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# BMJ Open

## Comparative safety and efficacy of cognitive enhancers for Alzheimer's dementia: An individual patient data network meta-analysis

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Complete List of Authors:	Veroniki, Areti; University of Ioannina, Department of Primary Education; St. Michael's Hospital, Knowledge Translation Program Ashoor, Huda; St Michael's Hospital, Knowledge Translation Program Rios, Patricia; St Michael's Hospital, Knowledge Translation Program Seitidis, Georgios; University of Ioannina, Department of Primary Education Stewart, Lesley; University of York, Centre for Reviews and Dissemination Clarke, Mike; Queen's University Belfast, Northern Ireland Hub for Trials Methodology Research Tudur-Smith, Catrin; University of Liverpool, Department of Biostatistics Mavridis, Dimitris ; University of Ioannina, Department of Primary Education Hemmelgarn, Brenda; University of Alberta, Department of Medicine Holroyd-Leduc, Jayna; University of Alberta, Department of Medicine Straus, Sharon; St Michael's Hospital, Knowledge Translation Program; University of Toronto, Department of Geriatric Medicine Tricco, Andrea; St Michael's Hospital, Knowledge Translation Program; University of Toronto, Dalla Lana School of Public Health
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3 **Comparative safety and efficacy of cognitive**  
4 **enhancers for Alzheimer's dementia: An individual**  
5 **patient data network meta-analysis**  
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10 Areti Angeliki Veroniki<sup>1,2,3\*</sup> PhD e-mail: [averoniki@uoi.gr](mailto:averoniki@uoi.gr)

11 Huda M. Ashoor<sup>2</sup> BSc e-mail: [huda.ashoor@unityhealth.to](mailto:huda.ashoor@unityhealth.to)

12 Patricia Rios<sup>2</sup> MSc e-mail:  
13 [patricia.rios@unityhealth.to](mailto:patricia.rios@unityhealth.to)

14 Georgios Seitidis<sup>1</sup> MSc e-mail: [g.seitidis@uoi.gr](mailto:g.seitidis@uoi.gr)

15 Lesley A. Stewart<sup>4</sup> PhD e-mail:  
16 [lesley.stewart@york.ac.uk](mailto:lesley.stewart@york.ac.uk)

17 Mike Clarke<sup>5</sup> PhD e-mail: [m.clarke@qub.ac.uk](mailto:m.clarke@qub.ac.uk)

18 Catrin Tudur Smith<sup>6</sup> PhD e-mail: [cat1@liverpool.ac.uk](mailto:cat1@liverpool.ac.uk)

19 Dimitris Mavridis<sup>1</sup> PhD e-mail: [dmavridi@uoi.gr](mailto:dmavridi@uoi.gr)

20 Brenda R. Hemmelgarn<sup>7</sup> PhD e-mail:  
21 [brenda.hemmelgarn@albertahealthservices.ca](mailto:brenda.hemmelgarn@albertahealthservices.ca)

22 Jayna Holroyd-Leduc<sup>7</sup> MD e-mail: [jayna.holroyd-  
24 leduc@albertahealthservices.ca](mailto:jayna.holroyd-<br/>23 leduc@albertahealthservices.ca)

25 Sharon E. Straus<sup>2,8</sup> MD e-mail:  
26 [sharon.straus@utoronto.ca](mailto:sharon.straus@utoronto.ca)

27 Andrea C. Tricco<sup>2,9</sup> PhD e-mail:  
28 [andrea.tricco@unityhealth.to](mailto:andrea.tricco@unityhealth.to)

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43  
44 <sup>1</sup> Department of Primary Education, School of Education,  
45 University of Ioannina, Ioannina, Greece

46 <sup>2</sup> Knowledge Translation Program, Li Ka Shing Knowledge  
47 Institute, St. Michael's Hospital, Toronto, Ontario, Canada

48 <sup>3</sup> Institute of Reproductive and Developmental Biology,  
49 Department of Surgery & Cancer, Faculty of Medicine, Imperial  
50 College, London, United Kingdom

51 <sup>4</sup> Centre for Reviews and Dissemination, University of York,  
52 York, United Kingdom  
53  
54  
55  
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60

1  
2  
3 <sup>5</sup> Northern Ireland Hub for Trials Methodology Research, Queen's  
4 University Belfast, Belfast, United Kingdom

5  
6 <sup>6</sup> Department of Biostatistics, University of Liverpool, Block  
7 F, Waterhouse Building, 1-5 Brownlow Hill, Liverpool, L69 3GL,  
8 UK  
9

10  
11 <sup>7</sup> Departments of Medicine, University of Alberta, Edmonton,  
12 Alberta, Canada;  
13

14  
15 <sup>8</sup> Department of Geriatric Medicine, University of Toronto,  
16 Toronto, Ontario, Canada  
17

18 <sup>9</sup> Epidemiology Division & Institute of Health Policy,  
19 Management, and Evaluation, Dalla Lana School of Public  
20 Health, University of Toronto, Toronto, Ontario, Canada  
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26

27 **\*Corresponding Author:**

28 Dr. Areti Angeliki Veroniki, MSc, PhD  
29 Research Fellow at the Department of Primary Education, School  
30 of Education, University of Ioannina, Ioannina, Greece  
31  
32 Phone: +30 26510 05694; fax: +30 26510 05854; e-mail:  
33 [averoniki@uoi.gr](mailto:averoniki@uoi.gr)  
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## 1 **Abstract**

2 Words: 291 (Max 300 words)

3 **Objective:** To examine the comparative efficacy and safety of  
4 cognitive enhancers by patient characteristics for managing  
5 Alzheimer's Dementia (AD).

6 **Design:** Systematic review and individual patient data (IPD)  
7 network meta-analysis (NMA)

8 **Participants:** 80 randomized controlled trials (RCTs)  
9 including 21,138 adults with AD, and 12 RCTs with IPD  
10 including 6,906 patients.

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

14 **Data extraction and Synthesis:** We requested IPD from authors,  
15 sponsors and data sharing platforms. When IPD were not  
16 available, we used aggregate data. We conducted a two-stage  
17 random-effects IPD-NMA, and assessed their findings using  
18 CINeMA (Confidence in Network meta-analysis).

19 **Primary and Secondary Outcomes:** We included trials assessing  
20 cognition with the Mini-Mental State Examination (MMSE), and  
21 serious adverse events (SAEs).

22 **Results:** Our IPD-NMA compared 9 treatments (including  
23 placebo). Donepezil (mean difference [MD] = 1.41, 95%  
24 confidence interval [CI]: 0.51 to 2.32) and  
25 donepezil+memantine (MD = 2.57, 95% CI: 0.07 to 5.07)  
26 improved MMSE score (56 RCTs, 11,619 participants; CINeMA  
27 score: moderate) compared to placebo. Oral rivastigmine (odds  
28 ratio [OR] = 1.26, 95% CI: 0.82 to 1.94) and donepezil (OR =  
29 1.08, 95% CI: 0.87 to 1.35) were associated with higher odds  
30 of a SAE than placebo (45 RCTs, 15,649 patients; CINeMA  
31 score: moderate to high). For moderate to severe impairment,

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3  
4 32 donepezil, memantine and their combination performed best,  
5  
6 33 but for mild to moderate impairment donepezil and transdermal  
7  
8 34 rivastigmine ranked best. Adjusting for MMSE baseline  
9  
10 35 differences, oral rivastigmine and galantamine improved MMSE  
11  
12 36 score, whereas when adjusting for comorbidities only oral  
13  
14 37 rivastigmine was effective.

14 38 **Conclusions:** The choice among the different cognitive  
15  
16 39 enhancers may depend on patient's characteristics. All  
17  
18 40 cognitive enhancers except for oral rivastigmine,  
19  
20 41 galantamine, and memantine, were clinically important for  
21  
22 42 cognition (MMSE score greater than 1.4).

23 43 **Protocol registration number:** PROSPERO # CRD42015023507

24 44  
25 45 **Keywords:** network meta-analysis; multiple treatments meta-  
26  
27 46 analysis; individual participant data; Nootropic Agents;  
28  
29 47 Alzheimer Disease

### 48 **Strengths and limitations of this study**

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- 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 the CINeMA quality assessment guidelines.
  - Access to individual patient data allowed us to 1) observe minor differences between the original published results and our re-analysis, 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

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4 64 effect modifiers that were not reported in the original  
5  
6 65 publications (e.g., comorbidities, additional  
7  
8 66 medications) and explore for treatment-by-covariate  
9  
10 67 interactions on the patient-level.

11 68 • Two thirds of the included RCTs, were associated with  
12  
13 69 high risk of bias for incomplete outcome data due to  
14  
15 70 attrition.

16 71 • We were unable to include individual patient data for  
17  
18 72 all RCTs (only 15% of the studies shared their  
19  
20 73 individual patient data), highlighting potential  
21  
22 74 availability bias.

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peer review only



## 75 Introduction

76  
77 Alzheimer's dementia (AD) is the most common type of dementia.<sup>1</sup>  
78 Patients living with AD have a lower quality of life due to  
79 deterioration in function, cognition, behavior, and mental  
80 health over time, as well as increased mortality.<sup>2</sup>  
81 Pharmacological treatment for AD predominantly consists of  
82 cholinesterase inhibitors (donepezil, galantamine, rivastigmine)  
83 and the N-methyl-d-aspartate (NMDA) receptor antagonist,  
84 memantine. It is unclear whether galantamine, rivastigmine, or  
85 donepezil should be used by patients with severe AD, or whether  
86 memantine is the optimal treatment for severe AD.<sup>3</sup>

87  
88 In AD, disease severity and sex are potential effect modifiers.  
89 However, aggregate data and covariates of interest (e.g., sex,  
90 disease severity) are not consistently reported across  
91 randomized clinical trials (RCTs).<sup>4</sup> The aim of this study was to  
92 examine the comparative efficacy and safety of cognitive  
93 enhancers for patients with different characteristics, such as  
94 severities of AD and for females versus males through a  
95 systematic review and individual patient data (IPD) NMA.

## 96 Methods

97  
98 We reported our results according to the Preferred Items for  
99 Systematic Reviews and Meta-analysis (PRISMA) Statement for NMA  
100 and PRISMA-IPD.<sup>5,6</sup>

101

## 102 Protocol

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3 104 The research question and protocol were based on our previous  
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5 105 systematic review and NMA.<sup>4</sup> We registered our systematic review  
6  
7 106 protocol with the prospective register of systematic reviews  
8  
9 107 (PROSPERO: CRD42015023507), and published our protocol.<sup>7</sup>  
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11 108 Additional information is also provided in Appendix 1. Herein,  
12  
13 109 we briefly summarize our methods.  
14

15

### 16 111 **Eligibility criteria**

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18  
19 113 We updated our previous systematic review,<sup>4</sup> using similar  
20  
21 114 population, interventions, comparators, study designs and time  
22  
23 115 period (PICOST) criteria. The literature search was updated from  
24  
25 116 January 2015 to March 2016. We included RCTs that assessed  
26  
27 117 cognition via the Mini-Mental State Examination (MMSE; efficacy  
28  
29 118 and primary outcome) and/or serious adverse events (SAE; safety  
30  
31 119 outcome) in adults with Alzheimer's dementia.  
32

33

### 34 121 **IPD collection process**

35 122

36 123 We contacted the corresponding author followed by the next-in-  
37  
38 124 order author, as presented in each eligible RCT, to obtain IPD.  
39  
40 125 The author contact process was part of a RCT that our team  
41  
42 126 conducted to assess methods that may optimize response rates for  
43  
44 127 IPD retrieval.<sup>8</sup> We also contacted sponsors of eligible trials, as  
45  
46 128 reported in the publications. We contacted industry sponsors  
47  
48 129 only, as we were not able to locate contact information for the  
49  
50 130 majority of non-industry sponsors (e.g., grants and university  
51  
52 131 funding). If a study had multiple sponsors, we contacted all of  
53  
54 132 them. To further facilitate IPD access, we contacted the  
55  
56 133 Clinical Study Data Request (CSDR)<sup>9</sup> and Yale University Open Data  
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3 134 Access (YODA) data sharing platforms.<sup>10</sup> If a data provider was  
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5 135 unable to provide IPD we noted the reason.

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### 8 9 137 **Risk of bias and quality appraisal**

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12 139 We appraised study quality using the Cochrane risk of bias  
13  
14 140 tool.<sup>11</sup> To ensure data consistency<sup>6</sup> we compared IPD with  
15  
16 141 aggregate data reported in the publication. We assessed whether  
17  
18 142 randomization of patients was adequate (i.e., intervention and  
19  
20 143 comparison groups were balanced for important patient  
21  
22 144 characteristics), by comparing numbers and types of patients in  
23  
24 145 each arm.

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27 147 When at least 10 studies were available for each treatment  
28  
29 148 against placebo, publication bias and small-study effects were  
30  
31 149 examined visually using funnel plots under the fixed-effect  
32  
33 150 model.<sup>12</sup> Confidence in NMA findings was assessed for each outcome  
34  
35 151 using CINeMA (Confidence in Network meta-analysis, see Appendix  
36  
37 152 1 for more details).<sup>13</sup>

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### 40 41 154 **Synthesis**

42  
43 155

44 156 We performed a descriptive analysis using frequencies and  
45  
46 157 distributions of the characteristics of the included patients  
47  
48 158 and treatments. For each outcome, we present the network  
49  
50 159 geometry according to IPD availability. We conducted a two-stage  
51  
52 160 IPD analysis, whereby data were analysed separately in each  
53  
54 161 trial in the first stage and the trial parameter estimates were  
55  
56 162 synthesised in a random-effects meta-analysis or NMA in the  
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58 163 second stage.

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3 165 The summary treatment effects are presented using the odds ratio  
4  
5 166 (OR) or mean difference (MD) along with their corresponding CIs  
6  
7 167 and predictive intervals (PrIs).<sup>14</sup> We ranked the interventions  
8  
9 168 for each outcome using the P-scores (and SUCRAs [surface under  
10  
11 169 the cumulative ranking curve] in meta-regression analysis), and  
12  
13 170 present them in a rank-heat plot.<sup>15,16</sup>  
14

## 15 171 **Results**

### 16 172 **Literature search, study selection and IPD obtained**

17  
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19 173  
20 174 After screening 20,410 titles and abstracts and 1,968 full-text  
21  
22 175 articles, 96 studies fulfilled the eligibility criteria; 80  
23  
24 176 unique studies and 16 companion reports (Figure 1a, Appendix 2).  
25

26 177  
27 178 (Figure 1 here)  
28

29 179  
30 180 Of the 80 RCTs, 55 reported at least one industry-sponsored  
31  
32 181 funder (i.e. 40 studies reported a single industry-sponsor and  
33  
34 182 15 multiple industry-sponsors). In the remaining studies, 9 were  
35  
36 183 publicly-sponsored and 16 did not report any information about  
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38 184 funding. We requested IPD by contacting the corresponding  
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40 185 authors for 80 RCTs that included 21,138 participants. None of the  
41  
42 186 original authors shared their IPD. Fifteen commercial sponsors  
43  
44 187 were then contacted and 6 (40%) sponsors shared their data  
45  
46 188 through proprietary sponsor-specific platforms. The 6 sponsors  
47  
48 189 were contacted for 46 RCTs (14,580 participants), and we  
49  
50 190 obtained IPD for 30% (14 RCTs, 8,007 participants) of these RCTs  
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52 191 (1,058 total waiting days up to March 9, 2020). The study flow  
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54 192 for obtaining IPD is depicted in Figure 1b.  
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3 194 We were able to include 12 (6,906 patients) of 14 RCTs in our  
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5 195 NMA due to incompleteness of provided IPD (Appendix 3). The  
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7 196 number of studies with available/non-available IPD from each  
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9 197 data provider along with reasons for non-availability of IPD are  
10  
11 198 presented in Appendix 4.  
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13 199

## 14 200 **Study and patient characteristics**

15 201  
16  
17 202 Most included studies (33%) were multi-national. The mean age of  
18  
19 203 patients ranged from 61 to 86 years. The majority of the RCTs  
20  
21 204 included patients with mild-moderate AD (56%), although the  
22  
23 205 diagnostic criteria used for AD varied widely (Table 1). The  
24  
25 206 most frequent longest duration of follow-up was 24 weeks (24  
26  
27 207 RCTs, 30%; Appendix 5). The intervention and comparison groups  
28  
29 208 were not balanced across all RCTs with provided IPD for  
30  
31 209 important patient characteristics, such as percent of male and  
32  
33 210 dropout rates (Appendix 6). Comparing study and patient  
34  
35 211 characteristics of available and non-available IPD when a study  
36  
37 212 was industry-sponsored, we found differences in the year of  
38  
39 213 study publication, study size, and absolute mean difference  
40  
41 214 (Appendix 7).  
42  
43 215

44 216 (Table 1 here)  
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## 47 218 **Risk of bias and IPD integrity**

48 219  
49 220 Using the Cochrane risk-of-bias tool, allocation concealment was  
50  
51 221 at low risk of bias for 43% and blinding of participants and  
52  
53 222 personnel was low for 64% of the RCTs (Appendix 8). One third of  
54  
55 223 the RCTs had low risk of incomplete outcome data bias due to  
56  
57 224 attrition and almost two thirds had high potential risk of  
58  
59 225 "other" bias, specifically, funding bias. The other risk of bias  
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3 226 item was scored as unclear for 32%. Overall risk of bias was  
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5 227 comparable in studies with available and unavailable IPD  
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7 228 (Appendix 9).

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10 230 All IPD provided were checked for consistency and results from  
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12 231 published RCTs were reproduced and provided in Appendix 10. High  
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14 232 dropout rates were observed in the IPD; experiencing an adverse  
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16 233 event was the most common reason for dropout. Despite the high  
17  
18 234 dropout rates observed in the individual studies, there was no  
19  
20 235 indication of correlation between age and dropout (Appendix 11).  
21  
22 236 Comparison-adjusted funnel plots suggested there is indication  
23  
24 237 for small-study effects (see Appendix 12).  
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### 26 239 **Network meta-analysis**

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29 241 In both MMSE and SAE outcomes, on average there were no  
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31 242 important concerns regarding the transitivity and consistency  
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33 243 assumptions (Appendices 13 and 14; design-by-treatment  
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35 244 interaction model MMSE:  $\chi^2 = 4.36$ , 13 degrees of freedom (df),  $P =$   
36  
37 245  $0.987$ ; SAE:  $\chi^2 = 3.57$ , 6 df,  $P = 0.735$ ). Below we present the main  
38  
39 246 analysis results compared to placebo. Additional analyses are  
40  
41 247 presented in Appendices 15-16). The network geometry is  
42  
43 248 presented in Figure 2.

44 249

45 250 (Figure 2 here)

46 251

### 47 252 **Cognition**

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49  
50 254 The NMA for MMSE included 56 RCTs, 9 treatments (including  
51  
52 255 placebo), and 11,619 participants. Nine RCTs (3,625 patients)  
53  
54 256 contributed IPD and 47 RCTs (7,994 patients) contributed  
55  
56 257 aggregated data to the NMA. Two studies<sup>17,18</sup> did not report MMSE

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3 258 in the final publication, but in the retrieved IPD we were able  
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5 259 to use data for this outcome.

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8 261 *NMA of studies with IPD and aggregate data*  
9 262 Studies in this NMA compared all available treatments. Donepezil  
10  
11 263 (MD= 1.41, 95% CI: 0.51 to 2.32) and donepezil+memantine (MD=  
12  
13 264 2.57, 95% CI: 0.07 to 5.07) were superior to placebo (Appendices  
14  
15 265 16-17). PrIs suggested results are not conclusive. Transdermal  
16  
17 266 rivastigmine, and the combinations donepezil+memantine,  
18  
19 267 galantamine+memantine, and transdermal rivastigmine+memantine  
20  
21 268 were associated with a minimal clinically important difference  
22  
23 269 (MCID; above 1.40)<sup>19</sup> (Figure 3a). However, donepezil+memantine had  
24  
25 270 the highest likelihood of being the most effective in improving  
26  
27 271 MMSE score (P-score range 79-80%, Figure 4). Confidence in NMA  
28  
29 272 results was moderate (Appendix 18).

30 273 (Figure 3 here)

31 274 (Figure 4 here)

32 275  
33  
34 276 *NMA of studies with aggregate data*  
35 277 Studies in this NMA compared also donepezil+memantine,  
36  
37 278 galantamine+memantine, and transdermal rivastigmine +memantine.  
38  
39 279 Donepezil improved MMSE score significantly (MD= 1.55 95% CI:  
40  
41 280 0.41 to 2.68). The MCID results were in agreement with the NMA of  
42  
43 281 IPD and aggregate data, and donepezil+memantine was likely the  
44  
45 282 most effective in improving MMSE score (P-score= 76%).

46 283  
47 284 *NMA of studies with IPD*  
48 285 Studies in this NMA compared placebo, donepezil, oral  
49  
50 286 rivastigmine, transdermal rivastigmine, galantamine, and  
51  
52 287 memantine. Donepezil (MD= 0.70, 95% CI: 0.01 to 1.40) and  
53  
54 288 transdermal rivastigmine (MD= 1.06, 95% CI: 0.04 to 2.08) were

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3 289 superior to placebo, but none was at a MCID. The most effective  
4  
5 290 treatment was likely transdermal rivastigmine (P-score= 82%).  
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### 8 292 ***Serious adverse events***

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10 293

11 294 A NMA was conducted on serious adverse events (study definitions  
12  
13 295 are provided in Appendix 19) with 45 RCTs, 9 treatments  
14  
15 296 (including placebo), and 15,649 patients (Figure 2b). In  
16  
17 297 particular, 12 RCTs (6420 patients) contributed to the NMA using  
18  
19 298 their IPD and 33 RCTs (9229 patients) using their data on their  
20  
21 299 aggregated form. The time taken to achieve at least one SAE was  
22  
23 300 available in 8 studies with available IPD and ranged between 45  
24  
25 301 and 2228 days (Appendix 20). Only one study included a patient  
26  
27 302 with a SAE occurring earlier than the trial opening and was  
28  
29 303 excluded from the study.<sup>20</sup>  
30  
31 304

#### 30 305 *NMA of studies with IPD and aggregate data*

31 306 Studies in this NMA compared all available treatments. Oral  
32  
33 307 rivastigmine had the least favourable safety profile regarding  
34  
35 308 SAE (OR= 1.26, 95% CI: 0.82 to 1.94, P-score= 16%). Donepezil (OR=  
36  
37 309 1.08, 95% CI: 0.87 to 1.35, P-score= 30%) and  
38  
39 310 galantamine+memantine (OR= 1.03, 95% CI: 0.45 to 2.39, P-score=  
40  
41 311 43%) were associated with higher odds of a SAE than placebo, yet  
42  
43 312 none of these comparisons were statistically significant (Figure  
44  
45 313 3b; Appendices 17, 21). All other treatments were considered to  
46  
47 314 have a favourable safety profile compared with placebo.  
48  
49 315 Confidence in NMA results ranged between moderate and high  
50  
51 316 (Appendix 18).  
52  
53 317

#### 52 318 *NMA of studies with aggregate data*

53 319 Studies in this NMA compared all available treatments. Results  
54  
55 320 were mainly consistent with NMA of IPD and aggregate data, but  
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3 321 for memantine which was statistically significantly associated  
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5 322 with lower odds of a SAE than placebo when using aggregate data  
6  
7 323 only (OR 0.70, 95% CI: 0.51 to 0.97, P-score= 77%, Appendix 16).  
8  
9 324

10 325 *NMA of studies with IPD*

11 326 Studies in this NMA compared placebo, donepezil, oral  
12  
13 327 rivastigmine, transdermal rivastigmine, galantamine, and  
14  
15 328 memantine. Results were on average consistent with NMA of IPD  
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17 329 and aggregate data.  
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20 330 **Discussion**

21 331  
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23 332 We compared the efficacy and safety of cognitive enhancers  
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25 333 regarding MMSE and SAE outcomes to update our previous  
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27 334 systematic review<sup>4</sup> and included studies with both aggregate data  
28  
29 335 and IPD. Our results are in agreement with our previous  
30  
31 336 systematic review,<sup>4</sup> and show that donepezil+memantine, donepezil  
32  
33 337 alone and transdermal rivastigmine were the most effective  
34  
35 338 treatments for improving MMSE score. However, heterogeneity was  
36  
37 339 a major concern, and this was also captured by PrIs. Both  
38  
39 340 donepezil+memantine and transdermal rivastigmine had a  
40  
41 341 favourable safety profile regarding SAE. Among all cognitive  
42  
43 342 enhancers, the therapy with the least favourable profile was  
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45 343 oral rivastigmine followed by donepezil. According to CINeMA  
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47 344 within-study bias and reporting bias were the highest concerns  
48  
49 345 for the MMSE outcome, whereas within-study bias and imprecision  
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51 346 of effect estimates were the highest concerns for the SAE  
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53 347 outcome.  
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56 349 Overall, the choice among the different cognitive enhancers may  
57  
58 350 depend on the patient's characteristics. In participants with  
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60 351 moderate to severe cognitive impairment (defined by MMSE), a

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3 352 larger improvement in cognitive performance was observed for  
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5 353 donepezil and memantine, and their combination  
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7 354 (donepezil+memantine), and these efficacy-related results are  
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9 355 expected to also be reflected when a future study becomes  
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11 356 available. The least effective cognitive enhancer in  
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13 357 participants with moderate to severe cognitive impairment was  
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15 358 oral rivastigmine. For patients with mild to moderate  
16  
17 359 impairments based on MMSE scores, donepezil and transdermal  
18  
19 360 rivastigmine were most likely the best performing cognitive  
20  
21 361 enhancers. For patients with moderate to severe cognitive  
22  
23 362 impairment, cognitive enhancers were well tolerated. For  
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25 363 patients with mild to moderate cognitive impairment, all except  
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27 364 for memantine and its combination with transdermal rivastigmine,  
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29 365 were associated with increased odds of a SAE, yet none of these  
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31 366 results reached statistical significance. Of note, the accuracy  
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33 367 of SAE reporting may be impacted by the degree of cognitive  
34  
35 368 impairment. Using IPD only and adjusting for MMSE baseline  
36  
37 369 differences, oral rivastigmine and galantamine improved MMSE  
38  
39 370 score, whereas when adjusting for comorbidities only oral  
40  
41 371 rivastigmine was effective, but results can change in a future  
42  
43 372 study. Considering a MCID equal to 1.4,<sup>19</sup> all cognitive enhancers  
44  
45 373 except for oral rivastigmine, galantamine, and memantine, were  
46  
47 374 clinically important for cognition. Our results did not differ  
48  
49 375 by participant characteristics sex, age, and other medications,  
50  
51 376 or by study characteristics, study duration and year of  
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53 377 publication. However, these findings might be due to low power  
54  
55 378 since meta-regression analyses depend on the number and size of  
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57 379 studies, magnitude of the relationship between the covariate and  
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59 380 effect size, along with its precision and heterogeneity.<sup>21</sup>

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3 382 To the best of our knowledge, our study was the first to add IPD in a NMA of  
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5 383 cognitive enhancers for patients with Alzheimer's Dementia to produce treatment  
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7 384 recommendations by patient characteristics. We followed the methods guidelines in the  
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9 385 Cochrane Handbook for systematic reviews,<sup>22</sup> the reporting guidelines in the PRISMA-NMA and  
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11 386 PRISMA-IPD statements,<sup>5,6</sup> and the CINeMA quality assessment guidelines.<sup>13</sup> Compared to  
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13 387 previous systematic reviews, we included a larger number of studies and/or studies with shared  
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15 388 IPD, compared in a wider range of cognitive enhancers.<sup>4,23</sup> Our results are in  
16  
17 389 agreement with previous studies overall. Access to IPD allowed us to  
18  
19 390 observe minor differences between the original published results and our re-analysis. An  
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21 391 explanation in these differences may be that many studies used the last-observation-carried-  
22  
23 392 forward imputation method, whereas we used the available case analysis when assessing MMSE.  
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25 393 Another potential explanation might be that original studies excluded some patients, and hence  
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27 394 used a smaller sample size.

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31 396 Comparing NMA, results between aggregate data and IPD were in agreement. The only  
32  
33 397 difference was observed in transdermal rivastigmine that was associated with a MCID of MMSE  
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35 398 in the aggregate data NMA compared to the IPD NMA, yet a statistically significant  
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37 399 improvement was achieved in the IPD NMA. The inclusion of IPD in our NMA,  
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39 400 allowed us to overcome potential reporting bias and to include  
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41 401 IPD for 1) a study that we previously were unable to include  
42  
43 402 since arm-level data were not reported in the RCT publication,<sup>20</sup>  
44  
45 403 and 2) two studies that did not report MMSE results in their  
46  
47 404 publications.<sup>17,18</sup> The use of IPD also allowed us to assess for  
48  
49 405 potential effect modifiers that were not reported in the  
50  
51 406 original publications (e.g., comorbidities, additional  
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53 407 medications) and explore for treatment-by-covariate interactions  
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55 408 on the patient-level. Several challenges were encountered during  
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57 409 the IPD request from sponsors, showing that repositories are not  
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59 410 a panacea (Appendix 22).

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3 412 An important finding of our review is that the two thirds of the  
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5 413 published RCTs, were associated with high risk of bias for  
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7 414 incomplete outcome data due to attrition, and the majority of  
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9 415 these RCTs used the last-observation-carried-forward technique  
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11 416 for missing data. This approach may bias results favouring  
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13 417 cognitive enhancers, since the dropout rates were greater in the  
14  
15 418 treatment group compared to the placebo group in 63% of the  
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17 419 included studies and because dementia is a progressive disease.  
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19 420 Of the 27 studies comparing treatment against placebo and  
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21 421 reporting the number of dropouts, 17 studies had a greater  
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23 422 dropout rate in the treatment group (treatment group: median  
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25 423 dropout rate= 28% IQR [17% to 39%]; placebo group: median  
26  
27 424 dropout rate= 21% IQR [15% to 31%]). Last-observation-carried-  
28  
29 425 forward is an inappropriate imputation method for Alzheimer's  
30  
31 426 Dementia studies, since it ignores expected deterioration of the  
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33 427 patient's condition and stabilizes the outcome at the value  
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35 428 observed at the time of dropout (i.e., the last observation).<sup>24</sup>  
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37 429 Restricting to low risk of attrition bias studies, we found that  
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39 430 galantamine was significantly associated with decreased odds of  
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41 431 experiencing a SAE.

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39 433 Our study has limitations worth mentioning. First, we were unable to include IPD for all eligible  
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41 434 studies (only 15% of the included RCTs shared their IPD), highlighting potential availability bias  
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43 435 for IPD. However, recent simulations have shown that combining IPD and aggregate data in a  
44  
45 436 NMA can significantly improve precision, reduce bias, and increase information compared to  
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47 437 NMA relying on aggregated data alone.<sup>25</sup> Second, missing data is a big concern in the  
48  
49 438 published RCTs for Alzheimer's Dementia. To assess the impact of missing data in our NMA,  
50  
51 439 we applied the informative missingness of difference in means.<sup>26</sup> Third, the lack of studies in  
52  
53 440 certain treatment comparisons may have affected the P-score calculation and treatment ranking.  
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55 441 In particular, polytherapies were informed by maximum two studies, and ranking may have been  
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57 442 in favour of the complex intervention group with the smaller number of studies.<sup>27</sup> For example,

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3 443 in MMSE the polytherapies including memantine in conjunction with one of the three treatments  
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5 444 donepezil, galantamine, transdermal rivastigmine had a P-score  $\geq 60\%$ , but these all had wide  
6  
7 445 95% CIs for MD. As such, ranking should be interpreted with caution and along with the  
8  
9 446 estimated effect sizes and their uncertainty measures. Fourth, the comparison-adjusted funnel  
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11 447 plot for MMSE suggested there is an indication for small-study effects pointing to the treatment  
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13 448 being better, and results should be interpreted with caution. Overall, MMSE score is only a  
14  
15 449 surrogate maker for determining the impact of treatments on dementia. A full assessment that  
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17 450 considers the potential impact of treatments on cognition, function and behavioural symptoms  
18  
19 451 needs to be considered within the clinical context.

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21 452  
22 453 We expect that our findings will increase scientific knowledge, because people  
23  
24 454 with Alzheimer's Dementia require personalized medicine to  
25  
26 455 optimize their healthcare. Well-conducted meta-analyses of IPD  
27  
28 456 are considered the 'gold-standard' and influence patient care  
29  
30 457 since patient-level data can be provided to facilitate tailored  
31  
32 458 decision making. However, results from meta-analyses of IPD are  
33  
34 459 likely subject to retrieval bias and awareness of these  
35  
36 460 limitations and their potential impact on findings is required.

## 461 **Contributors**

462  
463 AAV, SES and ACT conceived and designed the study. AAV conducted  
464 the analyses, abstracted data, contacted sponsors, analysed  
465 data, interpreted results, appraised quality of results, and  
466 wrote a draft manuscript. GS conducted the analyses, appraised  
467 quality of results, and edited the manuscript. HMA coordinated  
468 the review, screened citations and full-text articles,  
469 abstracted data, appraised quality, cleaned the data, contacted  
470 sponsors, and edited the manuscript. PR helped coordinate the  
471 study, screened citations and full-text articles, extracted and  
472 categorized data, appraised quality, and edited the manuscript.  
473 SES and ACT interpreted results and edited the manuscript. ACT  
474 and HMA contacted authors. LAS, MC, CTS, DM, BRH, JHL provided  
475 input into the design, interpreted results, and edited the  
476 manuscript. All authors read and approved the final manuscript.

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478  
479 The authors declare that they have no competing interests.

## 480 **Data sharing statement**

481 All data relevant to the study are included in the article or uploaded as supplementary  
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15

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27 501 [0/](http://creativecommons.org/licenses/by-nc/4.0/).  
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## 31 502 **Patient and public involvement**

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33  
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14 521 DEVELOPMENT, L.L.C.. The interpretation and reporting of research using this data are solely  
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16 522 the responsibility of the authors and does not necessarily represent the official views of the Yale  
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3 **528** **References**  
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## 591 **Figure Captions**

592  
593 **Figure 1.** Flow diagram for study inclusion in the review (a) and studies retrieved with  
594 individual patient data (b).  
595

596 **Figure 2.** Network diagrams for (a) MMSE and (b) SAE outcomes. The size of each node and  
597 line indicates the number of studies included in each treatment comparison. The number of  
598 studies per treatment comparison is presented on each edge, and the number of studies with  
599 individual patient data (IPD) is depicted in a parenthesis. Orange coloured edges are informed by  
600 both IPD and aggregate data, whereas black coloured edges are informed by aggregate data only.  
601

602 **Figure 3.** Forest plot of network meta-analysis (NMA) results for all cognitive enhancers versus  
603 placebo in (a) MMSE outcome, and (b) SAE outcome. NMA results are presented for i)  
604 aggregate data (AD) and fully adjusted results from studies with available individual patient data  
605 (IPD), ii) AD and crude results from studies with available IPD, iii) AD only (studies with  
606 available IPD are not included in the analysis), and iv) crude results from individual studies with  
607 individual patient data (IPD).  
608

609 **Figure 4.** Rank-heat plot of P-scores for 9 treatments, including placebo, studied in randomized  
610 clinical trials with patients with Alzheimer's Dementia assessing MMSE. Circles from inside out  
611 present results for different network meta-analyses including: i) aggregate data (AD) only  
612 (studies with available IPD are not included in the analysis), ii) crude results from individual  
613 studies with individual patient data (IPD), iii) AD and crude results from studies with available  
614 IPD, and iv) AD and fully adjusted results from studies with available IPD. Numbers within each  
615 sector correspond to the P-score values as calculated in each model.

616 **Tables**

617

<b>Table 1· Study and patient characteristics</b>		
	<b>AD (N=80)</b>	<b>IPD (N=12)</b>
<b>Total # participants</b>	21,138	5839
<b>Longest duration of follow-up in weeks: mean (range)</b>	28·28 (8 - 208)	29·33 (12 - 104)
<b>Mean number of patients (range)</b>	264·23 (14 - 2,045)	486·58 (123 - 2,045)
<b>Mean age in years (range)</b>	74·64 (61 - 85·7)	73·94 (70·4 - 78)
<b>Mean % Female (range)</b>	61·35 (3 - 89)	62·76 (53·68 - 81)
<b>Country of conduct: frequency (%)</b>		
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)	-
United Kingdom	6 (7·50)	1 (8·33)
United States	15 (18·75)	-
Multi-national	26 (32·50)	9 (75·00)
<b>Interventions examined: frequency*</b>		
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)
<b>Effectiveness outcomes reported: frequency*</b>		
Mini-Mental State Examination	57 (71·25)	6 (50·00)
Serious Adverse Events	46 (57·50)	12 (100·00)
<b>Funding</b>		
Industry-sponsored	48 (60·00)	12 (100·00)
Publicly-sponsored†	9 (11·25)	-
Mixed	7 (8·75)	-
Not Reported	16 (20·0)	-
<b>Severity of Alzheimer's dementia: frequency (%)</b>		
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)
<b>Diagnostic criteria for Alzheimer's dementia: frequency*</b>		
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)
Magnetic Resonance Imaging/Computerized Tomography	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)

**Abbreviations:** -, not applicable

\* 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

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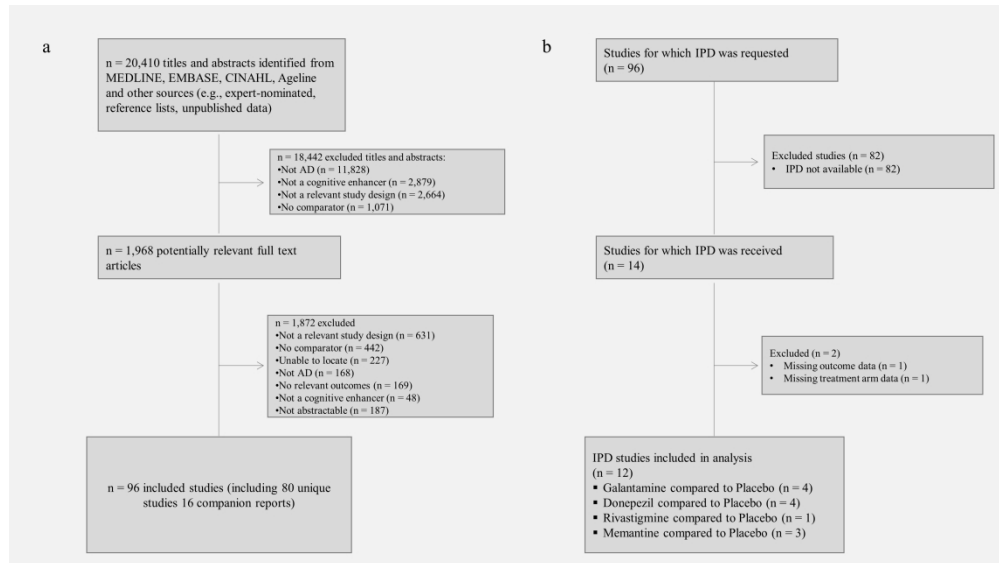


Figure 1. Flow diagram for study inclusion in the review (a) and studies retrieved with individual patient data (b).

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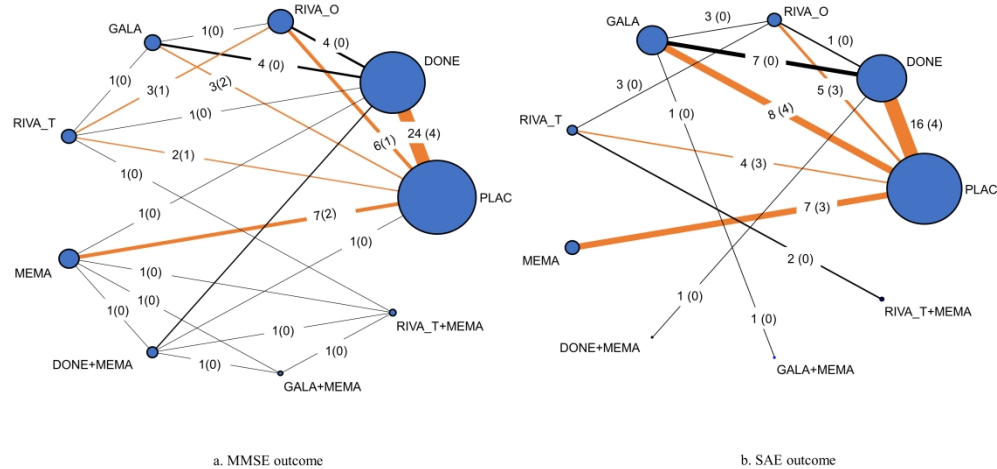


Figure 2. Network diagrams for (a) MMSE and (b) SAE outcomes. The size of each node and line indicates the number of studies included in each treatment comparison. The number of studies per treatment comparison is presented on each edge, and the number of studies with individual patient data (IPD) is 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.

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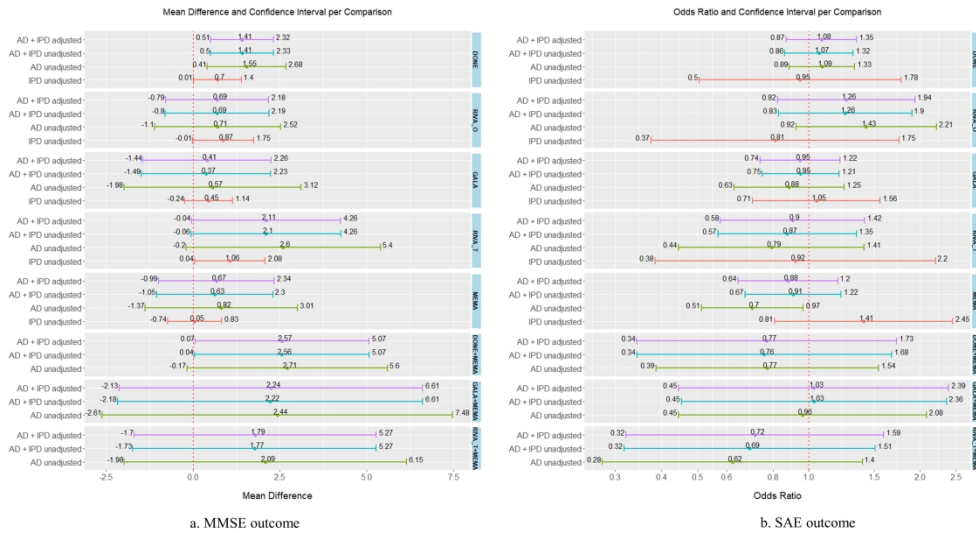


Figure 3. Forest plot of network meta-analysis (NMA) results for all cognitive enhancers versus placebo in (a) MMSE outcome, and (b) SAE outcome. NMA results are presented for i) aggregate data (AD) and fully adjusted results from studies with available individual patient data (IPD), ii) AD and crude 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 individual patient data (IPD).

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Figure 4. Rank-heat plot of P-scores for 9 treatments, including placebo, studied in randomized clinical trials with patients with Alzheimer’s Dementia assessing MMSE. 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.

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

### *Eligibility criteria, search strategy and study selection*

We considered a SAE as defined in the individual trials, specifically, when an event led to disability or hospitalization or was life-threatening or fatal. Study definitions for a SAE were also abstracted. 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,<sup>4</sup> 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.<sup>10</sup> 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:<sup>1</sup> 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.<sup>2</sup> 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 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 SAEs, 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.<sup>3</sup> 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. For imprecision, we considered a MD=1.4 and a OR=1 as a clinically important size of effect for MMSE

and SAE, 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.

### *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% confidence interval (CI). The first stage of the IPD analyses were conducted in RStudio,<sup>4</sup> 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 serious 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<sup>4</sup> 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.<sup>5</sup> We estimated the between-study variance using the DerSimonian and Laird<sup>6</sup> method and compared it with the relevant distributions provided by Turner et al<sup>7</sup> and Rhodes et al<sup>8</sup> 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.<sup>9-11</sup> 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<sup>12,13</sup> and the loop-specific method.<sup>14,15</sup> 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, and for studies with available IPD vs. studies with aggregate data (unadjusted estimates), 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,<sup>16</sup> and 4) the 'informative missingness difference of means' (IMDoM) imputation method<sup>17</sup> 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.

