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Comparative safety and efficacy of cognitive enhancers for Alzheimer's dementia: a systematic review with individual patient data network meta-analysis

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ABSTRACT

Objective To examine the comparative efficacy and safety of cognitive enhancers by patient characteristics for managing Alzheimer's dementia (AD).

Design Systematic review and individual patient data (IPD) network meta-analysis (NMA) based on our previously published systematic review and aggregate data NMA.

Data sources MEDLINE, Embase, Cochrane Methodology Register, CINAHL, AgeLine and Cochrane Central Register of Controlled Trials up to March 2016.

Participants 80 randomised controlled trials (RCTs) including 21 138 adults with AD, and 12 RCTs with IPD including 6906 patients.

Interventions Cognitive enhancers (donepezil, rivastigmine, galantamine and memantine) alone or in any combination against other cognitive enhancers or placebo.

Data extraction and synthesis We requested IPD from authors, sponsors and data sharing platforms. When IPD were not available, we used aggregate data. We appraised study quality with the Cochrane risk-of-bias. We conducted a two-stage random-effects IPD-NMA, and assessed their findings using CINeMA (Confidence in Network Meta-Analysis).

Primary and secondary outcomes We included trials assessing cognition with the Mini-Mental State Examination (MMSE), and adverse events.

Results Our IPD-NMA compared nine treatments (including placebo). Donepezil (mean difference (MD)=1.41, 95% CI: 0.51 to 2.32) and donepezil +memantine (MD=2.57, 95% CI: 0.07 to 5.07) improved MMSE score (56 RCTs, 11 619 participants; CINeMA score: moderate) compared with placebo. According to P-score, oral rivastigmine (OR=1.26, 95% CI: 0.82 to 1.94, P-score=16%) and donepezil (OR=1.08, 95% CI: 0.87 to 1.35, P-score=30%) had the least favourable safety profile, but none of the estimated treatment effects were sufficiently precise when compared with placebo (45 RCTs, 15 649 patients; CINeMA score: moderate to high). For moderate-to-severe impairment, donepezil, memantine and their combination performed best, but for mild-to-moderate impairment donepezil and transdermal rivastigmine ranked best. Adjusting for MMSE baseline differences, oral rivastigmine and galantamine

Strengths and limitations of this study

- This is one of the most comprehensive systematic reviews and network meta-analysis of cognitive enhancers including individual patient data for Alzheimer's dementia to produce treatment recommendations by patient characteristics.
- We followed the methodologically rigorous guidelines in the Cochrane Handbook for systematic reviews, and assessed credibility in the results using the Confidence in Network Meta-Analysis tool.
- Access to individual patient data allowed us to (1) observe minor differences between the original published results and our reanalysis, potentially due to differences in imputation methods for missing data or because original studies have excluded some patients, and hence have used a smaller sample size, (2) overcome potential reporting bias and (3) assess for potential effect modifiers that were not reported in the original publications (eg, comorbidities, additional medications) and explore for treatment-by-covariate interactions on the patient-level.
- Two-thirds of the included randomised controlled trials (RCTs), were associated with high risk of bias for incomplete outcome data due to attrition.
- We were unable to include individual patient data for all RCTs (only 15% of the studies shared their individual patient data), highlighting potential retrieval bias.
- Our literature searches were conducted 5 years ago and additional relevant studies may be available. However, obtaining individual patient data in a timely manner was very challenging and required more time than anticipated. Similar to all systematic reviews, the evidence should be updated regularly.

improved MMSE score, whereas when adjusting for comorbidities only oral rivastigmine was effective.

Conclusions The choice among the different cognitive enhancers may depend on patient's characteristics. The MDs of all cognitive enhancer regimens except for single-agent oral rivastigmine, galantamine and memantine, against placebo were clinically important for cognition (MD larger than 1.40 MMSE points), but results were quite imprecise. However, two-thirds of the published RCTs were associated with high risk of bias for incomplete outcome data, and IPD were only available for 15% of the included RCTs.

PROSPERO registration number CRD42015023507.

INTRODUCTION

Alzheimer's dementia (AD) is the most common type of dementia.[1] Patients living with AD have a lower quality of life due to deterioration in function, cognition, behaviour and mental health over time, as well as increased mortality.[2] Pharmacological treatment for AD predominantly consists of cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and the N-methyl-d-aspartate receptor antagonist, memantine. All three cholinesterase inhibitors and memantine are currently the only effective licenced treatments for dementia,[3] but their clinical effect can be small and there is no convincing evidence that they modify the disease process in AD.[4] Also, it is unclear whether galantamine, rivastigmine or donepezil should be used by patients with severe AD, or whether memantine is the optimal treatment for severe AD.[5]

In AD, disease severity and sex are potential effect modifiers. However, aggregate data and covariates of interest (eg, sex, disease severity) are not consistently reported across randomised clinical trials (RCTs).[6] The use of individual patient data (IPD) has several advantages, such as it allows for the exploration of the relationship between treatment effects and patient-level characteristics, and it overcomes restrictions in using the information reported in the publication among others. The aim of this study was to examine the comparative efficacy and safety of cognitive enhancers for patients with different characteristics, such as severities of AD and for women versus men through a systematic review and IPD network meta-analysis (NMA). This systematic review was based on our previously published systematic review and aggregate data NMA.[6] NMA is an extension of standard meta-analysis synthesising different sources of evidence from a network of RCTs comparing different treatments within a single model. NMA can provide treatment effect estimates for treatment comparisons that have not studied in a head-to-head study.

METHODS

We reported our results according to the Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for NMA and PRISMA-IPD.[7 8]

Protocol

The research question and protocol were based on our previous systematic review and NMA.[6] We registered our systematic review protocol with the prospective register of systematic reviews (PROSPERO), and published our protocol.[9] Additional information is also provided in online supplemental appendix 1 and online supplemental file 2. Herein, we briefly summarise our methods.

Eligibility criteria

We updated our previous systematic review,[6] using similar population, interventions, comparators, study designs and time period criteria. The literature search was updated from January 2015 to March 2016. We included published and English RCTs that assessed cognition via the Mini-Mental State Examination (MMSE; efficacy and primary outcome) and/or adverse events (AE; safety outcome) in adults with AD.

IPD collection process

We contacted the corresponding author followed by the next-in-order author, as presented in each eligible RCT, to obtain IPD. The author contact process was part of an RCT that our team conducted to assess methods that may optimise response rates for IPD retrieval.[10] We also contacted sponsors of eligible trials, as reported in the publications. We contacted industry sponsors only, as we were not able to locate contact information for non-industry sponsors (eg, grants and university funding). If a study had multiple sponsors, we contacted all of them. To further facilitate IPD access, we contacted the Clinical Study Data Request[11] and Yale University Open Data Access data sharing platforms.[12] If a data provider was unable to provide IPD we noted the reason.

Risk of bias and quality appraisal

We appraised study quality using the Cochrane risk of bias tool.[13] To ensure data consistency[8] we compared IPD with aggregate data reported in the publication. We assessed whether randomisation of patients was adequate (ie, intervention and comparison groups were balanced for important patient characteristics), by comparing numbers and types of patients in each arm.

When at least 10 studies were available for each treatment against placebo, publication bias and small-study effects were examined visually using the comparison adjusted funnel plot under the fixed-effect model.[3] When a funnel plot asymmetry was detected, we performed the Copas selection for the treatment comparisons that were informed by at least 10 studies and for which asymmetry was evident in the funnel plot. We explored the possibility that this was due to publication bias,[14] and made moderate assumptions about the probability of publication of the smaller and larger (in terms of SE) studies. We assumed that the smallest study had a probability of publication equal to 40%–50% and the largest study had a probability of 80%–90%. Confidence in NMA findings was assessed for each outcome using CINeMA (Confidence in Network

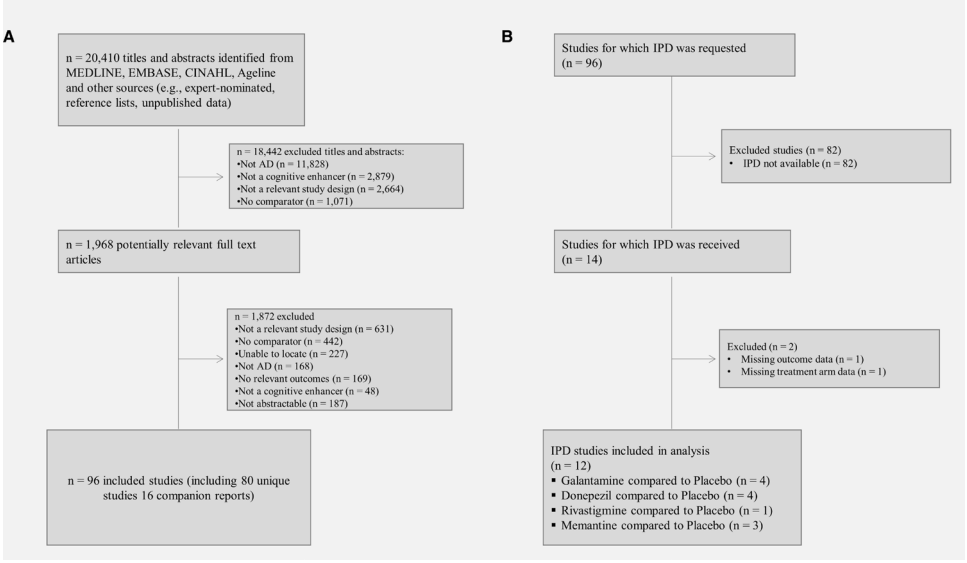

Figure 1 Flow diagram for study inclusion in the review (A) and studies retrieved with individual patient data (B). AD, Alzheimer's dementia; IPD, individual patient data.

Meta-Analysis, see online supplemental appendix 1 for more details).[15]

Synthesis

We performed a descriptive analysis using frequencies and distributions of the characteristics of the included patients and treatments. For each outcome, we present the network geometry according to IPD availability. We conducted a two-stage IPD analysis, whereby data were analysed separately in each trial in the first stage and the trial parameter estimates were synthesised in a random-effects meta-analysis or NMA in the second stage.

The summary treatment effects are presented using the OR or mean difference (MD) along with their corresponding CIs and prediction intervals (PIs).[16] We ranked the interventions for each outcome using the P-scores (and SUCRAs (surface under the cumulative ranking curve) in meta-regression analysis), and present them in a rank-heat plot.[17 18]

Patient and public involvement

Not applicable.

RESULTS

Literature search, study selection and IPD obtained

After screening 20 410 titles and abstracts and 1968 full-text articles, 96 studies fulfilled the eligibility criteria; 80 unique studies and 16 companion reports (figure 1A, online supplemental appendix 2).

Of the 80 unique RCTs, 55 reported at least one industry-sponsored funder (ie, 40 studies reported a single industry-sponsor and 15 multiple industry-sponsors). In the remaining studies, nine were publicly-sponsored and 16 did not report any information about funding. We requested IPD by contacting the corresponding authors for 80 RCTs that included 21 138 participants. None of the original authors shared their IPD. Fifteen commercial sponsors were then contacted and 6 (40%) sponsors shared their data through proprietary sponsor-specific platforms. The six sponsors were contacted for 46 RCTs (14 580 participants), and we obtained IPD for 30% (14 RCTs, 8007 participants) of these RCTs (1058 total waiting days up to 9 March 2020). The study flow for obtaining IPD is depicted in figure 1B.

We were able to include 12 (6906 patients) of 14 RCTs in our NMA due to incompleteness of provided IPD (online supplemental appendix 3). The number of studies with available/non-available IPD from each data provider along with reasons for non-availability of IPD are presented in online supplemental appendix 4.

Study and patient characteristics

Most included studies (33%) were multinational. The mean age of patients ranged from 61 to 86 years. The majority of the RCTs included patients with mild–moderate AD (55%), although the diagnostic criteria used for AD varied widely table 1. The most frequent longest duration of follow-up was 24 weeks (24 RCTs, 30%; online supplemental appendix 5). Important patient characteristics, such as per cent of men and dropout rates, were not balanced across groups in the RCTs with provided IPD (online supplemental appendix 6). Comparing study and patient characteristics of available and non-available IPD when a study was industry-sponsored, we found differences in the year of study publication, study size and absolute MD (online supplemental appendix 7).

Risk of bias and IPD integrity

Using the Cochrane risk-of-bias tool, allocation concealment was at low risk of bias for 43% and blinding of participants and personnel was low for 64% of the RCTs (online supplemental appendix 8). One-third of the RCTs had

Table 1 Study and patient characteristics

	AD (N=80)	IPD (N=12)
Total number of participants	21 138	6906
Longest duration of follow-up in weeks: mean (range)	28.28 (8.00–208.00)	29.33 (12.00–104.00)
Mean number of patients (range)	264 (14–2045)	4867 (123–2045)
Mean age in years (range)	74.64 (61.00–85.70)	73.94 (70.40–78.00)
Mean % female (range)	61.35 (3.00–89.00)	62.76 (53.68–81.00)
Country of conduct: frequency (%)		
Canada	2 (2.50)	1 (8.33)
China	6 (7.50)	–
Germany	1 (1.25)	–
Iran	2 (2.50)	–
Italy	6 (7.50)	–
Japan	7 (8.75)	1 (8.33)
Norway	1 (1.25)	–
Romania	1 (1.25)	–
South Korea	1 (1.25)	–
Spain	3 (3.75)	–
Sweden	2 (2.50)	–
Turkey	1 (1.25)	–
UK	6 (7.50)	1 (8.33)
USA	15 (18.75)	–
Multinational	26 (32.50)	9 (75.00)
Interventions examined: frequency*		
Placebo/no treatment	61 (76.25)	12 (100.00)
Donepezil	47 (58.75)	4 (33.33)
Galantamine	20 (25.00)	4 (33.33)
Memantine	20 (25.00)	3 (25.00)
Rivastigmine†	18 (22.50)	1 (8.33)
Outcomes reported: frequency*		
Mini-Mental State Examination	57 (71.25)	6 (50.00)
Adverse events	46 (57.50)	12 (100.00)
Funding		
Industry-sponsored	48 (60.00)	12 (100.00)
Publicly-sponsored‡	9 (11.25)	–
Mixed	7 (8.75)	–
Not reported	16 (20.0)	–
Severity of AD: frequency (%)		
Mild	3 (3.75)	–
Mild–moderate	44 (55.00)	7 (58.33)
Mild–severe	2 (2.50)	–
Moderate	3 (3.75)	–
Moderate–severe	11 (13.75)	1 (8.33)
Severe	6 (7.50)	2 (16.67)
Not reported	11 (13.75)	2 (16.67)
Diagnostic criteria for AD: frequency*		

Continued

Table 1 Continued

	AD (N=80)	IPD (N=12)
Mini-Mental State Examination	70 (87.50)	12 (100.00)
National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders Association	67 (83.75)	12 (100.00)
Diagnostic and Statistical Manual of Mental Disorders	39 (48.75)	5 (41.67)
MRI/CT	9 (11.25)	2 (16.67)
Clinical Dementia Rating	6 (7.50)	–
Hachinski Ischemic Score	5 (6.25)	–
Alzheimer's Disease Assessment Scale-Cognitive Subscale	3 (3.75)	1 (8.33)
Other	20 (25.00)	1 (8.33)

*Multiple interventions and outcomes reported per study.
†Rivastigmine refers to either oral or transdermal administration.
‡Including sponsors such as the National Institute of Aging, UK Medical Research Council and Veteran Affairs.
–, not applicable; AD, Alzheimer's dementia ; IPD, individual patient data .

low risk of incomplete outcome data bias due to attrition and almost two-thirds had high potential risk of 'other' bias, specifically, funding bias. The other risk of bias item was scored as unclear for 32%. Overall risk of bias was comparable in studies with available and unavailable IPD (online supplemental appendix 9).

All IPD provided were checked for consistency and results from published RCTs were reproduced and provided in online supplemental appendix 10. High dropout rates were observed in the IPD; experiencing an AE was the most common reason for dropout. Despite the high dropout rates observed in the individual studies, there was no indication of correlation between age and dropout (online supplemental appendix 11). Comparison-adjusted funnel plot for MMSE suggested there is indication for small-study effects (see online supplemental appendix 12). In contrast to the standard meta-analysis (MD=1.65, 95% CI: (0.16 to 3.14)), the Copas selection model estimated a pooled treatment effect for donepezil versus placebo (MD=1.87, 95% CI: (1.55 to 2.20)) with between-study variance τ^2=1.95, and correlation coefficient −0.45 (–0.76 to –0.01) reflecting the belief that the propensity for publication was associated with the observed effect size.

NMA

In both MMSE and AE outcomes, on average there were no important concerns regarding the transitivity and consistency assumptions (online supplemental appendices 13 and 14; design-by-treatment interaction test MMSE: χ^2=4.36, 13 df, p value=0.987; AE: χ^2=3.57, 6 df, p value=0.735). Below we present the main analysis results compared with placebo. Additional analyses are presented in online supplemental appendices 15 and 16. The network geometry is presented in figure 2.

Cognition

The NMA for MMSE included 56 RCTs, 9 treatments (including placebo) and 11 619 participants. Nine RCTs (3625 patients) contributed IPD and 47 RCTs (7994 patients) contributed aggregated data to the NMA. Two studies[19 20] did not report MMSE in the final publication, but in the retrieved IPD we were able to use data for this outcome.

NMA of studies with IPD and aggregate data

Studies in this NMA compared all available treatments. Donepezil (MD=1.41, 95% CI: 0.51 to 2.32) and donepezil +memantine (MD=2.57, 95% CI: 0.07 to 5.07) were superior to placebo in terms of MMSE score (online supplemental appendix 15). Transdermal rivastigmine

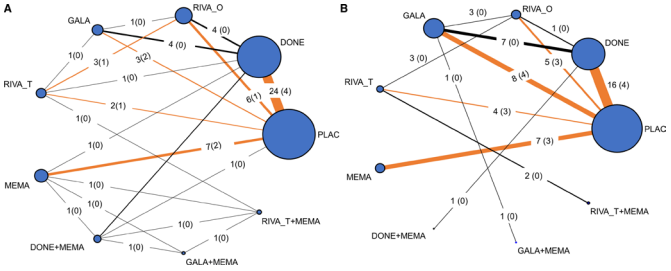

Figure 2 Network diagrams for (A) MMSE and (B) AE outcomes. The size of each node and line indicates the number of studies included in each treatment comparison. The number of studies per treatment comparison is presented on each edge, and the number of studies with individual patient data (IPD) is depicted in a parenthesis. Orange coloured edges are informed by both IPD and aggregate data, whereas black coloured edges are informed by aggregate data only. AE, adverse event; DONE, donepezil; GALA, galantamine; MEMA, memantine; MMSE, Mini-Mental State Examination; PLAC, placebo; RIVA_O, oral rivastigmine; RIVA_T, transdermal rivastigmine.

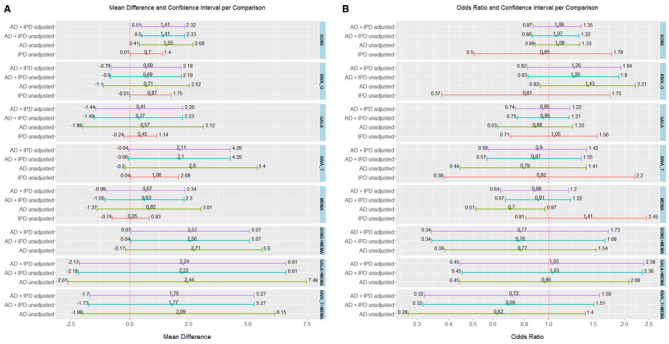

Figure 3 Forest plot of network meta-analysis (NMA) results for all cognitive enhancers versus placebo in (A) MMSE outcome, and (B) AE outcome. NMA results are presented for (i) aggregate data (AD) and fully adjusted results from studies with available individual patient data (IPD), (ii) AD and crude results from studies with available IPD, (iii) AD only (studies with available IPD are not included in the analysis) and (iv) crude results from individual studies with IPD. AD, Alzheimer's dementia; AE, adverse events; DONE, donepezil; GALA, galantamine; MEMA, memantine; MMSE, Mini-Mental State Examination; PLAC, placebo; RIVA_O, oral rivastigmine; RIVA_T, transdermal rivastigmine.

(MD=2.11, 95% CI: −0.04 to 4.26), and the combinations donepezil +memantine, galantamine +memantine (MD=2.24, 95% CI: −2.13 to 6.61), and transdermal rivastigmine +memantine (MD=1.79, 95% CI: −1.70 to 5.27) were associated with a MD from placebo of more than 1.40 MMSE points. A previous study suggested a MD larger than 1.40 is a minimal clinically important difference (MCID).[21] However, the associated 95% CIs were quite imprecise spanning between a mean decrease below and a mean increase above the suggested MCID value (figure 3A). However, donepezil +memantine had the highest likelihood of being the most effective in improving MMSE score (P-score range 79%–80%, figure 4). Confidence in NMA results was moderate (online supplemental appendix 17).

NMA of studies with aggregate data

Studies in this NMA compared all available treatments. Donepezil improved MMSE score significantly (MD=1.55, 95% CI: 0.41 to 2.68). Assuming an MCID of 1.40, results were in agreement with the NMA of IPD and aggregate data, and donepezil +memantine (MD=2.71, 95% CI: −0.17 to 5.60) was likely the most effective in improving MMSE score (P-score=76%).

NMA of studies with IPD

Studies in this NMA compared placebo, donepezil, oral rivastigmine, transdermal rivastigmine, galantamine and memantine. Donepezil (MD=0.70, 95% CI: 0.01 to 1.40) and transdermal rivastigmine (MD=1.06, 95% CI: 0.04 to 2.08) were superior to placebo, but none of the point estimates reached a previously suggested MCID.[21] The most effective treatment was likely transdermal rivastigmine (P-score=82%).

Figure 4 Rank-heat plot of P-scores for nine treatments, including placebo, studied in randomised clinical trials with patients with Alzheimer's dementia assessing Mini-Mental State Examination. Circles from inside out present results for different network meta-analyses including: (i) aggregate data (AD) only (studies with available IPD are not included in the analysis), (ii) crude results from individual studies with individual patient data (IPD), (iii) AD and crude results from studies with available IPD and (iv) AD and fully adjusted results from studies with available IPD. Numbers within each sector correspond to the P-score values as calculated in each model. AD, Alzheimer's dementia; adjMD, adjusted mean difference; DONE, donepezil; GALA, galantamine; MEMA, memantine; PLAC, placebo; RIVA_O, oral rivastigmine; RIVA_T, transdermal rivastigmine; unadjMD, unadjusted MD.

Additional analyses using IPD and aggregate data

Overall, additional analyses using both IPD and aggregate data were in agreement with the findings of the main analysis (online supplemental appendix 16). Cognitive performance was better in patients with mild-to-moderate MMSE receiving donepezil (MD=1.68, 95% CI: 0.31 to 3.06, P-score=69%) and most likely when receiving transdermal rivastigmine (MD=2.74, 95% CI: −0.68 to 6.16, P-score=81%). In patients with moderate-to-severe MMSE the combination donepezil +memantine improved MMSE score significantly (MD=2.49, 95% CI: 1.55 to 3.44, P-score=100%), but oral rivastigmine deteriorated MMSE score significantly (MD= −1.00, 95% CI: −1.87 to −0.12, P-score=4%). Donepezil (MD=1.31, 95% CI: 0.66 to 1.96, P-score=78%) and memantine (MD=0.69, 95% CI: 0.07 to 1.31, P-score=59%) also performed well for patients with moderate-to-severe cognitive impairment.

Accounting for the impact of the outlier studies, galantamine +memantine was the second-best cognitive enhancer (MD=1.87, 95% CI: 0.08 to 3.66, P-score=82%) after donepezil +memantine (MD=2.04, 95% CI: 1.03 to 3.05, P-score=92%). Using only IPD adjusted

for comorbidities suggested that oral rivastigmine improves MMSE score (MD=0.88, 95% CI: 0.31 to 1.45, P-score=75%). Similarly, using IPD adjusted for cognitive impairment assessed with MMSE at baseline suggested that oral rivastigmine (MD=0.88, 95% CI: 0.31 to 1.45, P-score=69%) and galantamine (MD=0.76, 95% CI: 0.34 to 1.18, P-score=62%) improve MMSE score, but in a future study, results are only stable for galantamine.

Heterogeneity in NMA was high (between-study variance=5.75, I^2=96%) compared also to the Rhodes *et al*[22] empirical distribution (median 0.05, 95% range: 0.00–7.56). However, heterogeneity decreased importantly when excluding outliers (between-study variance=0.59, I^2=73%), including only patients with moderate-to-severe AD (between-study variance=0.18, I2=44%), restricting to industry-sponsored trials (between-study variance=0.16, I^2=43%) and using IPD only (between-study variance=0.12, I^2=29%).

Adverse events

An NMA was conducted on AEs (study definitions are provided in online supplemental appendix 18) with 45 RCTs, 9 treatments (including placebo) and 15 649 patients (figure 2B). In particular, 12 RCTs (6420 patients) contributed to the NMA using their IPD and 33 RCTs (9229 patients) using their data on their aggregated form. The time taken to achieve at least one AE was available in eight studies with available IPD and ranged between 45 and 2228 days (online supplemental appendix 19). Only one study included a patient with an AE occurring earlier than the trial opening and was excluded from the study.[23]

NMA of studies with IPD and aggregate data

Studies in this NMA compared all available treatments. According to P-score, oral rivastigmine had the least favourable safety profile regarding AE (OR=1.26, 95% CI: 0.82 to 1.94, P-score=16%), followed by donepezil (OR=1.08, 95% CI: 0.87 to 1.35, P-score=30%) and galantamine +memantine (OR=1.03, 95% CI: 0.45 to 2.39, P-score=43%), yet in these comparisons the odds of experiencing an AE were imprecise and not importantly different from placebo (figure 3b; online supplemental appendices 16 and 20). Confidence in NMA results ranged between moderate and high (online supplemental appendix 17).

NMA of studies with aggregate data

Studies in this NMA compared all available treatments. Results were mainly consistent with NMA of IPD and aggregate data, but memantine was 0.70 times less likely to experience an AE than placebo, with an OR ranging from 0.51 to 0.97 (P-score=77%).

NMA of studies with IPD

Studies in this NMA compared placebo, donepezil, oral rivastigmine, transdermal rivastigmine, galantamine and memantine. Results were on average consistent with NMA of IPD and aggregate data.

Additional analyses using IPD and aggregate data

Additional analyses using both IPD and aggregate data, showed that memantine was 0.61 times less likely to experience an AE than placebo when using study duration as a covariate, with an OR ranging from 0.37 to 0.93 (P-score=88%). Restricting to low risk of bias for incomplete outcome data, galantamine was associated with significantly lower odds of an AE (OR=0.69, 95% CI: 0.50 to 0.97, P-score=80%).

Heterogeneity in NMA was low (between-study variance=0.04, I^2=22%) compared with the Turner *et al*[24] empirical distribution (median 0.12, 95% range: 0.01– 2.63). Heterogeneity decreased importantly when restricting to aggregate data (between-study variance=0.00, I^2=0%), low risk of bias for incomplete outcome data (between-study variance=0.02, I^2=10%), patients with moderate-to-severe cognitive impairment (between-study variance=0.00, I^2=0%) and when adjusting for study duration (between-study variance=0.03), year of publication (between-study variance=0.02), mean age (between-study variance=0.02) or sex (between-study variance=0.03).

