1	359	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [0.90, 2.39]

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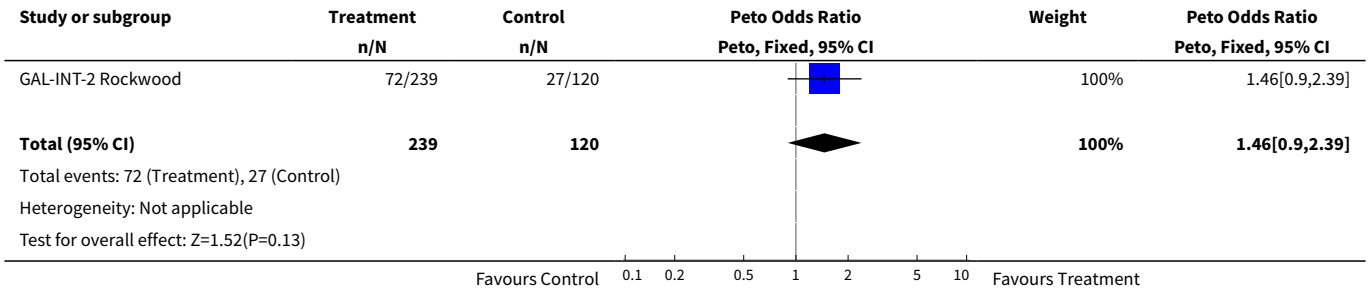
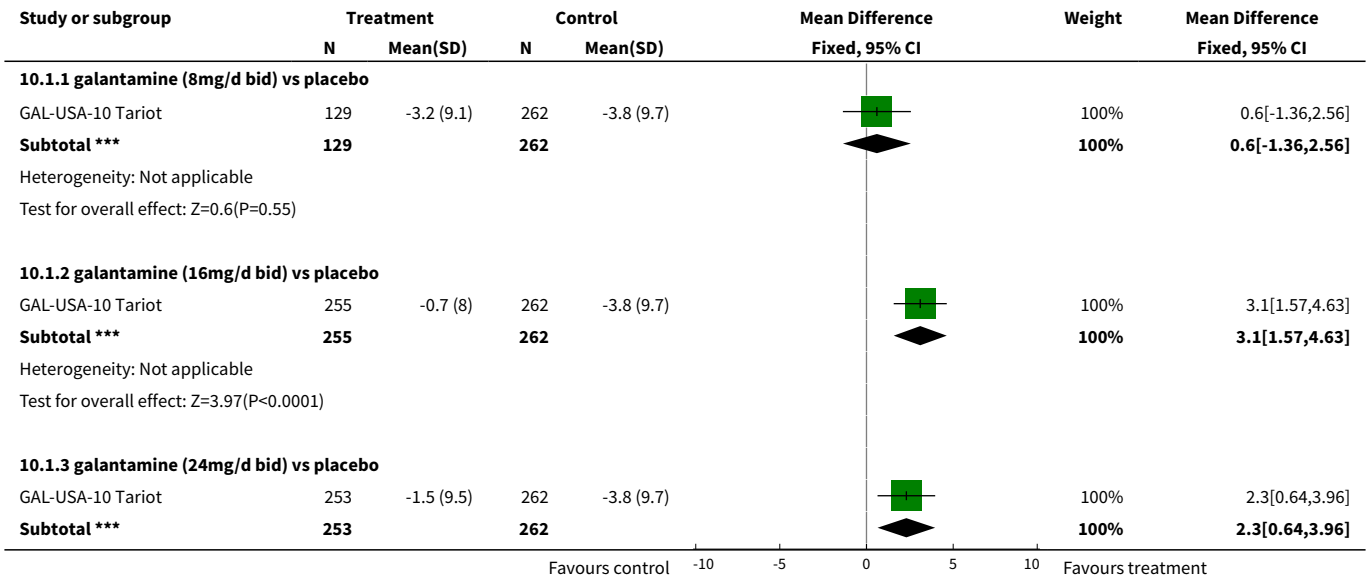
Analysis 9.1. Comparison 9 ADAS-cog (4 point or more improvement) ITT, Outcome 1 ADAS-cog (4 points or more improvement at 3 months) OC.



Comparison 10. ADCS-ADL (Change from baseline) ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADCS/ADL (Change from baseline at 6 months) ITT	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 galantamine (8mg/d bid) vs placebo	1	391	Mean Difference (IV, Fixed, 95% CI)	0.60 [-1.36, 2.56]
1.2 galantamine (16mg/d bid) vs placebo	1	517	Mean Difference (IV, Fixed, 95% CI)	3.10 [1.57, 4.63]
1.3 galantamine (24mg/d bid) vs placebo	1	515	Mean Difference (IV, Fixed, 95% CI)	2.3 [0.64, 3.96]

Analysis 10.1. Comparison 10 ADCS-ADL (Change from baseline) ITT, Outcome 1 ADCS/ADL (Change from baseline at 6 months) ITT.



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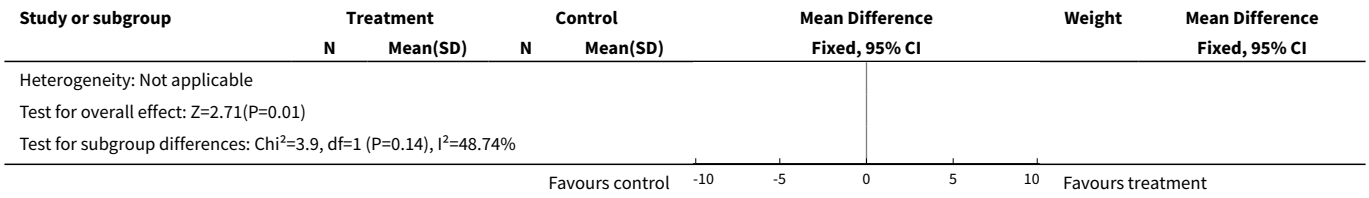
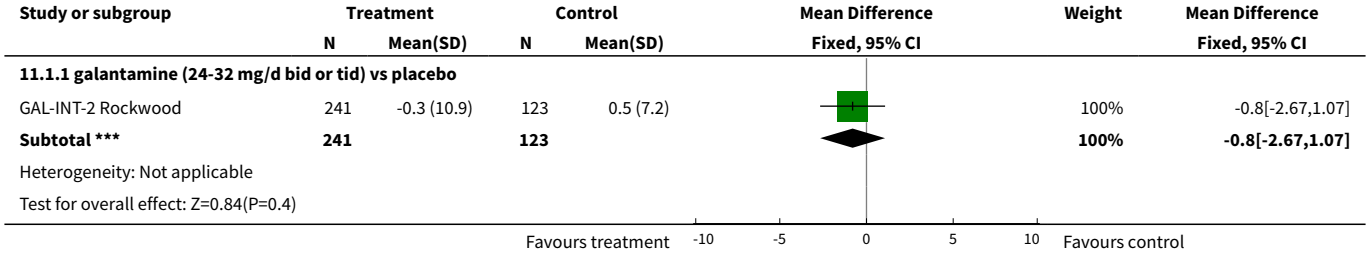


Comparison 11. NPI (Change from baseline) ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NPI (Change from baseline at 3 months) ITT	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 galantamine (24-32 mg/d bid or tid) vs placebo	1	364	Mean Difference (IV, Fixed, 95% CI)	-0.8 [-2.67, 1.07]
2 NPI (Change from baseline at 6 months) ITT	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 galantamine (8mg/d bid) vs placebo	1	391	Mean Difference (IV, Fixed, 95% CI)	0.30 [-2.09, 2.69]
2.2 galantamine (16mg/d bid) vs placebo	1	517	Mean Difference (IV, Fixed, 95% CI)	-2.1 [-4.04, -0.16]
2.3 galantamine (24mg/d bid) vs placebo	2	788	Mean Difference (IV, Fixed, 95% CI)	-1.49 [-3.11, 0.13]

Analysis 11.1. Comparison 11 NPI (Change from baseline) ITT, Outcome 1 NPI (Change from baseline at 3 months) ITT.



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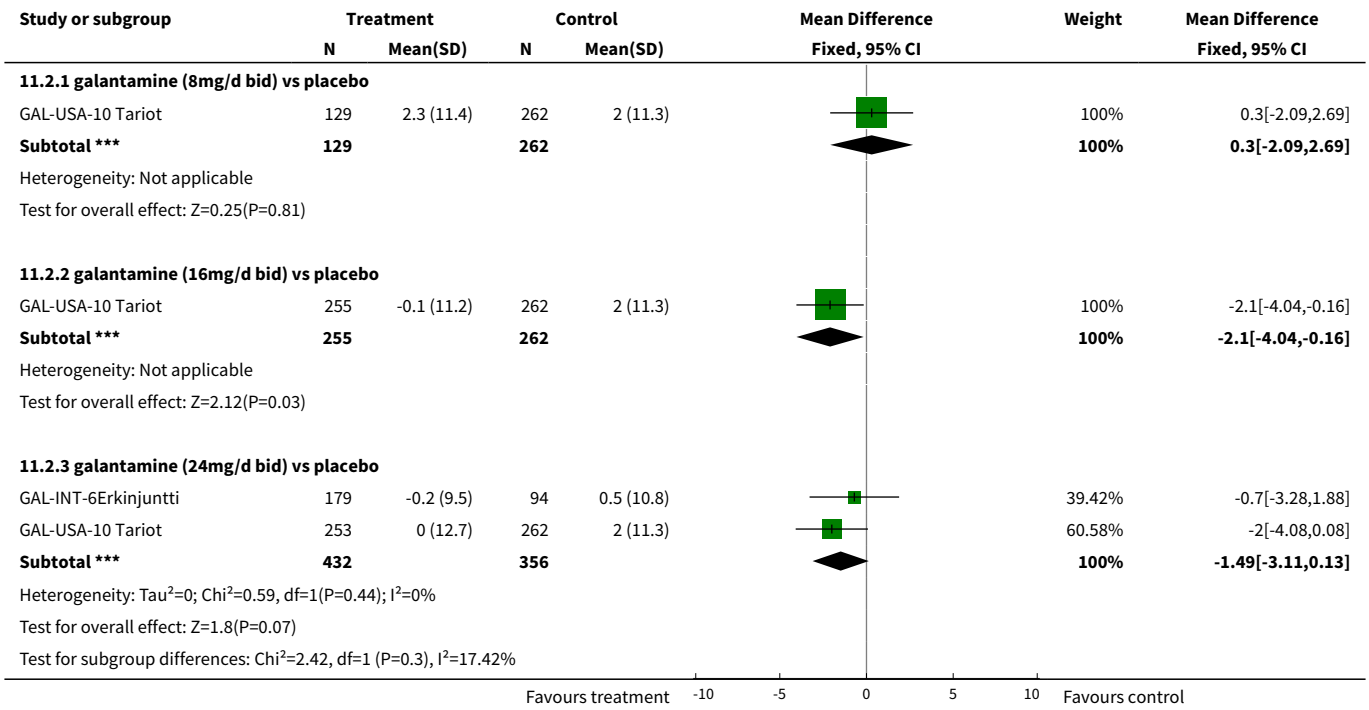
Analysis 11.2. Comparison 11 NPI (Change from baseline) ITT, Outcome 2 NPI (Change from baseline at 6 months) ITT.



Comparison 12. DAD (Change from baseline) ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAD (Change from baseline at 3 months) ITT	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 galantamine (24-32 mg/d bid or tid) vs placebo	1	364	Mean Difference (IV, Fixed, 95% CI)	4.8 [2.05, 7.55]
2 DAD (Change from baseline at 6 months) ITT	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 galantamine (24mg/d bid) vs placebo	2	701	Mean Difference (IV, Fixed, 95% CI)	3.66 [1.41, 5.90]
2.2 galantamine (32mg/d bid) vs placebo	1	424	Mean Difference (IV, Fixed, 95% CI)	3.5 [0.52, 6.48]

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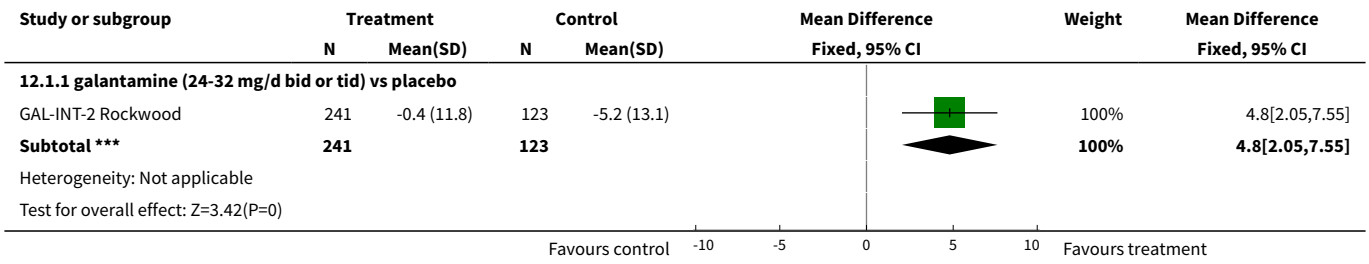
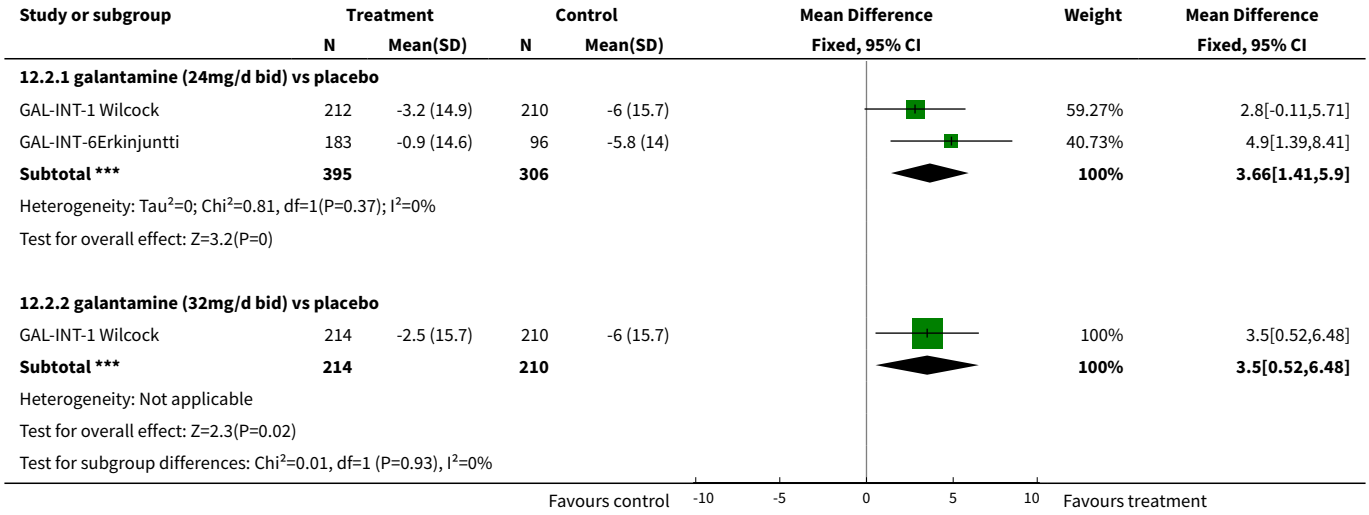
Analysis 12.1. Comparison 12 DAD (Change from baseline) ITT, Outcome 1 DAD (Change from baseline at 3 months) ITT.



Analysis 12.2. Comparison 12 DAD (Change from baseline) ITT, Outcome 2 DAD (Change from baseline at 6 months) ITT.



Comparison 13. Global Rating dose analyses OC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global Rating (no change or improvement; 8 mg) OC	1	340	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.71, 1.79]
2 Global Rating (no change or improvement 16-24mg/d) OC	3	1079	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.63 [1.28, 2.09]
3 Global Rating (no change or improvement 24mg/d to 24-32mg/d) OC	6	1713	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.06 [1.69, 2.52]
4 Global Rating (no change or improvement 32-36mg/d) OC	4	1123	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [1.35, 2.20]

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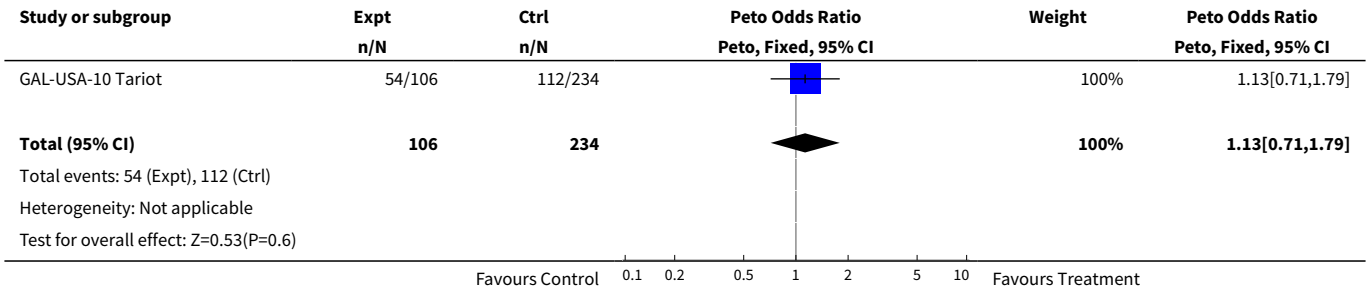
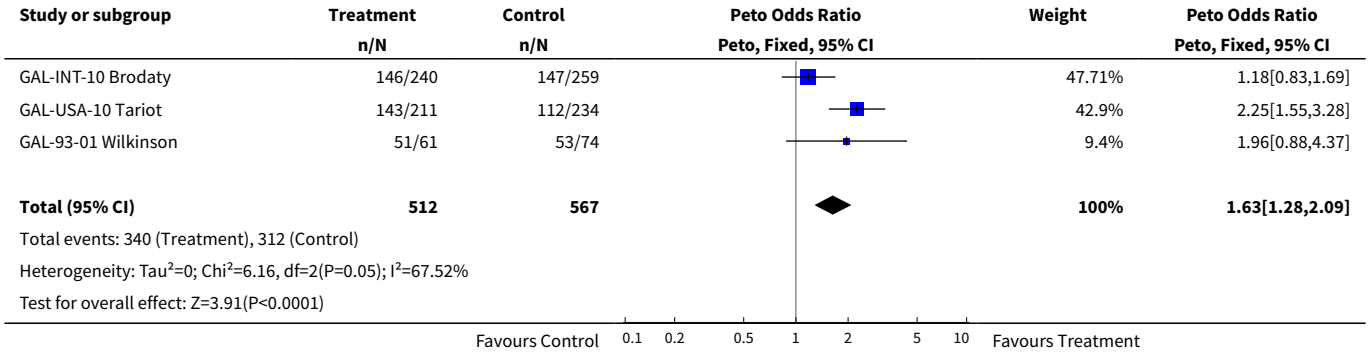
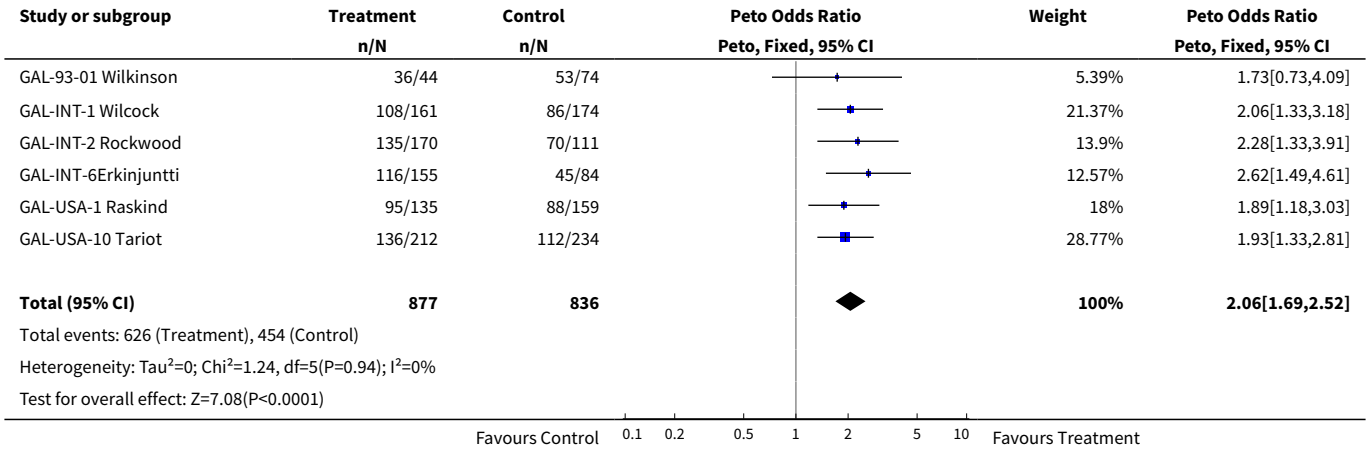
Analysis 13.1. Comparison 13 Global Rating dose analyses OC, Outcome 1 Global Rating (no change or improvement; 8 mg) OC.