Meta-analysis and NMA at the 2<sup>nd</sup> stage were conducted in the RStudio using R version 3.6.2 and the *meta*<sup>18</sup> and *netmeta*<sup>19</sup> 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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For peer review only

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

A study<sup>1</sup> of 859 participants comparing transdermal rivastigmine vs. placebo included only IPD for the placebo arm. Another study<sup>2</sup> 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 SAE 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 cm<sup>2</sup> group, 287 to the rivastigmine patch 10 cm<sup>2</sup> 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
SAE, 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 SAE 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 SAE 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
SAE, 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%)			

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

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## Appendix 4: List of studies requested and sponsor response

Sponsor	Author, year	Interventions compared	Sponsor Response	IPD Received
Abbvie	Gault, 2015	Placebo/No treatment, Donepezil	Available	Yes
	Haig, 2014	Placebo/No treatment, Donepezil	Available	Yes
	Marek, 2014	Placebo/No treatment, Donepezil	Unavailable (Cannot share data (Potential business considerations under review))	No
AstraZeneca	Frolich, 2011	Placebo/No treatment, Donepezil	Available	No
Daiichi-Sankyo	Shimizu, 2015	Donepezil, Galantamine, Rivastigmine	Unavailable (Do not own data)	No
Eisai	Black, 2007	Placebo/No treatment, Donepezil	Available	Yes
	Burns, 1999	Placebo/No treatment, Donepezil	Unavailable (Cannot share data (Old study))	No
	Feldman, 2001	Placebo/No treatment, Donepezil	Unavailable (Do not own data)	No
	Feldman, 2004	Placebo/No treatment, Donepezil	Unavailable (Do not own data)	No
	Feldman, 2005	Placebo/No treatment, Donepezil	Unavailable (Do not own data)	No
	Gauthier, 2002	Placebo/No treatment, Donepezil	Unavailable (Do not own data)	No
	Holmes, 2004	Placebo/No treatment, Donepezil	Unavailable (Do not own data)	No
	Homma, 2008	Placebo/No treatment, Donepezil	Unavailable (Cannot share data (Old study))	No
	Johannsen, 2006	Placebo/No treatment, Donepezil	Unavailable (Do not own data)	No
	Jones, 2004	Donepezil, Galantamine	Unavailable (Cannot share data (Old study))	No
	Mohs, 2001	Placebo/No treatment, Donepezil	Unavailable (Cannot share data (Old study))	No
	Rogers, 1996	Placebo/No treatment, Donepezil	Unavailable (Cannot share data (Old study))	No
	Rogers, 1998	Placebo/No treatment, Donepezil	Unavailable (Cannot share data (Old study))	No
	Rogers, 1998	Placebo/No treatment, Donepezil	Unavailable (Cannot share data (Old study))	No
	Schwam, 2010	Placebo/No treatment, Donepezil	Unavailable (Do not own data)	No
	Seltzer, 2004	Donepezil, Placebo/No treatment	Unavailable (Cannot share data (Old study))	No
	Shimizu, 2015	Donepezil, Galantamine, Rivastigmine	Unavailable (Do not own data)	No
	Sole-Padullas, 2013	Placebo/No treatment, Donepezil	Unavailable (Do not own data)	No
	Tariot, 2001	Placebo/No treatment, Donepezil	Unavailable (Cannot share data (Old study))	No
	Wilkinson, 2002	Donepezil, Rivastigmine	Unavailable (Do not own data)	No
Forest Laboratories/Allergen	Grossberg, 2013	Donepezil + Rivastigmine + Galantamine + Placebo, Donepezil + Rivastigmine + Galantamine + Memantine	Unavailable (Cannot share data (No details provided))	No
	Ott, 2007	Placebo/No treatment, Memantine	Unavailable (Cannot share data (No details provided))	No
	Peskind, 2006	Placebo/No treatment, Memantine	Unavailable (Cannot share data (No details provided))	No
	Saxton, 2012	Placebo/No treatment, Memantine	Unavailable (Cannot share data (No details provided))	No
	van Dyck, 2007	Placebo/No treatment, Memantine	Unavailable (Cannot share data (No details provided))	No
GlaxoSmithKline	Gold, 2010	Placebo/No treatment, Donepezil	Available	Yes
	Maher-Edwards, 2011	Placebo/No treatment, Donepezil	Unavailable (Do not own data)	No
Janssen	Ancoli-Israel, 2005	Donepezil, Galantamine	Unavailable (Cannot identify study)	No
	Aronson, 2009	Placebo/No treatment, Galantamine	Unavailable (Cannot identify study)	No
	Burns, 2009	Placebo/No treatment, Galantamine	Available	Yes
	Cummings, 2004	Placebo/No treatment, Galantamine	Available	Yes

Sponsor	Author, year	Interventions compared	Sponsor Response	IPD Received
	Gaudig, 2011	Placebo/No treatment, Galantamine	Unavailable (Cannot identify study)	No
	Hager K, 2014	Placebo/No treatment, Galantamine	Available	Yes
	Kadir, 2008	Placebo/No treatment, Galantamine	Unavailable (Cannot identify study)	No
	Likitjaroen, 2012	Placebo/No treatment, Galantamine	Unavailable(Do not own data)	No
	Rockwood, 2001	Placebo/No treatment, Galantamine	Available	Yes
	Rockwood, 2006	Placebo/No treatment, Galantamine	Unavailable (IPD not available)	No
	Scarpini, 2011	Placebo/No treatment, Galantamine	Unavailable (IPD not available)	No
	Shimizu, 2015	Donepezil, Galantamine, Rivastigmine	Unavailable (Cannot identify study)	No
	Tariot, 2000	Placebo/No treatment, Galantamine	Unavailable (Cannot identify study)	No
	Wilcock, 2003	Donepezil, Galantamine	Unavailable (Cannot identify study)	No
	Zhang, 2012	Donepezil, Galantamine	Unavailable (IPD not available)	No
	Wilkinson, 2001	Placebo/No treatment, Galantamine	Available	Yes
Lundbeck	Bakchine, 2008	Placebo/No treatment, Memantine	Available	Yes
	Fox, 2012	Placebo/No treatment, Memantine	Unavailable (Do not own data)	No
	Herrmann, 2013	Placebo/No treatment, Memantine	Available	Yes
	Lorenzi, 2011	Placebo/No treatment, Memantine	Unavailable (Do not own data)	No
	Wilkinson, 2012	Placebo/No treatment, Memantine	Available	Yes
Merz	Reisberg, 2003	Placebo/No treatment, Memantine	No response from sponsor	No
	Reisberg, 2006	Placebo/No treatment, Memantine	No response from sponsor	No
	Schmidt, 2008	Placebo/No treatment, Memantine	No response from sponsor	No
	Winblad, 2007	Placebo/No treatment, Rivastigmine	No response from sponsor	No
Novartis	Agid, 1998	Placebo/No treatment, Rivastigmine	Unavailable (Cannot identify study)	No
	Blesa González, 2011	Placebo/No treatment, Rivastigmine	Unavailable (Cannot share data)	No
	Choi, 2011	Placebo/No treatment, Memantine	Unavailable (Do not own data)	No
	Corey-Bloom, 1998	Placebo/No treatment, Rivastigmine	Unavailable (Cannot identify study)	No
	Farlow, 2013	Rivastigmine, Rivastigmine + Memantine	Unavailable (Cannot share data (Phase 4 study))	No
	Feldman, 2007	Placebo/No treatment, Rivastigmine	Unavailable (Cannot identify study)	No
	Grossberg, 2015	Rivastigmine, Rivastigmine + Memantine	Unavailable (Cannot share data (Phase 4 study))	No
	Han, 2012	Placebo/No treatment, Memantine	Unavailable (Cannot identify study)	No
	Kumar, 2000	Placebo/No treatment, Rivastigmine	Unavailable (Cannot identify study)	No
	Nakamura, 2011	Placebo/No treatment, Rivastigmine	Available	Yes
	Nordberg, 2009	Donepezil, Galantamine, Rivastigmine	Unavailable (Cannot share data (Phase 4 study))	No
	Shimizu, 2015	Donepezil, Galantamine, Rivastigmine	Unavailable (Cannot identify study)	No
	Winblad, 2007	Placebo/No treatment, Rivastigmine	Available	Yes
ONO	Nakamura, 2011	Placebo/No treatment, Rivastigmine	No response from sponsor	No
Pfizer	Black, 2007	Placebo/No treatment, Donepezil	Unavailable (Do not own data)	No
	Feldman, 2001	Placebo/No treatment, Donepezil	Available	No
	Feldman, 2004	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
	Feldman, 2005	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
	Gauthier, 2002	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
	Holmes, 2004	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
	Jelic, 2008	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
	Johannsen, 2006	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No



Sponsor	Author, year	Interventions compared	Sponsor Response	IPD Received
	Jones, 2004	Donepezil, Galantamine	Unavailable (Cannot identify study)	No
	Mohs, 2001	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
	Schwam, 2010	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
	Seltzer, 2004	Donepezil, Placebo/No treatment	Unavailable (Cannot identify study)	No
	Sole-Padulles, 2013	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
	Tariot, 2001	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
	Wilkinson, 2002	Donepezil, Rivastigmine	Unavailable (Cannot identify study)	No
	Wimo, 2003	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
	Winblad, 2001	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
	Winblad, 2006	Placebo/No treatment, Donepezil	Unavailable (Cannot identify study)	No
Roivant	Mahe-Edwards, 2011	Placebo/No treatment, Donepezil	No response from sponsor	No
Shire Pharmaceuticals	Wilcock, 2003	Donepezil, Galantamine	Unavailable (Do not own data)	No
	Wilkinson, 2001	Placebo/No treatment, Galantamine	Unavailable (Do not own data)	No
Takeda	Shimizu, 2015	Donepezil, Galantamine, Rivastigmine	Unavailable (Do not own data)	No
Non-Pharmaceutical	Andersen, 2012	Placebo/No treatment, Donepezil	NA	No
	Araki, 2014	Placebo/No treatment, Donepezil + Memantine	NA	No
	Burns, 2011	Placebo/No treatment, Donepezil	NA	No
	Dysken, 2014	Placebo/No treatment, Memantine	Available	No
	Greenberg, 2000	Placebo/No treatment, Donepezil	Unavailable (Need to contact PI)	No
	Howard, 2007	Placebo/No treatment, Donepezil	Unavailable (Do not own data)	No
	Howard, 2012	Donepezil + Memantine, Donepezil + Placebo	Unavailable (Do not own data)	No
	Mowla, 2007	Placebo/No treatment, Rivastigmine	NA	No
	Peters, 2015	Galantamine + Placebo, Galantamine + Memantine	NA	No
Not reported	Cretu, 2008	Placebo/No treatment, Memantine	NA	No
	Fuschillo, 2001	Donepezil, Rivastigmine	NA	No
	Hernández, 2007	Placebo/No treatment, Donepezil	NA	No
	Homma, 1998	Donepezil, Placebo/no treatment	NA	No
	Hong, 2006	Placebo/No treatment, Galantamine	NA	No
	Hu, 2006	Donepezil, Memantine	NA	No
	Kano, 2013	Donepezil, Donepezil + Memantine	NA	No
	Karaman, 2005	Placebo/No treatment, Rivastigmine	NA	No
	Mazza, 2006	Placebo/No treatment, Donepezil	NA	No
	Moretti, 2014	Placebo/No treatment, Rivastigmine	NA	No
	Nakano, 2001	Placebo/No treatment, Donepezil	NA	No
	Pakdaman H, 2015	Donepezil, Galantamine, Rivastigmine	NA	No
	Peng, 2005	Placebo/No treatment, Donepezil	NA	No
	Shao, 2015	Memantine + Placebo, Rivastigmine + Memantine, Donepezil + Memantine, Galantamine + Memantine	NA	No
	Thomas, 2001	Donepezil, Rivastigmine	NA	No
	Zhang-Yi, 2005	Placebo/No treatment, Donepezil	NA	No

**Abbreviations:** NA, not applicable; NPH, neutral protamine Hagedorn; PI, principle investigator

## 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs	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, SAEs, 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, SAEs, Headaches, Falls	Industry-sponsored	Not reported; December 2003; Not reported	Yes; NA
Burns, 2011	UK	62; 12	Donepezil, Placebo/no treatment; NPI, SAEs	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, SAEs, 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;	Memantine, Placebo/No treatment;	NA	Not reported;	No;

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		24	MMSE, ADAS-cog, NPI		Not reported; Not reported	NR
Dysken, 2014	USA	307; 26-208	Memantine, Placebo; MMSE, ADAS-cog, ADCS-ADL, NPI, Mortality, SAEs	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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs	Industry- sponsored	Not reported; February 2007; 2:2:2:1	Yes; Available
Greenberg, 2000	USA	103; 24	Donepezil, Placebo/no treatment; ADAS-cog, SAEs, 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, Headaches, Vomiting, Diarrhea,	Industry- sponsored	Not reported; June 2005; 1:1	No; Cannot share dat

## Nausea, SAEs

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, SAEs	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, SAEs	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, SAEs	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, SAEs, Headaches	NA	Not reported; Not reported; Not reported	No; NR
Homma, 2008	Japan	267; 24	Donepezil, Placebo/no treatment; ADCS-ADL, CIBIC-plus, Mortality, SAEs, 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, SAEs	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, SAEs, 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, SAEs	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, SAEs, 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, SAEs	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, SAEs, 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, SAEs, 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; SAEs, 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, Headaches, Vomiting, Diarrhea,	Industry- sponsored	Not reported; Not reported; Not reported	No; NR

## 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs	Industry- sponsored	Not reported; April 2007; Not reported	No; Cannot share data
Scarpini, 2011	Italy	139; 96	Galantamine, Placebo/no treatment; Mortality, SAEs	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;	Donepezil + Memantine, Galantamine	NA	Not reported;	No;

		24	+ Memantine, Memantine + Placebo, Rivastigmine + Memantine; MMSE, ADCS-ADL		October 2009; Not reported	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-Padullas, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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;	No; NR

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					Not reported	
Zhang, 2012	China	218; 16	Galantamine, Donepezil; MMSE, ADAS-cog, ADCS-ADL, NPI, Mortality, Vomiting, Diarrhea, Nausea, SAEs	Industry- sponsored	Not reported; Not reported; Not reported	No; IPD not available

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### 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 SAE	Missing data in SAE 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 SAE
Black 2007	21	0 (0%)	7.5 (3.3)	8.2 (5.2)	0.63 (3.1)	27 (15%)	176 (51%)	<ul style="list-style-type: none"> <li>intercurrent illness (1 [2%] – donepezil = 1; placebo = 0),</li> <li>request of patient or investigator (4 [7%] –</li> </ul>	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

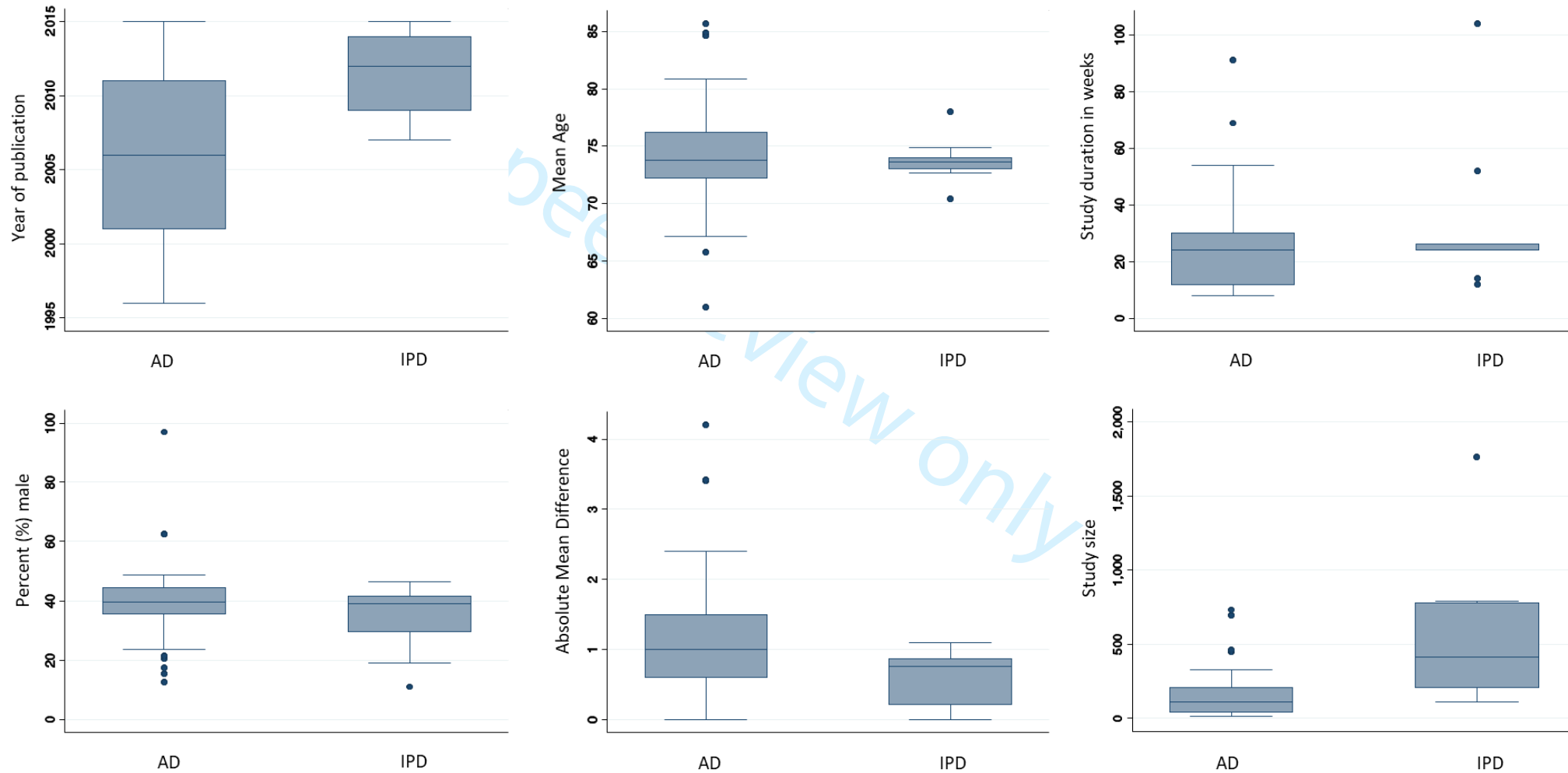
† The MMSE final value comes from visit 8 (last available visit in IPD). MMSE was not reported in study publication

**Abbreviations:** AD, Alzheimer's Dementia; IPD, individual patient data; MMSE, Mini-Mental State Examination; NR, not reported; N/A, not applicable; SAE, serious adverse event

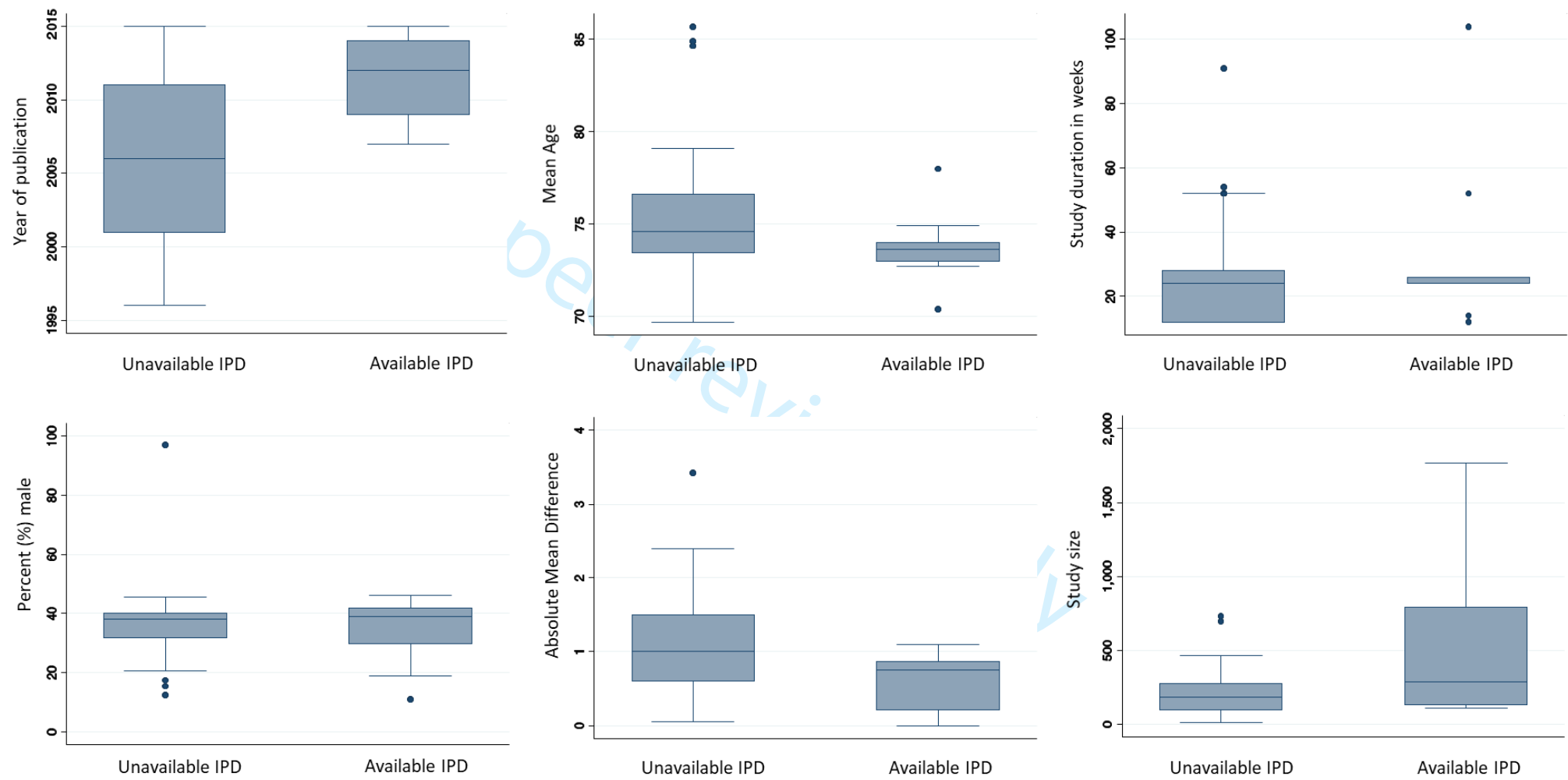
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**Appendix 7: Comparison of studies with shared IPD with (a) all remaining studies and (b) studies for which sponsors claimed unavailable IPD.** AD: aggregate data; IPD: individual patient data

**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)



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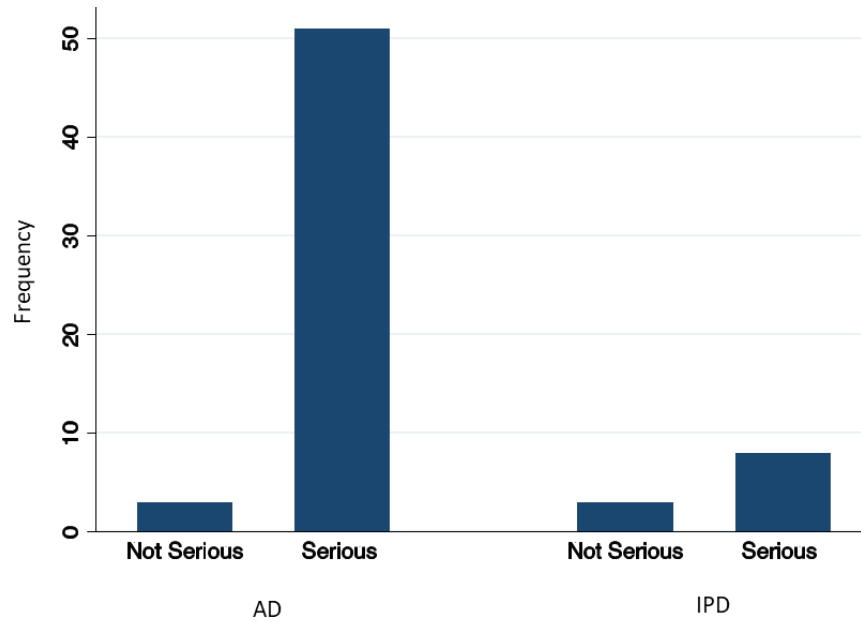
## Appendix 8: Cochrane Risk-of-bias appraisal results (n = 80)

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

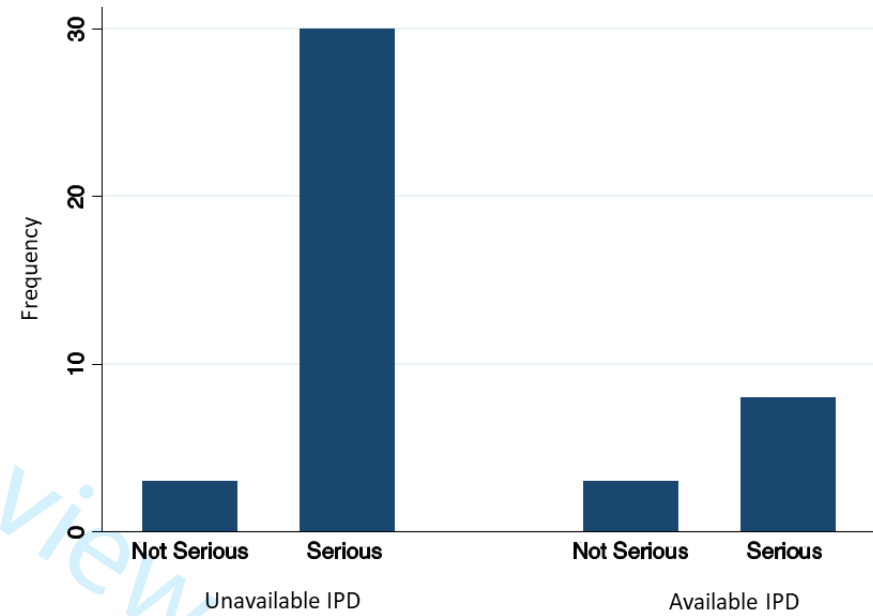
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3	Shao, 2015	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
4	Shimizu, 2015	Low	Unclear	High	Low	High	Unclear	Unclear
5	Sole-Padullas, 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
6	Tariot, 2000	Low	Unclear	Low	Low	High	Low	High
7	Tariot, 2001	Low	Low	Low	Low	Unclear	Unclear	High
8	Thomas, 2001	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
9	Wilcock, 2003	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
10	Wilkinson, 2001	Low	Low	Low	Low	High	Unclear	High
11	Wilkinson, 2002	Low	Low	Low	Low	High	Unclear	High
12	Wilkinson, 2012	Low	High	Low	Low	High	Low	High
13	Winblad, 2001	Low	Unclear	Unclear	Low	High	Unclear	High
14	Winblad, 2006	Low	Low	Low	Low	High	Low	High
15	Winblad, 2007	Low	Low	Low	Low	High	Unclear	High
16	Yi, 2005	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
17	Zhang, 2012	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
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**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**



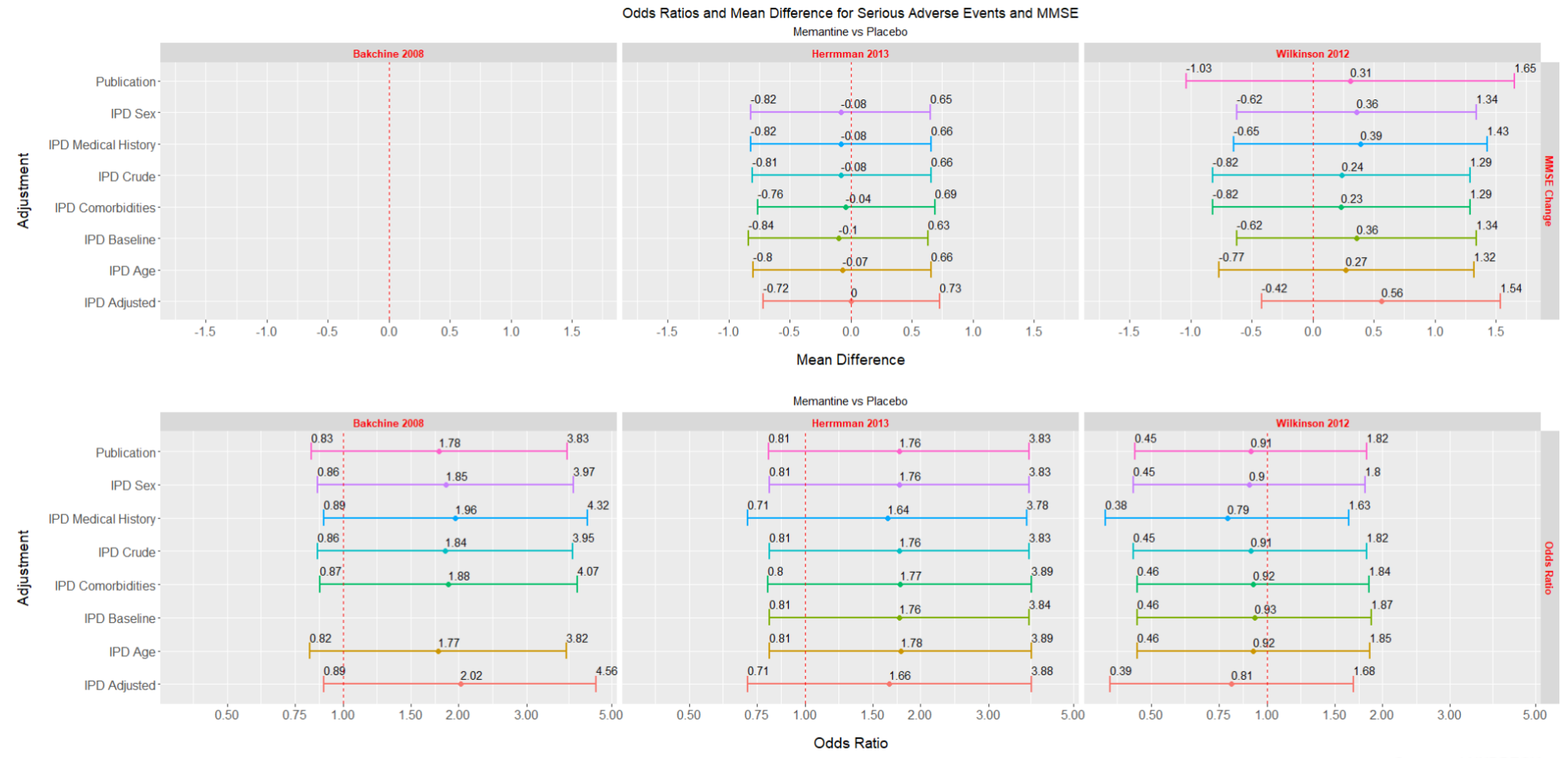
a. Comparison of studies with shared IPD with all remaining studies (irrespective type of sponsor)



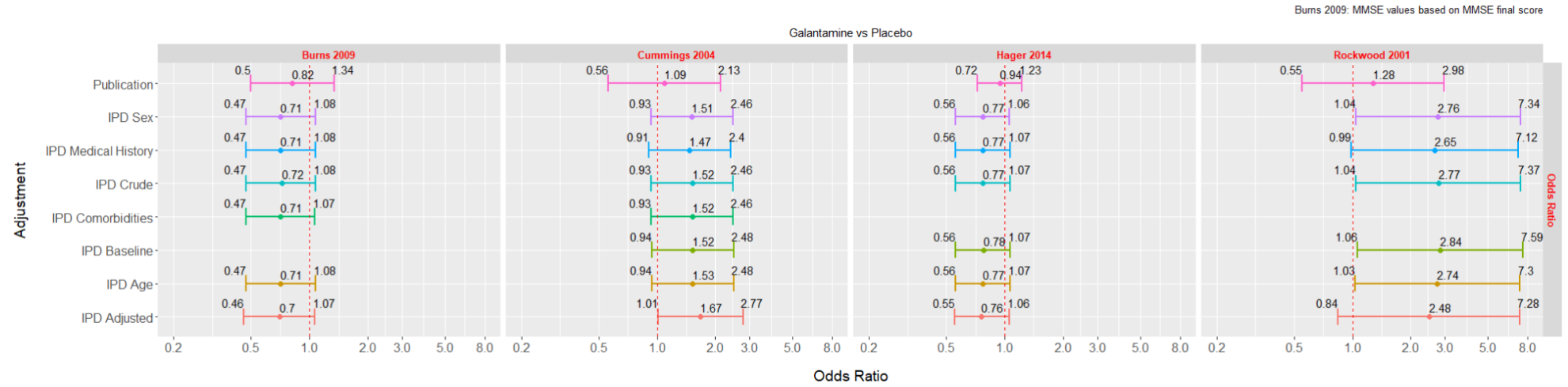
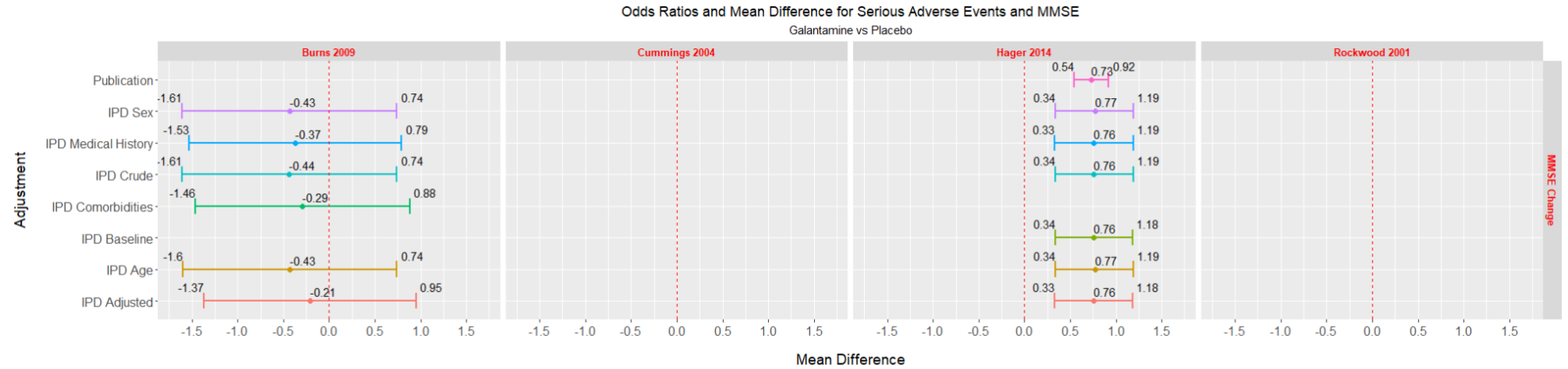
b. Comparison of studies with available and unavailable IPD (industry-sponsored studies only)



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

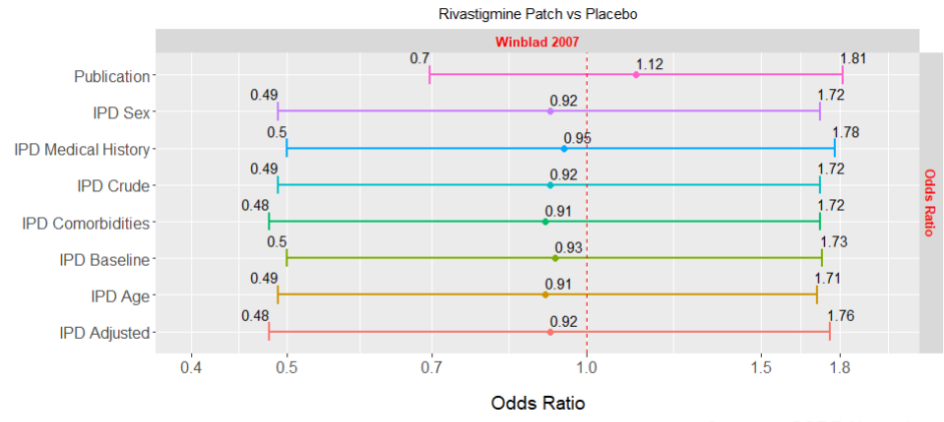
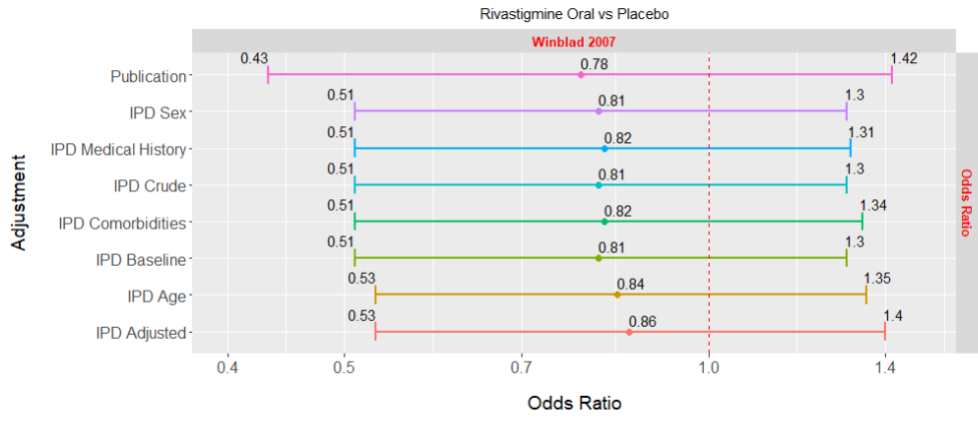
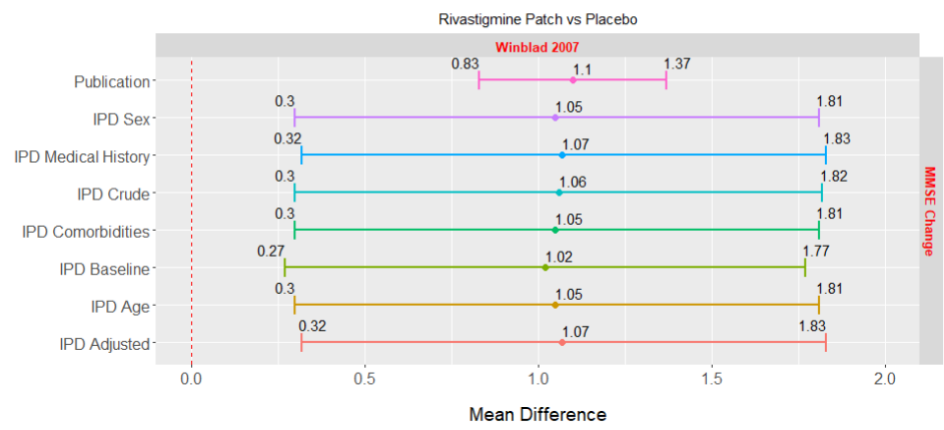
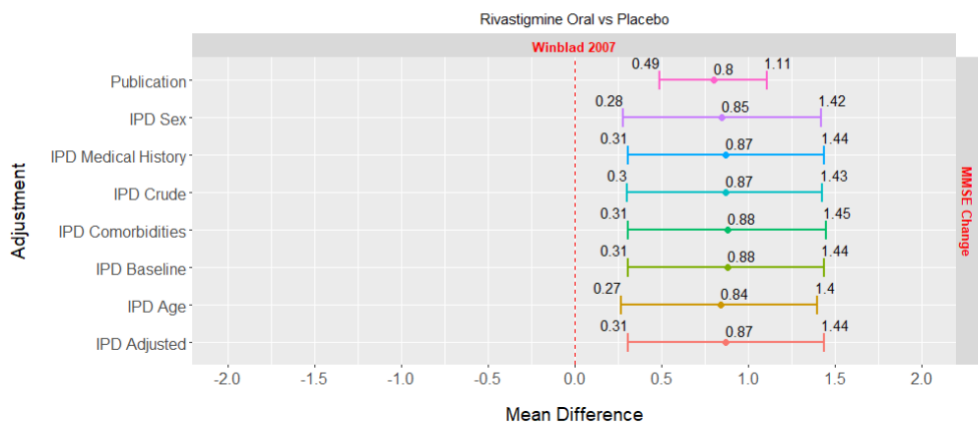


Sponsor: LUNDBECK

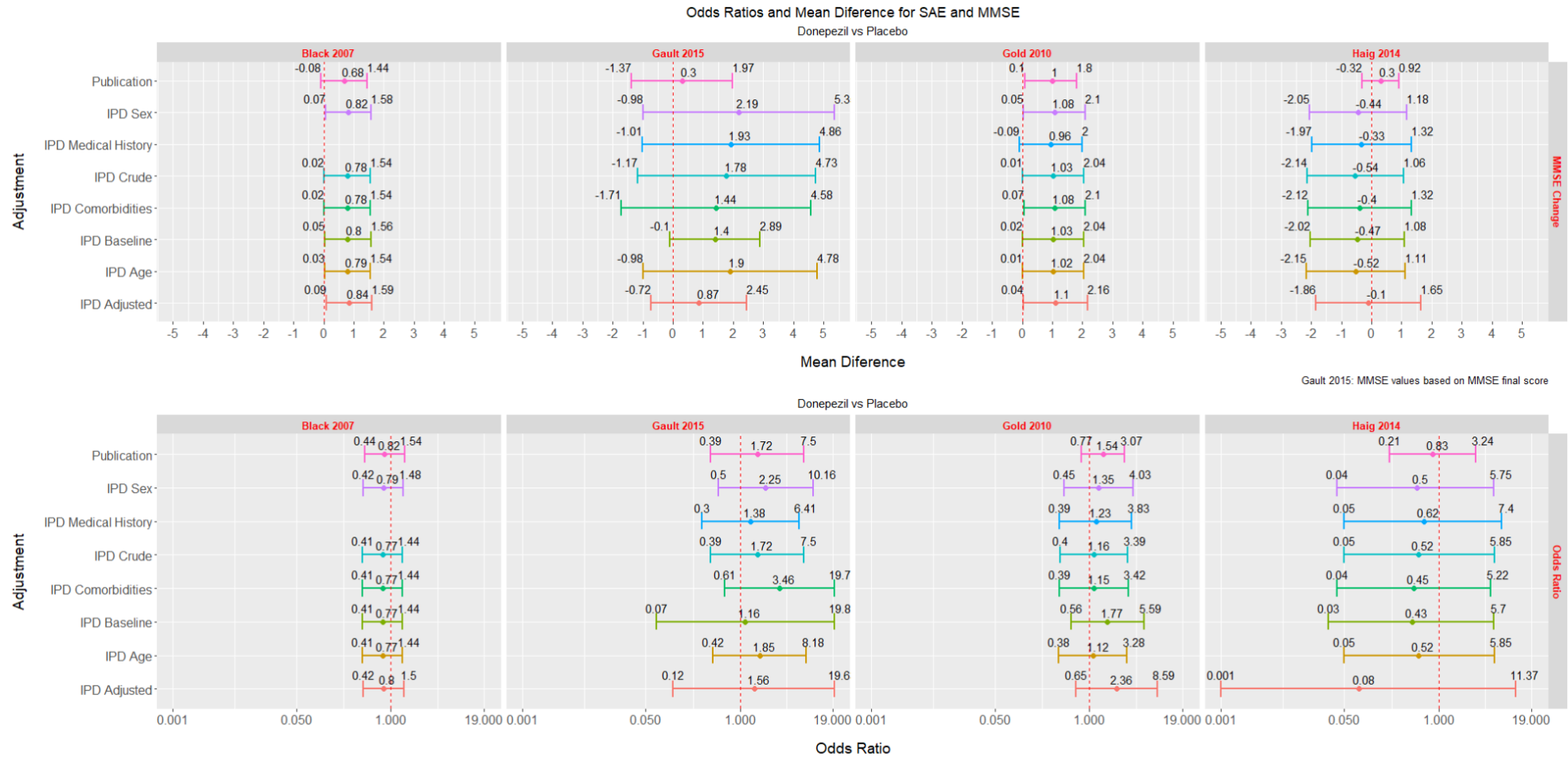


Sponsor: YODA

Odds Ratios and Mean Difference for Serious Adverse Events and MMSE



Sponsor: CSDR Novartis



Sponsor: CSDR, ABBVIE

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 SAE 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 assesment we did not have access to these data.

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**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)

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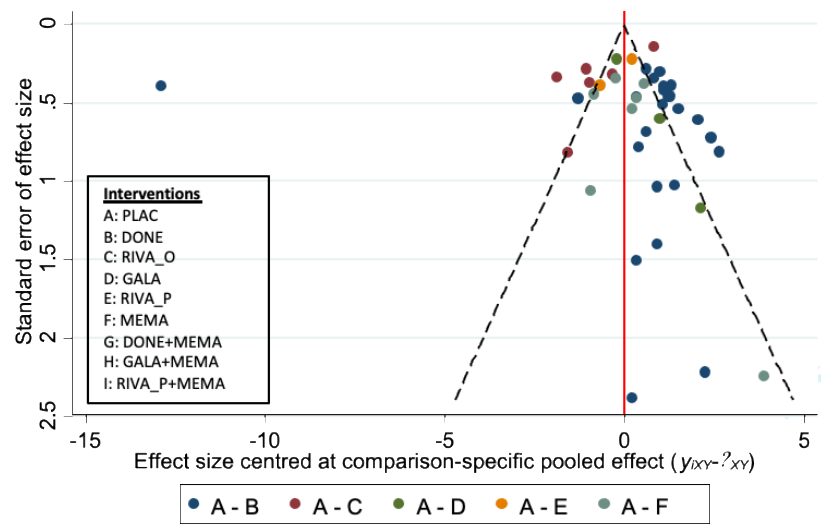
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3 **Appendix 11: Correlation between participant age and dropout in studies with IPD.** IPD: individual patient  
4 data  
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	<b>Study*</b>	<b>Correlation</b>	<b>P-Value</b>
<b>CSDR</b>	Black 2007 (EISAI)	0.079	0.147
	Gold 2010 (GSK)	0.141	0.072
	Winblad 2007 (Novartis)	0.016	0.584
<b>Lundbeck</b>	Wilkinson 2012	0.066	0.273
	Herrmman 2013	0.124	0.017

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13 \* We were unable to assess this correlation for studies obtained through YODA and AbbVie, since at the time of  
14 this assessment we did not have access to these data  
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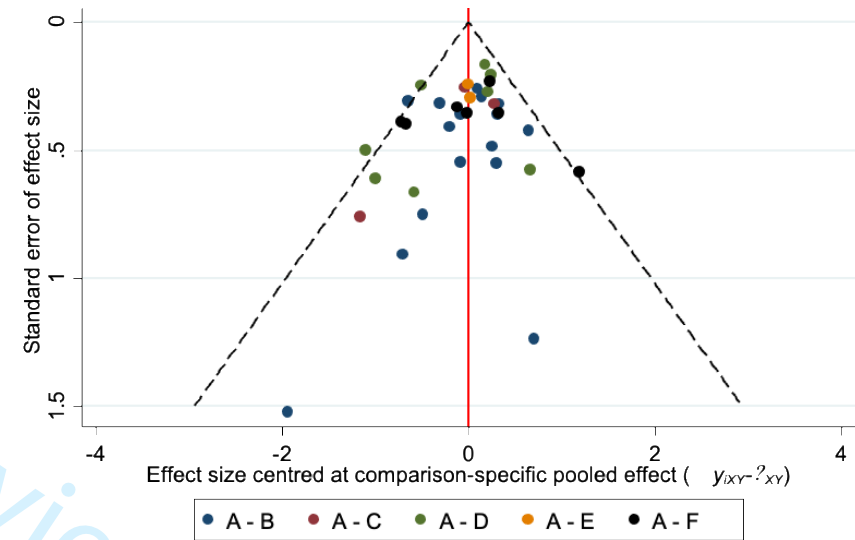
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Appendix 12: Comparison Adjusted Funnel plot (all treatments vs placebo)



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

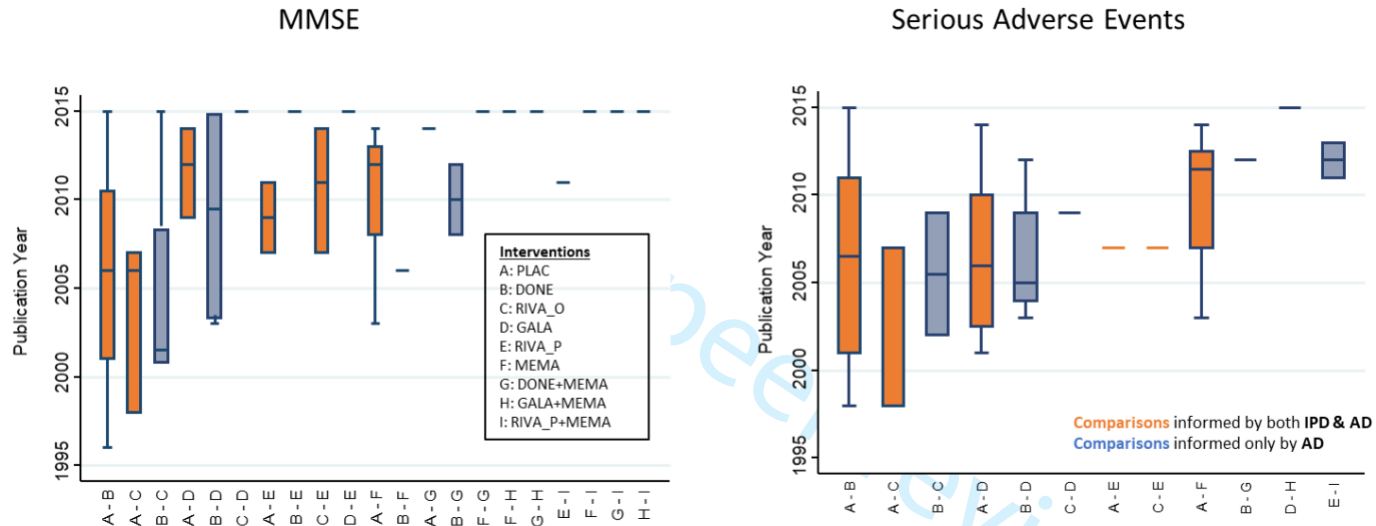
MMSE



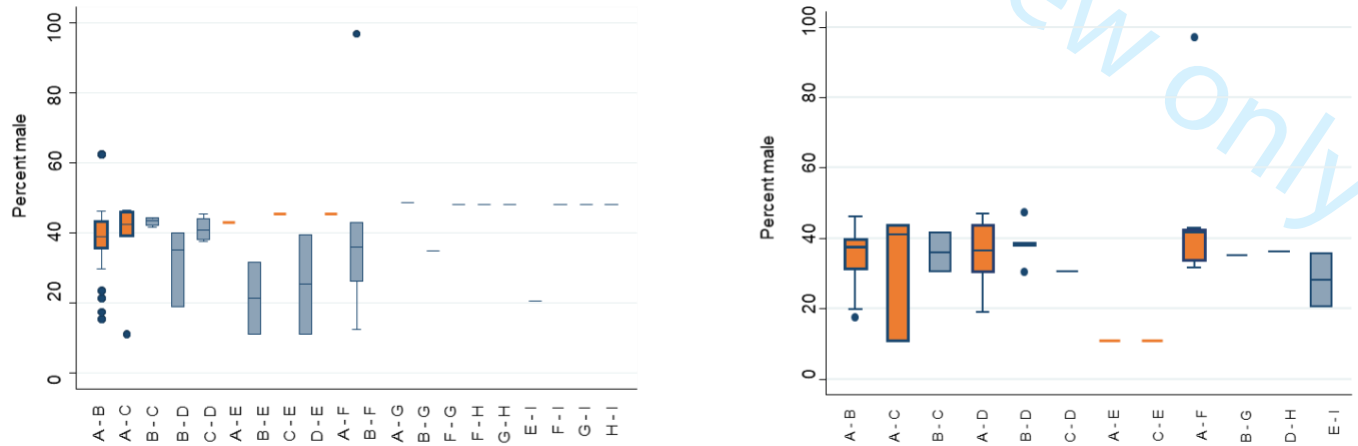
Note: Comparisons including only one study (when present) have been excluded

Serious Adverse Events

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

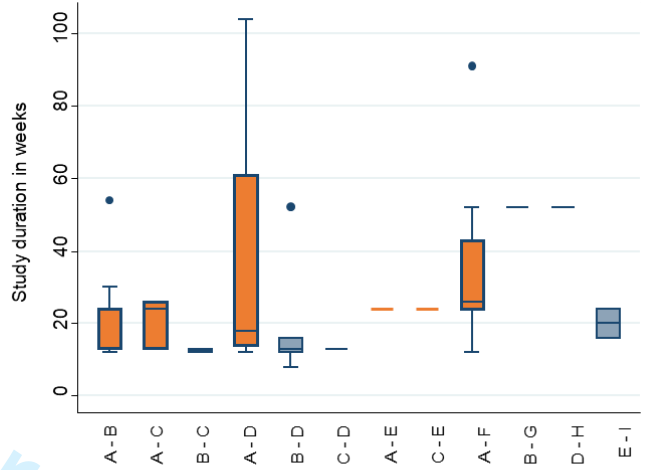
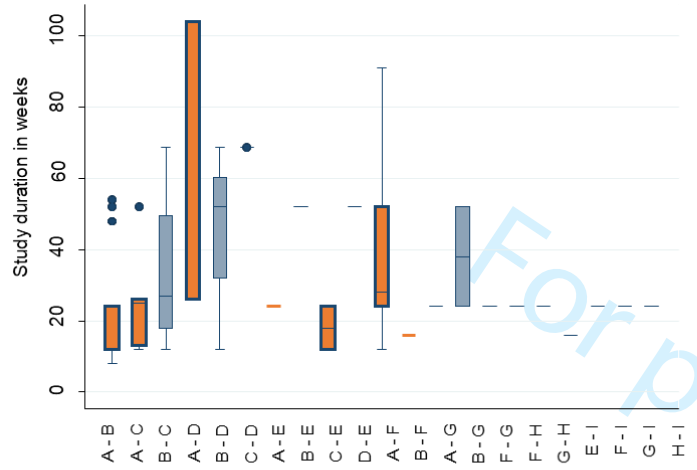


a. Publication year

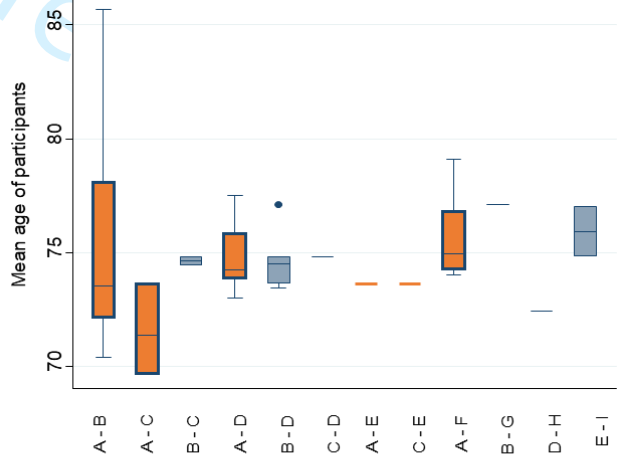
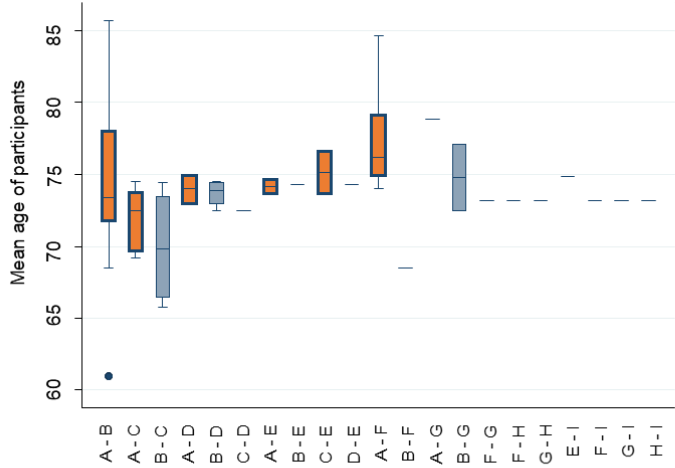


b. Percentage male



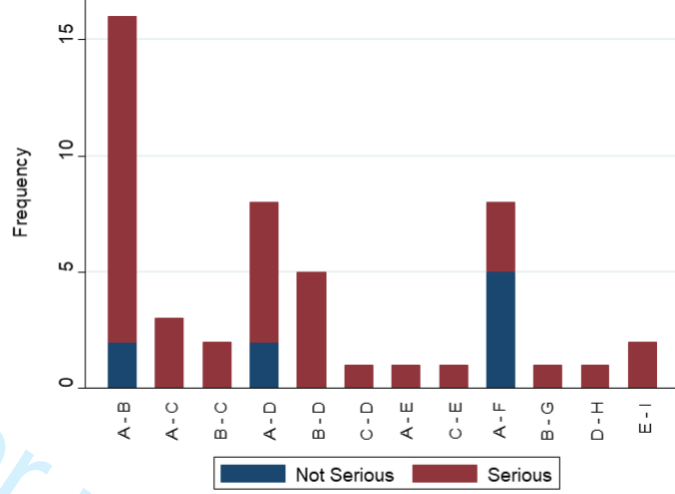
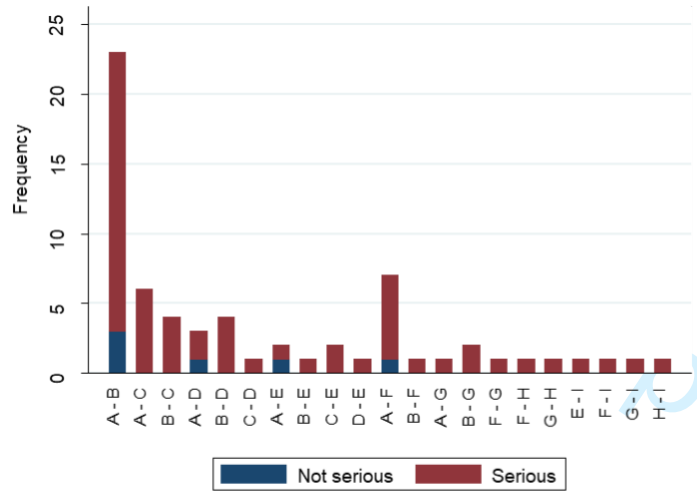


c. Study duration

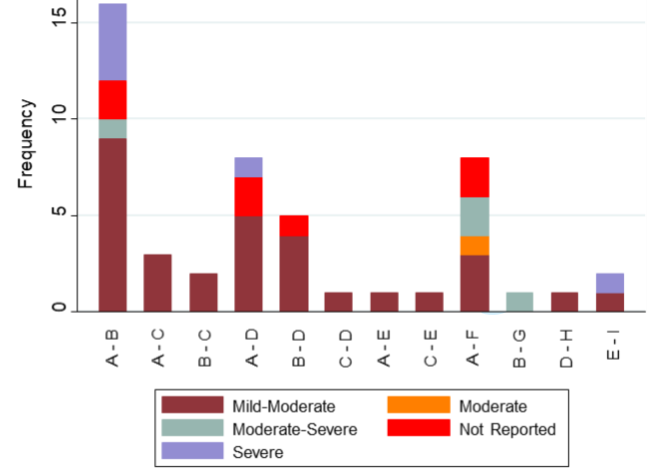
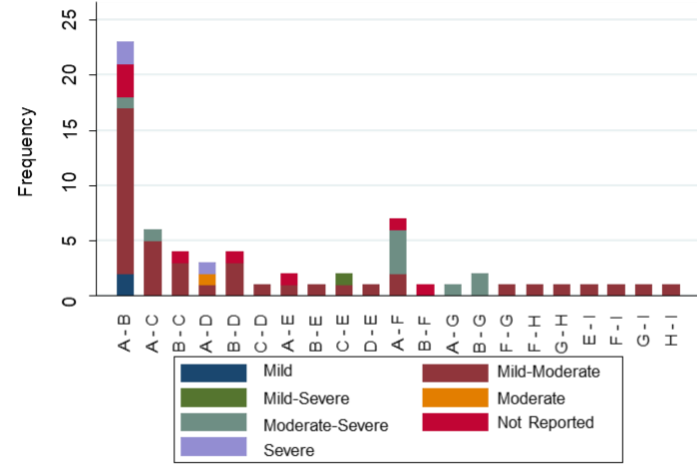


d. Mean participant age

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e. Overall Risk of Bias

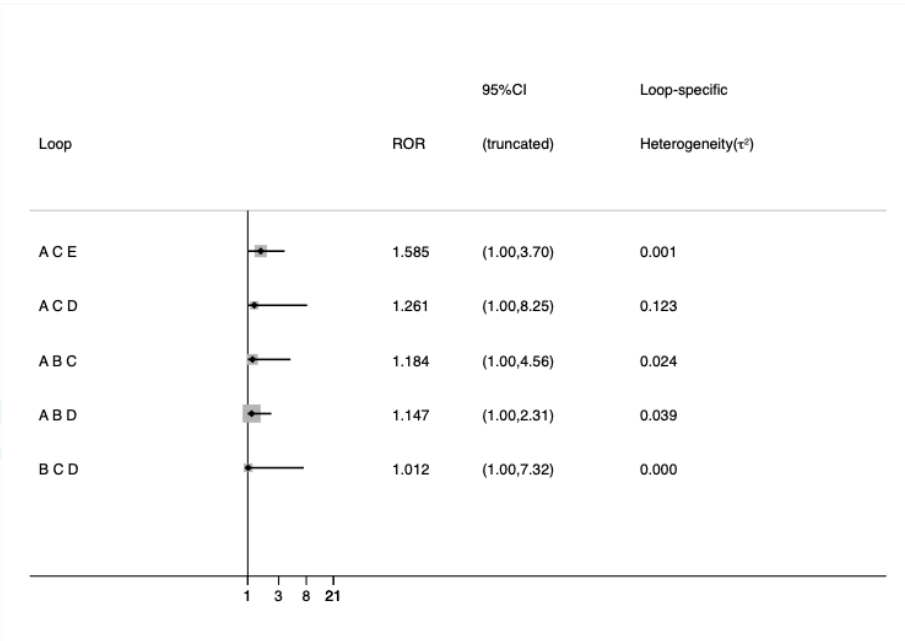
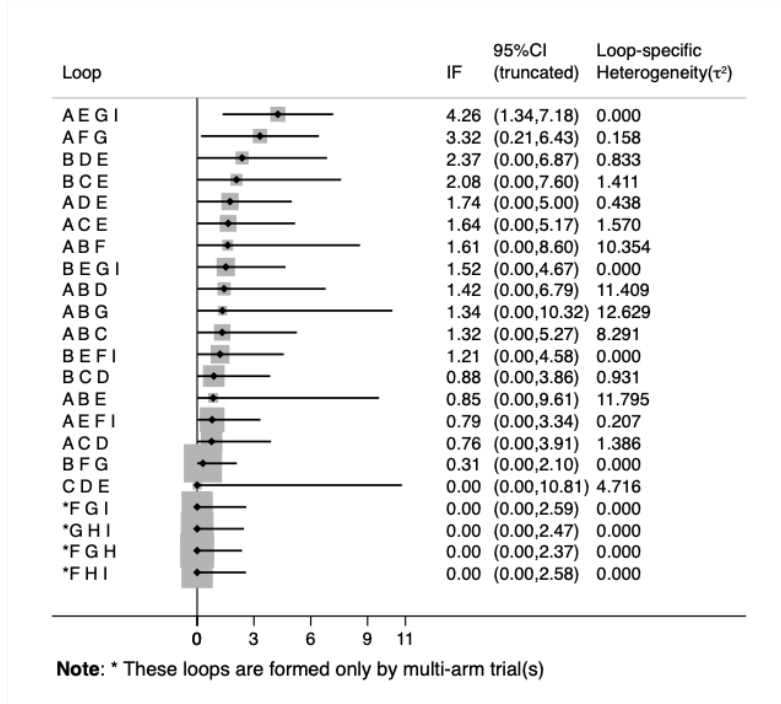


f. Alzheimer's Dementia Severity

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

MMSE

Serious Adverse Events



Design-by-treatment interaction model:  
 $\chi^2$  statistic: 4.36, 13 degrees of freedom, P value: 0.987, between-study variance: 7.34. I<sup>2</sup> statistic=96%

Design-by-treatment interaction model:  
 $\chi^2$  statistic: 3.57, 6 degrees of freedom, P value: 0.735, between-study variance: 0.06. I<sup>2</sup> 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
<b>Mini-Mental State Examination (MMSE)*†</b>								
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		
<i>Common within-network between-study variance <math>\tau^2 = 5.75</math>, <math>I^2 = 96\%</math> (96%, 97%)</i>								
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>								
<b>Serious Adverse Events (SAEs)*<sup>‡</sup></b>								
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
<i>Common within-network between-study variance <math>\tau^2 = 0.04</math>, <math>I^2 = 22\%</math> (0%, 48%)</i>								
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>								

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3 \* Aggregate data and fully adjusted results from studies with available individual patient data were used in both  
4 meta-analysis and NMA. The mean difference effect size is presented for MMSE and the odds ratio for SAE.