DISCUSSION

We compared the efficacy and safety of cognitive enhancers regarding MMSE and AE outcomes to update our previous systematic review[6] and included studies with both aggregate data and IPD. Our results are in agreement with our previous systematic review,[6] and show that donepezil +memantine, donepezil alone and transdermal rivastigmine were the most effective treatments for improving MMSE score. However, heterogeneity was a major concern, which requires careful consideration before suggesting the use of cognitive enhancers, and particularly when the efficacy is not clear on the patient's characteristics. This was also captured by PIs, but their interpretation requires caution due to evidence of funnel plot asymmetry in the MMSE outcome. Overall, PIs are expected to include the true intervention effect expected in future studies, and they incorporate an extra component of variance, specifically between-study heterogeneity. In the absence of heterogeneity, CIs and PIs are equal. According to the P-score intervention ranking, both donepezil +memantine and transdermal rivastigmine had a favourable safety profile regarding AE, whereas the therapy with the least favourable profile was oral rivastigmine followed by donepezil. However, none of the estimated treatment effects were sufficiently precise when cognitive enhancers were compared with the placebo group. CINeMA suggested that within-study bias and reporting bias were the highest concerns for the MMSE outcome, whereas within-study bias and imprecision of effect estimates were the highest concerns for the AE outcome.

Overall, the choice among the different cognitive enhancers may depend on the patient's characteristics. In participants with moderate-to-severe cognitive impairment (defined by MMSE), a larger improvement in

cognitive performance was observed for donepezil and memantine, and their combination (donepezil +memantine), and these efficacy-related results are expected to also be reflected when a future study becomes available. The least effective cognitive enhancer in participants with moderate-to-severe cognitive impairment was oral rivastigmine. For patients with mild-to-moderate impairments based on MMSE scores, donepezil and transdermal rivastigmine were most likely the best performing cognitive enhancers. For patients with moderate-to-severe cognitive impairment, cognitive enhancers were well tolerated. For patients with mild-to-moderate cognitive impairment, all except for memantine and its combination with transdermal rivastigmine, were associated with increased odds of an AE, yet none of these results reached statistical significance. Overall, memantine was associated with lower odds of an AE than placebo, yet this was statistically significant only in the subnetwork analysis including aggregate data (ie, studies without IPD) and the meta-regression analysis using study duration as a covariate. However, acknowledging for heterogeneity in the network, PIs suggested that results are inconclusive and the odds of AE could not be differentiated between memantine and placebo. Of note, the accuracy of AE reporting may be impacted by the degree of cognitive impairment. Using IPD only and adjusting for MMSE baseline differences, (as shown in online supplemental appendix 16, MD: NMA of studies with IPD adjusted for baseline cognitive impairment), oral rivastigmine and galantamine improved MMSE score, whereas when adjusting for comorbidities only oral rivastigmine was effective, but results can change in a future study. Considering a MCID equal to 1.40 points,[21] the MDs of all cognitive enhancer regimens except for single-agent oral rivastigmine, galantamine and memantine, against placebo were clinically important for cognition, but these were associated with high uncertainty. However, the 1.40 MMSE cut-off value is not a widely adopted MCID. Also, high variability may be related to different populations included in the studies, such as genetic profiles, race and gender identity. Future studies should report this information to enable exploration of population characteristics that would benefit more, with a clinically important improvement, when using these treatments. Our results did not differ by participant characteristics sex, age and other medications, or by study characteristics, study duration and year of publication. However, these findings might be due to low power since meta-regression analyses depend on the number and size of studies, magnitude of the relationship between the covariate and effect size, along with its precision and heterogeneity.[25]

To the best of our knowledge, our study was the first to add IPD in an NMA of cognitive enhancers for patients with AD to produce treatment recommendations by patient characteristics. We followed the methods guidelines in the Cochrane Handbook for systematic reviews,[26] the reporting guidelines in the PRISMA-NMA and PRISMA-IPD statements[7 8] and evaluated credibility of findings using CINeMA.[15] Compared with previous systematic reviews, we included a larger number of studies and/or studies with shared IPD, compared in a wider range of cognitive enhancers.[6 27] Our results are in agreement with previous studies overall. Access to IPD allowed us to observe minor differences between the original published results and our reanalysis. An explanation in these differences may be that many studies used the last-observation-carried-forward imputation method, whereas we used the available case analysis when assessing MMSE. Another potential explanation might be that original studies excluded some patients, and hence used a smaller sample size.

Comparing NMA, results between aggregate data and IPD were in agreement. The only difference was observed in transdermal rivastigmine that was associated with a MCID of greater than 1.40 MMSE points against placebo in the aggregate data NMA compared with the IPD NMA, yet a statistically significant improvement was achieved in the IPD NMA. The inclusion of IPD in our NMA, allowed us to overcome potential reporting bias and to include IPD for (1) a study that we previously were unable to include since arm-level data were not reported in the RCT publication,[23] and (2) two studies that did not report MMSE results in their publications.[19 20] The use of IPD also allowed us to assess for potential effect modifiers that were not reported in the original publications (eg, comorbidities, additional medications) and explore for treatment-by-covariate interactions on the patient level. Several challenges were encountered during the IPD request from sponsors, showing that repositories are not a panacea (online supplemental appendix 21).

An important finding of our review is that the two-thirds of the published RCTs, were associated with high risk of bias for incomplete outcome data due to attrition, and the majority of these RCTs used the last-observation-carried-forward technique for missing data. This approach may bias results favouring cognitive enhancers, since the dropout rates were greater in the treatment group compared with the placebo group in 63% of the included studies and because dementia is a progressive disease. Of the 27 studies comparing treatment against placebo and reporting the number of dropouts, 17 studies had a greater dropout rate in the treatment group (treatment group: median dropout rate=28%,IQR (17%–39%); placebo group: median dropout rate=21%,IQR (15%–31%)). Last-observation-carried-forward is an inappropriate imputation method for AD studies, since it ignores expected deterioration of the patient's condition and stabilises the outcome at the value observed at the time of dropout (ie, the last observation).[28] Restricting to low risk of attrition bias studies, we found that galantamine was significantly associated with decreased odds of experiencing an AE.

Our study has limitations worth mentioning. First, we were unable to include IPD for all eligible studies (only 15% of the included RCTs shared their IPD), highlighting potential retrieval bias for IPD. However, recent

simulations have shown that combining IPD and aggregate data in an NMA can significantly improve precision, reduce bias and increase information compared with NMA relying on aggregated data alone.[29] Second, missing data are a big concern in the published RCTs for AD. We found high rates of dropouts from experiencing an AE and the patients' characteristics that may increase the chances of such adverse reactions prior to administering these cognitive enhancers should further be explored. To assess the impact of missing data in our NMA, we applied the informative missingness of difference in means.[30] However, future studies should explore the characteristics of missing participants and specific AEs. Third, the lack of studies in certain treatment comparisons may have affected the P-score calculation and treatment ranking. In particular, polytherapies were informed by maximum two studies, and ranking may have been in favour of the complex intervention group with the smaller number of studies.[31] For example, in MMSE the polytherapies including memantine in conjunction with one of the three treatments donepezil, galantamine, transdermal rivastigmine had a P-score ≥60%, but these all had wide 95% CIs for MD. As such, ranking should be interpreted with caution and along with the estimated effect sizes and their uncertainty measures. Fourth, the comparison-adjusted funnel plot for MMSE suggested there is an indication for small-study effects pointing to the treatment being better, and results should be interpreted with caution. This may also be related to the potential risk of funding bias, since the majority of the included studies were industry-sponsored and IPD were retrieved only from industry-sponsored studies favouring cognitive enhancers over placebo. Overall, MMSE score is only a surrogate maker for determining the impact of treatments on dementia. A full assessment that considers the potential impact of treatments on cognition, function and behavioural symptoms needs to be considered within the clinical context. Fifth, differences in patient characteristics, such as sex, were observed in the RCTs with provided IPD, which increased heterogeneity across studies. To account for these differences, we used the fully adjusted treatment effect estimates in the IPD analyses and the primary NMA analysis. Also, at the NMA level, we found that on average there were no important differences across treatment comparisons to threaten the transitivity assumption. Sixth, there are clinically important limitations associated with this review, including consistent definition of outcome measures across studies, a well-established MCID for the MMSE score, lack of consideration of drug doses due to inconsistent reporting and data retrieval bias that we were unable to overcome (15% of the studies shared their IPD). Future studies are needed to establish ranking efficacy in drug doses and combination of interventions across different disease severity categories. Seventh, the literature searches were conducted 5 years ago and additional relevant studies may be available. However, obtaining IPD in a timely manner was very challenging and required more time than anticipated (challenges to obtain IPD are outlined in online supplemental appendix 21). Similar to all systematic reviews, the evidence should be updated regularly.[32]

We expect that our findings will increase scientific knowledge, because people with AD require personalised medicine to optimise their healthcare. Well-conducted meta-analyses of IPD are considered the 'gold-standard' and influence patient care since patient-level data can be provided to facilitate tailored decision-making. However, results from meta-analyses of IPD are likely subject to retrieval bias and awareness of these limitations and their potential impact on findings is required (table 1).

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Contributors AAV, SES and ACT conceived and designed the study. AAV conducted the analyses, abstracted data, contacted sponsors, analysed data, interpreted results, appraised quality of results and wrote a draft manuscript. She is the guarantor of the present study. GS conducted the analyses, appraised quality of results and edited the manuscript. HMA coordinated the review, screened citations and full-text articles, abstracted data, appraised quality, cleaned the data, contacted sponsors and edited the manuscript. PR helped coordinate the study, screened citations and full-text articles, extracted and categorised data, appraised quality and edited the manuscript. SES and ACT interpreted results and edited the manuscript. ACT and HMA contacted authors. LS, MC, CT-S, DM, BRH and JH-L provided input into the design, interpreted results and edited the manuscript. All authors read and approved the final manuscript.

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Additional File 1: ***Comparative safety and efficacy of cognitive enhancers for Alzheimer's dementia: A systematic review with individual patient data network meta-analysis***

Veroniki AA, *et al. BMJ Open* 2022; 12:e053012. doi: 10.1136/bmjopen-2021-053012

Appendix 1: Additional information on the methods used in the review

Eligibility criteria, search strategy and study selection

We considered an adverse event (AE) as defined in the individual trials. Definitions were captured for each study separately. We included donepezil, rivastigmine, galantamine, and memantine alone or in combination with other treatment and compared with each other, supportive care or placebo. We excluded studies examining other cognitive enhancers or including individuals with mixed causes of dementia. We included published studies written in any language and of any duration.

Using terms from our previous review,4 the MEDLINE literature search was drafted by an experienced librarian (Dr. Laure Perrier) and revised after another librarian (Ms. Becky Skidmore) peer-reviewed the search terms.10 Subsequently, we searched the following databases: MEDLINE, EMBASE, Cochrane Methodology Register, CINAHL, Ageline and Cochrane Central Register of Controlled Trials. We also scanned reference lists of included studies and relevant reviews to supplement the electronic literature searches.

After pilot-testing, the results from the literature search were screened by pairs of reviewers working independently. Pairs of reviewers independently abstracted data (e.g., study characteristics, patient characteristics, outcome results) after a pilot-test. We resolved conflicts through discussion. The overall agreement among the reviewers for screening was over 70%.

IPD collection process and data abstraction

During the author contact process, two authors (a senior scientist ACT and a research assistant SL) sent a data request following several strategies as outlined in the RCT protocol:[1] a) an email requesting their IPD, b) email reminders (4 in total) at 2, 6, 10, and 14-week intervals after the initial email, c) reminders by post in week 7, and d) reminders via telephone in week 15. We also invited eligible authors to be a co-author on our updated systematic review provided that they share their anonymized IPD, and meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship.[2] Our team (AAV, SL) also contacted sponsors of the eligible trials, as reported in the publications. If a sponsor was not reported in a publication, we contacted the author (whom we emailed during the RCT) to determine who sponsored the study. To contact industry sponsors, we navigated the data sharing process from their websites or via an email, online portal, or phone inquiry. When no response was received, two follow-up reminders were sent to the sponsors.

We requested IPD on 1) patients: age, sex, severity of Alzheimer's disease (e.g. baseline MMSE [Mini-Mental State Examination] level), presence of behavioral disturbance, comorbid conditions (e.g., stroke, cardiovascular conditions, Parkinson's disease), other medications used for each patient, number of drop-outs, reasons for drop-out, and number of participants, 2) medication: treatment each patient was allocated to, dosage, 3) outcomes: event, date of event, time taken to achieve the event for AEs, MMSE values and measurement dates, and 4) date and method of randomization. We checked IPD provided for consistency with results from published RCTs., and contacted IPD providers when data inconsistencies were found.

Data extraction items included a) study characteristics: year of publication, country and continent according to the first author, journal in which the study was published, funding information; b) aggregate patient characteristics: study size and percentage of males, c) outcome data: study data (e.g., events or mean and standard deviations, and sample size per arm), and d) treatments compared. We also abstracted the corresponding authors' contact details. We categorized each study according to funding source (industry-sponsored, publicly-sponsored, mixed, and non-sponsored).

Certainty of the evidence

We used CINeMA (Confidence in Network Meta-Analysis) to assess confidence in the NMA estimates.[3] Six domains were evaluated with scores 'no concerns', 'some concerns' and 'major concerns': 1) within-study bias, 2) reporting bias, 3) indirectness, 4) imprecision, 5) heterogeneity, and 6) incoherence. We used the overall risk of bias per study, and for each treatment comparison we applied the average risk of bias. Similarly, for all treatment comparisons we used the average for indirectness. We assessed reporting bias based on the comparison-adjusted funnel plot since there are no established statistical methods to explore reporting bias. We used a comparison-adjusted funnel to account for the fact that each set of studies estimates a different summary effect in NMA. This is a scatterplot of the difference between the study-specific effect sizes from the

corresponding comparison-specific effect (obtained from standard meta-analysis) against the corresponding study-specific standard error. We used the fixed effect model for the standard meta-analysis performed for each treatment comparison, ordered treatments chronologically according to year of availability in Canada, and used only treatment comparisons versus placebo. We used the *netfunnel* command in Stata to produce the comparison-adjusted funnel plot.[4]

For imprecision, we considered a MD=1.4 and a OR=1 as a clinically important size of effect for MMSE and AE, respectively, and followed the CINeMA guidelines for exploring whether statistical significance and clinical importance coincide. Similarly, heterogeneity and incoherence (i.e. inconsistency) were assessed by following the standard CINeMA approach.

CINeMA assesses the credibility of the NMA results and heterogeneity examining the range of both confidence intervals (CIs; which do not capture heterogeneity) and prediction intervals (PIs; which capture heterogeneity) in relation to their equivalence. If a PI includes values that lead to a different conclusion than an assessment based on the corresponding CI, then this suggests that there is considerable heterogeneity. PIs are expected to include the true intervention effects in future studies with characteristics similar to the existing studies, and they incorporate the extent of between-study heterogeneity.[5 6] In the presence of considerable heterogeneity, they are wide to include intervention effects with different implications for practice. However, caution is needed in the interpretation of results in the presence of funnel plot asymmetry, since PIs are based on the assumption of a normal distribution for the study-specific effects and as such they may be problematic if the data do not follow a normal distribution.

Statistical Analysis

We performed a descriptive analysis using frequencies and percentages of the discrete characteristics of the included patients and treatments of the eligible studies. We explored the distributions of the continuous patient characteristics per outcome and treatment group using means and standard deviations. For studies not providing outcome results for a certain outcome, we presented distributions of the available and requested patient characteristics, whenever available. Outliers for each patient characteristic were also explored in each study dataset using boxplots. We also recorded the number of missing participants per treatment group and overall. We compared the characteristics of the unavailable and the available by the sponsors' studies. In particular, we explored whether these were well-conducted according to overall risk of bias, and compared distributions of mean participant age, publication year, study duration, study size, percent male, and magnitude of treatment effect, to assess for potential bias in IPD sharing. We conducted a two-stage analysis for both standard meta-analysis and NMA. The network geometry was explored through the presentation of network plots.

First stage

All IPD from included studies were first aggregated to study-level summary statistics using each sponsor's portal. The use of different platforms and failure to obtain IPD from all studies restricted us from combining IPD in a one-stage analysis. For each separate study with IPD available, we fitted a logistic regression model for the binary outcome and a linear regression model for the continuous outcome. For MMSE, we considered the longest duration of follow-up per study (most frequently at week 24). In the shared IPD, when we were unable to make a judgement on first and last date of visit per patient, we used the older coded date and the newest coded date as baseline and final value for each patient respectively.

Initially, we did not adjust for any of the patient characteristics provided, but in a subsequent analysis we included patient-level covariates with as many interaction terms in the model as the patient characteristics were provided (considering only the ones we have asked for). For each study, we obtained the adjusted odds ratio (OR) for binary data and adjusted mean difference (MD) for continuous data, along their corresponding 95% CI. We adjusted for any of the following variables that were available in each study: age, sex, severity of Alzheimer's disease (e.g., baseline Mini-Mental State Examination [MMSE] level), presence of behavioural disturbance, comorbidity, and other medications. The first stage of the IPD analyses were conducted in RStudio,[7] which was available in data providers. Additional medications and comorbid conditions were grouped into broader categories according to their clinical relevance to increase power in our analysis (e.g., grouped medications as anti-psychotics, anti-depressants, and cognitive enhancers, as well as comorbid conditions as psychiatric, neurological, and cardiac disorders). Eligible studies with insufficient data to derive a pairwise estimate for NMA were summarized descriptively without performing a statistical analysis.

We applied an available case analysis for each study, since we were unable to install R packages in most sponsor-specific platforms, and hence we applied a consistent approach across all IPD datasets. We explored the impact of missing data during the second stage of analysis. Reasons for missing participants and time taken to have a adverse event were captured (when available).

We synthesized IPD at the first stage in four different proprietary sponsor-specific platforms. Analyses were conducted in the RStudio using different R versions[7] according to what was provided in each sponsor's platform: R version 3.4.1 for AbbVie, R version 3.4.3 for CSDR, R version 3.5.1 for YODA, R version 3.6.0 for Lundbeck.

Second stage

Since we were not successful in obtaining IPD for all eligible studies, we combined both IPD and aggregate data in a single meta-analysis or NMA model. Both IPD and aggregate data studies shared the same amount of heterogeneity. In both meta-analysis and NMA models, we combined the adjusted IPD estimates with the aggregate data (main analysis). As a secondary analysis, we combined the unadjusted estimates from retrieved IPD with the evidence provided by the aggregated data studies in a joint NMA model. A common-within network between-study variance was assumed across comparisons for all NMA models.[8] We estimated the between-study variance using the DerSimonian and Laird[9] method and compared it with the relevant distributions provided by Turner et al[10] and Rhodes et al[11] to assess heterogeneity. We also calculated I^2 on the NMA level to quantify overall heterogeneity and inconsistency in each outcome.

To assess the validity of the transitivity assumption for each outcome, we assessed the distribution of potential effect modifiers (e.g., age, sex) across treatment comparisons in each network.[12-14] We visually inspected similarity and assessed whether these characteristics were likely to modify the treatment effect. We evaluated the consistency assumption using the design-by-treatment interaction model[15 16] and the loop-specific method.[17 18] In the presence of statistically significant inconsistency, we checked the data for discrepancies and if none were identified, we planned to conduct subgroup NMA or network meta-regression analysis adjusting for potential variables influencing the results.

We conducted additional NMA analyses for all potential effect modifiers requested from data providers. If relevant data were not available in the IPD, we used aggregate data of the relevant publications. Additional NMA analyses included: 1) subgroup analysis for industry vs. publicly sponsored studies, for studies with available IPD vs. studies with aggregate data (unadjusted estimates), and for AD severity, classified according to MMSE scores using the National Institute for Health and Care Excellence categories: mild (21–24), moderate (10–20), severe (<10),[19] 2) network meta-regression accounting for study duration, year of publication, mean age, and sex (% of male participants) effect modifiers separately and assuming a common regression coefficient across comparisons (studies with aggregate data were used only; studies with available IPD were pooled in a NMA separately adjusted for available covariates at first stage), 3) sensitivity analysis including studies with low risk of bias for allocation concealment and incomplete outcome data items, as these items may have an important impact on the meta-analysis results according to our previous NMA,[20] and 4) the 'informative missingness difference of means' (IMDoM) imputation method[21] for MMSE for the aggregate data studies to assess the impact of missing data in our NMA. In all additional NMA analyses, we used the adjusted effect estimates derived from the IPD within-study analysis and the aggregate data extracted from the eligible publications. Network meta-regression was performed in a Bayesian setting using OpenBUGS version 3.2.3, non-informative priors for all parameters in the model and a half-normal prior for the between standard deviation. We compared the results of the additional models by evaluating the treatment effect estimates and ranking statistics, as well as monitoring the reduction in the between-study variance.

We present the results using summary effect sizes, and in particular the MD for MMSE and the OR for AE, along with their corresponding CIs and PIs.[6] We ranked the interventions for each outcome according to their efficacy and safety using P-scores in frequentist analyses and SUCRAs (surface under the cumulative ranking curve) in Bayesian analyses (e.g., meta-regression analysis).[22 23] SUCRA is the numeric presentation of the intervention ranking and is based on the surface under the cumulative ranking probability function for each treatment. An equivalent frequentist statistic is the P-score measure that is based on the observed treatment effect estimates and their uncertainty. Both measures summarize the estimated probabilities for all possible ranks, account for uncertainty in relative ranking, and range between 0-100%, with 100% reflecting the best intervention with no uncertainty and 0% reflecting the worst intervention with no uncertainty. Ranking strategies are commonly encountered in NMAs,[24-26] and we present the hierarchy of cognitive enhancers in a rank-heat plot.[27]

Meta-analysis and NMA at the 2nd stage were conducted in the RStudio using R version 3.6.2 and the *meta*[28] and *netmeta*[29] packages, respectively.

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Appendix 2: Studies included in the systematic review

80 Main Studies:

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16 Companion Reports

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Appendix 3: Studies with available IPD but insufficient data to be included in the analysis

A study[1] of 859 participants comparing transdermal rivastigmine vs. placebo included only IPD for the placebo arm. Another study[2] of 285 participants comparing 22·5 mg of galantamine vs. 30 mg of galantamine vs. 45 mg of galantamine vs. placebo did not provide information about the AE or MMSE outcomes in the shared IPD.

CSDR: Novartis (study: NVT_SA_ENA713D1301) – Nakamura 2011

The study compares rivastigmine patch vs. placebo, but includes data only on placebo. Hence, we cannot conduct an analysis to convert data on their aggregated form so that to be included in our network meta-analysis. The IPD of this study included 288 participants in total.
According to the publication, 284 were allocated to the rivastigmine patch 5 cm2 group, 287 to the rivastigmine patch 10 cm2 group, and 288 to the placebo group.

Baseline characteristics of included patients

Characteristics	PLAC	Total	Missing Data	P-value	Outliers
Males	92 (32 %)	92 (32 %)	No	-	No
Age, mean (SD)	74.6 (7.4)	74.6 (7.4)	No	-	Yes - 1 value
AE, events/sample size	19/288	19/288	No	-	-
Baseline MMSE, mean (SD)	16.6 (2.9)	16.6 (2.9)	Yes - 1 value	-	No
MMSE, mean (SD)	17.5 (3.4)	17.5 (3.4)	No	-	No
Change score, mean (SD)	0.9 (1.6)	0.9 (1.6)	Yes - 2 values	-	Yes - 41 values
Total number of patients	288 (100 %)	288			

YODA: JNJ-Study-GAL-93-01 –Wilkinson 2001

The study compares galantamine 22.5mg, 30mg and 45mg vs placebo. In our analysis we combined galantamine 22.5mg, 30mg and 45mg in a single group. However, we only descriptively can include this study in our paper - not in the network meta-analysis – as it does not provide any info about the AE or MMSE outcomes (only total score for baseline). The IPD of this study included 285 participants in total.
According to the publication, 285 patients were randomized to: galantamine 18mg, 24mg, 36mg/day and placebo. Of the outcomes of interest, publication reported the AE outcome. According to the sponsor there are no differences in the reporting of doses:

- galantamine hydrobromide 7.5 mg =6 mg galantamine base was administered tid i.e galantamine hydrobromide 22.5 mg/d = galantamine base **18mg/day**
- galantamine hydrobromide 10 mg =8 mg galantamine base was administered tid i.e galantamine hydrobromide 30mg/d= galantamine base **24mg/day** and
- galantamine hydrobromide 15 mg =12 mg galantamine base was administered tid i.e galantamine hydrobromide 45mg/d= galantamine base **36mg/day**

Baseline characteristics of included patients

Characteristics	GALA	PLAC	Total	Missing Data	P-value	Outliers
Males	85 (30%)	36 (12%)	121 (42%)	No	<0.001	No
Age, mean (SD)	73.5 (8.2)	74.2 (9.0)	73.8 (8.5)	No	0.242	Yes - 1 value
AE, events/sample size*	-	-	-	-	-	-
Baseline MMSE, mean (SD)	18.6 (3.2)	18.8 (3.1)	18.7 (3.2)	No	0.616	No
MMSE, mean (SD)	-	-	-	-	-	-
Change score, mean (SD)	-	-	-	-	-	-
Total number of patients	198 (69%)	87 (31%)	285 (100%)			

*AE in publication is as follows, PLAC: 3/87, GALA 18mg: 6/88, GALA 24mg: 0/56, GALA 36mg: 5/54

[1]Nakamura Y, Imai Y, Shigeta M, et al. A 24-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of the rivastigmine patch in Japanese patients with Alzheimer's disease. Dement Geriatr Cogn Dis Extra 2011; 1(1): 163-79.
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Appendix 4: List of studies requested and sponsor response