Analysis 13.2. Comparison 13 Global Rating dose analyses OC, Outcome 2 Global Rating (no change or improvement 16-24mg/d) OC.



Analysis 13.3. Comparison 13 Global Rating dose analyses OC, Outcome 3 Global Rating (no change or improvement 24mg/d to 24-32mg/d) OC.



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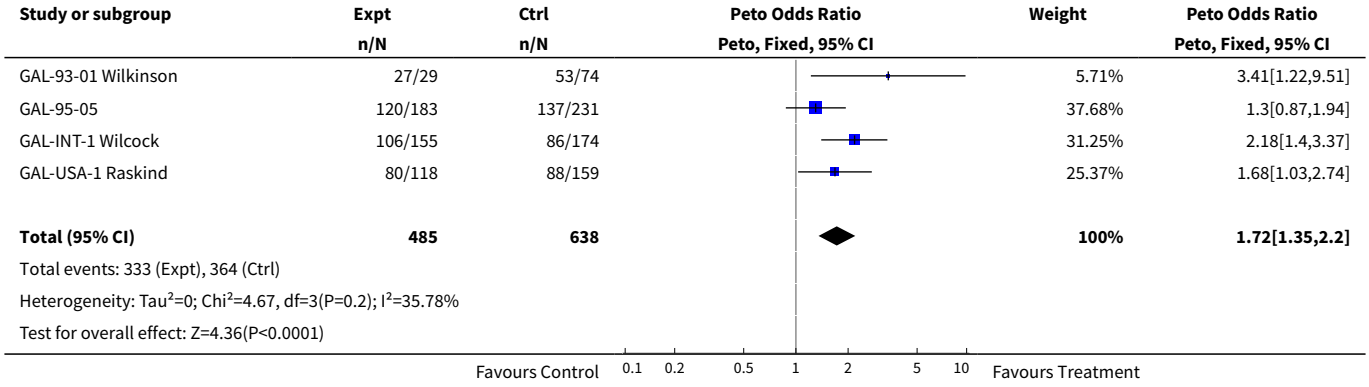
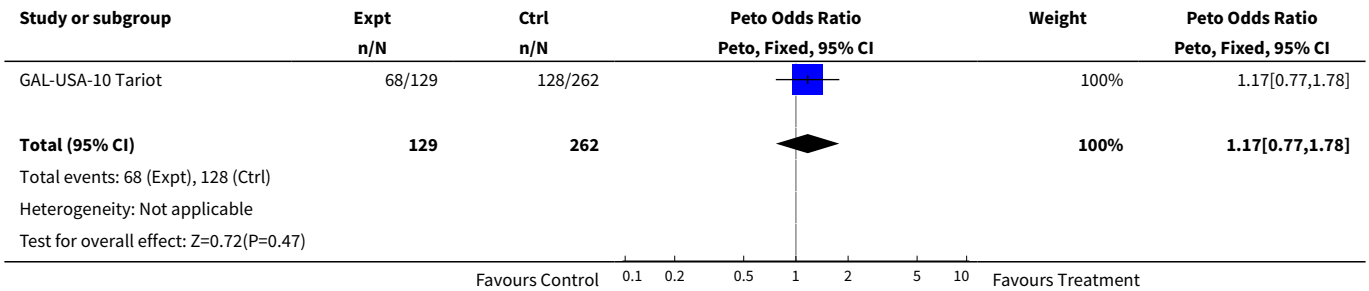
Analysis 13.4. Comparison 13 Global Rating dose analyses OC, Outcome 4 Global Rating (no change or improvement 32-36mg/d) OC.



Comparison 14. Global Rating dose analyses ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global Rating (no change or improvement; 8 mg) ITT	1	391	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.77, 1.78]
2 Global Rating (no change or improvement 16-24mg/d) ITT	3	1282	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [1.32, 2.07]
3 Global Rating (no change or improvement 24mg/d to 24-32mg/d) ITT	6	2069	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.84 [1.53, 2.21]
4 Global Rating (no change or improvement 32-36mg/d) ITT	4	1423	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.63 [1.31, 2.02]

Analysis 14.1. Comparison 14 Global Rating dose analyses ITT, Outcome 1 Global Rating (no change or improvement; 8 mg) ITT.



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Analysis 14.2. Comparison 14 Global Rating dose analyses ITT, Outcome 2 Global Rating (no change or improvement 16-24mg/d) ITT.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
GAL-93-01 Wilkinson	67/79	57/83		9.74%	2.44[1.18,5.04]
GAL-INT-10 Brodaty	191/302	173/301		48.11%	1.27[0.92,1.76]
GAL-USA-10 Tariot	169/255	128/262		42.15%	2.04[1.44,2.89]
Total (95% CI)	**636**	**646**		**100%**	**1.65[1.32,2.07]**
Total events: 427 (Treatment), 358 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.97, df=2(P=0.08); I^2=59.75%					
Test for overall effect: Z=4.36(P<0.0001)					

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Analysis 14.3. Comparison 14 Global Rating dose analyses ITT, Outcome 3 Global Rating (no change or improvement 24mg/d to 24-32mg/d) ITT.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
GAL-93-01 Wilkinson	44/53	57/83		5.39%	2.11[0.96,4.62]
GAL-INT-1 Wilcock	127/206	101/203		21.87%	1.62[1.1,2.39]
GAL-INT-2 Rockwood	174/240	79/123		14.9%	1.48[0.92,2.37]
GAL-INT-6Erkinjuntti	127/172	50/92		11.5%	2.41[1.41,4.12]
GAL-USA-1 Raskind	136/186	111/196		18.91%	2.05[1.35,3.12]
GAL-USA-10 Tariot	162/253	128/262		27.44%	1.85[1.31,2.62]
Total (95% CI)	**1110**	**959**		**100%**	**1.84[1.53,2.21]**
Total events: 770 (Treatment), 526 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.59, df=5(P=0.76); I^2=0%					
Test for overall effect: Z=6.55(P<0.0001)					

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Analysis 14.4. Comparison 14 Global Rating dose analyses ITT, Outcome 4 Global Rating (no change or improvement 32-36mg/d) ITT.

Study or subgroup	Expt n/N	Ctrl n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
GAL-93-01 Wilkinson	41/47	57/83		6.91%	2.7[1.18,6.17]
GAL-95-05	174/253	172/272		36.35%	1.28[0.89,1.83]
GAL-INT-1 Wilcock	129/198	101/203		30.27%	1.87[1.26,2.78]
GAL-USA-1 Raskind	118/171	111/196		26.47%	1.69[1.11,2.58]
Total (95% CI)	**669**	**754**		**100%**	**1.63[1.31,2.02]**
Total events: 462 (Expt), 441 (Ctrl)					
Heterogeneity: Tau^2=0; Chi^2=3.67, df=3(P=0.3); I^2=18.21%					
Test for overall effect: Z=4.39(P<0.0001)					

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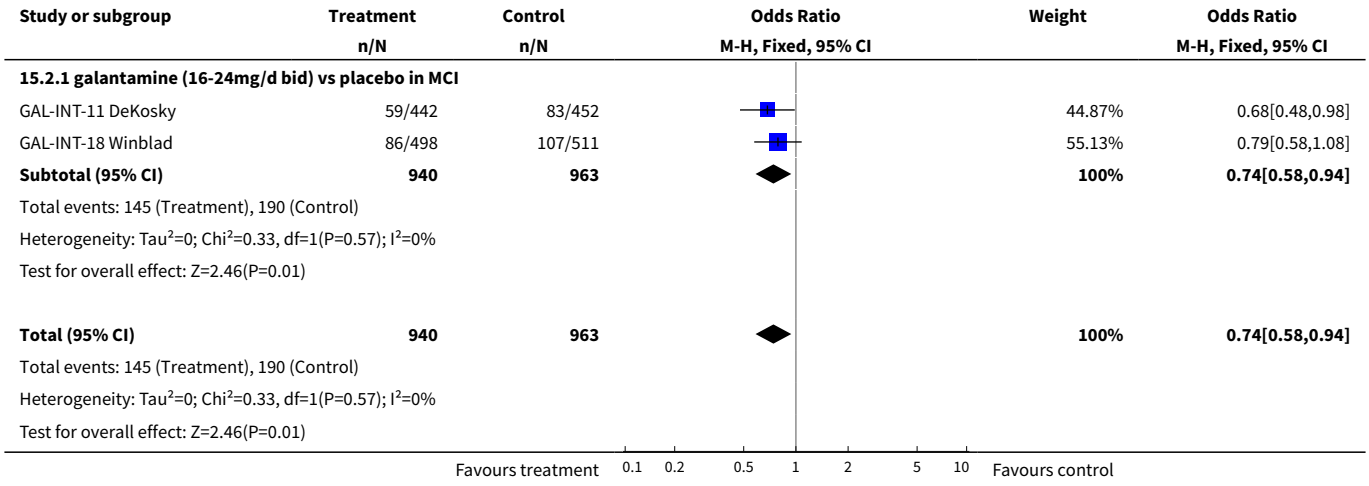
Comparison 15. Conversion from MCI to dementia (change of CDR-SB from 0.5 to >=1) ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Conversion from MCI to dementia at 24 months	2	1903	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.58, 0.94]
2.1 galantamine (16-24mg/d bid) vs placebo in MCI	2	1903	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.58, 0.94]

Analysis 15.2. Comparison 15 Conversion from MCI to dementia (change of CDR-SB from 0.5 to >=1) ITT, Outcome 2 Conversion from MCI to dementia at 24 months.



Comparison 16. Withdrawals before end of treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of all cause discontinuations (3 months)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 galantamine (18mg/d bid) vs placebo	1	175	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [1.00, 4.13]
1.2 galantamine (24mg/d bid) vs placebo	1	143	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.75 [0.75, 4.08]
1.3 galantamine (24mg/d to 24-32mg/d) vs placebo	1	386	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.42 [2.10, 5.58]
1.4 galantamine (36mg/d bid) vs placebo	1	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.79 [2.26, 10.14]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Proportion of discontinuations due to adverse events (3 months)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 galantamine (18mg/d bid) vs placebo	1	175	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.57 [1.13, 5.83]
2.2 galantamine (24mg/d bid) vs placebo	1	143	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.99 [1.03, 8.64]
2.3 galantamine (24mg/d to 24-32mg/d) vs placebo	1	386	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.11 [2.37, 7.13]
2.4 galantamine (36mg/d bid) vs placebo	1	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.26 [4.05, 21.17]
3 Proportion of all cause discontinuations (6 months)	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 galantamine (8mg/d bid) vs placebo	1	426	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [0.93, 2.65]
3.2 galantamine (16mg/d bid) vs placebo	1	565	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.94, 2.18]
3.3 galantamine (16-24mg/d bid) vs placebo	1	651	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.39 [0.95, 2.03]
3.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	640	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.84, 1.83]
3.5 galantamine (24mg/d bid) vs placebo	3	1419	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.67 [1.29, 2.17]
3.6 galantamine (32mg/d bid) vs placebo	2	857	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.55 [1.87, 3.48]
3.7 galantamine (32mg/d tds) vs placebo	1	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.36 [1.62, 3.45]
4 Proportion of discontinuations due to adverse events (6 months)	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 galantamine (8mg/d bid) vs placebo	1	426	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.41, 2.04]
4.2 galantamine (16mg/d bid) vs placebo	1	565	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.51, 1.86]
4.3 galantamine (16-24mg/d bid) vs placebo	1	651	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.62 [0.85, 3.09]
4.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	644	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [1.04, 3.59]

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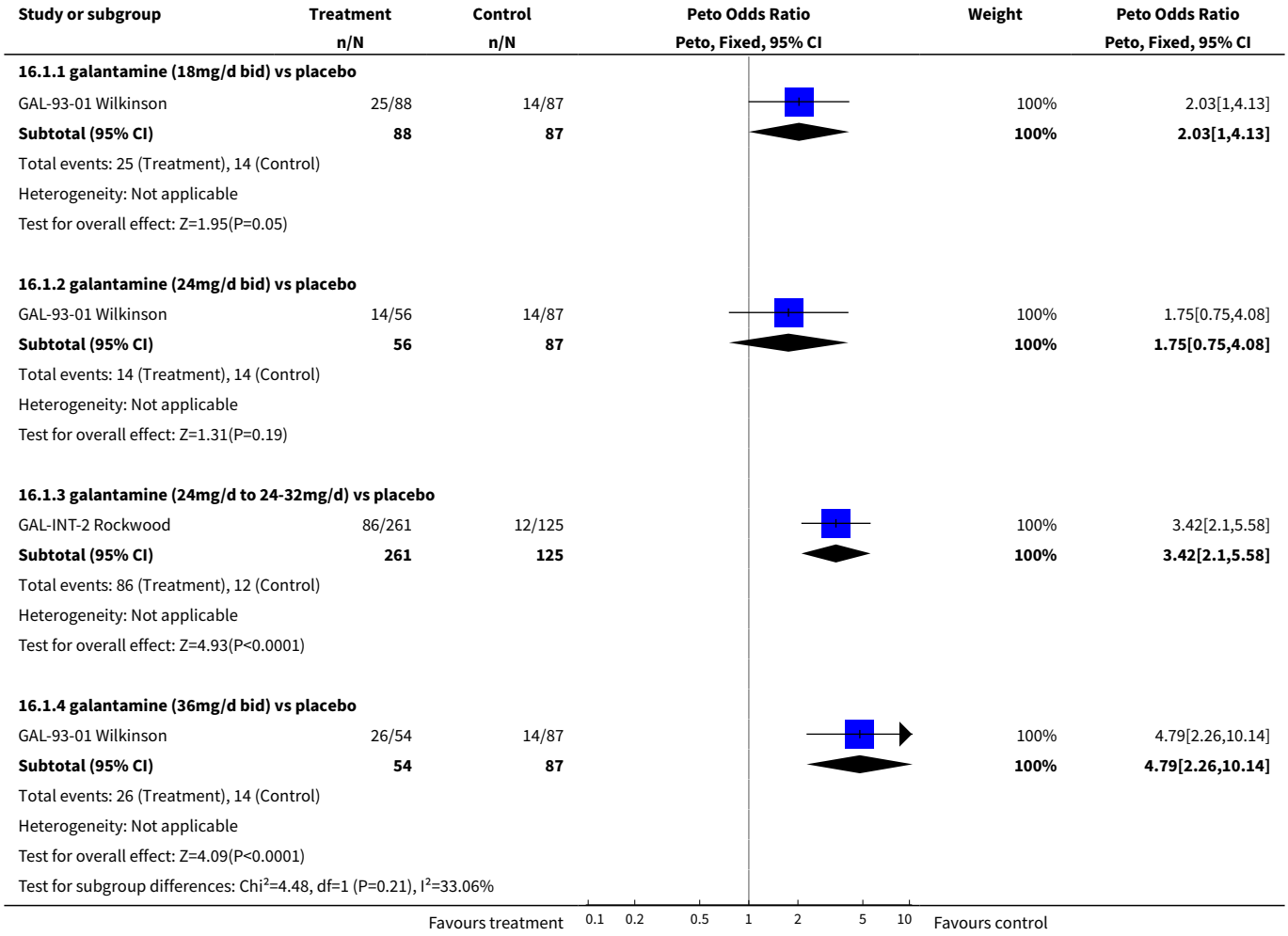
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.5 galantamine (24mg/d bid) vs placebo	3	1419	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.09 [1.51, 2.91]
4.6 galantamine (32mg/d bid) vs placebo	2	857	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.64 [2.56, 5.18]
4.7 galantamine (32mg/d tds) vs placebo	1	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.79 [1.81, 4.28]

Analysis 16.1. Comparison 16 Withdrawals before end of treatment, Outcome 1 Proportion of all cause discontinuations (3 months).