5 † MMSE: Studies with available IPD included only available participants –to assess the missing data impact on  
6 the second stage (IMDoM) a separate analysis was applied

7 ‡ SAE: Studies with available IPD included all randomized participants  
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## Appendix 16: Additional analyses using IPD and aggregate data

### *Cognition*

Additional analyses using both IPD and aggregate data, were in agreement with the main analysis findings, overall (Appendix 17). 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 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. However, PrIs are wide suggesting results are not conclusive.

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, but results are inconclusive (MD= 0.88 95% CI: 0.31 to 1.45, 95% PI: -0.05 to 1.81, P-score= 75%). Similarly, using IPD adjusted for MMSE 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<sup>2</sup>= 96%) compared also to the Rhodes et al<sup>21</sup> empirical distribution (median 0.05, 95% range: 0.00 to 7.56). However, heterogeneity decreased importantly when excluding outliers (between-study variance = 0.59, I<sup>2</sup>= 73%), when including only patients with moderate to severe AD (between-study variance = 0.18, I<sup>2</sup>= 44%), restricting to industry-sponsored trials (between-study variance = 0.16, I<sup>2</sup>= 43%), and when using IPD only (between-study variance = 0.12, I<sup>2</sup>= 29%).

### *Serious adverse events*

Additional analyses using both IPD and aggregate data, showed that memantine was statistically significantly associated with lower odds of a SAE than placebo when using study duration as a covariate (OR= 0.61, 95% CI: 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 a SAE (OR= 0.69, 95% CI: 0.50 to 0.97, P-score= 80%). The available case analysis for studies with available IPD showed that donepezil (OR= 1.63, 95% CI: 0.49 to 5.41) and oral rivastigmine (OR= 1.28, 95% CI: 0.08 to 19.94) were associated with higher odds of a SAE, yet these were non-statistically significant, and overall there were no major differences with the intention to treat IPD NMA results.

Heterogeneity in NMA was low (between-study variance = 0.04, I<sup>2</sup>= 22%) compared to the Turner et al<sup>20</sup> empirical distribution (median 0.12, 95% range: 0.01 to 2.63). Heterogeneity decreased importantly when restricting to aggregate data (between-study variance = 0.00, I<sup>2</sup>= 0%), low risk of bias for incomplete outcome data (between-study variance = 0.02, I<sup>2</sup>= 10%), patients with moderate to severe cognitive impairment (between-study variance = 0.00, I<sup>2</sup>= 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).

Appendix 17: Network subgroup and meta-regression analysis results

Treatment Comparison	NMA estimate	95% CI	95%PI	P-score
<b>Mini-Mental State Examination (MMSE)†</b>				
<b>Mean Difference: Aggregate data and crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 5.81, I^2 = 96\%</math> (96%, 97%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.42 (13, 0.986, 7.44)</i>				
<b>Mean Difference: Aggregate data results**</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 7.66, I^2 = 97\%</math> (96%, 97%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.92 (11, 0.972, 8.76)</i>				
<b>Mean Difference: Crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.12, I^2 = 29\%</math> (0%, 71%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Mean Difference: Low Risk of Bias for Allocation Concealment*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 13.82, I^2 = 98\%</math> (98%, 99%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.13 (3, 0.99, 19.10)</i>				
<b>Mean Difference: Low risk of bias for Incomplete Data*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 1.16, I^2 = 79\%</math> (65%, 88%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 12.15 (3, 0.007, 0.863)</i>				
<b>Mean Difference: Publicly-Sponsored Studies*</b>				
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



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<i>Common within-network between-study variance: <math>\tau^2 = 81.93, I^2 = 99\%</math> (99%, 100%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.05 (1, 0.815, 116.71)</i>				
<b>Mean Difference: Industry-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.16, I^2 = 43\%</math> (15%, 62%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 8.06 (7, 0.327, 0.16)</i>				
<b>Mean Difference: Studies with Mild to Moderate baseline MMSE*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 9.67, I^2 = 97\%</math> (97%, 98%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.22 (9, 0.96, 13.28)</i>				
<b>Mean Difference: Studies with Moderate to Severe baseline MMSE*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.18, I^2 = 44\%</math> (0%, 75%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.60 (1, 0.11, 0.11)</i>				
<b>Mean Difference: Excluding outlier studies**</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.59, I^2 = 73\%</math> (64%, 79%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 10.60 (13, 0.64, 0.61)</i>				
<b>Accounting for missing outcome data - Informative Missingness Difference of Means<sup>§</sup></b>				
Donepezil vs Placebo	1.42	0.51 to 2.33	0.51 to 2.33	0.59 <sup>  </sup>
Rivastigmine oral vs Placebo	0.45	-1.09 to 1.99	-1.09 to 1.99	0.30 <sup>  </sup>
Galantamine vs Placebo	0.19	-1.78 to 2.17	-1.78 to 2.17	0.25 <sup>  </sup>
Rivastigmine transdermal vs Placebo	2.37	-0.03 to 4.79	-0.03 to 4.79	0.76 <sup>  </sup>
Memantine vs Placebo	0.60	-1.09 to 2.42	-1.09 to 2.42	0.36 <sup>  </sup>
Donepezil + Memantine vs Placebo	2.55	0.09 to 5.01	0.09 to 5.01	0.80 <sup>  </sup>
Galantamine + Memantine vs Placebo	2.26	-2.03 to 6.56	-2.03 to 6.56	0.68 <sup>  </sup>
Rivastigmine transdermal + Memantine vs Placebo	1.81	-1.66 to 5.28	-1.66 to 5.28	0.61 <sup>  </sup>
Placebo (reference)				0.16 <sup>  </sup>
<i>Common within-network between-study variance: <math>\tau^2 = 5.47</math><sup>  </sup></i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.45 (11, 0.955, 6.45)</i>				
<b>Mean Difference: Meta-regression, Trial Mean Age**</b>				
Donepezil vs Placebo	1.53	0.52 to 2.53	-3.17 to 6.27	0.50 <sup>††</sup>
Rivastigmine oral vs Placebo	0.80	-0.84 to 2.44	-4.15 to 5.79	0.37 <sup>††</sup>
Galantamine vs Placebo	0.60	-1.63 to 2.83	-4.57 to 5.72	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.53	0.06 to 4.98	-2.72 to 7.80	0.75 <sup>††</sup>
Memantine vs Placebo	0.79	-1.18 to 2.74	-4.33 to 5.85	0.37 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.66	0.09 to 5.19	-2.70 to 7.97	0.87 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.39	-2.02 to 6.84	-4.14 to 8.83	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.05	-1.53 to 5.59	-3.83 to 7.94	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
Regression coefficient	0.03	-0.14 to 0.20		
<i>Common within-network between-study variance: <math>\tau^2 = 5.50</math></i>				

<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.92 (11, 0.972, 8.76)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for Age</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.12</math>, <math>I^2 = 29\%</math> (0%, 71%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: Meta-regression, Percent of Male Participants**</b>				
Donepezil vs Placebo	1.62	0.58 to 2.65	-3.40 to 6.61	0.62 <sup>††</sup>
Rivastigmine oral vs Placebo	0.73	-0.90 to 2.35	-4.30 to 5.81	0.37 <sup>††</sup>
Galantamine vs Placebo	0.62	-1.65 to 2.89	-4.75 to 5.93	0.25 <sup>††</sup>
Rivastigmine Transdermal vs Placebo	2.51	0.01 to 5.04	-2.78 to 7.94	0.75 <sup>††</sup>
Memantine vs Placebo	0.66	-1.47 to 2.77	-4.54 to 5.88	0.25 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.52	-0.40 to 5.45	-3.09 to 8.17	0.75 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.27	-2.28 to 6.83	-4.37 to 8.90	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	1.98	-1.67 to 5.65	-4.02 to 7.99	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
<i>Regression coefficient</i>	0.01	-0.05 to 0.06		
<i>Common within-network between-study variance: <math>\tau^2 = 5.73</math> 3.83 to 8.84</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.72 (10, 0.959, 8.97)</i>				
<b>Mean difference: NMA of studies with IPD adjusted for Percent of Male Participants</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.13</math>, <math>I^2 = 32\%</math> (0%, 72%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for MMSE baseline</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 79%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for comorbidities</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 67%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for other medications</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.17</math>, <math>I^2 = 35\%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: Meta-regression, Study Duration**</b>				
Donepezil vs Placebo	1.66	0.67 to 2.66	-3.12 to 6.32	0.62 <sup>††</sup>
Rivastigmine oral vs Placebo	0.80	-0.77 to 2.37	-4.14 to 5.69	0.37 <sup>††</sup>
Galantamine vs Placebo	0.47	-1.75 to 2.68	-4.64 to 5.66	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.38	-0.04 to 4.83	-2.87 to 7.56	0.75 <sup>††</sup>
Memantine vs Placebo	0.67	-1.27 to 2.58	-4.35 to 5.79	0.25 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.67	0.18 to 5.16	-2.60 to 7.97	0.88 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.43	-1.94 to 6.79	-3.94 to 8.81	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.13	-1.40 to 5.63	-3.62 to 7.87	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>

<i>Regression coefficient</i>	0.02	-0.01 to 0.06		
<i>Common within-network between-study variance: <math>\tau^2 = 5.40</math></i>	3.63 to 8.29			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>				
<b>Mean Difference: Meta-regression, Year of Publication**</b>				
Donepezil vs Placebo	1.53	0.51 to 2.54	-3.27 to 6.31	0.50 <sup>††</sup>
Rivastigmine oral vs Placebo	0.66	-1.01 to 2.32	-4.31 to 5.65	0.25 <sup>††</sup>
Galantamine vs Placebo	0.60	-1.65 to 2.85	-4.65 to 5.83	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.59	0.09 to 5.12	-2.73 to 7.95	0.75 <sup>††</sup>
Memantine vs Placebo	0.89	-1.05 to 2.80	-4.17 to 5.90	0.38 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.82	0.19 to 5.44	-2.57 to 8.21	0.88 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.59	-1.93 to 7.16	-3.98 to 9.12	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.21	-1.49 to 5.95	-3.81 to 8.24	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
<i>Regression coefficient</i>	-0.02	-0.17 to 0.14		
<i>Common within-network between-study variance: <math>\tau^2 = 5.53</math></i>	3.71 to 8.48			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>				
<b>Serious Adverse Events (SAEs)‡</b>				
<b>Odds Ratio: Aggregate data and crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.04</math>, <math>I^2 = 20%</math> (0%, 47%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.58 (6, 0.733, 0.05)</i>				
<b>Odds Ratio: Aggregate data results**</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.00</math>, <math>I^2 = 0%</math> (0%, 42%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.29 (4, 0.682, 0.01)</i>				
<b>Odds Ratio: Crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.10</math>, <math>I^2 = 48%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: Low Risk of Bias for Allocation Concealment*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.08</math>, <math>I^2 = 37%</math> (0%, 64%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.19 (3, 0.53, 0.1)</i>				
<b>Odds Ratio: Low Risk of Bias for Incomplete Data*</b>				
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

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<i>Common within-network between-study variance: <math>\tau^2 = 0.02</math>, <math>I^2 = 10\%</math> (0%, 50%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.00 (1, 0.95, 0.04)</i>				
<b>Odds Ratio: Publicly-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = \text{N/A}</math> (each comparison includes a single study)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: Industry-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.05</math>, <math>I^2 = 25\%</math> (0%, 50%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.68 (6, 0.72, 0.07)</i>				
<b>Odds Ratio: Studies with Mild to Moderate baseline MMSE*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.09</math>, <math>I^2 = 29\%</math> (0%, 57%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.29 (5, 0.66, 0.13)</i>				
<b>Odds Ratio: Studies with Moderate to Severe baseline MMSE*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 72%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.90 (1, 0.09, 0.00)</i>				
<b>Odds Ratio: NMA of studies with IPD – available case analysis</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.13</math>, <math>I^2 = 50\%</math> (0%, 77%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, heterogeneity): N/A (no closed loops)</i>				
<b>Odds Ratio: Meta-regression, Trial Mean Age**</b>				
Donepezil vs Placebo	1.13	0.88 to 1.43	0.68 to 1.86	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.52	0.89 to 2.53	0.77 to 3.04	0.00 <sup>††</sup>
Galantamine vs Placebo	0.91	0.60 to 1.30	0.52 to 1.59	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.84	0.39 to 1.58	0.34 to 1.80	0.75 <sup>††</sup>
Memantine vs Placebo	0.74	0.48 to 1.07	0.39 to 1.26	0.75 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.92	0.38 to 1.89	0.33 to 2.15	0.62 <sup>††</sup>
Galantamine + Memantine vs Placebo	0.99	0.37 to 2.27	0.33 to 2.55	0.50 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.73	0.24 to 1.70	0.22 to 1.87	0.87 <sup>††</sup>
Placebo (reference)				0.37 <sup>††</sup>
<i>Regression coefficient (log-scale)</i>	-0.03	-0.08 to 0.02		
<i>Common within-network between-study variance: <math>\tau^2 = 0.02</math></i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for Age</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.10</math>, <math>I^2 = 48\%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				

<b>Odds Ratio: Meta-regression, Percent of Male Participants**</b>				
Donepezil vs Placebo	1.12	0.87 to 1.44	0.64 to 2.01	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.71	0.97 to 2.92	0.83 to 3.67	0.00 <sup>††</sup>
Galantamine vs Placebo	0.93	0.62 to 1.36	0.49 to 1.77	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.89	0.39 to 1.79	0.34 to 2.05	0.63 <sup>††</sup>
Memantine vs Placebo	0.64	0.37 to 1.00	0.29 to 1.21	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.88	0.35 to 1.88	0.30 to 2.13	0.63 <sup>††</sup>
Galantamine + Memantine vs Placebo	1.13	0.39 to 2.58	0.36 to 2.95	0.38 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.77	0.24 to 1.93	0.21 to 2.13	0.88 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): 3.57 (6, 0.735, 0.06)				
<b>Odds Ratio: NMA of studies with IPD adjusted for Percent of Male Participants</b>				
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): N/A (no closed loops)				
<b>Odds Ratio: NMA of studies with IPD adjusted for MMSE baseline</b>				
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): N/A (no closed loops)				
<b>Odds Ratio: NMA of studies with IPD adjusted for comorbidities</b>				
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): N/A (no closed loops)				
<b>Odds Ratio: NMA of studies with IPD adjusted for other medications</b>				
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): N/A (no closed loops)				
<b>Odds Ratio: Meta-regression, Study Duration**</b>				
Donepezil vs Placebo	1.12	0.87 to 1.43	0.63 to 1.95	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.76	1.00 to 2.99	0.88 to 3.68	0.00 <sup>††</sup>
Galantamine vs Placebo	0.92	0.62 to 1.36	0.50 to 1.69	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.87	0.39 to 1.70	0.34 to 1.96	0.63 <sup>††</sup>
Memantine vs Placebo	0.61	0.37 to 0.93	0.31 to 1.13	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.76	0.29 to 1.69	0.26 to 1.90	0.75 <sup>††</sup>
Galantamine + Memantine vs Placebo	0.98	0.34 to 2.26	0.30 to 2.53	0.50 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.75	0.25 to 1.81	0.23 to 1.97	0.75 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): 3.57 (6, 0.735, 0.06)				
<b>Odds Ratio: Meta-regression, Year of Publication**</b>				
Donepezil vs Placebo	1.05	0.79 to 1.38	0.61 to 1.77	0.38 <sup>††</sup>
Rivastigmine oral vs Placebo	1.68	0.98 to 2.77	0.85 to 3.37	0.00 <sup>††</sup>
Galantamine vs Placebo	0.91	0.61 to 1.32	0.50 to 1.64	0.63 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.92	0.40 to 1.84	0.36 to 2.04	0.63 <sup>††</sup>
Memantine vs Placebo	0.73	0.46 to 1.05	0.38 to 1.28	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.88	0.35 to 1.83	0.31 to 2.15	0.75 <sup>††</sup>

Galantamine + Memantine vs Placebo	1.24	0.43 to 2.85	0.39 to 3.25	0.25 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.88	0.24 to 2.24	0.24 to 2.42	0.75 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): 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)

‡ SAE: 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)

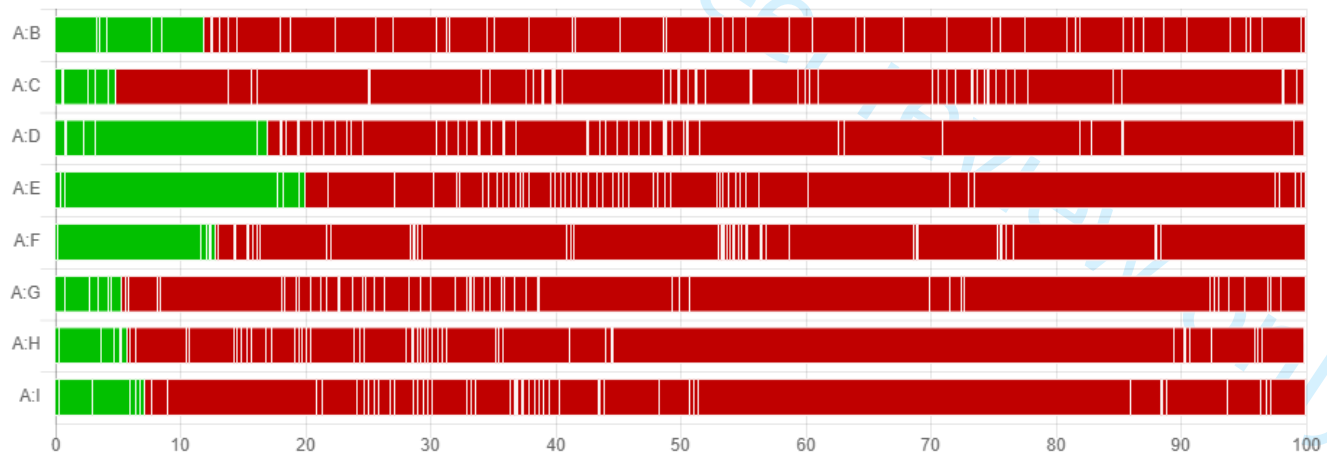
†† Analyses were conducted in OpenBUGS, and SUCRA values were calculated instead of P-scores

Appendix 18: CINeMA results

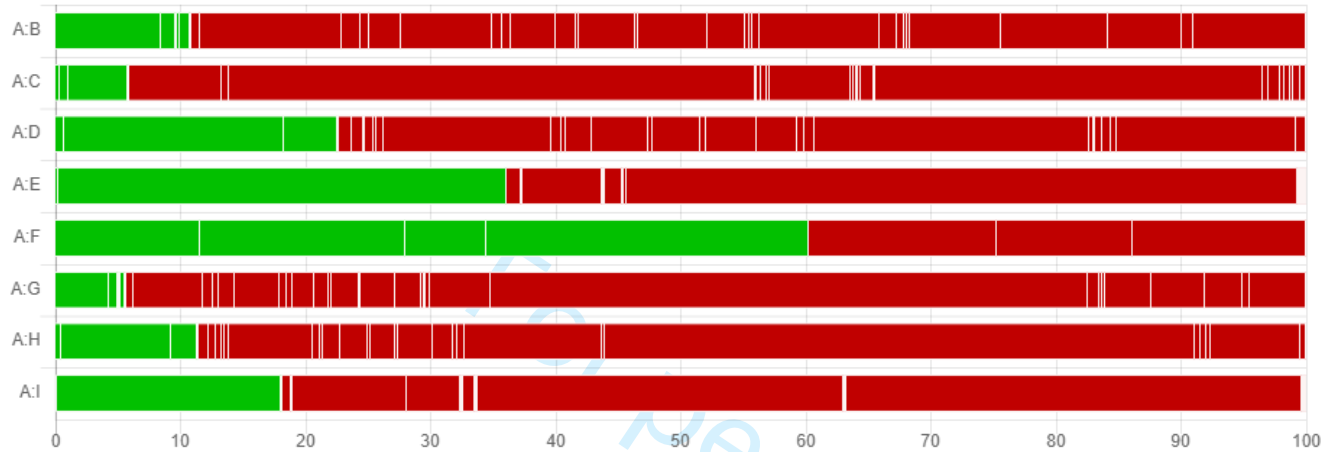
Risk of bias contributions: The bar chart shows the contributions of each piece of study to the network estimate

- 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



SAE 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

**SAE outcome**

Comparison	# of	Nature of	Type of	Within-study	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence	Downgrading
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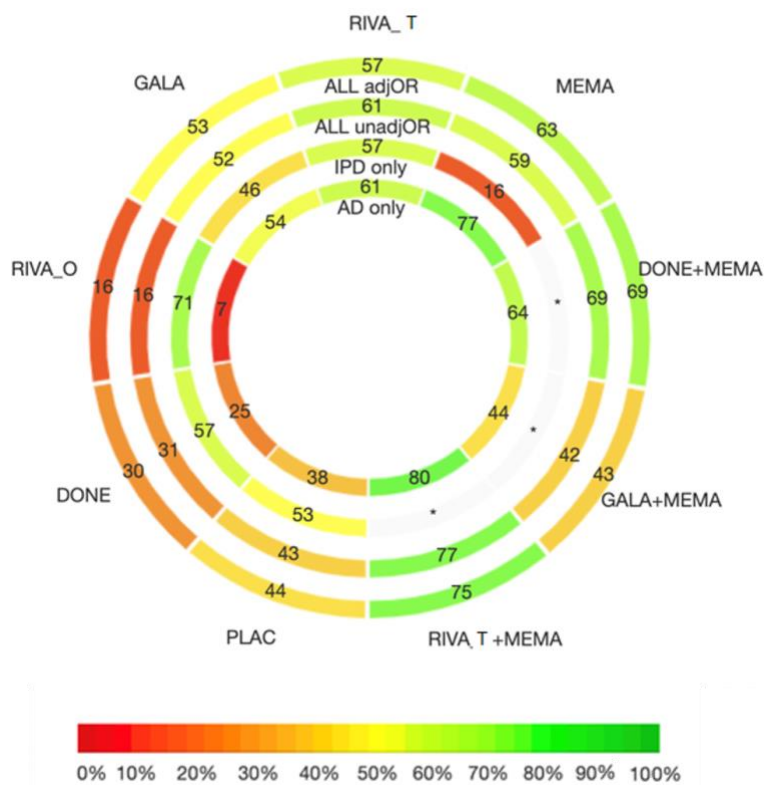
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	studies	evidence	data	bias (D1)	(D2)	(D3)	(D4)	(D5)	(D6)	rating	due to
DONE vs PLAC	16	Mixed	IPD+AD	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate	D1
RIVA_O vs PLAC	3	Mixed	IPD+AD	Major concerns	Undetected	No 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 19: Rank-heat plot for serious 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 20: Study definitions for serious 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	"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	"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	"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	NR
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	NR	NR
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		
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	NR	NR
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	NR	NR
Schmidt, 2008	NA	NA
Seltzer, 2004	NA	NA
Shao, 2015	NA	NA
Shimizu, 2015	NA	NA
Sole-Padulles, 2013	NA	NA
Tariot, 2000	NR	NR
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	NR	NR
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"

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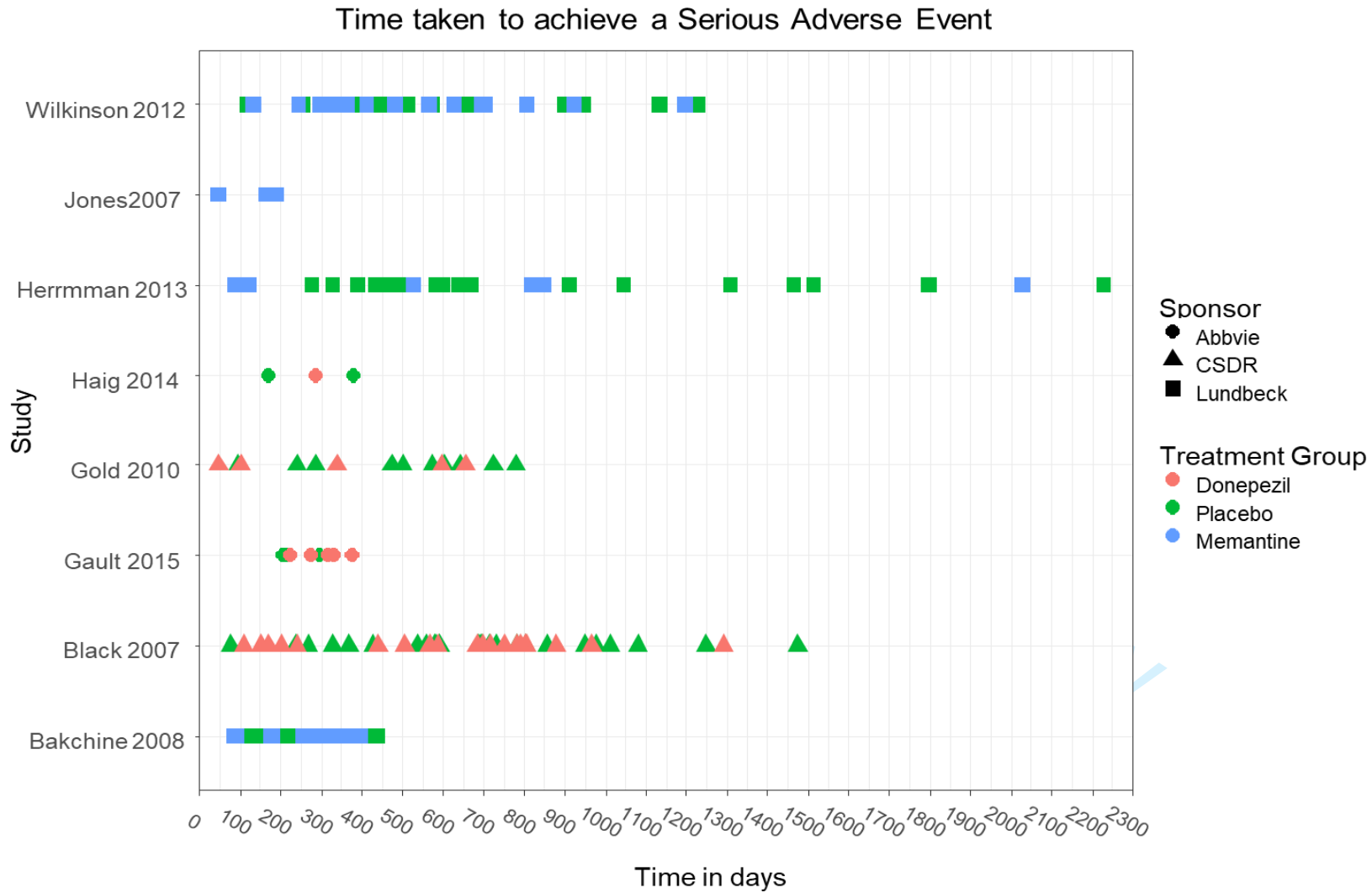
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**Notes:** <sup>a</sup>Unpublished data, <sup>b</sup>Non-English studies  
**Abbreviations:** CR, companion report; NA, not applicable; NR, not reported.

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For peer review only

Appendix 21: Time taken to achieve at least one serious adverse event using individual patient data



**Appendix 22: 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.

## PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
<b>Title</b>			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
<b>Abstract</b>			
Structured summary	2	Provide a structured summary including as applicable:	3-4
		<b>Background:</b> state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		<b>Methods:</b> report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		<b>Results:</b> provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		<b>Discussion:</b> state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		<b>Other:</b> report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
<b>Introduction</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	5
<b>Methods</b>			



Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	5, Appendix 1
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	5-6, Appendix 1
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	6, Appendix 1
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	N/A (see published protocol)
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	6, Appendix 1
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study). If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	6, Appendix 1
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	6, Appendix 1

IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	Appendix 1
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	6, Appendix 1
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	7, Appendix 1
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): <ul style="list-style-type: none"> <li>• Use of a one-stage or two-stage approach.</li> <li>• How effect estimates were generated separately within each study and combined across studies (where applicable).</li> <li>• Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for.</li> <li>• Use of fixed or random effects models and any other model assumptions, such as proportional hazards.</li> <li>• How (summary) survival curves were generated (where applicable).</li> <li>• Methods for quantifying statistical heterogeneity (such as <math>I^2</math> and <math>\tau^2</math>).</li> <li>• How studies providing IPD and not providing IPD were analysed together (where applicable).</li> <li>• How missing data within the IPD were dealt with (where applicable).</li> </ul>	7, Appendix 1
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	Appendix 1
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	6, Appendix 1

Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	7, Appendix 1
<b>Results</b>			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	7 – Figure 1
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	8 – Table 1, Appendix 5
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	8-9, Appendices 5 and 10
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	8-9 – Appendix 8
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Appendices 6 and 10 (full data can be provided by the

			first author)
Results of syntheses	21	<p>Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.</p> <p>When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.</p> <p>Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.</p>	9-11 – Appendix 15
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	9-11 - Appendix 12
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	9-11 - Appendices 16 and 17
<b>Discussion</b>			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	11-13
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	13-14
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	13-14
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	12-13

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Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	15

**A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.**

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## PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: <b>Background:</b> main objectives <b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . <b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> <b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings. <b>Other:</b> primary source of funding; systematic review registration number with registry name.	3-4
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5, Appendix 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	6, Appendix 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6, Appendix 1

1	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	N/A (see published protocol)
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4	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, Appendix 1
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7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, Appendix 1
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11	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, Appendix 1
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14	<b>Geometry of the network</b>	<b>S1</b>	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	7, Appendix 1
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21	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6, Appendix 1
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25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	7, Appendix 1
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses; and</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>	7, Appendix 1
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40	<b>Assessment of Inconsistency</b>	<b>S2</b>	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	7, Appendix 1
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44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6, Appendix 1
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47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network; and</i></li> <li>• <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i></li> </ul>	7, Appendix 1
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## RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 – Figure 1
<b>Presentation of network structure</b>	<b>S3</b>	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	9 – Figure 2
<b>Summary of network geometry</b>	<b>S4</b>	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	7-8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8 – Table 1, Appendix 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	8-9 – Appendix 8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Appendices 6 and 10 (full data can be provided by the first author)
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	9-11 – Appendix 15
<b>Exploration for inconsistency</b>	<b>S5</b>	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	9 - Appendix 14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	9-11 - Appendix 12
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i> ).	9-11 - Appendices 16 and 17



1	<b>DISCUSSION</b>			
2	Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	11-13
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6	Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	13-14
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14	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
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18	<b>FUNDING</b>			
19	Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	15
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PICOS = population, intervention, comparators, outcomes, study design.

\* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

# BMJ Open

## 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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Complete List of Authors:	Veroniki, Areti; St. Michael's Hospital, Knowledge Translation Program; Imperial College London, Department of Surgery & Cancer, Faculty of Medicine Ashoor, Huda; St Michael's Hospital, Knowledge Translation Program Rios, Patricia; St Michael's Hospital, Knowledge Translation Program Seitidis, Georgios; University of Ioannina, Department of Primary Education Stewart, Lesley; University of York, Centre for Reviews and Dissemination Clarke, Mike; Queen's University Belfast, Northern Ireland Hub for Trials Methodology Research Tudur-Smith, Catrin; University of Liverpool, Department of Biostatistics Mavridis, Dimitris ; University of Ioannina, Department of Primary Education Hemmelgarn, Brenda; University of Alberta, Department of Medicine Holroyd-Leduc, Jayna; University of Calgary, Department of Medicine Straus, Sharon; St Michael's Hospital, Knowledge Translation Program; University of Toronto, Department of Geriatric Medicine Tricco, Andrea; St Michael's Hospital, Knowledge Translation Program; University of Toronto, Dalla Lana School of Public Health
<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Neurology
Keywords:	STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY, Dementia < NEUROLOGY

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3 **Comparative safety and efficacy of cognitive enhancers for Alzheimer's**  
4 **dementia: A systematic review with individual patient data network**  
5 **meta-analysis**  
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10 Areti Angeliki Veroniki<sup>1,2\*</sup> PhD e-mail: [averoniki@uoi.gr](mailto:averoniki@uoi.gr)  
11 Huda M. Ashoor<sup>1</sup> BSc e-mail: [huda.ashoor@unityhealth.to](mailto:huda.ashoor@unityhealth.to)  
12 Patricia Rios<sup>1</sup> MSc e-mail: [patricia.rios@unityhealth.to](mailto:patricia.rios@unityhealth.to)  
13 Georgios Seitidis<sup>3</sup> MSc e-mail: [g.seitidis@uoi.gr](mailto:g.seitidis@uoi.gr)  
14 Lesley A. Stewart<sup>4</sup> PhD e-mail: [lesley.stewart@york.ac.uk](mailto:lesley.stewart@york.ac.uk)  
15 Mike Clarke<sup>5</sup> PhD e-mail: [m.clarke@qub.ac.uk](mailto:m.clarke@qub.ac.uk)  
16 Catrin Tudur Smith<sup>6</sup> PhD e-mail: [cat1@liverpool.ac.uk](mailto:cat1@liverpool.ac.uk)  
17 Dimitris Mavridis<sup>3</sup> PhD e-mail: [dmavridi@uoi.gr](mailto:dmavridi@uoi.gr)  
18 Brenda R. Hemmelgarn<sup>7</sup> PhD e-mail: [brenda.hemmelgarn@albertahealthservices.ca](mailto:brenda.hemmelgarn@albertahealthservices.ca)  
19 Jayna Holroyd-Leduc<sup>8</sup> MD e-mail: [jayna.holroyd-leduc@albertahealthservices.ca](mailto:jayna.holroyd-leduc@albertahealthservices.ca)  
20 Sharon E. Straus<sup>1,9</sup> MD e-mail: [sharon.straus@utoronto.ca](mailto:sharon.straus@utoronto.ca)  
21 Andrea C. Tricco<sup>1,10</sup> PhD e-mail: [andrea.tricco@unityhealth.to](mailto:andrea.tricco@unityhealth.to)  
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<sup>1</sup> Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

<sup>2</sup> Institute of Reproductive and Developmental Biology, Department of Surgery & Cancer, Faculty of Medicine, Imperial College, London, United Kingdom

<sup>3</sup> Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece

<sup>4</sup> Centre for Reviews and Dissemination, University of York, York, United Kingdom

<sup>5</sup> Northern Ireland Hub for Trials Methodology Research, Queen's University Belfast, Belfast, United Kingdom

<sup>6</sup> Department of Biostatistics, University of Liverpool, Block F, Waterhouse Building, 1-5 Brownlow Hill, Liverpool, L69 3GL, UK

<sup>7</sup> Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

<sup>8</sup> Department of Medicine, University of Calgary, Calgary, Alberta, Canada

<sup>9</sup> Department of Geriatric Medicine, University of Toronto, Toronto, Ontario, Canada

1  
2  
3 <sup>10</sup> Epidemiology Division & Institute of Health Policy, Management, and Evaluation, Dalla  
4 Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada  
5  
6  
7  
8  
9

10 **\*Corresponding Author:**

11 Dr. Areti Angeliki Veroniki, MSc, PhD

12 209 Victoria Street, East Building, Toronto, Ontario

13 M5B 1T8, Canada

14  
15  
16  
17  
18 Phone: 416-564-5015; Fax: 416-564-5735; Email: [averoniki@uoi.gr](mailto:averoniki@uoi.gr)  
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22 **Word count:** 4,076 (max 4000); 1 table; 4 figures; 2 additional files (21 appendices in  
23 additional file 1); 31 references  
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## 1 **Abstract**

2 Words: 367 (Max 300 words)

3 **Objective:** To examine the comparative efficacy and safety of cognitive enhancers by  
4 patient characteristics for managing Alzheimer's Dementia (AD).

5 **Design:** Systematic review and individual patient data (IPD) network meta-analysis  
6 (NMA)

7 **Data Sources:** MEDLINE, EMBASE, Cochrane Methodology Register, CINAHL,  
8 Ageline and Cochrane Central Register of Controlled Trials up to March 2016.

9 **Participants:** 80 randomized controlled trials (RCTs) including 21,138 adults with AD,  
10 and 12 RCTs with IPD including 6,906 patients.

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

13 **Data extraction and Synthesis:** We requested IPD from authors, sponsors and data  
14 sharing platforms. When IPD were not available, we used aggregate data. We appraised  
15 study quality with the Cochrane risk-of-bias. We conducted a two-stage random-effects  
16 IPD-NMA, and assessed their findings using CINeMA (Confidence in Network meta-  
17 analysis).

18 **Primary and Secondary Outcomes:** We included trials assessing cognition with the  
19 Mini-Mental State Examination (MMSE), and serious adverse events (SAEs).

20 **Results:** Our IPD-NMA compared 9 treatments (including placebo). Donepezil (mean  
21 difference [MD] = 1.41, 95% confidence interval [CI]: 0.51 to 2.32) and  
22 donepezil+memantine (MD = 2.57, 95% CI: 0.07 to 5.07) improved MMSE score (56  
23 RCTs, 11,619 participants; CINeMA score: moderate) compared with placebo. According  
24 to P-score, oral rivastigmine (odds ratio [OR] = 1.26, 95% CI: 0.82 to 1.94, P-score= 16%)  
25 and donepezil (OR = 1.08, 95% CI: 0.87 to 1.35, P-score= 30%) had the least favourable  
26 safety profile, but none of the estimated treatment effects were sufficiently precise when  
27 compared with placebo (45 RCTs, 15,649 patients; CINeMA score: moderate to high). For  
28 moderate to severe impairment, donepezil, memantine and their combination performed  
29 best, but for mild to moderate impairment donepezil and transdermal rivastigmine ranked  
30 best. Adjusting for MMSE baseline differences, oral rivastigmine and galantamine

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4 31 improved MMSE score, whereas when adjusting for comorbidities only oral rivastigmine  
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6 32 was effective.

7 33 **Conclusions:** The choice among the different cognitive enhancers may depend on patient's  
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9 34 characteristics. All cognitive enhancer regimens except for single-agent oral rivastigmine,  
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11 35 galantamine, and memantine, were clinically important for cognition (MMSE score greater  
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13 36 than 1.4). However, two thirds of the published RCTs were associated with high risk of  
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15 37 bias for incomplete outcome data, and IPD were only available for 15% of the included  
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17 38 RCTs.

18 39  
19 40 **Registration:** PROSPERO # CRD42015023507

20 41 **Funding:** This research was funded by the CIHR Drug Safety and Effectiveness Network  
21  
22 42 (grant number 137713).

23 43 **Keywords:** network meta-analysis; multiple treatments meta-analysis; individual  
24  
25 44 participant data; Nootropic Agents; Alzheimer Disease

### 26 27 28 29 30 45 **Strengths and limitations of this study**

- 31  
32 46 • This is one of the most comprehensive systematic reviews and network meta-analysis  
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34 47 of cognitive enhancers including individual patient data for Alzheimer's Dementia to  
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36 48 produce treatment recommendations by patient characteristics.
- 37 49 • We followed the methodologically rigorous guidelines in the Cochrane Handbook for  
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39 50 systematic reviews, and the CINeMA quality assessment guidelines.
- 40 51 • Access to individual patient data allowed us to 1) observe minor differences between  
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42 52 the original published results and our re-analysis, potentially due to differences in  
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44 53 imputation methods for missing data or because original studies have excluded some  
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46 54 patients, and hence have used a smaller sample size, 2) overcome potential reporting  
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48 55 bias, and 3) assess for potential effect modifiers that were not reported in the original  
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50 56 publications (e.g., comorbidities, additional medications) and explore for treatment-by-  
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52 57 covariate interactions on the patient-level.
- 53 58 • Two thirds of the included RCTs, were associated with high risk of bias for incomplete  
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55 59 outcome data due to attrition.
- 56 60 • We were unable to include individual patient data for all RCTs (only 15% of the  
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58 61 studies shared their individual patient data), highlighting potential availability bias.

## 62 Introduction

63  
64 Alzheimer's dementia (AD) is the most common type of dementia.<sup>1</sup> Patients living with AD have  
65 a lower quality of life due to deterioration in function, cognition, behavior, and mental health  
66 over time, as well as increased mortality.<sup>2</sup> Pharmacological treatment for AD predominantly  
67 consists of cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and the N-methyl-d-  
68 aspartate (NMDA) receptor antagonist, memantine. All three cholinesterase inhibitors and  
69 memantine are currently the only effective licensed treatments for dementia,<sup>3</sup> but their clinical  
70 effect can be small and there is no convincing evidence that they modify the disease process in  
71 AD.<sup>4</sup> Also, it is unclear whether galantamine, rivastigmine, or donepezil should be used by  
72 patients with severe AD, or whether memantine is the optimal treatment for severe AD.<sup>5</sup>

73  
74 In AD, disease severity and sex are potential effect modifiers. However, aggregate data and  
75 covariates of interest (e.g., sex, disease severity) are not consistently reported across randomized  
76 clinical trials (RCTs).<sup>6</sup> The use of IPD has several advantages, such as it allows for the  
77 exploration of the relationship between treatment effects and patient-level characteristics, and it  
78 overcomes restrictions in using the information reported in the publication among others. The  
79 aim of this study was to examine the comparative efficacy and safety of cognitive enhancers for  
80 patients with different characteristics, such as severities of AD and for females versus males  
81 through a systematic review and individual patient data (IPD) NMA. NMA is an extension of  
82 standard meta-analysis synthesizing different sources of evidence from a network of RCTs  
83 comparing different treatments within a single model. NMA can provide treatment effect  
84 estimates for treatment comparisons that have not studied in a head-to-head study.