Sponsor	Author, year	Interventions compared (dosage mg)*	Sponsor Response	IPD Received
Abbvie	Gault, 2015	Placebo/No treatment, Donepezil (10 mg)	Available	Yes
	Haig, 2014	Placebo/No treatment, Donepezil (5 – 10 mg)	Available	Yes
	Marek, 2014	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot share data (Potential business considerations under review))	No
AstraZeneca	Frolich, 2011	Placebo/No treatment, Donepezil (5 – 10 mg)	Available	No
Daiichi-Sankyo	Shimizu, 2015	Donepezil (5 mg), Galantamine (24 mg), Rivastigmine (18 mg)	Unavailable (Do not own data)	No
Eisai	Black, 2007	Placebo/No treatment, Donepezil (5 – 10 mg)	Available	Yes
	Burns, 1999	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot share data (Old study))	No
	Feldman, 2001	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Do not own data)	No
	Feldman, 2004	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Do not own data)	No
	Feldman, 2005	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Do not own data)	No
	Gauthier, 2002	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Do not own data)	No
	Holmes, 2004	Placebo/No treatment, Donepezil (10 mg)	Unavailable (Do not own data)	No
	Homma, 2008	Placebo/No treatment, Donepezil (10 mg)	Unavailable (Cannot share data (Old study))	No
	Johannsen, 2006	Placebo/No treatment, Donepezil (10 mg)	Unavailable (Do not own data)	No
	Jones, 2004	Donepezil (5 – 10 mg), Galantamine (8 – 24 mg)	Unavailable (Cannot share data (Old study))	No
	Mohs, 2001	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot share data (Old study))	No
	Rogers, 1996	Placebo/No treatment, Donepezil (5 mg)	Unavailable (Cannot share data (Old study))	No
	Rogers, 1998	Placebo/No treatment, Donepezil (10 mg)	Unavailable (Cannot share data (Old study))	No
	Rogers, 1998	Placebo/No treatment, Donepezil (10 mg)	Unavailable (Cannot share data (Old study))	No
	Schwam, 2010	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Do not own data)	No
	Seltzer, 2004	Donepezil (5 – 10 mg), Placebo/No treatment	Unavailable (Cannot share data (Old study))	No
	Shimizu, 2015	Donepezil (5 mg), Galantamine (24 mg), Rivastigmine (18 mg)	Unavailable (Do not own data)	No
	Sole-Padulles, 2013	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Do not own data)	No
	Tariot, 2001	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot share data (Old study))	No
	Wilkinson, 2002	Donepezil (5 – 10 mg), Rivastigmine (6 – 12 mg)	Unavailable (Do not own data)	No
Forest Laboratories/Allergen	Grossberg, 2013	Donepezil (NR) + Rivastigmine (13.3 mg) + Galantamine + Placebo, Donepezil (NR) + Rivastigmine (4.6 mg) + Galantamine (NR)+ Memantine (NR)	Unavailable (Cannot share data (No details provided))	No
	Ott, 2007	Placebo/No treatment, Memantine (5 -20 mg)	Unavailable (Cannot share data (No details provided))	No
	Peskind, 2006	Placebo/No treatment, Memantine (5 -20 mg)	Unavailable (Cannot share data (No details provided))	No
	Saxton, 2012	Placebo/No treatment, Memantine (20 mg)	Unavailable (Cannot share data (No details provided))	No
	van Dyck, 2007	Placebo/No treatment, Memantine (20 mg)	Unavailable (Cannot share data (No details provided))	No
GlaxoSmithKline	Gold, 2010	Placebo/No treatment, Donepezil (10 mg)	Available	Yes
	Maher-Edwards, 2011	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Do not own data)	No
Janssen	Ancoli-Israel, 2005	Donepezil (10 mg), Galantamine (8 mg)	Unavailable (Cannot identify study)	No
	Aronson, 2009	Placebo/No treatment, Galantamine (16 – 24 mg)	Unavailable (Cannot identify study)	No
	Burns, 2009	Placebo/No treatment, Galantamine (8-24 mg)	Available	Yes
	Cummings, 2004	Placebo/No treatment, Galantamine (4, 8, 12 mg)	Available	Yes
	Gaudig, 2011	Placebo/No treatment, Galantamine (8 mg)	Unavailable (Cannot identify study)	No
	Hager K, 2014	Placebo/No treatment, Galantamine (8 – 24 mg)	Available	Yes
	Kadir, 2008	Placebo/No treatment, Galantamine (16 – 24 mg)	Unavailable (Cannot identify study)	No
	Likitjaroen, 2012	Placebo/No treatment, Galantamine (8 – 24 mg)	Unavailable(Do not own data)	No
	Rockwood, 2001	Placebo/No treatment, Galantamine (24, 32 mg)	Available	Yes
	Rockwood, 2006	Placebo/No treatment, Galantamine (16 – 24 mg)	Unavailable (IPD not available)	No
	Scarpini, 2011	Placebo/No treatment, Galantamine (16 mg)	Unavailable (IPD not available)	No

Sponsor	Author, year	Interventions compared (dosage mg)*	Sponsor Response	IPD Received
	Shimizu, 2015	Donepezil (5 mg), Galantamine (24 mg), Rivastigmine (18 mg)	Unavailable (Cannot identify study)	No
	Tariot, 2000	Placebo/No treatment, Galantamine (8 mg)	Unavailable (Cannot identify study)	No
	Wilcock, 2003	Donepezil (5 – 10 mg), Galantamine (16 – 24 mg)	Unavailable (Cannot identify study)	No
	Zhang, 2012	Donepezil (5 – 10 mg), Galantamine (6 – 16 mg or 6 – 24 mg)	Unavailable (IPD not available)	No
	Wilkinson, 2001	Placebo/No treatment, Galantamine (18 - 36 mg)	Available	Yes
Lundbeck	Bakchine, 2008	Placebo/No treatment, Memantine (20 mg)	Available	Yes
	Fox, 2012	Placebo/No treatment, Memantine (5 – 20 mg)	Unavailable (Do not own data)	No
	Herrmann, 2013	Placebo/No treatment, Memantine (5 – 20 mg)	Available	Yes
	Lorenzi, 2011	Placebo/No treatment, Memantine (5 – 20 mg)	Unavailable (Do not own data)	No
	Wilkinson, 2012	Placebo/No treatment, Memantine (5 – 20 mg)	Available	Yes
Merz	Reisberg, 2003	Placebo/No treatment, Memantine (20 mg)	No response from sponsor	No
	Reisberg, 2006	Placebo/No treatment, Memantine (20 mg)	No response from sponsor	No
	Schmidt, 2008	Placebo/No treatment, Memantine (5 – 20 mg)	No response from sponsor	No
	Winblad, 2007	Placebo/No treatment, Rivastigmine (3 – 12 mg)	No response from sponsor	No
Novartis	Agid, 1998	Placebo/No treatment, Rivastigmine (6 mg)	Unavailable (Cannot identify study)	No
	Blesa González, 2011	Placebo/No treatment, Rivastigmine (6 – 12 mg)	Unavailable (Cannot share data)	No
	Choi, 2011	Placebo/No treatment, Memantine (5 – 20 mg)	Unavailable (Do not own data)	No
	Corey-Bloom, 1998	Placebo/No treatment, Rivastigmine (6 – 12 mg)	Unavailable (Cannot identify study)	No
	Farlow, 2013	Rivastigmine (4.6 - 13.3 mg), Rivastigmine (4.6 mg) + Memantine (20 mg)	Unavailable (Cannot share data (Phase 4 study))	No
	Feldman, 2007	Placebo/No treatment, Rivastigmine (2 – 12 mg)	Unavailable (Cannot identify study)	No
	Grossberg, 2015	Rivastigmine (4.6 - 13.3 mg), Rivastigmine (4.6 mg) + Memantine (20 mg)	Unavailable (Cannot share data (Phase 4 study))	No
	Han, 2012	Placebo/No treatment, Memantine (5 – 20 mg)	Unavailable (Cannot identify study)	No
	Kumar, 2000	Placebo/No treatment, Rivastigmine (1 – 12 mg)	Unavailable (Cannot identify study)	No
	Nakamura, 2011	Placebo/No treatment, Rivastigmine (4.5 – 9.5 mg)	Available	Yes
	Nordberg, 2009	Donepezil (5 – 10 mg), Galantamine (8 – 24 mg), Rivastigmine (3 – 12 mg)	Unavailable (Cannot share data (Phase 4 study))	No
	Shimizu, 2015	Donepezil (5 mg), Galantamine (24 mg), Rivastigmine (18 mg)	Unavailable (Cannot identify study)	No
	Winblad, 2007	Placebo/No treatment, Rivastigmine (3 – 12 mg)	Available	Yes
ONO	Nakamura, 2011	Placebo/No treatment, Rivastigmine (4.5 – 9.5 mg)	No response from sponsor	No
Pfizer	Black, 2007	Placebo/No treatment, Donepezil (10 mg)	Unavailable (Do not own data)	No
	Feldman, 2001	Placebo/No treatment, Donepezil (5 – 10 mg)	Available	No
	Feldman, 2004	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot identify study)	No
	Feldman, 2005	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot identify study)	No
	Gauthier, 2002	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot identify study)	No
	Holmes, 2004	Placebo/No treatment, Donepezil (10 mg)	Unavailable (Cannot identify study)	No
	Jelic, 2008	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot identify study)	No
	Johannsen, 2006	Placebo/No treatment, Donepezil (10 mg)	Unavailable (Cannot identify study)	No
	Jones, 2004	Donepezil, Galantamine (8 – 24 mg)	Unavailable (Cannot identify study)	No
	Mohs, 2001	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot identify study)	No
	Schwam, 2010	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot identify study)	No
	Seltzer, 2004	Donepezil (5 – 10 mg), Placebo/No treatment	Unavailable (Cannot identify study)	No
	Sole-Padulles, 2013	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot identify study)	No
	Tariot, 2001	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot identify study)	No

Sponsor	Author, year	Interventions compared (dosage mg)*	Sponsor Response	IPD Received
	Wilkinson, 2002	Donepezil (5 – 10 mg), Rivastigmine (6 – 12 mg)	Unavailable (Cannot identify study)	No
	Wimo, 2003	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot identify study)	No
	Winblad, 2001	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot identify study)	No
	Winblad, 2006	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Cannot identify study)	No
Roivant	Maher-Edwards, 2011	Placebo/No treatment, Donepezil (5 – 10 mg)	No response from sponsor	No
Shire Pharmaceuticals	Wilcock, 2003	Donepezil (5 – 10 mg), Galantamine (16 – 24 mg)	Unavailable (Do not own data)	No
	Wilkinson, 2001	Placebo/No treatment, Galantamine (24 mg)	Unavailable (Do not own data)	No
Takeda	Shimizu, 2015	Donepezil (5 mg), Galantamine (24 mg), Rivastigmine (18 mg)	Unavailable (Do not own data)	No
Non-Pharmaceutical	Andersen, 2012	Placebo/No treatment, Donepezil (5 – 10 mg)	NA	No
	Araki, 2014	Placebo/No treatment, Donepezil (NR) + Memantine (5 – 20 mg)	NA	No
	Burns, 2011	Placebo/No treatment, Donepezil (5 – 10 mg)	NA	No
	Dysken, 2014	Placebo/No treatment, Memantine (20 mg)	Available	No
	Greenberg, 2000	Placebo/No treatment, Donepezil (5 mg)	Unavailable (Need to contact PI)	No
	Howard, 2007	Placebo/No treatment, Donepezil (5 – 10 mg)	Unavailable (Do not own data)	No
	Howard, 2012	Donepezil (10 mg) + Memantine (5 – 20 mg), Donepezil (10 mg) + Placebo	Unavailable (Do not own data)	No
	Mowla, 2007	Placebo/No treatment, Rivastigmine (3 – 12 mg)	NA	No
	Peters, 2015	Galantamine (24 mg) + Placebo, Galantamine (24 mg) + Memantine (20 mg)	NA	No
Not reported	Cretu, 2008	Placebo/No treatment, Memantine (5 – 20 mg)	NA	No
	Fuschillo, 2001	Donepezil (5 mg), Rivastigmine (6 – 9 mg)	NA	No
	Hernández, 2007	Placebo/No treatment, Donepezil (10 mg)	NA	No
	Homma, 1998	Donepezil (3 – 5 mg), Placebo/no treatment	NA	No
	Hong, 2006	Placebo/No treatment, Galantamine (8 – 24 mg)	NA	No
	Hu, 2006	Donepezil (5 mg), Memantine (5 – 10 mg)	NA	No
	Kano, 2013	Donepezil(10 mg), Donepezil (10 mg) + Memantine (20 mg)	NA	No
	Karaman, 2005	Placebo/No treatment, Rivastigmine (3 – 12 mg)	NA	No
	Mazza, 2006	Placebo/No treatment, Donepezil (5 mg)	NA	No
	Moretti, 2014	Placebo/No treatment, Rivastigmine (3 – 12 mg)	NA	No
	Nakano, 2001	Placebo/No treatment, Donepezil (5 mg)	NA	No
	Pakdaman H, 2015	Donepezil (NR), Galantamine (NR), Rivastigmine (NR)	NA	No
	Peng, 2005	Placebo/No treatment, Donepezil (5 mg)	NA	No
	Shao, 2015	Memantine (5 – 10 mg)+ Placebo, Rivastigmine (1.5 – 3 mg) + Memantine (5 – 10 mg), Donepezil (5 – 10 mg) + Memantine (5 – 10 mg), Galantamine (2 – 6 mg) + Memantine (5 – 10 mg)	NA	No
	Thomas, 2001	Donepezil (5 – 10 mg), Rivastigmine (6 – 12 mg)	NA	No
	Zhang-Yi, 2005	Placebo/No treatment, Donepezil (5 mg)	NA	No

Abbreviations: NA, not applicable; NPH, neutral protamine Hagedorn; NR, not reported; PI, principal investigator

* In studies that examined different dosages of the same intervention, we selected the dosages that were consistent with those approved for use in Canada.

Appendix 5: Study characteristics of the included RCTs

Study	Country of conduct	Sample size; Longest duration of follow-up (weeks)	Treatments compared; Outcomes	Funding information	Date of randomization; Date trial opened; Randomization ratio	IPD available; Reasons for not providing IPD by the data providers
Agid, 1998	12 countries - Austria, Belgium, Czechoslovakia, Denmark, Finland, France, Germany, Ireland, Norway, Sweden, Switzerland, and the UK	402; 13	Rivastigmine, Placebo/No treatment; MMSE, Nausea, Vomiting, Diarrhea, AEs, Headaches	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot identify study
Ancoli-Israel, 2005	USA	63; 8	Galantamine, Donepezil; CIBIC-plus, Mortality, Nausea, Diarrhea, AEs, Headaches	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot identify study
Andersen, 2012	Norway	180; 52	Donepezil, Placebo; MMSE, ADAS-cog	Publicly-sponsored	Not reported; June 2003; Not reported	No; NA
Araki, 2014	Japan	37; 24	Donepezil + Memantine, Placebo; MMSE, NPI	Publicly-sponsored	Not reported; Not reported; Not reported	No; NA
Bakchine, 2008	12 countries -Austria, Belgium, Denmark, Finland, France, Greece, Lithuania, the Netherlands, Poland, Spain, Sweden and UK	470; 24	Memantine, Placebo/no treatment; ADAS-cog, ADCS-ADL, NPI, CIBIC-plus, Mortality, AEs, Headaches, Falls	Industry-sponsored	Not reported; Not reported; Not reported	Yes; NA
Black, 2007	5 countries - USA, Canada, France, UK, Australia	343; 24	Donepezil, Placebo/No treatment; MMSE, ADCS-ADL, NPI, CIBIC-plus, Nausea, Vomiting, Diarrhea, AEs	Industry-sponsored	Not reported; January 2001; Not reported	Yes; Do not own data
Blesa González, 2011	Spain	139; 12	Rivastigmine Patch, Rivastigmine Oral; MMSE, Nausea, Vomiting, Diarrhea	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot share data (Phase 4 study)
Burns, 1999	Australia, Belgium, Canada, France, Germany,Ireland, New Zealand, South Africa and the UK	818; 30	Donepezil, Placebo/no treatment; ADAS-cog, CIBIC-plus, Mortality, Diarrhea, Nausea, AEs, Vomiting	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot share data (Old study)
Burns, 2009	Belgium, Finland, France, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, UK	407; 26	Galantamine, Placebo/no treatment; Mortality, Nausea, Vomiting, Diarrhea, AEs, Headaches, Falls	Industry-sponsored	Not reported; December 2003; Not reported	Yes; NA
Burns, 2011	UK	62; 12	Donepezil, Placebo/no treatment; NPI, AEs	Publicly-sponsored	Not reported; January 2006; Not reported	No; NA
Choi, 2011	South Korea	171; 16	Memantine, Placebo/No treatment; MMSE, ADAS-cog, ADCS-ADL, NPI, AEs, Nausea, Diarrhea, Vomiting, Headaches	Publicly-sponsored + Industry-sponsored	Not reported; December 2008; Not reported	No; Do not own data
Corey-Bloom, 1998	USA	699; 26	Rivastigmine, Placebo/No treatment; MMSE, ADAS-cog, CIBIC-plus, Mortality, Nausea, Vomiting	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot identify study

Cretu, 2008	Romania	43; 24	Memantine, Placebo/No treatment; MMSE, ADAS-cog, NPI	NA	Not reported; Not reported; Not reported	No; NR
Dysken, 2014	USA	307; 26-208	Memantine, Placebo; MMSE, ADAS-cog, ADCS-ADL, NPI, Mortality, AEs	Publicly-sponsored	Not reported; August 2007; 1:1:1:1	No; NA
Farlow, 2013	USA	716; 24	Rivastigmine + Memantine, Rivastigmine; NPI, Mortality, Falls, Vomiting, Diarrhea, Nausea	Industry-sponsored	Not reported; July 2009; 1:1	No; Cannot share data (Phase 4 study)
Feldman, 2001	Canada, Australia, France	290; 24	Donepezil, Placebo/No treatment; MMSE, NPI, CIBIC-plus, Mortality, Vomiting, Nausea, Diarrhea, AEs, Headaches	Industry-sponsored	Not reported; Not reported; "50/50 split"	No; NA
Feldman, 2007	Australia, Canada, Ireland, Italy, South Africa, UK	450; 26	Rivastigmine, Placebo/No treatment; MMSE, ADAS-cog, CIBIC-plus, AEs, Bradycardia, Headaches, Vomiting, Diarrhea, Nausea	Industry-sponsored	Not reported; Not reported; 1:1:1	No; Cannot identify study
Fox, 2012	UK	149; 12	Memantine, Placebo; MMSE, NPI, Mortality	Industry-sponsored	Not reported; September 2007; "assigned with equal probability"	No; Unavailable (Do not own data)
Frolich, 2011	Austria, Belgium, Bulgaria, Czech Republic, Germany, Romania, Russia, Spain, UK, Canada	324; 12	Donepezil, Placebo/No treatment; MMSE, ADAS-cog, Nausea, Vomiting, Diarrhea, Headaches	Industry-sponsored	Not reported; July 2007; Not reported	No; Available
Fuschillo, 2001	Italy	27; 30	Donepezil, Rivastigmine; MMSE, ADAS-cog, Headaches, Vomiting, Diarrhea, Nausea	NA	Not reported; Not reported; Not reported	No; NR
Gault, 2015	USA, Bulgaria, Czech Republic, Slovakia, UK, South Africa	136; 14	Donepezil, Placebo; MMSE, ADAS-cog, ADCS-ADL, NPI, CIBIC-plus, Mortality, AEs, Bradycardia, Falls, Headaches, Vomiting, Diarrhea, Nausea	Industry-sponsored	Not reported; October 2009; Not reported	Yes; Available
Gold, 2010	Austria, Bulgaria, Chile, China, Croatia, Estonia, Germany, Greece, Hungary, Mexico, New Zealand, Pakistan, Peru, Republic of the Philippines, Puerto Rico, Republic of Korea, Russian Federation, UK and USA	248; 24	Donepezil, Placebo/no treatment; ADAS-cog, CIBIC-plus, Mortality, Headaches, Nausea, Diarrhea, AEs	Industry-sponsored	Not reported; February 2007; 2:2:2:1	Yes; Available
Greenberg, 2000	USA	103; 24	Donepezil, Placebo/no treatment; ADAS-cog, AEs, Diarrhea, Nausea	Publicly-sponsored	Not reported; Not reported; Not reported	No; Contact PI
Grossberg, 2013	Argentina, USA, Mexico, Chile	676; 24	Donepezil + Rivastigmine + Galantamine + Memantine, Donepezil + Rivastigmine + Galantamine + Placebo; NPI, CIBIC-plus, Mortality, Falls,	Industry-sponsored	Not reported; June 2005; 1:1	No; Cannot share dat

			Headaches, Vomiting, Diarrhea, Nausea, AEs			
Hager K, 2014	Czech Republic, Estonia, France, Germany, Greece, Italy, Latvia, Lithuania, Romania, Russia, Slovakia, Slovenia, Ukraine	2045; 104	Galantamine, Placebo; MMSE, Mortality, Headaches, Vomiting, Diarrhea, Nausea, AEs	Industry-sponsored	Not reported; May 2008; 1:1	Yes; NA
Haig, 2014	Russia, Ukraine	123; 12	Donepezil, Placebo; MMSE, ADAS-cog, ADCS-ADL, NPI, Headaches, Nausea, AEs	Industry-sponsored	Not reported; Not reported; 1:1:1	Yes; NA
Hernández, 2007	Spain	20; 48	Donepezil, Placebo/No treatment; MMSE, ADAS-cog	NA	Not reported; Not reported; Not reported	No; NR
Herrmann, 2013	Canada	369; 24	Memantine, Placebo; NPI, Mortality, Falls, Nausea, AEs	Industry-sponsored	Not reported; December 2003; "equally allocated"	Yes; NA
Holmes, 2004	UK	96; 24	Donepezil, Placebo/No treatment; MMSE, NPI	Industry-sponsored	Not reported; Not reported; 3:2	No; Cannot identify study
Homma, 1998	Japan	187; 12	Donepezil, Placebo/no treatment; ADAS-cog, Mortality, AEs, Headaches	NA	Not reported; Not reported; Not reported	No; NR
Homma, 2008	Japan	267; 24	Donepezil, Placebo/no treatment; ADCS-ADL, CIBIC-plus, Mortality, AEs, Falls, Vomiting, Diarrhea	Industry-sponsored	Not reported; Not reported; 1:1:1	No; Cannot share data (Old study)
Hong, 2006	China	218; 16	Galantamine, Placebo/no treatment; ADAS-cog, ADCS-ADL, NPI, AEs	NA	Not reported; Not reported; Not reported	No; NR
Howard, 2007	England	259; 12	Donepezil, Placebo/No treatment; MMSE, NPI, Mortality, Falls, Diarrhea	Publicly-sponsored	Not reported; November 2003; "probability ratios of 0.75 and 0.25 to assign treatment"	No; NA
Howard, 2012	Europe	295; 52	Donepezil + Placebo, Donepezil + Memantine; MMSE, Mortality, AEs, Falls	Publicly-sponsored	Not reported; February 2008; Not reported	No; Do not own data
Hu, 2006	China	97; 16	Memantine, Donepezil; MMSE	NA	Not reported; Not reported; Not reported	No; NA
Johannsen, 2006	Belgium, Denmark, Germany, Greece, Hungary, Iceland, The Netherlands, Poland, USA	202; 48	Donepezil, Placebo/No treatment; MMSE, ADAS-cog, NPI, Headaches, Diarrhea, Nausea	Industry-sponsored	Not reported; February 1999; Not reported	No; Do not own data
Jones, 2004	UK, Finland, Germany and Norway	120; 12	Donepezil, Galantamine; MMSE, ADAS-cog, Headaches, Vomiting, Diarrhea, Nausea, AEs	Industry-sponsored	Not reported; Not reported; 1:1	No; Cannot share data (Old study)
Kadir, 2008	Sweden	18; 48	Galantamine, Placebo/No treatment; MMSE, ADAS-cog	Industry-sponsored + Other	Not reported; Not reported; Not reported	No; Cannot identify study

Kano, 2013;	Japan	30; 28	Donepezil, Donepezil + Memantine ; MMSE	NA	Not reported; August 2011; Not reported	No; NR
Karaman, 2005	Turkey	44; 52	Rivastigmine, Placebo/No treatment; MMSE, ADAS-cog, ADAS-ADL, CIBIC-plus, Headaches, Vomiting, Nausea	NA	Not reported; Not reported; Not reported	No; NR
Likitjaroen, 2012	Germany	25; 26	Galantamine, Placebo; MMSE	Publicly-sponsored + Industry-sponsored	Not reported; September 2006; Not reported	No; Do not own data
Lorenzi, 2011	Italy	15; 24	Memantine, Placebo/No treatment; MMSE	Publicly-sponsored + Industry-sponsored	Not reported; Not reported; Not reported	No; Do not own data
Maher-Edwards, 2011	Austria, Bulgaria, Chile, Estonia, Germany, Russia, Slovakia, and UK	129; 24	Donepezil, Placebo/no treatment; ADAS-cog, CIBIC-plus, Mortality, AEs, Headaches, Nausea	Industry-sponsored	Not reported; May 2006; 1:1:1	No; No response from sponsor
Marek, 2014	UK, Ukraine, South Africa, Russia	132; 16	Donepezil, Placebo; MMSE, ADAS-cog, NPI, CIBIC-plus, Mortality, Headaches, Vomiting, Diarrhea, AEs	Industry-sponsored	Not reported; May 2010; "equal proportions"	No; Cannot share data
Mazza, 2006	Italy	51; 24	Donepezil, Placebo/No treatment; MMSE	NA	Not reported; March 2003; 1:1:1	No; NR
Mohs, 2001	USA	431; 54	Donepezil, Placebo/No treatment; MMSE, Mortality, AEs, Headaches, Diarrhea, Nausea	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot share data
Moretti, 2014	Italy	20; 78	Rivastigmine Patch, Rivastigmine Oral; MMSE	NA	Not reported; Not reported; Not reported	No; NA
Mowla, 2007	Iran	81; 12	Rivastigmine, Placebo/No treatment; MMSE	Publicly-sponsored	Not reported; Not reported; Not reported	No; NA
Nakamura, 2011	Japan	855; 24	Rivastigmine, Placebo/No treatment; MMSE, AEs, Vomiting, Nausea, Diarrhea	Industry-sponsored	Not reported; January 2007; Not reported	Yes; NA
Nakano, 2001	Japan	35; 48	Donepezil, Placebo/No treatment; MMSE	NA	Not reported; Not reported; Not reported	No; NR
Nordberg, 2009	USA	63; 13	Rivastigmine, Donepezil, Galantamine; AEs, Headaches, Vomiting, Diarrhea, Nausea	Industry-sponsored	Not reported; Not reported; 1:1:1	No; Cannot share data
Pakdaman H, 2015	Iran	198; 68.8	Donepezil, Galantamine, Rivastigmine; MMSE, ADAS-cog, Mortality,	Industry-sponsored	Not reported; Not reported; Not reported	No; NR

			Headaches, Vomiting, Diarrhea, Nausea			
Peng, 2005	China	89; 12	Donepezil, Placebo/No treatment; MMSE	NA	Not reported; 1998; Not reported	No; NR
Peskind, 2006	USA	403; 24	Memantine, Placebo/no treatment; ADAS-cog, ADCS-ADL, NPI, CIBIC-plus, Nausea, Vomiting, Diarrhea	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot share data
Peters, 2015	Europe	226; 52	Galantamine + Memantine, Galantamine + Placebo; ADAS-cog, ADCS-ADL, NPI, Mortality, AEs, Falls	Publicly-sponsored	Not reported; Not reported; Not reported	No; NA
Reisberg, 2003	USA	252; 28	Memantine, Placebo/No treatment; MMSE, ADCS-ADL, NPI, CIBIC-plus, Mortality, AEs, Diarrhea	Publicly-sponsored + Industry-sponsored	Not reported; August 1998; Not reported	No; No response from sponsor
Rockwood, 2001	Australia, Canada, Great Britian, New Zealand, South Africa, USA	386; 12	Galantamine, Placebo/no treatment; ADAS-cog, NPI, CIBIC-plus, Mortality, AEs, Vomiting, Nausea	Industry-sponsored	Not reported; Not reported; Not reported	Yes; NA
Rockwood, 2006	Canada	130; 16	Galantamine, Placebo/no treatment; ADAS-cog, CIBIC-plus, AEs, Vomiting, Nausea	Publicly-sponsored + Industry-sponsored	Not reported; November 2001; Not reported	No; IPD not available
Rogers, 1996	USA	161; 12	Donepezil, Placebo/No treatment; MMSE, ADAS-cog, Headaches, Diarrhea	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot share data
Rogers, 1998	USA	468; 12	Donepezil, Placebo/No treatment; MMSE, ADAS-cog, CIBIC-plus, AEs, Headaches, Vomiting, Diarrhea, Nausea	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot share data
Rogers, 1998	USA	473; 24	Donepezil, Placebo/No treatment; MMSE, ADAS-cog, CIBIC-plus, Mortality, AEs, Vomiting, Diarrhea, Nausea	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot share data
Saxton, 2012	Australia, South Africa, New Zealand	264; 12	Memantine, Placebo; Mortality, Falls, Headaches, Diarrhea, Nausea, AEs	Industry-sponsored	Not reported; April 2007; Not reported	No; Cannot share data
Scarpini, 2011	Italy	139; 96	Galantamine, Placebo/no treatment; Mortality, AEs	Industry-sponsored	Not reported; July 2001; Not reported	No; IPD not available
Schmidt, 2008	Europe	36; 52	Memantine, Placebo/No treatment; MMSE, ADAS-cog, ADCS-ADL	Industry-sponsored	Not reported; Not reported; Not reported	No; No response from sponsor
Seltzer, 2004	USA	153; 24	Donepezil, Placebo/No treatment; MMSE, ADAS-cog, Diarrhea, Nausea	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot identify study