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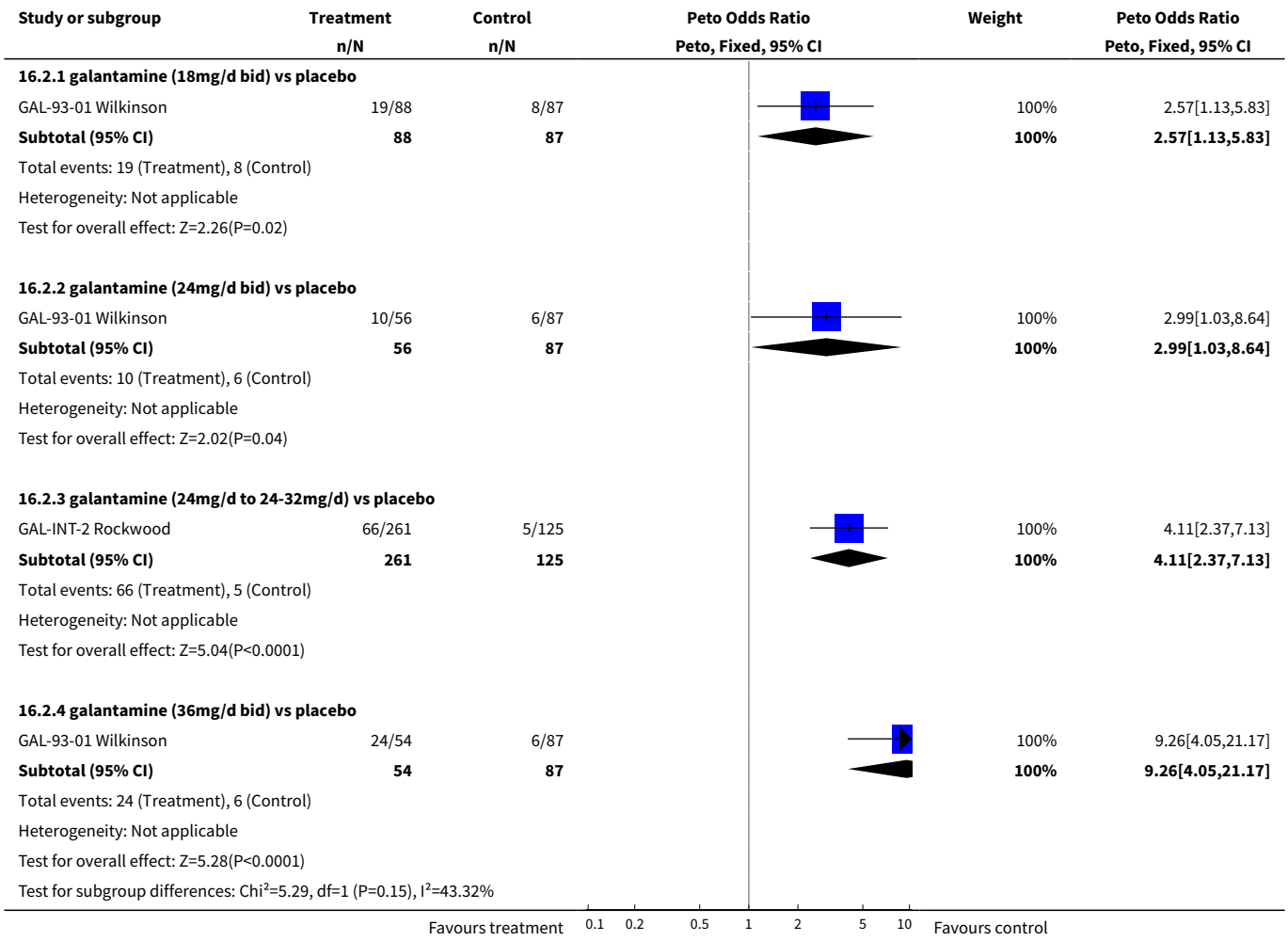
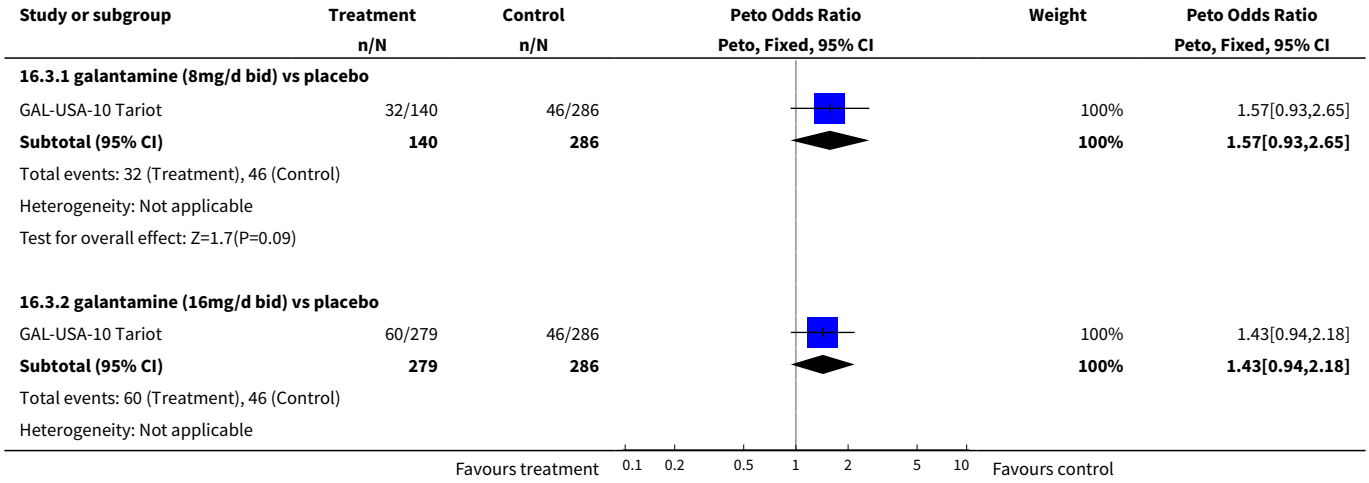
Analysis 16.2. Comparison 16 Withdrawals before end of treatment, Outcome 2 Proportion of discontinuations due to adverse events (3 months).



Analysis 16.3. Comparison 16 Withdrawals before end of treatment, Outcome 3 Proportion of all cause discontinuations (6 months).



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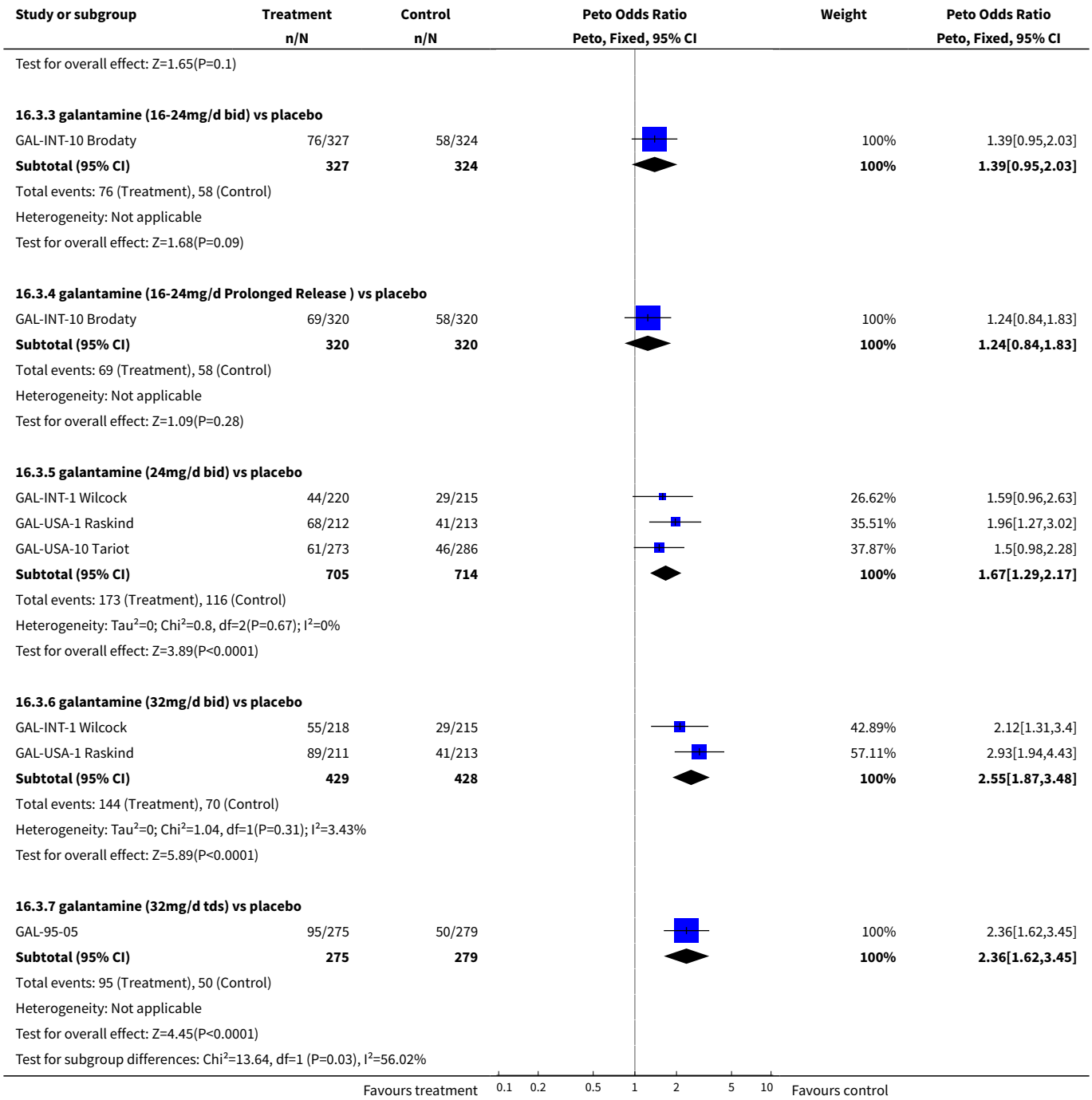
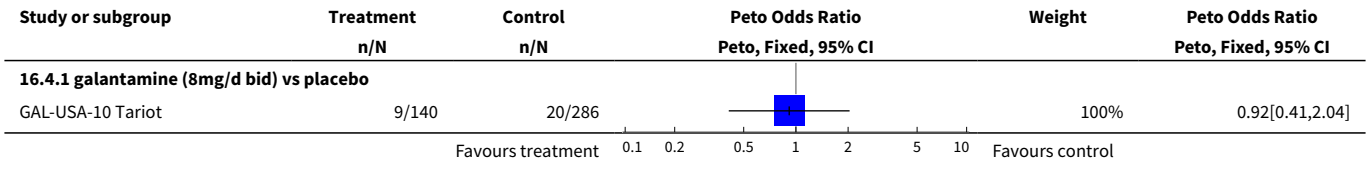


Analysis 16.4. Comparison 16 Withdrawals before end of treatment, Outcome 4 Proportion of discontinuations due to adverse events (6 months).



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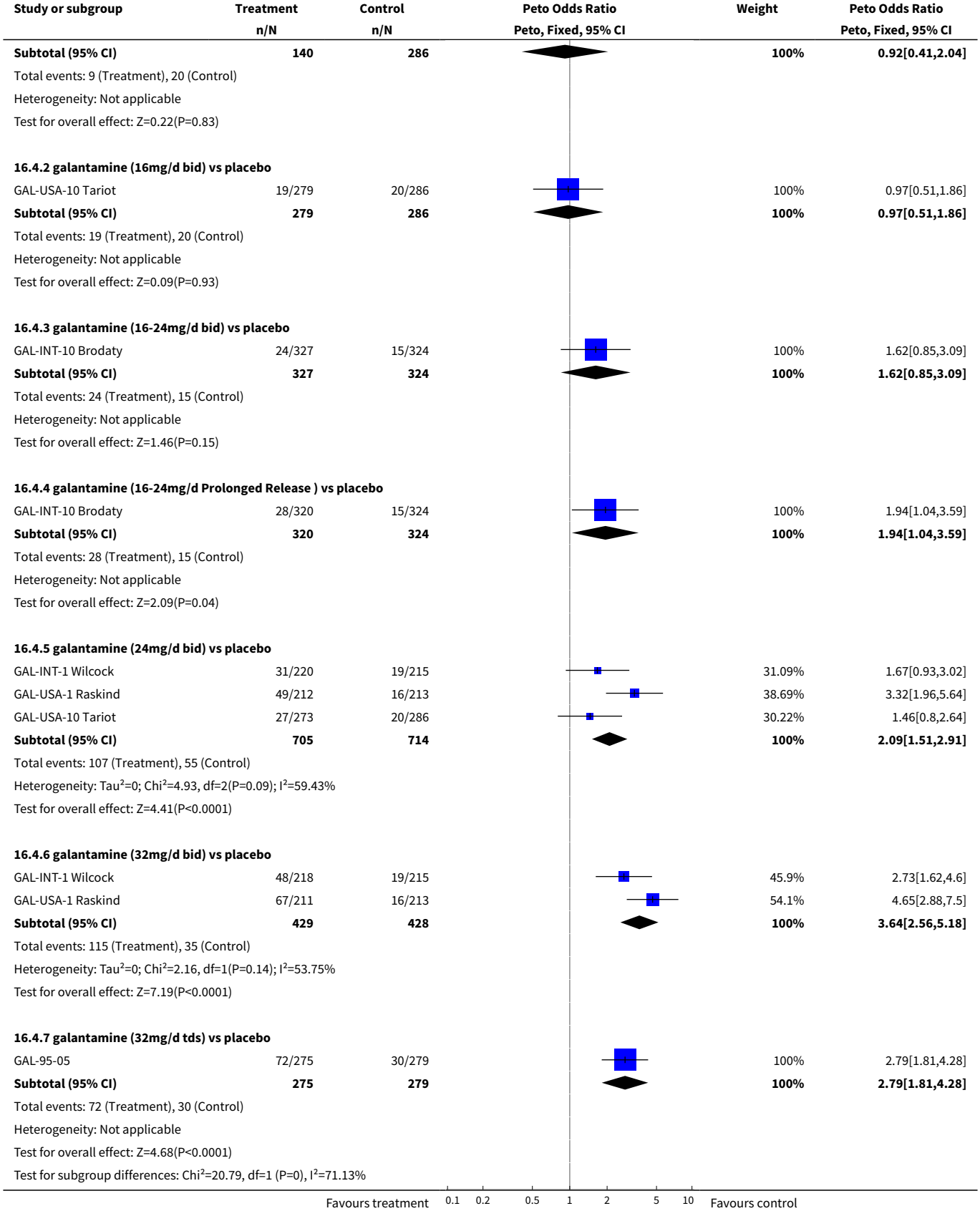

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Comparison 17. Specific adverse events (3 months)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of subjects experiencing nausea (3 months)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 galantamine (18mg/d bid) vs placebo	1	175	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.33 [1.64, 11.45]
1.2 galantamine (24-32mg/d bid) vs placebo	2	529	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.32 [2.11, 5.21]
1.4 galantamine (36mg/d bid) vs placebo	1	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	11.51 [4.61, 28.75]
2 Proportion of subjects experiencing vomiting (3 months)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 galantamine (18mg/d bid) vs placebo	1	175	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.59 [1.39, 9.29]
2.2 galantamine (24-32mg/d bid) vs placebo	2	529	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.14 [1.75, 5.63]
2.3 galantamine (36mg/d bid) vs placebo	1	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.19 [1.30, 13.48]
3 Proportion of subjects experiencing dizziness (3 months)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 galantamine (18mg/d bid) vs placebo	1	175	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.29, 6.00]
3.2 galantamine (24-32mg/d bid) vs placebo	2	529	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.60 [1.39, 4.88]
3.3 galantamine (36mg/d bid) vs placebo	1	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.30 [0.48, 10.92]
4 Proportion of subjects experiencing diarrhea (3 months)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 galantamine (18mg/d bid) vs placebo	1	175	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.14, 7.14]
4.2 galantamine (24-32mg/d bid) vs placebo	1	143	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.46 [0.40, 15.20]
4.3 galantamine (36mg/d bid) vs placebo	1	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.66 [0.22, 12.73]
5 Proportion of subjects experiencing anorexia (3 months)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

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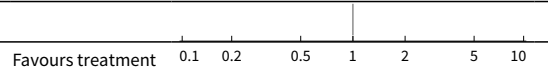
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 galantamine (24-32mg/d bid) vs placebo	1	386	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.24 [1.53, 6.88]
6 Proportion of subjects experiencing somnolence (3 months)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 galantamine (24-32mg/d bid) vs placebo	1	386	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.78 [1.48, 9.67]
7 Proportion of subjects experiencing abdominal pain (3 months)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 galantamine (24-32mg/d bid) vs placebo	1	386	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.93 [1.12, 7.66]
8 Proportion of subjects experiencing decreased appetite (3 months)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 galantamine (18mg/d bid) vs placebo	1	175	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.40 [0.53, 10.85]
8.2 galantamine (24-32mg/d bid) vs placebo	1	143	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [0.21, 12.11]
8.3 galantamine (36mg/d bid) vs placebo	1	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.47 [0.65, 18.56]
9 Proportion of subjects experiencing agitation (3 months)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 galantamine (24-32mg/d bid) vs placebo	1	386	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.54 [1.25, 9.98]
10 Proportion of subjects experiencing headache (3 months)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 galantamine (18mg/d bid) vs placebo	1	175	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.33, 4.75]
10.2 galantamine (24-32mg/d bid) vs placebo	1	143	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.54 [0.69, 9.45]
10.3 galantamine (36mg/d bid) vs placebo	1	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.80 [1.36, 16.96]

Analysis 17.1. Comparison 17 Specific adverse events (3 months), Outcome 1 Proportion of subjects experiencing nausea (3 months).

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
17.1.1 galantamine (18mg/d bid) vs placebo					



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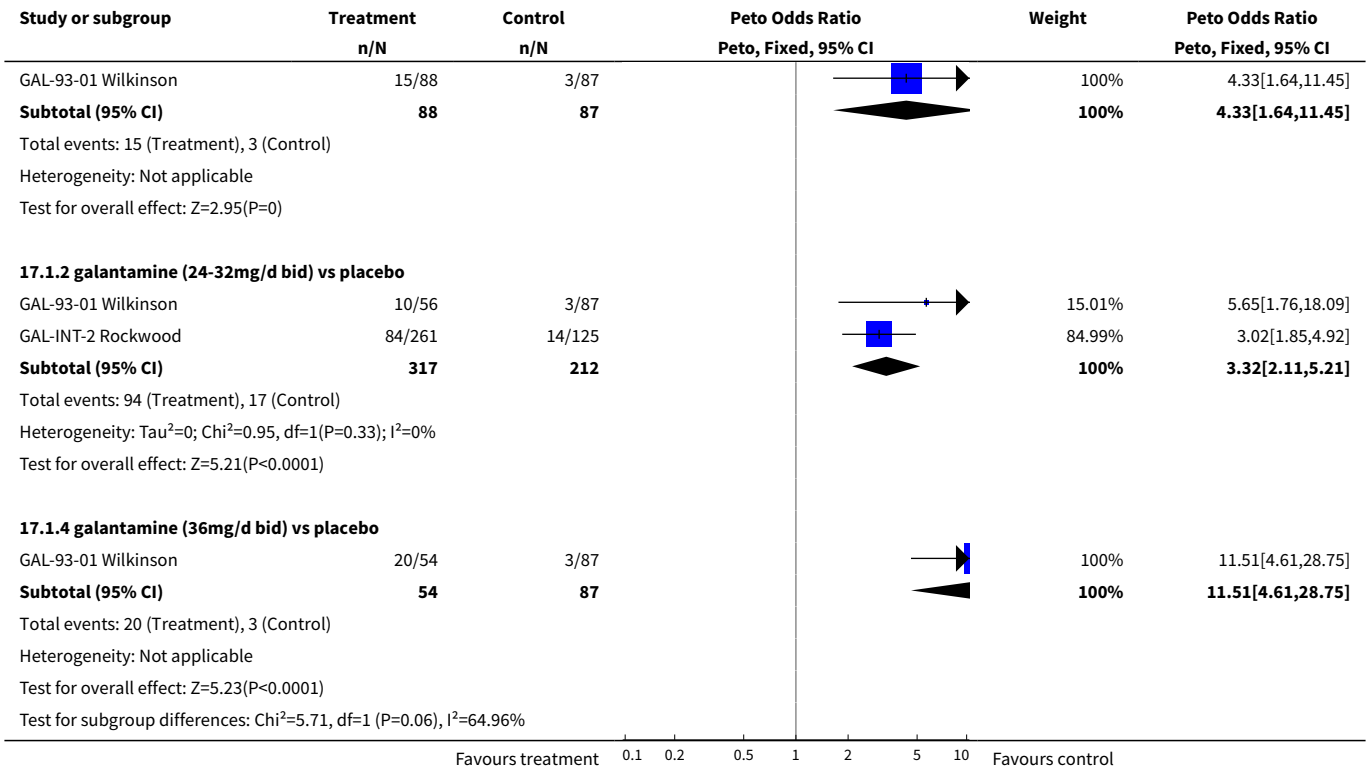
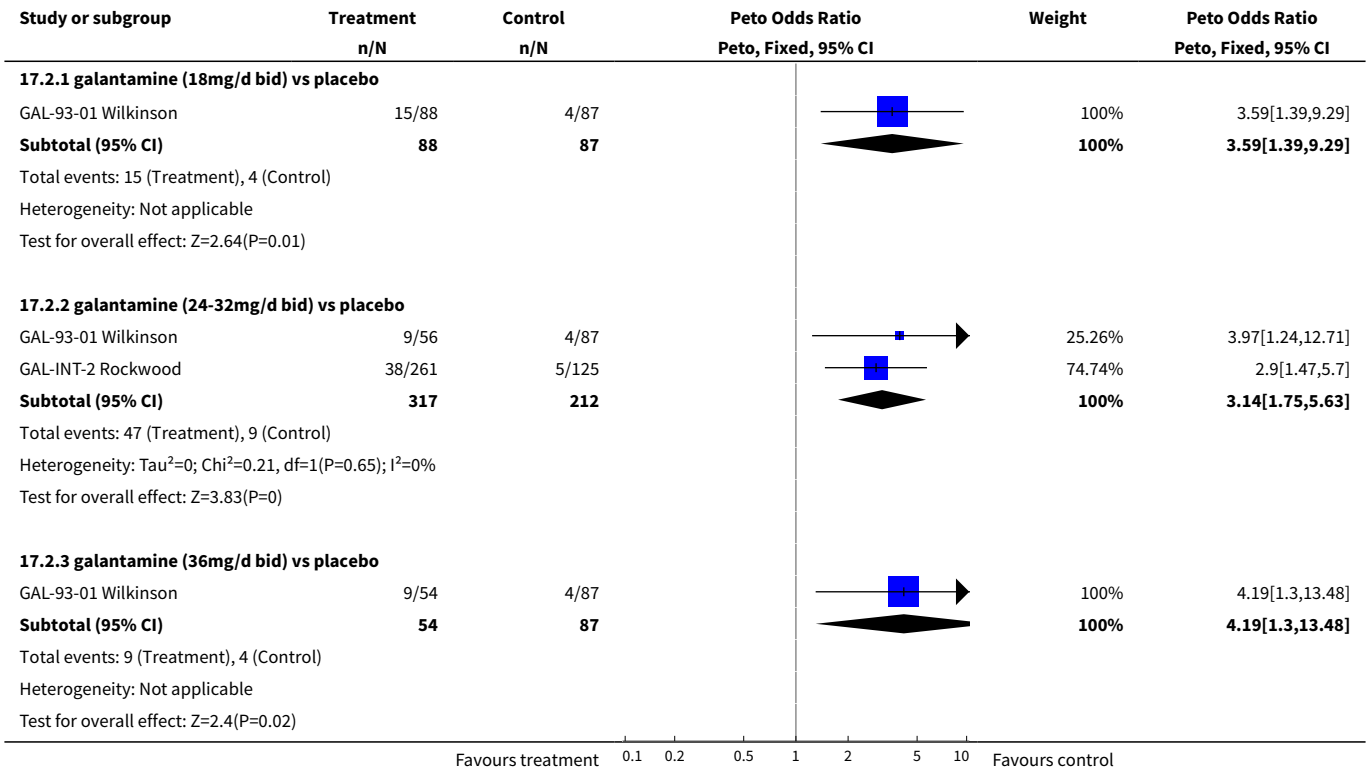


Analysis 17.2. Comparison 17 Specific adverse events (3 months), Outcome 2 Proportion of subjects experiencing vomiting (3 months).