## 85 Methods

86  
87 We reported our results according to the Preferred Items for Systematic Reviews and Meta-  
88 analysis (PRISMA) Statement for NMA and PRISMA-IPD.<sup>7,8</sup>

## 90 Protocol



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5 92 The research question and protocol were based on our previous systematic review and NMA.<sup>6</sup>  
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7 93 We registered our systematic review protocol with the prospective register of systematic reviews  
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9 94 (PROSPERO: CRD42015023507), and published our protocol.<sup>9</sup> Additional information is also  
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11 95 provided in Appendix 1 and Additional File 2. Herein, we briefly summarize our methods.  
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### 14 97 **Eligibility criteria**

15 98  
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17 99 We updated our previous systematic review,<sup>6</sup> using similar population, interventions,  
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19 100 comparators, study designs and time period (PICOST) criteria. The literature search was updated  
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21 101 from January 2015 to March 2016. We included published and English RCTs that assessed  
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23 102 cognition via the Mini-Mental State Examination (MMSE; efficacy and primary outcome) and/or  
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25 103 serious adverse events (SAE; safety outcome) in adults with Alzheimer's dementia.  
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### 28 105 **IPD collection process**

29 106  
30  
31 107 We contacted the corresponding author followed by the next-in-order author, as presented in  
32  
33 108 each eligible RCT, to obtain IPD. The author contact process was part of a RCT that our team  
34  
35 109 conducted to assess methods that may optimize response rates for IPD retrieval.<sup>10</sup> We also  
36  
37 110 contacted sponsors of eligible trials, as reported in the publications. We contacted industry  
38  
39 111 sponsors only, as we were not able to locate contact information for the majority of non-industry  
40  
41 112 sponsors (e.g., grants and university funding). If a study had multiple sponsors, we contacted all  
42  
43 113 of them. To further facilitate IPD access, we contacted the Clinical Study Data Request  
44  
45 114 (CSDR)<sup>11</sup> and Yale University Open Data Access (YODA) data sharing platforms.<sup>12</sup> If a data  
46  
47 115 provider was unable to provide IPD we noted the reason.  
48  
49 116

### 49 117 **Risk of bias and quality appraisal**

50 118  
51  
52 119 We appraised study quality using the Cochrane risk of bias tool.<sup>13</sup> To ensure data consistency<sup>8</sup>  
53  
54 120 we compared IPD with aggregate data reported in the publication. We assessed whether  
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3 121 randomization of patients was adequate (i.e., intervention and comparison groups were balanced  
4 for important patient characteristics), by comparing numbers and types of patients in each arm.  
5 122  
6  
7 123

8 124 When at least 10 studies were available for each treatment against placebo, publication bias and  
9 small-study effects were examined visually using the comparison adjusted funnel plot under the  
10 125 fixed-effect model.<sup>3</sup> When a funnel plot asymmetry was detected, we performed the Copas  
11 126 selection for the treatment comparisons that were informed by at least 10 studies and for which  
12 127 asymmetry was evident in the funnel plot. We explored the possibility that this was due to  
13 128 publication bias,<sup>14</sup> and made moderate assumptions about the probability of publication of the  
14 129 smaller and larger (in terms of standard error) studies. We assumed that the smallest study had a  
15 130 probability of publication equal to 40-50% and the largest study had a probability of 80-90%.  
16 131 Confidence in NMA findings was assessed for each outcome using CINeMA (Confidence in  
17 132 Network meta-analysis, see Appendix 1 for more details).<sup>15</sup>  
18  
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## 28 135 **Synthesis**

29 136  
30  
31 137 We performed a descriptive analysis using frequencies and distributions of the characteristics of  
32 138 the included patients and treatments. For each outcome, we present the network geometry  
33 139 according to IPD availability. We conducted a two-stage IPD analysis, whereby data were  
34 140 analysed separately in each trial in the first stage and the trial parameter estimates were  
35 141 synthesised in a random-effects meta-analysis or NMA in the second stage.  
36  
37  
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41

42 143 The summary treatment effects are presented using the odds ratio (OR) or mean difference (MD)  
43 144 along with their corresponding CIs and predictive intervals (PIs).<sup>16</sup> We ranked the interventions  
44 145 for each outcome using the P-scores (and SUCRAs [surface under the cumulative ranking curve]  
45 146 in meta-regression analysis), and present them in a rank-heat plot.<sup>17,18</sup>  
46  
47  
48  
49

## 50 147 **Patient and public involvement**

51  
52 148 Not applicable.  
53  
54  
55  
56  
57  
58  
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60

## 149 **Results**

### 150 **Literature search, study selection and IPD obtained**

151  
152 After screening 20,410 titles and abstracts and 1,968 full-text articles, 96 studies fulfilled the  
153 eligibility criteria; 80 unique studies and 16 companion reports (Figure 1a, Appendix 2).

154  
155 (Figure 1 here)

156  
157 Of the 80 RCTs, 55 reported at least one industry-sponsored funder (i.e. 40 studies reported a  
158 single industry-sponsor and 15 multiple industry-sponsors). In the remaining studies, 9 were  
159 publicly-sponsored and 16 did not report any information about funding. We requested IPD by  
160 contacting the corresponding authors for 80 RCTs that included 21,138 participants. None of the  
161 original authors shared their IPD. Fifteen commercial sponsors were then contacted and 6 (40%)  
162 sponsors shared their data through proprietary sponsor-specific platforms. The 6 sponsors were  
163 contacted for 46 RCTs (14,580 participants), and we obtained IPD for 30% (14 RCTs, 8,007  
164 participants) of these RCTs (1,058 total waiting days up to March 9, 2020). The study flow for  
165 obtaining IPD is depicted in Figure 1b.

166  
167 We were able to include 12 (6,906 patients) of 14 RCTs in our NMA due to incompleteness of  
168 provided IPD (Appendix 3). The number of studies with available/non-available IPD from each  
169 data provider along with reasons for non-availability of IPD are presented in Appendix 4.

170

### 171 **Study and patient characteristics**

172  
173 Most included studies (33%) were multi-national. The mean age of patients ranged from 61 to 86  
174 years. The majority of the RCTs included patients with mild-moderate AD (56%), although the  
175 diagnostic criteria used for AD varied widely (Table 1). The most frequent longest duration of  
176 follow-up was 24 weeks (24 RCTs, 30%; Appendix 5). Important patient characteristics, such as  
177 percent of male and dropout rates, were not balanced across groups in the RCTs with provided  
178 IPD (Appendix 6). Comparing study and patient characteristics of available and non-available

1  
2  
3 179 IPD when a study was industry-sponsored, we found differences in the year of study publication,  
4 study size, and absolute mean difference (Appendix 7).

5 180  
6 181  
7  
8 182 (Table 1 here)

9 183

### 11 184 **Risk of bias and IPD integrity**

12 185

13  
14 186 Using the Cochrane risk-of-bias tool, allocation concealment was at low risk of bias for 43% and  
15 blinding of participants and personnel was low for 64% of the RCTs (Appendix 8). One third of  
16 187 the RCTs had low risk of incomplete outcome data bias due to attrition and almost two thirds had  
17 high potential risk of “other” bias, specifically, funding bias. The other risk of bias item was  
18 188 scored as unclear for 32%. Overall risk of bias was comparable in studies with available and  
19 unavailable IPD (Appendix 9).

20 192

21 193 All IPD provided were checked for consistency and results from published RCTs were  
22 reproduced and provided in Appendix 10. High dropout rates were observed in the IPD;  
23 194 experiencing an adverse event was the most common reason for dropout. Despite the high  
24 dropout rates observed in the individual studies, there was no indication of correlation between  
25 195 age and dropout (Appendix 11). Comparison-adjusted funnel plot for MMSE suggested there is  
26 196 indication for small-study effects (see Appendix 12). In contrast to the standard meta-analysis  
27 197 (MD=1.65 95% CI (0.16, 3.14)), the Copas selection model estimated a pooled treatment effect  
28 198 for donepezil vs. placebo MD=1.87 95% CI (1.55, 2.20) with between-study variance  $\tau^2= 1.95$ ,  
29 200 and correlation coefficient -0.45 (-0.76, -0.01) reflecting the belief that the propensity for  
30 201 publication was associated with the observed effect size.

31 202

### 32 203 33 204 **Network meta-analysis**

34 205

35 206 In both MMSE and SAE outcomes, on average there were no important concerns regarding the  
36 207 transitivity and consistency assumptions (Appendices 13 and 14; design-by-treatment interaction  
37 208 model MMSE:  $\chi^2= 4.36$ , 13 degrees of freedom (df), P= 0.987; SAE:  $\chi^2= 3.57$ , 6 df, P= 0.735).

209 Below we present the main analysis results compared to placebo. Additional analyses are  
210 presented in Appendix 15-16). The network geometry is presented in Figure 2.

211  
212 (Figure 2 here)

### 213 214 **Cognition**

215  
216 The NMA for MMSE included 56 RCTs, 9 treatments (including placebo), and 11,619  
217 participants. Nine RCTs (3,625 patients) contributed IPD and 47 RCTs (7,994 patients)  
218 contributed aggregated data to the NMA. Two studies<sup>19,20</sup> did not report MMSE in the final  
219 publication, but in the retrieved IPD we were able to use data for this outcome.

#### 220 221 *NMA of studies with IPD and aggregate data*

222  
223 Studies in this NMA compared all available treatments. Donepezil (MD= 1·41, 95% CI: 0·51 to  
224 2·32) and donepezil+memantine (MD= 2·57, 95% CI: 0·07 to 5·07) were superior to placebo in  
225 terms of MMSE score (Appendix 15). PIs suggested results are not conclusive. Transdermal  
226 rivastigmine (MD= 2·11, 95% CI: -0·04 to 4·26), and the combinations donepezil+memantine,  
227 galantamine+memantine (MD= 2·24, 95% CI: -2·13 to 6·61), and transdermal  
228 rivastigmine+memantine (MD= 1·79, 95% CI: -1·70 to 5·27) were associated with a minimal  
229 clinically important difference (MCID; above 1·40)<sup>21</sup> (Figure 3a). However,  
230 donepezil+memantine had the highest likelihood of being the most effective in improving  
231 MMSE score (P-score range 79-80%, Figure 4). Confidence in NMA results was moderate  
232 (Appendix 17).

233 (Figure 3 here)

234 (Figure 4 here)

#### 235 236 *NMA of studies with aggregate data*

237  
238 Studies in this NMA compared all available treatments. Donepezil improved MMSE score  
239 significantly (MD= 1·55 95% CI: 0·41 to 2·68). The MCID results were in agreement with the

240 NMA of IPD and aggregate data, and donepezil+memantine (MD= 2.71, 95% CI: -0.17 to 5.60)  
241 was likely the most effective in improving MMSE score (P-score= 76%).

242

#### 243 *NMA of studies with IPD*

244

245 Studies in this NMA compared placebo, donepezil, oral rivastigmine, transdermal rivastigmine,  
246 galantamine, and memantine. Donepezil (MD= 0.70, 95% CI: 0.01 to 1.40) and transdermal  
247 rivastigmine (MD= 1.06, 95% CI: 0.04 to 2.08) were superior to placebo, but none was at a  
248 MCID. The most effective treatment was likely transdermal rivastigmine (P-score= 82%).

249

#### 250 *Additional analyses using IPD and aggregate data*

251

252 Overall, additional analyses using both IPD and aggregate data were in agreement with the  
253 findings of the main analysis (Appendix 16). Cognitive performance was better in patients with  
254 mild to moderate MMSE receiving donepezil (MD= 1.68 95% CI: 0.31 to 3.06, P-score= 69%)  
255 and most likely when receiving transdermal rivastigmine (MD= 2.74 95% CI: -0.68 to 6.16, P-  
256 score= 81%). In patients with moderate to severe MMSE the combination donepezil+memantine  
257 improved MMSE score significantly (MD= 2.49 95% CI: 1.55 to 3.44, P-score=100%), but oral  
258 rivastigmine deteriorated MMSE score significantly (MD= -1.00 95% CI: -1.87 to -0.12, P-  
259 score= 4%). Donepezil (MD= 1.31 95% CI: 0.66 to 1.96, P-score= 78%) and memantine  
260 (MD=0.69 95% CI: 0.07 to 1.31, P-score= 59%) also performed well for patients with moderate  
261 to severe cognitive impairment. However, PIs are wide suggesting results are not conclusive.

262

263 Accounting for the impact of the outlier studies, galantamine+memantine was the second-best  
264 cognitive enhancer (MD= 1.87 95% CI: 0.08 to 3.66, P-score=82%) after donepezil+memantine  
265 (MD= 2.04 95% CI: 1.03 to 3.05, P-score= 92%). Using only IPD adjusted for comorbidities  
266 suggested that oral rivastigmine improves MMSE score, but results are inconclusive as indicated  
267 in the prediction interval (MD= 0.88 95% CI: 0.31 to 1.45, 95% PI: -0.05 to 1.81, P-score=  
268 75%). Similarly, using IPD adjusted for cognitive impairment assessed with MMSE at baseline  
269 suggested that oral rivastigmine (MD= 0.88 95% CI: 0.31 to 1.45, P-score= 69%) and  
270 galantamine (MD= 0.76 95% CI: 0.34 to 1.18, P-score= 62%) improve MMSE score, but in a  
271 future study, results are only stable for galantamine.

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3 272  
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5 273 Heterogeneity in NMA was high (between-study variance = 5.75,  $I^2= 96%$ ) compared also to the  
6  
7 274 Rhodes et al.<sup>22</sup> empirical distribution (median 0.05, 95% range: 0.00 to 7.56). However,  
8  
9 275 heterogeneity decreased importantly when excluding outliers (between-study variance = 0.59,  
10  
11 276  $I^2= 73%$ ), when including only patients with moderate to severe AD (between-study variance =  
12  
13 277 0.18,  $I^2= 44%$ ), restricting to industry-sponsored trials (between-study variance = 0.16,  $I^2=$   
14  
15 278 43%), and when using IPD only (between-study variance = 0.12,  $I^2= 29%$ ).

16 279

### 17 280 *Serious adverse events*

18 281  
19  
20 282 A NMA was conducted on serious adverse events (study definitions are provided in Appendix  
21  
22 283 19) with 45 RCTs, 9 treatments (including placebo), and 15,649 patients (Figure 2b). In  
23  
24 284 particular, 12 RCTs (6420 patients) contributed to the NMA using their IPD and 33 RCTs (9229  
25  
26 285 patients) using their data on their aggregated form. The time taken to achieve at least one SAE  
27  
28 286 was available in 8 studies with available IPD and ranged between 45 and 2228 days (Appendix  
29  
30 287 20). Only one study included a patient with a SAE occurring earlier than the trial opening and  
31  
32 288 was excluded from the study.<sup>23</sup>

33 289

### 34 290 *NMA of studies with IPD and aggregate data*

35 291  
36  
37 292 Studies in this NMA compared all available treatments. According to P-score, oral rivastigmine  
38  
39 293 had the least favourable safety profile regarding SAE (OR= 1.26, 95% CI: 0.82 to 1.94, P-  
40  
41 294 score= 16%), followed by donepezil (OR= 1.08, 95% CI: 0.87 to 1.35, P-score= 30%) and  
42  
43 295 galantamine+memantine (OR= 1.03, 95% CI: 0.45 to 2.39, P-score= 43%), yet none of these  
44  
45 296 comparisons were statistically significant different from placebo (Figure 3b; Appendices 16, 18).  
46  
47 297 Confidence in NMA results ranged between moderate and high (Appendix 17).

48 298

### 49 299 *NMA of studies with aggregate data*

50 300  
51  
52 301 Studies in this NMA compared all available treatments. Results were mainly consistent with  
53  
54 302 NMA of IPD and aggregate data, but for memantine which was statistically significantly

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3 303 associated with lower odds of a SAE than placebo when using aggregate data only (OR 0·70,  
4 304 95% CI: 0·51 to 0·97, P-score= 77%),

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6 305

7  
8 306 *NMA of studies with IPD*

9 307

10  
11 308 Studies in this NMA compared placebo, donepezil, oral rivastigmine, transdermal rivastigmine,  
12 309 galantamine, and memantine. Results were on average consistent with NMA of IPD and  
13 310 aggregate data.

14  
15 311

16  
17 312 *Additional analyses using IPD and aggregate data*

18 313

19  
20 314 Additional analyses using both IPD and aggregate data, showed that memantine was statistically  
21 315 significantly associated with lower odds of a SAE than placebo when using study duration as a  
22 316 covariate (OR= 0·61, 95% CI: 0·37 to 0·93, P-score= 88%). Restricting to low risk of bias for  
23 317 incomplete outcome data, galantamine was associated with significantly lower odds of a SAE  
24 318 (OR= 0·69, 95% CI: 0·50 to 0·97, P-score= 80%).

25  
26 319

27 320 Heterogeneity in NMA was low (between-study variance = 0·04, I<sup>2</sup>= 22%) compared to the  
28 321 Turner et al.<sup>24</sup> empirical distribution (median 0·12, 95% range: 0·01 to 2·63). Heterogeneity  
29 322 decreased importantly when restricting to aggregate data (between-study variance = 0·00, I<sup>2</sup>=  
30 323 0%), low risk of bias for incomplete outcome data (between-study variance = 0·02, I<sup>2</sup>= 10%),  
31 324 patients with moderate to severe cognitive impairment (between-study variance = 0·00, I<sup>2</sup>= 0%),  
32 325 and when adjusting for study duration (between-study variance = 0·03), year of publication  
33 326 (between-study variance = 0·02), mean age (between-study variance = 0·02) or sex (between-  
34 327 study variance = 0·03).

## 35 36 37 38 39 328 **Discussion**

40 329

41 330 We compared the efficacy and safety of cognitive enhancers regarding MMSE and SAE  
42 331 outcomes to update our previous systematic review<sup>6</sup> and included studies with both aggregate  
43 332 data and IPD. Our results are in agreement with our previous systematic review,<sup>6</sup> and show that  
44 333 donepezil+memantine, donepezil alone and transdermal rivastigmine were the most effective



1  
2  
3 334 treatments for improving MMSE score. However, heterogeneity was a major concern, and this  
4 was also captured by PIs. According to the P-score intervention ranking, both  
5 335 donepezil+memantine and transdermal rivastigmine had a favourable safety profile regarding  
6 336 SAE, whereas the therapy with the least favourable profile was oral rivastigmine followed by  
7 337 donepezil. However, none of the estimated treatment effects were sufficiently precise when  
8 338 cognitive enhancers were compared with the placebo group. CINeMA suggested that within-  
9 339 study bias and reporting bias were the highest concerns for the MMSE outcome, whereas within-  
10 340 study bias and imprecision of effect estimates were the highest concerns for the SAE outcome.  
11 341  
12 342

13  
14  
15 343 Overall, the choice among the different cognitive enhancers may depend on the patient's  
16 344 characteristics. In participants with moderate to severe cognitive impairment (defined by  
17 345 MMSE), a larger improvement in cognitive performance was observed for donepezil and  
18 346 memantine, and their combination (donepezil+memantine), and these efficacy-related results are  
19 347 expected to also be reflected when a future study becomes available. The least effective  
20 348 cognitive enhancer in participants with moderate to severe cognitive impairment was oral  
21 349 rivastigmine. For patients with mild to moderate impairments based on MMSE scores, donepezil  
22 350 and transdermal rivastigmine were most likely the best performing cognitive enhancers. For  
23 351 patients with moderate to severe cognitive impairment, cognitive enhancers were well tolerated.  
24 352 For patients with mild to moderate cognitive impairment, all except for memantine and its  
25 353 combination with transdermal rivastigmine, were associated with increased odds of a SAE, yet  
26 354 none of these results reached statistical significance. Overall, memantine was associated with  
27 355 lower odds of a SAE than placebo, yet this was statistically significant only in the subnetwork  
28 356 analysis including aggregate data (i.e., studies without IPD) and the meta-regression analysis  
29 357 using study duration as a covariate. However, acknowledging for heterogeneity in the network,  
30 358 prediction intervals suggested that results are inconclusive and the odds of SAE could not be  
31 359 differentiated between memantine and placebo. Of note, the accuracy of SAE reporting may be  
32 360 impacted by the degree of cognitive impairment. Using IPD only and adjusting for MMSE  
33 361 baseline differences, (as shown in Appendix 16, Mean Difference: NMA of studies with IPD  
34 362 adjusted for baseline cognitive impairment), oral rivastigmine and galantamine improved MMSE  
35 363 score, whereas when adjusting for comorbidities only oral rivastigmine was effective, but results  
36 364 can change in a future study. Considering a MCID equal to 1·4,<sup>21</sup> all cognitive enhancer

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2  
3 365 regiments except for single-agent oral rivastigmine, galantamine, and memantine, were clinically  
4  
5 366 important for cognition. Our results did not differ by participant characteristics sex, age, and  
6  
7 367 other medications, or by study characteristics, study duration and year of publication. However,  
8  
9 368 these findings might be due to low power since meta-regression analyses depend on the number  
10  
11 369 and size of studies, magnitude of the relationship between the covariate and effect size, along  
12  
13 370 with its precision and heterogeneity.<sup>25</sup>

14 371  
15 372 To the best of our knowledge, our study was the first to add IPD in a NMA of cognitive  
16  
17 373 enhancers for patients with Alzheimer's Dementia to produce treatment recommendations by  
18  
19 374 patient characteristics. We followed the methods guidelines in the Cochrane Handbook for  
20  
21 375 systematic reviews,<sup>26</sup> the reporting guidelines in the PRISMA-NMA and PRISMA-IPD  
22  
23 376 statements,<sup>7,8</sup> and the CINeMA quality assessment guidelines.<sup>15</sup> Compared to previous  
24  
25 377 systematic reviews, we included a larger number of studies and/or studies with shared IPD,  
26  
27 378 compared in a wider range of cognitive enhancers.<sup>6,27</sup> Our results are in agreement with previous  
28  
29 379 studies overall. Access to IPD allowed us to observe minor differences between the original  
30  
31 380 published results and our re-analysis. An explanation in these differences may be that many  
32  
33 381 studies used the last-observation-carried-forward imputation method, whereas we used the  
34  
35 382 available case analysis when assessing MMSE. Another potential explanation might be that  
36  
37 383 original studies excluded some patients, and hence used a smaller sample size.

38 384  
39 385 Comparing NMA, results between aggregate data and IPD were in agreement. The only  
40  
41 386 difference was observed in transdermal rivastigmine that was associated with a MCID of MMSE  
42  
43 387 in the aggregate data NMA compared to the IPD NMA, yet a statistically significant  
44  
45 388 improvement was achieved in the IPD NMA. The inclusion of IPD in our NMA, allowed us to  
46  
47 389 overcome potential reporting bias and to include IPD for 1) a study that we previously were  
48  
49 390 unable to include since arm-level data were not reported in the RCT publication,<sup>23</sup> and 2) two  
50  
51 391 studies that did not report MMSE results in their publications.<sup>19,20</sup> The use of IPD also allowed  
52  
53 392 us to assess for potential effect modifiers that were not reported in the original publications (e.g.,  
54  
55 393 comorbidities, additional medications) and explore for treatment-by-covariate interactions on the  
56  
57 394 patient-level. Several challenges were encountered during the IPD request from sponsors,  
58  
59 395 showing that repositories are not a panacea (Appendix 21).

1  
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3 396  
4  
5 397 An important finding of our review is that the two thirds of the published RCTs, were associated  
6  
7 398 with high risk of bias for incomplete outcome data due to attrition, and the majority of these  
8  
9 399 RCTs used the last-observation-carried-forward technique for missing data. This approach may  
10  
11 400 bias results favouring cognitive enhancers, since the dropout rates were greater in the treatment  
12  
13 401 group compared to the placebo group in 63% of the included studies and because dementia is a  
14  
15 402 progressive disease. Of the 27 studies comparing treatment against placebo and reporting the  
16  
17 403 number of dropouts, 17 studies had a greater dropout rate in the treatment group (treatment  
18  
19 404 group: median dropout rate= 28% IQR [17% to 39%]; placebo group: median dropout rate= 21%  
20  
21 405 IQR [15% to 31%]). Last-observation-carried-forward is an inappropriate imputation method for  
22  
23 406 Alzheimer's Dementia studies, since it ignores expected deterioration of the patient's condition  
24  
25 407 and stabilizes the outcome at the value observed at the time of dropout (i.e., the last  
26  
27 408 observation).<sup>28</sup> Restricting to low risk of attrition bias studies, we found that galantamine was  
28  
29 409 significantly associated with decreased odds of experiencing a SAE.

30  
31 411 Our study has limitations worth mentioning. First, we were unable to include IPD for all eligible  
32  
33 412 studies (only 15% of the included RCTs shared their IPD), highlighting potential availability bias  
34  
35 413 for IPD. However, recent simulations have shown that combining IPD and aggregate data in a  
36  
37 414 NMA can significantly improve precision, reduce bias, and increase information compared to  
38  
39 415 NMA relying on aggregated data alone.<sup>29</sup> Second, missing data is a big concern in the published  
40  
41 416 RCTs for Alzheimer's Dementia. To assess the impact of missing data in our NMA, we applied  
42  
43 417 the informative missingness of difference in means.<sup>30</sup> Third, the lack of studies in certain  
44  
45 418 treatment comparisons may have affected the P-score calculation and treatment ranking. In  
46  
47 419 particular, polytherapies were informed by maximum two studies, and ranking may have been in  
48  
49 420 favour of the complex intervention group with the smaller number of studies.<sup>31</sup> For example, in  
50  
51 421 MMSE the polytherapies including memantine in conjunction with one of the three treatments  
52  
53 422 donepezil, galantamine, transdermal rivastigmine had a P-score  $\geq 60\%$ , but these all had wide  
54  
55 423 95% CIs for MD. As such, ranking should be interpreted with caution and along with the  
56  
57 424 estimated effect sizes and their uncertainty measures. Fourth, the comparison-adjusted funnel  
58  
59 425 plot for MMSE suggested there is an indication for small-study effects pointing to the treatment  
60  
61 426 being better, and results should be interpreted with caution. Overall, MMSE score is only a

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3 427 surrogate maker for determining the impact of treatments on dementia. A full assessment that  
4  
5 428 considers the potential impact of treatments on cognition, function and behavioural symptoms  
6  
7 429 needs to be considered within the clinical context. Fifth, differences in patient characteristics,  
8  
9 430 such as sex, were observed in the RCTs with provided IPD, which increased heterogeneity across  
10  
11 431 studies. To account for these differences, we used the fully adjusted treatment effect estimates in  
12  
13 432 the IPD analyses and the primary NMA analysis. Also, at the NMA level, we found that on  
14  
15 433 average there were no important differences across treatment comparisons to threaten the  
16  
17 434 transitivity assumption. Sixth, there are clinically important limitations associated with this  
18  
19 435 review, including consistent definition of outcome measures across studies, a well-established  
20  
21 436 MCID for the MMSE score, lack of consideration of drug doses due to inconsistent reporting and  
22  
23 437 data availability bias that we were unable to overcome (15% of the studies shared their IPD).  
24  
25 438 Future studies are needed to establish ranking efficacy in drug doses and combination of  
26  
27 439 interventions across different disease severity categories. Seventh, the literature searches were  
28  
29 440 conducted 5 years ago and additional relevant studies may be available. However, obtaining IPD  
30  
31 441 in a timely manner was very challenging and required more time than anticipated (challenges to  
32  
33 442 obtain IPD are outlined in Appendix 21). Similar to all systematic reviews, the evidence should  
34  
35 443 be regularly updated.

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37 444  
38 445 We expect that our findings will increase scientific knowledge, because people with Alzheimer's  
39  
40 446 Dementia require personalized medicine to optimize their healthcare. Well-conducted meta-  
41  
42 447 analyses of IPD are considered the 'gold-standard' and influence patient care since patient-level  
43  
44 448 data can be provided to facilitate tailored decision making. However, results from meta-analyses  
45  
46 449 of IPD are likely subject to retrieval bias and awareness of these limitations and their potential  
47  
48 450 impact on findings is required.

## 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. 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 categorized data, appraised quality, and edited the manuscript. SES and ACT interpreted results and edited the manuscript. ACT and HMA contacted authors. LAS, MC, CTS, DM, BRH, JHL provided input into the design, interpreted results, and edited the manuscript. All authors read and approved the final manuscript.

## Declaration of interests

The authors declare that they have no competing interests.

## Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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54 506 DEVELOPMENT, L.L.C.. The interpretation and reporting of research using this data are solely

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4 588 **Figure Captions**

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6 590 **Figure 1.** Flow diagram for study inclusion in the review (a) and studies retrieved with  
7 591 individual patient data (b).  
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9 593 **Figure 2.** Network diagrams for (a) MMSE and (b) SAE outcomes. The size of each node and  
10 594 line indicates the number of studies included in each treatment comparison. The number of  
11 595 studies per treatment comparison is presented on each edge, and the number of studies with  
12 596 individual patient data (IPD) is depicted in a parenthesis. Orange coloured edges are informed by  
13 597 both IPD and aggregate data, whereas black coloured edges are informed by aggregate data only.  
14 598

15 599 **Figure 3.** Forest plot of network meta-analysis (NMA) results for all cognitive enhancers versus  
16 600 placebo in (a) MMSE outcome, and (b) SAE outcome. NMA results are presented for i)  
17 601 aggregate data (AD) and fully adjusted results from studies with available individual patient data  
18 602 (IPD), ii) AD and crude results from studies with available IPD, iii) AD only (studies with  
19 603 available IPD are not included in the analysis), and iv) crude results from individual studies with  
20 604 individual patient data (IPD).  
21 605

22 606 **Figure 4.** Rank-heat plot of P-scores for 9 treatments, including placebo, studied in randomized  
23 607 clinical trials with patients with Alzheimer's Dementia assessing MMSE. Circles from inside out  
24 608 present results for different network meta-analyses including: i) aggregate data (AD) only  
25 609 (studies with available IPD are not included in the analysis), ii) crude results from individual  
26 610 studies with individual patient data (IPD), iii) AD and crude results from studies with available  
27 611 IPD, and iv) AD and fully adjusted results from studies with available IPD. Numbers within each  
28 612 sector correspond to the P-score values as calculated in each model.  
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613 **Tables**

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<b>Table 1· Study and patient characteristics</b>		
	<b>AD (N=80)</b>	<b>IPD (N=12)</b>
<b>Total # participants</b>	21,138	5839
<b>Longest duration of follow-up in weeks: mean (range)</b>	28·28 (8 - 208)	29·33 (12 - 104)
<b>Mean number of patients (range)</b>	264·23 (14 - 2,045)	486·58 (123 - 2,045)
<b>Mean age in years (range)</b>	74·64 (61 - 85·7)	73·94 (70·4 - 78)
<b>Mean % Female (range)</b>	61·35 (3 - 89)	62·76 (53·68 - 81)
<b>Country of conduct: frequency (%)</b>		
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)	-
United Kingdom	6 (7·50)	1 (8·33)
United States	15 (18·75)	-
Multi-national	26 (32·50)	9 (75·00)
<b>Interventions examined: frequency*</b>		
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)
<b>Effectiveness outcomes reported: frequency*</b>		
Mini-Mental State Examination	57 (71·25)	6 (50·00)
Serious Adverse Events	46 (57·50)	12 (100·00)
<b>Funding</b>		
Industry-sponsored	48 (60·00)	12 (100·00)
Publicly-sponsored†	9 (11·25)	-
Mixed	7 (8·75)	-
Not Reported	16 (20·0)	-
<b>Severity of Alzheimer's dementia: frequency (%)</b>		
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)
<b>Diagnostic criteria for Alzheimer's dementia: frequency*</b>		
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)
Magnetic Resonance Imaging/Computerized Tomography	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)

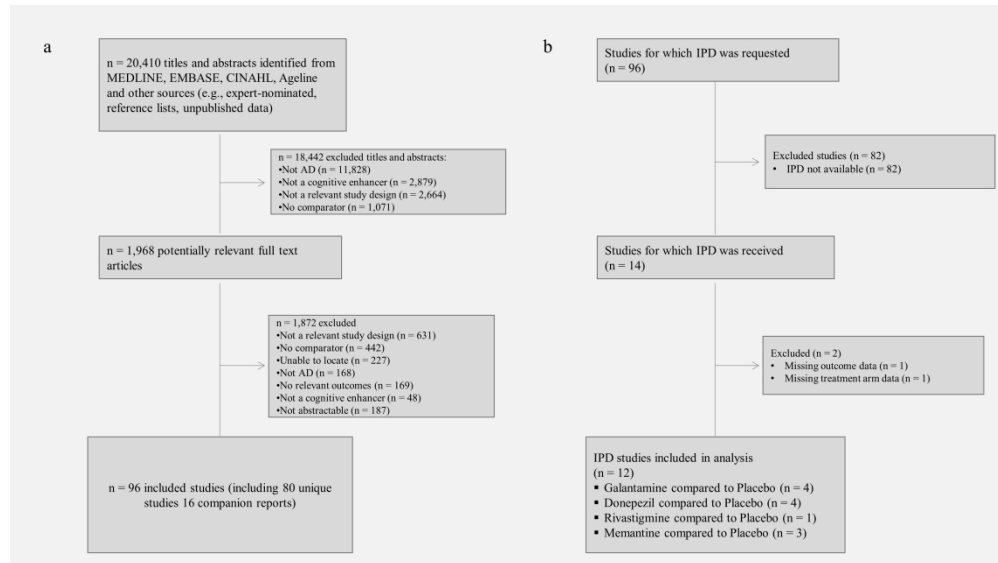
**Abbreviations:** -, not applicable

\* 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

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25 Figure 1. Flow diagram for study inclusion in the review (a) and studies retrieved with individual patient data  
26 (b).

27 338x190mm (300 x 300 DPI)

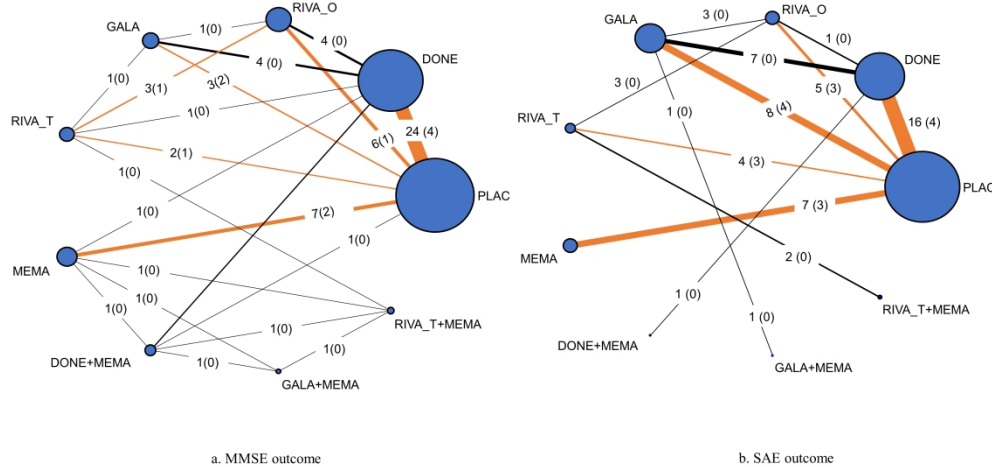


Figure 2. Network diagrams for (a) MMSE and (b) SAE outcomes. The size of each node and line indicates the number of studies included in each treatment comparison. The number of studies per treatment comparison is presented on each edge, and the number of studies with individual patient data (IPD) is 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.

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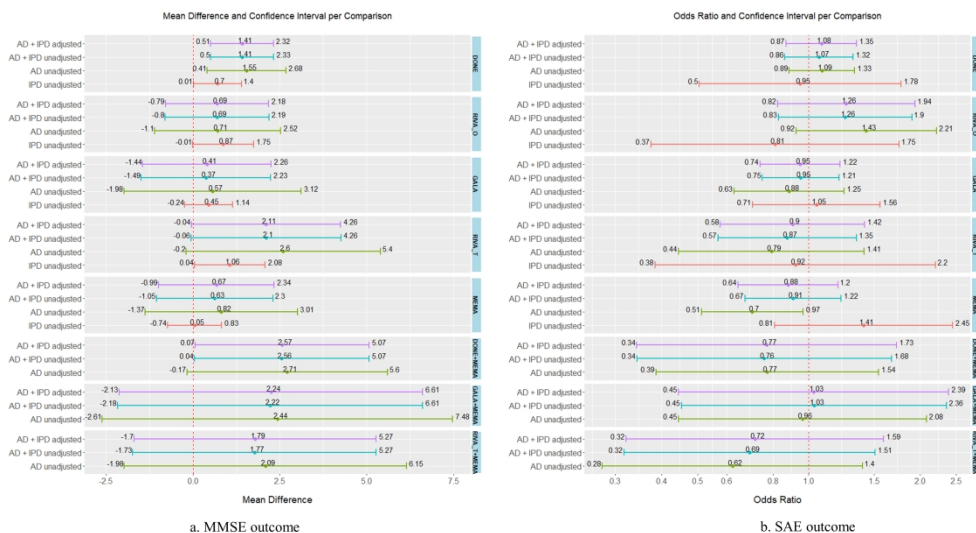


Figure 3. Forest plot of network meta-analysis (NMA) results for all cognitive enhancers versus placebo in (a) MMSE outcome, and (b) SAE outcome. NMA results are presented for i) aggregate data (AD) and fully adjusted results from studies with available individual patient data (IPD), ii) AD and crude 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 individual patient data (IPD).

338x190mm (300 x 300 DPI)



Figure 4. Rank-heat plot of P-scores for 9 treatments, including placebo, studied in randomized clinical trials with patients with Alzheimer’s Dementia assessing MMSE. 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.

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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***

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

### *Eligibility criteria, search strategy and study selection*

We considered a SAE as defined in the individual trials, specifically, when an event led to disability or hospitalization or was life-threatening or fatal. Study definitions for a SAE were also abstracted. 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,<sup>4</sup> 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.<sup>10</sup> 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:<sup>1</sup> 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.<sup>2</sup> 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 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 SAEs, 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.<sup>3</sup> 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 the *netfunnel* command in Stata to produce the comparison-adjusted funnel plot.<sup>4</sup> For imprecision,

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

### 7 8 *Statistical Analysis*

9  
10 We performed a descriptive analysis using frequencies and percentages of the discrete characteristics of  
11 the included patients and treatments of the eligible studies. We explored the distributions of the continuous  
12 patient characteristics per outcome and treatment group using means and standard deviations. For studies not  
13 providing outcome results for a certain outcome, we presented distributions of the available and requested  
14 patient characteristics, whenever available. Outliers for each patient characteristic were also explored in each  
15 study dataset using boxplots. We also recorded the number of missing participants per treatment group and  
16 overall. We compared the characteristics of the unavailable and the available by the sponsors' studies. In  
17 particular, we explored whether these were well-conducted according to overall risk of bias, and compared  
18 distributions of mean participant age, publication year, study duration, study size, percent male, and magnitude  
19 of treatment effect, to assess for potential bias in IPD sharing. We conducted a two-stage analysis for both  
20 standard meta-analysis and NMA. The network geometry was explored through the presentation of network  
21 plots.

### 22 23 *First stage*

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

31  
32 Initially, we did not adjust for any of the patient characteristics provided, but in a subsequent analysis  
33 we included patient-level covariates with as many interaction terms in the model as the patient characteristics  
34 were provided (considering only the ones we have asked for). For each study, we obtained the adjusted odds  
35 ratio (OR) for binary data and adjusted mean difference (MD) for continuous data, along their corresponding  
36 95% confidence interval (CI). We adjusted for any of the following variables that were available in each study:  
37 age, sex, severity of Alzheimer's disease (e.g., baseline Mini-Mental State Examination [MMSE] level),  
38 presence of behavioural disturbance, comorbidity, and other medications. The first stage of the IPD analyses  
39 were conducted in RStudio,<sup>5</sup> which was available in data providers. Additional medications and comorbid  
40 conditions were grouped into broader categories according to their clinical relevance to increase power in our  
41 analysis (e.g., grouped medications as anti-psychotics, anti-depressants, and cognitive enhancers, as well as  
42 comorbid conditions as psychiatric, neurological, and cardiac disorders). Eligible studies with insufficient data  
43 to derive a pairwise estimate for NMA were summarized descriptively without performing a statistical analysis.

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

48  
49 We synthesized IPD at the first stage in four different proprietary sponsor-specific platforms. Analyses  
50 were conducted in the RStudio using different R versions<sup>5</sup> according to what was provided in each sponsor's  
51 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  
52 Lundbeck.

### 53 54 *Second stage*

55 Since we were not successful in obtaining IPD for all eligible studies, we combined both IPD and aggregate data  
56 in a single meta-analysis or NMA model. Both IPD and aggregate data studies shared the same amount of  
57 heterogeneity. In both meta-analysis and NMA models, we combined the adjusted IPD estimates with the  
58 aggregate data (main analysis). As a secondary analysis, we combined the unadjusted estimates from retrieved  
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3 IPD with the evidence provided by the aggregated data studies in a joint NMA model. A common-within network  
4 between-study variance was assumed across comparisons for all NMA models.<sup>6</sup> We estimated the between-study  
5 variance using the DerSimonian and Laird<sup>7</sup> method and compared it with the relevant distributions provided by  
6 Turner et al<sup>8</sup> and Rhodes et al<sup>9</sup> to assess heterogeneity. We also calculated  $I^2$  on the NMA level to quantify overall  
7 heterogeneity and inconsistency in each outcome.  
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10 To assess the validity of the transitivity assumption for each outcome, we assessed the distribution of  
11 potential effect modifiers (e.g., age, sex) across treatment comparisons in each network.<sup>10-12</sup> We visually inspected  
12 similarity and assessed whether these characteristics were likely to modify the treatment effect. We evaluated the  
13 consistency assumption using the design-by-treatment interaction model<sup>13,14</sup> and the loop-specific method.<sup>15,16</sup> In  
14 the presence of statistically significant inconsistency, we checked the data for discrepancies and if none were  
15 identified, we planned to conduct subgroup NMA or network meta-regression analysis adjusting for potential  
16 variables influencing the results.  
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21 We conducted additional NMA analyses for all potential effect modifiers requested from data  
22 providers. If relevant data were not available in the IPD, we used aggregate data of the relevant publications.  
23 Additional NMA analyses included: 1) subgroup analysis for industry vs. publicly sponsored studies, for studies  
24 with available IPD vs. studies with aggregate data (unadjusted estimates), and for AD severity, classified  
25 according to MMSE scores using the National Institute for Health and Care Excellence categories: mild (21–  
26 24), moderate (10–20), severe (<10),<sup>17</sup> 2) network meta-regression accounting for study duration, year of  
27 publication, mean age, and sex (% of male participants) effect modifiers separately and assuming a common  
28 regression coefficient across comparisons (studies with aggregate data were used only; studies with available  
29 IPD were pooled in a NMA separately adjusted for available covariates at first stage), 3) sensitivity analysis  
30 including studies with low risk of bias for allocation concealment and incomplete outcome data items, as these  
31 items may have an important impact on the meta-analysis results according to our previous NMA,<sup>18</sup> and 4) the  
32 ‘informative missingness difference of means’ (IMDoM) imputation method<sup>19</sup> for MMSE for the aggregate data  
33 studies to assess the impact of missing data in our NMA. In all additional NMA analyses, we used the adjusted  
34 effect estimates derived from the IPD within-study analysis and the aggregate data extracted from the eligible  
35 publications. Network meta-regression was performed in a Bayesian setting using OpenBUGS version 3.2.3,  
36 non-informative priors for all parameters in the model and a half-normal prior for the between standard  
37 deviation. We compared the results of the additional models by evaluating the treatment effect estimates and  
38 ranking statistics, as well as monitoring the reduction in the between-study variance.  
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40 Meta-analysis and NMA at the 2<sup>nd</sup> stage were conducted in the RStudio using R version 3.6.2 and the *meta*<sup>20</sup> and  
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## Appendix 2: Studies included in the systematic review

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

A study<sup>1</sup> of 859 participants comparing transdermal rivastigmine vs. placebo included only IPD for the placebo arm. Another study<sup>2</sup> 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 SAE 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 cm<sup>2</sup> group, 287 to the rivastigmine patch 10 cm<sup>2</sup> 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
SAE, 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 SAE 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 SAE 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
SAE, 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%)			

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

<sup>1</sup>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/Allergan	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-Padullles, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs	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, SAEs, 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, SAEs, Headaches, Falls	Industry-sponsored	Not reported; December 2003; Not reported	Yes; NA
Burns, 2011	UK	62; 12	Donepezil, Placebo/no treatment; NPI, SAEs	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, SAEs, 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, SAEs	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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs	Industry- sponsored	Not reported; February 2007; 2:2:2:1	Yes; Available
Greenberg, 2000	USA	103; 24	Donepezil, Placebo/no treatment; ADAS-cog, SAEs, 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, SAEs			
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, SAEs	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, SAEs	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, SAEs	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, SAEs, Headaches	NA	Not reported; Not reported; Not reported	No; NR
Homma, 2008	Japan	267; 24	Donepezil, Placebo/no treatment; ADCS-ADL, CIBIC-plus, Mortality, SAEs, 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, SAEs	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, SAEs, 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, SAEs	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, SAEs, 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, SAEs	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, SAEs, 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, SAEs, 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; SAEs, 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, SAEs, 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, SAEs, Diarrhea	Publicly- sponsored + Industry- sponsored	Not reported; August 1998; Not reported	No; No response from sponsor
Rockwood, 2001	Australia, Canada, Great Britain, New Zealand, South Africa, USA	386; 12	Galantamine, Placebo/no treatment; ADAS-cog, NPI, CIBIC-plus, Mortality, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs	Industry- sponsored	Not reported; April 2007; Not reported	No; Cannot share data
Scarpini, 2011	Italy	139; 96	Galantamine, Placebo/no treatment; Mortality, SAEs	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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, 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, SAEs, Headaches, Vomiting, Diarrhea, Nausea	Industry-sponsored	Not reported; November 2003; Not reported	No; No response from sponsor

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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, SAEs	Industry- sponsored	Not reported; Not reported; Not reported	No; IPD not available

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## 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 SAE	Missing data in SAE 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 SAE
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

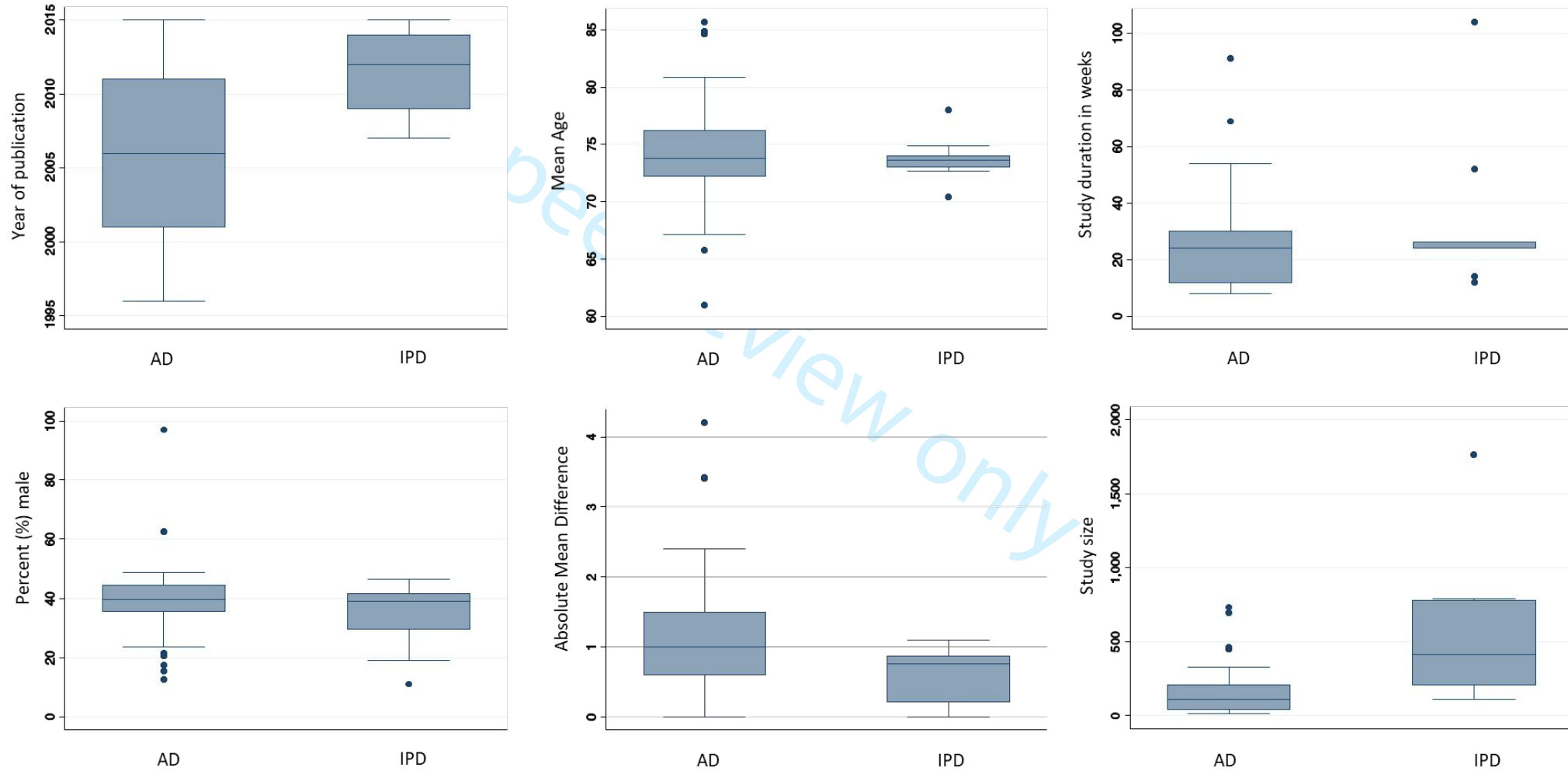
† The MMSE final value comes from visit 8 (last available visit in IPD). MMSE was not reported in study publication

**Abbreviations:** AD, Alzheimer's Dementia; IPD, individual patient data; MMSE, Mini-Mental State Examination; NR, not reported; N/A, not applicable; SAE, serious adverse event

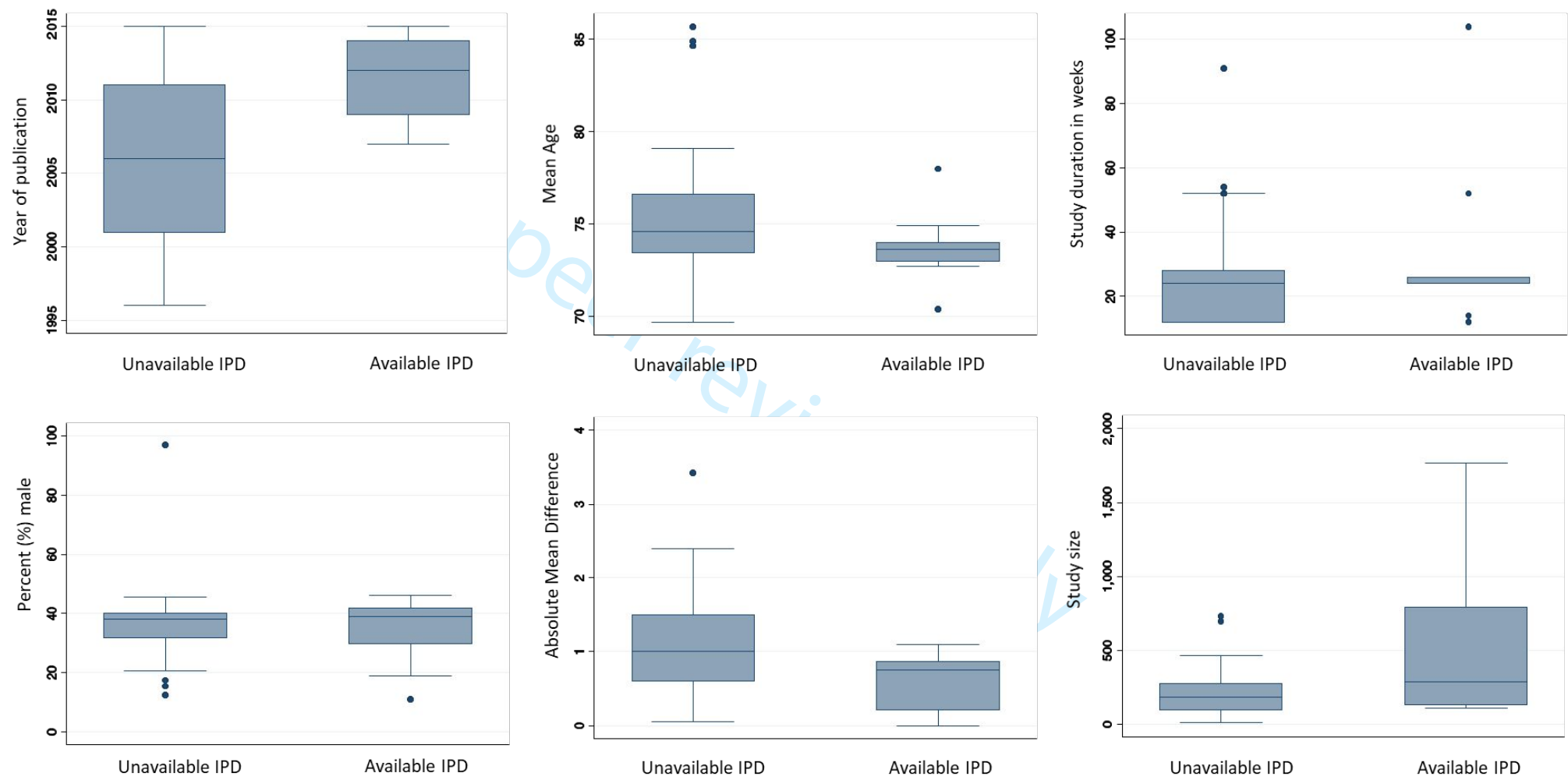
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**Appendix 7: Comparison of studies with shared IPD with (a) all remaining studies and (b) studies for which sponsors claimed unavailable IPD.** AD: aggregate data; IPD: individual patient data