Shao, 2015	China	110; 24	Donepezil + Memantine, Galantamine + Memantine, Memantine + Placebo, Rivastigmine + Memantine; MMSE, ADCS-ADL	NA	Not reported; October 2009; Not reported	No; NR
Shimizu, 2015	Japan	75; 52	Donepezil, Galantamine, Rivastigmine; MMSE, ADAS-cog, NPI, Headaches, Vomiting, Nausea	Industry-sponsored	Not reported; Not reported; Not reported	No; Do not own data
Sole-Padulles, 2013	Spain	14; 13	No treatment, Donepezil; MMSE, NPI	Industry-sponsored	Not reported; Not reported; Not reported	No; Do not own data
Tariot, 2000	USA	978; 20	Galantamine, Placebo/no treatment; ADAS-cog, ADCS-ADL, NPI, Mortality, AEs, Vomiting, Diarrhea, Nausea	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot identify study
Tariot, 2001	USA	208; 24	Donepezil, Placebo/No treatment; MMSE, Mortality, AEs, Bradycardia, Headaches, Vomiting, Diarrhea, Nausea	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot identify study
Thomas, 2001	Italy	40; 24	Donepezil, Rivastigmine; MMSE, ADAS-cog	NA	Not reported; Not reported; Not reported	No; NR
Wilcock, 2003	UK	188; 52	Galantamine, Donepezil; MMSE, ADAS-cog, Mortality, AEs, Falls, Headaches, Vomiting, Nausea	Industry-sponsored	Not reported; June 2000; Not reported	No; Cannot identify study
Wilkinson, 2001	UK	180; 12	Galantamine, Placebo/no treatment; ADAS-cog, AEs, Headaches, Vomiting, Diarrhea, Nausea	Industry-sponsored	Not reported; May 1994; Not reported	Yes; NA
Wilkinson, 2002	UK, South Africa, and Switzerland	111; 12	Donepezil, Rivastigmine; MMSE, ADAS-cog, Mortality, AEs, Bradycardia, Headaches, Vomiting, Nausea	Industry-sponsored	Not reported; Not reported; 1:1	No; Cannot identify study
Wilkinson, 2012	France, Germany, Switzerland, UK	277; 52	Memantine, Placebo/No treatment; MMSE, NPI, Mortality, AEs, Falls	Industry-sponsored	Not reported; September 2005; 1:1	Yes; NA
Winblad, 2001	Denmark, Finland, Norway, Sweden, the Netherlands	286; 52	Donepezil, Placebo/No treatment; MMSE, AEs, Bradycardia, Headaches, Diarrhea, Nausea	Industry-sponsored	Not reported; Not reported; Not reported	No; Cannot identify study
Winblad, 2006	Sweden	248; 24	Donepezil, Placebo/No treatment; MMSE, NPI, Mortality, AEs, Falls, Diarrhea, Nausea	Industry-sponsored	Not reported; October 2002; Not reported	No; Cannot identify study
Winblad, 2007	Chile, Czech Republic, Denmark, Finland, Germany, Guatemala, Israel, Italy, Korea, Mexico, Norway, Peru, Poland, Portugal, Russia, Slovak Republic, Sweden, Taiwan, USA, Uruguay, Venezuela	1190; 24	Rivastigmine, Placebo/No treatment; MMSE, ADAS-cog, ADCS-ADL, NPI, Mortality, AEs, Headaches, Vomiting, Diarrhea, Nausea	Industry-sponsored	Not reported; November 2003; Not reported	No; No response from sponsor

Zhang-Yi, 2005	China	120; 8	Donepezil, Placebo/No treatment; MMSE	NA	Not reported; Not reported; Not reported	No; NR
Zhang, 2012	China	218; 16	Galantamine, Donepezil; MMSE, ADAS-cog, ADCS-ADL, NPI, Mortality, Vomiting, Diarrhea, Nausea, AEs	Industry-sponsored	Not reported; Not reported; Not reported	No; IPD not available

Appendix 6. Characteristics of studies with shared IPD

Study	Provided by	Severity of AD*	Previous response to treatment for AD	Presence of behavioural disturbance	Comorbid conditions	Other medications used	Treatment Group	Males (%)	Age, mean (SD)
Black 2007	CSDR - EISAI	Severe	NR	NR	All patients included the same exact comorbidities	NR	Donepezil	48 (27%)	78 (7.9)
							Placebo	54 (32%)	78 (8.1)
Gold 2010	CSDR - GSK	Mild-Moderate	NR	NR	Multiple reported	Multiple reported	Donepezil	16 (29%)	76.6 (8.2)
							Placebo	49 (46%)	75.5 (8.2)
Winblad 2007	CSDR - Novartis	Mild-Moderate	NR	NR	Multiple reported	Multiple reported	Rivastigmine patch	198 (33 %)	73.9 (8.0)
							Rivastigmine oral	102 (34 %)	72.9 (8.2)
							Placebo	101 (33%)	73.8 (7.5)
Hager 2014	YODA - Janssen	Mild-Moderate	NR	NR	NR	Multiple reported	Galantamine	354 (34%)	73 (8.9)
							Placebo	367 (36%)	73 (8.7)
Rockwood 2001	YODA - Janssen	Mild-Moderate	NR	NR	NR	Multiple reported	Galantamine	113 (43%)	75 (7.3)
							Placebo	58 (46%)	75 (7.6)
Cummings 2004	YODA - Janssen	NR	NR	NR	Multiple reported	Multiple reported	Galantamine	245 (35%)	76.9 (7.8)
							Placebo	108 (38%)	77.2 (7.9)
Burns 2009	YODA - Janssen	Severe	NR	NR	Multiple reported	Multiple reported	Galantamine	42 (20%)	84.0 (6.5)
							Placebo	39 (19%)	83.8 (6.7)
Gault 2015	AbbVie	Mild-Moderate	NR	NR	NR	Multiple reported	Donepezil	37 (54%)	72.4 (8.4)
							Placebo	26 (38%)	73.6 (8.2)
Haig 2014	AbbVie	Mild-Moderate	NR	NR	Multiple reported	Multiple reported	Donepezil	24 (40%)	70 (8.3)
							Placebo	24 (38%)	70 (7.8)
Bakchine 2008	Lundbeck	Mild-Moderate	NR	NR	NR	Multiple reported	Memantine	112 (35%)	74 (7.4)
							Placebo	61 (40%)	73 (6.9)
Herrman 2013	Lundbeck	69 (48%)	NR	NR	NR	Multiple reported	Memantine	77 (42%)	75 (7.9)
							Placebo	77 (41%)	75 (6.9)
Wilkinson 2012	Lundbeck	NR	NR	NR	NR	Multiple reported	Memantine	50 (38%)	74 (8.8)
							Placebo	69 (48%)	74 (7.8)

Additional characteristics of studies with shared IPD

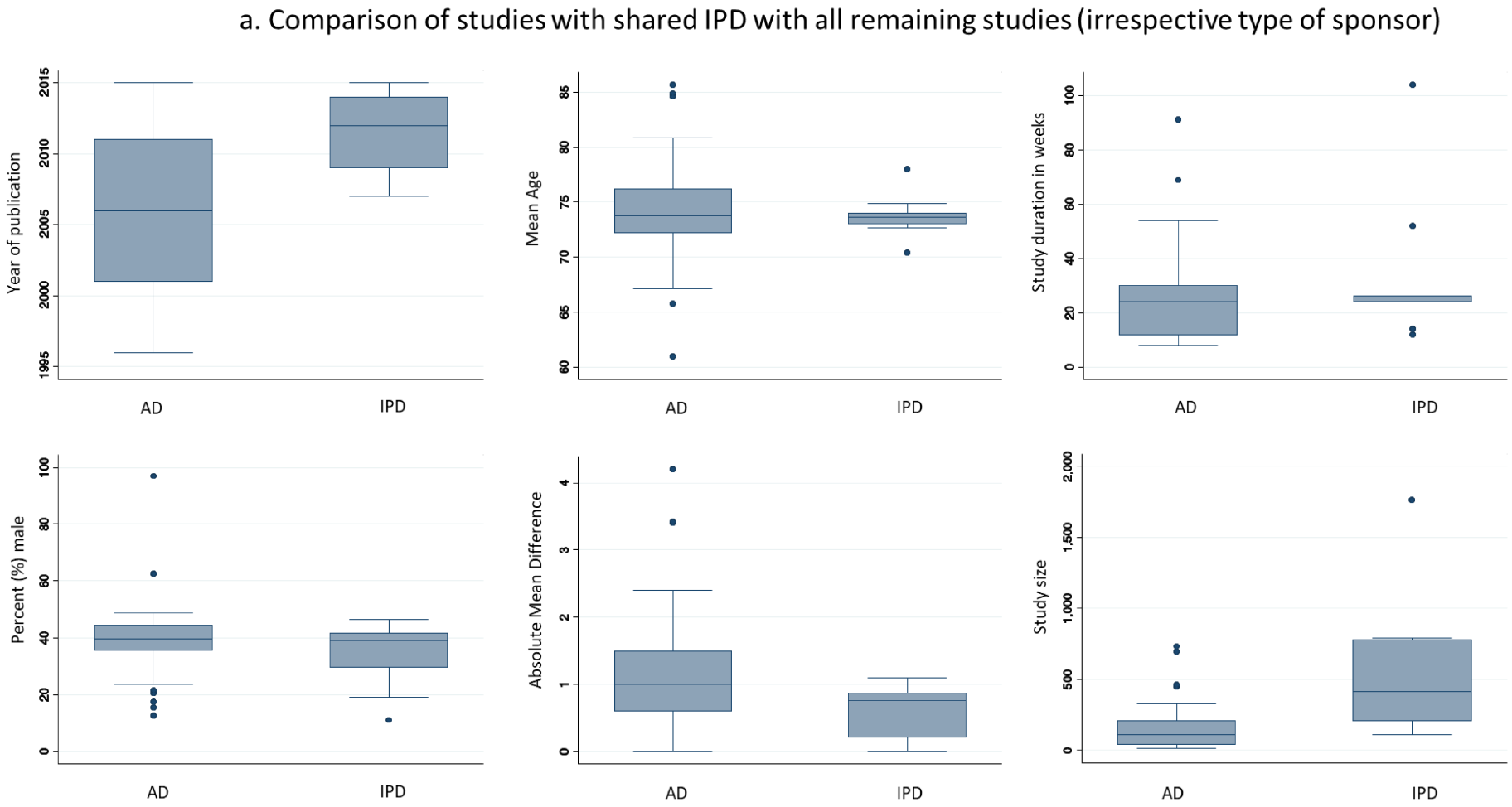
Study	Patients experiencing at least one AE	Missing data in AE outcome	Baseline MMSE, mean (SD)	Final MMSE, mean (SD)	Change score, mean (SD)	Missing data in MMSE outcome	Total number of patients	Reasons for dropouts as indicated in the provided IPD	Time taken for the 1st AE
Black 2007	21	0 (0%)	7.5 (3.3)	8.2 (5.2)	0.63 (3.1)	27 (15%)	176 (51%)	• intercurrent illness (1 [2%] – donepezil = 1; placebo = 0), • request of patient or investigator (4 [7%] –	617 days (range [110, 1292])

	25	0 (0%)	7.4 (3.6)	7.6 (4.8)	-0.15 (3.5)	27 (16%)	167 (49%)	donepezil = 3; placebo = 1), • patient entered nursing home/facility (5 [9%] – donepezil = 1; placebo =) 4, • due to adverse experience (30 [56%] – donepezil = 15; placebo = 15), and • other (14 [26%] – donepezil = 7; placebo = 7)	691 days (range [78, 1475]).
Gold 2010	6	0 (0%)	20 (3.7)	21 (4.6)	1.11 (2.3)	18 (32%)	56 (34%)	• Adverse Event (16 [39%] – donepezil = 9; placebo = 7), • Lost to Follow-Up (4 [10%] – donepezil = 3; placebo = 1), • Non-compliance (6 [15%] – donepezil = 2; placebo = 4), • Subject decided to withdraw (11 [26%] – donepezil = 4; placebo = 7)	349 days (range [48, 656])
	10	0 (0%)	20.1 (4.2)	20.4 (5.4)	0.08 (2.7)	23 (22%)	107 (66%)		492 days (range [95, 780])
Winblad 2007	83	0 (0%)	16.6 (3.0)	17.7 (4.7)	1 (3.4)	74 (10%)	598 (50 %)	NR	NR
	37	0 (0%)	16.4 (3.1)	17.2 (4.6)	0.8 (3.2)	31 (12%)	297 (25 %)	NR	NR
	45	0 (0%)	16.4 (3.0)	16.4 (5.3)	-0.1 (3.6)	21 (7%)	302 (25 %)	NR	NR
Hager 2014	73	0 (0%)	19.0 (4.1)	17.81 (6.2)	-1.38 (4.3)	228 (22%)	1027 (50%)	NR	NR
	92	0 (0%)	19.0 (4.0)	16.99 (6.3)	-2.15 (4.4)	236 (23%)	1022 (50%)	NR	NR
Rockwood 2001	27	0 (0%)	23.2 (5.2)	NR	NR	NR	261 (68%)	NR	NR
	5	0 (0%)	22.9 (5.0)	NR	NR	NR	125 (32%)	NR	NR
Cummings 2004	23	0 (0%)	20.7 (4.9)	NR	NR	NR	692 (71%)	NR	NR
	81	0 (0%)	20.6 (4.9)	NR	NR	NR	286 (29%)	NR	NR
Burns 2009	62	0 (0%)	NR	9.2 (4.5)†	NR	NR	211 (51%)	NR	NR
	75	0 (0%)	NR	9.6 (4.9)†	NR	NR	204 (49%)	NR	NR
Gault 2015	5	0 (0%)	19.2 (4.1)	20.7 (5.1)	1.5 (2.6)	48 (71%)	68 (50%)	NR	305 days (range [224, 377])
	3	0 (0%)	18.8 (4)	18.9 (4.8)	0.1 (2.4)	45 (66%)	68 (50%)	NR	239 days (range [206, 295])
Haig 2014	2	0 (0%)	17.9 (4.2)	19.7 (3.9)	1.2 (2.8)	41 (68%)	60 (49%)	NR	286 days (range N/A – a single date was provided)
	1	0 (0%)	17.8 (3.8)	19.9 (4.2)	1.8 (1.8)	47 (75%)	63 (51%)	NR	270 days (range [161, 379]).
Bakchine 2008	33	0 (0%)	18.7 (3.3)	NR	NR	NR	318 (68%)	NR	NR
	9	0 (0%)	18.9 (3.2)	NR	NR	NR	152 (32%)	NR	NR
Herrman 2013	18	0 (0%)	11.9 (3.1)	11.3 (4.9)	-0.76 (3.4)	31 (8%)	182 (49%)	NR	NR
	11	0 (0%)	11.8 (2.9)	11.1 (4.7)	-0.68 (3.2)	32 (9%)	187 (51%)	NR	NR

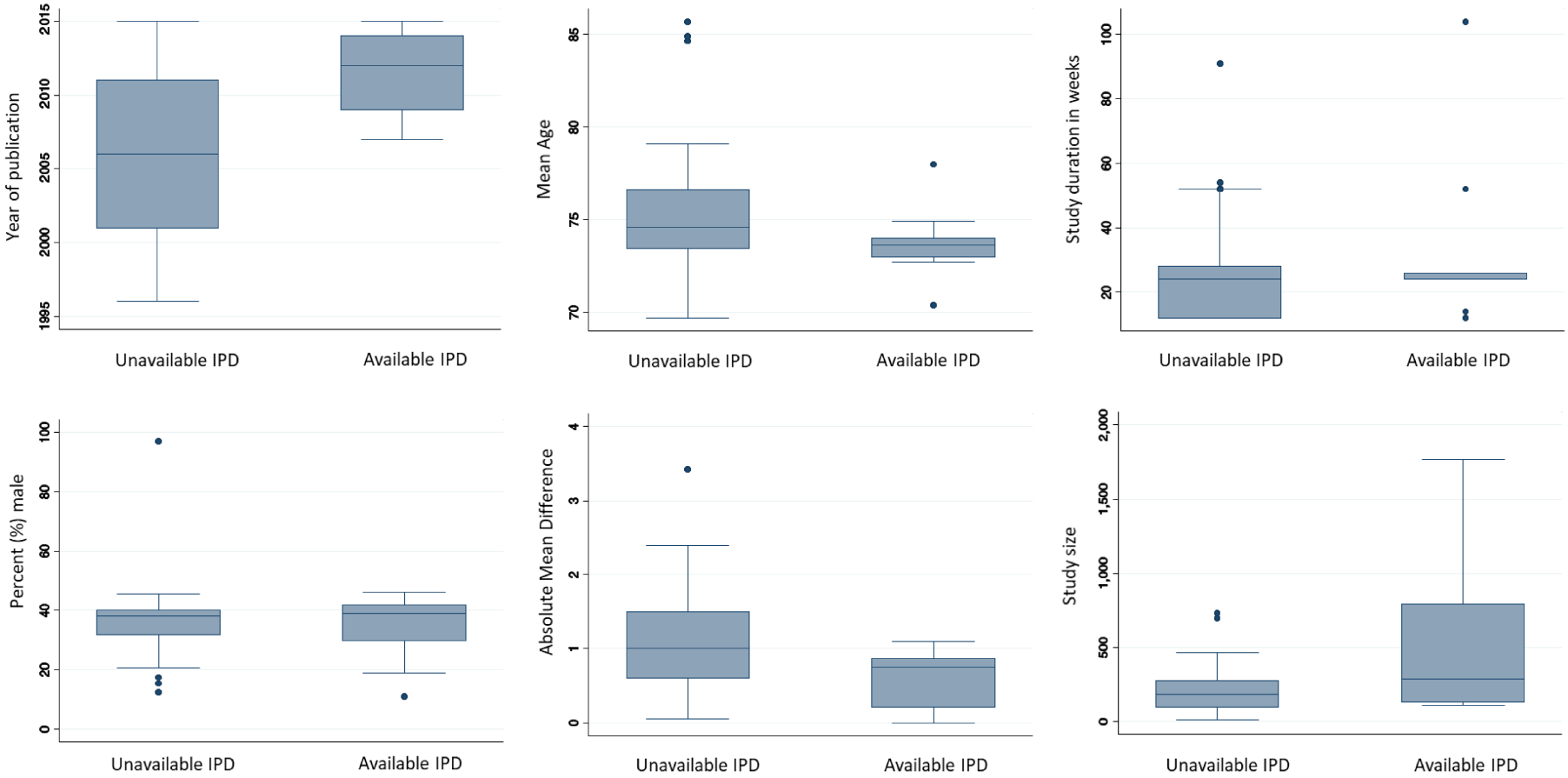
Wilkinson 2012	17	0 (0%)	16.7 (2.5)	16.4 (5.2)	-0.46 (3.9)	30 (11%)	133 (48%)	NR	NR
	20	0 (0%)	17.1 (2.4)	16.4 (5.6)	-0.69 (4.0)	30 (11%)	144 (52%)	NR	NR

* According to publication
† The MMSE final value comes from visit 8 (last available visit in IPD). MMSE was not reported in study publication
Abbreviations: AD, Alzheimer's Dementia; IPD, individual patient data; MMSE, Mini-Mental State Examination; NR, not reported; N/A, not applicable; AE, adverse event

Appendix 7: Comparison of studies with shared IPD with (a) all remaining studies and (b) studies for which sponsors claimed unavailable IPD. AD: aggregate data; IPD: individual patient data



b. Comparison of studies with available and unavailable IPD (industry-sponsored studies only)



Appendix 8: Cochrane Risk-of-bias appraisal results (n = 80)

Study	1. Random sequence generation	2. Allocation concealment	3. Blinding of participants and personnel	4. Blinding of outcome assessment	5. Incomplete outcome data	6. Selective reporting	7. Other bias*
Agid, 1998	Low	High	Low	Unclear	High	Unclear	High
Ancoli-Israel, 2005	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
Andersen, 2012	Unclear	Low	Low	Low	High	Low	Low
Araki, 2014	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear
Bakchine, 2008	Low	Low	Low	Low	Low	High	High
Black, 2007	Low	Low	Low	Low	Low	Unclear	High
Blesa Gonzalez, 2011	Unclear	Unclear	High	Unclear	High	Low	High
Burns, 1999	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
Burns, 2009	Low	Low	Low	Low	Low	Unclear	High
Burns, 2011	Low	Unclear	Low	Low	High	Unclear	Unclear
Choi, 2011	Unclear	Unclear	High	High	High	Low	Low
Corey-Bloom, 1998	Low	Low	Low	Low	High	Unclear	High
Cretu, 2008	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Dysken, 2014	Low	Low	Low	Unclear	Low	Low	Low
Farlow, 2013	Low	Unclear	Low	Low	High	Unclear	High
Feldman, 2001	Low	Unclear	Low	Low	High	Unclear	High
Feldman, 2007	Low	Low	Low	Low	High	Unclear	High
Fox, 2012	Low	Low	High	Low	High	High	Unclear
Frolich, 2011	Unclear	Unclear	Low	Low	High	Low	High
Fuschillo, 2001	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Gault, 2015	Low	Low	Low	Unclear	Low	Low	High
Gold, 2010	Low	Unclear	Low	Low	High	Low	High
Greenberg, 2000	Low	Low	Low	Unclear	High	Low	Low
Grossberg, 2013	Low	Low	Low	Low	High	Low	High
Hager K, 2014	Low	Low	Low	Low	High	High	High
Haig, 2014	Low	Low	Low	Low	High	Low	High
Hernández, 2007	Low	Low	Low	Low	Unclear	Low	Low
Herrmann, 2013	Low	Low	Low	Low	High	Low	High
Holmes, 2004	Low	Unclear	Low	Low	High	Low	High
Homma, 1998	Low	Low	Low	Low	Low	Unclear	High
Homma, 2008	Low	Low	Low	Low	High	Unclear	Unclear
Hong, 2006	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Howard, 2007	Low	Low	Low	Low	Low	Unclear	Low
Howard, 2012	Low	Low	Low	Low	High	Low	Low
Hu, 2006	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Johannsen, 2006	Unclear	Unclear	Low	Low	Low	Unclear	High
Jones, 2004	Low	Unclear	Unclear	Low	Low	Unclear	High
Kadir, 2008	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
Kano, 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Karaman, 2005	Low	Unclear	Low	Low	Unclear	Unclear	Unclear
Likitjaroen, 2012	Low	Low	Low	Unclear	High	High	Unclear
Lorenzi, 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Maher-Edwards, 2011	Low	Unclear	Unclear	Unclear	High	Unclear	High
Marek, 2014	Low	Low	Low	Low	High	Low	High
Mazza, 2006	Low	Unclear	Low	Low	High	Unclear	Unclear
Mohs, 2001	Low	Low	Low	Low	High	Unclear	High
Moretti, 2014	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Mowla, 2007	Low	Unclear	Low	Unclear	High	Unclear	Unclear
Nakamura, 2011	Unclear	Low	Low	Low	Low	Low	High
Nakano, 2001	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Nordberg, 2009	Unclear	Unclear	High	High	Unclear	Unclear	High
Pakdaman H, 2015	Low	Unclear	High	High	High	Unclear	Unclear
Peng, 2005	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Peskind, 2006	Low	Low	Low	Unclear	Low	Unclear	High
Peters, 2015	Unclear	Unclear	Low	Low	High	Low	Low
Reisberg, 2003	Low	Unclear	Low	Unclear	High	Low	Unclear
Rockwood, 2001	Low	Low	Low	Low	Unclear	Low	High
Rockwood, 2006	Low	Low	Low	Low	Low	Unclear	Unclear
Rogers, 1996	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear
Rogers, 1998	Unclear	Unclear	Low	Low	Low	Unclear	High
Rogers, 1998	Low	Unclear	Low	Unclear	High	Unclear	High
Saxton, 2012	Low	Low	Low	Low	Low	Low	High
Scarpini, 2011	Low	Low	Low	Unclear	High	Unclear	High
Schmidt, 2008	Low	Low	Low	Low	High	Unclear	High
Seltzer, 2004	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High

Shao, 2015	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Shimizu, 2015	Low	Unclear	High	Low	High	Unclear	Unclear
Sole-Padulles, 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Tariot, 2000	Low	Unclear	Low	Low	High	Low	High
Tariot, 2001	Low	Low	Low	Low	Unclear	Unclear	High
Thomas, 2001	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wilcock, 2003	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wilkinson, 2001	Low	Low	Low	Low	High	Unclear	High
Wilkinson, 2002	Low	Low	Low	Low	High	Unclear	High
Wilkinson, 2012	Low	High	Low	Low	High	Low	High
Winblad, 2001	Low	Unclear	Unclear	Low	High	Unclear	High
Winblad, 2006	Low	Low	Low	Low	High	Low	High
Winblad, 2007	Low	Low	Low	Low	High	Unclear	High
Yi, 2005	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Zhang, 2012	Unclear	Unclear	Unclear	Unclear	High	Unclear	High

* Other bias was categorized as:

a) *low risk of bias* when the study appeared to be free of other sources of bias,

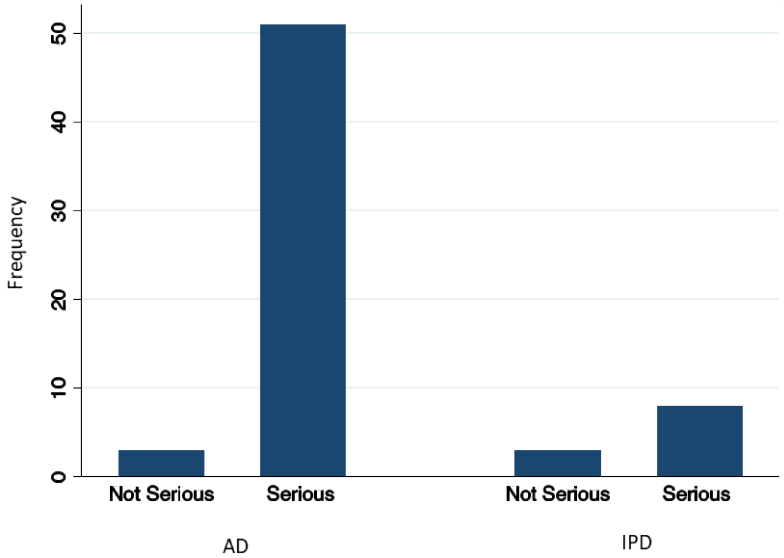
b) *high risk of bias* when there was at least one important risk of bias. For example, when the study had:

- A potential source of bias related to the specific study design used; or
- A conflict of interest related to funding source; or
- An author was an employee of the drug company that sponsored the study; or
- Been claimed to have been fraudulent; or
- Other potential biases.