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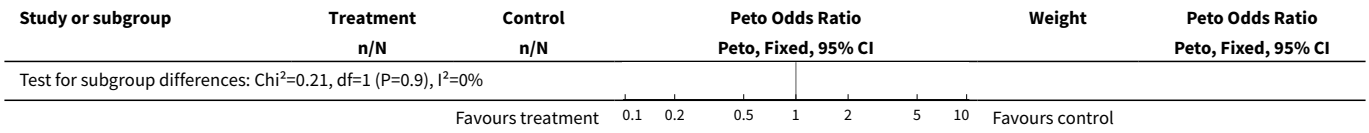
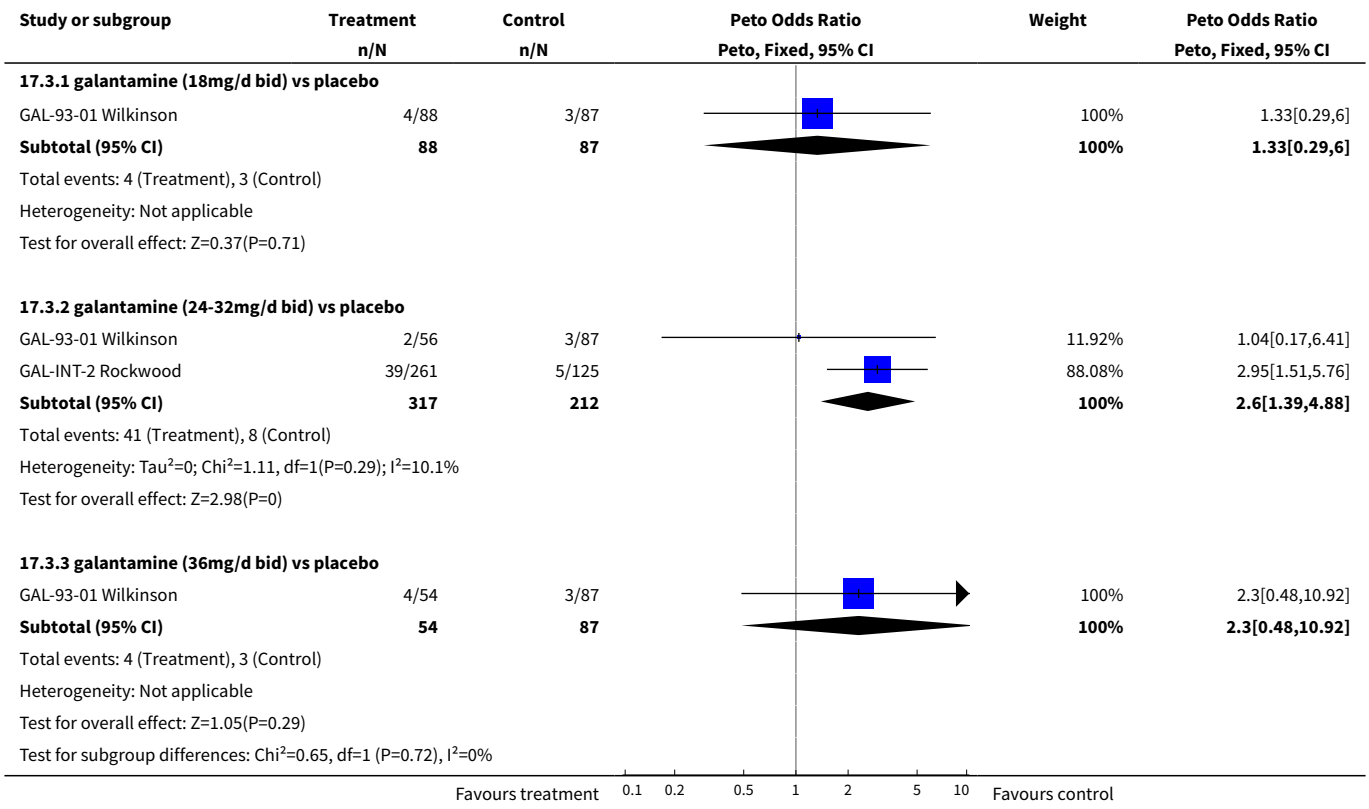
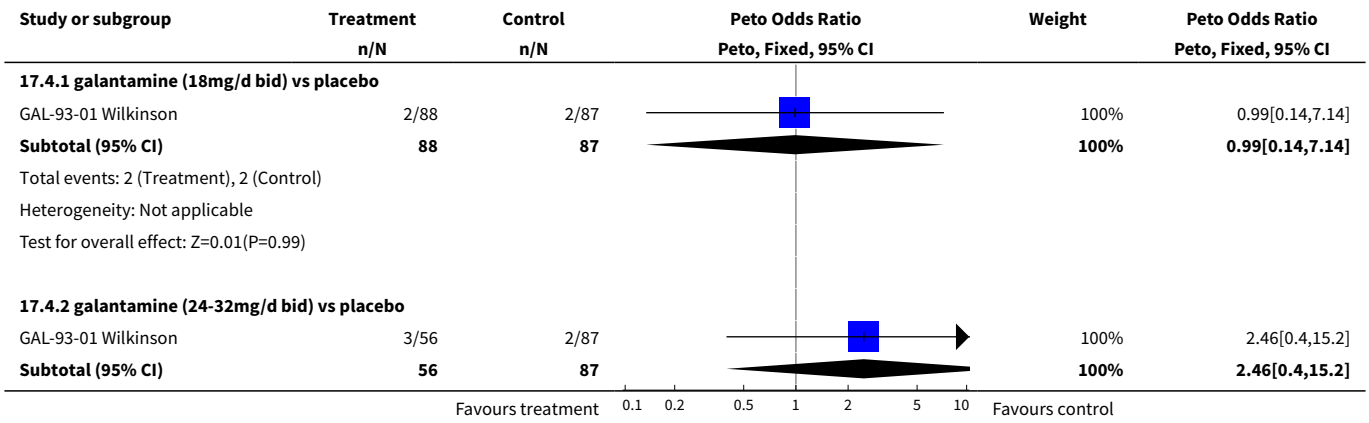


Analysis 17.3. Comparison 17 Specific adverse events (3 months), Outcome 3 Proportion of subjects experiencing dizziness (3 months).



Analysis 17.4. Comparison 17 Specific adverse events (3 months), Outcome 4 Proportion of subjects experiencing diarrhea (3 months).



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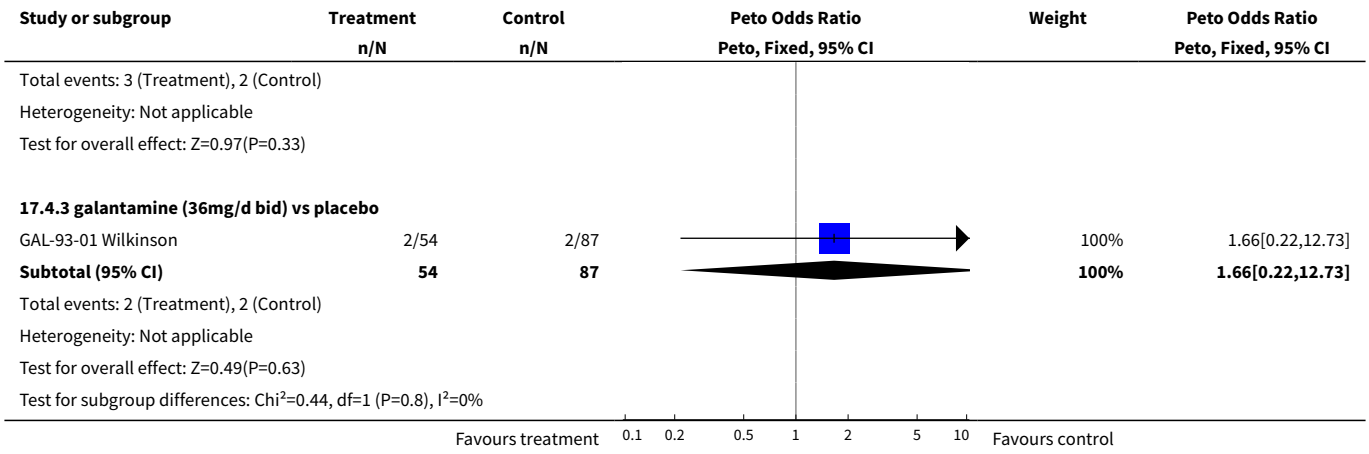
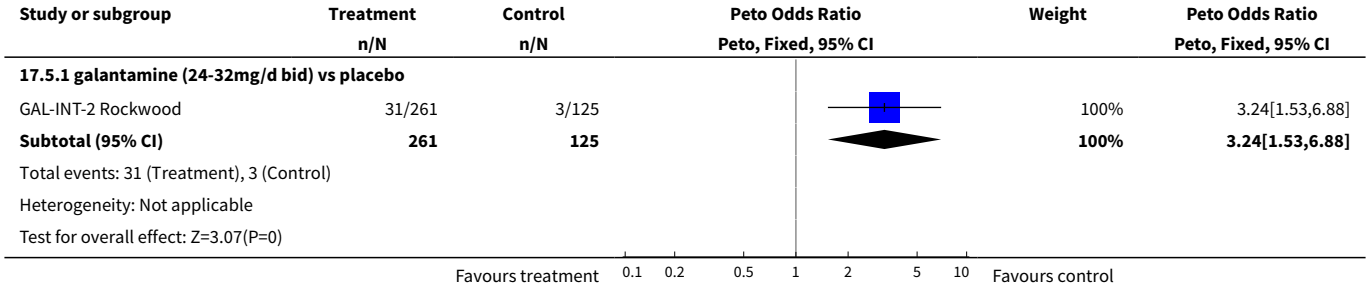
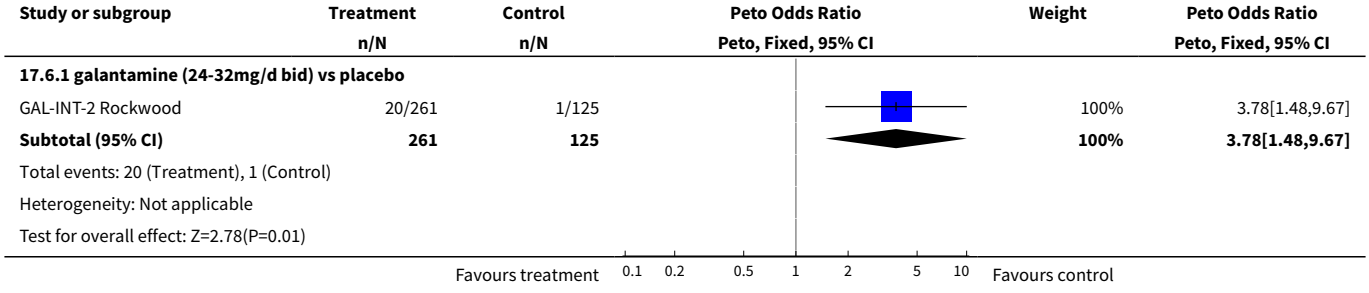


Analysis 17.5. Comparison 17 Specific adverse events (3 months), Outcome 5 Proportion of subjects experiencing anorexia (3 months).



Analysis 17.6. Comparison 17 Specific adverse events (3 months), Outcome 6 Proportion of subjects experiencing somnolence (3 months).



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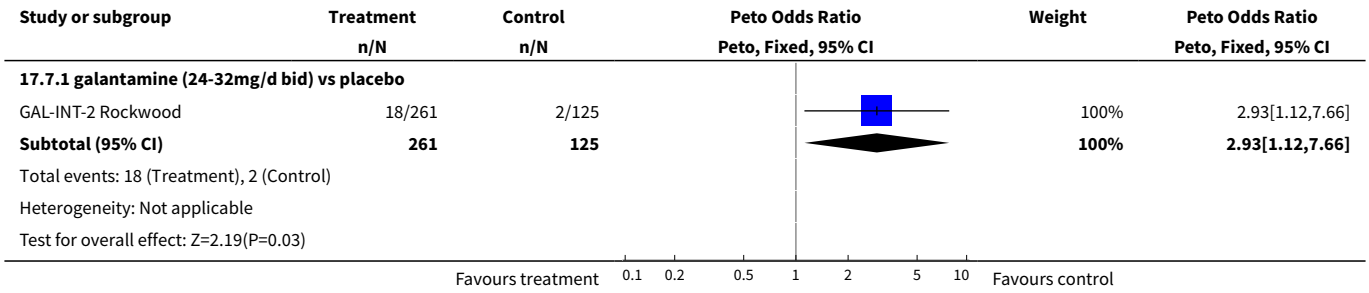
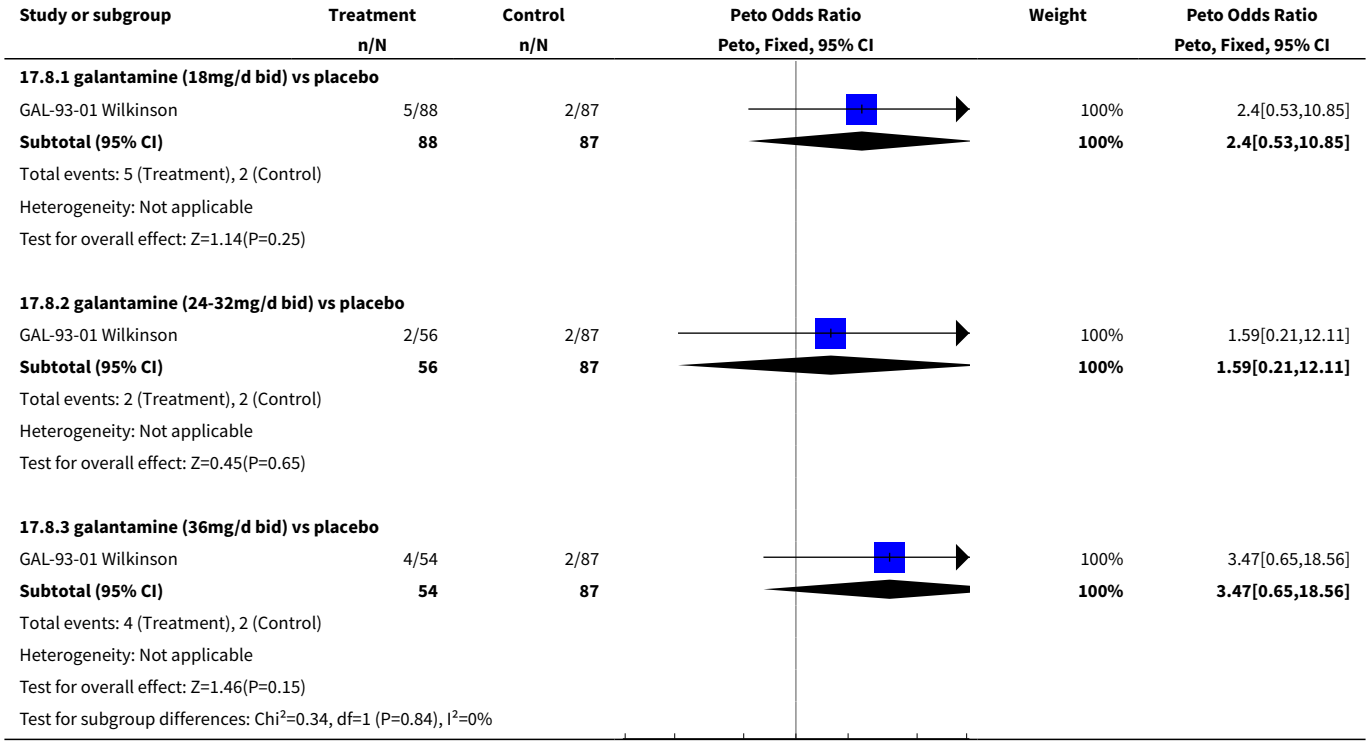
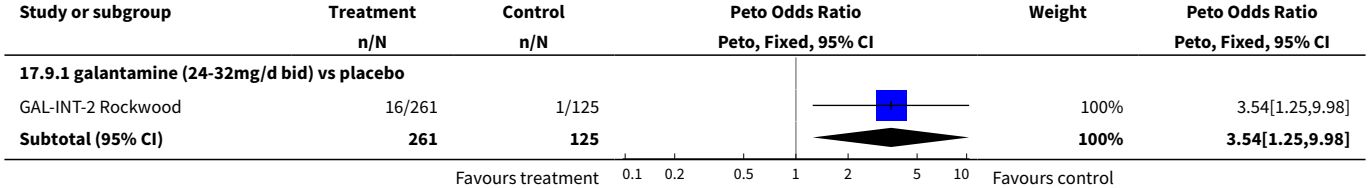
Analysis 17.7. Comparison 17 Specific adverse events (3 months), Outcome 7 Proportion of subjects experiencing abdominal pain (3 months).



Analysis 17.8. Comparison 17 Specific adverse events (3 months), Outcome 8 Proportion of subjects experiencing decreased appetite (3 months).



Analysis 17.9. Comparison 17 Specific adverse events (3 months), Outcome 9 Proportion of subjects experiencing agitation (3 months).