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)



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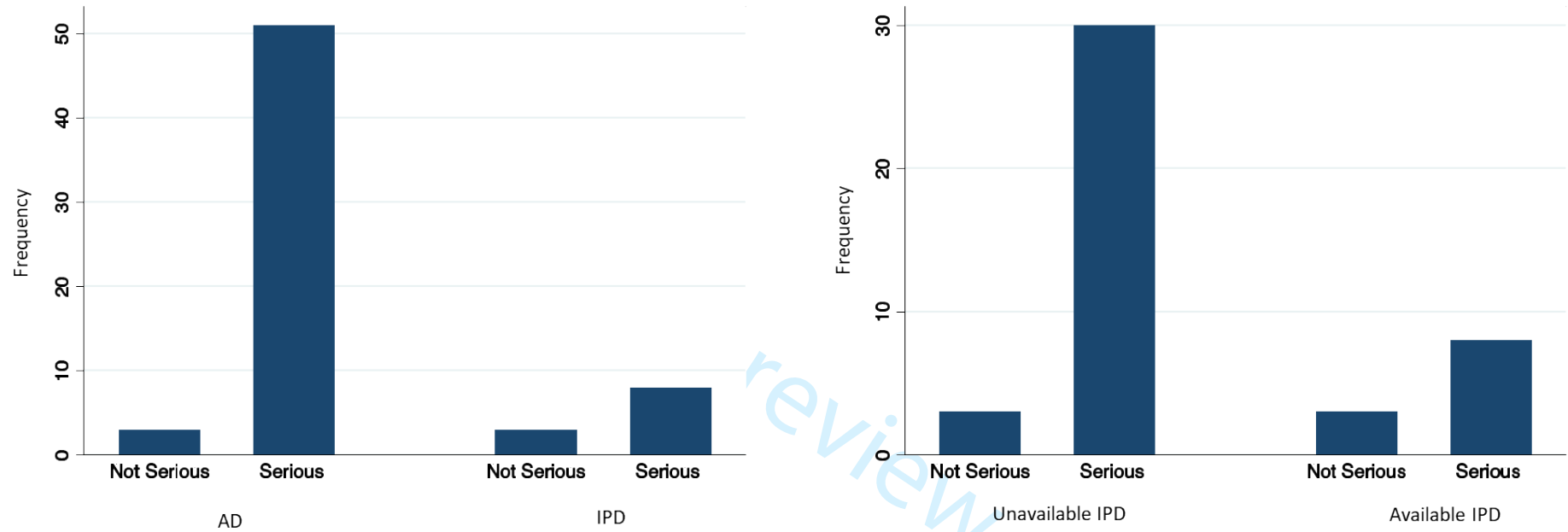
## Appendix 8: Cochrane Risk-of-bias appraisal results (n = 80)

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

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3	Shao, 2015	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
4	Shimizu, 2015	Low	Unclear	High	Low	High	Unclear	Unclear
5	Sole-Padullas, 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
6	Tariot, 2000	Low	Unclear	Low	Low	High	Low	High
7	Tariot, 2001	Low	Low	Low	Low	Unclear	Unclear	High
8	Thomas, 2001	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
9	Wilcock, 2003	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
10	Wilkinson, 2001	Low	Low	Low	Low	High	Unclear	High
11	Wilkinson, 2002	Low	Low	Low	Low	High	Unclear	High
12	Wilkinson, 2012	Low	High	Low	Low	High	Low	High
13	Winblad, 2001	Low	Unclear	Unclear	Low	High	Unclear	High
14	Winblad, 2006	Low	Low	Low	Low	High	Low	High
15	Winblad, 2007	Low	Low	Low	Low	High	Unclear	High
16	Yi, 2005	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
17	Zhang, 2012	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
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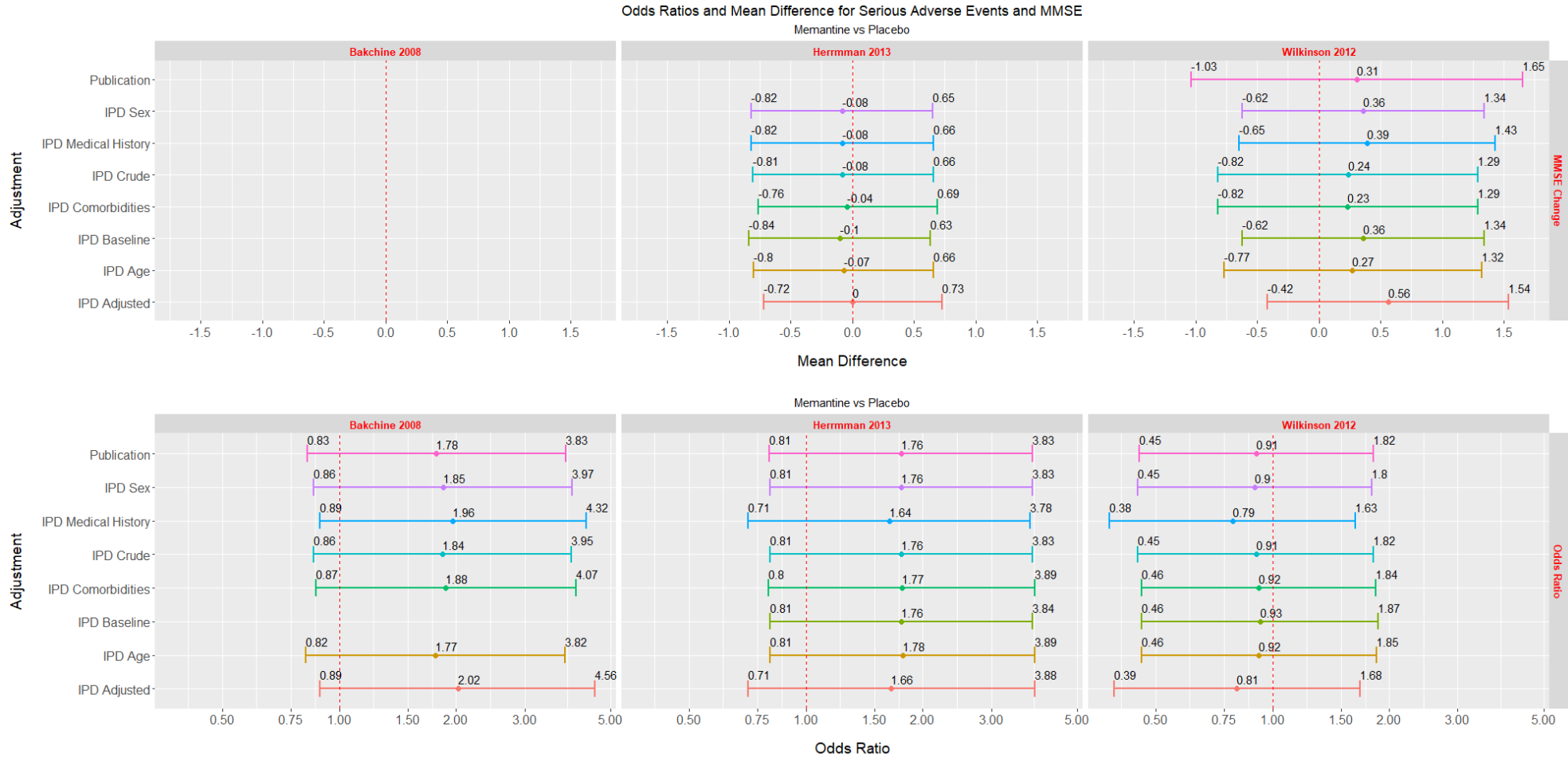
**Appendix 9: Overall risk of bias for studies with shared IPD against (a) all remaining studies and (b) studies for which sponsors claimed unavailable IPD. AD: aggregate data; IPD: individual patient data**



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)

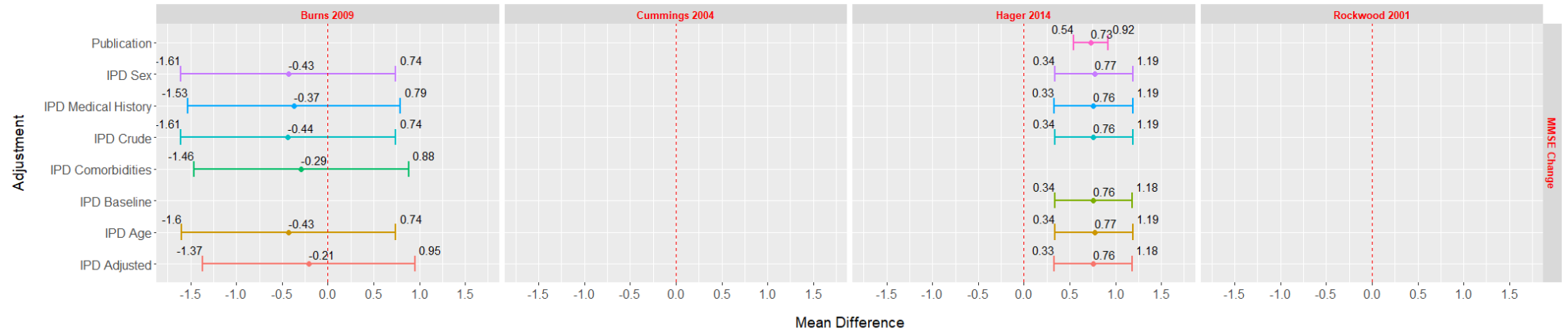
Appendix 10: Study-specific effect sizes calculated from shared IPD and published data. IPD: individual patient data



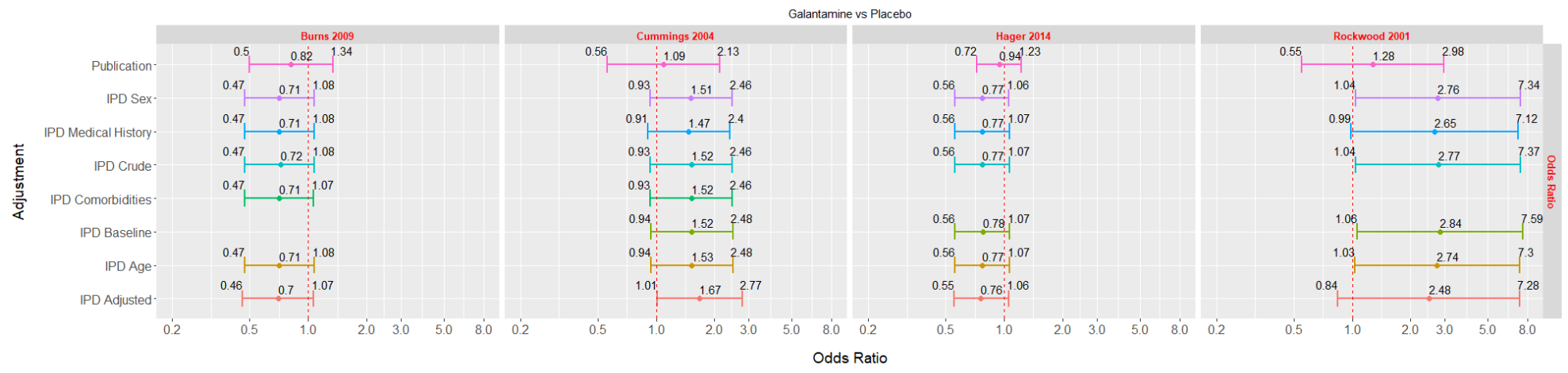
Sponsor: LUNDBECK

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Odds Ratios and Mean Difference for Serious Adverse Events and MMSE  
Galantamine vs Placebo



Burns 2009: MMSE values based on MMSE final score



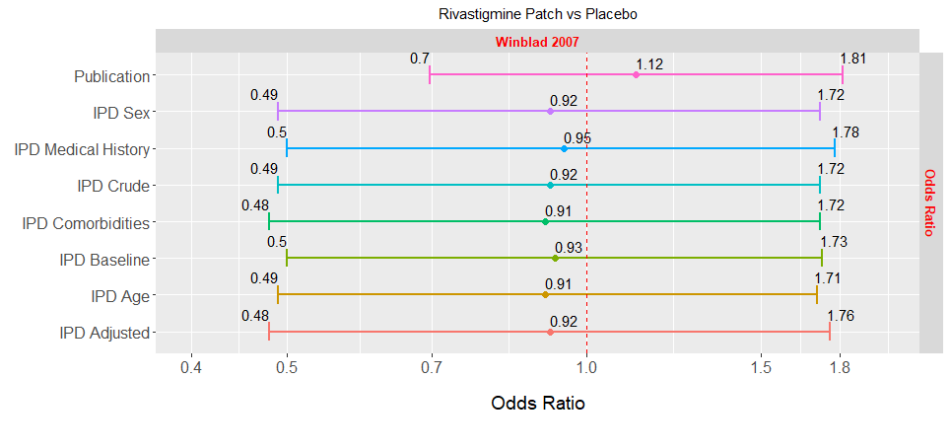
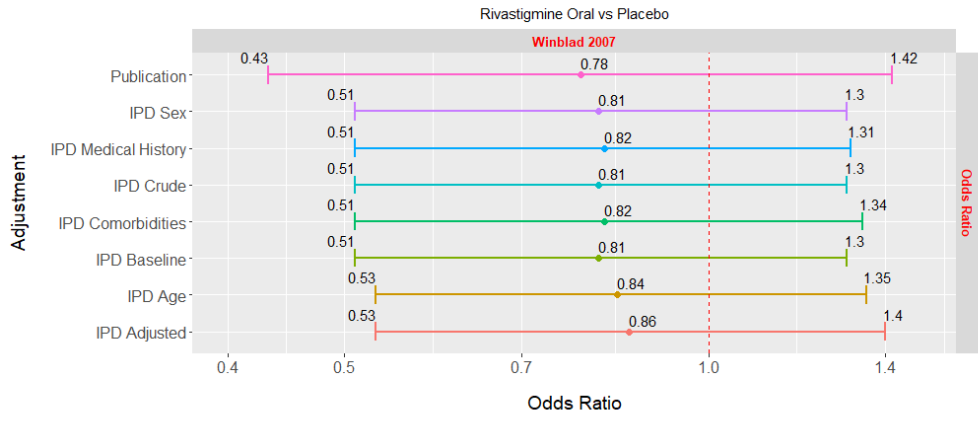
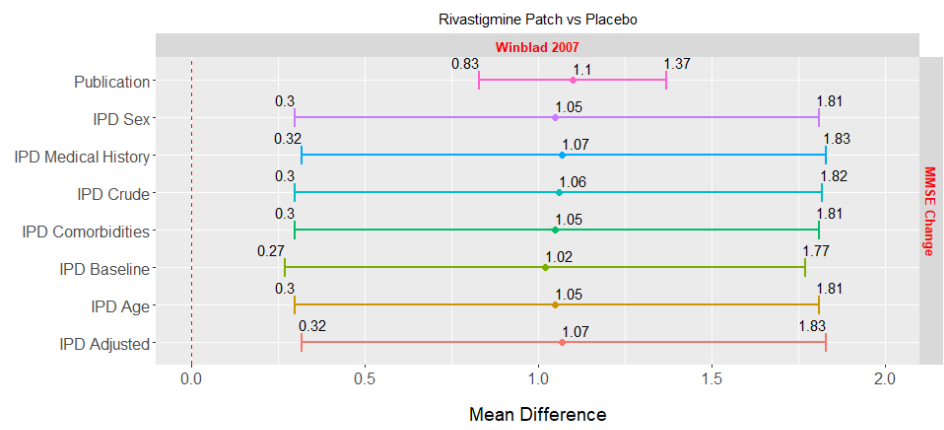
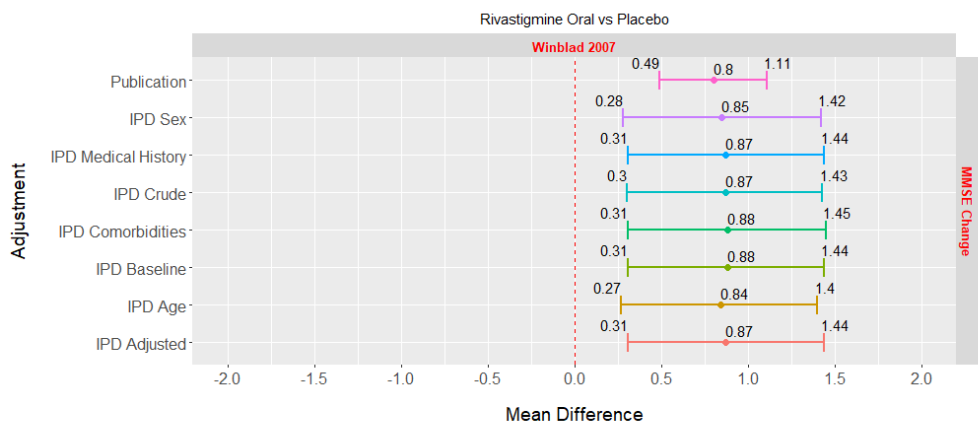
Sponsor: YODA

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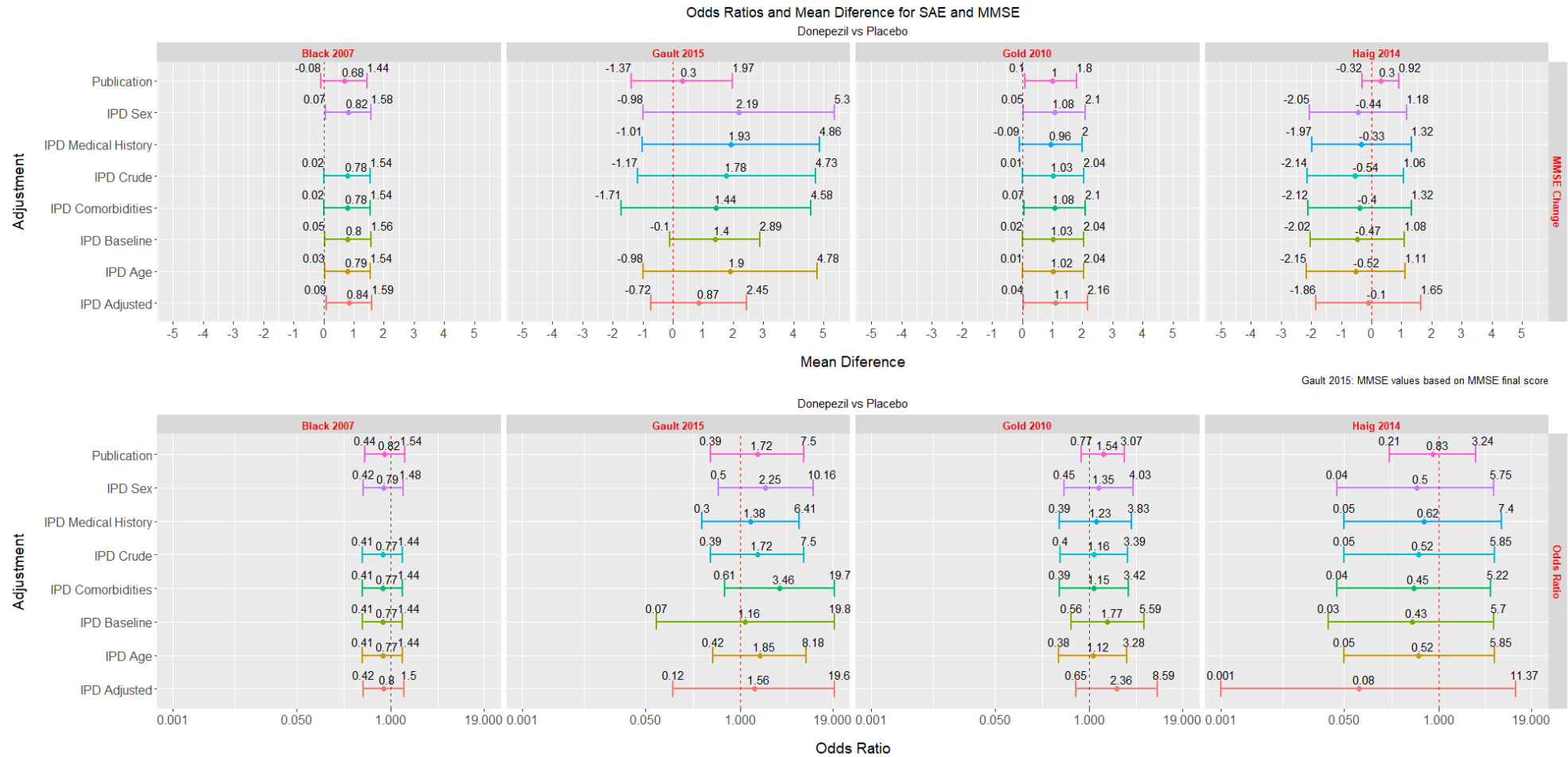


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Odds Ratios and Mean Difference for Serious Adverse Events and MMSE



Sponsor: CSDR Novartis



Sponsor: CSDR, ABBVIE

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 SAE 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 assesment we did not have access to these data.

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**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)

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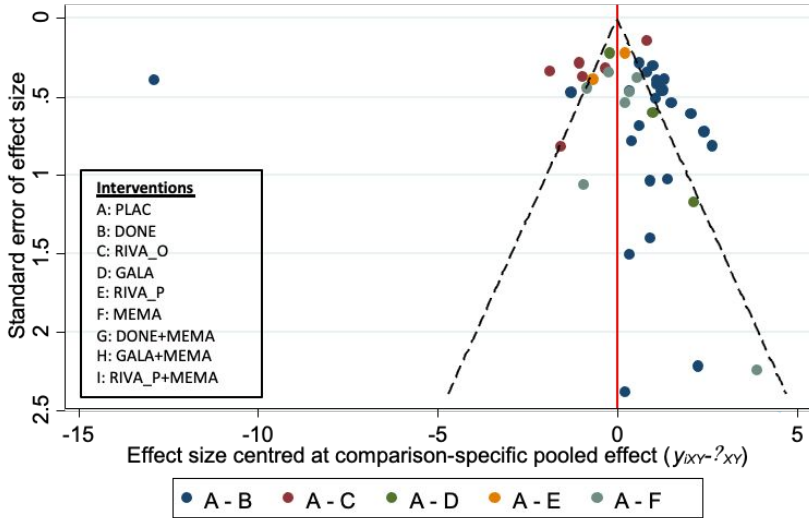
**Appendix 11: Correlation between participant age and dropout in studies with IPD.** IPD: individual patient data

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

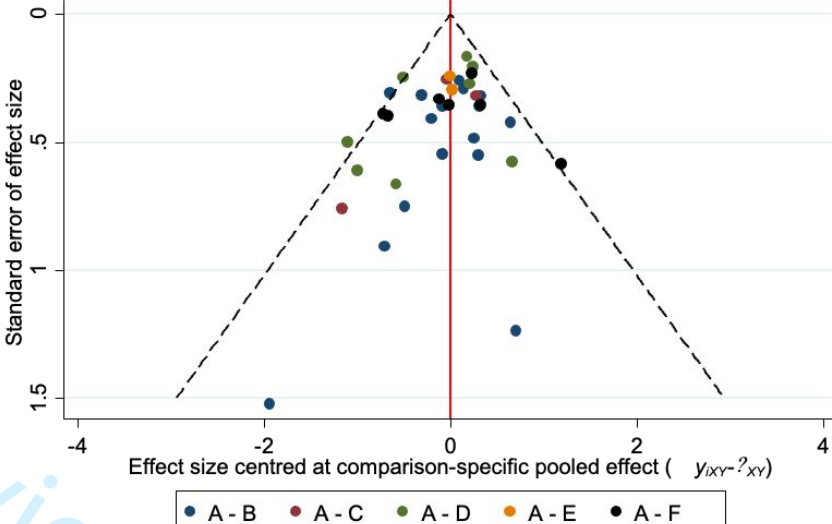
\* We were unable to assess this correlation for studies obtained through YODA and AbbVie, since at the time of this assessment we did not have access to these data

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

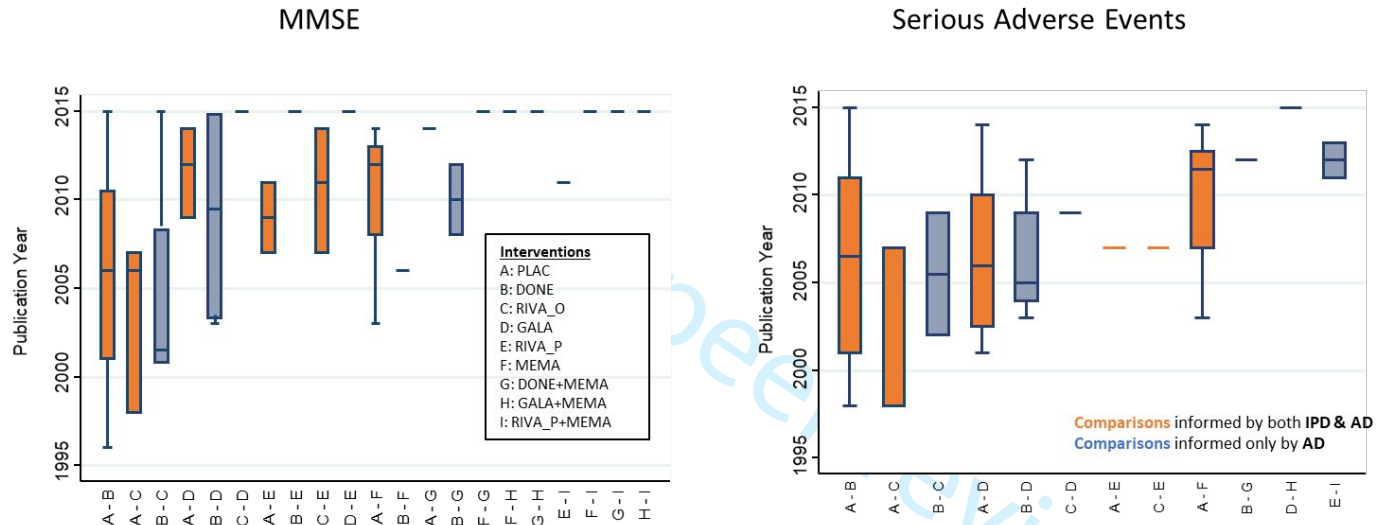


MMSE

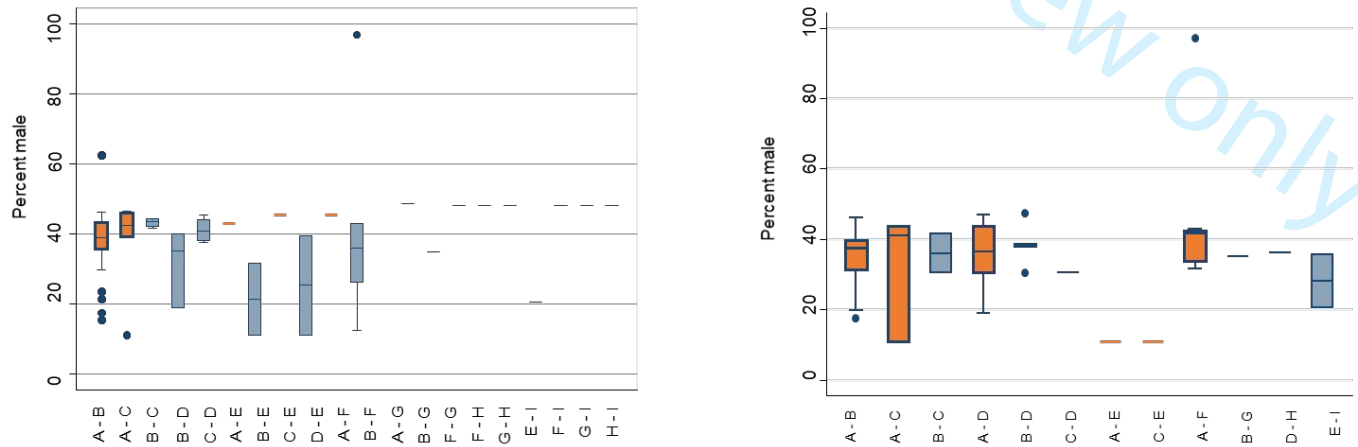


Serious Adverse Events

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

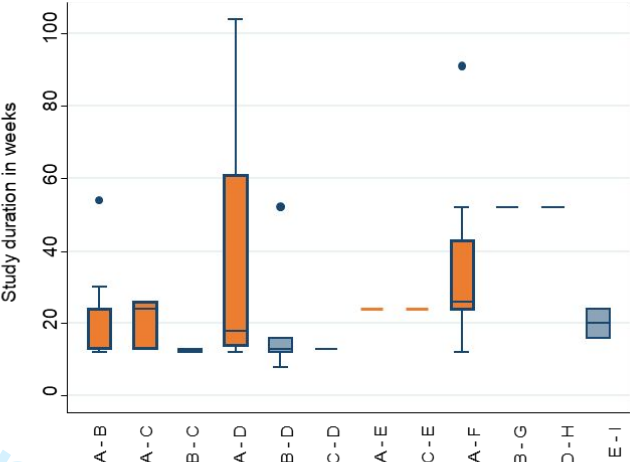
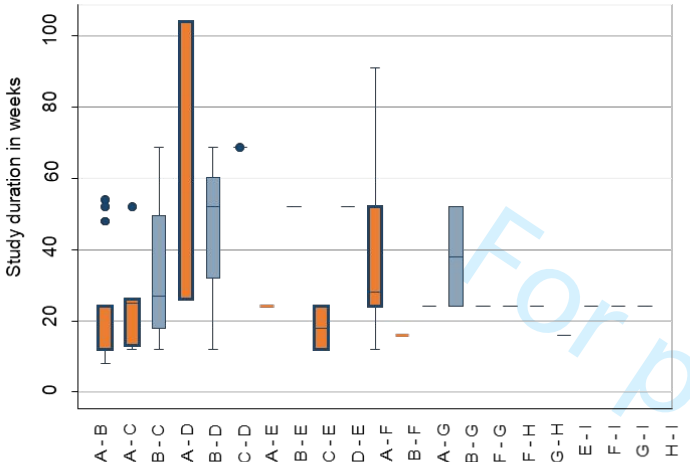


a. Publication year

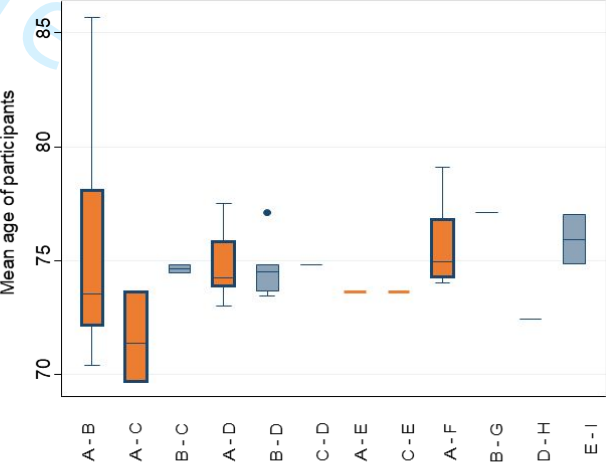
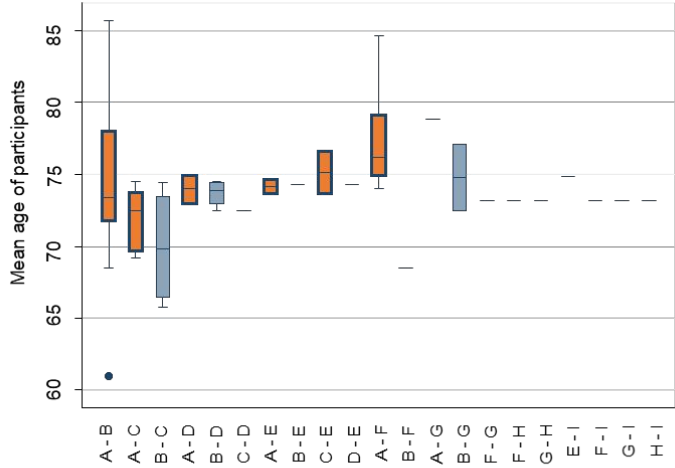


b. Percentage male

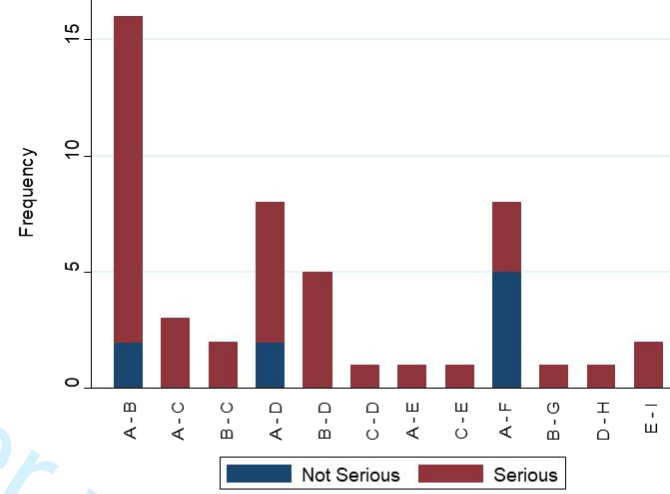
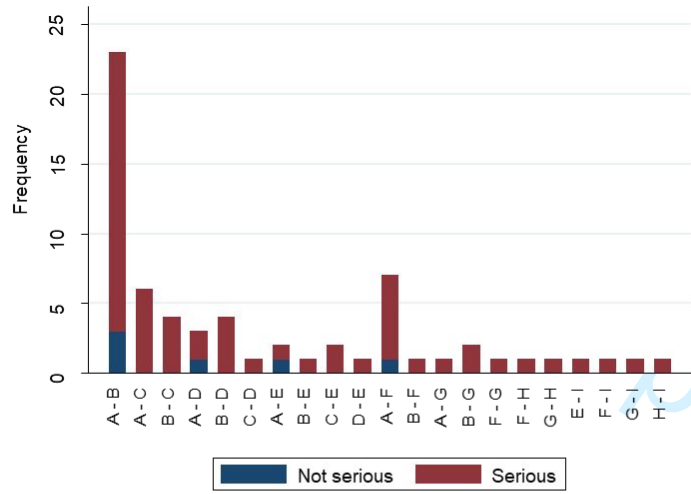
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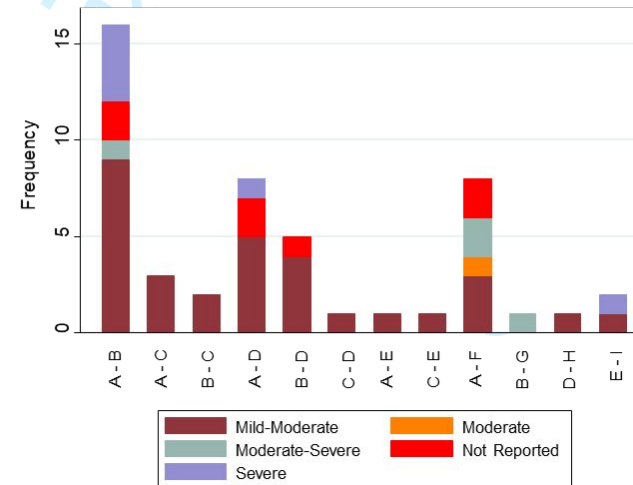
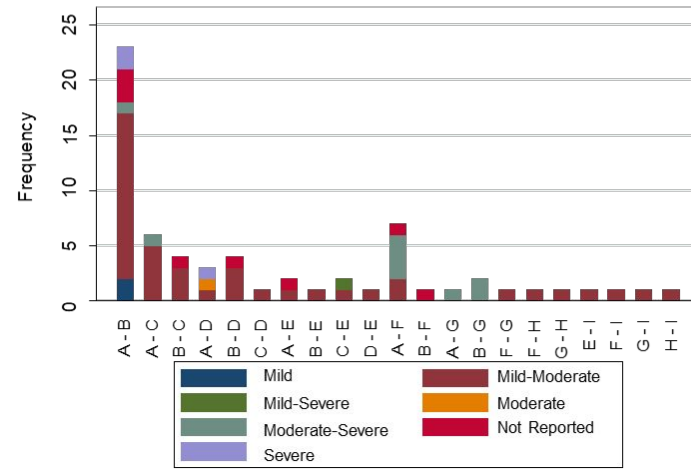
c. Study duration



d. Mean participant age



e. Overall Risk of Bias

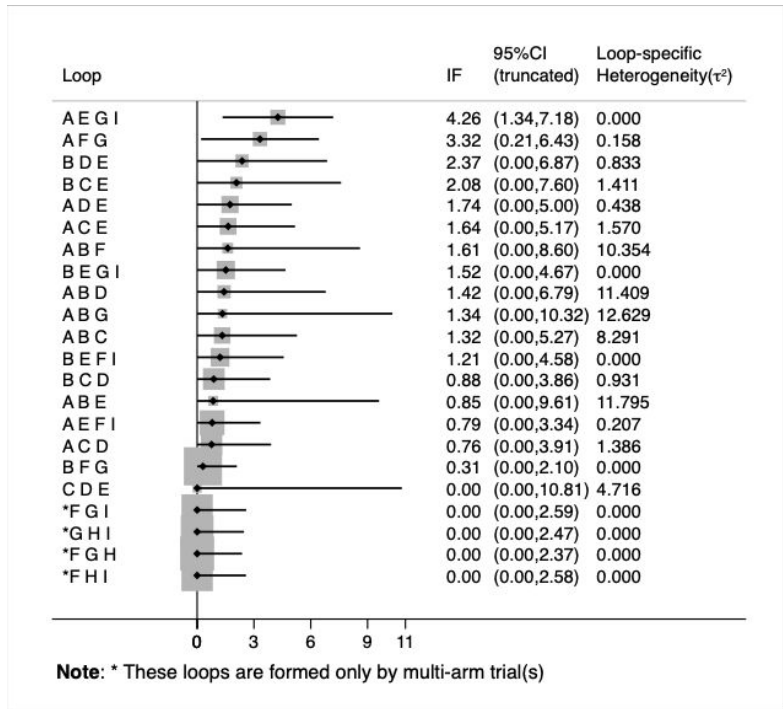


f. Alzheimer's Dementia Severity



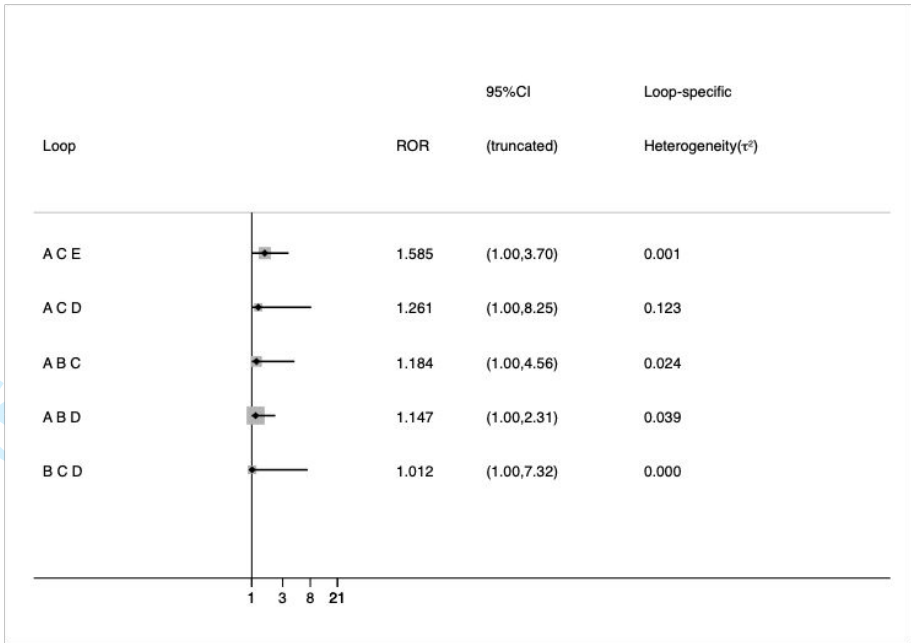
Appendix 14: Consistency Assessment – Loop-specific approach (using adjusted treatment effects)

MMSE



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

Serious Adverse Events



Design-by-treatment interaction model:  
 $\chi^2$  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
<b>Mini-Mental State Examination (MMSE)*†</b>								
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		
<i>Common within-network between-study variance <math>\tau^2 = 5.75</math>, <math>I^2 = 96\%</math> (96%, 97%)</i>								
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>								
<b>Serious Adverse Events (SAEs)*<sup>‡</sup></b>								
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 vs Donepezil	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
<i>Common within-network between-study variance <math>\tau^2 = 0.04</math>, <math>I^2 = 22\%</math> (0%, 48%)</i>						
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>						

\* 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 SAE.

† 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

‡ SAE: Studies with available IPD included all randomized participants

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## Appendix 16: Network subgroup and meta-regression analysis results

Treatment Comparison	NMA estimate	95% CI	95%PI	P-score
<b>Mini-Mental State Examination (MMSE)†</b>				
<b>Mean Difference: Aggregate data and crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 5.81</math>, <math>I^2 = 96%</math> (96%, 97%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.42 (13, 0.986, 7.44)</i>				
<b>Mean Difference: Aggregate data results**</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 7.66</math>, <math>I^2 = 97%</math> (96%, 97%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.92 (11, 0.972, 8.76)</i>				
<b>Mean Difference: Crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.12</math>, <math>I^2 = 29%</math> (0%, 71%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Mean Difference: Low Risk of Bias for Allocation Concealment*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 13.82</math>, <math>I^2 = 98%</math> (98%, 99%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.13 (3, 0.99, 19.10)</i>				
<b>Mean Difference: Low risk of bias for Incomplete Data*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 1.16</math>, <math>I^2 = 79%</math> (65%, 88%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 12.15 (3, 0.007, 0.863)</i>				
<b>Mean Difference: Publicly-Sponsored Studies*</b>				
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

<i>Common within-network between-study variance: <math>\tau^2 = 81.93</math>, <math>I^2 = 99\%</math> (99%, 100%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.05 (1, 0.815, 116.71)</i>				
<b>Mean Difference: Industry-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.16</math>, <math>I^2 = 43\%</math> (15%, 62%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 8.06 (7, 0.327, 0.16)</i>				
<b>Mean Difference: Studies with Mild to Moderate cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 9.67</math>, <math>I^2 = 97\%</math> (97%, 98%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.22 (9, 0.96, 13.28)</i>				
<b>Mean Difference: Studies with Moderate to Severe cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.18</math>, <math>I^2 = 44\%</math> (0%, 75%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.60 (1, 0.11, 0.11)</i>				
<b>Mean Difference: Excluding outlier studies**</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.59</math>, <math>I^2 = 73\%</math> (64%, 79%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 10.60 (13, 0.64, 0.61)</i>				
<b>Accounting for missing outcome data - Informative Missingness Difference of Means<sup>§</sup></b>				
Donepezil vs Placebo	1.42	0.51 to 2.33	0.51 to 2.33	0.59 <sup>  </sup>
Rivastigmine oral vs Placebo	0.45	-1.09 to 1.99	-1.09 to 1.99	0.30 <sup>  </sup>
Galantamine vs Placebo	0.19	-1.78 to 2.17	-1.78 to 2.17	0.25 <sup>  </sup>
Rivastigmine transdermal vs Placebo	2.37	-0.03 to 4.79	-0.03 to 4.79	0.76 <sup>  </sup>
Memantine vs Placebo	0.60	-1.09 to 2.42	-1.09 to 2.42	0.36 <sup>  </sup>
Donepezil + Memantine vs Placebo	2.55	0.09 to 5.01	0.09 to 5.01	0.80 <sup>  </sup>
Galantamine + Memantine vs Placebo	2.26	-2.03 to 6.56	-2.03 to 6.56	0.68 <sup>  </sup>
Rivastigmine transdermal + Memantine vs Placebo	1.81	-1.66 to 5.28	-1.66 to 5.28	0.61 <sup>  </sup>
Placebo (reference)				0.16 <sup>  </sup>
<i>Common within-network between-study variance: <math>\tau^2 = 5.47</math><sup>  </sup></i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.45 (11, 0.955, 6.45)</i>				
<b>Mean Difference: Meta-regression, Trial Mean Age**</b>				
Donepezil vs Placebo	1.53	0.52 to 2.53	-3.17 to 6.27	0.50 <sup>††</sup>
Rivastigmine oral vs Placebo	0.80	-0.84 to 2.44	-4.15 to 5.79	0.37 <sup>††</sup>
Galantamine vs Placebo	0.60	-1.63 to 2.83	-4.57 to 5.72	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.53	0.06 to 4.98	-2.72 to 7.80	0.75 <sup>††</sup>
Memantine vs Placebo	0.79	-1.18 to 2.74	-4.33 to 5.85	0.37 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.66	0.09 to 5.19	-2.70 to 7.97	0.87 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.39	-2.02 to 6.84	-4.14 to 8.83	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.05	-1.53 to 5.59	-3.83 to 7.94	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
Regression coefficient	0.03	-0.14 to 0.20		
<i>Common within-network between-study variance: <math>\tau^2 = 5.50</math></i>				
<i>3.72 to 8.51</i>				

<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.92 (11, 0.972, 8.76)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for Age</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.12</math>, <math>I^2 = 29\%</math> (0%, 71%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: Meta-regression, Percent of Male Participants**</b>				
Donepezil vs Placebo	1.62	0.58 to 2.65	-3.40 to 6.61	0.62 <sup>††</sup>
Rivastigmine oral vs Placebo	0.73	-0.90 to 2.35	-4.30 to 5.81	0.37 <sup>††</sup>
Galantamine vs Placebo	0.62	-1.65 to 2.89	-4.75 to 5.93	0.25 <sup>††</sup>
Rivastigmine Transdermal vs Placebo	2.51	0.01 to 5.04	-2.78 to 7.94	0.75 <sup>††</sup>
Memantine vs Placebo	0.66	-1.47 to 2.77	-4.54 to 5.88	0.25 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.52	-0.40 to 5.45	-3.09 to 8.17	0.75 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.27	-2.28 to 6.83	-4.37 to 8.90	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	1.98	-1.67 to 5.65	-4.02 to 7.99	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
<i>Regression coefficient</i>	0.01	-0.05 to 0.06		
<i>Common within-network between-study variance: <math>\tau^2 = 5.73</math>, 3.83 to 8.84</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.72 (10, 0.959, 8.97)</i>				
<b>Mean difference: NMA of studies with IPD adjusted for Percent of Male Participants</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.13</math>, <math>I^2 = 32\%</math> (0%, 72%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for cognitive impairment, assessed with MMSE at baseline</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 79%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for comorbidities</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 67%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for other medications</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.17</math>, <math>I^2 = 35\%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: Meta-regression, Study Duration**</b>				
Donepezil vs Placebo	1.66	0.67 to 2.66	-3.12 to 6.32	0.62 <sup>††</sup>
Rivastigmine oral vs Placebo	0.80	-0.77 to 2.37	-4.14 to 5.69	0.37 <sup>††</sup>
Galantamine vs Placebo	0.47	-1.75 to 2.68	-4.64 to 5.66	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.38	-0.04 to 4.83	-2.87 to 7.56	0.75 <sup>††</sup>
Memantine vs Placebo	0.67	-1.27 to 2.58	-4.35 to 5.79	0.25 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.67	0.18 to 5.16	-2.60 to 7.97	0.88 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.43	-1.94 to 6.79	-3.94 to 8.81	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.13	-1.40 to 5.63	-3.62 to 7.87	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>

<i>Regression coefficient</i>	0.02	-0.01 to 0.06		
<i>Common within-network between-study variance: <math>\tau^2 = 5.40</math></i>	3.63 to 8.29			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>				
<b>Mean Difference: Meta-regression, Year of Publication**</b>				
Donepezil vs Placebo	1.53	0.51 to 2.54	-3.27 to 6.31	0.50 <sup>††</sup>
Rivastigmine oral vs Placebo	0.66	-1.01 to 2.32	-4.31 to 5.65	0.25 <sup>††</sup>
Galantamine vs Placebo	0.60	-1.65 to 2.85	-4.65 to 5.83	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.59	0.09 to 5.12	-2.73 to 7.95	0.75 <sup>††</sup>
Memantine vs Placebo	0.89	-1.05 to 2.80	-4.17 to 5.90	0.38 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.82	0.19 to 5.44	-2.57 to 8.21	0.88 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.59	-1.93 to 7.16	-3.98 to 9.12	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.21	-1.49 to 5.95	-3.81 to 8.24	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
<i>Regression coefficient</i>	-0.02	-0.17 to 0.14		
<i>Common within-network between-study variance: <math>\tau^2 = 5.53</math></i>	3.71 to 8.48			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>				
<b>Serious Adverse Events (SAEs)‡</b>				
<b>Odds Ratio: Aggregate data and crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.04</math>, <math>I^2 = 20\%</math> (0%, 47%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.58 (6, 0.733, 0.05)</i>				
<b>Odds Ratio: Aggregate data results**</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 42%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.29 (4, 0.682, 0.01)</i>				
<b>Odds Ratio: Crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.10</math>, <math>I^2 = 48\%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: Low Risk of Bias for Allocation Concealment*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.08</math>, <math>I^2 = 37\%</math> (0%, 64%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.19 (3, 0.53, 0.1)</i>				
<b>Odds Ratio: Low Risk of Bias for Incomplete Data*</b>				
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