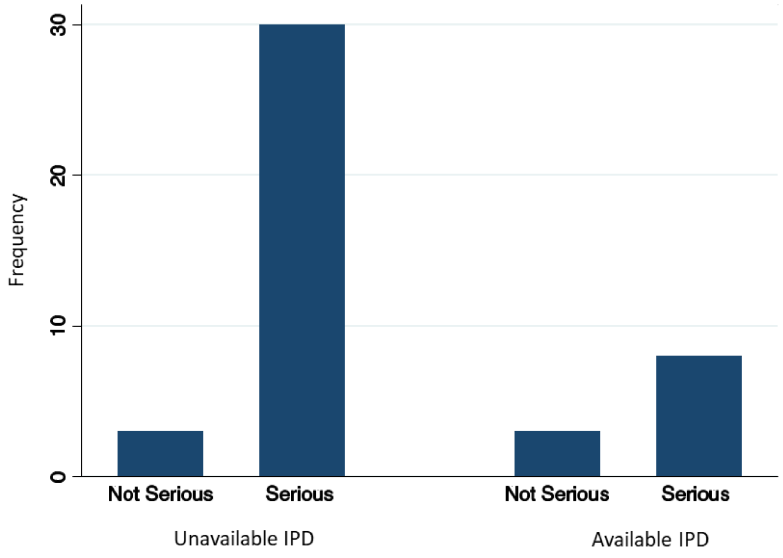
c) *unclear risk of bias* when there was a potential for bias, but there was either:

- Insufficient information to assess whether an important risk of bias exists; or
- Insufficient rationale/evidence that an identified problem would introduce bias; or
- Funding by drug company, but conflicts were not described

Appendix 9: Overall risk of bias for studies with shared IPD against (a) all remaining studies and (b) studies for which sponsors claimed unavailable IPD. AD: aggregate data; IPD: individual patient data

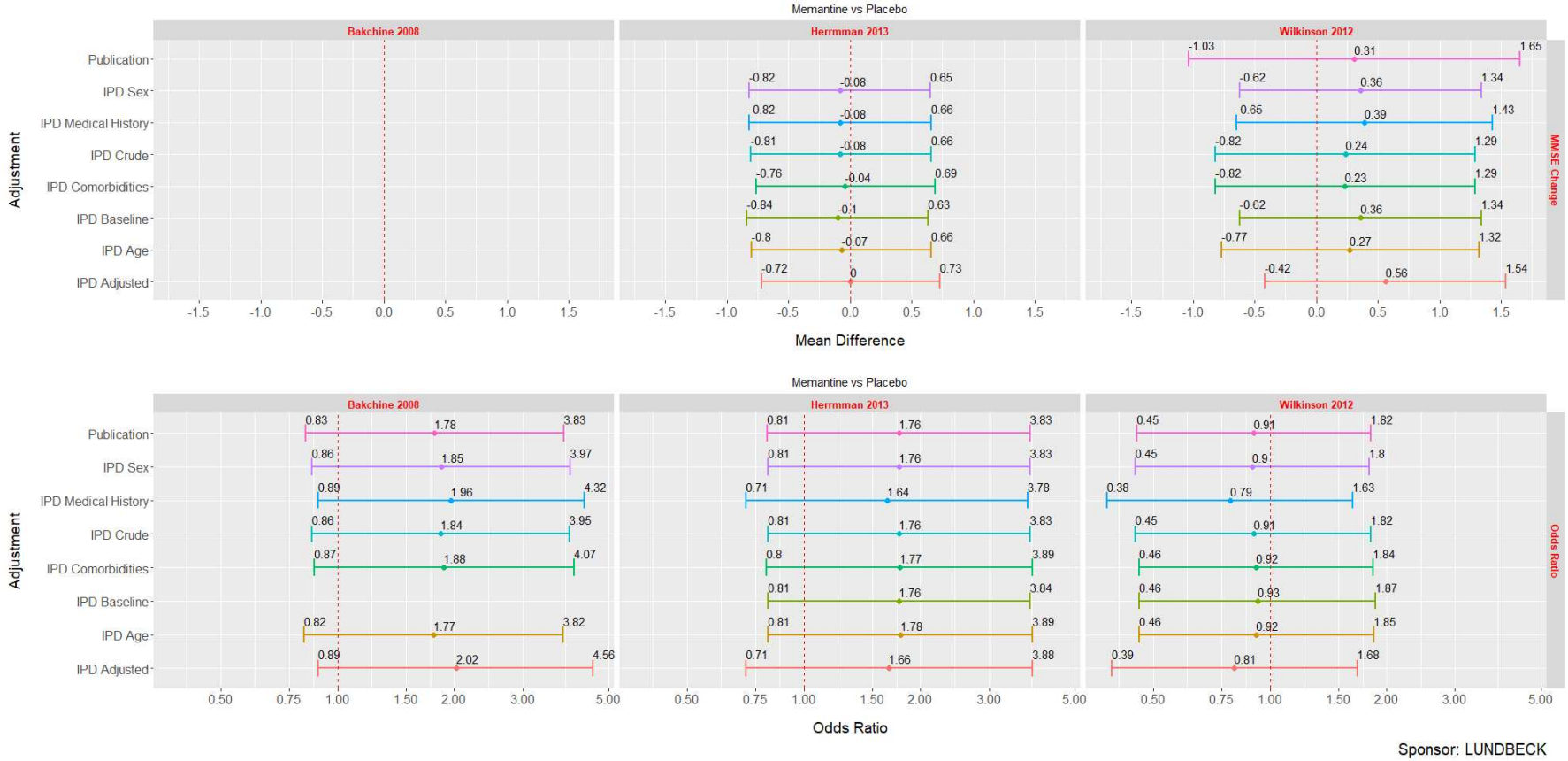


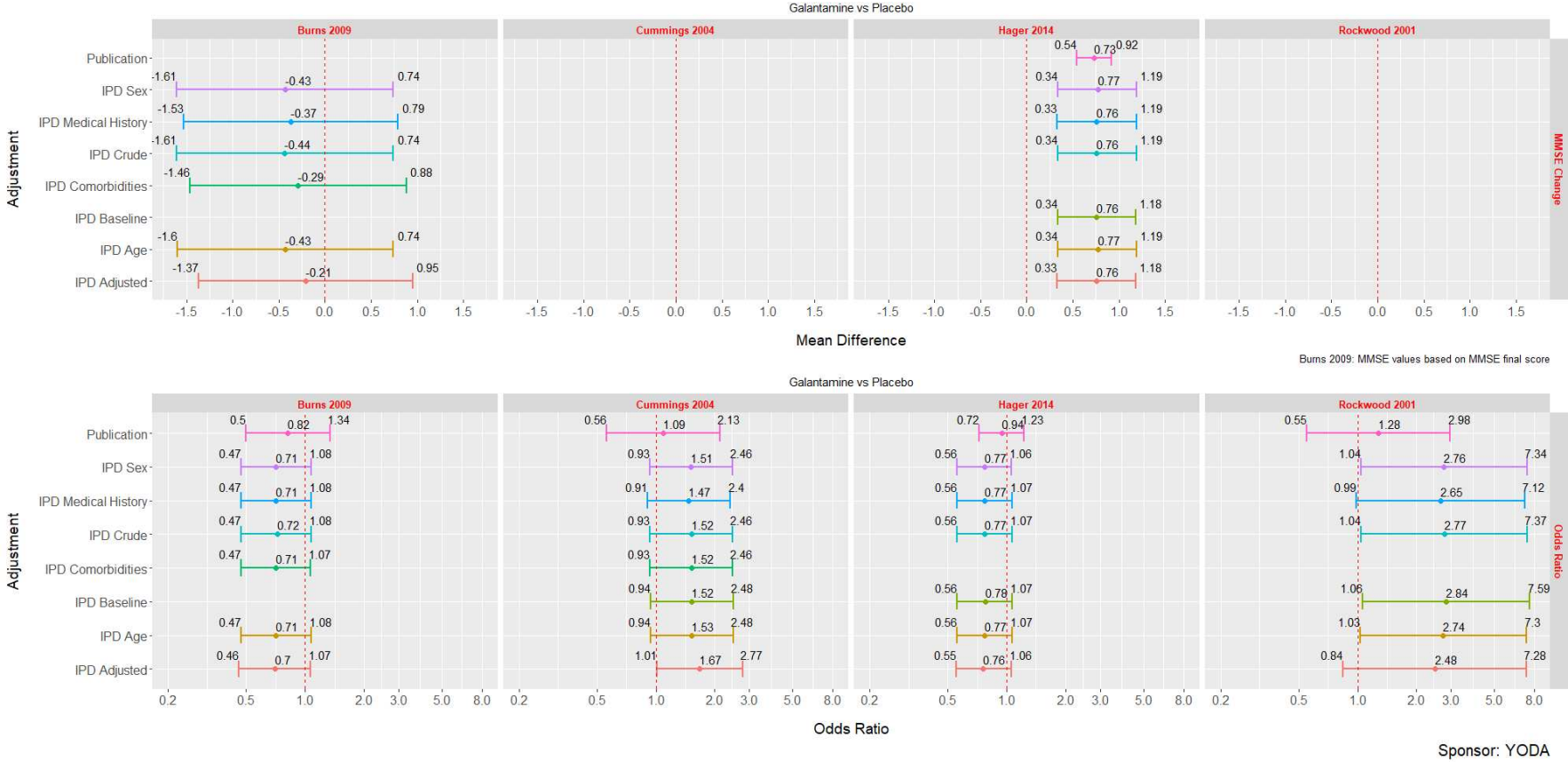
a. Comparison of studies with shared IPD with all remaining studies (irrespective type of sponsor)

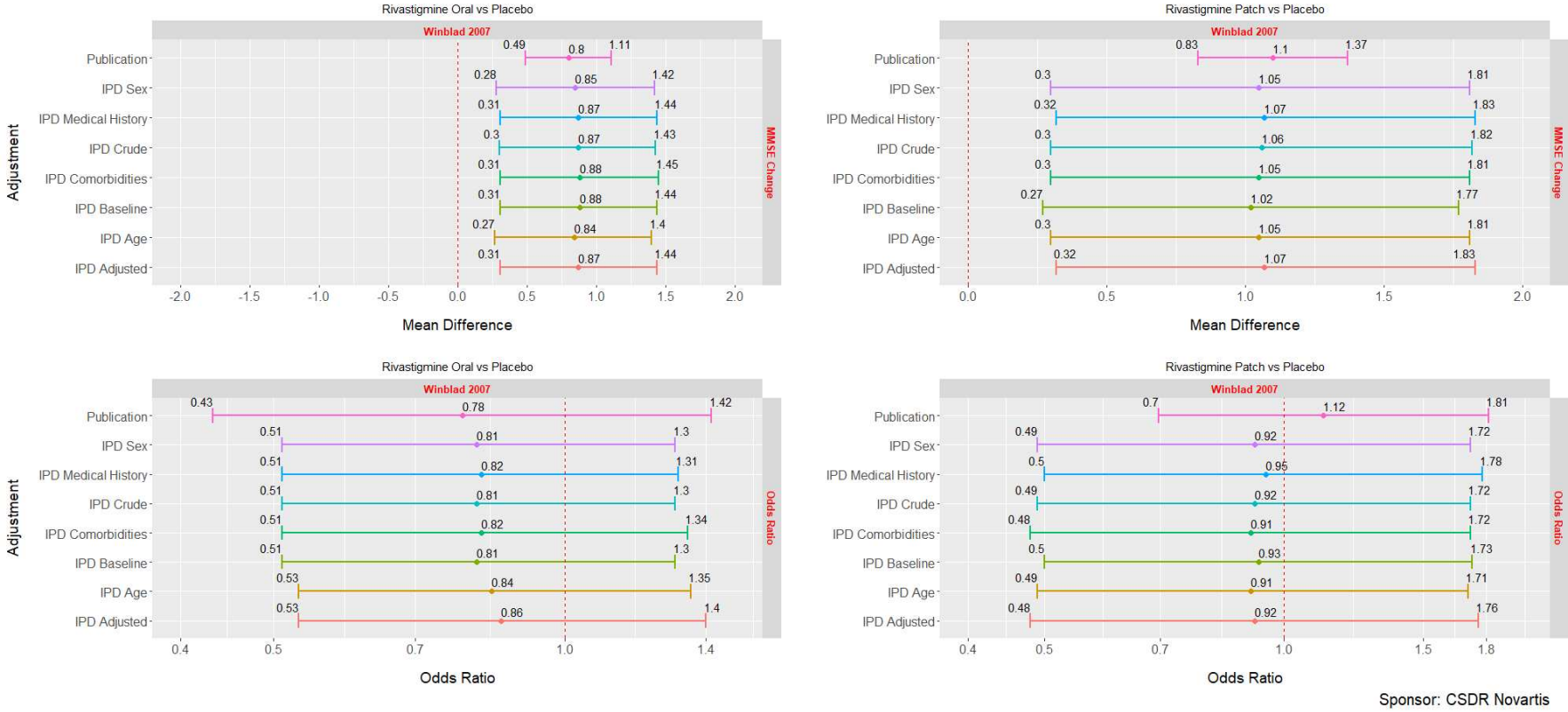


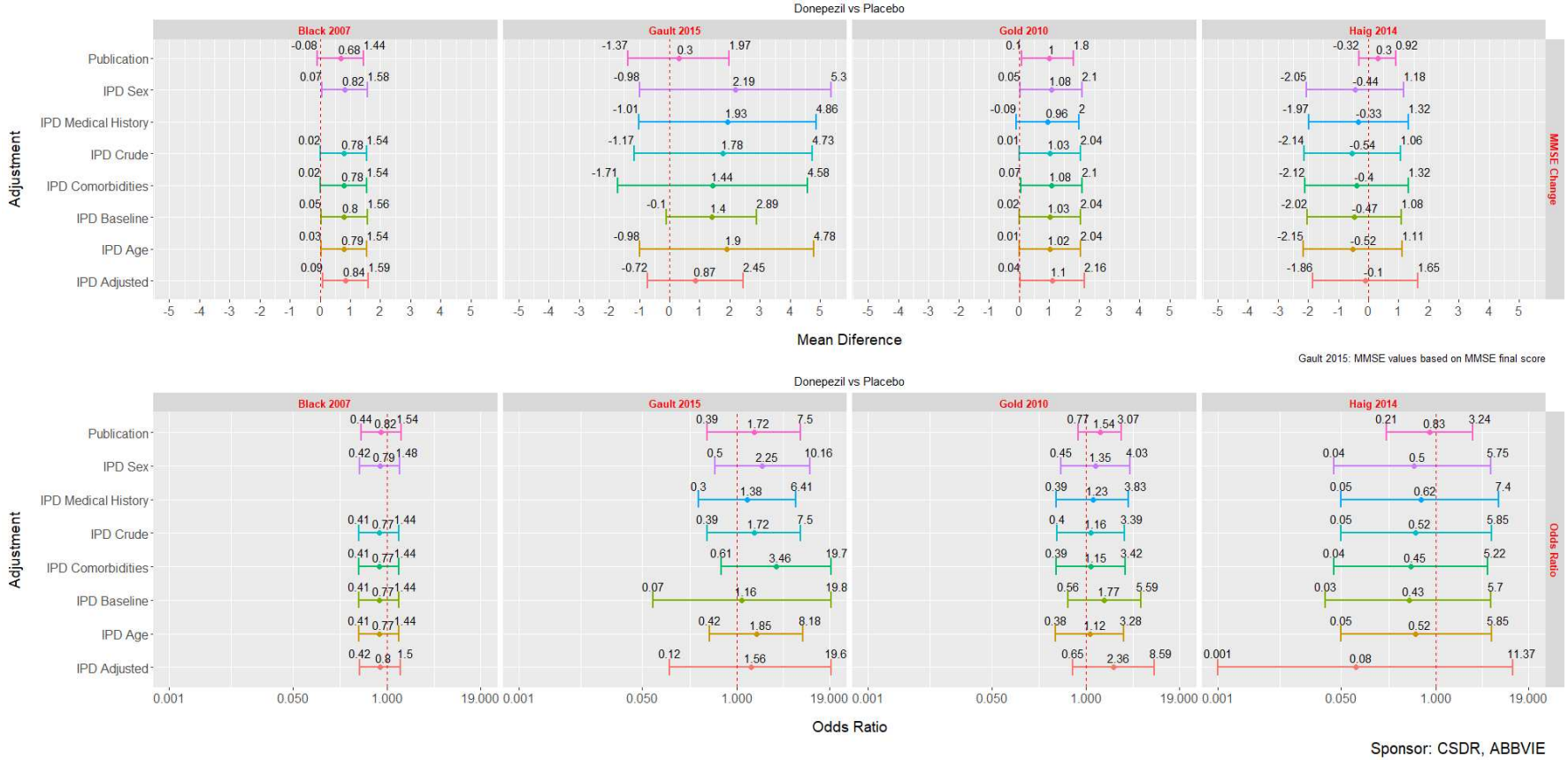
b. Comparison of studies with available and unavailable IPD (industry-sponsored studies only)

Appendix 10: Study-specific effect sizes calculated from shared IPD and published data. IPD: individual patient data




Galantamine vs Placebo
Burns 2009
Cummings 2004
Hager 2014
Rockwood 2001
Publication
IPD Sex
IPD Medical History
IPD Crude
IPD Comorbidities
IPD Baseline
IPD Age
IPD Adjusted
Adjustment
MMSE Change
Mean Difference
Burns 2009: MMSE values based on MMSE final score
Odds Ratio
Sponsor: YODA


Rivastigmine Oral vs Placebo
Winblad 2007
Publication 0.49 0.8 1.11
IPD Sex 0.28 0.85 1.42
IPD Medical History 0.31 0.87 1.44
IPD Crude 0.3 0.87 1.43
IPD Comorbidities 0.31 0.88 1.45
IPD Baseline 0.31 0.88 1.44
IPD Age 0.27 0.84 1.4
IPD Adjusted 0.31 0.87 1.44
Adjustment
MMSE Change
-2.0 -1.5 -1.0 -0.5 0.0 0.5 1.0 1.5 2.0
Mean Difference
Rivastigmine Patch vs Placebo
Winblad 2007
Publication 0.83 1.1 1.37
IPD Sex 0.3 1.05 1.81
IPD Medical History 0.32 1.07 1.83
IPD Crude 0.3 1.06 1.82
IPD Comorbidities 0.3 1.05 1.81
IPD Baseline 0.27 1.02 1.77
IPD Age 0.3 1.05 1.81
IPD Adjusted 0.32 1.07 1.83
MMSE Change
0.0 0.5 1.0 1.5 2.0
Mean Difference
Rivastigmine Oral vs Placebo
Winblad 2007
Publication 0.43 0.78 1.42
IPD Sex 0.51 0.81 1.3
IPD Medical History 0.51 0.82 1.31
IPD Crude 0.51 0.81 1.3
IPD Comorbidities 0.51 0.82 1.34
IPD Baseline 0.51 0.81 1.3
IPD Age 0.53 0.84 1.35
IPD Adjusted 0.53 0.86 1.4
Adjustment
Odds Ratio
0.4 0.5 0.7 1.0 1.4
Odds Ratio
Rivastigmine Patch vs Placebo
Winblad 2007
Publication 0.7 1.12 1.81
IPD Sex 0.49 0.92 1.72
IPD Medical History 0.5 0.95 1.78
IPD Crude 0.49 0.92 1.72
IPD Comorbidities 0.48 0.91 1.72
IPD Baseline 0.5 0.93 1.73
IPD Age 0.49 0.91 1.71
IPD Adjusted 0.48 0.92 1.76
Odds Ratio
0.4 0.5 0.7 1.0 1.5 1.8
Odds Ratio
Sponsor: CSDR Novartis



CSDR includes studies sponsored by GlaxoSmithKline, Eisai, Novartis, whereas YODA includes studies sponsored by Janssen

We also calculated the odds ratio for patients experiencing at least one AE excluding missing participants as shown in the MMSE outcome: Gold 2010: OR 2.78, 95% CI: 0.63-12.25; Black 2007: OR 1.19, 95% CI: 0.08-17.96; Winbland 2007: rivastigmine oral, OR 1.28, 95% CI: 0.09-18.16, rivastigmine patch, OR 0.81, 95% CI: 0.02-33.59; Wilkinson 2012: OR 0.84, 95% CI: 0.38-1.86; Herrmman 2013: OR 1.70, 95% CI: 0.71-4.08; Bachine 2008: OR 1.83, 95% CI: 0.77-4.32.

We were unable to assess this for studies obtained through YODA and AbbVie, since at the time of this assessement we did not have access to these data.

Abbreviations: IPD sex, regression analysis adjusting for sex; IPD medical history, regression analysis adjusting for medical history; IPD crude, analysis with no adjustments; IPD comorbidities, regression analysis adjusting for comorbidities; IPD baseline, regression analysis adjusting for MMSE baseline; IPD age, regression analysis adjusting for age; IPD adjusted, regression analysis adjusting for all available variables (we only considered those that we initially requested from sponsor)

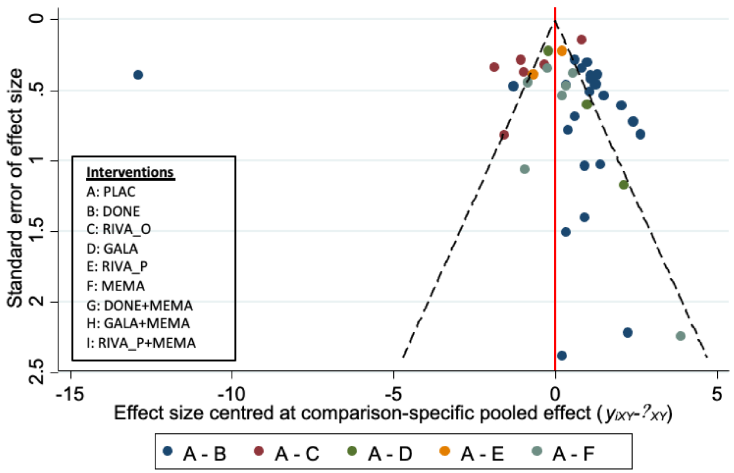
Appendix 11: Correlation between participant age and dropout in studies with IPD. IPD: individual patient data

	Study*	Correlation	P-Value
CSDR	Black 2007 (EISAI)	0.079	0.147
	Gold 2010 (GSK)	0.141	0.072
	Winblad 2007 (Novartis)	0.016	0.584
Lundbeck	Wilkinson 2012	0.066	0.273
	Herrmman 2013	0.124	0.017

* We were unable to assess this correlation for studies obtained through YODA and AbbVie, since at the time of this assessment we did not have access to these data

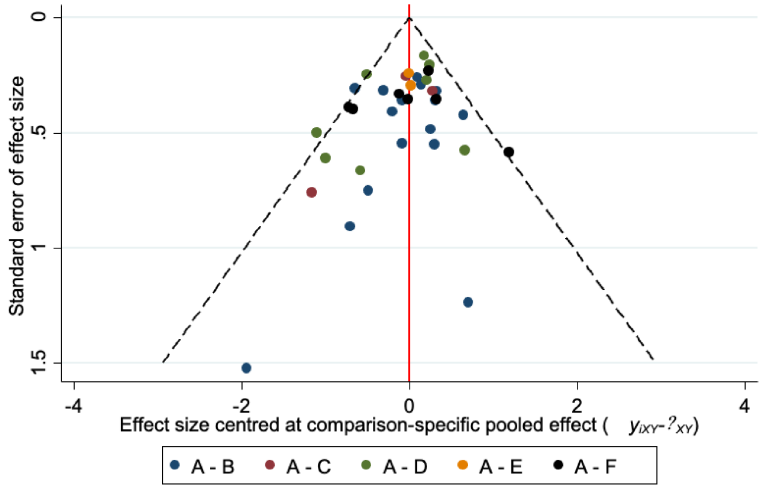
Appendix 12: Comparison Adjusted Funnel plot (all treatments vs placebo)

(a) MMSE



Note: Comparisons including only one study (when present) have been excluded

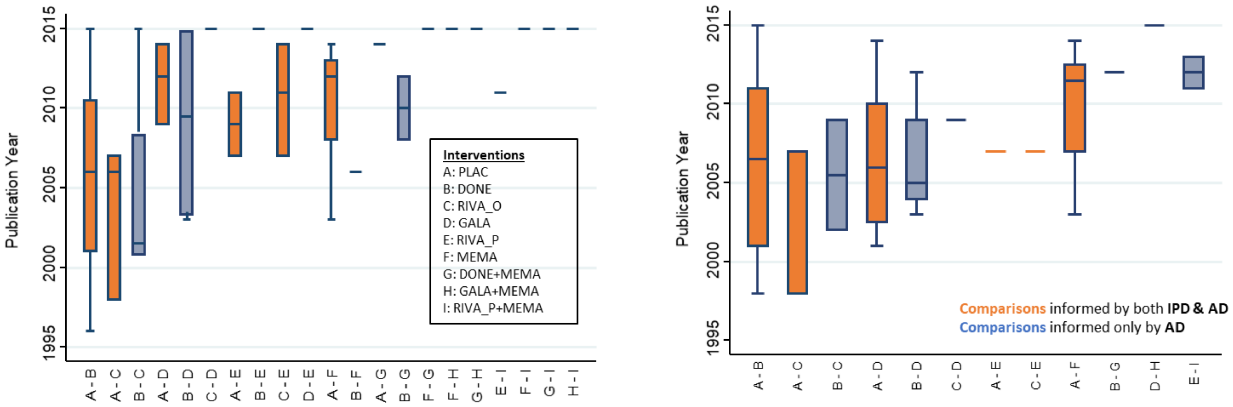
(b) Adverse Events



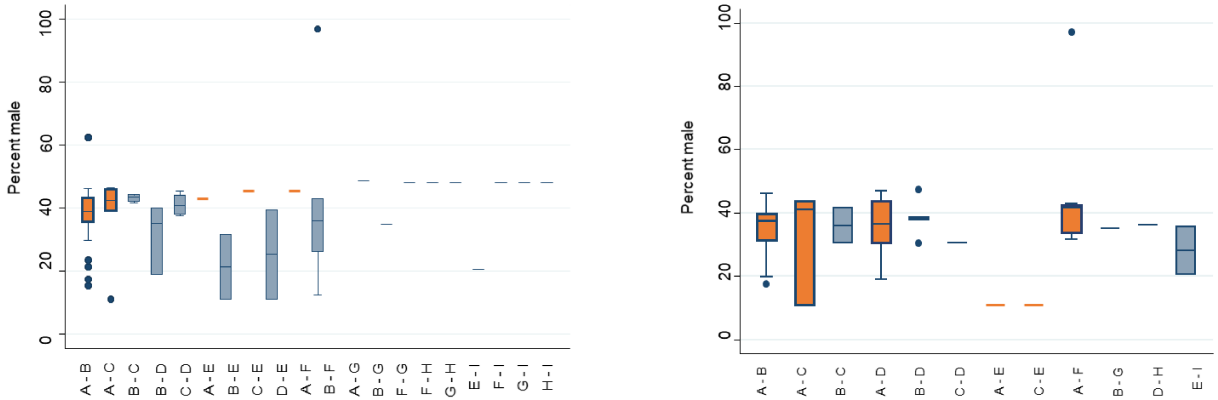
Note: Comparisons including only one study (when present) have been excluded

Appendix 13: Distribution of potential effect modifiers per treatment comparison and outcome