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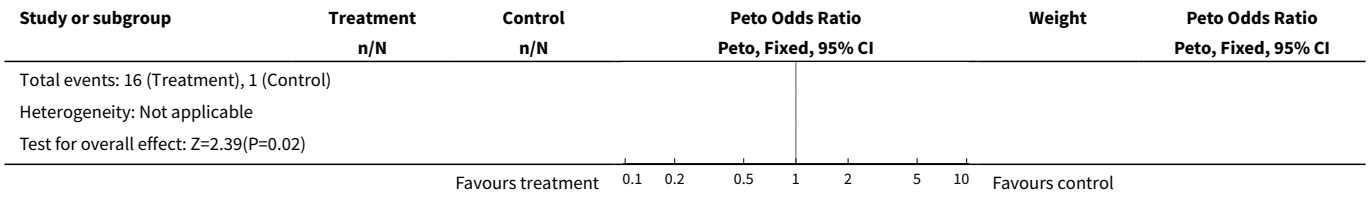
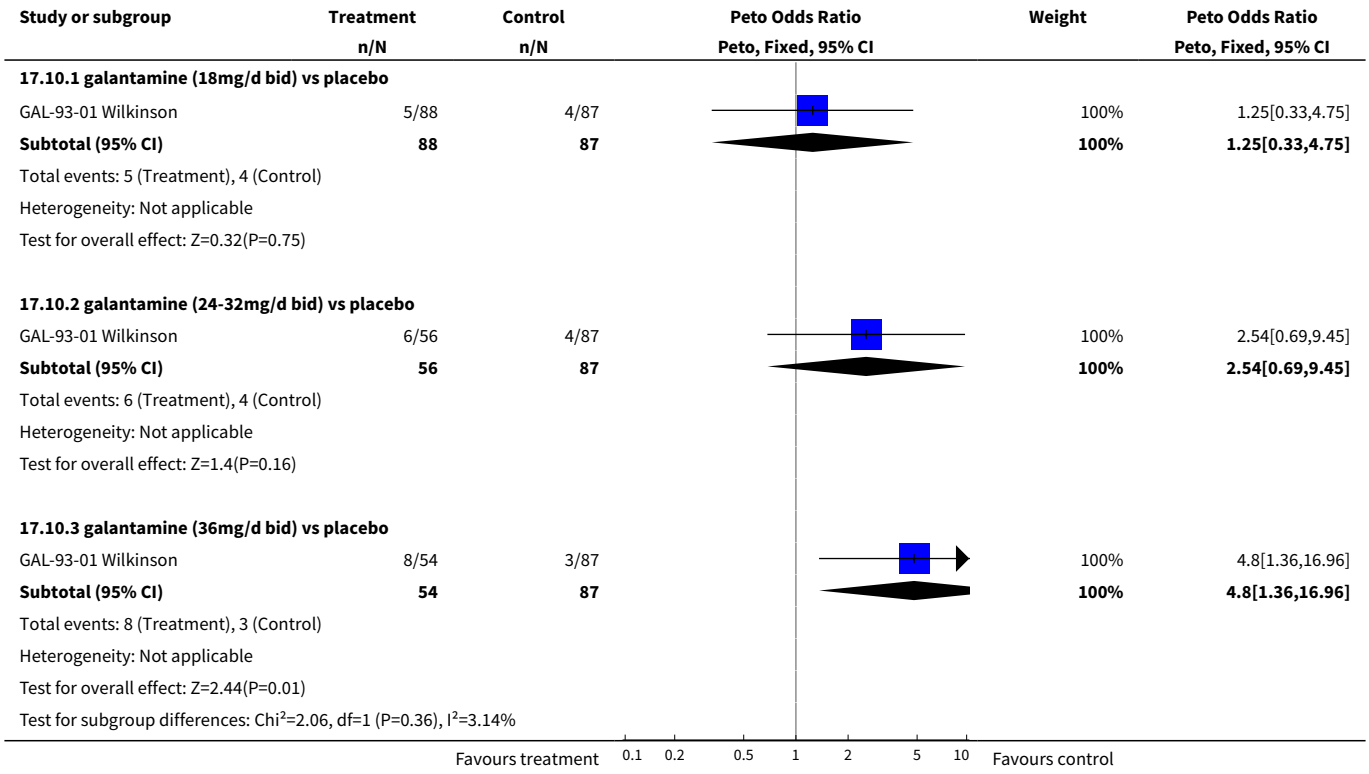


Analysis 17.10. Comparison 17 Specific adverse events (3 months), Outcome 10 Proportion of subjects experiencing headache (3 months).



Comparison 18. Specific adverse events (6 months)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of subjects experiencing nausea (6 months)	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 galantamine (8mg/d bid) vs placebo	1	426	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.50, 3.26]
1.2 galantamine (16mg/d bid) vs placebo	1	565	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.94 [1.65, 5.25]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 galantamine (16-24mg/d bid) vs placebo	1	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.80 [1.65, 4.73]
1.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	639	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.39 [2.06, 5.57]
1.5 galantamine (24mg/d bid) vs placebo	3	1419	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.69 [2.82, 4.82]
1.6 galantamine (32mg/d bid) vs placebo	2	856	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.21 [1.66, 2.94]
1.7 galantamine (32mg/d tds) vs placebo	1	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.58 [3.00, 6.98]
2 Proportion of subjects experiencing vomiting (6 months)	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 galantamine (8mg/d bid) vs placebo	1	426	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.85 [0.70, 11.62]
2.2 galantamine (16mg/d bid) vs placebo	1	565	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.70 [1.55, 8.85]
2.3 galantamine (16-24mg/d bid) vs placebo	1	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.48 [1.76, 6.88]
2.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	639	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.85 [1.34, 6.08]
2.5 galantamine (24mg/d bid) vs placebo	3	1419	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.01 [2.15, 4.21]
2.6 galantamine (32mg/d bid) vs placebo	2	857	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.07 [2.09, 4.50]
2.7 galantamine (32mg/d tds) vs placebo	1	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.33 [3.33, 12.03]
3 Proportion of subjects experiencing dizziness (6 months)	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 galantamine (8mg/d bid) vs placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 galantamine (16mg/d bid) vs placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 galantamine (16-24mg/d bid) vs placebo	1	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.71 [0.89, 3.30]
3.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	639	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.40 [1.32, 4.34]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5 galantamine (24mg/d bid) vs placebo	2	860	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.62 [1.04, 2.52]
3.6 galantamine (32mg/d bid) vs placebo	2	857	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.04 [1.34, 3.11]
3.7 galantamine (32mg/d tds) vs placebo	1	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.47 [1.03, 5.90]
4 Proportion of subjects experiencing diarrhea (6 months)	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 galantamine (8mg/d bid) vs placebo	1	426	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.35, 2.01]
4.2 galantamine (16mg/d bid) vs placebo	1	565	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.14 [1.20, 3.80]
4.3 galantamine (16-24mg/d bid) vs placebo	1	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.53, 1.81]
4.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	639	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.35, 1.30]
4.5 galantamine (24mg/d bid) vs placebo	3	1419	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [0.91, 2.05]
4.6 galantamine (32mg/d bid) vs placebo	2	857	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [1.35, 3.04]
4.7 galantamine (32mg/d tds) vs placebo	1	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.14 [1.43, 6.89]
5 Proportion of subjects experiencing anorexia (6 months)	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 galantamine (8mg/d bid) vs placebo	1	426	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.95 [0.70, 5.47]
5.2 galantamine (16mg/d bid) vs placebo	1	565	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.06 [0.95, 4.47]
5.3 galantamine (16-24mg/d bid) vs placebo	1	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.61 [1.25, 5.42]
5.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	639	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.35 [1.09, 5.07]
5.5 galantamine (24mg/d bid) vs placebo	3	1425	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.84 [1.24, 2.73]
5.6 galantamine (32mg/d bid) vs placebo	2	857	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.71 [2.95, 7.53]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.7 galantamine (32mg/d tds) vs placebo	1	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.47 [1.87, 10.68]
6 Proportion of subjects experiencing weight loss (6 months)	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 galantamine (8mg/d bid) vs placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 galantamine (16mg/d bid) vs placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 galantamine (16-24mg/d bid) vs placebo	1	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.52 [1.48, 8.40]
6.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	639	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.14 [1.23, 8.01]
6.5 galantamine (24mg/d bid) vs placebo	2	860	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.55 [2.04, 6.17]
6.6 galantamine (32mg/d bid) vs placebo	2	857	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.98 [1.63, 5.46]
7 Proportion of subjects experiencing abdominal pain (6 months)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 galantamine (8mg/d bid) vs placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 galantamine (16mg/d bid) vs placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 galantamine (24mg/d bid) vs placebo	1	425	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [0.69, 3.68]
7.4 galantamine (32mg/d bid) vs placebo	1	424	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.60 [1.26, 5.33]
7.5 galantamine (32mg/d tds) vs placebo	1	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.84 [1.05, 7.66]
8 Proportion of subjects experiencing tremor (6 months)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 galantamine (8mg/d bid) vs placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 galantamine (16mg/d bid) vs placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 galantamine (24mg/d bid) vs placebo	1	425	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.56 [1.77, 17.50]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.4 galantamine (32mg/d bid) vs placebo	1	424	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.64 [1.15, 18.77]
9 Proportion of subjects experiencing agitation (6 months)	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 galantamine (8mg/d bid) vs placebo	1	426	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [0.92, 3.30]
9.2 galantamine (16mg/d bid) vs placebo	1	565	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.61, 1.87]
9.3 galantamine (16-24mg/d bid) vs placebo	1	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.49, 1.75]
9.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	639	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.57, 1.96]
9.5 galantamine (24mg/d bid) vs placebo	1	559	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.47, 1.51]
9.6 galantamine (32mg/d bid) vs placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.7 galantamine (32mg/d tds) vs placebo	1	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.58, 3.07]
10 Proportion of subjects experiencing headache (6 months)	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 galantamine (8mg/d bid) vs placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 galantamine (16mg/d bid) vs placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 galantamine (16-24mg/d bid) vs placebo	1	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.50, 1.92]
10.4 galantamine (16-24mg/d Prolonged Release) vs placebo	1	639	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.54 [0.84, 2.83]
10.5 galantamine (24mg/d bid) vs placebo	1	435	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.83 [1.32, 6.09]
10.6 galantamine (32mg/d bid) vs placebo	1	433	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.31 [1.61, 6.80]
10.7 galantamine (32mg/d tds) vs placebo	1	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.45, 2.30]

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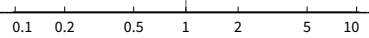
Analysis 18.1. Comparison 18 Specific adverse events (6 months), Outcome 1 Proportion of subjects experiencing nausea (6 months).

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
18.1.1 galantamine (8mg/d bid) vs placebo					
GAL-USA-10 Tariot	8/140	13/286		100%	1.28[0.5,3.26]
Subtotal (95% CI)	**140**	**286**		**100%**	**1.28[0.5,3.26]**
Total events: 8 (Treatment), 13 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.52(P=0.6)					
18.1.2 galantamine (16mg/d bid) vs placebo					
GAL-USA-10 Tariot	37/279	13/286		100%	2.94[1.65,5.25]
Subtotal (95% CI)	**279**	**286**		**100%**	**2.94[1.65,5.25]**
Total events: 37 (Treatment), 13 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.64(P=0)					
18.1.3 galantamine (16-24mg/d bid) vs placebo					
GAL-INT-10 Brodaty	45/326	16/320		100%	2.8[1.65,4.73]
Subtotal (95% CI)	**326**	**320**		**100%**	**2.8[1.65,4.73]**
Total events: 45 (Treatment), 16 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.82(P=0)					
18.1.4 galantamine (16-24mg/d Prolonged Release) vs placebo					
GAL-INT-10 Brodaty	54/319	16/320		100%	3.39[2.06,5.57]
Subtotal (95% CI)	**319**	**320**		**100%**	**3.39[2.06,5.57]**
Total events: 54 (Treatment), 16 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.82(P<0.0001)					
18.1.5 galantamine (24mg/d bid) vs placebo					
GAL-INT-1 Wilcock	82/220	26/215		38.08%	3.84[2.49,5.93]
GAL-USA-1 Raskind	79/212	28/213		37.56%	3.59[2.32,5.56]
GAL-USA-10 Tariot	45/273	13/286		24.36%	3.6[2.09,6.2]
Subtotal (95% CI)	**705**	**714**		**100%**	**3.69[2.82,4.82]**
Total events: 206 (Treatment), 67 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=2(P=0.97); I^2=0%					
Test for overall effect: Z=9.53(P<0.0001)					
18.1.6 galantamine (32mg/d bid) vs placebo					
GAL-INT-1 Wilcock	87/218	26/215		45.05%	4.22[2.75,6.47]
GAL-USA-1 Raskind	92/211	79/212		54.95%	1.3[0.88,1.92]
Subtotal (95% CI)	**429**	**427**		**100%**	**2.21[1.66,2.94]**
Total events: 179 (Treatment), 105 (Control)					
Heterogeneity: Tau^2=0; Chi^2=15.91, df=1(P<0.0001); I^2=93.72%					
Test for overall effect: Z=5.4(P<0.0001)					
18.1.7 galantamine (32mg/d tds) vs placebo					
GAL-95-05	86/275	21/279		100%	4.58[3,6.98]
Subtotal (95% CI)	**275**	**279**		**100%**	**4.58[3,6.98]**
Total events: 86 (Treatment), 21 (Control)					



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Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=7.07(P<0.0001)					
Test for subgroup differences: Chi²=13.92, df=1 (P=0.03), I²=56.91%					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 18.2. Comparison 18 Specific adverse events (6 months), Outcome 2 Proportion of subjects experiencing vomiting (6 months).

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
18.2.1 galantamine (8mg/d bid) vs placebo					
GAL-USA-10 Tariot	5/140	4/286		100%	2.85[0.7,11.62]
Subtotal (95% CI)	**140**	**286**		**100%**	**2.85[0.7,11.62]**
Total events: 5 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.46(P=0.14)					
18.2.2 galantamine (16mg/d bid) vs placebo					
GAL-USA-10 Tariot	17/279	4/286		100%	3.7[1.55,8.85]
Subtotal (95% CI)	**279**	**286**		**100%**	**3.7[1.55,8.85]**
Total events: 17 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.95(P=0)					
18.2.3 galantamine (16-24mg/d bid) vs placebo					
GAL-INT-10 Brodaty	28/326	7/320		100%	3.48[1.76,6.88]
Subtotal (95% CI)	**326**	**320**		**100%**	**3.48[1.76,6.88]**
Total events: 28 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.59(P=0)					
18.2.4 galantamine (16-24mg/d Prolonged Release) vs placebo					
GAL-INT-10 Brodaty	21/319	7/320		100%	2.85[1.34,6.08]
Subtotal (95% CI)	**319**	**320**		**100%**	**2.85[1.34,6.08]**
Total events: 21 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.71(P=0.01)					
18.2.5 galantamine (24mg/d bid) vs placebo					
GAL-INT-1 Wilcock	45/220	9/215		34.68%	4.45[2.52,7.86]
GAL-USA-1 Raskind	44/212	28/213		43.86%	1.72[1.03,2.85]
GAL-USA-10 Tariot	27/273	4/286		21.45%	5.04[2.45,10.4]
Subtotal (95% CI)	**705**	**714**		**100%**	**3.01[2.15,4.21]**
Total events: 116 (Treatment), 41 (Control)					
Heterogeneity: Tau²=0; Chi²=8.5, df=2(P=0.01); I²=76.48%					
Test for overall effect: Z=6.44(P<0.0001)					
18.2.6 galantamine (32mg/d bid) vs placebo					
GAL-INT-1 Wilcock	37/218	16/215		44.31%	2.42[1.36,4.3]

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

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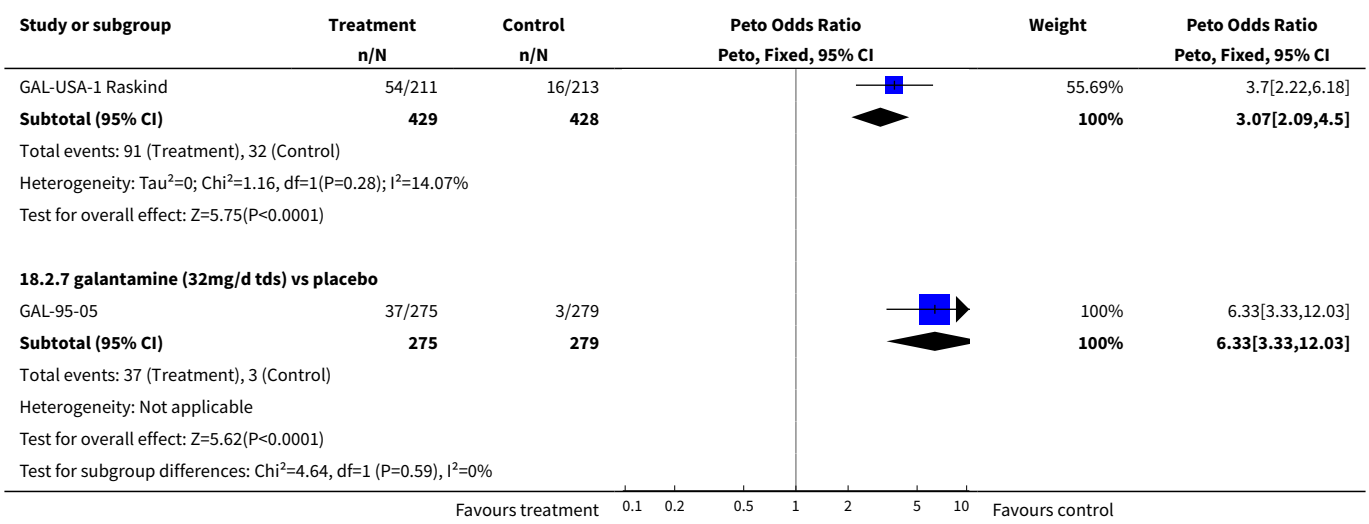
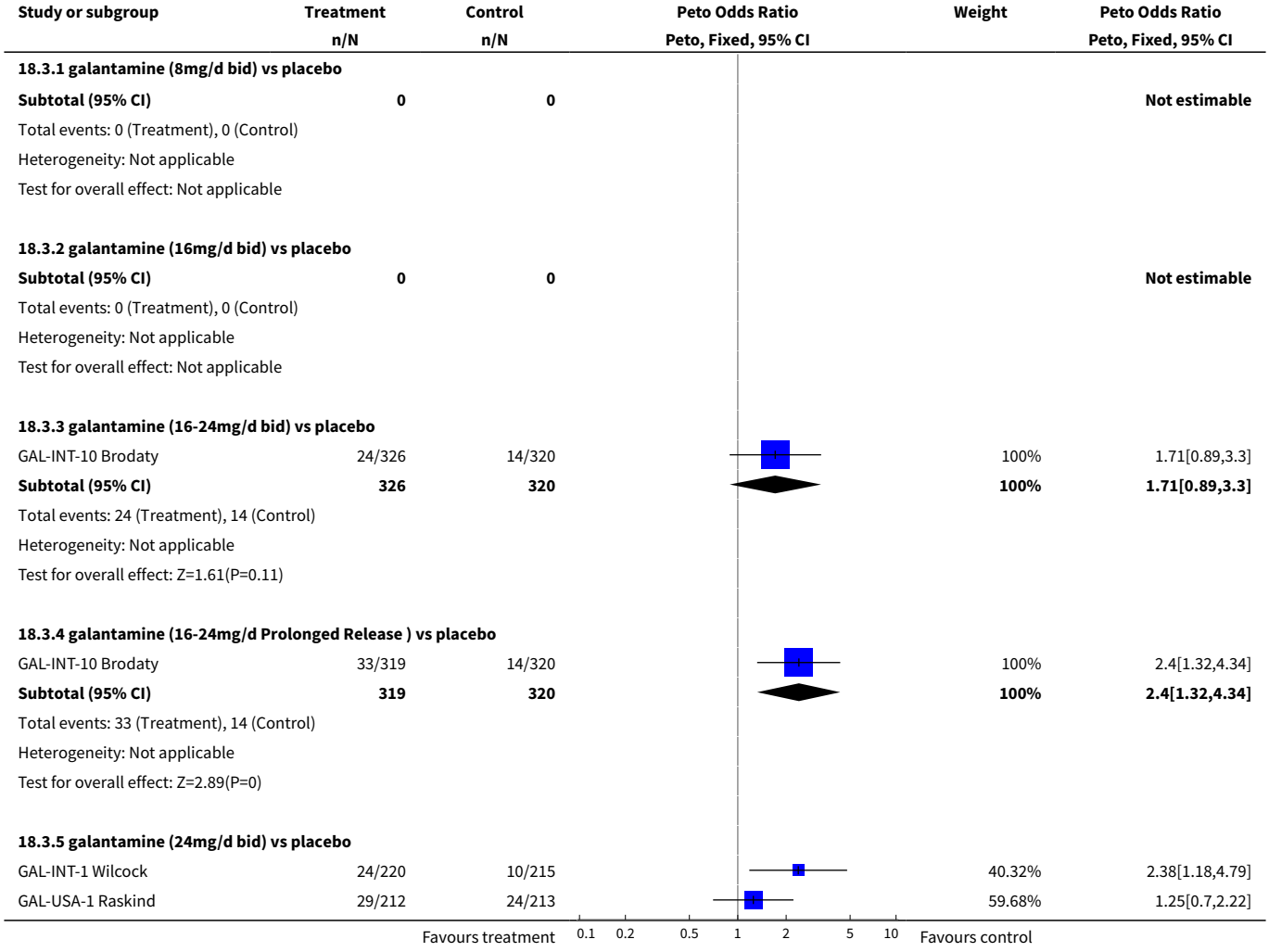


Analysis 18.3. Comparison 18 Specific adverse events (6 months), Outcome 3 Proportion of subjects experiencing dizziness (6 months).