<i>Common within-network between-study variance: <math>\tau^2 = 0.02</math>, <math>I^2 = 10\%</math> (0%, 50%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.00 (1, 0.95, 0.04)</i>				
<b>Odds Ratio: Publicly-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = N/A</math> (each comparison includes a single study)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: Industry-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.05</math>, <math>I^2 = 25\%</math> (0%, 50%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.68 (6, 0.72, 0.07)</i>				
<b>Odds Ratio: Studies with Mild to Moderate cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.09</math>, <math>I^2 = 29\%</math> (0%, 57%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.29 (5, 0.66, 0.13)</i>				
<b>Odds Ratio: Studies with Moderate to Severe cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 72%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.90 (1, 0.09, 0.00)</i>				
<b>Odds Ratio: NMA of studies with IPD – available case analysis</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.13</math>, <math>I^2 = 50\%</math> (0%, 77%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, heterogeneity): N/A (no closed loops)</i>				
<b>Odds Ratio: Meta-regression, Trial Mean Age**</b>				
Donepezil vs Placebo	1.13	0.88 to 1.43	0.68 to 1.86	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.52	0.89 to 2.53	0.77 to 3.04	0.00 <sup>††</sup>
Galantamine vs Placebo	0.91	0.60 to 1.30	0.52 to 1.59	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.84	0.39 to 1.58	0.34 to 1.80	0.75 <sup>††</sup>
Memantine vs Placebo	0.74	0.48 to 1.07	0.39 to 1.26	0.75 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.92	0.38 to 1.89	0.33 to 2.15	0.62 <sup>††</sup>
Galantamine + Memantine vs Placebo	0.99	0.37 to 2.27	0.33 to 2.55	0.50 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.73	0.24 to 1.70	0.22 to 1.87	0.87 <sup>††</sup>
Placebo (reference)				0.37 <sup>††</sup>
<i>Regression coefficient (log-scale)</i>	-0.03	-0.08 to 0.02		
<i>Common within-network between-study variance: <math>\tau^2 = 0.02</math></i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for Age</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.10</math>, <math>I^2 = 48\%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				

<b>Odds Ratio: Meta-regression, Percent of Male Participants**</b>				
Donepezil vs Placebo	1.12	0.87 to 1.44	0.64 to 2.01	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.71	0.97 to 2.92	0.83 to 3.67	0.00 <sup>††</sup>
Galantamine vs Placebo	0.93	0.62 to 1.36	0.49 to 1.77	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.89	0.39 to 1.79	0.34 to 2.05	0.63 <sup>††</sup>
Memantine vs Placebo	0.64	0.37 to 1.00	0.29 to 1.21	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.88	0.35 to 1.88	0.30 to 2.13	0.63 <sup>††</sup>
Galantamine + Memantine vs Placebo	1.13	0.39 to 2.58	0.36 to 2.95	0.38 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.77	0.24 to 1.93	0.21 to 2.13	0.88 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): 3.57 (6, 0.735, 0.06)				
<b>Odds Ratio: NMA of studies with IPD adjusted for Percent of Male Participants</b>				
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): N/A (no closed loops)				
<b>Odds Ratio: NMA of studies with IPD adjusted for cognitive impairment, assessed with MMSE at baseline</b>				
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): N/A (no closed loops)				
<b>Odds Ratio: NMA of studies with IPD adjusted for comorbidities</b>				
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): N/A (no closed loops)				
<b>Odds Ratio: NMA of studies with IPD adjusted for other medications</b>				
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): N/A (no closed loops)				
<b>Odds Ratio: Meta-regression, Study Duration**</b>				
Donepezil vs Placebo	1.12	0.87 to 1.43	0.63 to 1.95	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.76	1.00 to 2.99	0.88 to 3.68	0.00 <sup>††</sup>
Galantamine vs Placebo	0.92	0.62 to 1.36	0.50 to 1.69	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.87	0.39 to 1.70	0.34 to 1.96	0.63 <sup>††</sup>
Memantine vs Placebo	0.61	0.37 to 0.93	0.31 to 1.13	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.76	0.29 to 1.69	0.26 to 1.90	0.75 <sup>††</sup>
Galantamine + Memantine vs Placebo	0.98	0.34 to 2.26	0.30 to 2.53	0.50 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.75	0.25 to 1.81	0.23 to 1.97	0.75 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): 3.57 (6, 0.735, 0.06)				
<b>Odds Ratio: Meta-regression, Year of Publication**</b>				
Donepezil vs Placebo	1.05	0.79 to 1.38	0.61 to 1.77	0.38 <sup>††</sup>
Rivastigmine oral vs Placebo	1.68	0.98 to 2.77	0.85 to 3.37	0.00 <sup>††</sup>
Galantamine vs Placebo	0.91	0.61 to 1.32	0.50 to 1.64	0.63 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.92	0.40 to 1.84	0.36 to 2.04	0.63 <sup>††</sup>
Memantine vs Placebo	0.73	0.46 to 1.05	0.38 to 1.28	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.88	0.35 to 1.83	0.31 to 2.15	0.75 <sup>††</sup>

Galantamine + Memantine vs Placebo	1.24	0.43 to 2.85	0.39 to 3.25	0.25 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.88	0.24 to 2.24	0.24 to 2.42	0.75 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): 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)

‡ SAE: 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)

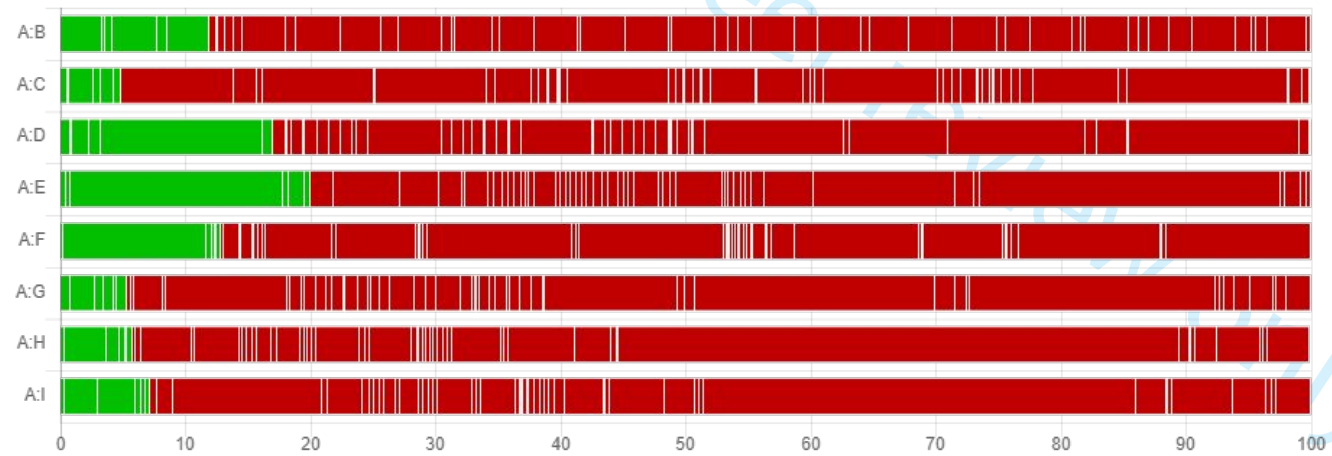
†† Analyses were conducted in OpenBUGS, and SUCRA values were calculated instead of P-scores

Appendix 17: CINeMA results

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

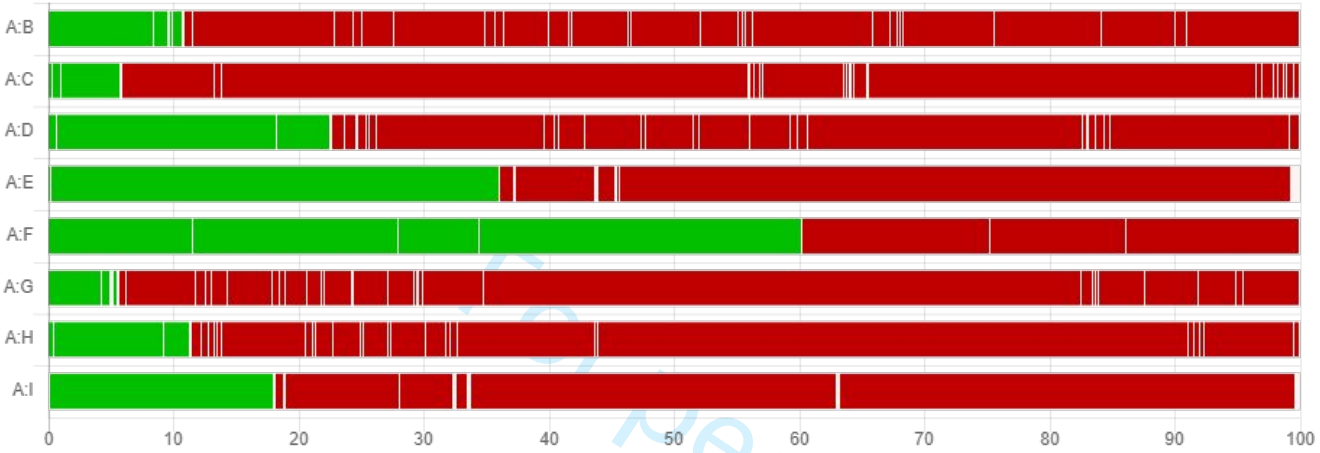
Interventions	
A:	PLAC
B:	DONE
C:	RIVA_O
D:	GALA
E:	RIVA_P
F:	MEMA
G:	DONE+MEMA
H:	GALA+MEMA
I:	RIVA_P+MEMA

MMSE outcome



SAE outcome

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**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

**SAE outcome**

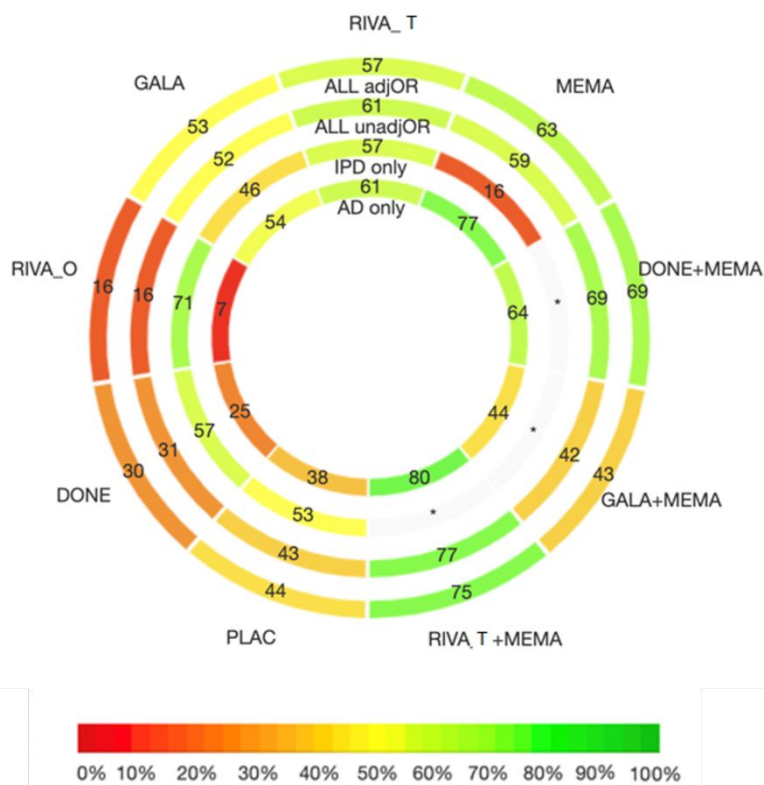
53

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: Rank-heat plot for serious 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 19: Study definitions for serious 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	"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	"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	"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	NR
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	NR	NR
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		
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



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3	Johannsen, 2006	NA	NA
4	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"
5			
6	Kadir, 2008	NA	NA
7	Kano, 2013	NA	NA
8	Karaman, 2005	NA	NA
9	Likitjaroen, 2012	NA	NA
10	Lorenzi, 2011	NA	NA
11	Maher-Edwards, 2011	Determined by Investigator	"Eight subjects experienced nonfatal serious AEs; all were considered unrelated to the study drug"
12	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"
13			
14	Mazza, 2006	NA	NA
15	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."
16			
17	Moretti, 2014	NA	NA
18	Mowla, 2007	NA	NA
19	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."
20			
21			
22	Nakano, 2001	NA	NA
23	Nordberg, 2009	Determined by Investigator	"Safety and tolerability were monitored throughout the study by recording all adverse events (AEs)."
24			
25	Pakdaman H, 2015	NA	NA
26	Peng, 2005	NA	NA
27	Peskind, 2006	NR	NR
28	Peters O, 2015	NR	NR
29	Reisberg, 2003	NR	NR
30	Rockwood, 2001	World Health Organisation preferred terms	"adverse events (classified according to World Health Organisation preferred terms)."
31	Rockwood, 2006	NR	NR
32	Rogers, 1996		
33	Rogers, 1998	COSTART	"Events, recorded using investigator terminology, were grouped and coded into common terms using a modified COSTART dictionary"
34	Rogers, 1998	COSTART	"Events, recorded using investigator terminology, were grouped and coded into common terms using a modified COSTART dictionary."
35			
36	Saxton, 2012	Determined by Investigator	"Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were recorded at all post-Screening study visits"
37	Scarpini, 2011	NR	NR
38	Schmidt, 2008	NA	NA
39	Seltzer, 2004	NA	NA
40	Shao, 2015	NA	NA
41	Shimizu, 2015	NA	NA
42	Sole-Padulles, 2013	NA	NA
43	Tariot, 2000	NR	NR
44	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."
45			
46	Thomas, 2001		
47	Wilcock, 2003	World Health Organisation preferred terms	"monitoring for adverse events (classified according to WHO preferred terms)"
48			
49	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."
50			
51			
52	Wilkinson, 2002	NR	NR
53	Wilkinson, 2012	NR	NR
54	Winblad, 2001	NR	NR
55	Winblad, 2006	COSTART	"We recorded all treatment emergent adverse events, coding them according to a modified COSTART dictionary."
56	Winblad, 2007	Determined by Investigator	"Safety evaluations included recording all adverse events, which were coded using a standard glossary."
57			
58	Zhang-Yi, 2005	NA	NA
59	Zhang, 2012	Determined by Investigator	"Serious adverse events considered to be possibly related to treatment occurred in one patient in each treatment arm"
60			

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**Notes:** <sup>a</sup>Unpublished data, <sup>b</sup>Non-English studies

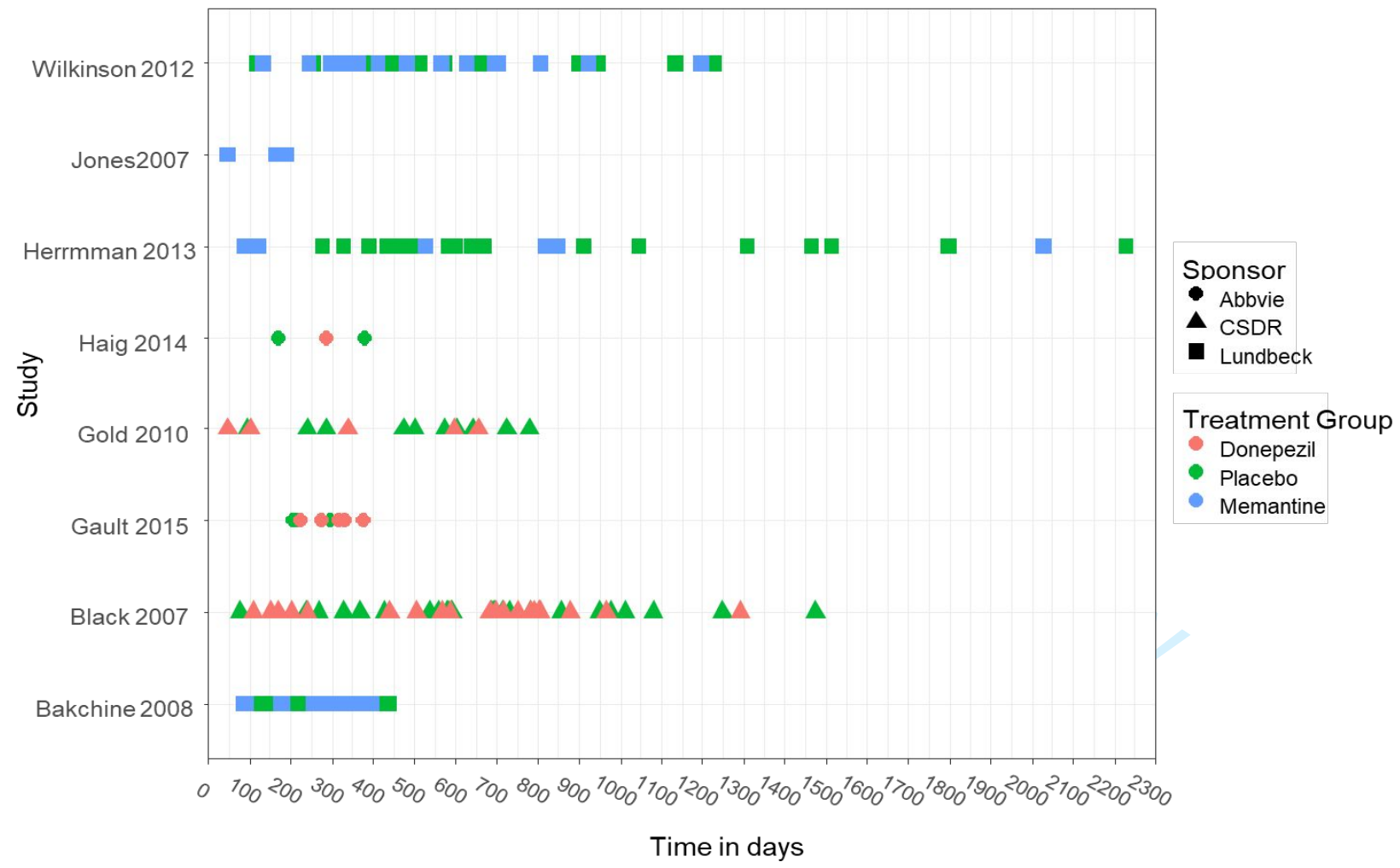
**Abbreviations:** CR, companion report; NA, not applicable; NR, not reported.

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Appendix 20: Time taken to achieve at least one serious adverse event using individual patient data

Time taken to achieve a Serious Adverse Event



#### 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.

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## 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:

-----

- 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.tw.
- 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.

1  
2  
3 36 memantin\$.tw.  
4 37 memox.tw.  
5 38 namenda.tw.  
6 39 nimvastid.tw.  
7 40 nivalin\$.tw.  
8 41 "N-Methyl-D-aspartic acid receptor antagonist\$.tw.  
9 42 prometax.tw.  
10 43 razadyne.tw.  
11 44 reminyl.tw.  
12 45 rivastigmine.mp.  
13 46 exp Cholinesterase Inhibitors/  
14 47 Galantamine/  
15 48 Memantine/  
16 49 Galantamin.rn.  
17 50 Memantine.rn.  
18 51 Donepezil.rn.  
19 52 Donepezil Hydrochloride.rn.  
20 53 Rivastigmine.rn.  
21 54 or/21-53  
22 55 20 and 54  
23 56 exp Animals/ not (exp Animals/ and Humans/)  
24 57 55 and 56  
25 58 (comment or editorial or interview or news).pt.  
26 59 (letter not (letter and randomized controlled trial)).pt.  
27 60 57 not (58 or 59)  
28 61 (201111\* or 201112\* or 2012\* or 2013\* or 2014\*).ed.  
29 62 60 and 61  
30 63 alzheimer\$.mp.  
31 64 "benign senescent forgetfulness".mp.  
32 65 (cognit\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
33 disorder\$ or complain\$ or disturb\$)).mp.  
34 66 (cerebr\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or disorder\$ or  
35 complain\$ or disturb\$)).mp.  
36 67 (mental adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
37 disorder\$ or complain\$ or disturb\$)).mp.  
38 68 (ne?rocognit\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
39 disorder\$ or complain\$ or disturb\$)).mp.  
40 69 (ne?ro-cognit\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
41 disorder\$ or complain\$ or disturb\$)).mp.  
42 70 ((cognit\$ or memory or cerebral or brain) adj2 (improv\$ or enhanc\$ or perform\$ or  
43 process\$ or function\$ or rehabilitation or aid\$ or stimulat\$)).mp.  
44 71 cognition.ti.  
45 72 (confusion\$ or confused).tw.  
46 73 dement\$.mp.  
47 74 ("normal pressure hydrocephalus" and shunt\$.mp.  
48 75 "organic brain disease\$.mp.  
49 76 "organic brain syndrome".mp.  
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3 77 (presenil\$ or pre-senil\$ or senil\$.tw  
4 78 Alzheimer disease/  
5 79 cognitive defect/  
6 80 confusion/  
7 81 dementia/  
8 82 organic brain syndrome/  
9 83 or/63-82  
10 84 abixa.tw.  
11 85 aricept.tw.  
12 86 (acetylcholinesteraseadj inhibitor\$.tw.  
13 87 axura.tw.  
14 88 akatinol.tw.  
15 89 (anticholinesterase? or anti-cholinesterase?).tw.  
16 90 (cognitive adjenhanc\$.mp.  
17 91 (cholinesterase adj inhibitor\$.mp.  
18 92 ChEI.tw.  
19 93 donepezil.mp.  
20 94 ebixa.tw.  
21 95 eranz.tw.  
22 96 exelon.tw.  
23 97 galant?amin\$.tw.  
24 98 lycoremine.tw.  
25 99 memantin\$.tw.  
26 100 memox.tw.  
27 101 namenda.tw.  
28 102 nimvastid.tw.  
29 103 nivalin\$.tw.  
30 104 "N-Methyl-D-aspartic acid receptor antagonist\$.tw.  
31 105 prometax.tw.  
32 106 razadyne.tw.  
33 107 reminyl.tw.  
34 108 rivastigmine.mp.  
35 109 exp cholinesterase inhibitor/  
36 110 donepezil/ or donepezil plus memantine/  
37 111 galantamine/  
38 112 memantine/  
39 113 rivastigmine/  
40 114 357-70-0.rn.  
41 115 19982-08-2.rn.  
42 116 120011-70-3.rn.  
43 117 120014-06-4.rn.  
44 118 rivastigmine.rn.  
45 119 or/84-118  
46 120 83 and 119  
47 121 randomized controlled trial/ or controlled clinical trial/  
48 122 exp "clinical trial (topic)"/  
49 123 (randomi#ed or randomly or RCT\$1 or placebo\*).tw.  
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3 124 ((singl\* or doubl\* or trebl\* or tripl\*) adj (mask\* or blind\* or dumm\*)).tw.  
4 125 trial.ti.  
5 126 or/121-125  
6 127 120 and 126  
7 128 exp controlled clinical trial/  
8 129 exp "controlled clinical trial (topic)"/  
9 130 (control\* adj2 trial\*).tw.  
10 131 (nonrandom\* or non-random\* or quasi-random\* or quasi-experiment\*).tw.  
11 132 (nRCT or nRCTs or non-RCT\$1).tw.  
12 133 (control\* adj3 ("before and after" or "before after")).tw.  
13 134 time series analysis/  
14 135 (time series adj3 interrupt\*).tw.  
15 136 pretest posttest control group design/  
16 137 (pre- adj3 post-).tw.  
17 138 (pretest adj3 posttest).tw.  
18 139 controlled study/  
19 140 (control\* adj2 stud\$3).tw.  
20 141 control group/  
21 142 (control\$ adj2 group\$1).tw.  
22 143 or/128-142  
23 144 120 and 143  
24 145 cohort analysis/  
25 146 cohort.tw.  
26 147 retrospective study/  
27 148 longitudinal study/  
28 149 prospective study/  
29 150 (longitudinal or prospective or retrospective).tw.  
30 151 follow up/  
31 152 ((followup or follow-up) adj (study or studies)).tw.  
32 153 observational study/  
33 154 (observation\$2 adj (study or studies)).tw.  
34 155 population research/  
35 156 ((population or population-based) adj (study or studies or analys#s)).tw.  
36 157 ((multidimensional or multi-dimensional) adj (study or studies)).tw.  
37 158 exp comparative study/  
38 159 ((comparative or comparison) adj (study or studies)).tw.  
39 160 exp case control study/  
40 161 ((case-control\* or case-based or case-comparison) adj (study or studies)).tw.  
41 162 or/145-161  
42 163 120 and 162  
43 164 127 or 144 or 163  
44 165 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or  
45 nonhuman/ or exp vertebrate/  
46 166 exp humans/ or exp human experimentation/ or exp human experiment/  
47 167 165 not 166  
48 168 164 not 167  
49 169 editorial.pt.

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2  
3 170 letter.pt.not (letter.pt. and randomized controlled trial/)  
4 171 168 not (169 or 170)  
5 172 (2011112\* or 2011113\* or 201112\* or 2012\* or 2013\* or 2014\*).dd.  
6 173 171 and 172  
7 174 62 use prmz  
8 175 173 use emez  
9 176 174 or 175  
10 177 remove duplicates from 176  
11 178 177 use prmz [MEDLINE UNIQUE HITS]  
12 179 177 use emez [EMBASE UNIQUE HITS]  
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**PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)**

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
<b>Title</b>			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
<b>Abstract</b>			
Structured summary	2	Provide a structured summary including as applicable:	3-4
		<b>Background:</b> state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		<b>Methods:</b> report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		<b>Results:</b> provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		<b>Discussion:</b> state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		<b>Other:</b> report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
<b>Introduction</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	5
<b>Methods</b>			

Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	5, Appendix 1
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	5-6, Appendix 1
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	6, Appendix 1
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	N/A (see published protocol)
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	6, Appendix 1
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study). If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	6, Appendix 1
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	6, Appendix 1

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IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	Appendix 1
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	6, Appendix 1
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	7, Appendix 1
Synthesis methods	14	<p>Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to):</p> <ul style="list-style-type: none"> <li>• Use of a one-stage or two-stage approach.</li> <li>• How effect estimates were generated separately within each study and combined across studies (where applicable).</li> <li>• Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for.</li> <li>• Use of fixed or random effects models and any other model assumptions, such as proportional hazards.</li> <li>• How (summary) survival curves were generated (where applicable).</li> <li>• Methods for quantifying statistical heterogeneity (such as <math>I^2</math> and <math>\tau^2</math>).</li> <li>• How studies providing IPD and not providing IPD were analysed together (where applicable).</li> <li>• How missing data within the IPD were dealt with (where applicable).</li> </ul>	7, Appendix 1
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	Appendix 1
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	6, Appendix 1

Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	7, Appendix 1
<b>Results</b>			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	7 – Figure 1
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	8 – Table 1, Appendix 5
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	8-9, Appendices 5 and 10
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	8-9 – Appendix 8
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Appendices 6 and 10 (full data can be provided by the

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			first author)
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	9-11 – Appendix 15
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	9-11 - Appendix 12
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	9-11 - Appendices 16 and 17
<b>Discussion</b>			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	11-13
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	13-14
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	13-14
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	12-13

Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	15

**A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.**

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## PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: <b>Background:</b> main objectives <b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . <b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> <b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings. <b>Other:</b> primary source of funding; systematic review registration number with registry name.	3-4
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5, Appendix 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	6, Appendix 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6, Appendix 1

1	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	N/A (see published protocol)
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3				
4	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, Appendix 1
5				
6				
7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, Appendix 1
8				
9				
10				
11	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, Appendix 1
12				
13				
14	<b>Geometry of the network</b>	<b>S1</b>	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	7, Appendix 1
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21	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6, Appendix 1
22				
23				
24				
25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	7, Appendix 1
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses; and</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>	7, Appendix 1
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40	<b>Assessment of Inconsistency</b>	<b>S2</b>	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	7, Appendix 1
41				
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44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6, Appendix 1
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46				
47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network; and</i></li> <li>• <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i></li> </ul>	7, Appendix 1
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## RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 – Figure 1
<b>Presentation of network structure</b>	<b>S3</b>	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	9 – Figure 2
<b>Summary of network geometry</b>	<b>S4</b>	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	7-8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8 – Table 1, Appendix 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	8-9 – Appendix 8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Appendices 6 and 10 (full data can be provided by the first author)
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	9-11 – Appendix 15
<b>Exploration for inconsistency</b>	<b>S5</b>	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	9 - Appendix 14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	9-11 - Appendix 12
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i> ).	9-11 - Appendices 16 and 17

<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	15

PICOS = population, intervention, comparators, outcomes, study design.

\* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.



## PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Yes
<b>BACKGROUND</b>			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
<b>METHODS</b>			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
<b>RESULTS</b>			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
<b>DISCUSSION</b>			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
<b>OTHER</b>			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

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# BMJ Open

## 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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Complete List of Authors:	Veroniki, Areti; St. Michael's Hospital, Knowledge Translation Program; Imperial College London, Department of Surgery & Cancer, Faculty of Medicine Ashoor, Huda; St Michael's Hospital, Knowledge Translation Program Rios, Patricia; St Michael's Hospital, Knowledge Translation Program Seitidis, Georgios; University of Ioannina, Department of Primary Education Stewart, Lesley; University of York, Centre for Reviews and Dissemination Clarke, Mike; Queen's University Belfast, Northern Ireland Hub for Trials Methodology Research Tudur-Smith, Catrin; University of Liverpool, Department of Biostatistics Mavridis, Dimitris ; University of Ioannina, Department of Primary Education Hemmelgarn, Brenda; University of Alberta, Department of Medicine Holroyd-Leduc, Jayna; University of Calgary, Department of Medicine Straus, Sharon; St Michael's Hospital, Knowledge Translation Program; University of Toronto, Department of Geriatric Medicine Tricco, Andrea; St Michael's Hospital, Knowledge Translation Program; University of Toronto, Dalla Lana School of Public Health
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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

Areti Angeliki Veroniki <sup>1,*</sup>	PhD	e-mail: <a href="mailto:aretangeliki.veroniki@unityhealth.to">aretangeliki.veroniki@unityhealth.to</a>
Huda M. Ashoor <sup>1</sup>	BSc	e-mail: <a href="mailto:huda.ashoor@unityhealth.to">huda.ashoor@unityhealth.to</a>
Patricia Rios <sup>1</sup>	MSc	e-mail: <a href="mailto:patricia.rios@unityhealth.to">patricia.rios@unityhealth.to</a>
Georgios Seitidis <sup>2</sup>	MSc	e-mail: <a href="mailto:g.seitidis@uoi.gr">g.seitidis@uoi.gr</a>
Lesley A. Stewart <sup>3</sup>	PhD	e-mail: <a href="mailto:lesley.stewart@york.ac.uk">lesley.stewart@york.ac.uk</a>
Mike Clarke <sup>4</sup>	PhD	e-mail: <a href="mailto:m.clarke@qub.ac.uk">m.clarke@qub.ac.uk</a>
Catrin Tudur Smith <sup>5</sup>	PhD	e-mail: <a href="mailto:cat1@liverpool.ac.uk">cat1@liverpool.ac.uk</a>
Dimitris Mavridis <sup>2</sup>	PhD	e-mail: <a href="mailto:dmavridi@uoi.gr">dmavridi@uoi.gr</a>
Brenda R. Hemmelgarn <sup>6</sup>	PhD	e-mail: <a href="mailto:brenda.hemmelgarn@albertahealthservices.ca">brenda.hemmelgarn@albertahealthservices.ca</a>
Jayna Holroyd-Leduc <sup>7</sup>	MD	e-mail: <a href="mailto:jayna.holroyd-leduc@albertahealthservices.ca">jayna.holroyd-leduc@albertahealthservices.ca</a>
Sharon E. Straus <sup>1,8</sup>	MD	e-mail: <a href="mailto:sharon.straus@utoronto.ca">sharon.straus@utoronto.ca</a>
Andrea C. Tricco <sup>1,9</sup>	PhD	e-mail: <a href="mailto:andrea.tricco@unityhealth.to">andrea.tricco@unityhealth.to</a>

<sup>1</sup> Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

<sup>2</sup> Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece

<sup>3</sup> Centre for Reviews and Dissemination, University of York, York, United Kingdom

<sup>4</sup> Northern Ireland Hub for Trials Methodology Research, Queen's University Belfast, Belfast, United Kingdom

<sup>5</sup> Department of Biostatistics, University of Liverpool, Block F, Waterhouse Building, 1-5 Brownlow Hill, Liverpool, L69 3GL, UK

<sup>6</sup> Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

<sup>7</sup> Department of Medicine, University of Calgary, Calgary, Alberta, Canada

<sup>8</sup> Department of Geriatric Medicine, University of Toronto, Toronto, Ontario, Canada

<sup>9</sup> Epidemiology Division & Institute of Health Policy, Management, and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada



1  
2  
3  
4  
5 **\*Corresponding Author:**

6 Dr. Areti Angeliki Veroniki, MSc, PhD

7  
8 209 Victoria Street, East Building, Toronto, Ontario

9  
10 M5B 1T8, Canada

11  
12  
13 Phone: 416-564-5015; Fax: 416-564-5735; Email: areti-angeliki.veroniki@unityhealth.to

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18 additional file 1); 31 references  
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## 1 **Abstract**

2 Words: 377 (Max 300 words)

3 **Objective:** To examine the comparative efficacy and safety of cognitive enhancers by  
4 patient characteristics for managing Alzheimer's Dementia (AD).

5 **Design:** Systematic review and individual patient data (IPD) network meta-analysis  
6 (NMA)

7 **Data Sources:** MEDLINE, EMBASE, Cochrane Methodology Register, CINAHL,  
8 Ageline and Cochrane Central Register of Controlled Trials up to March 2016.

9 **Participants:** 80 randomized controlled trials (RCTs) including 21,138 adults with AD,  
10 and 12 RCTs with IPD including 6,906 patients.

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

13 **Data extraction and Synthesis:** We requested IPD from authors, sponsors and data  
14 sharing platforms. When IPD were not available, we used aggregate data. We appraised  
15 study quality with the Cochrane risk-of-bias. We conducted a two-stage random-effects  
16 IPD-NMA, and assessed their findings using CINeMA (Confidence in Network meta-  
17 analysis).

18 **Primary and Secondary Outcomes:** We included trials assessing cognition with the  
19 Mini-Mental State Examination (MMSE), and adverse events (AEs).

20 **Results:** Our IPD-NMA compared 9 treatments (including placebo). Donepezil (mean  
21 difference [MD] = 1.41, 95% confidence interval [CI]: 0.51 to 2.32) and  
22 donepezil+memantine (MD = 2.57, 95% CI: 0.07 to 5.07) improved MMSE score (56  
23 RCTs, 11,619 participants; CINeMA score: moderate) compared with placebo. According  
24 to P-score, oral rivastigmine (odds ratio [OR] = 1.26, 95% CI: 0.82 to 1.94, P-score= 16%)  
25 and donepezil (OR = 1.08, 95% CI: 0.87 to 1.35, P-score= 30%) had the least favourable  
26 safety profile, but none of the estimated treatment effects were sufficiently precise when  
27 compared with placebo (45 RCTs, 15,649 patients; CINeMA score: moderate to high). For  
28 moderate to severe impairment, donepezil, memantine and their combination performed  
29 best, but for mild to moderate impairment donepezil and transdermal rivastigmine ranked  
30 best. Adjusting for MMSE baseline differences, oral rivastigmine and galantamine

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4 31 improved MMSE score, whereas when adjusting for comorbidities only oral rivastigmine  
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6 32 was effective.

7 33 **Conclusions:** The choice among the different cognitive enhancers may depend on patient's  
8  
9 34 characteristics. The MDs of all cognitive enhancer regimens except for single-agent oral  
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11 35 rivastigmine, galantamine, and memantine, against placebo were clinically important for  
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13 36 cognition (MD larger than 1.40 MMSE points), but results were quite imprecise. However,  
14  
15 37 two thirds of the published RCTs were associated with high risk of bias for incomplete  
16  
17 38 outcome data, and IPD were only available for 15% of the included RCTs.  
18  
19 39

20 40 **Registration:** PROSPERO # CRD42015023507

21 41 **Funding:** This research was funded by the CIHR Drug Safety and Effectiveness Network  
22  
23 42 (grant number 137713).

24 43 **Keywords:** network meta-analysis; multiple treatments meta-analysis; individual  
25  
26 44 participant data; Nootropic Agents; Alzheimer Disease  
27  
28  
29

### 30 45 **Strengths and limitations of this study**

- 31 46
- 32 47 • This is one of the most comprehensive systematic reviews and network meta-analysis  
33 48 of cognitive enhancers including individual patient data for Alzheimer's Dementia to  
34 49 produce treatment recommendations by patient characteristics.
  - 35 50 • We followed the methodologically rigorous guidelines in the Cochrane Handbook for  
36 51 systematic reviews, and the CINeMA quality assessment guidelines.
  - 37 52 • Access to individual patient data allowed us to 1) observe minor differences between  
38 53 the original published results and our re-analysis, potentially due to differences in  
39 54 imputation methods for missing data or because original studies have excluded some  
40 55 patients, and hence have used a smaller sample size, 2) overcome potential reporting  
41 56 bias, and 3) assess for potential effect modifiers that were not reported in the original  
42 57 publications (e.g., comorbidities, additional medications) and explore for treatment-by-  
43 58 covariate interactions on the patient-level.
  - 44 59 • Two thirds of the included RCTs, were associated with high risk of bias for incomplete  
45 60 outcome data due to attrition.
  - 46 61 • We were unable to include individual patient data for all RCTs (only 15% of the  
47 62 studies shared their individual patient data), highlighting potential availability bias.
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## 62 Introduction

63  
64 Alzheimer's dementia (AD) is the most common type of dementia.<sup>1</sup> Patients living with AD have  
65 a lower quality of life due to deterioration in function, cognition, behavior, and mental health  
66 over time, as well as increased mortality.<sup>2</sup> Pharmacological treatment for AD predominantly  
67 consists of cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and the N-methyl-d-  
68 aspartate (NMDA) receptor antagonist, memantine. All three cholinesterase inhibitors and  
69 memantine are currently the only effective licensed treatments for dementia,<sup>3</sup> but their clinical  
70 effect can be small and there is no convincing evidence that they modify the disease process in  
71 AD.<sup>4</sup> Also, it is unclear whether galantamine, rivastigmine, or donepezil should be used by  
72 patients with severe AD, or whether memantine is the optimal treatment for severe AD.<sup>5</sup>

73  
74 In AD, disease severity and sex are potential effect modifiers. However, aggregate data and  
75 covariates of interest (e.g., sex, disease severity) are not consistently reported across randomized  
76 clinical trials (RCTs).<sup>6</sup> The use of IPD has several advantages, such as it allows for the  
77 exploration of the relationship between treatment effects and patient-level characteristics, and it  
78 overcomes restrictions in using the information reported in the publication among others. The  
79 aim of this study was to examine the comparative efficacy and safety of cognitive enhancers for  
80 patients with different characteristics, such as severities of AD and for females versus males  
81 through a systematic review and individual patient data (IPD) NMA. NMA is an extension of  
82 standard meta-analysis synthesizing different sources of evidence from a network of RCTs  
83 comparing different treatments within a single model. NMA can provide treatment effect  
84 estimates for treatment comparisons that have not studied in a head-to-head study.

## 85 Methods

86  
87 We reported our results according to the Preferred Items for Systematic Reviews and Meta-  
88 analysis (PRISMA) Statement for NMA and PRISMA-IPD.<sup>7,8</sup>

## 90 Protocol

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3 91  
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5 92 The research question and protocol were based on our previous systematic review and NMA.<sup>6</sup>  
6  
7 93 We registered our systematic review protocol with the prospective register of systematic reviews  
8  
9 94 (PROSPERO: CRD42015023507), and published our protocol.<sup>9</sup> Additional information is also  
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11 95 provided in Appendix 1 and Additional File 2. Herein, we briefly summarize our methods.  
12  
13 96

### 14 97 **Eligibility criteria**

15 98  
16  
17 99 We updated our previous systematic review,<sup>6</sup> using similar population, interventions,  
18  
19 100 comparators, study designs and time period (PICOST) criteria. The literature search was updated  
20  
21 101 from January 2015 to March 2016. We included published and English RCTs that assessed  
22  
23 102 cognition via the Mini-Mental State Examination (MMSE; efficacy and primary outcome) and/or  
24  
25 103 adverse events (AE; safety outcome) in adults with Alzheimer's dementia.  
26  
27 104

### 28 105 **IPD collection process**

29 106  
30  
31 107 We contacted the corresponding author followed by the next-in-order author, as presented in  
32  
33 108 each eligible RCT, to obtain IPD. The author contact process was part of a RCT that our team  
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35 109 conducted to assess methods that may optimize response rates for IPD retrieval.<sup>10</sup> We also  
36  
37 110 contacted sponsors of eligible trials, as reported in the publications. We contacted industry  
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39 111 sponsors only, as we were not able to locate contact information for the majority of non-industry  
40  
41 112 sponsors (e.g., grants and university funding). If a study had multiple sponsors, we contacted all  
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43 113 of them. To further facilitate IPD access, we contacted the Clinical Study Data Request  
44  
45 114 (CSDR)<sup>11</sup> and Yale University Open Data Access (YODA) data sharing platforms.<sup>12</sup> If a data  
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47 115 provider was unable to provide IPD we noted the reason.  
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49 116

### 49 117 **Risk of bias and quality appraisal**

50 118  
51  
52 119 We appraised study quality using the Cochrane risk of bias tool.<sup>13</sup> To ensure data consistency<sup>8</sup>  
53  
54 120 we compared IPD with aggregate data reported in the publication. We assessed whether  
55  
56  
57  
58  
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60

1  
2  
3 121 randomization of patients was adequate (i.e., intervention and comparison groups were balanced  
4  
5 122 for important patient characteristics), by comparing numbers and types of patients in each arm.  
6  
7 123

8 124 When at least 10 studies were available for each treatment against placebo, publication bias and  
9  
10 125 small-study effects were examined visually using the comparison adjusted funnel plot under the  
11  
12 126 fixed-effect model.<sup>3</sup> When a funnel plot asymmetry was detected, we performed the Copas  
13  
14 127 selection for the treatment comparisons that were informed by at least 10 studies and for which  
15  
16 128 asymmetry was evident in the funnel plot. We explored the possibility that this was due to  
17  
18 129 publication bias,<sup>14</sup> and made moderate assumptions about the probability of publication of the  
19  
20 130 smaller and larger (in terms of standard error) studies. We assumed that the smallest study had a  
21  
22 131 probability of publication equal to 40-50% and the largest study had a probability of 80-90%.  
23  
24 132 Confidence in NMA findings was assessed for each outcome using CINeMA (Confidence in  
25  
26 133 Network meta-analysis, see Appendix 1 for more details).<sup>15</sup>  
27  
28 134

## 28 135 **Synthesis**

29 136  
30  
31 137 We performed a descriptive analysis using frequencies and distributions of the characteristics of  
32  
33 138 the included patients and treatments. For each outcome, we present the network geometry  
34  
35 139 according to IPD availability. We conducted a two-stage IPD analysis, whereby data were  
36  
37 140 analysed separately in each trial in the first stage and the trial parameter estimates were  
38  
39 141 synthesised in a random-effects meta-analysis or NMA in the second stage.  
40  
41 142

42 143 The summary treatment effects are presented using the odds ratio (OR) or mean difference (MD)  
43  
44 144 along with their corresponding CIs and prediction intervals (PIs).<sup>16</sup> We ranked the interventions  
45  
46 145 for each outcome using the P-scores (and SUCRAs [surface under the cumulative ranking curve]  
47  
48 146 in meta-regression analysis), and present them in a rank-heat plot.<sup>17,18</sup>  
49

## 50 147 **Patient and public involvement**

51  
52 148 Not applicable.  
53  
54  
55  
56  
57  
58  
59  
60

## 149 **Results**

### 150 **Literature search, study selection and IPD obtained**

151  
152 After screening 20,410 titles and abstracts and 1,968 full-text articles, 96 studies fulfilled the  
153 eligibility criteria; 80 unique studies and 16 companion reports (Figure 1a, Appendix 2).

154  
155 (Figure 1 here)

156  
157 Of the 80 RCTs, 55 reported at least one industry-sponsored funder (i.e. 40 studies reported a  
158 single industry-sponsor and 15 multiple industry-sponsors). In the remaining studies, 9 were  
159 publicly-sponsored and 16 did not report any information about funding. We requested IPD by  
160 contacting the corresponding authors for 80 RCTs that included 21,138 participants. None of the  
161 original authors shared their IPD. Fifteen commercial sponsors were then contacted and 6 (40%)  
162 sponsors shared their data through proprietary sponsor-specific platforms. The 6 sponsors were  
163 contacted for 46 RCTs (14,580 participants), and we obtained IPD for 30% (14 RCTs, 8,007  
164 participants) of these RCTs (1,058 total waiting days up to March 9, 2020). The study flow for  
165 obtaining IPD is depicted in Figure 1b.

166  
167 We were able to include 12 (6,906 patients) of 14 RCTs in our NMA due to incompleteness of  
168 provided IPD (Appendix 3). The number of studies with available/non-available IPD from each  
169 data provider along with reasons for non-availability of IPD are presented in Appendix 4.

### 171 **Study and patient characteristics**

172  
173 Most included studies (33%) were multi-national. The mean age of patients ranged from 61 to 86  
174 years. The majority of the RCTs included patients with mild-moderate AD (56%), although the  
175 diagnostic criteria used for AD varied widely (Table 1). The most frequent longest duration of  
176 follow-up was 24 weeks (24 RCTs, 30%; Appendix 5). Important patient characteristics, such as  
177 percent of male and dropout rates, were not balanced across groups in the RCTs with provided  
178 IPD (Appendix 6). Comparing study and patient characteristics of available and non-available

1  
2  
3 179 IPD when a study was industry-sponsored, we found differences in the year of study publication,  
4 study size, and absolute mean difference (Appendix 7).

5 180  
6 181  
7  
8 182 (Table 1 here)

9 183

### 11 184 **Risk of bias and IPD integrity**

12 185

13  
14 186 Using the Cochrane risk-of-bias tool, allocation concealment was at low risk of bias for 43% and  
15 blinding of participants and personnel was low for 64% of the RCTs (Appendix 8). One third of  
16 187 the RCTs had low risk of incomplete outcome data bias due to attrition and almost two thirds had  
17 high potential risk of “other” bias, specifically, funding bias. The other risk of bias item was  
18 188 scored as unclear for 32%. Overall risk of bias was comparable in studies with available and  
19 unavailable IPD (Appendix 9).

20 191

21 192  
22 193 All IPD provided were checked for consistency and results from published RCTs were  
23 reproduced and provided in Appendix 10. High dropout rates were observed in the IPD;  
24 194 experiencing an adverse event was the most common reason for dropout. Despite the high  
25 dropout rates observed in the individual studies, there was no indication of correlation between  
26 195 age and dropout (Appendix 11). Comparison-adjusted funnel plot for MMSE suggested there is  
27 indication for small-study effects (see Appendix 12). In contrast to the standard meta-analysis  
28 196 (MD=1.65 95% CI (0.16, 3.14)), the Copas selection model estimated a pooled treatment effect  
29 for donepezil vs. placebo MD=1.87 95% CI (1.55, 2.20) with between-study variance  $\tau^2= 1.95$ ,  
30 197 and correlation coefficient -0.45 (-0.76, -0.01) reflecting the belief that the propensity for  
31 publication was associated with the observed effect size.

32 201

### 34 204 **Network meta-analysis**

35 205

36 206 In both MMSE and AE outcomes, on average there were no important concerns regarding the  
37 207 transitivity and consistency assumptions (Appendices 13 and 14; design-by-treatment interaction  
38 model MMSE:  $\chi^2= 4.36$ , 13 degrees of freedom (df), p-value= 0.987; AE:  $\chi^2= 3.57$ , 6 df, p-



209 value= 0.735). Below we present the main analysis results compared to placebo. Additional  
210 analyses are presented in Appendix 15-16). The network geometry is presented in Figure 2.

211

212 (Figure 2 here)

213

### 214 **Cognition**

215

216 The NMA for MMSE included 56 RCTs, 9 treatments (including placebo), and 11,619  
217 participants. Nine RCTs (3,625 patients) contributed IPD and 47 RCTs (7,994 patients)  
218 contributed aggregated data to the NMA. Two studies<sup>19,20</sup> did not report MMSE in the final  
219 publication, but in the retrieved IPD we were able to use data for this outcome.

220

#### 221 *NMA of studies with IPD and aggregate data*

222

223 Studies in this NMA compared all available treatments. Donepezil (MD= 1.41, 95% CI: 0.51 to  
224 2.32) and donepezil+memantine (MD= 2.57, 95% CI: 0.07 to 5.07) were superior to placebo in  
225 terms of MMSE score (Appendix 15). Transdermal rivastigmine (MD= 2.11, 95% CI: -0.04 to  
226 4.26), and the combinations donepezil+memantine, galantamine+memantine (MD= 2.24, 95%  
227 CI: -2.13 to 6.61), and transdermal rivastigmine+memantine (MD= 1.79, 95% CI: -1.70 to 5.27)  
228 were associated with a MD from placebo of more than 1.40 MMSE points. A previous study  
229 suggested a MD larger than 1.40 is a minimal clinically important difference (MCID).<sup>21</sup>

230 However, the associated 95% CIs were quite imprecise spanning between a mean decrease below  
231 and a mean increase above the suggested MCID value (Figure 3a). However,

232 donepezil+memantine had the highest likelihood of being the most effective in improving

233 MMSE score (P-score range 79-80%, Figure 4). Confidence in NMA results was moderate

234 (Appendix 17).