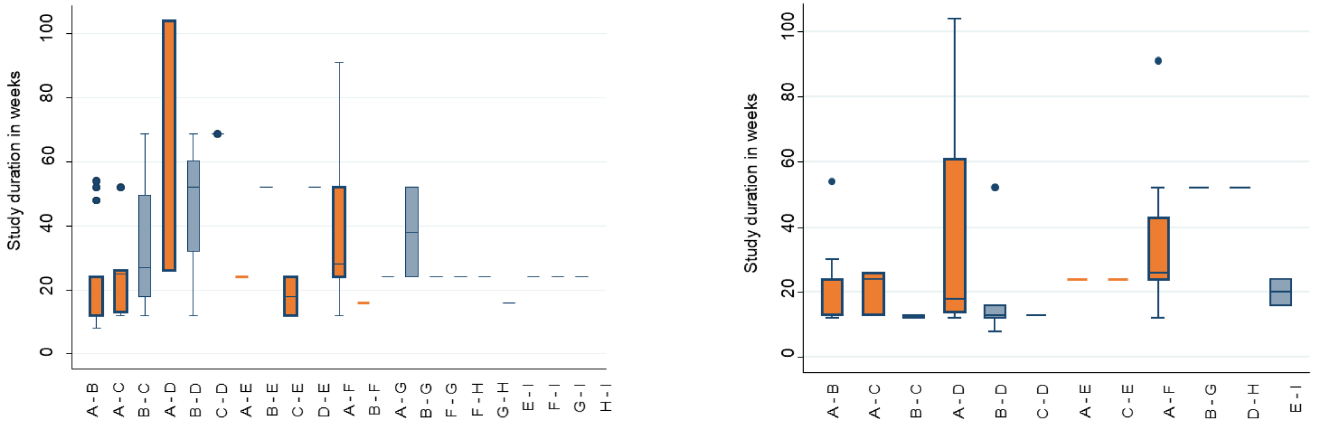
(a) MMSE (b) Adverse Events



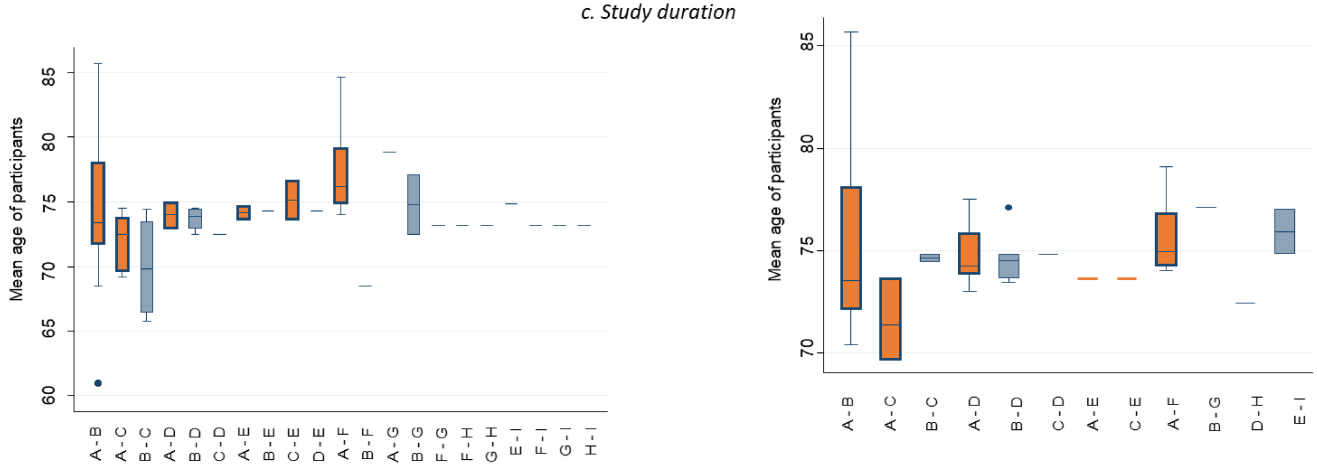
a. Publication year



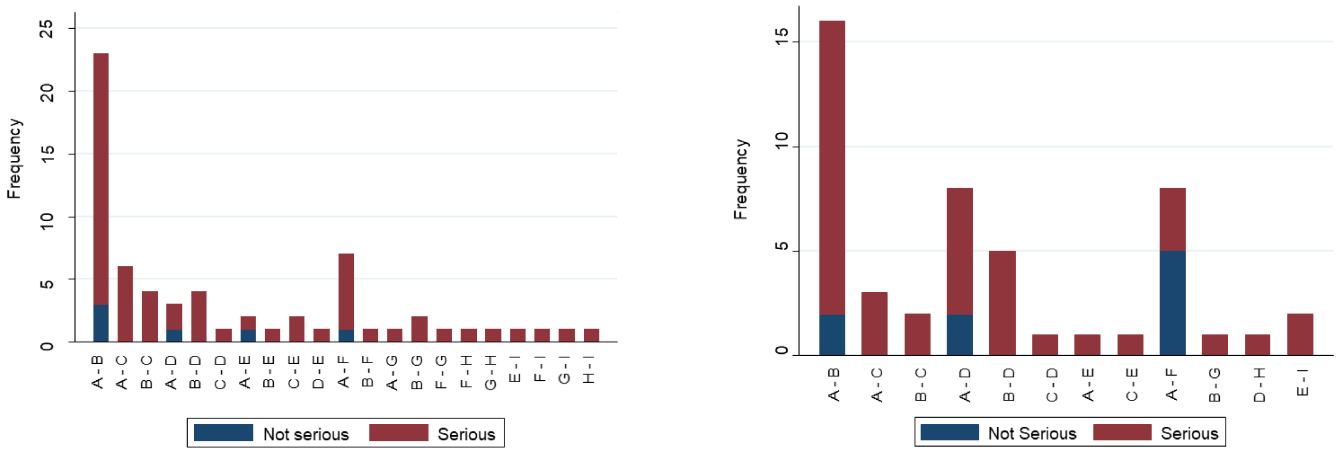
b. Percentage male



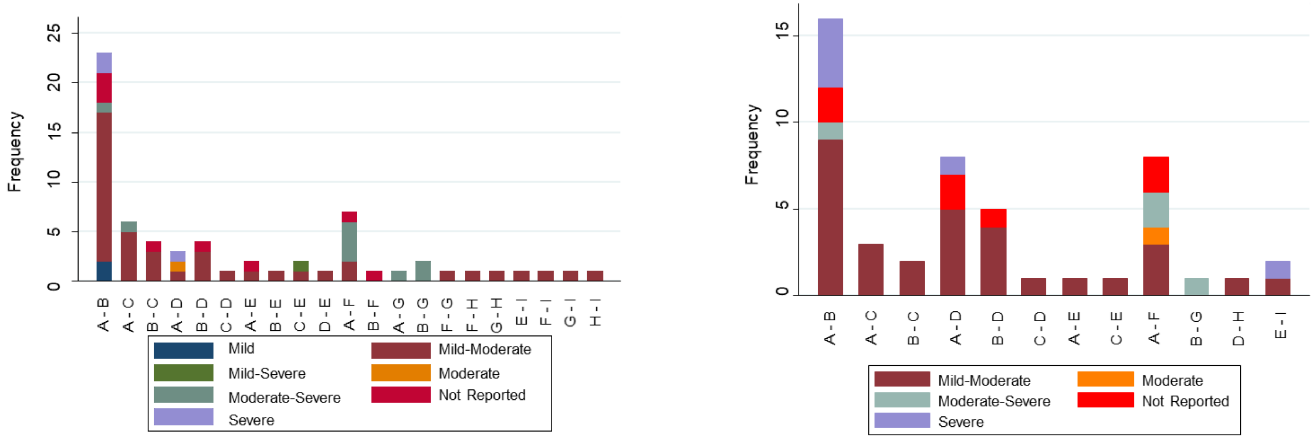
c. Study duration



d. Mean participant age



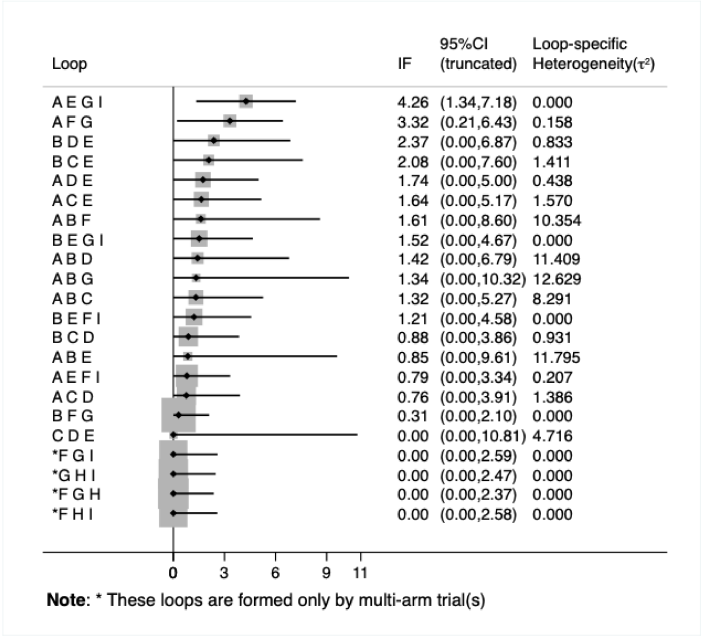
e. Overall Risk of Bias



f. Alzheimer's Dementia Severity

Appendix 14: Consistency Assessment – Loop-specific approach (using adjusted treatment effects)

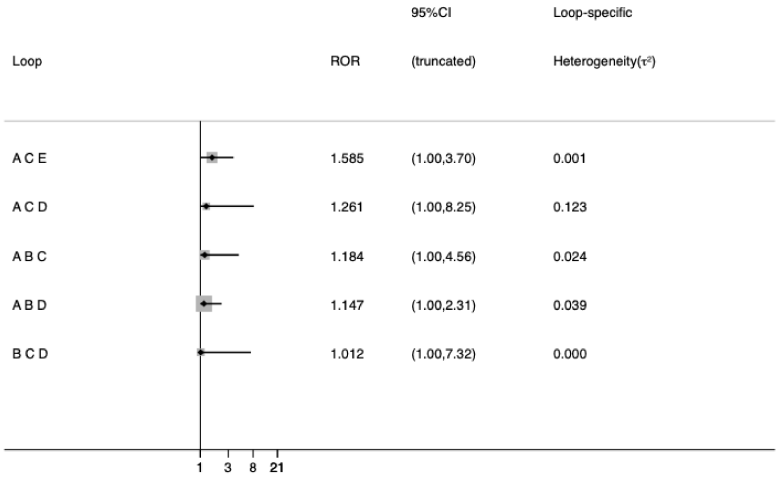
(a) MMSE



Note: * These loops are formed only by multi-arm trial(s)

Design-by-treatment interaction model:
χ^2 statistic: 4.36, 13 degrees of freedom, P value: 0.987, between-study variance: 7.34. I^2 statistic=96%

(b) Adverse Events



Design-by-treatment interaction model:
χ^2 statistic: 3.57, 6 degrees of freedom, P value: 0.735, between-study variance: 0.06. I^2 statistic=22%

Appendix 15: Network and standard meta-analysis results

Treatment Comparison	NMA estimate	95% CI	95% PI	P-score	MA estimate	95% CI	95% PI	#studies
Mini-Mental State Examination (MMSE)*†								
Donepezil vs Placebo	1.41	0.51 to 2.32	-3.48 to 6.31	0.59	1.65	0.16 to 3.14	-6.02 to 9.32	24
Rivastigmine oral vs Placebo	0.69	-0.79 to 2.18	-4.35 to 5.74	0.36	0.60	-0.43 to 1.62	-3.07 to 4.26	6
Galantamine vs Placebo	0.41	-1.44 to 2.26	-4.76 to 5.58	0.28	0.04	-1.09 to 1.17	-12.39 to 12.47	3
Rivastigmine transdermal vs Placebo	2.11	-0.04 to 4.26	-3.18 to 7.40	0.72	0.56	-0.33 to 1.45	--	2
Memantine vs Placebo	0.67	-0.99 to 2.34	-4.43 to 5.78	0.35	0.52	0.03 to 1.01	-0.69 to 1.73	7
Donepezil + Memantine vs Placebo	2.57	0.07 to 5.07	-2.88 to 8.02	0.80	4.21	1.94 to 6.48	--	1
Galantamine + Memantine vs Placebo	2.24	-2.13 to 6.61	-4.33 to 8.81	0.66				
Rivastigmine transdermal + Memantine vs Placebo	1.79	-1.70 to 5.27	-4.20 to 7.78	0.60				
Placebo (reference)				0.14				
Rivastigmine transdermal vs Rivastigmine oral	1.41	-0.80 to 3.62	-3.90 to 6.73		2.26	-0.48 to 4.99	-30.56 to 35.07	3
Rivastigmine oral vs Donepezil	-0.72	-2.28 to 0.84	-5.79 to 4.35		0.16	-0.57 to 0.90	-1.45 to 1.77	4
Galantamine vs Rivastigmine oral	-0.29	-2.48 to 1.91	-5.60 to 5.02		0.06	-1.05 to 1.17		1
Rivastigmine transdermal vs Donepezil	0.69	-1.52 to 2.91	-4.62 to 6.01		-0.20	-2.78 to 2.38		1
Rivastigmine transdermal vs Galantamine	1.70	-0.93 to 4.33	-3.81 to 7.21		2.20	-0.19 to 4.59		1
Rivastigmine transdermal + Memantine vs Rivastigmine transdermal	-0.32	-3.82 to 3.18	-6.32 to 5.68		-0.40	-1.40 to 0.60		1
Memantine vs Donepezil	-0.74	-2.56 to 1.08	-5.90 to 4.42		0.20	0.88 to 1.28		1
Donepezil + Memantine vs Donepezil	1.15	-1.33 to 3.64	-4.29 to 6.59		0.88	0.64 to 1.11		2
Galantamine vs Donepezil	-1.01	-2.86 to 0.84	-6.18 to 4.16		-0.35	-1.52 to 0.83	-5.31 to 4.62	4
Donepezil + Memantine vs Memantine	1.89	-0.88 to 4.67	-3.69 to 7.48		0.37	-1.04 to 1.78		1
Galantamine + Memantine vs Memantine	1.57	-2.78 to 5.92	-4.98 to 8.12		0.82	-0.58 to 2.22		1

Rivastigmine transdermal + Memantine vs Memantine	1.12	-2.47 to 4.70	-4.93 to 7.16		0.41	-1.17 to 1.99		1
Galantamine + Memantine vs Donepezil + Memantine	-0.33	-4.72 to 4.06	-6.91 to 6.23		0.45	-0.85 to 1.75		1
Rivastigmine transdermal + Memantine vs Donepezil + Memantine	-0.78	-4.53 to 2.97	-6.93 to 5.38		0.04	-1.45 to 1.53		1
Rivastigmine transdermal + Memantine vs Galantamine + Memantine	-0.45	-5.05 to 4.14	-7.18 to 6.28		-0.41	-1.89 to 1.07		1
Common within-network between-study variance $\tau^2 = 5.75$, $I^2 = 96\%$ (96%, 97%)								
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 4.36 (13, 0.987, 7.35)								
Adverse Events (AEs)*‡								
Donepezil vs Placebo	1.08	0.87 to 1.35	0.67 to 1.75	0.30	1.07	0.88 to 1.31	0.84 to 1.37	16
Rivastigmine oral vs Placebo	1.26	0.82 to 1.94	0.69 to 2.33	0.16	1.26	0.75 to 2.12	0.01 to 161.35	3
Galantamine vs Placebo	0.95	0.74 to 1.22	0.58 to 1.55	0.53	1.02	0.71 to 1.46	0.38 to 2.77	8
Rivastigmine transdermal vs Placebo	0.90	0.58 to 1.42	0.48 to 1.69	0.57	0.86	0.53 to 1.40		1
Memantine vs Placebo	0.88	0.64 to 1.20	0.52 to 1.49	0.63	0.87	0.63 to 1.20	0.38 to 1.99	8
Donepezil + Memantine vs Placebo	0.77	0.34 to 1.73	0.30 to 1.96	0.69				
Galantamine + Memantine vs Placebo	1.03	0.45 to 2.39	0.39 to 2.70	0.43				
Rivastigmine transdermal + Memantine vs Placebo	0.72	0.32 to 1.59	0.28 to 1.81	0.75				
Placebo (reference)				0.44				
Rivastigmine oral Donepezil vs	1.17	0.73 to 1.87	0.61 to 2.22		2.08	0.21 to 20.73		2
Galantamine vs Donepezil	0.88	0.64 to 1.19	0.52 to 1.49		0.79	0.46 to 1.39	0.32 to 1.96	5
Donepezil + Memantine vs Donepezil	0.71	0.33 to 1.55	0.29 to 1.76		0.71	0.37 to 1.38		1
Rivastigmine transdermal vs Rivastigmine oral	0.72	0.42 to 1.23	0.36 to 1.44		0.94	0.52 to 1.68		1
Rivastigmine transdermal + Memantine vs Rivastigmine transdermal	0.79	0.41 to 1.54	0.36 to 1.77		0.79	0.45 to 1.39		2
Galantamine vs Rivastigmine oral	0.75	0.46 to 1.22	0.39 to 1.45		0.63	0.15 to 2.64		1

Galantamine + Memantine vs Galantamine	1.09	0.49 to 2.42	0.43 to 2.75	1.09	0.55 to 2.17	1
Common within-network between-study variance $\tau 2 = 0.04$, $I^2 = 22\%$ (0%, 48%)						
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 3.57 (6, 0.735, 0.06)						

* Aggregate data and fully adjusted results from studies with available individual patient data were used in both meta-analysis and NMA. The mean difference effect size is presented for MMSE and the odds ratio for AE.
† MMSE: Studies with available IPD included only available participants –to assess the missing data impact on the second stage (IMDoM) a separate analysis was applied
‡ AE: Studies with available IPD included all randomized participants

Appendix 16: Network subgroup and meta-regression analysis results

Treatment Comparison	NMA estimate	95% CI	95%PI	P-score
Mini-Mental State Examination (MMSE)†				
Mean Difference: Aggregate data and crude results from studies with available individual patient data				
Donepezil vs Placebo	1.41	0.50 to 2.33	-3.51 to 6.34	0.59
Rivastigmine oral vs Placebo	0.69	-0.80 to 2.19	-4.38 to 5.76	0.36
Galantamine vs Placebo	0.37	-1.49 to 2.23	-4.82 to 5.57	0.28
Rivastigmine transdermal vs Placebo	2.10	-0.06 to 4.26	-3.22 to 7.42	0.72
Memantine vs Placebo	0.63	-1.05 to 2.30	-4.51 to 5.76	0.34
Donepezil + Memantine vs Placebo	2.56	0.04 to 5.07	-2.92 to 8.04	0.79
Galantamine + Memantine vs Placebo	2.22	-2.18 to 6.61	-4.39 to 8.82	0.66
Rivastigmine transdermal + Memantine vs Placebo	1.77	-1.73 to 5.27	-4.25 to 7.79	0.60
Placebo (reference)				0.14
Common within-network between-study variance τ^2 = 5.81, I^2 = 96% (96%, 97%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 4.42 (13, 0.986, 7.44)				
Mean Difference: Aggregate data results**				
Donepezil vs Placebo	1.55	0.41 to 2.68	-4.16 to 7.25	0.57
Rivastigmine oral vs Placebo	0.71	-1.10 to 2.52	-5.18 to 6.60	0.34
Galantamine vs Placebo	0.57	-1.98 to 3.12	-5.61 to 6.74	0.32
Rivastigmine transdermal vs Placebo	2.60	-0.20 to 5.40	-3.69 to 8.89	0.75
Memantine vs Placebo	0.82	-1.37 to 3.01	-5.21 to 6.84	0.37
Donepezil + Memantine vs Placebo	2.71	-0.17 to 5.60	-3.62 to 9.04	0.76
Galantamine + Memantine vs Placebo	2.44	-2.61 to 7.48	-5.19 to 10.07	0.65
Rivastigmine transdermal + Memantine vs Placebo	2.09	-1.98 to 6.15	-4.89 to 9.07	0.61
Placebo (reference)				0.15
Common within-network between-study variance τ^2 = 7.66, I2 = 97% (96%, 97%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 3.92 (11, 0.972, 8.76)				
Mean Difference: Crude results from studies with available individual patient data				
Donepezil vs Placebo	0.70	0.01 to 1.40	-0.67 to 2.07	0.65
Rivastigmine oral vs Placebo	0.87	-0.01 to 1.75	-0.70 to 2.44	0.73
Galantamine vs Placebo	0.45	-0.24 to 1.14	-0.91 to 1.82	0.48
Rivastigmine transdermal vs Placebo	1.06	0.04 to 2.08	-0.67 to 2.79	0.82
Memantine vs Placebo	0.05	-0.74 to 0.83	-1.42 to 1.51	0.20
Placebo (reference)				0.13
Common within-network between-study variance τ^2 = 0.12, I^2 = 29% (0%, 71%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: N/A (no closed loops)				
Mean Difference: Low Risk of Bias for Allocation Concealment*				
Donepezil vs Placebo	2.02	-0.24 to 4.28	-6.19 to 10.23	0.70
Rivastigmine oral vs Placebo	1.38	-2.27 to 5.02	-7.39 to 10.14	0.57
Galantamine vs Placebo	-0.31	-4.61 to 3.98	-9.42 to 8.79	0.31
Rivastigmine transdermal vs Placebo	0.82	-4.08 to 5.72	-8.63 to 10.27	0.48
Memantine vs Placebo	0.69	-3.01 to 4.39	-8.10 to 9.49	0.46
Donepezil + Memantine vs Placebo	2.88	-4.75 to 10.51	-8.48 to 14.23	0.69
Placebo (reference)				0.30
Common within-network between-study variance: τ^2 = 13.82, I^2 = 98% (98%, 99%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 0.13 (3, 0.99, 19.10)				
Mean Difference: Low risk of bias for Incomplete Data*				
Donepezil vs Placebo	0.87	0.07 to 1.66	-1.67 to 3.40	0.61
Rivastigmine oral vs Placebo	-1.52	-4.41 to 1.37	-5.54 to 2.50	0.10
Galantamine vs Placebo	0.52	-0.94 to 1.99	-2.36 to 3.41	0.48
Rivastigmine transdermal vs Placebo	1.37	-0.64 to 3.38	-1.91 to 4.65	0.71
Memantine vs Placebo	0.57	-1.12 to 2.27	-2.47 to 3.62	0.48
Donepezil + Memantine vs Placebo	0.94	-2.11 to 4.00	-3.23 to 5.11	0.57
Galantamine + Memantine vs Placebo	1.39	-1.66 to 4.44	-2.77 to 5.56	0.70
Rivastigmine transdermal + Memantine vs Placebo	0.98	-2.15 to 4.12	-3.26 to 5.23	0.58
Placebo (reference)				0.27
Common within-network between-study variance: τ^2 = 1.16, I^2 = 79% (65%, 88%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 12.15 (3, 0.007, 0.863)				
Mean Difference: Publicly-Sponsored Studies*				
Donepezil vs Placebo	6.57	-4.68 to 17.81	-129.61 to 142.74	0.71
Rivastigmine oral vs Placebo	1.40	-16.41 to 19.21	-161.58 to 164.38	0.44
Memantine vs Placebo	0.11	-17.65 to 17.87	-162.64 to 162.86	0.39
Rivastigmine transdermal + Memantine vs Placebo	5.83	-7.98 to 19.64	-139.93 to 151.59	0.65
Placebo (reference)				0.32

Common within-network between-study variance: τ^2 = 81.93, I^2 = 99% (99%, 100%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 0.05 (1, 0.815, 116.71)				
Mean Difference: Industry-Sponsored Studies*				
Donepezil vs Placebo	0.98	0.69 to 1.27	0.10 to 1.86	0.85
Rivastigmine oral vs Placebo	0.82	0.35 to 1.29	-0.14 to 1.78	0.69
Galantamine vs Placebo	0.41	-0.15 to 0.96	-0.60 to 1.41	0.34
Rivastigmine transdermal vs Placebo	0.80	0.18 to 1.41	-0.25 to 1.84	0.67
Memantine vs Placebo	0.60	0.06 to 1.15	-0.39 to 1.60	0.50
Rivastigmine transdermal + Memantine vs Placebo	0.40	-1.02 to 1.81	-1.29 to 2.08	0.39
Placebo (reference)				0.06
Common within-network between-study variance: τ^2 = 0.16, I^2 = 43% (15%, 62%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 8.06 (7, 0.327, 0.16)				
Mean Difference: Studies with Mild to Moderate cognitive impairment, assessed with MMSE at baseline *				
Donepezil vs Placebo	1.68	0.31 to 3.06	-4.81 to 8.18	0.69
Rivastigmine oral vs Placebo	0.88	-1.29 to 3.05	-5.85 to 7.61	0.51
Galantamine vs Placebo	0.31	-2.47 to 3.09	-6.66 to 7.28	0.40
Rivastigmine transdermal vs Placebo	2.74	-0.68 to 6.16	-4.53 to 10.01	0.81
Memantine vs Placebo	-0.58	-4.84 to 3.69	-8.31 to 7.16	0.28
Donepezil + Memantine vs Placebo	0.43	-6.36 to 7.21	-9.06 to 9.91	0.45
Galantamine + Memantine vs Placebo	0.88	-5.90 to 7.66	-8.61 to 10.37	0.51
Rivastigmine transdermal + Memantine vs Placebo	1.11	-4.20 to 6.42	-7.30 to 9.52	0.55
Placebo (reference)				0.31
Common within-network between-study variance: τ^2 = 9.67, I^2 = 97% (97%, 98%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 3.22 (9, 0.96, 13.28)				
Mean Difference: Studies with Moderate to Severe cognitive impairment, assessed with MMSE at baseline *				
Donepezil vs Placebo	1.31	0.66 to 1.96	-0.01 to 2.63	0.78
Rivastigmine oral vs Placebo	-1.00	-1.87 to -0.12	-2.51 to 0.51	0.04
Galantamine vs Placebo	-0.21	-1.64 to 1.21	-2.28 to 1.86	0.28
Memantine vs Placebo	0.69	0.07 to 1.31	-0.61 to 2.00	0.59
Donepezil + Memantine vs Placebo	2.49	1.55 to 3.44	0.92 to 4.07	1.00
Placebo (reference)				0.32
Common within-network between-study variance: τ^2 = 0.18, I^2 = 44% (0%, 75%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 2.60 (1, 0.11, 0.11)				
Mean Difference: Excluding outlier studies*[§]				
Donepezil vs Placebo	0.95	0.59 to 1.32	-0.64 to 2.54	0.57
Rivastigmine oral vs Placebo	0.65	0.09 to 1.22	-1.00 to 2.30	0.37
Galantamine vs Placebo	0.36	-0.38 to 1.09	-1.36 to 2.07	0.22
Rivastigmine transdermal vs Placebo	1.03	0.15 to 1.91	-0.76 to 2.82	0.59
Memantine vs Placebo	0.67	0.02 to 1.32	-1.01 to 2.35	0.39
Donepezil + Memantine vs Placebo	2.04	1.03 to 3.05	0.18 to 3.90	0.92
Galantamine + Memantine vs Placebo	1.87	0.08 to 3.66	-0.53 to 4.26	0.82
Rivastigmine transdermal + Memantine vs Placebo	1.10	-0.33 to 2.53	-1.03 to 3.23	0.58
Placebo (reference)				0.04
Common within-network between-study variance: τ^2 = 0.59, I^2 = 73% (64%, 79%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 10.60 (13, 0.64, 0.61)				
Accounting for missing outcome data - Informative Missingness Difference of Means[¶]				
Donepezil vs Placebo	1.42	0.51 to 2.33	0.51 to 2.33	0.59[‖]
Rivastigmine oral vs Placebo	0.45	-1.09 to 1.99	-1.09 to 1.99	0.30[‖]
Galantamine vs Placebo	0.19	-1.78 to 2.17	-1.78 to 2.17	0.25[‖]
Rivastigmine transdermal vs Placebo	2.37	-0.03 to 4.79	-0.03 to 4.79	0.76[‖]
Memantine vs Placebo	0.60	-1.09 to 2.42	-1.09 to 2.42	0.36[‖]
Donepezil + Memantine vs Placebo	2.55	0.09 to 5.01	0.09 to 5.01	0.80[‖]
Galantamine + Memantine vs Placebo	2.26	-2.03 to 6.56	-2.03 to 6.56	0.68[‖]
Rivastigmine transdermal + Memantine vs Placebo	1.81	-1.66 to 5.28	-1.66 to 5.28	0.61[‖]
Placebo (reference)				0.16[‖]
Common within-network between-study variance: τ^2 = 5.47[‖]				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 4.45 (11, 0.955, 6.45)				
Mean Difference: Meta-regression, Trial Mean Age[**]				
Donepezil vs Placebo	1.53	0.52 to 2.53	-3.17 to 6.27	0.50[††]
Rivastigmine oral vs Placebo	0.80	-0.84 to 2.44	-4.15 to 5.79	0.37[††]
Galantamine vs Placebo	0.60	-1.63 to 2.83	-4.57 to 5.72	0.25[††]
Rivastigmine transdermal vs Placebo	2.53	0.06 to 4.98	-2.72 to 7.80	0.75[††]
Memantine vs Placebo	0.79	-1.18 to 2.74	-4.33 to 5.85	0.37[††]
Donepezil + Memantine vs Placebo	2.66	0.09 to 5.19	-2.70 to 7.97	0.87[††]
Galantamine + Memantine vs Placebo	2.39	-2.02 to 6.84	-4.14 to 8.83	0.75[††]
Rivastigmine transdermal + Memantine vs Placebo	2.05	-1.53 to 5.59	-3.83 to 7.94	0.75[††]
Placebo (reference)				0.12[††]
Regression coefficient	0.03	-0.14 to 0.20		
Common within-network between-study variance: τ^2 = 5.50	3.72 to 8.51			

Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 3.92 (11, 0.972, 8.76)				
Mean Difference: NMA of studies with IPD adjusted for Age				
Donepezil vs Placebo	0.72	0.03 to 1.42	-0.66 to 2.10	0.66
Rivastigmine oral vs Placebo	0.84	-0.05 to 1.73	-0.75 to 2.43	0.70
Galantamine vs Placebo	0.46	-0.24 to 1.15	-0.92 to 1.83	0.48
Rivastigmine transdermal vs Placebo	1.05	0.04 to 2.06	-0.68 to 2.78	0.83
Memantine vs Placebo	0.06	-0.72 to 0.84	-1.40 to 1.53	0.21
Placebo (reference)				0.12
Common within-network between-study variance: $\tau^2 = 0.12$, $I^2 = 29\%$ (0%, 71%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: N/A (one closed loop with a single multi-arm trial)				
Mean Difference: Meta-regression, Percent of Male Participants[**]				
Donepezil vs Placebo	1.62	0.58 to 2.65	-3.40 to 6.61	0.62[††]
Rivastigmine oral vs Placebo	0.73	-0.90 to 2.35	-4.30 to 5.81	0.37[††]
Galantamine vs Placebo	0.62	-1.65 to 2.89	-4.75 to 5.93	0.25[††]
Rivastigmine Transdermal vs Placebo	2.51	0.01 to 5.04	-2.78 to 7.94	0.75[††]
Memantine vs Placebo	0.66	-1.47 to 2.77	-4.54 to 5.88	0.25[††]
Donepezil + Memantine vs Placebo	2.52	-0.40 to 5.45	-3.09 to 8.17	0.75[††]
Galantamine + Memantine vs Placebo	2.27	-2.28 to 6.83	-4.37 to 8.90	0.75[††]
Rivastigmine transdermal + Memantine vs Placebo	1.98	-1.67 to 5.65	-4.02 to 7.99	0.75[††]
Placebo (reference)				0.12[††]
Regression coefficient	0.01	-0.05 to 0.06		
Common within-network between-study variance: $\tau^2 = 5.73$	3.83 to 8.84			
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 3.72 (10, 0.959, 8.97)				
Mean difference: NMA of studies with IPD adjusted for Percent of Male Participants				
Donepezil vs Placebo	0.76	0.05 to 1.47	-0.67 to 2.19	0.67
Rivastigmine oral vs Placebo	0.85	-0.07 to 1.77	-0.80 to 2.50	0.69
Galantamine vs Placebo	0.45	-0.27 to 1.16	-0.99 to 1.88	0.46
Rivastigmine transdermal vs Placebo	1.05	0.01 to 2.09	-0.74 to 2.84	0.81
Memantine vs Placebo	0.10	-0.68 to 0.89	-1.40 to 1.61	0.23
Placebo (reference)				0.11
Common within-network between-study variance: $\tau^2 = 0.13$, $I^2 = 32\%$ (0%, 72%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: N/A (one closed loop with a single multi-arm trial)				
Mean Difference: NMA of studies with IPD adjusted for cognitive impairment, assessed with MMSE at baseline				
Donepezil vs Placebo	0.79	0.26 to 1.32	-0.06 to 1.64	0.64
Rivastigmine oral vs Placebo	0.88	0.31 to 1.45	-0.05 to 1.81	0.69
Galantamine vs Placebo	0.76	0.34 to 1.18	0.08 to 1.44	0.62
Rivastigmine transdermal vs Placebo	1.02	0.27 to 1.77	-0.20 to 2.24	0.82
Memantine vs Placebo	0.07	-0.52 to 0.66	-0.89 to 1.03	0.14
Placebo (reference)				0.08
Common within-network between-study variance: $\tau^2 = 0.00$, $I^2 = 0\%$ (0%, 79%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: N/A (one closed loop with a single multi-arm trial)				
Mean Difference: NMA of studies with IPD adjusted for comorbidities				
Donepezil vs Placebo	0.77	0.21 to 1.33	-0.15 to 1.68	0.71
Rivastigmine oral vs Placebo	0.88	0.31 to 1.45	-0.05 to 1.81	0.75
Galantamine vs Placebo	-0.29	-1.46 to 0.88	-2.19 to 1.61	0.15
Rivastigmine transdermal vs Placebo	1.05	0.30 to 1.80	-0.17 to 2.27	0.88
Memantine vs Placebo	0.05	-0.55 to 0.64	-0.92 to 1.01	0.27
Placebo (reference)				0.15
Common within-network between-study variance: $\tau^2 = 0.00$, $I^2 = 0\%$ (0%, 67%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: N/A (one closed loop with a single multi-arm trial)				
Mean Difference: NMA of studies with IPD adjusted for other medications				
Donepezil vs Placebo	0.67	-0.34 to 1.69	-1.44 to 2.79	0.61
Rivastigmine oral vs Placebo	0.87	-0.12 to 1.86	-1.21 to 2.95	0.71
Galantamine vs Placebo	0.42	-0.35 to 1.19	-1.40 to 2.25	0.47
Rivastigmine transdermal vs Placebo	1.07	-0.04 to 2.18	-1.16 to 3.30	0.81
Memantine vs Placebo	0.11	-0.74 to 0.96	-1.80 to 2.02	0.26
Placebo (reference)				0.14
Common within-network between-study variance: $\tau^2 = 0.17$, $I^2 = 35\%$ (0%, 76%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: N/A (one closed loop with a single multi-arm trial)				
Mean Difference: Meta-regression, Study Duration[**]				
Donepezil vs Placebo	1.66	0.67 to 2.66	-3.12 to 6.32	0.62[††]
Rivastigmine oral vs Placebo	0.80	-0.77 to 2.37	-4.14 to 5.69	0.37[††]
Galantamine vs Placebo	0.47	-1.75 to 2.68	-4.64 to 5.66	0.25[††]
Rivastigmine transdermal vs Placebo	2.38	-0.04 to 4.83	-2.87 to 7.56	0.75[††]
Memantine vs Placebo	0.67	-1.27 to 2.58	-4.35 to 5.79	0.25[††]
Donepezil + Memantine vs Placebo	2.67	0.18 to 5.16	-2.60 to 7.97	0.88[††]
Galantamine + Memantine vs Placebo	2.43	-1.94 to 6.79	-3.94 to 8.81	0.75[††]
Rivastigmine transdermal + Memantine vs Placebo	2.13	-1.40 to 5.63	-3.62 to 7.87	0.75[††]
Placebo (reference)				0.12[††]

Regression coefficient	0.02	-0.01 to 0.06		
Common within-network between-study variance: τ^2 = 5.40	3.63 to 8.29			
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 4.36 (13, 0.987, 7.35)				
Mean Difference: Meta-regression, Year of Publication**				
Donepezil vs Placebo	1.53	0.51 to 2.54	-3.27 to 6.31	0.50 ††
Rivastigmine oral vs Placebo	0.66	-1.01 to 2.32	-4.31 to 5.65	0.25 ††
Galantamine vs Placebo	0.60	-1.65 to 2.85	-4.65 to 5.83	0.25 ††
Rivastigmine transdermal vs Placebo	2.59	0.09 to 5.12	-2.73 to 7.95	0.75 ††
Memantine vs Placebo	0.89	-1.05 to 2.80	-4.17 to 5.90	0.38 ††
Donepezil + Memantine vs Placebo	2.82	0.19 to 5.44	-2.57 to 8.21	0.88 ††
Galantamine + Memantine vs Placebo	2.59	-1.93 to 7.16	-3.98 to 9.12	0.75 ††
Rivastigmine transdermal + Memantine vs Placebo	2.21	-1.49 to 5.95	-3.81 to 8.24	0.75 ††
Placebo (reference)				0.12 ††
Regression coefficient	-0.02	-0.17 to 0.14		
Common within-network between-study variance: τ^2 = 5.53	3.71 to 8.48			
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 4.36 (13, 0.987, 7.35)				
Adverse Events (AEs)‡				
Odds Ratio: Aggregate data and crude results from studies with available individual patient data				
Donepezil vs Placebo	1.07	0.86 to 1.32	0.68 to 1.67	0.31
Rivastigmine oral vs Placebo	1.26	0.83 to 1.90	0.70 to 2.24	0.16
Galantamine vs Placebo	0.95	0.75 to 1.21	0.60 to 1.51	0.52
Rivastigmine transdermal vs Placebo	0.87	0.57 to 1.35	0.48 to 1.58	0.61
Memantine vs Placebo	0.91	0.67 to 1.22	0.55 to 1.49	0.59
Donepezil + Memantine vs Placebo	0.76	0.34 to 1.68	0.31 to 1.88	0.69
Galantamine + Memantine vs Placebo	1.03	0.45 to 2.36	0.41 to 2.64	0.42
Rivastigmine transdermal + Memantine vs Placebo	0.69	0.32 to 1.51	0.28 to 1.70	0.77
Placebo (reference)				0.43
Common within-network between-study variance τ^2 = 0.04, I^2 = 20% (0%, 47%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 3.58 (6, 0.733, 0.05)				
Odds Ratio: Aggregate data results**				
Donepezil vs Placebo	1.09	0.89 to 1.33	0.88 to 1.35	0.25
Rivastigmine oral vs Placebo	1.43	0.92 to 2.21	0.90 to 2.26	0.07
Galantamine vs Placebo	0.88	0.63 to 1.25	0.62 to 1.27	0.54
Rivastigmine transdermal vs Placebo	0.79	0.44 to 1.41	0.43 to 1.45	0.61
Memantine vs Placebo	0.70	0.51 to 0.97	0.50 to 0.98	0.77
Donepezil + Memantine vs Placebo	0.77	0.39 to 1.54	0.37 to 1.60	0.64
Galantamine + Memantine vs Placebo	0.96	0.45 to 2.08	0.43 to 2.16	0.44
Rivastigmine transdermal + Memantine vs Placebo	0.62	0.28 to 1.40	0.27 to 1.46	0.80
Placebo (reference)				0.38
Common within-network between-study variance τ^2 = 0.00, I^2 = 0% (0%, 42%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 2.29 (4, 0.682, 0.01)				
Odds Ratio: Crude results from studies with available individual patient data				
Donepezil vs Placebo	0.95	0.50 to 1.78	0.33 to 2.70	0.57
Rivastigmine oral vs Placebo	0.81	0.37 to 1.75	0.25 to 2.61	0.71
Galantamine vs Placebo	1.05	0.71 to 1.56	0.44 to 2.50	0.46
Rivastigmine transdermal vs Placebo	0.92	0.38 to 2.20	0.26 to 3.31	0.57
Memantine vs Placebo	1.41	0.81 to 2.45	0.53 to 3.79	0.16
				0.53
Common within-network between-study variance τ^2 = 0.10, I^2 = 48% (0%, 76%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: N/A (no closed loops)				
Odds Ratio: Low Risk of Bias for Allocation Concealment*				
Donepezil vs Placebo	0.88	0.60 to 1.29	0.42 to 1.83	0.52
Rivastigmine oral vs Placebo	1.15	0.67 to 1.98	0.50 to 2.68	0.21
Galantamine vs Placebo	0.94	0.64 to 1.38	0.45 to 1.95	0.44
Rivastigmine transdermal vs Placebo	0.88	0.52 to 1.49	0.39 to 2.02	0.51
Memantine vs Placebo	0.86	0.55 to 1.36	0.40 to 1.88	0.54
Donepezil + Memantine vs Placebo	0.63	0.24 to 1.62	0.19 to 2.05	0.75
Rivastigmine transdermal + Memantine vs Placebo	0.67	0.25 to 1.80	0.20 to 2.28	0.71
Placebo (reference)				0.33
Common within-network between-study variance: τ^2 = 0.08, I^2 = 37% (0%, 64%)				
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 2.19 (3, 0.53, 0.1)				
Odds Ratio: Low Risk of Bias for Incomplete Data*				
Donepezil vs Placebo	0.83	0.53 to 1.29	0.45 to 1.51	0.51
Galantamine vs Placebo	0.69	0.50 to 0.97	0.42 to 1.13	0.80
Rivastigmine transdermal vs Placebo	0.79	0.42 to 1.49	0.36 to 1.76	0.56
Memantine vs Placebo	0.86	0.60 to 1.22	0.51 to 1.43	0.47
Placebo (reference)				0.16

Common within-network between-study variance: τ^2 = 0.02, I^2 = 10% (0%, 50%)				
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): 0.00 (1, 0.95, 0.04)				
Odds Ratio: Publicly-Sponsored Studies*				
Donepezil vs Placebo	2.15	0.36 to 12.69	--	0.16
Memantine vs Placebo	0.71	0.45 to 1.12	--	0.86
Donepezil + Memantine vs Placebo	1.53	0.23 to 10.18	--	0.46
Placebo (reference)				0.51
Common within-network between-study variance: τ^2 = N/A (each comparison includes a single study)				
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): N/A (no closed loops)				
Odds Ratio: Industry-Sponsored Studies*				
Donepezil vs Placebo	1.08	0.86 to 1.35	0.64 to 1.82	0.34
Rivastigmine oral vs Placebo	1.27	0.82 to 1.98	0.66 to 2.44	0.16
Galantamine vs Placebo	0.99	0.75 to 1.31	0.57 to 1.71	0.52
Rivastigmine transdermal vs Placebo	0.91	0.57 to 1.44	0.46 to 1.77	0.62
Memantine vs Placebo	0.95	0.65 to 1.37	0.52 to 1.73	0.58
Rivastigmine transdermal + Memantine vs Placebo	0.72	0.31 to 1.64	0.27 to 1.90	0.79
Placebo (reference)				0.50
Common within-network between-study variance: τ^2 = 0.05, I^2 = 25% (0%, 50%)				
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): 3.68 (6, 0.72, 0.07)				
Odds Ratio: Studies with Mild to Moderate cognitive impairment, assessed with MMSE at baseline *				
Donepezil vs Placebo	1.27	0.88 to 1.83	0.61 to 2.65	0.29
Rivastigmine oral vs Placebo	1.36	0.83 to 2.24	0.60 to 3.09	0.25
Galantamine vs Placebo	1.01	0.67 to 1.55	0.47 to 2.19	0.56
Rivastigmine transdermal vs Placebo	1.02	0.50 to 2.05	0.39 to 2.69	0.55
Memantine vs Placebo	0.86	0.54 to 1.37	0.39 to 1.91	0.73
Galantamine + Memantine vs Placebo	1.10	0.40 to 3.00	0.32 to 3.78	0.48
Rivastigmine transdermal + Memantine vs Placebo	0.96	0.18 to 5.19	0.14 to 6.37	0.55
Placebo (reference)				0.59
Common within-network between-study variance: τ^2 = 0.09, I^2 = 29% (0%, 57%)				
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): 3.29 (5, 0.66, 0.13)				
Odds Ratio: Studies with Moderate to Severe cognitive impairment, assessed with MMSE at baseline *				
Donepezil vs Placebo	0.92	0.67 to 1.27	0.59 to 1.45	0.38
Galantamine vs Placebo	0.70	0.46 to 1.07	0.38 to 1.28	0.76
Memantine vs Placebo	0.95	0.55 to 1.62	0.44 to 2.02	0.36
Donepezil + Memantine vs Placebo	0.66	0.32 to 1.37	0.23 to 1.86	0.76
Placebo (reference)				0.23
Common within-network between-study variance: τ^2 = 0.00, I^2 = 0% (0%, 72%)				
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): 2.90 (1, 0.09, 0.00)				
Odds Ratio: NMA of studies with IPD – available case analysis				
Donepezil vs Placebo	1.63	0.49 to 5.41	0.30 to 8.73	0.33
Rivastigmine oral vs Placebo	1.28	0.08 to 19.94	0.04 to 39.11	0.46
Galantamine vs Placebo	1.05	0.67 to 1.63	0.38 to 2.85	0.58
Rivastigmine transdermal vs Placebo	0.81	0.02 to 35.04	0.01 to 82.49	0.59
Memantine vs Placebo	1.35	0.72 to 2.55	0.43 to 4.24	0.38
Placebo (reference)				0.64
Common within-network between-study variance: τ^2 = 0.13, I^2 = 50% (0%, 77%)				
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, heterogeneity): N/A (no closed loops)				
Odds Ratio: Meta-regression, Trial Mean Age**				
Donepezil vs Placebo	1.13	0.88 to 1.43	0.68 to 1.86	0.25 ††
Rivastigmine oral vs Placebo	1.52	0.89 to 2.53	0.77 to 3.04	0.00 ††
Galantamine vs Placebo	0.91	0.60 to 1.30	0.52 to 1.59	0.50 ††
Rivastigmine transdermal vs Placebo	0.84	0.39 to 1.58	0.34 to 1.80	0.75 ††
Memantine vs Placebo	0.74	0.48 to 1.07	0.39 to 1.26	0.75 ††
Donepezil + Memantine vs Placebo	0.92	0.38 to 1.89	0.33 to 2.15	0.62 ††
Galantamine + Memantine vs Placebo	0.99	0.37 to 2.27	0.33 to 2.55	0.50 ††
Rivastigmine transdermal + Memantine vs Placebo	0.73	0.24 to 1.70	0.22 to 1.87	0.87 ††
Placebo (reference)				0.37 ††
Regression coefficient (log-scale)	-0.03	-0.08 to 0.02		
Common within-network between-study variance: τ^2 = 0.02	0.00 to 0.19			
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): 3.57 (6, 0.735, 0.06)				
Odds Ratio: NMA of studies with IPD adjusted for Age				
Donepezil vs Placebo	0.95	0.50 to 1.78	0.33 to 2.73	0.57
Rivastigmine oral vs Placebo	0.84	0.39 to 1.81	0.26 to 2.74	0.68
Galantamine vs Placebo	1.04	0.70 to 1.55	0.43 to 2.52	0.46
Rivastigmine transdermal vs Placebo	0.91	0.38 to 2.17	0.25 to 3.28	0.58
Memantine vs Placebo	1.39	0.80 to 2.44	0.52 to 3.79	0.17
Placebo (reference)				0.53
Common within-network between-study variance: τ^2 = 0.10, I^2 = 48% (0%, 76%)				
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): N/A (no closed loops)				

Odds Ratio: Meta-regression, Percent of Male Participants[**]				
Donepezil vs Placebo	1.12	0.87 to 1.44	0.64 to 2.01	0.25 [††]
Rivastigmine oral vs Placebo	1.71	0.97 to 2.92	0.83 to 3.67	0.00 [††]
Galantamine vs Placebo	0.93	0.62 to 1.36	0.49 to 1.77	0.50 [††]
Rivastigmine transdermal vs Placebo	0.89	0.39 to 1.79	0.34 to 2.05	0.63 [††]
Memantine vs Placebo	0.64	0.37 to 1.00	0.29 to 1.21	0.88 [††]
Donepezil + Memantine vs Placebo	0.88	0.35 to 1.88	0.30 to 2.13	0.63 [††]
Galantamine + Memantine vs Placebo	1.13	0.39 to 2.58	0.36 to 2.95	0.38 [††]
Rivastigmine transdermal + Memantine vs Placebo	0.77	0.24 to 1.93	0.21 to 2.13	0.88 [††]
Placebo (reference)				0.38 [††]
Regression coefficient (log-scale)	0.00	0.00 to 0.02		
Common within-network between-study variance: $\tau^2 = 0.03$	0.00 to 0.23			
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): 3.57 (6, 0.735, 0.06)				
Odds Ratio: NMA of studies with IPD adjusted for Percent of Male Participants				
Donepezil vs Placebo	1.04	0.54 to 1.99	0.34 to 3.16	0.49
Rivastigmine oral vs Placebo	0.81	0.37 to 1.80	0.24 to 2.79	0.72
Galantamine vs Placebo	1.05	0.70 to 1.59	0.42 to 2.65	0.48
Rivastigmine transdermal vs Placebo	0.92	0.37 to 2.27	0.24 to 3.52	0.58
Memantine vs Placebo	1.40	0.80 to 2.48	0.50 to 3.98	0.19
Placebo (reference)				0.55
Common within-network between-study variance: $\tau^2 = 0.11$, $I^2 = 51\%$ (0%, 77%)				
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): N/A (no closed loops)				
Odds Ratio: NMA of studies with IPD adjusted for cognitive impairment, assessed with MMSE at baseline				
Donepezil vs Placebo	0.97	0.46 to 2.06	0.23 to 4.03	0.56
Rivastigmine oral vs Placebo	0.81	0.33 to 2.01	0.17 to 3.91	0.70
Galantamine vs Placebo	1.29	0.74 to 2.25	0.37 to 4.55	0.28
Rivastigmine transdermal vs Placebo	0.93	0.34 to 2.53	0.18 to 4.91	0.57
Memantine vs Placebo	1.26	0.59 to 2.70	0.30 to 5.28	0.33
Placebo (reference)				0.56
Common within-network between-study variance: $\tau^2 = 0.16$, $I^2 = 52\%$ (0%, 80%)				
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): N/A (no closed loops)				
Odds Ratio: NMA of studies with IPD adjusted for comorbidities				
Donepezil vs Placebo	1.01	0.52 to 1.96	0.29 to 3.50	0.51
Rivastigmine oral vs Placebo	0.82	0.36 to 1.87	0.20 to 3.32	0.69
Galantamine vs Placebo	1.02	0.57 to 1.80	0.32 to 3.26	0.50
Rivastigmine transdermal vs Placebo	0.91	0.36 to 2.31	0.20 to 4.11	0.58
Memantine vs Placebo	1.42	0.79 to 2.55	0.44 to 4.59	0.18
Placebo (reference)				0.53
Common within-network between-study variance: $\tau^2 = 0.12$, $I^2 = 44\%$ (0%, 77%)				
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): N/A (no closed loops)				
Odds Ratio: NMA of studies with IPD adjusted for other medications				
Donepezil vs Placebo	1.17	0.49 to 3.03	0.28 to 4.88	0.41
Rivastigmine oral vs Placebo	0.82	0.37 to 1.81	0.23 to 2.91	0.72
Galantamine vs Placebo	1.03	0.69 to 1.55	0.40 to 2.65	0.51
Rivastigmine transdermal vs Placebo	0.95	0.39 to 2.34	0.24 to 2.91	0.56
Memantine vs Placebo	1.34	0.75 to 2.39	0.46 to 3.92	0.25
Placebo (reference)				0.56
Common within-network between-study variance: $\tau^2 = 0.11$, $I^2 = 51\%$ (0%, 78%)				
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): N/A (no closed loops)				
Odds Ratio: Meta-regression, Study Duration[**]				
Donepezil vs Placebo	1.12	0.87 to 1.43	0.63 to 1.95	0.25 [††]
Rivastigmine oral vs Placebo	1.76	1.00 to 2.99	0.88 to 3.68	0.00 [††]
Galantamine vs Placebo	0.92	0.62 to 1.36	0.50 to 1.69	0.50 [††]
Rivastigmine transdermal vs Placebo	0.87	0.39 to 1.70	0.34 to 1.96	0.63 [††]
Memantine vs Placebo	0.61	0.37 to 0.93	0.31 to 1.13	0.88 [††]
Donepezil + Memantine vs Placebo	0.76	0.29 to 1.69	0.26 to 1.90	0.75 [††]
Galantamine + Memantine vs Placebo	0.98	0.34 to 2.26	0.30 to 2.53	0.50 [††]
Rivastigmine transdermal + Memantine vs Placebo	0.75	0.25 to 1.81	0.23 to 1.97	0.75 [††]
Placebo (reference)				0.38 [††]
Regression coefficient (log-scale)	0.00	0.00 to 0.01		
Common within-network between-study variance: $\tau^2 = 0.03$	0.00 to 0.22			
Design-by-treatment interaction model for inconsistency χ^2 (d.f., P-value, τ^2): 3.57 (6, 0.735, 0.06)				
Odds Ratio: Meta-regression, Year of Publication[**]				
Donepezil vs Placebo	1.05	0.79 to 1.38	0.61 to 1.77	0.38 [††]
Rivastigmine oral vs Placebo	1.68	0.98 to 2.77	0.85 to 3.37	0.00 [††]
Galantamine vs Placebo	0.91	0.61 to 1.32	0.50 to 1.64	0.63 [††]
Rivastigmine transdermal vs Placebo	0.92	0.40 to 1.84	0.36 to 2.04	0.63 [††]
Memantine vs Placebo	0.73	0.46 to 1.05	0.38 to 1.28	0.88 [††]
Donepezil + Memantine vs Placebo	0.88	0.35 to 1.83	0.31 to 2.15	0.75 [††]

Galantamine + Memantine vs Placebo	1.24	0.43 to 2.85	0.39 to 3.25	0.25 ††
Rivastigmine transdermal + Memantine vs Placebo	0.88	0.24 to 2.24	0.24 to 2.42	0.75 ††
Placebo (reference)				0.38 ††
Regression coefficient (log-scale)	-0.02	-0.06 to 0.03		
Common within-network between-study variance: $\tau^2 = 0.02$	0.00 to 0.21			
Design-by-treatment interaction model for inconsistency χ^2 *(d.f., P-value,* τ^2*)*: 3.57 (6, 0.735, 0.06)				

* Aggregate data and fully adjusted results from studies with available individual patient data
† MMSE: Studies with available IPD included only available participants – to assess the missing data impact on the second stage a separate analysis was applied (IMDoM)
‡ AE: Studies with available IPD included all randomized participants
§ Outlier studies:

- Hernandez C, Unturbe F, Martinez-Lage P, Lucas A, Gregorio P, Alonso T. Effects of combined pharmacologic and cognitive treatment in the progression of moderate dementia: a two-year follow-up. REVISTA ESPANOLA DE GERIATRIA Y GERONTOLOGIA. 2007;42(1):3
- Moretti DV. Alpha rhythm oscillations and MMSE scores are differently modified by transdermal or oral rivastigmine in patients with Alzheimer's disease. American journal of neurodegenerative disease. 2014;3(2):72-83.