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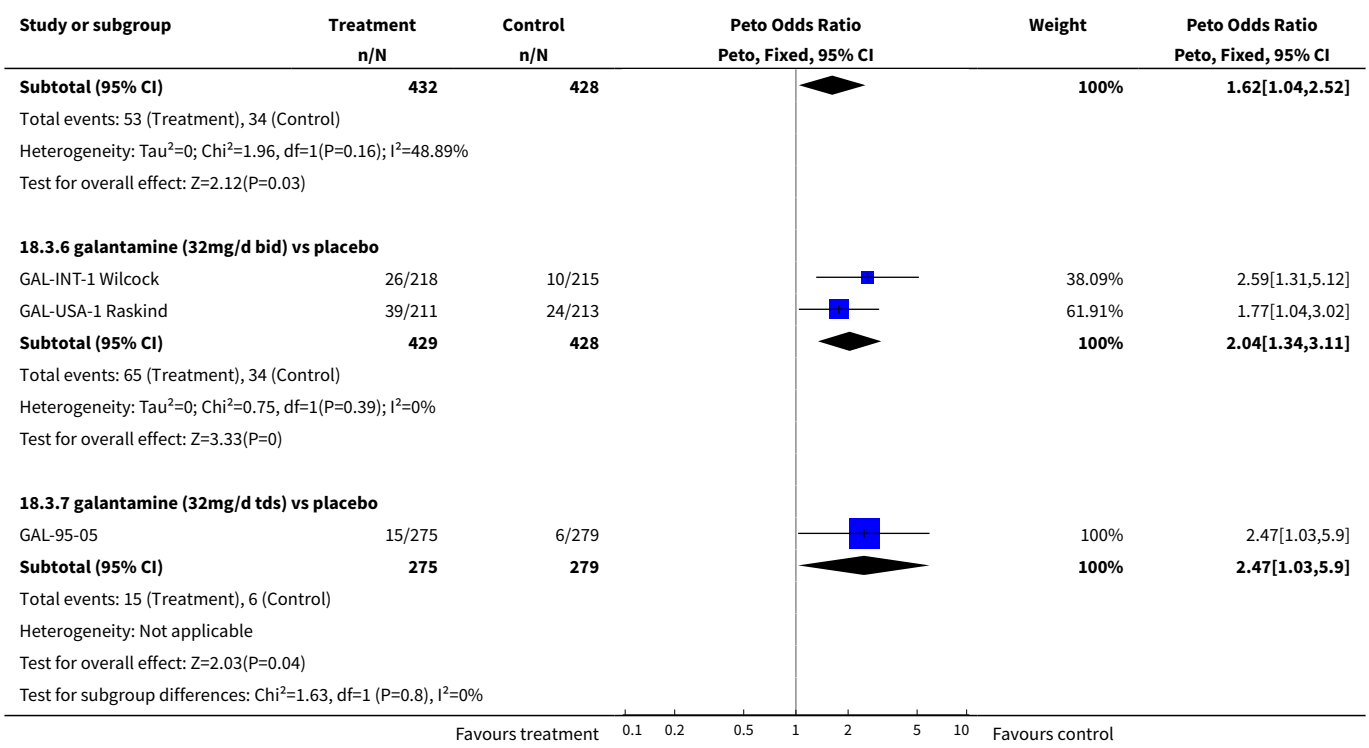
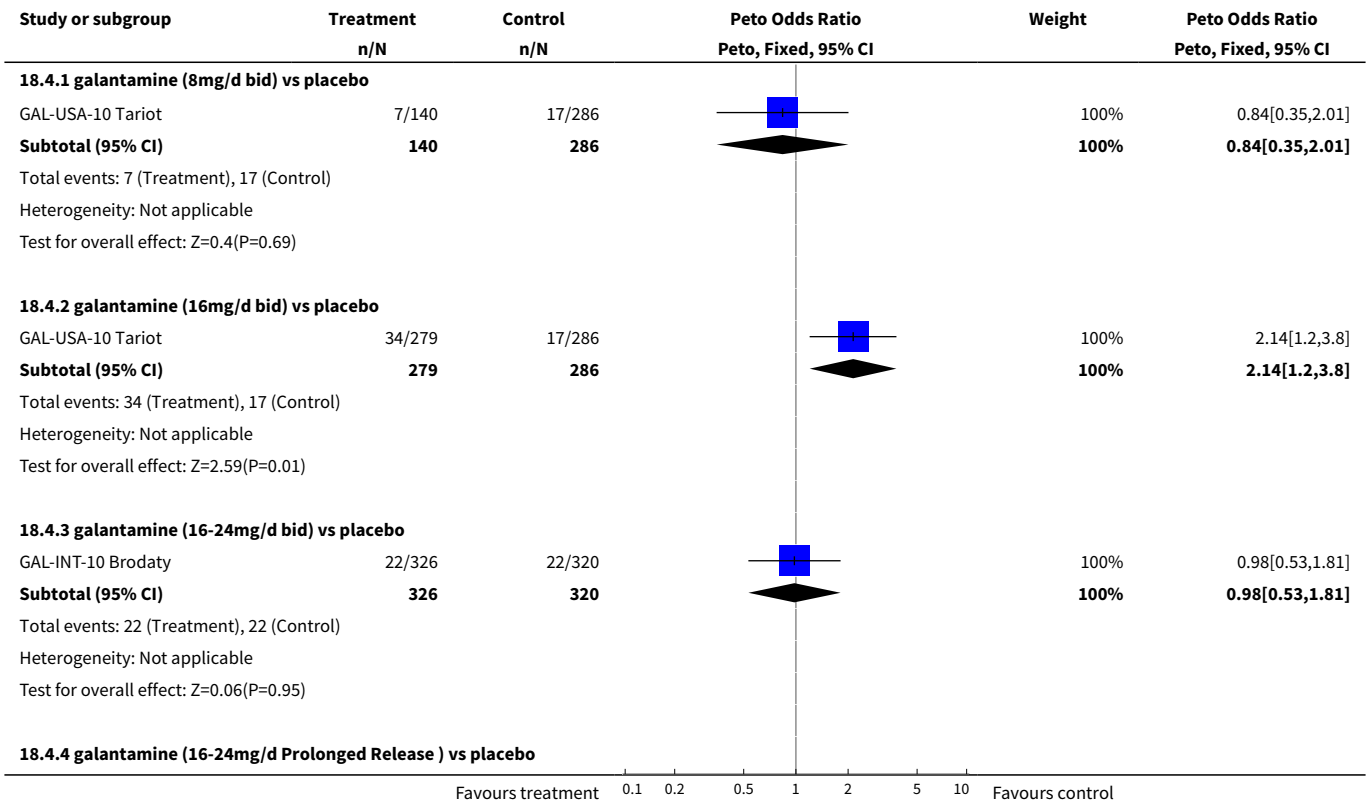


Analysis 18.4. Comparison 18 Specific adverse events (6 months), Outcome 4 Proportion of subjects experiencing diarrhea (6 months).



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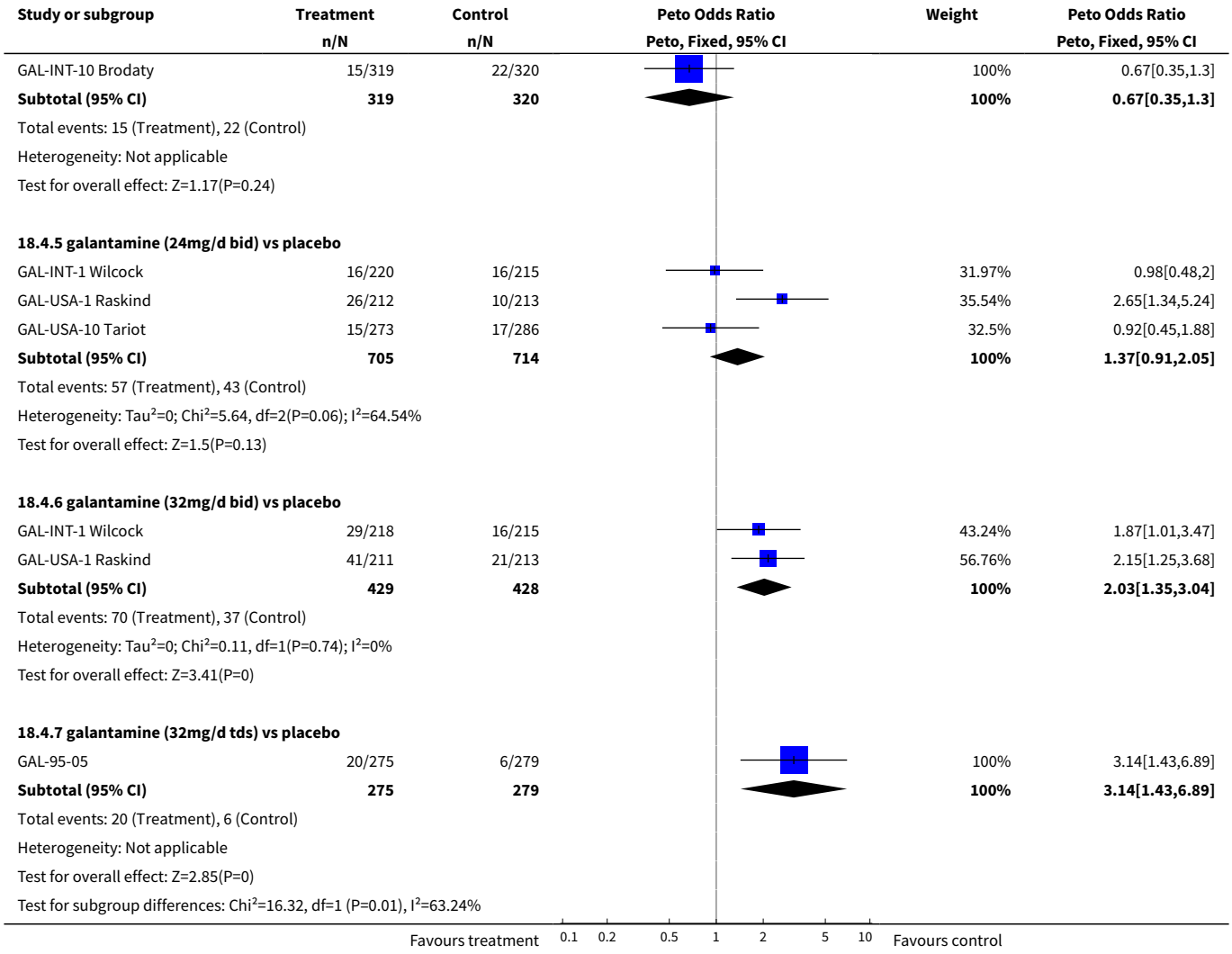
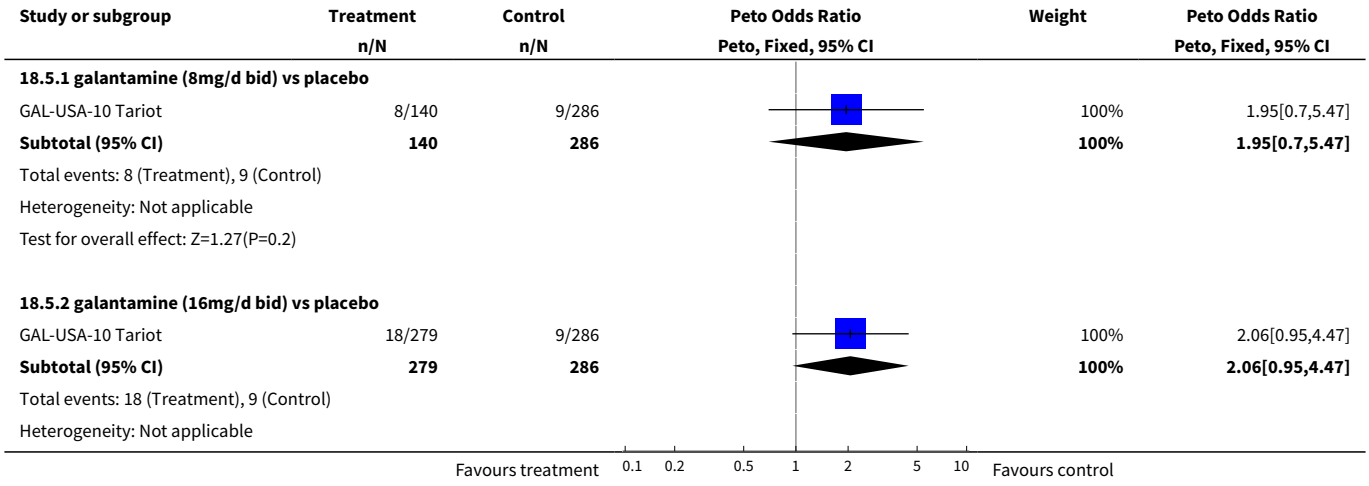


Analysis 18.5. Comparison 18 Specific adverse events (6 months), Outcome 5 Proportion of subjects experiencing anorexia (6 months).



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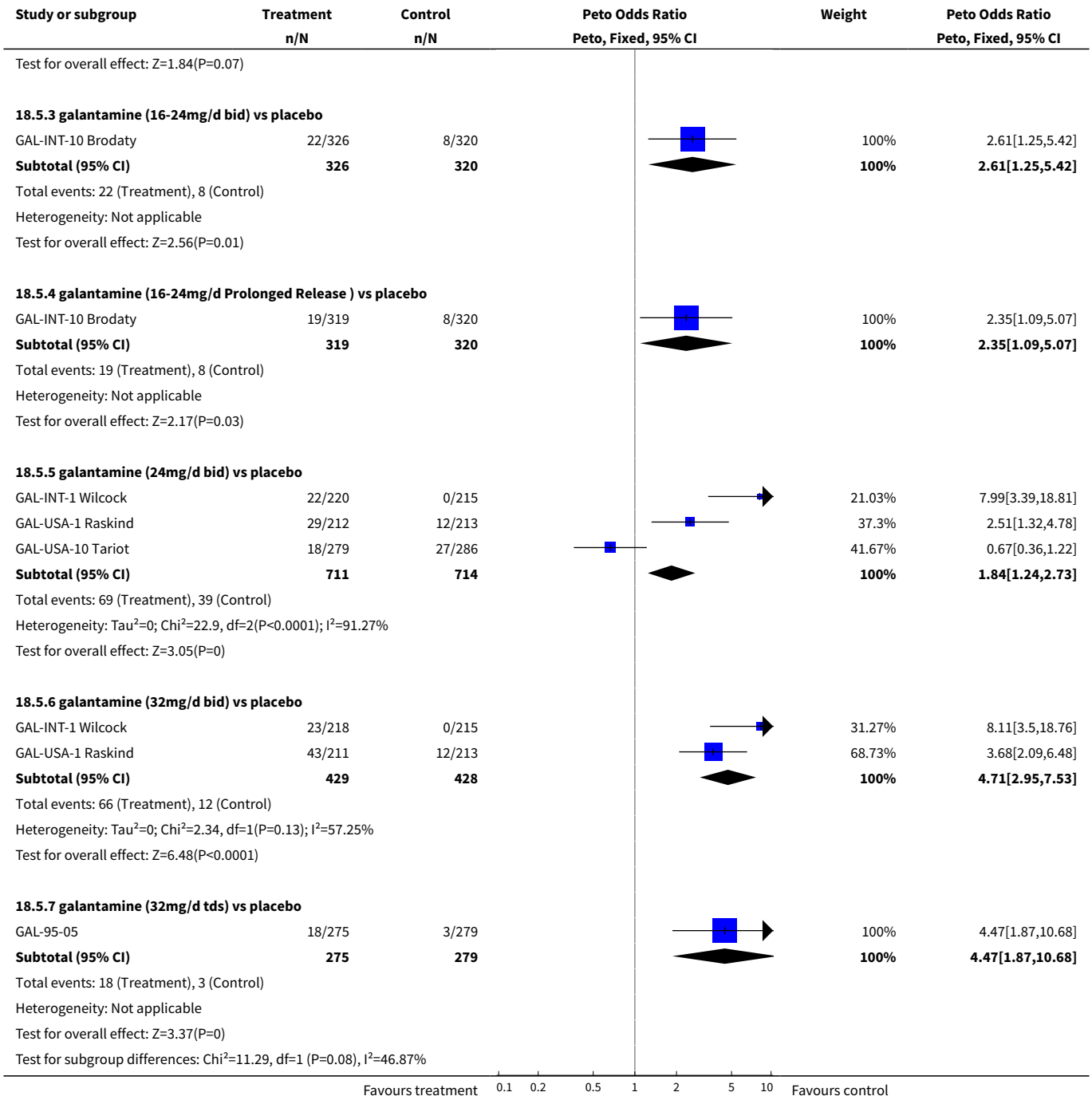
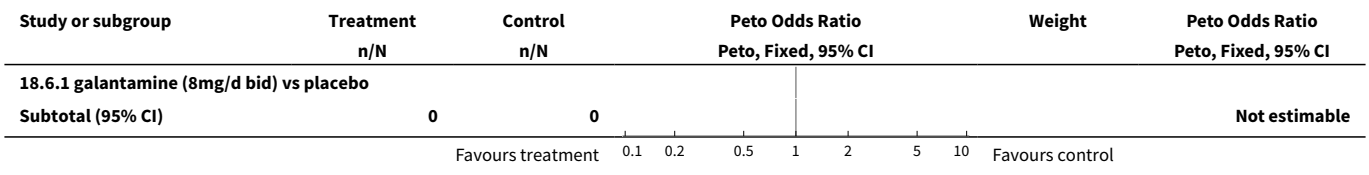


Analysis 18.6. Comparison 18 Specific adverse events (6 months), Outcome 6 Proportion of subjects experiencing weight loss (6 months).