235 (Figure 3 here)

236 (Figure 4 here)

237

#### 238 *NMA of studies with aggregate data*

239

1  
2  
3 240 Studies in this NMA compared all available treatments. Donepezil improved MMSE score  
4 significantly (MD= 1·55 95% CI: 0·41 to 2·68). Assuming an MCID of 1·40, results were in  
5 241 agreement with the NMA of IPD and aggregate data, and donepezil+memantine (MD= 2·71,  
6 242 95% CI: -0·17 to 5·60) was likely the most effective in improving MMSE score (P-score= 76%).  
7  
8  
9

10 244

11  
12 245 *NMA of studies with IPD*

13 246

14  
15 247 Studies in this NMA compared placebo, donepezil, oral rivastigmine, transdermal rivastigmine,  
16 248 galantamine, and memantine. Donepezil (MD= 0·70, 95% CI: 0·01 to 1·40) and transdermal  
17 249 rivastigmine (MD= 1·06, 95% CI: 0·04 to 2·08) were superior to placebo, but none of the point  
18 250 estimates reached a previously suggested MCID.<sup>21</sup> The most effective treatment was likely  
19 251 transdermal rivastigmine (P-score= 82%).  
20  
21  
22  
23

24 252

25 253 *Additional analyses using IPD and aggregate data*

26 254

27  
28 255 Overall, additional analyses using both IPD and aggregate data were in agreement with the  
29 256 findings of the main analysis (Appendix 16). Cognitive performance was better in patients with  
30 257 mild to moderate MMSE receiving donepezil (MD= 1·68 95% CI: 0·31 to 3·06, P-score= 69%)  
31 258 and most likely when receiving transdermal rivastigmine (MD= 2·74 95% CI: -0·68 to 6·16, P-  
32 259 score= 81%). In patients with moderate to severe MMSE the combination donepezil+memantine  
33 260 improved MMSE score significantly (MD= 2·49 95% CI: 1·55 to 3·44, P-score=100%), but oral  
34 261 rivastigmine deteriorated MMSE score significantly (MD= -1·00 95% CI: -1·87 to -0·12, P-  
35 262 score= 4%). Donepezil (MD= 1·31 95% CI: 0·66 to 1·96, P-score= 78%) and memantine  
36 263 (MD=0·69 95% CI: 0·07 to 1·31, P-score= 59%) also performed well for patients with moderate  
37 264 to severe cognitive impairment.  
38  
39  
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46 265

47 266 Accounting for the impact of the outlier studies, galantamine+memantine was the second-best  
48 267 cognitive enhancer (MD= 1·87 95% CI: 0·08 to 3·66, P-score=82%) after donepezil+memantine  
49 268 (MD= 2·04 95% CI: 1·03 to 3·05, P-score= 92%). Using only IPD adjusted for comorbidities  
50 269 suggested that oral rivastigmine improves MMSE score (MD= 0·88 95% CI: 0·31 to 1·45, P-  
51 270 score= 75%). Similarly, using IPD adjusted for cognitive impairment assessed with MMSE at  
52 271 baseline suggested that oral rivastigmine (MD= 0·88 95% CI: 0·31 to 1·45, P-score= 69%) and  
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272 galantamine (MD= 0.76 95% CI: 0.34 to 1.18, P-score= 62%) improve MMSE score, but in a  
273 future study, results are only stable for galantamine.

274  
275 Heterogeneity in NMA was high (between-study variance = 5.75, I<sup>2</sup>= 96%) compared also to the  
276 Rhodes et al.<sup>22</sup> empirical distribution (median 0.05, 95% range: 0.00 to 7.56). However,  
277 heterogeneity decreased importantly when excluding outliers (between-study variance = 0.59,  
278 I<sup>2</sup>= 73%), including only patients with moderate to severe AD (between-study variance = 0.18,  
279 I<sup>2</sup>= 44%), restricting to industry-sponsored trials (between-study variance = 0.16, I<sup>2</sup>= 43%), and  
280 using IPD only (between-study variance = 0.12, I<sup>2</sup>= 29%).

281

### 282 *Adverse events*

283

284 A NMA was conducted on adverse events (study definitions are provided in Appendix 18) with  
285 45 RCTs, 9 treatments (including placebo), and 15,649 patients (Figure 2b). In particular, 12  
286 RCTs (6420 patients) contributed to the NMA using their IPD and 33 RCTs (9229 patients)  
287 using their data on their aggregated form. The time taken to achieve at least one AE was  
288 available in 8 studies with available IPD and ranged between 45 and 2228 days (Appendix 19).  
289 Only one study included a patient with a AE occurring earlier than the trial opening and was  
290 excluded from the study.<sup>23</sup>

291

### 292 *NMA of studies with IPD and aggregate data*

293

294 Studies in this NMA compared all available treatments. According to P-score, oral rivastigmine  
295 had the least favourable safety profile regarding AE (OR= 1.26, 95% CI: 0.82 to 1.94, P-score=  
296 16%), followed by donepezil (OR= 1.08, 95% CI: 0.87 to 1.35, P-score= 30%) and  
297 galantamine+memantine (OR= 1.03, 95% CI: 0.45 to 2.39, P-score= 43%), yet in these  
298 comparisons the odds of experiencing an AE were imprecise and not importantly different from  
299 placebo (Figure 3b; Appendices 16, 20). Confidence in NMA results ranged between moderate  
300 and high (Appendix 17).

301

### 302 *NMA of studies with aggregate data*

303

1  
2  
3 304 Studies in this NMA compared all available treatments. Results were mainly consistent with  
4  
5 305 NMA of IPD and aggregate data, but memantine was 0·70 times less likely to experience an AE  
6  
7 306 than placebo, with an OR ranging from 0·51 to 0·97 (P-score= 77%).  
8  
9 307

#### 10 308 *NMA of studies with IPD*

11 309  
12  
13 310 Studies in this NMA compared placebo, donepezil, oral rivastigmine, transdermal rivastigmine,  
14  
15 311 galantamine, and memantine. Results were on average consistent with NMA of IPD and  
16  
17 312 aggregate data.  
18  
19 313

#### 20 314 *Additional analyses using IPD and aggregate data*

21 315  
22  
23 316 Additional analyses using both IPD and aggregate data, showed that memantine was 0·61 times  
24  
25 317 less likely to experience an AE than placebo when using study duration as a covariate, with an  
26  
27 318 OR ranging from 0·37 to 0·93 (P-score= 88%). Restricting to low risk of bias for incomplete  
28  
29 319 outcome data, galantamine was associated with significantly lower odds of a AE (OR= 0·69,  
30  
31 320 95% CI: 0·50 to 0·97, P-score= 80%).  
32  
321

33 322 Heterogeneity in NMA was low (between-study variance = 0·04, I<sup>2</sup>= 22%) compared to the  
34  
35 323 Turner *et al.*<sup>24</sup> empirical distribution (median 0·12, 95% range: 0·01 to 2·63). Heterogeneity  
36  
37 324 decreased importantly when restricting to aggregate data (between-study variance = 0·00, I<sup>2</sup>=  
38  
39 325 0%), low risk of bias for incomplete outcome data (between-study variance = 0·02, I<sup>2</sup>= 10%),  
40  
41 326 patients with moderate to severe cognitive impairment (between-study variance = 0·00, I<sup>2</sup>= 0%),  
42  
43 327 and when adjusting for study duration (between-study variance = 0·03), year of publication  
44  
45 328 (between-study variance = 0·02), mean age (between-study variance = 0·02) or sex (between-  
46  
47 329 study variance = 0·03).  
48

## 49 330 **Discussion**

50 331  
51  
52 332 We compared the efficacy and safety of cognitive enhancers regarding MMSE and AE outcomes  
53  
54 333 to update our previous systematic review<sup>6</sup> and included studies with both aggregate data and  
55  
56 334 IPD. Our results are in agreement with our previous systematic review,<sup>6</sup> and show that  
57  
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59  
60

1  
2  
3 335 donepezil+memantine, donepezil alone and transdermal rivastigmine were the most effective  
4  
5 336 treatments for improving MMSE score. However, heterogeneity was a major concern, which  
6  
7 337 requires careful consideration before suggesting the use of cognitive enhancers, and particularly  
8  
9 338 when the efficacy is not clear on the patient's characteristics. This was also captured by PIs, but  
10  
11 339 their interpretation requires caution due to evidence of funnel plot asymmetry in the MMSE  
12  
13 340 outcome. Overall, PIs are expected to include the true intervention effect expected in future  
14  
15 341 studies, and they incorporate an extra component of variance, specifically between-study  
16  
17 342 heterogeneity. In the absence of heterogeneity, confidence intervals and PIs are equal. According  
18  
19 343 to the P-score intervention ranking, both donepezil+memantine and transdermal rivastigmine had  
20  
21 344 a favourable safety profile regarding AE, whereas the therapy with the least favourable profile  
22  
23 345 was oral rivastigmine followed by donepezil. However, none of the estimated treatment effects  
24  
25 346 were sufficiently precise when cognitive enhancers were compared with the placebo group.  
26  
27 347 CINeMA suggested that within-study bias and reporting bias were the highest concerns for the  
28  
29 348 MMSE outcome, whereas within-study bias and imprecision of effect estimates were the highest  
30  
31 349 concerns for the AE outcome.

30  
31 350  
32  
33 351 Overall, the choice among the different cognitive enhancers may depend on the patient's  
34  
35 352 characteristics. In participants with moderate to severe cognitive impairment (defined by  
36  
37 353 MMSE), a larger improvement in cognitive performance was observed for donepezil and  
38  
39 354 memantine, and their combination (donepezil+memantine), and these efficacy-related results are  
40  
41 355 expected to also be reflected when a future study becomes available. The least effective  
42  
43 356 cognitive enhancer in participants with moderate to severe cognitive impairment was oral  
44  
45 357 rivastigmine. For patients with mild to moderate impairments based on MMSE scores, donepezil  
46  
47 358 and transdermal rivastigmine were most likely the best performing cognitive enhancers. For  
48  
49 359 patients with moderate to severe cognitive impairment, cognitive enhancers were well tolerated.  
50  
51 360 For patients with mild to moderate cognitive impairment, all except for memantine and its  
52  
53 361 combination with transdermal rivastigmine, were associated with increased odds of an AE, yet  
54  
55 362 none of these results reached statistical significance. Overall, memantine was associated with  
56  
57 363 lower odds of an AE than placebo, yet this was statistically significant only in the subnetwork  
58  
59 364 analysis including aggregate data (i.e., studies without IPD) and the meta-regression analysis  
60  
365 using study duration as a covariate. However, acknowledging for heterogeneity in the network,

1  
2  
3 366 PIs suggested that results are inconclusive and the odds of AE could not be differentiated  
4  
5 367 between memantine and placebo. Of note, the accuracy of AE reporting may be impacted by the  
6  
7 368 degree of cognitive impairment. Using IPD only and adjusting for MMSE baseline differences,  
8  
9 369 (as shown in Appendix 16, Mean Difference: NMA of studies with IPD adjusted for baseline  
10  
11 370 cognitive impairment), oral rivastigmine and galantamine improved MMSE score, whereas when  
12  
13 371 adjusting for comorbidities only oral rivastigmine was effective, but results can change in a  
14  
15 372 future study. Considering a MCID equal to 1·40 points,<sup>21</sup> the MDs of all cognitive enhancer  
16  
17 373 regimens except for single-agent oral rivastigmine, galantamine, and memantine, against placebo  
18  
19 374 were clinically important for cognition, but these were associated with high uncertainty.  
20  
21 375 However, the 1·40 MMSE cut-off value is not a widely adopted MCID. Our results did not differ  
22  
23 376 by participant characteristics sex, age, and other medications, or by study characteristics, study  
24  
25 377 duration and year of publication. However, these findings might be due to low power since meta-  
26  
27 378 regression analyses depend on the number and size of studies, magnitude of the relationship  
28  
29 379 between the covariate and effect size, along with its precision and heterogeneity.<sup>25</sup>

30  
31 380  
32  
33 381 To the best of our knowledge, our study was the first to add IPD in a NMA of cognitive  
34  
35 382 enhancers for patients with Alzheimer's Dementia to produce treatment recommendations by  
36  
37 383 patient characteristics. We followed the methods guidelines in the Cochrane Handbook for  
38  
39 384 systematic reviews,<sup>26</sup> the reporting guidelines in the PRISMA-NMA and PRISMA-IPD  
40  
41 385 statements,<sup>7,8</sup> and the CINeMA quality assessment guidelines.<sup>15</sup> Compared to previous  
42  
43 386 systematic reviews, we included a larger number of studies and/or studies with shared IPD,  
44  
45 387 compared in a wider range of cognitive enhancers.<sup>6,27</sup> Our results are in agreement with previous  
46  
47 388 studies overall. Access to IPD allowed us to observe minor differences between the original  
48  
49 389 published results and our re-analysis. An explanation in these differences may be that many  
50  
51 390 studies used the last-observation-carried-forward imputation method, whereas we used the  
52  
53 391 available case analysis when assessing MMSE. Another potential explanation might be that  
54  
55 392 original studies excluded some patients, and hence used a smaller sample size.

56  
57 393  
58  
59 394 Comparing NMA, results between aggregate data and IPD were in agreement. The only  
60  
61 395 difference was observed in transdermal rivastigmine that was associated with a MCID of greater  
62  
63 396 than 1·40 MMSE points against placebo in the aggregate data NMA compared to the IPD NMA,

1  
2  
3 397 yet a statistically significant improvement was achieved in the IPD NMA. The inclusion of IPD  
4  
5 398 in our NMA, allowed us to overcome potential reporting bias and to include IPD for 1) a study  
6  
7 399 that we previously were unable to include since arm-level data were not reported in the RCT  
8  
9 400 publication,<sup>23</sup> and 2) two studies that did not report MMSE results in their publications.<sup>19,20</sup> The  
10  
11 401 use of IPD also allowed us to assess for potential effect modifiers that were not reported in the  
12  
13 402 original publications (e.g., comorbidities, additional medications) and explore for treatment-by-  
14  
15 403 covariate interactions on the patient-level. Several challenges were encountered during the IPD  
16  
17 404 request from sponsors, showing that repositories are not a panacea (Appendix 21).  
18  
19 405

20  
21 406 An important finding of our review is that the two thirds of the published RCTs, were associated  
22  
23 407 with high risk of bias for incomplete outcome data due to attrition, and the majority of these  
24  
25 408 RCTs used the last-observation-carried-forward technique for missing data. This approach may  
26  
27 409 bias results favouring cognitive enhancers, since the dropout rates were greater in the treatment  
28  
29 410 group compared to the placebo group in 63% of the included studies and because dementia is a  
30  
31 411 progressive disease. Of the 27 studies comparing treatment against placebo and reporting the  
32  
33 412 number of dropouts, 17 studies had a greater dropout rate in the treatment group (treatment  
34  
35 413 group: median dropout rate= 28% IQR [17% to 39%]; placebo group: median dropout rate= 21%  
36  
37 414 IQR [15% to 31%]). Last-observation-carried-forward is an inappropriate imputation method for  
38  
39 415 Alzheimer's Dementia studies, since it ignores expected deterioration of the patient's condition  
40  
41 416 and stabilizes the outcome at the value observed at the time of dropout (i.e., the last  
42  
43 417 observation).<sup>28</sup> Restricting to low risk of attrition bias studies, we found that galantamine was  
44  
45 418 significantly associated with decreased odds of experiencing an AE.  
46  
47 419

48  
49 420 Our study has limitations worth mentioning. First, we were unable to include IPD for all eligible  
50  
51 421 studies (only 15% of the included RCTs shared their IPD), highlighting potential availability bias  
52  
53 422 for IPD. However, recent simulations have shown that combining IPD and aggregate data in a  
54  
55 423 NMA can significantly improve precision, reduce bias, and increase information compared to  
56  
57 424 NMA relying on aggregated data alone.<sup>29</sup> Second, missing data is a big concern in the published  
58  
59 425 RCTs for AD. We found high rates of dropouts from experiencing an adverse event and the  
60  
426 patients' characteristics that may increase the chances of such adverse reactions prior to  
427 administering these cognitive enhancers should further be explored. To assess the impact of

1  
2  
3 428 missing data in our NMA, we applied the informative missingness of difference in means.<sup>30</sup>  
4  
5 429 However, future studies should explore the characteristics of missing participants and specific  
6  
7 430 adverse events. Third, the lack of studies in certain treatment comparisons may have affected the  
8  
9 431 P-score calculation and treatment ranking. In particular, polytherapies were informed by  
10  
11 432 maximum two studies, and ranking may have been in favour of the complex intervention group  
12  
13 433 with the smaller number of studies.<sup>31</sup> For example, in MMSE the polytherapies including  
14  
15 434 memantine in conjunction with one of the three treatments donepezil, galantamine, transdermal  
16  
17 435 rivastigmine had a P-score  $\geq 60\%$ , but these all had wide 95% CIs for MD. As such, ranking  
18  
19 436 should be interpreted with caution and along with the estimated effect sizes and their uncertainty  
20  
21 437 measures. Fourth, the comparison-adjusted funnel plot for MMSE suggested there is an  
22  
23 438 indication for small-study effects pointing to the treatment being better, and results should be  
24  
25 439 interpreted with caution. This may also be related to the potential risk of funding bias, since the  
26  
27 440 majority of the included studies were industry-sponsored and IPD were retrieved only from  
28  
29 441 industry-sponsored studies favouring cognitive enhancers over placebo. Overall, MMSE score is  
30  
31 442 only a surrogate maker for determining the impact of treatments on dementia. A full assessment  
32  
33 443 that considers the potential impact of treatments on cognition, function and behavioural  
34  
35 444 symptoms needs to be considered within the clinical context. Fifth, differences in patient  
36  
37 445 characteristics, such as sex, were observed in the RCTs with provided IPD, which increased  
38  
39 446 heterogeneity across studies. To account for these differences, we used the fully adjusted  
40  
41 447 treatment effect estimates in the IPD analyses and the primary NMA analysis. Also, at the NMA  
42  
43 448 level, we found that on average there were no important differences across treatment  
44  
45 449 comparisons to threaten the transitivity assumption. Sixth, there are clinically important  
46  
47 450 limitations associated with this review, including consistent definition of outcome measures  
48  
49 451 across studies, a well-established MCID for the MMSE score, lack of consideration of drug  
50  
51 452 doses due to inconsistent reporting and data availability bias that we were unable to overcome  
52  
53 453 (15% of the studies shared their IPD). Future studies are needed to establish ranking efficacy in  
54  
55 454 drug doses and combination of interventions across different disease severity categories.  
56  
57 455 Seventh, the literature searches were conducted 5 years ago and additional relevant studies may  
58  
59 456 be available. However, obtaining IPD in a timely manner was very challenging and required  
60  
457 more time than anticipated (challenges to obtain IPD are outlined in Appendix 21). Similar to all  
458  
systematic reviews, the evidence should be regularly updated.



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3 459  
4  
5 460 We expect that our findings will increase scientific knowledge, because people with Alzheimer's  
6  
7 461 Dementia require personalized medicine to optimize their healthcare. Well-conducted meta-  
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9 462 analyses of IPD are considered the 'gold-standard' and influence patient care since patient-level  
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11 463 data can be provided to facilitate tailored decision making. However, results from meta-analyses  
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13 464 of IPD are likely subject to retrieval bias and awareness of these limitations and their potential  
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15 465 impact on findings is required.  
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For peer review only

## 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.

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 categorized data, appraised quality, and edited the manuscript.

SES and ACT interpreted results and edited the manuscript.

ACT and HMA contacted authors. LAS, MC, CTS, DM, BRH, JHL provided input into the design, interpreted results, and edited the manuscript.

All authors read and approved the final manuscript.

## Declaration of interests

The authors declare that they have no competing interests.

## Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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21 530 Not applicable.  
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## 606 Figure Captions

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608 **Figure 1.** Flow diagram for study inclusion in the review (a) and studies retrieved with  
609 individual patient data (b).

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611 **Figure 2.** Network diagrams for (a) MMSE and (b) AE outcomes. The size of each node and line  
612 indicates the number of studies included in each treatment comparison. The number of studies  
613 per treatment comparison is presented on each edge, and the number of studies with individual  
614 patient data (IPD) is depicted in a parenthesis. Orange coloured edges are informed by both IPD  
615 and aggregate data, whereas black coloured edges are informed by aggregate data only.

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617 **Figure 3.** Forest plot of network meta-analysis (NMA) results for all cognitive enhancers versus  
618 placebo in (a) MMSE outcome, and (b) AE outcome. NMA results are presented for i) aggregate  
619 data (AD) and fully adjusted results from studies with available individual patient data (IPD), ii)  
620 AD and crude results from studies with available IPD, iii) AD only (studies with available IPD  
621 are not included in the analysis), and iv) crude results from individual studies with individual  
622 patient data (IPD).

623

624 **Figure 4.** Rank-heat plot of P-scores for 9 treatments, including placebo, studied in randomized  
625 clinical trials with patients with Alzheimer's Dementia assessing MMSE. Circles from inside out  
626 present results for different network meta-analyses including: i) aggregate data (AD) only  
627 (studies with available IPD are not included in the analysis), ii) crude results from individual  
628 studies with individual patient data (IPD), iii) AD and crude results from studies with available  
629 IPD, and iv) AD and fully adjusted results from studies with available IPD. Numbers within each  
630 sector correspond to the P-score values as calculated in each model.

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631 **Tables**

632

<b>Table 1· Study and patient characteristics</b>		
	<b>AD (N=80)</b>	<b>IPD (N=12)</b>
<b>Total # participants</b>	21,138	5839
<b>Longest duration of follow-up in weeks: mean (range)</b>	28·28 (8 - 208)	29·33 (12 - 104)
<b>Mean number of patients (range)</b>	264·23 (14 - 2,045)	486·58 (123 - 2,045)
<b>Mean age in years (range)</b>	74·64 (61 - 85·7)	73·94 (70·4 - 78)
<b>Mean % Female (range)</b>	61·35 (3 - 89)	62·76 (53·68 - 81)
<b>Country of conduct: frequency (%)</b>		
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)	-
United Kingdom	6 (7·50)	1 (8·33)
United States	15 (18·75)	-
Multi-national	26 (32·50)	9 (75·00)
<b>Interventions examined: frequency*</b>		
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)
<b>Effectiveness outcomes reported: frequency*</b>		
Mini-Mental State Examination	57 (71·25)	6 (50·00)
Adverse Events	46 (57·50)	12 (100·00)
<b>Funding</b>		
Industry-sponsored	48 (60·00)	12 (100·00)
Publicly-sponsored†	9 (11·25)	-
Mixed	7 (8·75)	-
Not Reported	16 (20·0)	-
<b>Severity of Alzheimer's dementia: frequency (%)</b>		
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)
<b>Diagnostic criteria for Alzheimer's dementia: frequency*</b>		
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)
Magnetic Resonance Imaging/Computerized Tomography	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)

**Abbreviations:** -, not applicable

\* 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

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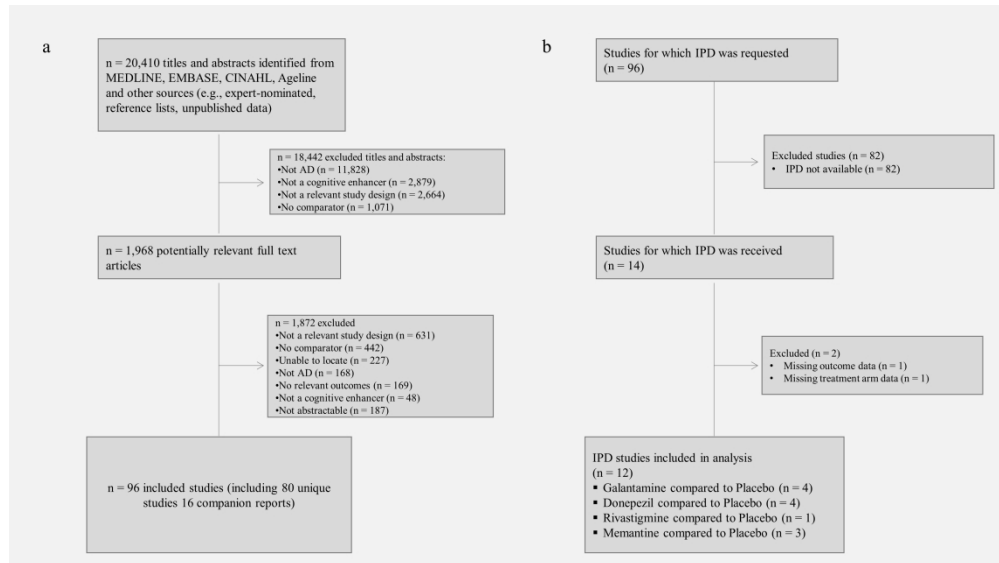
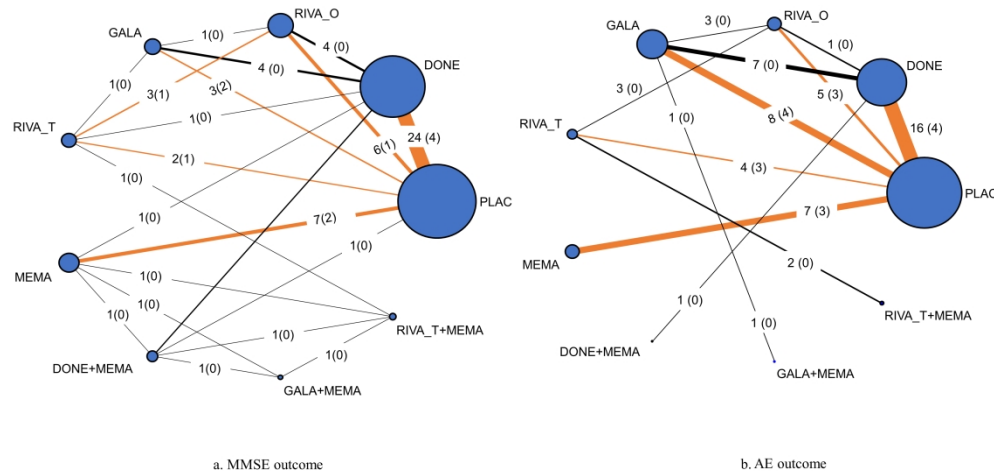


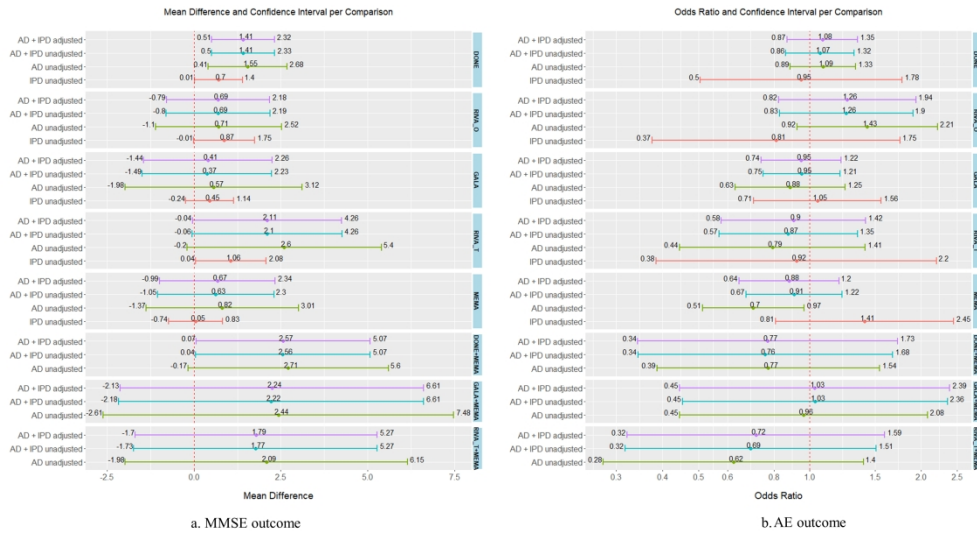
Figure 1. Flow diagram for study inclusion in the review (a) and studies retrieved with individual patient data (b).

338x190mm (300 x 300 DPI)



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.

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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 individual patient data (IPD).

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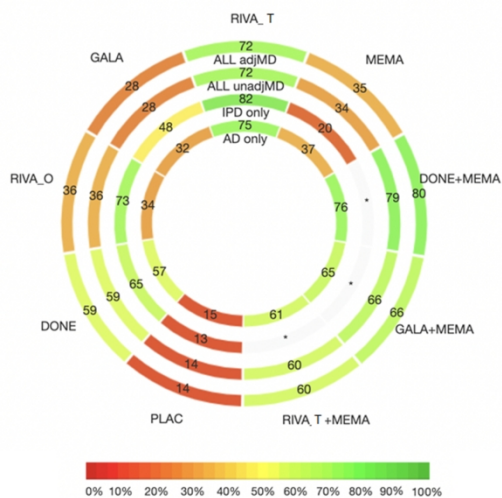


Figure 4. Rank-heat plot of P-scores for 9 treatments, including placebo, studied in randomized clinical trials with patients with Alzheimer’s Dementia assessing MMSE. Circles from inside out present results for different network meta-analyses including: i) aggregate data (AD) only (studies with available 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.

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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**

Appendix 1: Additional information on the methods used in the review .....	2
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## 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,<sup>4</sup> 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.<sup>10</sup> 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:<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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

1  
2  
3 corresponding comparison-specific effect (obtained from standard meta-analysis) against the corresponding  
4 study-specific standard error. We used the fixed effect model for the standard meta-analysis performed for each  
5 treatment comparison, ordered treatments chronologically according to year of availability in Canada, and used  
6 only treatment comparisons versus placebo. We used the *netfunnel* command in Stata to produce the  
7 comparison-adjusted funnel plot.<sup>4</sup>

8  
9 For imprecision, we considered a MD=1.4 and a OR=1 as a clinically important size of effect for  
10 MMSE and AE, respectively, and followed the CINeMA guidelines for exploring whether statistical  
11 significance and clinical importance coincide. Similarly, heterogeneity and incoherence (i.e. inconsistency) were  
12 assessed by following the standard CINeMA approach.

13  
14 CINeMA assesses the credibility of the NMA results and heterogeneity examining the range of both  
15 confidence intervals (CIs; which do not capture heterogeneity) and prediction intervals (PIs; which capture  
16 heterogeneity) in relation to their equivalence. If a PI includes values that lead to a different conclusion than an  
17 assessment based on the corresponding CI, then this suggests that there is considerable heterogeneity. PIs are  
18 expected to include the true intervention effects in future studies with characteristics similar to the existing  
19 studies, and they incorporate the extent of between-study heterogeneity.<sup>5,6</sup> In the presence of considerable  
20 heterogeneity, they are wide to include intervention effects with different implications for practice. However,  
21 caution is needed in the interpretation of results in the presence of funnel plot asymmetry, since PIs are based on  
22 the assumption of a normal distribution for the study-specific effects and as such they may be problematic if the  
23 data do not follow a normal distribution.

### 24 *Statistical Analysis*

25  
26 We performed a descriptive analysis using frequencies and percentages of the discrete characteristics of  
27 the included patients and treatments of the eligible studies. We explored the distributions of the continuous  
28 patient characteristics per outcome and treatment group using means and standard deviations. For studies not  
29 providing outcome results for a certain outcome, we presented distributions of the available and requested  
30 patient characteristics, whenever available. Outliers for each patient characteristic were also explored in each  
31 study dataset using boxplots. We also recorded the number of missing participants per treatment group and  
32 overall. We compared the characteristics of the unavailable and the available by the sponsors' studies. In  
33 particular, we explored whether these were well-conducted according to overall risk of bias, and compared  
34 distributions of mean participant age, publication year, study duration, study size, percent male, and magnitude  
35 of treatment effect, to assess for potential bias in IPD sharing. We conducted a two-stage analysis for both  
36 standard meta-analysis and NMA. The network geometry was explored through the presentation of network  
37 plots.

### 38 *First stage*

39  
40 All IPD from included studies were first aggregated to study-level summary statistics using each  
41 sponsor's portal. The use of different platforms and failure to obtain IPD from all studies restricted us from  
42 combining IPD in a one-stage analysis. For each separate study with IPD available, we fitted a logistic  
43 regression model for the binary outcome and a linear regression model for the continuous outcome. For MMSE,  
44 we considered the longest duration of follow-up per study (most frequently at week 24). In the shared IPD,  
45 when we were unable to make a judgement on first and last date of visit per patient, we used the older coded  
46 date and the newest coded date as baseline and final value for each patient respectively.

47  
48 Initially, we did not adjust for any of the patient characteristics provided, but in a subsequent analysis  
49 we included patient-level covariates with as many interaction terms in the model as the patient characteristics  
50 were provided (considering only the ones we have asked for). For each study, we obtained the adjusted odds  
51 ratio (OR) for binary data and adjusted mean difference (MD) for continuous data, along their corresponding  
52 95% CI. We adjusted for any of the following variables that were available in each study: age, sex, severity of  
53 Alzheimer's disease (e.g., baseline Mini-Mental State Examination [MMSE] level), presence of behavioural  
54 disturbance, comorbidity, and other medications. The first stage of the IPD analyses were conducted in  
55 RStudio,<sup>7</sup> which was available in data providers. Additional medications and comorbid conditions were grouped  
56 into broader categories according to their clinical relevance to increase power in our analysis (e.g., grouped  
57 medications as anti-psychotics, anti-depressants, and cognitive enhancers, as well as comorbid conditions as  
58 psychiatric, neurological, and cardiac disorders). Eligible studies with insufficient data to derive a pairwise  
59 estimate for NMA were summarized descriptively without performing a statistical analysis.



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3 We applied an available case analysis for each study, since we were unable to install R packages in  
4 most sponsor-specific platforms, and hence we applied a consistent approach across all IPD datasets. We  
5 explored the impact of missing data during the second stage of analysis. Reasons for missing participants and  
6 time taken to have a adverse event were captured (when available).  
7

8 We synthesized IPD at the first stage in four different proprietary sponsor-specific platforms. Analyses  
9 were conducted in the RStudio using different R versions<sup>7</sup> according to what was provided in each sponsor's  
10 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  
11 Lundbeck.  
12

### 13 *Second stage*

14 Since we were not successful in obtaining IPD for all eligible studies, we combined both IPD and  
15 aggregate data in a single meta-analysis or NMA model. Both IPD and aggregate data studies shared the same  
16 amount of heterogeneity. In both meta-analysis and NMA models, we combined the adjusted IPD estimates with  
17 the aggregate data (main analysis). As a secondary analysis, we combined the unadjusted estimates from retrieved  
18 IPD with the evidence provided by the aggregated data studies in a joint NMA model. A common-within network  
19 between-study variance was assumed across comparisons for all NMA models.<sup>8</sup> We estimated the between-study  
20 variance using the DerSimonian and Laird<sup>9</sup> method and compared it with the relevant distributions provided by  
21 Turner et al<sup>10</sup> and Rhodes et al<sup>11</sup> to assess heterogeneity. We also calculated  $I^2$  on the NMA level to quantify  
22 overall heterogeneity and inconsistency in each outcome.  
23

24 To assess the validity of the transitivity assumption for each outcome, we assessed the distribution of  
25 potential effect modifiers (e.g., age, sex) across treatment comparisons in each network.<sup>12-14</sup> We visually inspected  
26 similarity and assessed whether these characteristics were likely to modify the treatment effect. We evaluated the  
27 consistency assumption using the design-by-treatment interaction model<sup>15 16</sup> and the loop-specific method.<sup>17 18</sup> In  
28 the presence of statistically significant inconsistency, we checked the data for discrepancies and if none were  
29 identified, we planned to conduct subgroup NMA or network meta-regression analysis adjusting for potential  
30 variables influencing the results.  
31

32 We conducted additional NMA analyses for all potential effect modifiers requested from data  
33 providers. If relevant data were not available in the IPD, we used aggregate data of the relevant publications.  
34 Additional NMA analyses included: 1) subgroup analysis for industry vs. publicly sponsored studies, for studies  
35 with available IPD vs. studies with aggregate data (unadjusted estimates), and for AD severity, classified  
36 according to MMSE scores using the National Institute for Health and Care Excellence categories: mild (21–  
37 24), moderate (10–20), severe (<10),<sup>19</sup> 2) network meta-regression accounting for study duration, year of  
38 publication, mean age, and sex (% of male participants) effect modifiers separately and assuming a common  
39 regression coefficient across comparisons (studies with aggregate data were used only; studies with available  
40 IPD were pooled in a NMA separately adjusted for available covariates at first stage), 3) sensitivity analysis  
41 including studies with low risk of bias for allocation concealment and incomplete outcome data items, as these  
42 items may have an important impact on the meta-analysis results according to our previous NMA,<sup>20</sup> and 4) the  
43 'informative missingness difference of means' (IMDoM) imputation method<sup>21</sup> for MMSE for the aggregate data  
44 studies to assess the impact of missing data in our NMA. In all additional NMA analyses, we used the adjusted  
45 effect estimates derived from the IPD within-study analysis and the aggregate data extracted from the eligible  
46 publications. Network meta-regression was performed in a Bayesian setting using OpenBUGS version 3.2.3,  
47 non-informative priors for all parameters in the model and a half-normal prior for the between standard  
48 deviation. We compared the results of the additional models by evaluating the treatment effect estimates and  
49 ranking statistics, as well as monitoring the reduction in the between-study variance.  
50

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

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4 Meta-analysis and NMA at the 2<sup>nd</sup> stage were conducted in the RStudio using R version 3.6.2 and the  
5 *meta*<sup>28</sup> and *netmeta*<sup>29</sup> packages, respectively.  
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## Appendix 2: Studies included in the systematic review

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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<sup>1</sup> of 859 participants comparing transdermal rivastigmine vs. placebo included only IPD for the placebo arm. Another study<sup>2</sup> 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 cm<sup>2</sup> group, 287 to the rivastigmine patch 10 cm<sup>2</sup> 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

<sup>1</sup>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.

<sup>2</sup>Wilkinson D, Murray J. Galantamine: a randomized, double-blind, dose comparison in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2001; 16(9): 852-7.

## 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
	Johansen, 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/Allergan	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-Padullés, 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 Britain, 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

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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

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## 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%)	<ul style="list-style-type: none"> <li>• intercurrent illness (1 [2%] – donepezil = 1; placebo = 0),</li> <li>• request of patient or investigator (4 [7%] –</li> </ul>	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

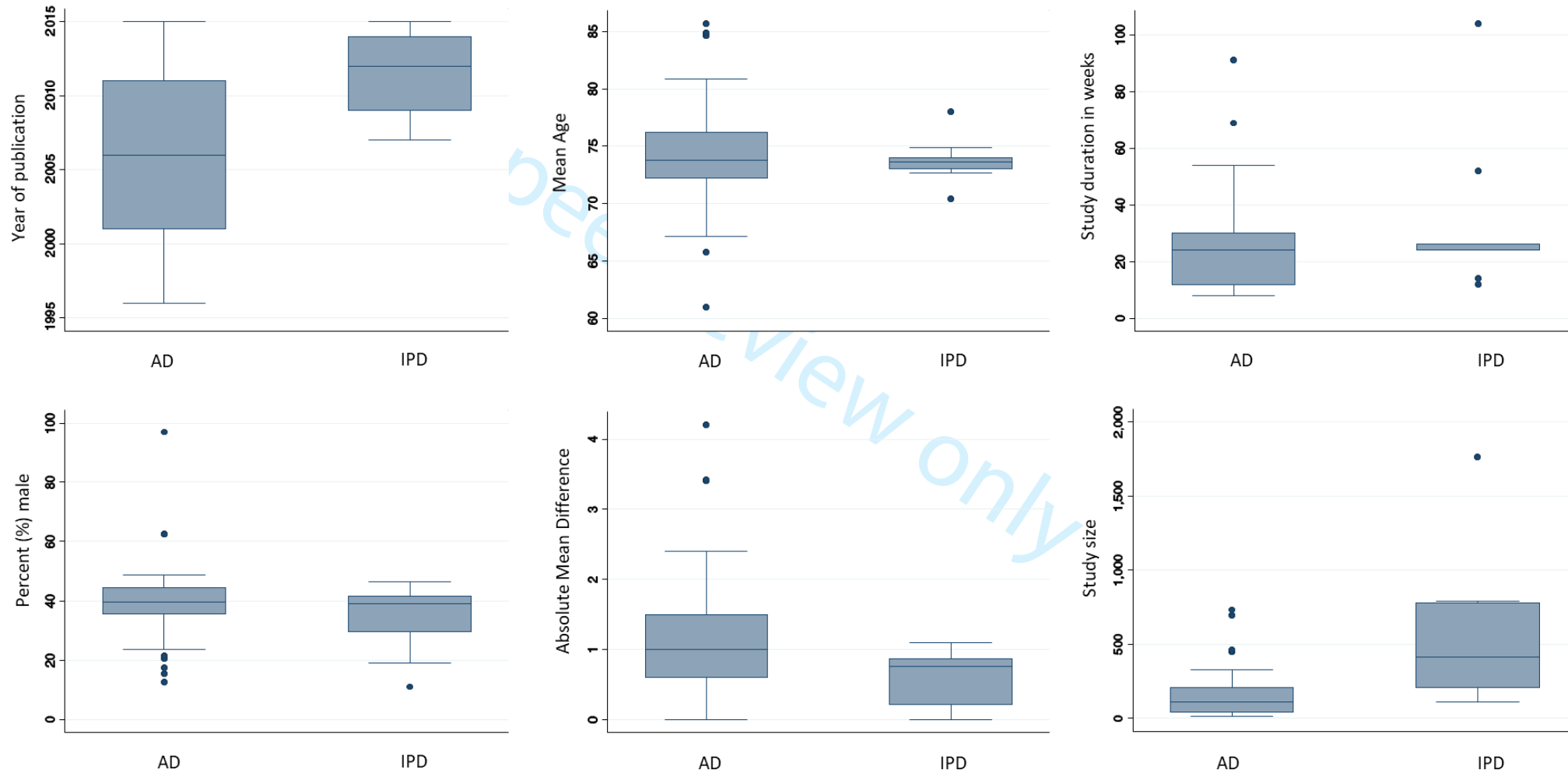
† The MMSE final value comes from visit 8 (last available visit in IPD). MMSE was not reported in study publication

**Abbreviations:** AD, Alzheimer's Dementia; IPD, individual patient data; MMSE, Mini-Mental State Examination; NR, not reported; N/A, not applicable; AE, adverse event

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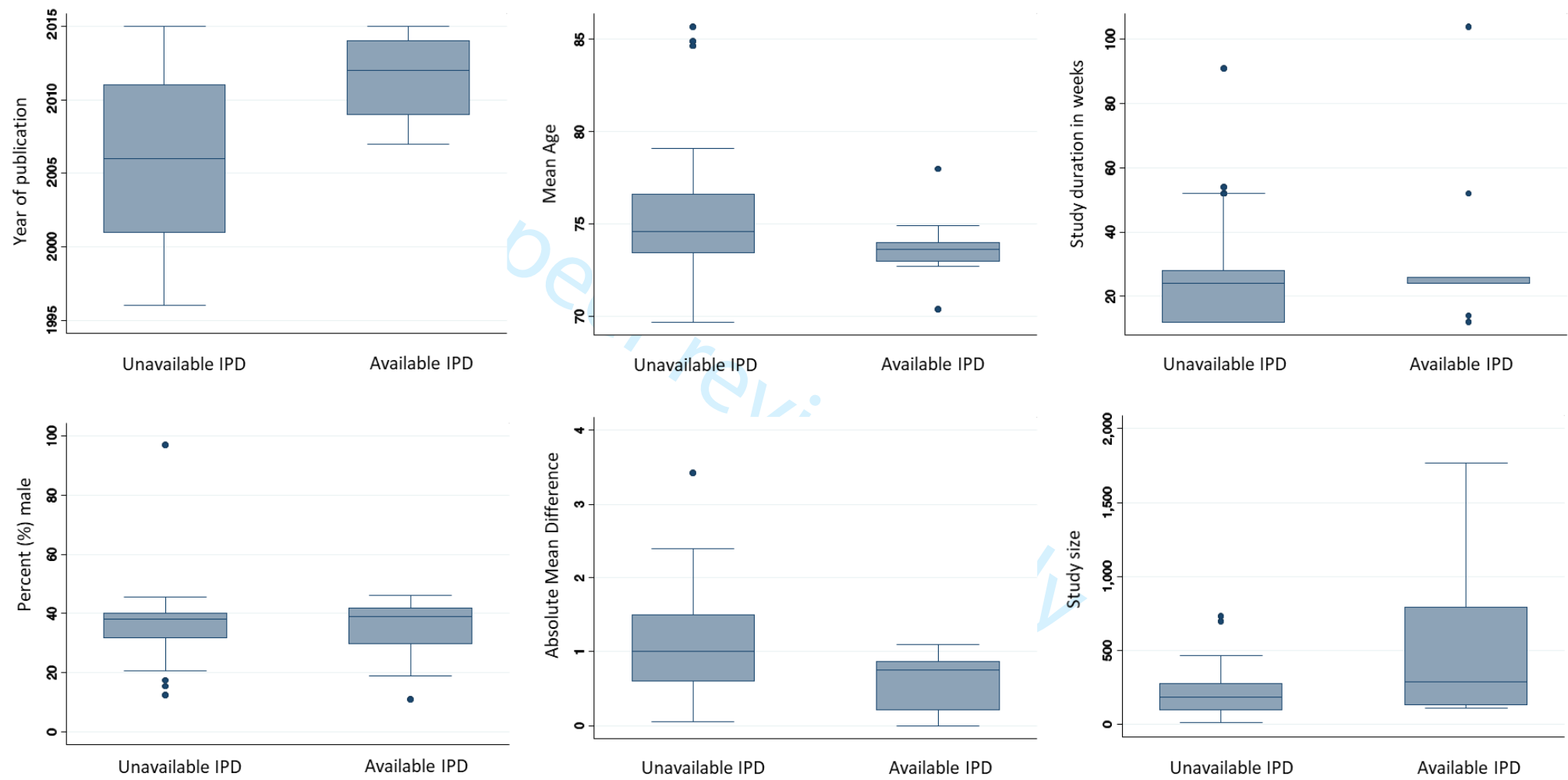
**Appendix 7: Comparison of studies with shared IPD with (a) all remaining studies and (b) studies for which sponsors claimed unavailable IPD.** AD: aggregate data; IPD: individual patient data

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)



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## 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

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3	Shao, 2015	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
4	Shimizu, 2015	Low	Unclear	High	Low	High	Unclear	Unclear
5	Sole-Padulles, 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
6	Tariot, 2000	Low	Unclear	Low	Low	High	Low	High
7	Tariot, 2001	Low	Low	Low	Low	Unclear	Unclear	High
8	Thomas, 2001	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
9	Wilcock, 2003	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
10	Wilkinson, 2001	Low	Low	Low	Low	High	Unclear	High
11	Wilkinson, 2002	Low	Low	Low	Low	High	Unclear	High
12	Wilkinson, 2012	Low	High	Low	Low	High	Low	High
13	Winblad, 2001	Low	Unclear	Unclear	Low	High	Unclear	High
14	Winblad, 2006	Low	Low	Low	Low	High	Low	High
15	Winblad, 2007	Low	Low	Low	Low	High	Unclear	High
16	Yi, 2005	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
17	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,

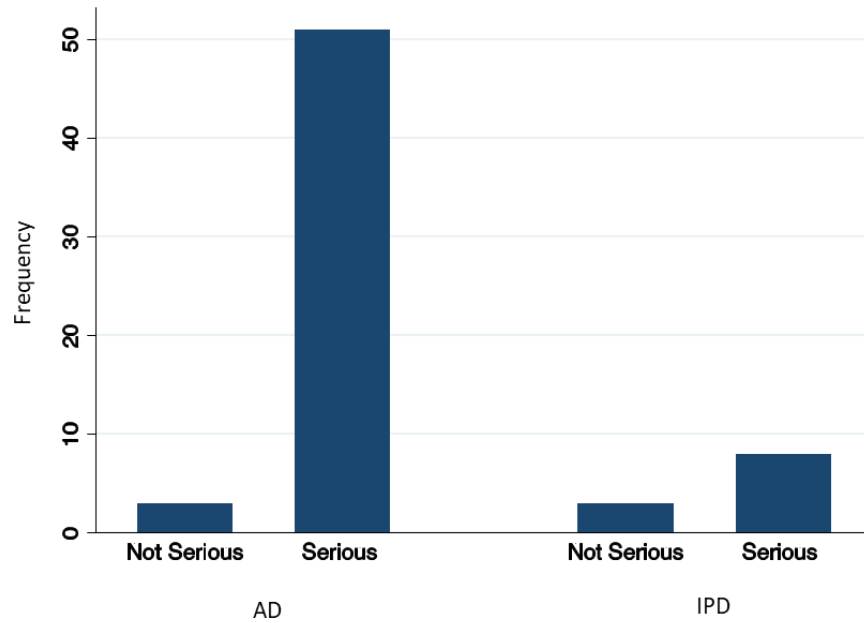
b) *high risk of bias* when there was at least one important risk of bias. For example, when the study had:

- 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.