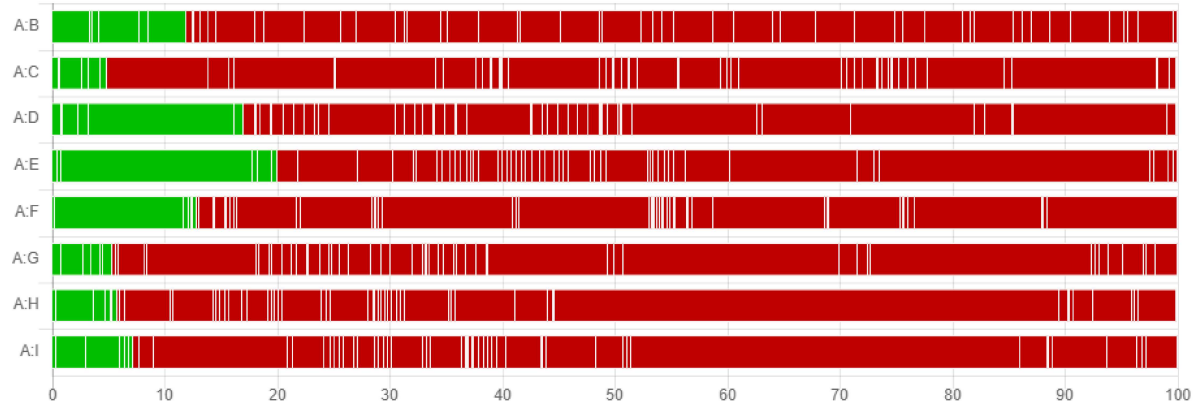
¶ Included studies with available raw data only, irrespective having access to individual patient data
‖ Analyses were conducted in Stata using the *metamiss2* and *network* commands; I2 is not available; SUCRA values are presented instead of P-scores
** Studies with aggregate data were used (studies with available individual patient data were not included in this analysis)
†† Analyses were conducted in OpenBUGS, and SUCRA values were calculated instead of P-scores

Appendix 17: CINeMA results

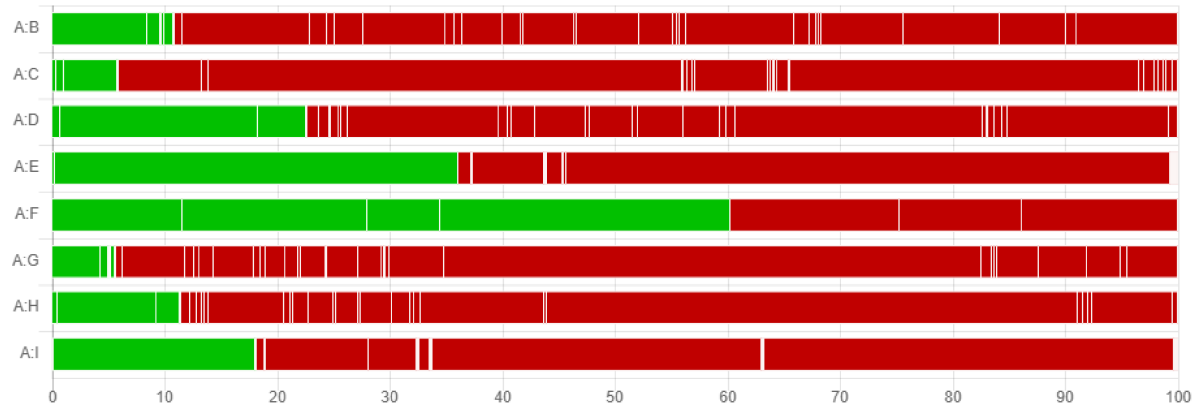
Risk of bias contributions: The bar chart shows the contributions of each piece of study to the network estimate

Interventions
A: PLAC
B: DONE
C: RIVA_O
D: GALA
E: RIVA_P
F: MEMA
G: DONE+MEMA
H: GALA+MEMA
I: RIVA_P+MEMA

MMSE outcome



AE outcome



CINeMA report

MMSE outcome

Comparison	# of studies	Nature of evidence	Type of data	Within-study bias (D1)	Reporting bias (D2)	Indirectness (D3)	Imprecision (D4)	Heterogeneity (D5)	Incoherence (D6)	Confidence rating	Downgrading due to
DONE vs PLAC	24	Mixed	IPD+AD	Major concerns	Suspected	No concerns	No concerns	Major concerns	No concerns	Moderate	D5
RIVA_O vs PLAC	6	Mixed	IPD+AD	Major concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Moderate	D4;D5
GALA vs PLAC	3	Mixed	IPD+AD	Major concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Moderate	D4
RIVA_P vs PLAC	2	Mixed	IPD+AD	Major concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Moderate	D4;D5
MEMA vs PLAC	7	Mixed	IPD+AD	Major concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Moderate	D4;D5
DONE+MEMA vs PLAC	1	Mixed	AD	Major concerns	Suspected	No concerns	No concerns	Major concerns	No concerns	Moderate	D5
GALA+MEMA vs PLAC	0	Indirect	-	Major concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Moderate	D4
RIVA_P+MEMA vs PLAC	0	Indirect	-	Major concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Moderate	D4

AE outcome

Comparison	# of studies	Nature of evidence	Type of data	Within-study bias (D1)	Reporting bias (D2)	Indirectness (D3)	Imprecision (D4)	Heterogeneity (D5)	Incoherence (D6)	Confidence rating	Downgrading due to
DONE vs PLAC	16	Mixed	IPD+AD	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate	D1
RIVA_O vs PLAC	3	Mixed	IPD+AD	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate	D1
GALA vs PLAC	8	Mixed	IPD+AD	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate	D1
RIVA_P vs PLAC	2	Mixed	IPD+AD	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	High	
MEMA vs PLAC	7	Mixed	IPD+AD	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	High	
DONE+MEMA vs PLAC	2	Mixed	AD	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate	D1
GALA+MEMA vs PLAC	0	Indirect	-	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate	D1
RIVA_P+MEMA vs PLAC	0	Indirect	-	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate	D1

Abbreviations: DONE, donepezil; GALA, galantamine; MEMA, memantine; PLAC, placebo; RIVA_O, rivastigmine oral; RIVA_P, rivastigmine patch

Appendix 18: Study definitions for adverse events

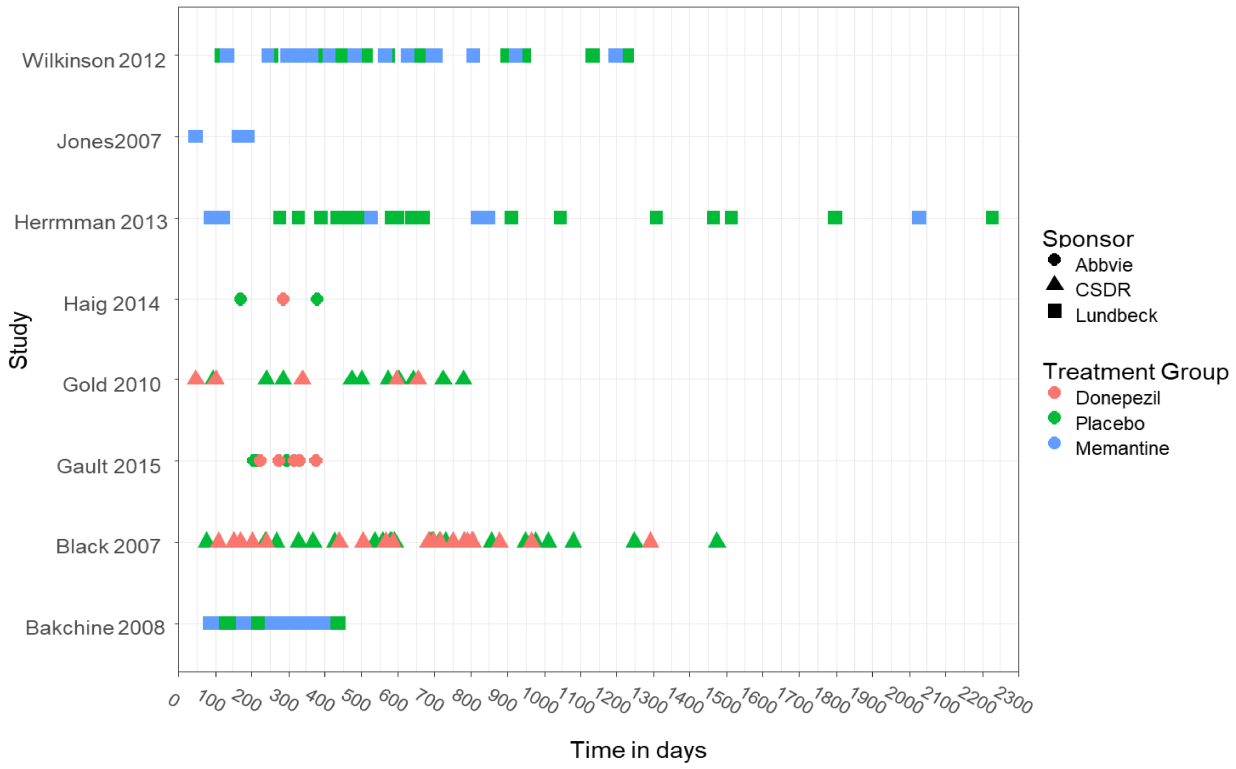
Author, Year	Source of Definition	Definition
Agid, 1998	Determined by Investigator	"Patients and caregivers were questioned systematically regarding the occurrence of adverse events at each clinical visit"
Ancoli-Israel, 2005	Determined by Investigator	"Only one serious AE leading to discontinuation, hepatic failure, in the donepezil-treated group was considered to be possibly due to study treatment by the investigator."
Andersen, 2012	NA	NA
Araki, 2014	NA	NA
Bakchine, 2008	Determined by Investigator	" A patient could also be withdrawn from the study if: they had a serious adverse event (SAE: death, life-threatening condition, hospitalisation) [..] Three patients had an SAE that was considered by the investigator to be possibly or probably related to treatment."
Black, 2007	Determined by Investigator	"AEs were considered serious (SAEs) when death occurred, life was threatened, hospitalization or prolonged hospitalization was required, or a significant disability occurred."
Blesa González, 2011	NA	NA
Burns,1999	COSTART	"Serious adverse events (SAE) included fatal or life-threatening situations, permanently disabling conditions or incidents that required or prolonged hospitalisation […] Events were coded using a modified COSTART dictionary, and the assessment of relationship to treatment for all adverse events was conducted blind to treatment assignment."
Burns, 2009	NR	NR
Burns, 2011	NR	NR
Choi, 2011	Determined by Investigator	"Investigators were asked to evaluate severity (mild, moderate, or severe), relationship to study drug (not related, probable relationship with rivastigmine patch, probable relationship with memantine, or probable relationship with an interaction of the two drugs), and seriousness of the AEs."
Corey-Bloom, 1998	NA	NA
Cretu, 2008	NA	NA
Dysken, 2014	Medical Dictionary for Regulatory Activities	"Serious AEs were coded according to the Medical Dictionary for Regulatory Activities."
Farlow, 2013	NA	NA
Feldman, 2001	Determined by Investigator	"Serious AE was defined as any AE that was life threatening or resulted in death, hospitalization, prolongation of hospitalization, or significant disability."
Feldman, 2007	World Health Organisation preferred terms	" A similar proportion of patients in each treatment group experienced at least one serious adverse event (any event that was fatal, considered life threatening or required hospitalisation) […] All adverse events were recorded using the Novartis Medical Terminology Thesaurus (a modified version of the WHO adverse reaction terminology dictionary)."
Fox, 2012	NA	NA
Frolich, 2011	NA	NA
Fuschillo, 2001	NA	NA
Gault L, 2015	Medical Dictionary for Regulatory Activities	"AEs were coded using the Medical Dictionary for Regulatory Activities"
Gold, 2010	NR	"SAE (fatal or nonfatal) "
Greenberg, 2000	Determined by Investigator	"Of 9 withdrawals from the study after randomization, 2 were due to serious adverse events judged to be possibly related to donepezil therapy: syncope and generalized seizure (1 patient each). "
Grossberg, 2013	Medical Dictionary for Regulatory Activities	"Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 7.0 or newer), and an assessment of the severity, chronicity, causal relationship to study medication, and seriousness of the event was provided by an investigator"
Hager, 2014	Determined by Investigator	"Safety data were monitored during the study by a company-commissioned, external, independent, blinded Data Safety Monitoring Board (DSMB). Secondary safety outcomes were the number of treatment emergent adverse events (TEAEs), including serious TEAEs."
Haig, 2014	Determined by Investigator	"The incidence of adverse events considered possibly or probably related to study drug as assessed by the investigator was generally similar across treatment groups (range 20.6% to 26.8%)." "Treatment emergent adverse events were tabulated by primary Medical Dictionary for Regulatory Activities (MedDRA) [23] version 13.1 System Organ Class and Preferred Term"
Hernández, 2007	NA	NA
Herrmann, 2013	Determined by Investigator	"The incidence of adverse events considered related to the study drug by the investigator was 30% in the placebo group and 36% in the memantine group"
Holmes, 2004	Determined by Investigator	"During these (clinic) visits, psychometric evaluations, medication compliance checks, and adverse event (AE) monitoring took place"

Homma, 1998	NR	NR
Homma, 2008	Medical Dictionary for Regulatory Activities – Japanese Version	"AE terms were standardized according to the Medical Dictionary for Regulatory Activities – Japanese Version . AEs were graded on a 3-point scale (mild: discomfort noticed, but no disruption of normal daily activity; moderate: discomfort sufficient to reduce or affect normal daily activity; severe: incapacitating, with inability to work or to perform normal daily activity). "
Hong, 2006	NR	NR
Howard, 2007	NA	NA
Howard, 2012	NR	NR
Hu, 2006	NA	NA
Johannsen, 2006	NA	NA
Jones, 2004	Determined by Investigator	"A serious adverse event (SAE) was defined as any AE that was life threatening or resulted in death, hospitalisation, prolongation of hospitalisation, or significant disability"
Kadir, 2008	NA	NA
Kano, 2013	NA	NA
Karaman, 2005	NA	NA
Likitjaroen, 2012	NA	NA
Lorenzi, 2011	NA	NA
Maher-Edwards, 2011	Determined by Investigator	"Eight subjects experienced nonfatal serious AEs; all were considered unrelated to the study drug"
Marek, 2014	Medical Dictionary for Regulatory Activities	"Aes were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 14.0) by system organ class and preferred term"
Mazza, 2006	NA	NA
Mohs, 2001	Determined by Investigator	"In all cases, judgment of the relationship of study treatment to an adverse event and of the severity of the event was made by the investigator under double-blind conditions. "
Moretti, 2014	NA	NA
Mowla, 2007	NA	NA
Nakamura, 2011	Determined by Investigator	"Safety evaluations included recording all adverse events on Adverse Event Case Report Forms. Every serious adverse event occurring after the patient provided informed consent and until 28 days after the patient stopped the study was reported. "
Nakano, 2001	NA	NA
Nordberg, 2009	Determined by Investigator	"Safety and tolerability were monitored throughout the study by recording all adverse events (AEs). "
Pakdaman H, 2015	NA	NA
Peng, 2005	NA	NA
Peskind, 2006	Determined by Investigator	"Overall, the type and incidence of SAEs were similar between the memantine and placebo groups. One participant death occurred in each group during the trial; neither was rated by the investigator as being treatment-related"
Peters O, 2015	NR	NR
Reisberg, 2003	NR	NR
Rockwood, 2001	World Health Organisation preferred terms	"adverse events (classified according to World Health Organisation preferred terms)."
Rockwood, 2006	NR	NR
Rogers, 1996		
Rogers, 1998	COSTART	"Events, recorded using investigator terminology, were grouped and coded into common terms using a modified COSTART dictionary"
Rogers, 1998	COSTART	"Events, recorded using investigator terminology, were grouped and coded into common terms using a modified COSTART dictionary. "
Saxton, 2012	Determined by Investigator	"Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were recorded at all post-Screening study visits"
Scarpini, 2011	Determined by Investigator	"Subjects with a treatment 51 (20.1) 2 (2.6) 4 (6.3) related AE, as judged by the investigator"
Schmidt, 2008	NA	NA
Seltzer, 2004	NA	NA
Shao, 2015	NA	NA
Shimizu, 2015	NA	NA
Sole-Padulles, 2013	NA	NA
Tariot, 2000	World Health Organisation preferred terms	"adverse events (classified according to World Health Organization Preferred Term). "
Tariot, 2001	COSTART	"Investigator terms describing AEs were coded to standard preferred terms using a modified Coding Symbols for Thesaurus of Adverse Reaction Terms dictionary. "
Thomas, 2001		

Wilcock, 2003	World Health Organisation preferred terms	"monitoring for adverse events (classified according to WHO preferred terms) "
Wilkinson, 2001	Determined by Investigator	"All adverse events were recorded, regardless of the considered relationship to treatment. All details of adverse events and their outcomes were recorded including severity and relationship to treatment. Serious adverse events were documented separately. "
Wilkinson, 2002	NR	NR
Wilkinson, 2012	Determined by Investigator	"Tolerability and safety were based on the incidence of adverse events, either reported spontaneously by the patients or in response to a non-leading question by the investigator throughout the study"
Winblad, 2001	NR	NR
Winblad, 2006	COSTART	"We recorded all treatment emergent adverse events, coding them according to a modified COSTART dictionary. "
Winblad, 2007	Determined by Investigator	"Safety evaluations included recording all adverse events, which were coded using a standard glossary."
Zhang-Yi, 2005	NA	NA
Zhang, 2012	Determined by Investigator	"Serious adverse events considered to be possibly related to treatment occurred in one patient in each treatment arm"

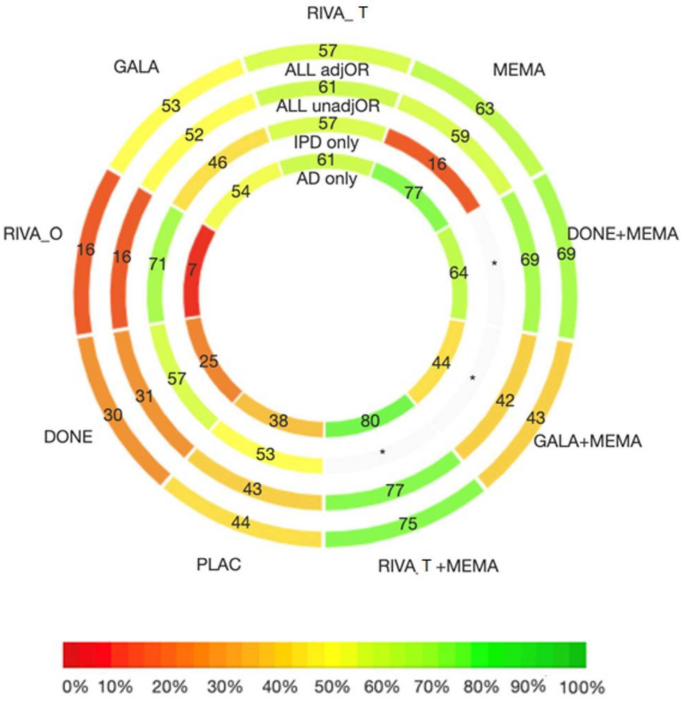
Notes: [a]Unpublished data, [b]Non-English studies
Abbreviations: CR, companion report; NA, not applicable; NR, not reported.

Appendix 19: Time taken to achieve at least an adverse event using individual patient data



Appendix 20: Rank-heat plot for adverse events

Circles from inside out present results for different network meta-analyses including: i) aggregate data (AD) only (studies with available IPD are not included in the analysis), ii) crude results from individual studies with individual patient data (IPD), iii) AD and crude results from studies with available IPD, and iv) AD and fully adjusted results from studies with available IPD. Numbers within each sector correspond to the P-score values as calculated in each model.



Appendix 21: Challenges encountered during the individual patient data request from sponsors

- The identification of the trial data set when certain details were not available (e.g. NCT number; particularly for studies published before 2005 that this was established).
- Data ownership.
- Sponsors switched platforms, while we were navigating the data.
- IPD available through proprietary sponsor-specific platforms did not allow for combination of IPD from different sponsor platforms; hence a one-stage analysis as planned in our protocol, was impossible.
- Software availability: Required R packages (e.g., mice) were not available/provided, and we were not allowed to install any new R packages; some R packages were older versions (e.g. lme4).
- Time that the platform permitted access to the IPD was often limited. This is a significant constraint given that IPD from different studies became available at different time points.
- Cost associated with obtaining access to the data for a certain amount of time. Additionally, cost associated with the WHO Drug Dictionary license to obtain access to the additional medications used for each patient; this license's approximate cost was $8,958·25 USD per sponsor.
- Available IPD did not include the full information as shown in the publication: For example, only data for placebo were available, or did not give information about a reported outcome (e.g. only baseline MMSE values were available). Also, date of follow-up was coded in some studies and it was impossible to make a judgement on first and last date.

Additional File 2: MEDLINE Search Strategy

MEDLINE Search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase<1980 to 2014 Week 50> Search Strategy:

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1 alzheimer$.mp.
2 "benign senescent forgetfulness".mp.
3 (cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
4 (cerebr$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
5 (mental adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
6 (ne?rocognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.)
7 (ne?ro-cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
8 ((cognit$ or memory or cerebral or brain) adj2 (improv$ or enhanc$ or perform$ or process$ or function$ or rehabilitation or aid$ or stimulat$)).mp.
9 cognition.ti.
10 (confusion$ or confused).tw.
11 dement$.mp.
12 ("normal pressure hydrocephalus" and shunt$).mp.
13 "organic brain disease$".mp.
14 "organic brain syndrome".mp.
15 (presenil$ or pre-senil$ or senil$).tw.
16 Alzheimer Disease/
17 Cognition/de
18 Confusion/
19 Dementia/
20 or/1-19
21 abixa.tw.
22 aricept.tw.
23 (acetylcholinesteraseadj inhibitor$).tw.
24 axura.tw.
25 akatinol.tw.
26 (anticholinesterase? or anti-cholinesterase?).tw.
27 (cognitive adjenhanc$).mp.
28 (cholinesterase adj inhibitor$).mp.
29 ChEI.tw.
30 donepezil.mp.
31 ebixa.tw.
32 eranz.tw.
33 exelon.tw.
34 galant?amin$.tw.
35 lycoremine.tw.

36 memantin$.tw.
37 memox.tw.
38 namenda.tw.
39 nimvastid.tw.
40 nivalin$.tw.
41 "N-Methyl-D-aspartic acid receptor antagonist$".tw.
42 prometax.tw.
43 razadyne.tw.
44 reminyl.tw.
45 rivastigmine.mp.
46 exp Cholinesterase Inhibitors/
47 Galantamine/
48 Memantine/
49 Galantamin.rn.
50 Memantine.rn.
51 Donepezil.rn.
52 Donepezil Hydrochloride.rn.
53 Rivastigmine.rn.
54 or/21-53
55 20 and 54
56 exp Animals/ not (exp Animals/ and Humans/)
57 55 and 56
58 (comment or editorial or interview or news).pt.
59 (letter not (letter and randomized controlled trial)).pt.
60 57 not (58 or 59)
61 (201111* or 201112* or 2012* or 2013* or 2014*).ed.
62 60 and 61
63 alzheimer$.mp.
64 "benign senescent forgetfulness".mp.
65 (cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
66 (cerebr$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
67 (mental adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
68 (ne?rocognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
69 (ne?ro-cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
70 ((cognit$ or memory or cerebral or brain) adj2 (improv$ or enhanc$ or perform$ or process$ or function$ or rehabilitation or aid$ or stimulat$)).mp.
71 cognition.ti.
72 (confusion$ or confused).tw.
73 dement$.mp.
74 ("normal pressure hydrocephalus" and shunt$).mp.
75 "organic brain disease$".mp.
76 "organic brain syndrome".mp.

77 (presenil$ or pre-senil$ or senil$).tw
78 Alzheimer disease/
79 cognitive defect/
80 confusion/
81 dementia/
82 organic brain syndrome/
83 or/63-82
84 abixa.tw.
85 aricept.tw.
86 (acetylcholinesteraseadj inhibitor$).tw.
87 axura.tw.
88 akatinol.tw.
89 (anticholinesterase? or anti-cholinesterase?).tw.
90 (cognitive adjenhanc$).mp.
91 (cholinesterase adj inhibitor$).mp.
92 ChEI.tw.
93 donepezil.mp.
94 ebixa.tw.
95 eranz.tw.
96 exelon.tw.
97 galant?amin$.tw.
98 lycoremine.tw.
99 memantin$.tw.
100 memox.tw.
101 namenda.tw.
102 nimvastid.tw.
103 nivalin$.tw.
104 "N-Methyl-D-aspartic acid receptor antagonist$".tw.
105 prometax.tw.
106 razadyne.tw.
107 reminyl.tw.
108 rivastigmine.mp.
109 exp cholinesterase inhibitor/
110 donepezil/ or donepezil plus memantine/
111 galantamine/
112 memantine/
113 rivastigmine/
114 357-70-0.rn.
115 19982-08-2.rn.
116 120011-70-3.rn.
117 120014-06-4.rn.
118 rivastigmine.rn.
119 or/84-118
120 83 and 119
121 randomized controlled trial/ or controlled clinical trial/
122 exp "clinical trial (topic)"/
123 (randomi#ed or randomly or RCT$1 or placebo*).tw.

124 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
125 trial.ti.
126 or/121-125
127 120 and 126
128 exp controlled clinical trial/
129 exp "controlled clinical trial (topic)"/
130 (control* adj2 trial*).tw.
131 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw.
132 (nRCT or nRCTs or non-RCT$1).tw.
133 (control* adj3 ("before and after" or "before after")).tw.
134 time series analysis/
135 (time series adj3 interrupt*).tw.
136 pretest posttest control group design/
137 (pre- adj3 post-).tw.
138 (pretest adj3 posttest).tw.
139 controlled study/
140 (control* adj2 stud$3).tw.
141 control group/
142 (control$ adj2 group$1).tw.
143 or/128-142
144 120 and 143
145 cohort analysis/
146 cohort.tw.
147 retrospective study/
148 longitudinal study/
149 prospective study/
150 (longitudinal or prospective or retrospective).tw.
151 follow up/
152 ((followup or follow-up) adj (study or studies)).tw.
153 observational study/
154 (observation$2 adj (study or studies)).tw.
155 population research/
156 ((population or population-based) adj (study or studies or analys#s)).tw.
157 ((multidimensional or multi-dimensional) adj (study or studies)).tw.
158 exp comparative study/
159 ((comparative or comparison) adj (study or studies)).tw.
160 exp case control study/
161 ((case-control* or case-based or case-comparison) adj (study or studies)).tw.
162 or/145-161
163 120 and 162
164 127 or 144 or 163
165 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
166 exp humans/ or exp human experimentation/ or exp human experiment/
167 165 not 166
168 164 not 167
169 editorial.pt.

170 letter.pt.not (letter.pt. and randomized controlled trial/)
171 168 not (169 or 170)
172 (2011112* or 2011113* or 201112* or 2012* or 2013* or 2014*).dd.
173 171 and 172
174 62 use prmz
175 173 use emez
176 174 or 175
177 remove duplicates from 176
178 177 use prmz [MEDLINE UNIQUE HITS]
179 177 use emez [EMBASE UNIQUE HITS]
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