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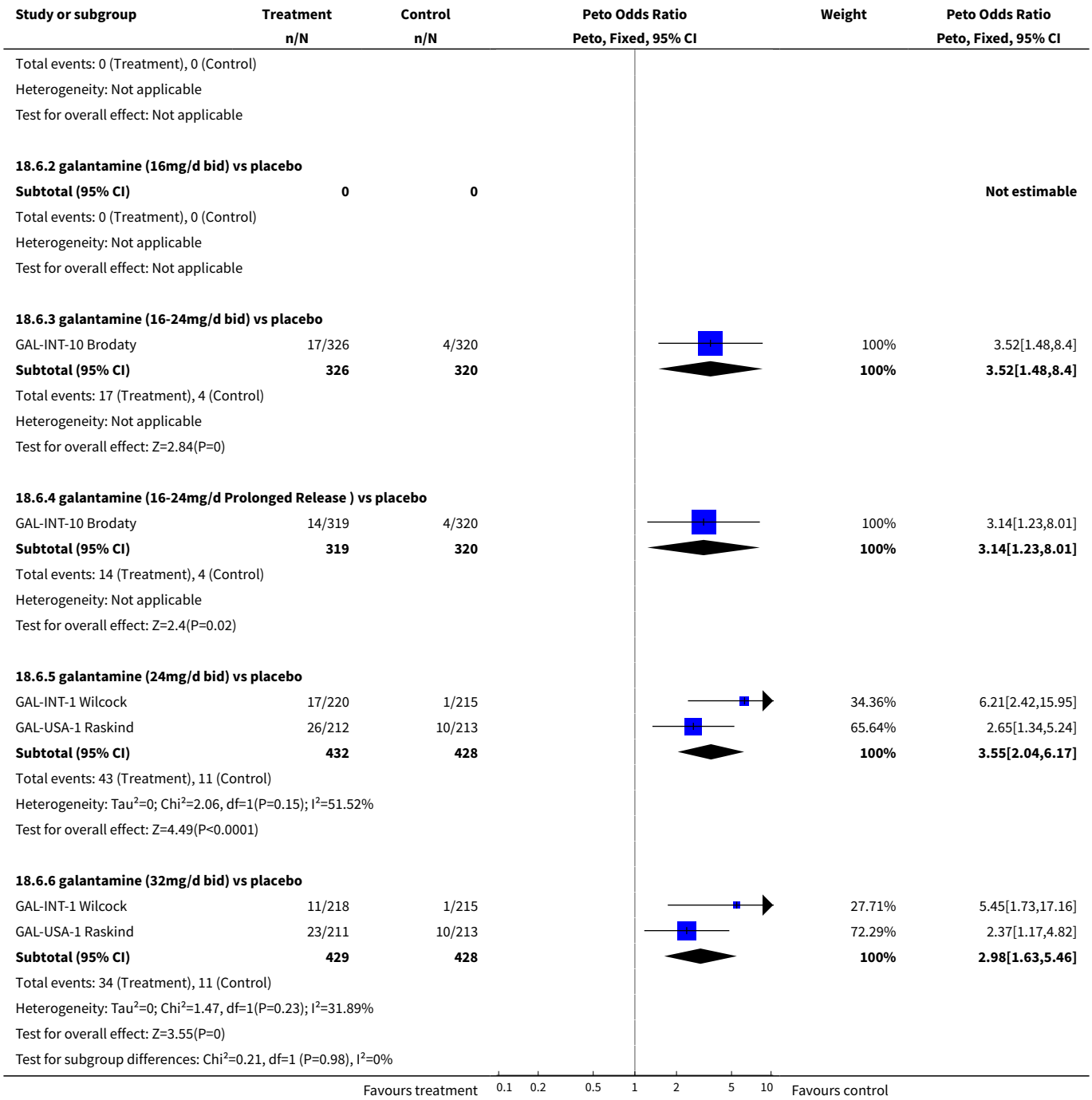
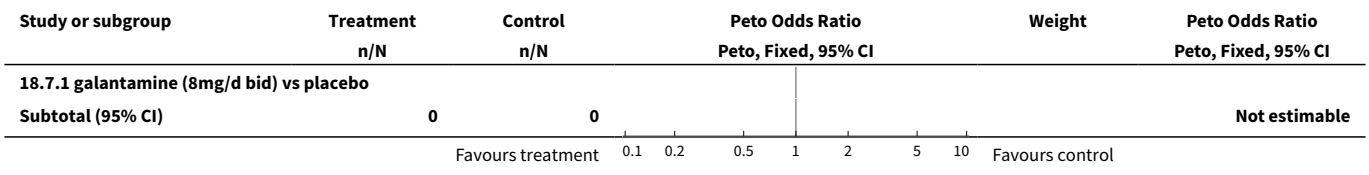


Analysis 18.7. Comparison 18 Specific adverse events (6 months), Outcome 7 Proportion of subjects experiencing abdominal pain (6 months).



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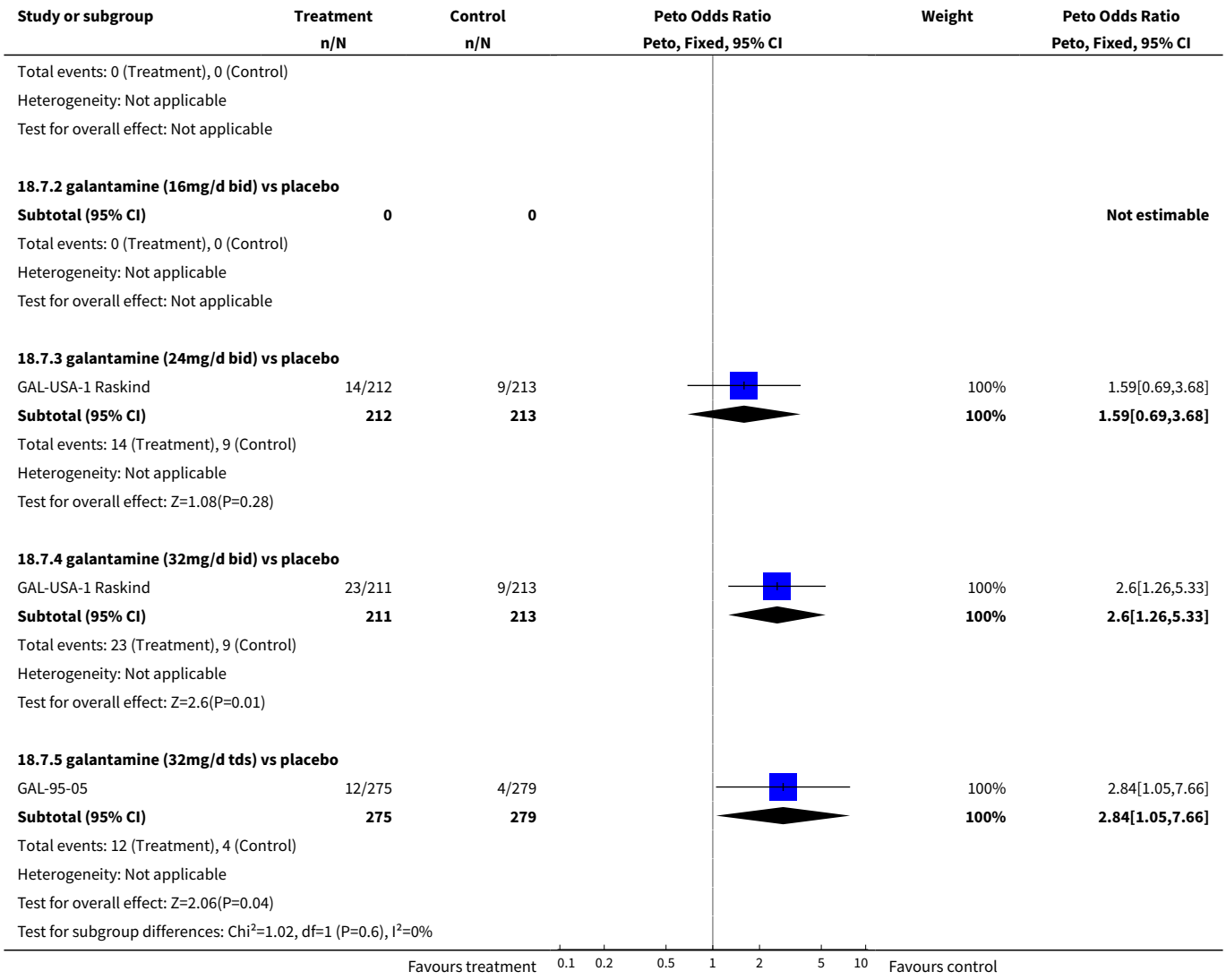
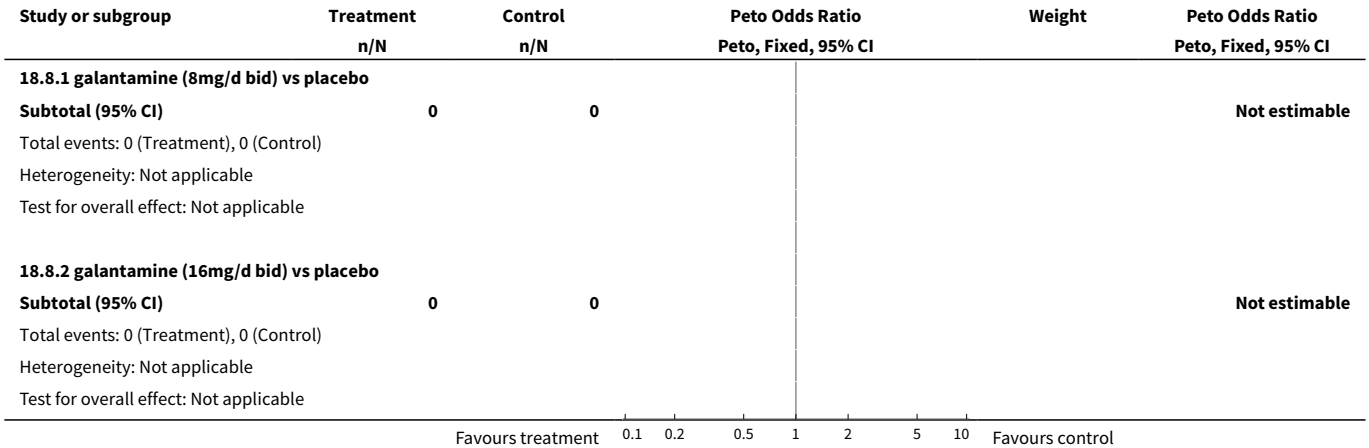


Analysis 18.8. Comparison 18 Specific adverse events (6 months), Outcome 8 Proportion of subjects experiencing tremor (6 months).



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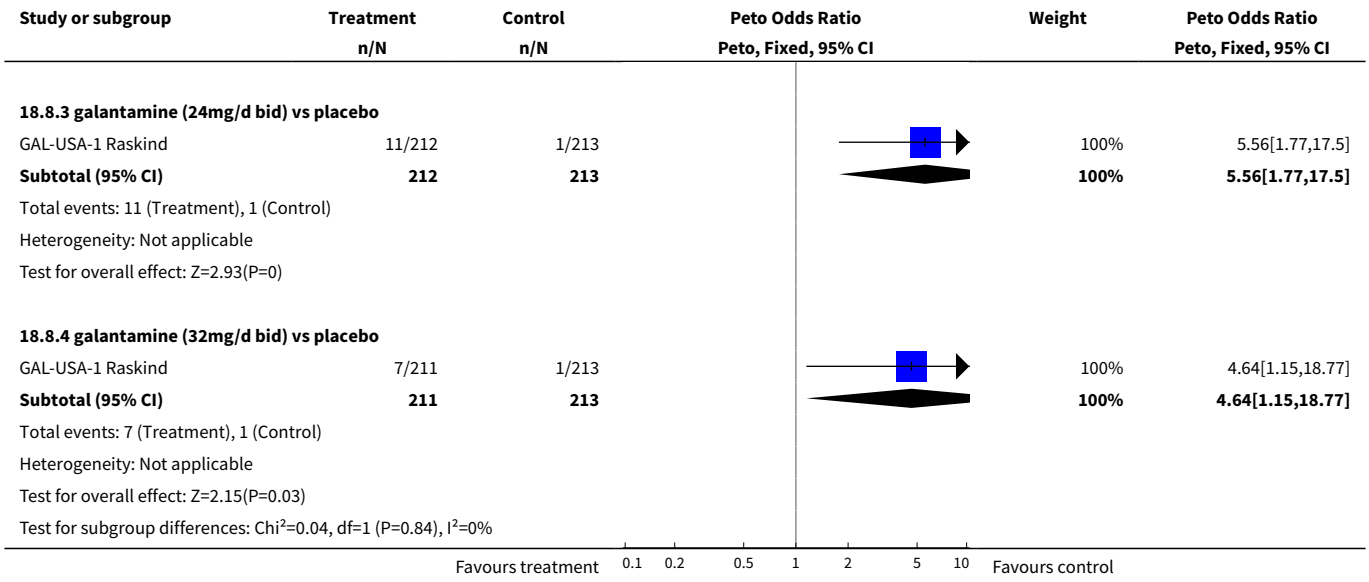
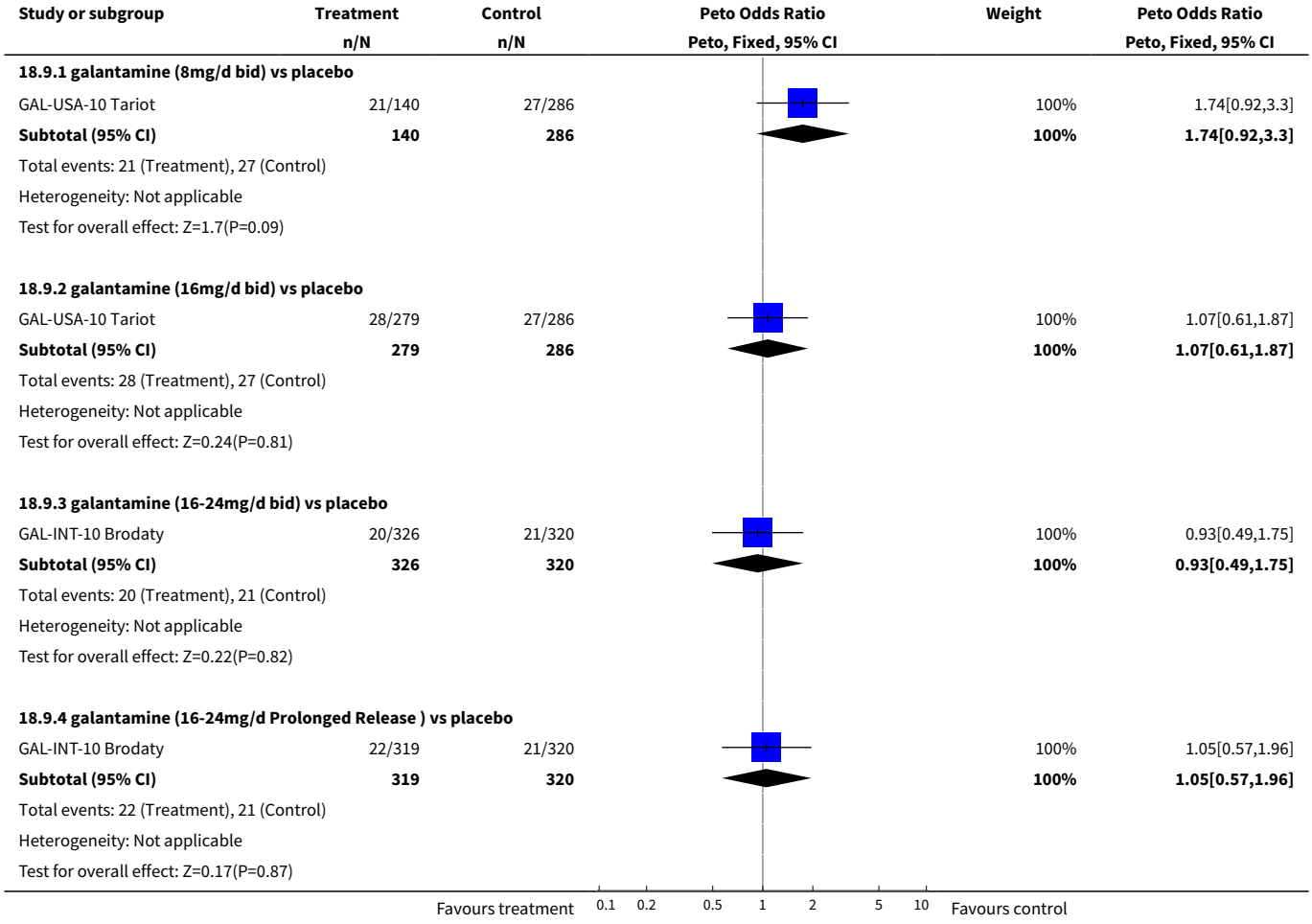


Analysis 18.9. Comparison 18 Specific adverse events (6 months), Outcome 9 Proportion of subjects experiencing agitation (6 months).



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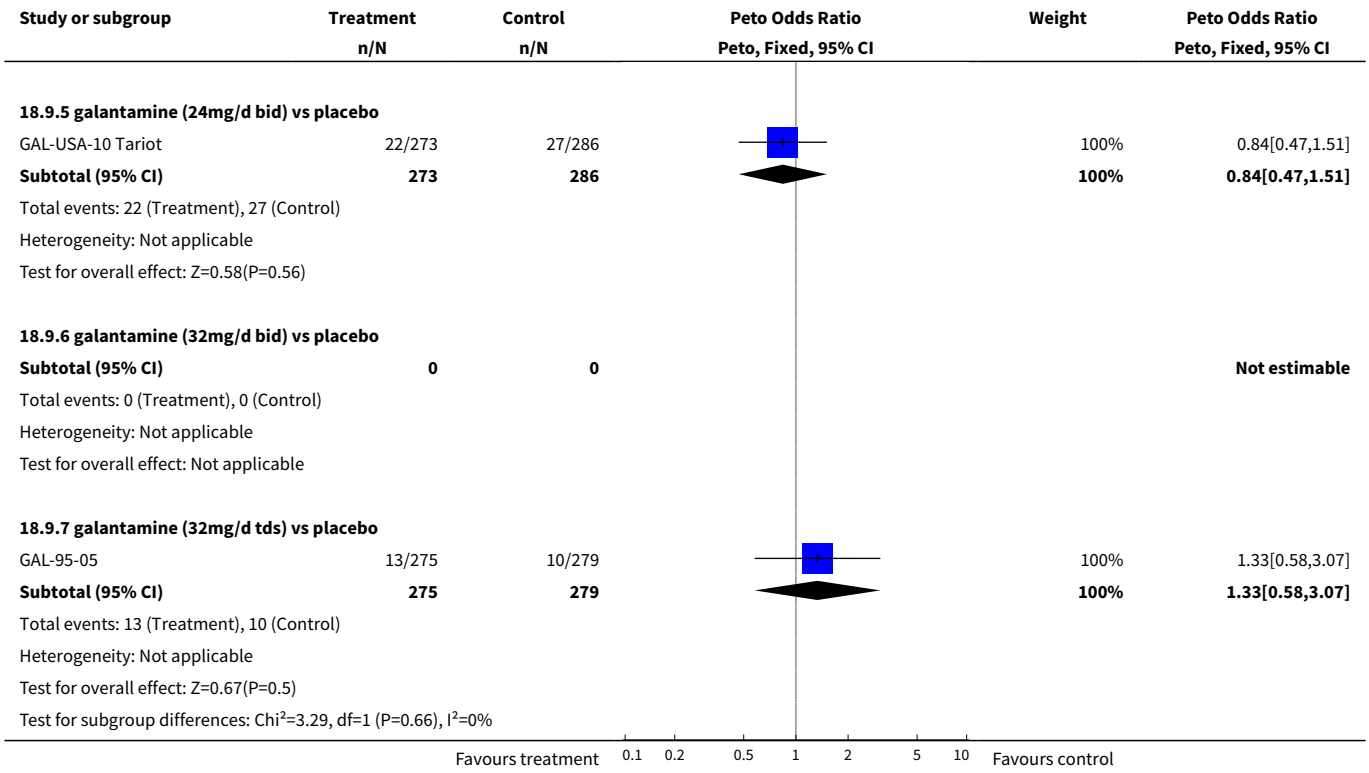
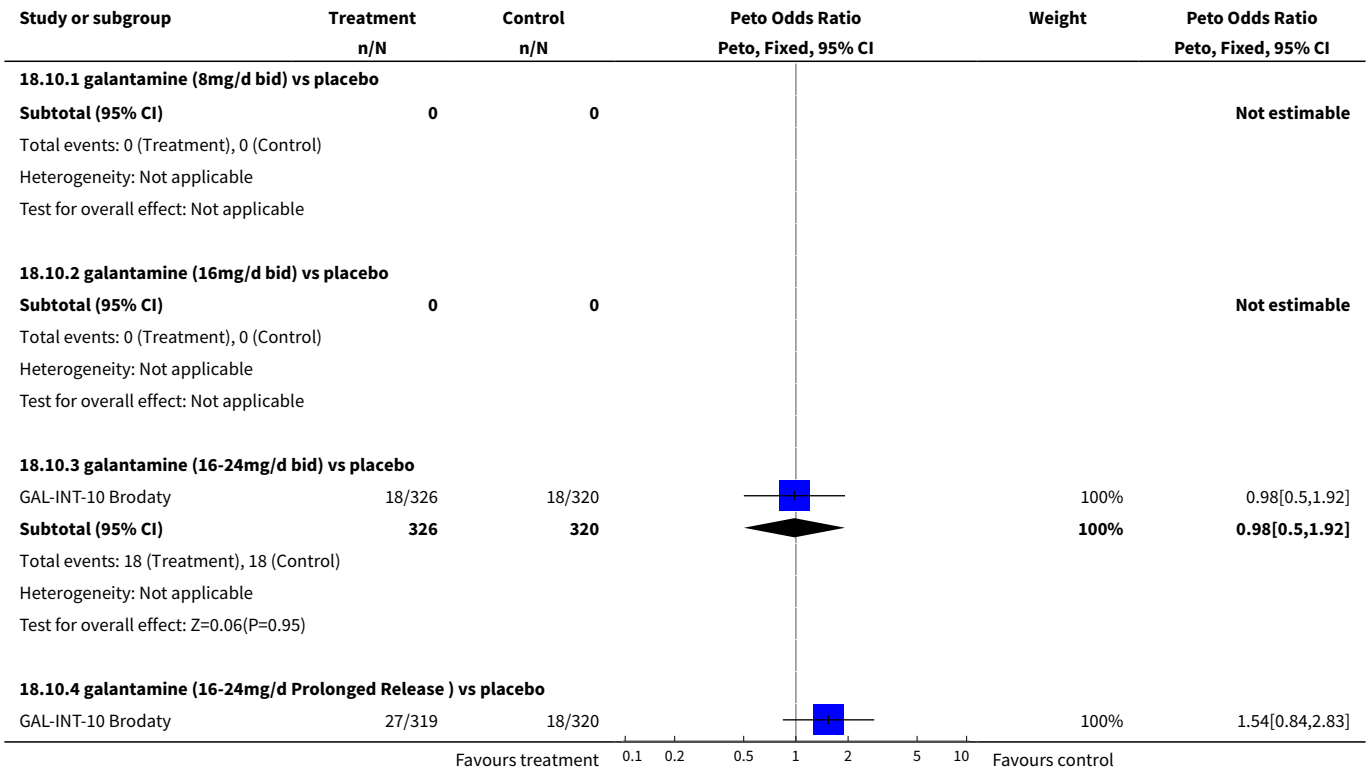


Analysis 18.10. Comparison 18 Specific adverse events (6 months), Outcome 10 Proportion of subjects experiencing headache (6 months).



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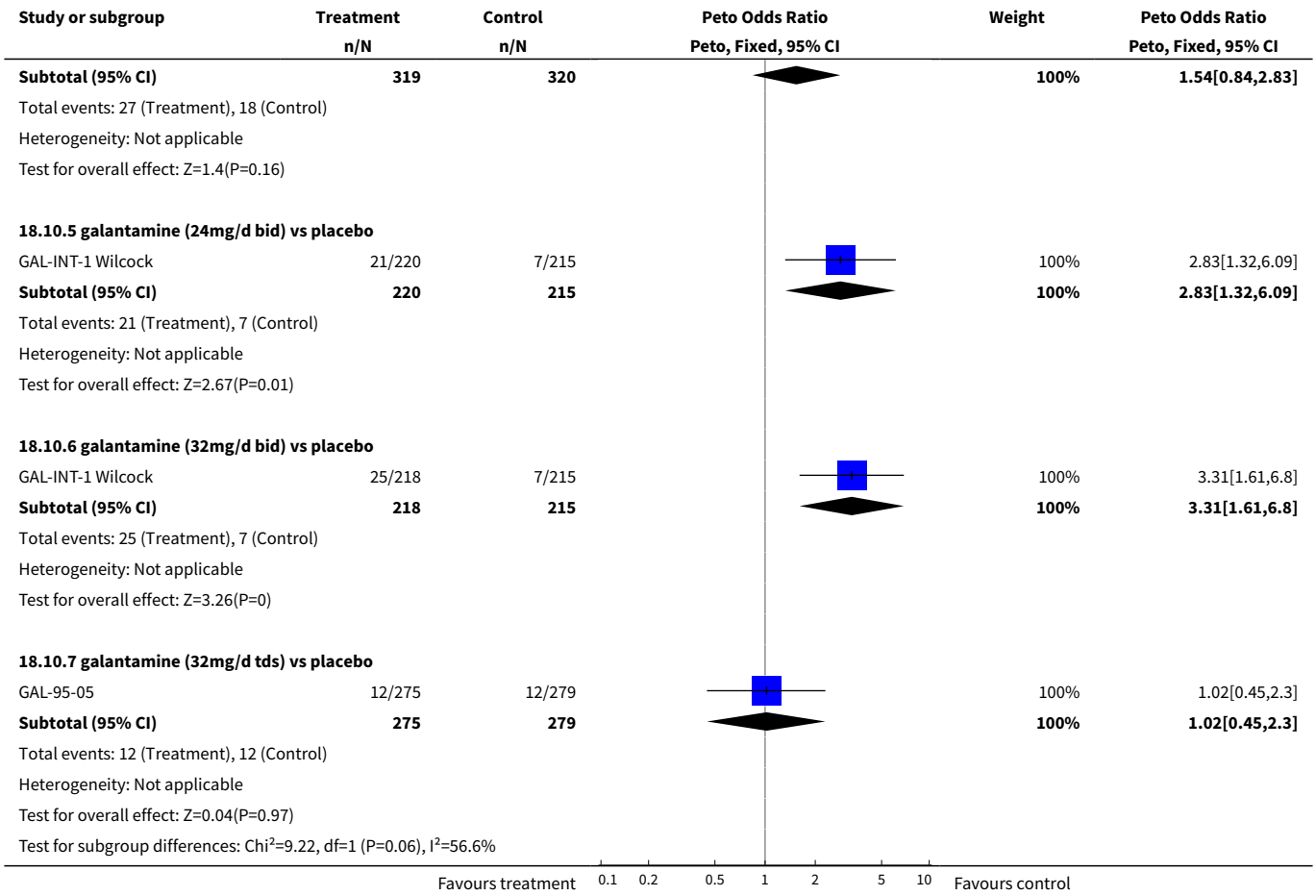

Comparison 19. Proportion of subjects deceased

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of subjects deceased (3 months)	2	940	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.10, 1.95]
1.1 galantamine (24-32mg/d bid) vs placebo	1	386	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.98]
1.2 galantamine (32mg/d tds) vs placebo	1	554	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.14, 7.25]
2 Proportion of subjects deceased (6 months)	4	4286	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.50, 1.78]
2.1 galantamine (16-24mg/d bid) vs placebo	1	651	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.06, 15.91]
2.2 galantamine (16-24mg/d Prolonged Release) vs placebo	1	644	Odds Ratio (M-H, Fixed, 95% CI)	3.06 [0.32, 29.54]

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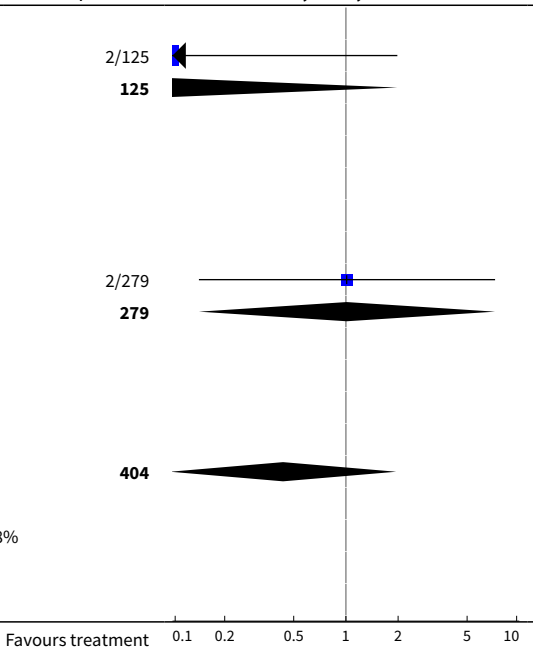
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 galantamine (24mg/d bid) vs placebo	3	1576	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.35, 1.98]
2.4 galantamine (32mg/d bid or tds) vs placebo	1	424	Odds Ratio (M-H, Fixed, 95% CI)	3.04 [0.12, 75.12]
2.5 galantamine (8mg/d bid) vs placebo	1	426	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.06, 4.58]
2.6 galantamine (16mg/d bid) vs placebo	1	565	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.17, 3.46]
3 Proportion of subjects deceased (24 months in MCI)	2	1903	Odds Ratio (M-H, Fixed, 95% CI)	9.33 [1.72, 50.54]
3.1 galantamine (16-24mg/d bid) vs. placebo in MCI	2	1903	Odds Ratio (M-H, Fixed, 95% CI)	9.33 [1.72, 50.54]

Analysis 19.1. Comparison 19 Proportion of subjects deceased, Outcome 1 Proportion of subjects deceased (3 months).

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
19.1.1 galantamine (24-32mg/d bid) vs placebo					
GAL-INT-2 Rockwood	0/261	2/125		63.09%	0.09[0,1.98]
Subtotal (95% CI)	**261**	**125**		**63.09%**	**0.09[0,1.98]**
Total events: 0 (Treatment), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					
19.1.2 galantamine (32mg/d tds) vs placebo					
GAL-95-05	2/275	2/279		36.91%	1.01[0.14,7.25]
Subtotal (95% CI)	**275**	**279**		**36.91%**	**1.01[0.14,7.25]**
Total events: 2 (Treatment), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
Total (95% CI)	**536**	**404**		**100%**	**0.43[0.1,1.95]**
Total events: 2 (Treatment), 4 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.68, df=1(P=0.19); I^2=40.48%					
Test for overall effect: Z=1.09(P=0.28)					
Test for subgroup differences: Not applicable					



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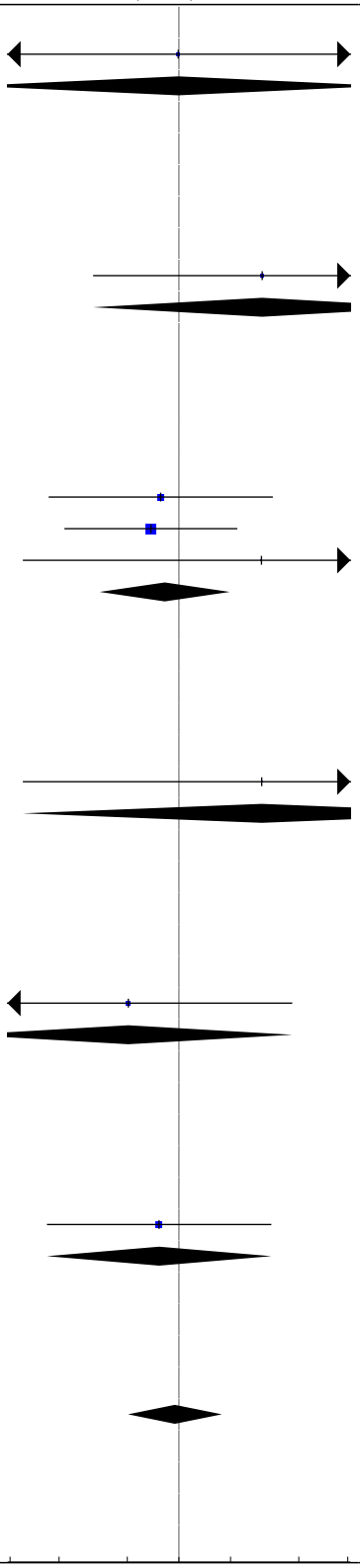
Analysis 19.2. Comparison 19 Proportion of subjects deceased, Outcome 2 Proportion of subjects deceased (6 months).

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
19.2.1 galantamine (16-24mg/d bid) vs placebo					
GAL-INT-10 Brodaty	1/327	1/324		5.03%	0.99[0.06,15.91]
Subtotal (95% CI)	**327**	**324**		**5.03%**	**0.99[0.06,15.91]**
Total events: 1 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
19.2.2 galantamine (16-24mg/d Prolonged Release) vs placebo					
GAL-INT-10 Brodaty	3/320	1/324		4.94%	3.06[0.32,29.54]
Subtotal (95% CI)	**320**	**324**		**4.94%**	**3.06[0.32,29.54]**
Total events: 3 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.97(P=0.33)					
19.2.3 galantamine (24mg/d bid) vs placebo					
GAL-USA-10 Tariot	3/273	4/286		19.39%	0.78[0.17,3.53]
GAL-INT-6Erkinjuntti	7/396	5/196		32.97%	0.69[0.22,2.19]
GAL-USA-1 Raskind	1/212	0/213		2.49%	3.03[0.12,74.76]
Subtotal (95% CI)	**881**	**695**		**54.85%**	**0.83[0.35,1.98]**
Total events: 11 (Treatment), 9 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.73, df=2(P=0.69); I^2=0%					
Test for overall effect: Z=0.43(P=0.67)					
19.2.4 galantamine (32mg/d bid or tds) vs placebo					
GAL-USA-1 Raskind	1/211	0/213		2.48%	3.04[0.12,75.12]
Subtotal (95% CI)	**211**	**213**		**2.48%**	**3.04[0.12,75.12]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					
19.2.5 galantamine (8mg/d bid) vs placebo					
GAL-USA-10 Tariot	1/140	4/286		13.1%	0.51[0.06,4.58]
Subtotal (95% CI)	**140**	**286**		**13.1%**	**0.51[0.06,4.58]**
Total events: 1 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.6(P=0.55)					
19.2.6 galantamine (16mg/d bid) vs placebo					
GAL-USA-10 Tariot	3/279	4/286		19.61%	0.77[0.17,3.46]
Subtotal (95% CI)	**279**	**286**		**19.61%**	**0.77[0.17,3.46]**
Total events: 3 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.35(P=0.73)					
Total (95% CI)	**2158**	**2128**		**100%**	**0.95[0.5,1.78]**
Total events: 20 (Treatment), 19 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.78, df=7(P=0.9); I^2=0%					
Test for overall effect: Z=0.17(P=0.86)					
Test for subgroup differences: Not applicable					



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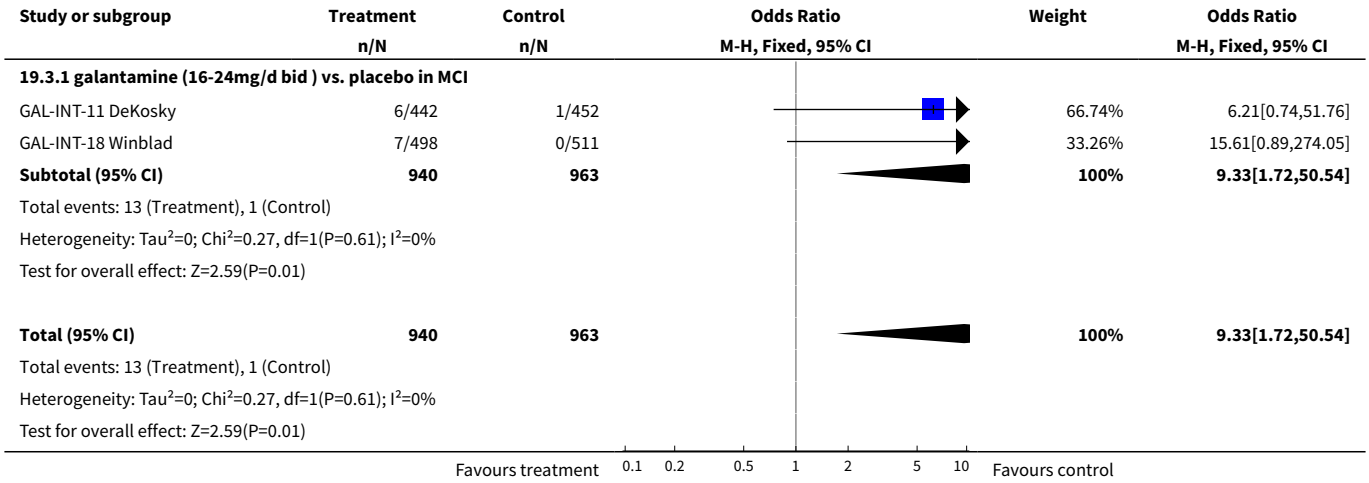
Analysis 19.3. Comparison 19 Proportion of subjects deceased, Outcome 3 Proportion of subjects deceased (24 months in MCI).



WHAT'S NEW

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

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 1, 2001

Date	Event	Description
16 November 2005	New citation required and conclusions have changed	November 2005 Update: additional trials and data have been added to the analyses and two MCI trials have been included for the first time, so altering the title of the review.

CONTRIBUTIONS OF AUTHORS

Clement Loy took over from Jason Olin as main reviewer for the updates of this review from November 2003. He dealt with article collection, in- and exclusion of new references, updated the data- analyses and rewrote the manuscript where necessary

Lon Schneider co-wrote, reviewed article coding, and assisted with editing the manuscript, for the original review as well as all subsequent updates.

Consumer Editors: Enid Light and Mervyn Richardson
Contact Editor: Leon Flicker

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DECLARATIONS OF INTEREST

Dr. Schneider and the University of Southern California have received clinical trials-and other contracts from Janssen Pharmaceutica and Johnson and Johnson, Inc. Dr. Schneider has served as a consultant to Janssen, Pfizer, and Novartis, all manufacturers of cholinesterase inhibitors used to treat AD, and to Forest Pharmaceuticals, manufacturer of memantine used to treat AD, for which he received payments. Dr. Loy has received a Wellcome Trust Travelling Award in relation to his work with the Cochrane Collaboration.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute of Mental Health (MH01368 (OLIN), MH19074, MH48759), USA.
- National Institute on Aging (AG05142), USA.
- NIMH Clinical Antipsychotic Trials of Interventions Effectiveness, USA.

NOTES

August 2004:

A trial studying the efficacy of Galantamine in mixed Alzheimer's Disease/ vascular dementia was added.

Analyses for GAL-INT-2 and GAL-93-01 were amended based on press reports, slightly changing existing analyses, and adding additional data that was previously unavailable. Added references for publication of GAL-INT-1 and GAL-93-01.

Notes:
-Tariot global rating formerly was stated as cibic-plus. The citation for the was the ADCS-CGIC. This has been corrected.
-Raskind global rating formerly was stated as cibic-plus. The citation for the was the ADCS-CGIC. This has been corrected.
-Rockwood global rating was formerly stated as cibic-plus. The citation for the was the ADCS-CGIC. This has been corrected.
-Wilcock global rating was formerly stated as cibic-plus. The citation for the was the ADCS-CGIC. This has been corrected.

New data tables were added for 3-month adverse events and discontinuations.

November 2005

Trials were added, studying the efficacy of Galantamine in Mild Cognitive Impairment, and the efficacy of Prolonged Release formulation of Galantamine in Alzheimer's Disease.

Death rates for the Galantamine trials were also recorded.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*drug therapy]; Cholinesterase Inhibitors [*therapeutic use]; Cognition Disorders [*drug therapy]; Double-Blind Method; Galantamine [*therapeutic use]; Multicenter Studies as Topic; Nootropic Agents [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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