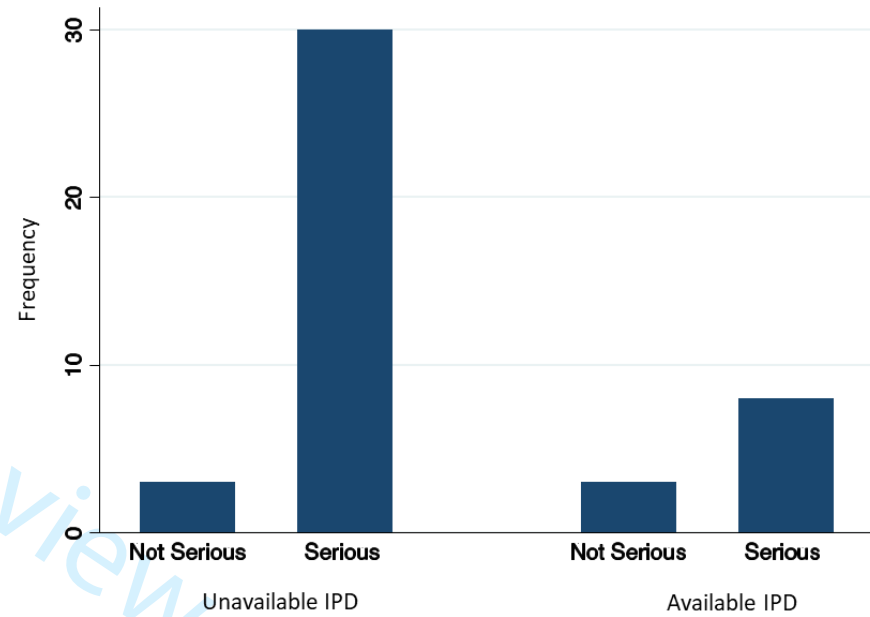
c) *unclear risk of bias* when there was a potential for bias, but there was either:

- 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**

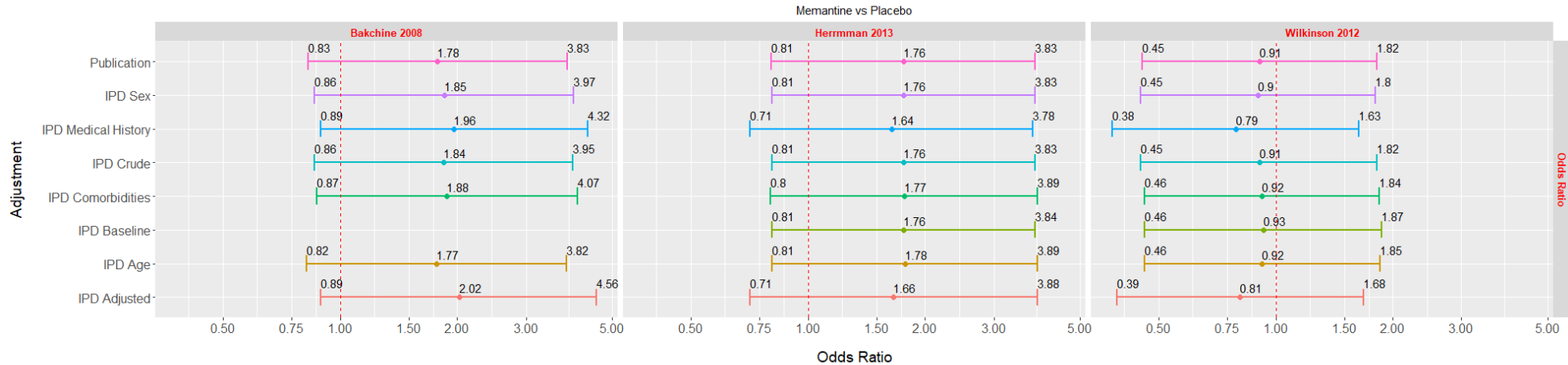
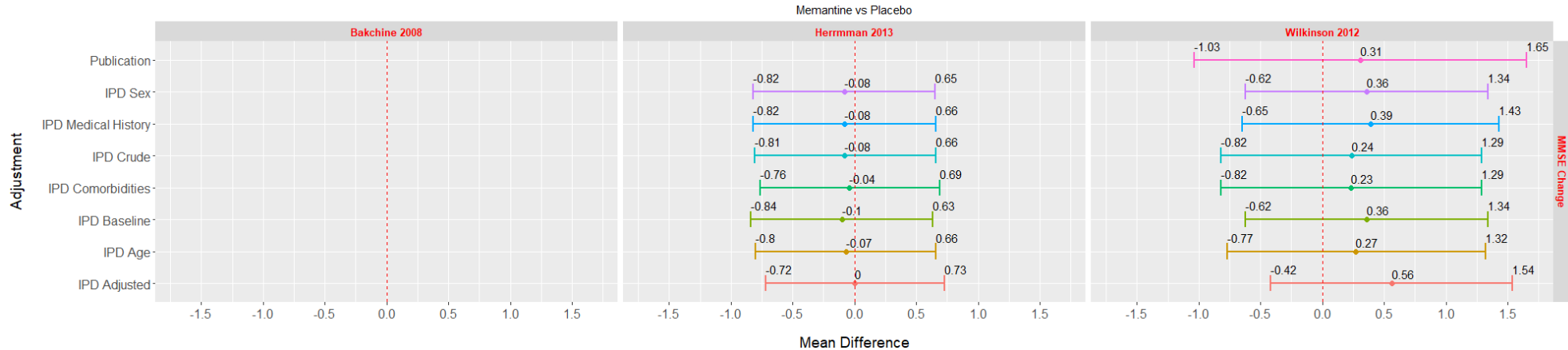


a. Comparison of studies with shared IPD with all remaining studies (irrespective type of sponsor)

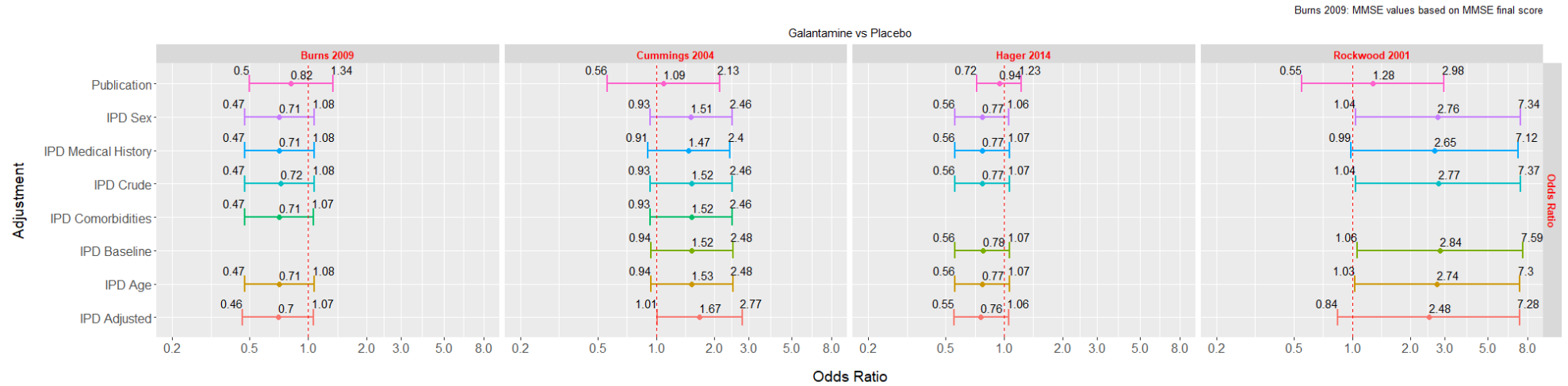
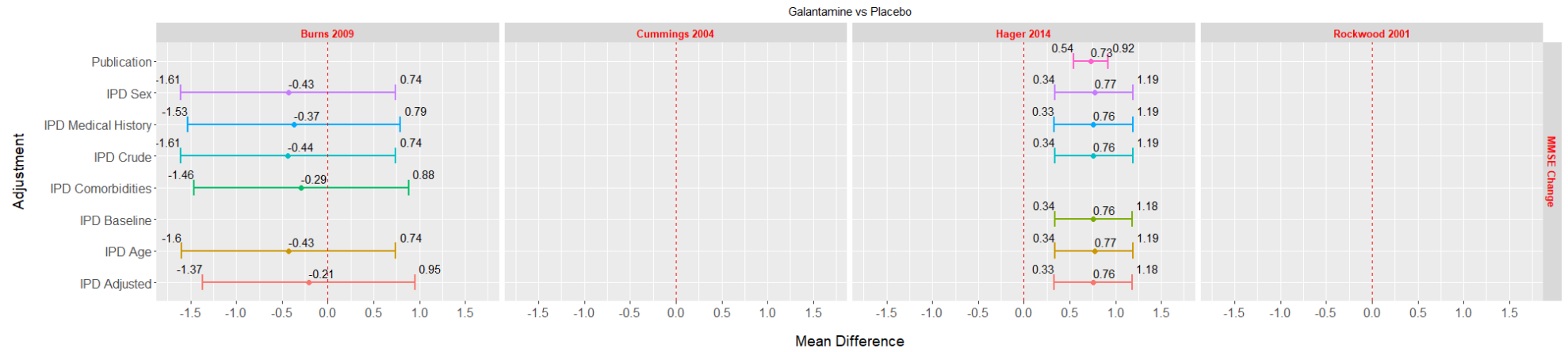


b. Comparison of studies with available and unavailable IPD (industry-sponsored studies only)

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

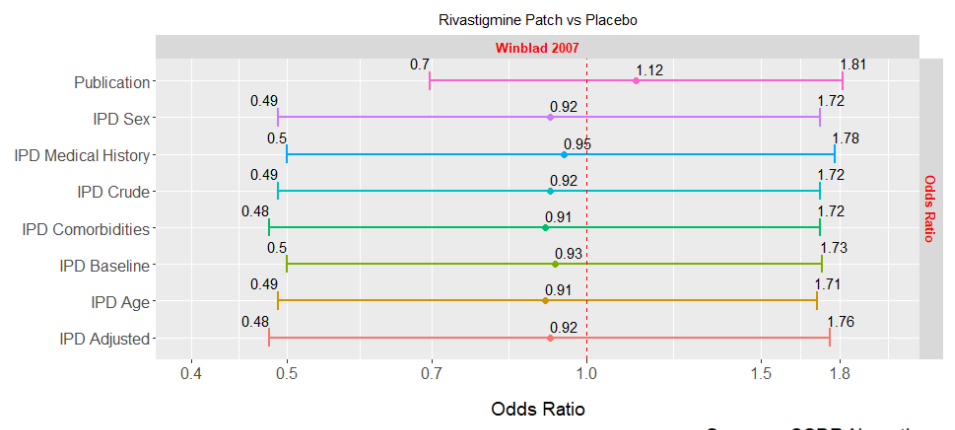
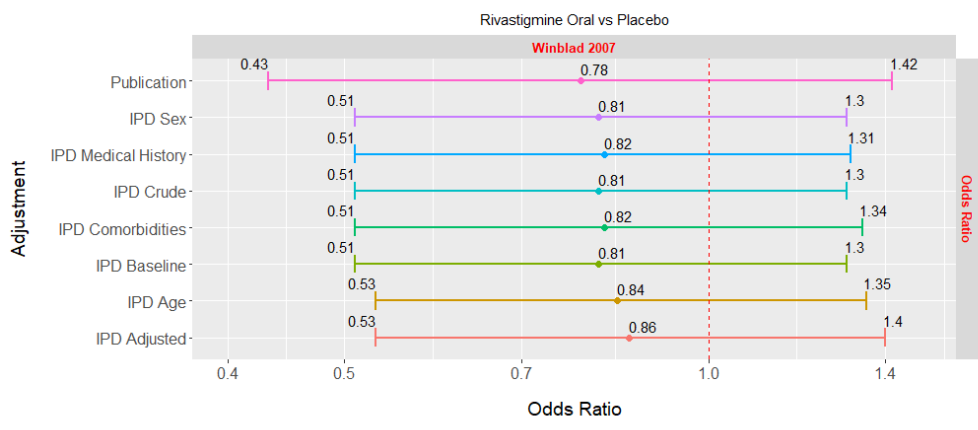
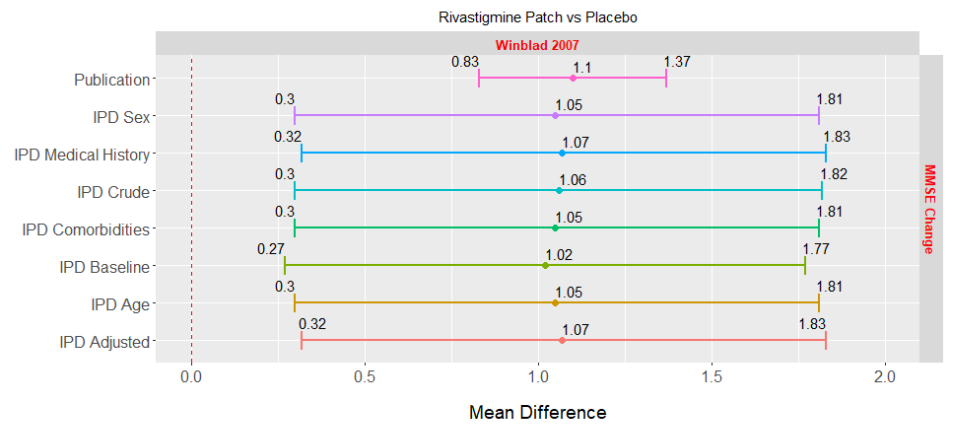
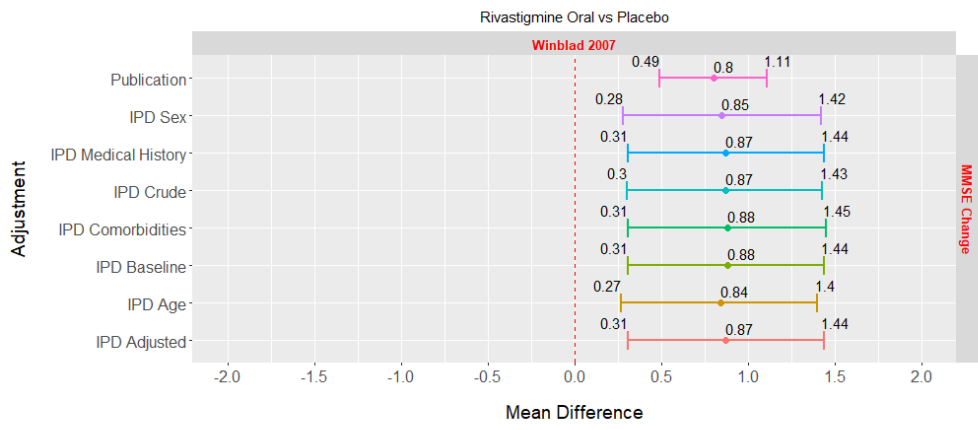


Sponsor: LUNDBECK

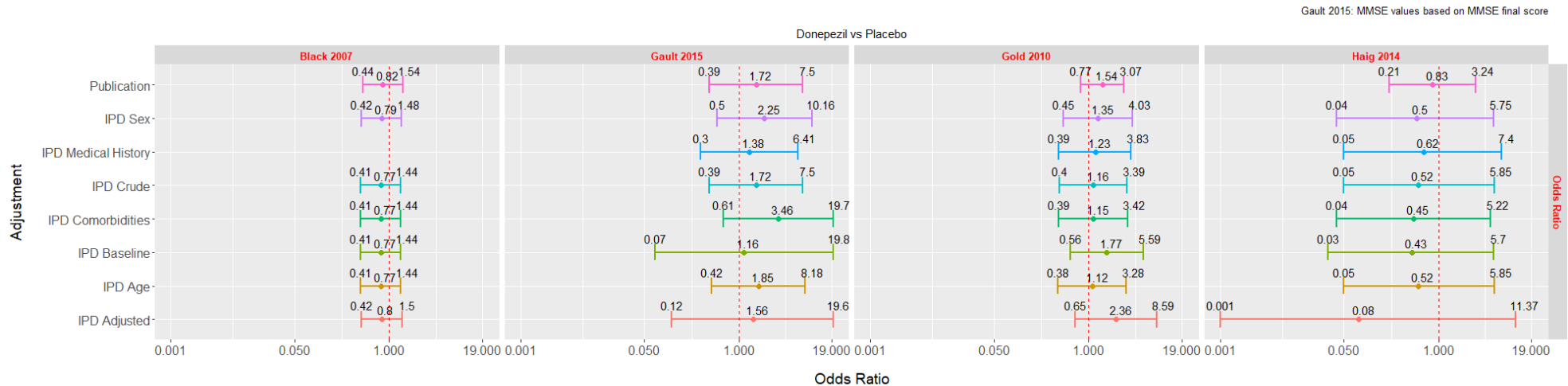
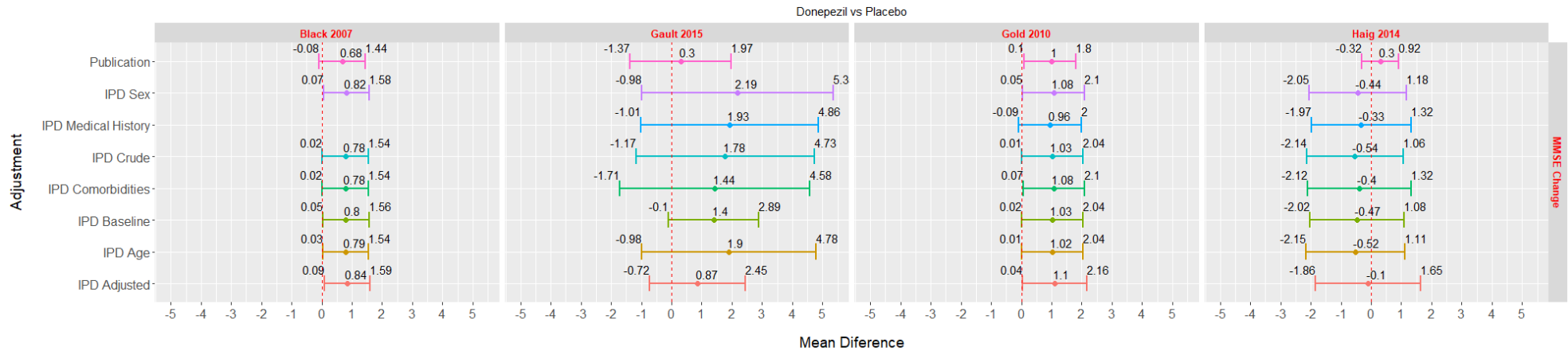


Sponsor: YODA

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Sponsor: CSDR Novartis



Sponsor: CSDR, ABBVIE

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 assesment we did not have access to these data.



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**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)

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

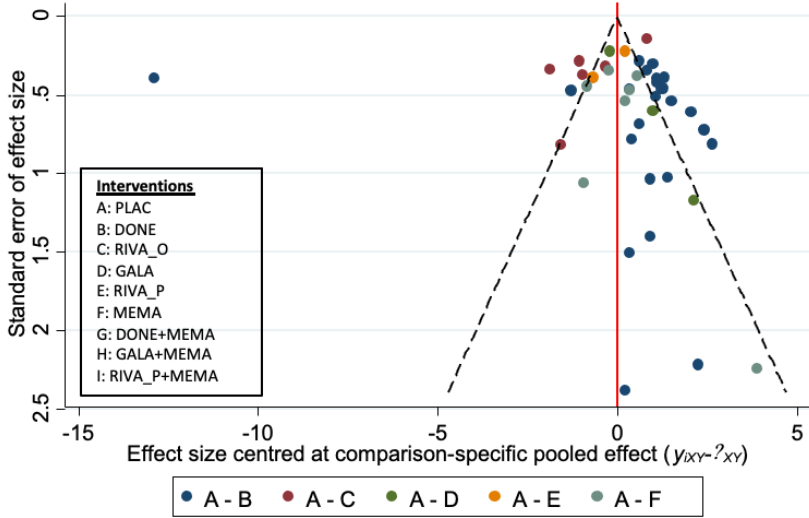
	<b>Study*</b>	<b>Correlation</b>	<b>P-Value</b>
<b>CSDR</b>	Black 2007 (EISA)	0.079	0.147
	Gold 2010 (GSK)	0.141	0.072
	Winblad 2007 (Novartis)	0.016	0.584
<b>Lundbeck</b>	Wilkinson 2012	0.066	0.273
	Herrmman 2013	0.124	0.017

\* 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

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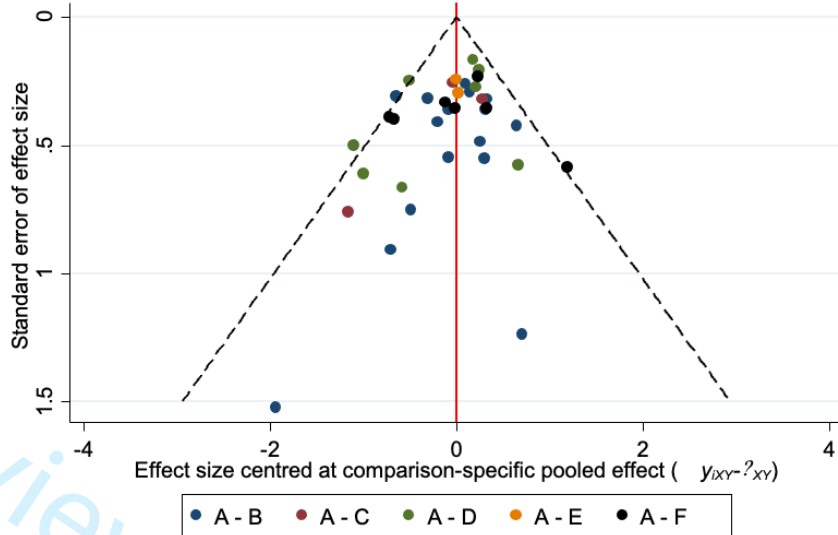
Appendix 12: Comparison Adjusted Funnel plot (all treatments vs placebo)

(a) MMSE



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

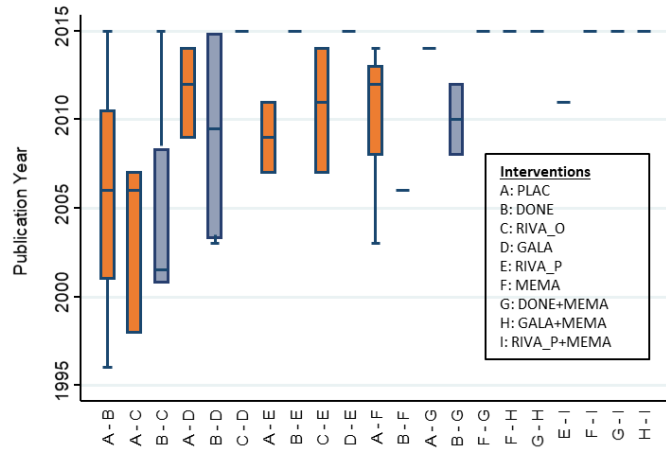
(b) Adverse Events



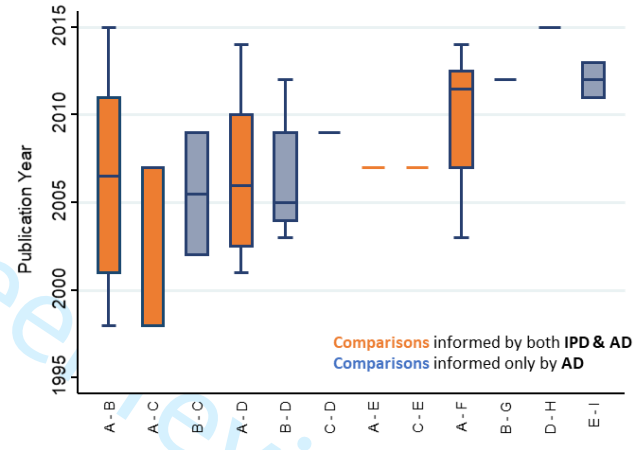
Note: Comparisons including only one study (when present) have been excluded

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

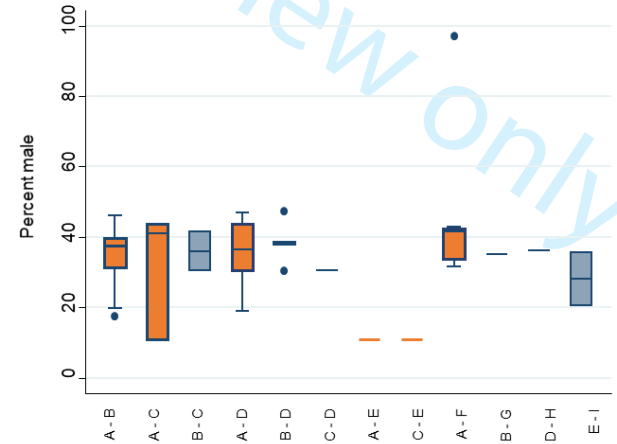
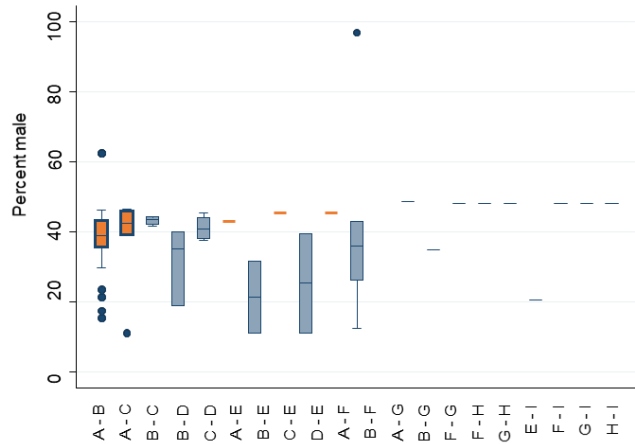
(a) MMSE



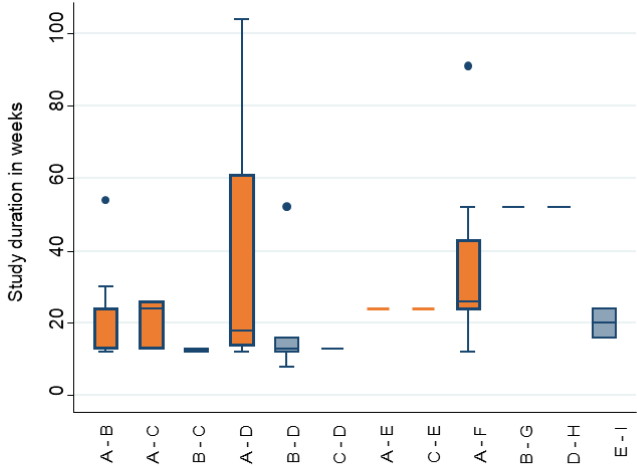
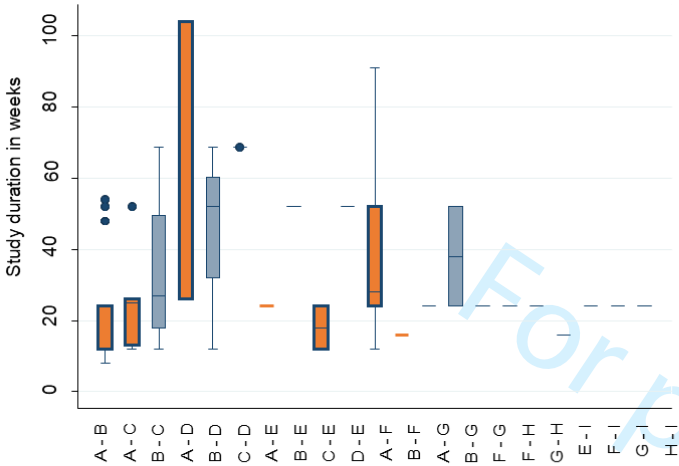
(b) Adverse Events



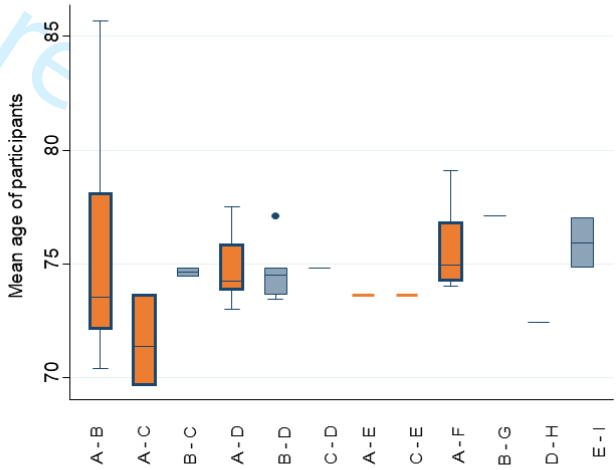
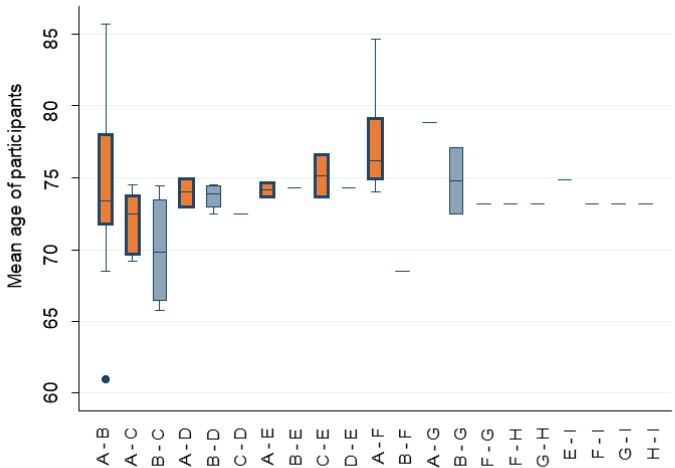
a. Publication year



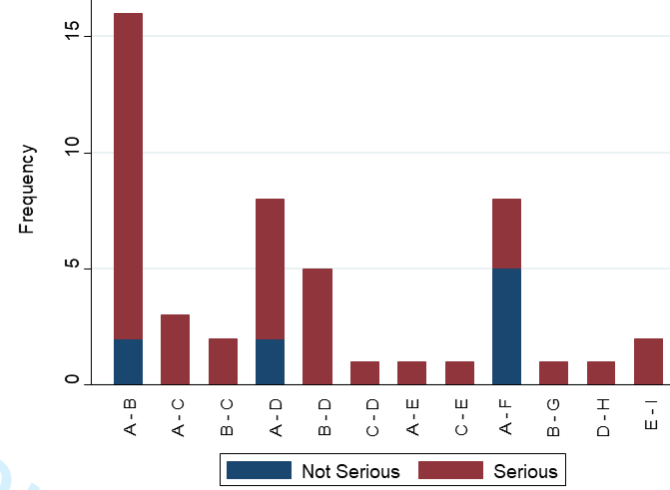
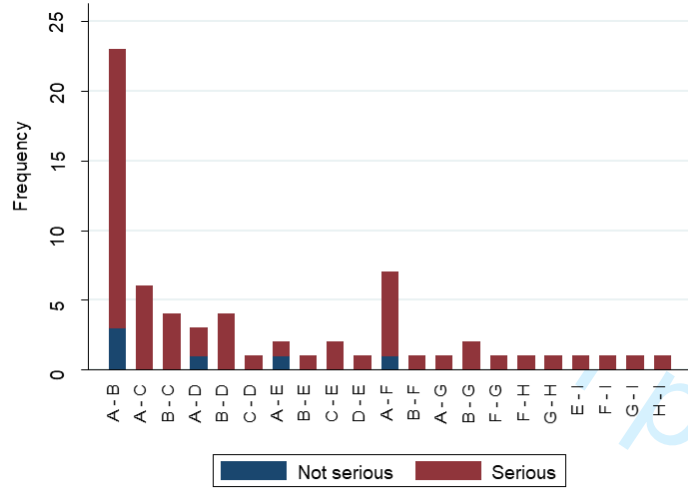
b. Percentage male



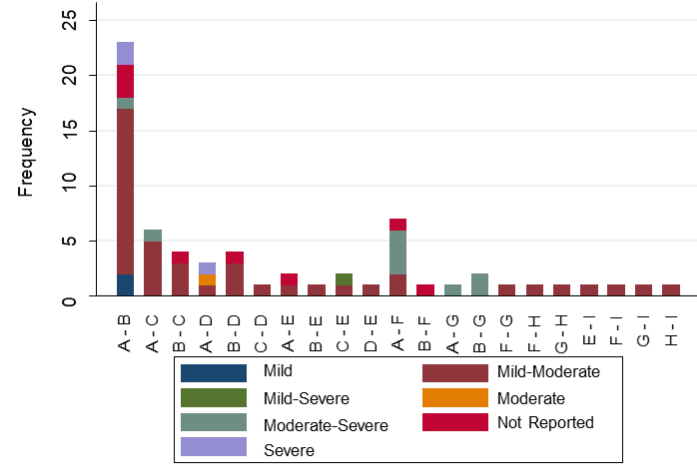
c. Study duration



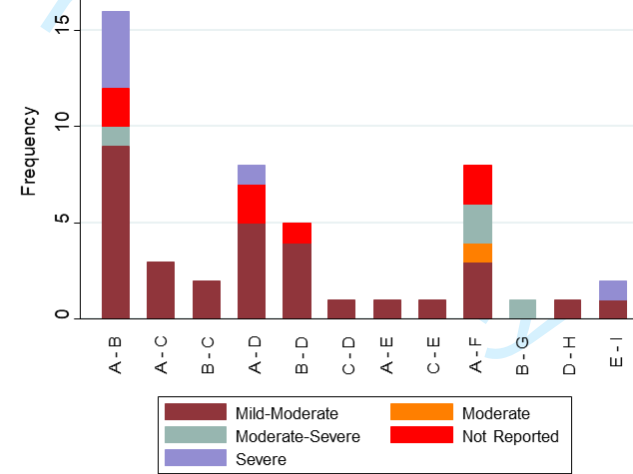
d. Mean participant age



e. Overall Risk of Bias

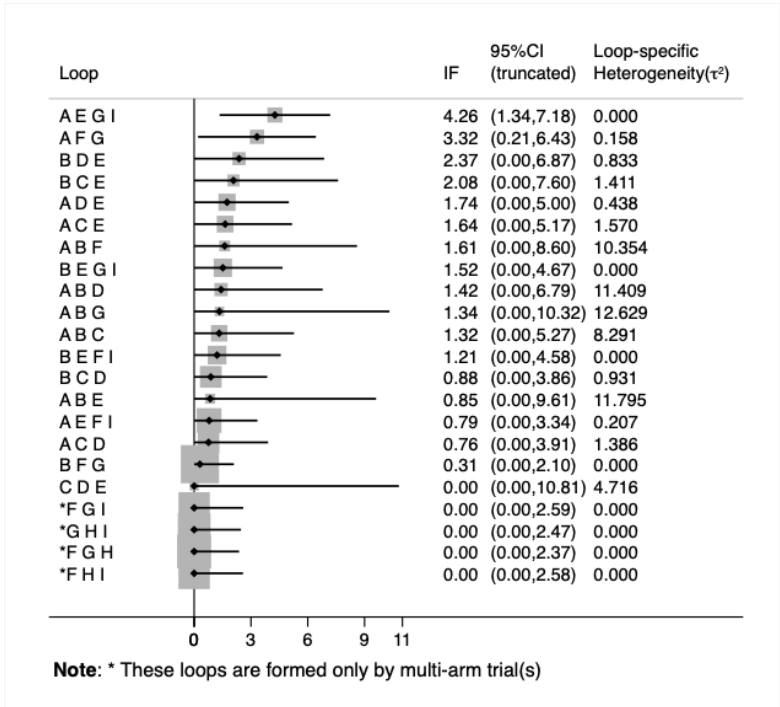


f. Alzheimer's Dementia Severity



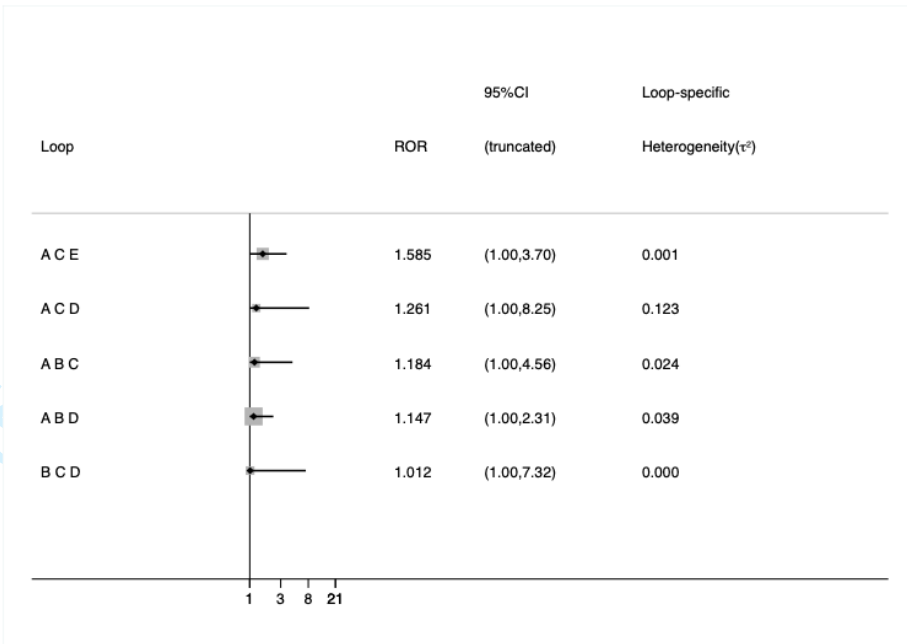
Appendix 14: Consistency Assessment – Loop-specific approach (using adjusted treatment effects)

(a) MMSE



Design-by-treatment interaction model:  
 $\chi^2$  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:  
 $\chi^2$  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
<b>Mini-Mental State Examination (MMSE)*†</b>								
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
<i>Common within-network between-study variance <math>\tau^2 = 5.75</math>, <math>I^2 = 96\%</math> (96%, 97%)</i>								
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>								
<b>Adverse Events (AEs)*<sup>‡</sup></b>								
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 vs Donepezil	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
<i>Common within-network between-study variance <math>\tau^2 = 0.04</math>, <math>I^2 = 22\%</math> (0%, 48%)</i>						
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>						

\* 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

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## Appendix 16: Network subgroup and meta-regression analysis results

Treatment Comparison	NMA estimate	95% CI	95%PI	P-score
<b>Mini-Mental State Examination (MMSE)†</b>				
<b>Mean Difference: Aggregate data and crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 5.81</math>, <math>I^2 = 96%</math> (96%, 97%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.42 (13, 0.986, 7.44)</i>				
<b>Mean Difference: Aggregate data results**</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 7.66</math>, <math>I^2 = 97%</math> (96%, 97%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.92 (11, 0.972, 8.76)</i>				
<b>Mean Difference: Crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.12</math>, <math>I^2 = 29%</math> (0%, 71%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Mean Difference: Low Risk of Bias for Allocation Concealment*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 13.82</math>, <math>I^2 = 98%</math> (98%, 99%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.13 (3, 0.99, 19.10)</i>				
<b>Mean Difference: Low risk of bias for Incomplete Data*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 1.16</math>, <math>I^2 = 79%</math> (65%, 88%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 12.15 (3, 0.007, 0.863)</i>				
<b>Mean Difference: Publicly-Sponsored Studies*</b>				
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

<i>Common within-network between-study variance: <math>\tau^2 = 81.93, I^2 = 99\%</math> (99%, 100%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.05 (1, 0.815, 116.71)</i>				
<b>Mean Difference: Industry-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.16, I^2 = 43\%</math> (15%, 62%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 8.06 (7, 0.327, 0.16)</i>				
<b>Mean Difference: Studies with Mild to Moderate cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 9.67, I^2 = 97\%</math> (97%, 98%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.22 (9, 0.96, 13.28)</i>				
<b>Mean Difference: Studies with Moderate to Severe cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.18, I^2 = 44\%</math> (0%, 75%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.60 (1, 0.11, 0.11)</i>				
<b>Mean Difference: Excluding outlier studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.59, I^2 = 73\%</math> (64%, 79%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 10.60 (13, 0.64, 0.61)</i>				
<b>Accounting for missing outcome data - Informative Missingness Difference of Means<sup>§</sup></b>				
Donepezil vs Placebo	1.42	0.51 to 2.33	0.51 to 2.33	0.59 <sup>  </sup>
Rivastigmine oral vs Placebo	0.45	-1.09 to 1.99	-1.09 to 1.99	0.30 <sup>  </sup>
Galantamine vs Placebo	0.19	-1.78 to 2.17	-1.78 to 2.17	0.25 <sup>  </sup>
Rivastigmine transdermal vs Placebo	2.37	-0.03 to 4.79	-0.03 to 4.79	0.76 <sup>  </sup>
Memantine vs Placebo	0.60	-1.09 to 2.42	-1.09 to 2.42	0.36 <sup>  </sup>
Donepezil + Memantine vs Placebo	2.55	0.09 to 5.01	0.09 to 5.01	0.80 <sup>  </sup>
Galantamine + Memantine vs Placebo	2.26	-2.03 to 6.56	-2.03 to 6.56	0.68 <sup>  </sup>
Rivastigmine transdermal + Memantine vs Placebo	1.81	-1.66 to 5.28	-1.66 to 5.28	0.61 <sup>  </sup>
Placebo (reference)				0.16 <sup>  </sup>
<i>Common within-network between-study variance: <math>\tau^2 = 5.47^{  }</math></i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.45 (11, 0.955, 6.45)</i>				
<b>Mean Difference: Meta-regression, Trial Mean Age<sup>**</sup></b>				
Donepezil vs Placebo	1.53	0.52 to 2.53	-3.17 to 6.27	0.50 <sup>††</sup>
Rivastigmine oral vs Placebo	0.80	-0.84 to 2.44	-4.15 to 5.79	0.37 <sup>††</sup>
Galantamine vs Placebo	0.60	-1.63 to 2.83	-4.57 to 5.72	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.53	0.06 to 4.98	-2.72 to 7.80	0.75 <sup>††</sup>
Memantine vs Placebo	0.79	-1.18 to 2.74	-4.33 to 5.85	0.37 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.66	0.09 to 5.19	-2.70 to 7.97	0.87 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.39	-2.02 to 6.84	-4.14 to 8.83	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.05	-1.53 to 5.59	-3.83 to 7.94	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
Regression coefficient	0.03	-0.14 to 0.20		
<i>Common within-network between-study variance: <math>\tau^2 = 5.50</math></i>				
<i>3.72 to 8.51</i>				

<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.92 (11, 0.972, 8.76)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for Age</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.12</math>, <math>I^2 = 29\%</math> (0%, 71%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: Meta-regression, Percent of Male Participants**</b>				
Donepezil vs Placebo	1.62	0.58 to 2.65	-3.40 to 6.61	0.62 <sup>††</sup>
Rivastigmine oral vs Placebo	0.73	-0.90 to 2.35	-4.30 to 5.81	0.37 <sup>††</sup>
Galantamine vs Placebo	0.62	-1.65 to 2.89	-4.75 to 5.93	0.25 <sup>††</sup>
Rivastigmine Transdermal vs Placebo	2.51	0.01 to 5.04	-2.78 to 7.94	0.75 <sup>††</sup>
Memantine vs Placebo	0.66	-1.47 to 2.77	-4.54 to 5.88	0.25 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.52	-0.40 to 5.45	-3.09 to 8.17	0.75 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.27	-2.28 to 6.83	-4.37 to 8.90	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	1.98	-1.67 to 5.65	-4.02 to 7.99	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
<i>Regression coefficient</i>	0.01	-0.05 to 0.06		
<i>Common within-network between-study variance: <math>\tau^2 = 5.73</math>, 3.83 to 8.84</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.72 (10, 0.959, 8.97)</i>				
<b>Mean difference: NMA of studies with IPD adjusted for Percent of Male Participants</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.13</math>, <math>I^2 = 32\%</math> (0%, 72%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for cognitive impairment, assessed with MMSE at baseline</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 79%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for comorbidities</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 67%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for other medications</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.17</math>, <math>I^2 = 35\%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: Meta-regression, Study Duration**</b>				
Donepezil vs Placebo	1.66	0.67 to 2.66	-3.12 to 6.32	0.62 <sup>††</sup>
Rivastigmine oral vs Placebo	0.80	-0.77 to 2.37	-4.14 to 5.69	0.37 <sup>††</sup>
Galantamine vs Placebo	0.47	-1.75 to 2.68	-4.64 to 5.66	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.38	-0.04 to 4.83	-2.87 to 7.56	0.75 <sup>††</sup>
Memantine vs Placebo	0.67	-1.27 to 2.58	-4.35 to 5.79	0.25 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.67	0.18 to 5.16	-2.60 to 7.97	0.88 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.43	-1.94 to 6.79	-3.94 to 8.81	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.13	-1.40 to 5.63	-3.62 to 7.87	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>

<i>Regression coefficient</i>	0.02	-0.01 to 0.06		
<i>Common within-network between-study variance: <math>\tau^2 = 5.40</math></i>	3.63 to 8.29			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>				
<b>Mean Difference: Meta-regression, Year of Publication**</b>				
Donepezil vs Placebo	1.53	0.51 to 2.54	-3.27 to 6.31	0.50 <sup>††</sup>
Rivastigmine oral vs Placebo	0.66	-1.01 to 2.32	-4.31 to 5.65	0.25 <sup>††</sup>
Galantamine vs Placebo	0.60	-1.65 to 2.85	-4.65 to 5.83	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.59	0.09 to 5.12	-2.73 to 7.95	0.75 <sup>††</sup>
Memantine vs Placebo	0.89	-1.05 to 2.80	-4.17 to 5.90	0.38 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.82	0.19 to 5.44	-2.57 to 8.21	0.88 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.59	-1.93 to 7.16	-3.98 to 9.12	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.21	-1.49 to 5.95	-3.81 to 8.24	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
<i>Regression coefficient</i>	-0.02	-0.17 to 0.14		
<i>Common within-network between-study variance: <math>\tau^2 = 5.53</math></i>	3.71 to 8.48			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>				
<b>Adverse Events (AEs)‡</b>				
<b>Odds Ratio: Aggregate data and crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.04</math>, <math>I^2 = 20\%</math> (0%, 47%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.58 (6, 0.733, 0.05)</i>				
<b>Odds Ratio: Aggregate data results**</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 42%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.29 (4, 0.682, 0.01)</i>				
<b>Odds Ratio: Crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.10</math>, <math>I^2 = 48\%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: Low Risk of Bias for Allocation Concealment*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.08</math>, <math>I^2 = 37\%</math> (0%, 64%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.19 (3, 0.53, 0.1)</i>				
<b>Odds Ratio: Low Risk of Bias for Incomplete Data*</b>				
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

<i>Common within-network between-study variance: <math>\tau^2 = 0.02</math>, <math>I^2 = 10\%</math> (0%, 50%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.00 (1, 0.95, 0.04)</i>				
<b>Odds Ratio: Publicly-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = \text{N/A}</math> (each comparison includes a single study)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: Industry-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.05</math>, <math>I^2 = 25\%</math> (0%, 50%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.68 (6, 0.72, 0.07)</i>				
<b>Odds Ratio: Studies with Mild to Moderate cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.09</math>, <math>I^2 = 29\%</math> (0%, 57%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.29 (5, 0.66, 0.13)</i>				
<b>Odds Ratio: Studies with Moderate to Severe cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 72%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.90 (1, 0.09, 0.00)</i>				
<b>Odds Ratio: NMA of studies with IPD – available case analysis</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.13</math>, <math>I^2 = 50\%</math> (0%, 77%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, heterogeneity): N/A (no closed loops)</i>				
<b>Odds Ratio: Meta-regression, Trial Mean Age*</b>				
Donepezil vs Placebo	1.13	0.88 to 1.43	0.68 to 1.86	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.52	0.89 to 2.53	0.77 to 3.04	0.00 <sup>††</sup>
Galantamine vs Placebo	0.91	0.60 to 1.30	0.52 to 1.59	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.84	0.39 to 1.58	0.34 to 1.80	0.75 <sup>††</sup>
Memantine vs Placebo	0.74	0.48 to 1.07	0.39 to 1.26	0.75 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.92	0.38 to 1.89	0.33 to 2.15	0.62 <sup>††</sup>
Galantamine + Memantine vs Placebo	0.99	0.37 to 2.27	0.33 to 2.55	0.50 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.73	0.24 to 1.70	0.22 to 1.87	0.87 <sup>††</sup>
Placebo (reference)				0.37 <sup>††</sup>
<i>Regression coefficient (log-scale)</i>	-0.03	-0.08 to 0.02		
<i>Common within-network between-study variance: <math>\tau^2 = 0.02</math></i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for Age</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.10</math>, <math>I^2 = 48\%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				

<b>Odds Ratio: Meta-regression, Percent of Male Participants**</b>				
Donepezil vs Placebo	1.12	0.87 to 1.44	0.64 to 2.01	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.71	0.97 to 2.92	0.83 to 3.67	0.00 <sup>††</sup>
Galantamine vs Placebo	0.93	0.62 to 1.36	0.49 to 1.77	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.89	0.39 to 1.79	0.34 to 2.05	0.63 <sup>††</sup>
Memantine vs Placebo	0.64	0.37 to 1.00	0.29 to 1.21	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.88	0.35 to 1.88	0.30 to 2.13	0.63 <sup>††</sup>
Galantamine + Memantine vs Placebo	1.13	0.39 to 2.58	0.36 to 2.95	0.38 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.77	0.24 to 1.93	0.21 to 2.13	0.88 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
<i>Regression coefficient (log-scale)</i>	0.00	0.00 to 0.02		
<i>Common within-network between-study variance: <math>\tau^2 = 0.03</math></i>	0.00 to 0.23			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for Percent of Male Participants</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.11</math>, <math>I^2 = 51\%</math> (0%, 77%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for cognitive impairment, assessed with MMSE at baseline</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.16</math>, <math>I^2 = 52\%</math> (0%, 80%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for comorbidities</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.12</math>, <math>I^2 = 44\%</math> (0%, 77%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for other medications</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.11</math>, <math>I^2 = 51\%</math> (0%, 78%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: Meta-regression, Study Duration**</b>				
Donepezil vs Placebo	1.12	0.87 to 1.43	0.63 to 1.95	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.76	1.00 to 2.99	0.88 to 3.68	0.00 <sup>††</sup>
Galantamine vs Placebo	0.92	0.62 to 1.36	0.50 to 1.69	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.87	0.39 to 1.70	0.34 to 1.96	0.63 <sup>††</sup>
Memantine vs Placebo	0.61	0.37 to 0.93	0.31 to 1.13	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.76	0.29 to 1.69	0.26 to 1.90	0.75 <sup>††</sup>
Galantamine + Memantine vs Placebo	0.98	0.34 to 2.26	0.30 to 2.53	0.50 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.75	0.25 to 1.81	0.23 to 1.97	0.75 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
<i>Regression coefficient (log-scale)</i>	0.00	0.00 to 0.01		
<i>Common within-network between-study variance: <math>\tau^2 = 0.03</math></i>	0.00 to 0.22			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>				
<b>Odds Ratio: Meta-regression, Year of Publication**</b>				
Donepezil vs Placebo	1.05	0.79 to 1.38	0.61 to 1.77	0.38 <sup>††</sup>
Rivastigmine oral vs Placebo	1.68	0.98 to 2.77	0.85 to 3.37	0.00 <sup>††</sup>
Galantamine vs Placebo	0.91	0.61 to 1.32	0.50 to 1.64	0.63 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.92	0.40 to 1.84	0.36 to 2.04	0.63 <sup>††</sup>
Memantine vs Placebo	0.73	0.46 to 1.05	0.38 to 1.28	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.88	0.35 to 1.83	0.31 to 2.15	0.75 <sup>††</sup>



Galantamine + Memantine vs Placebo	1.24	0.43 to 2.85	0.39 to 3.25	0.25 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.88	0.24 to 2.24	0.24 to 2.42	0.75 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): 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)

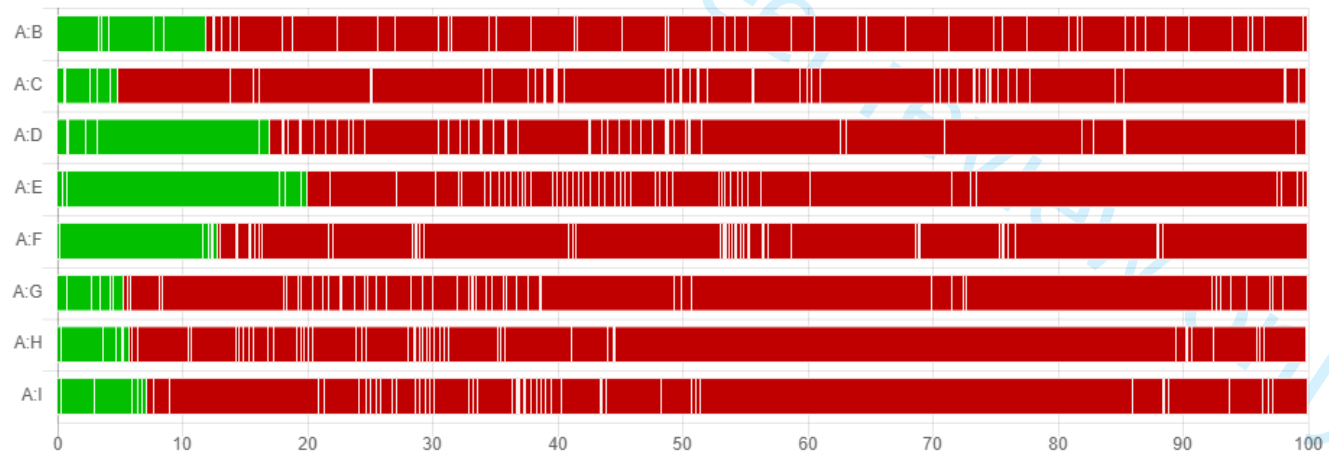
†† Analyses were conducted in OpenBUGS, and SUCRA values were calculated instead of P-scores

Appendix 17: CINeMA results

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

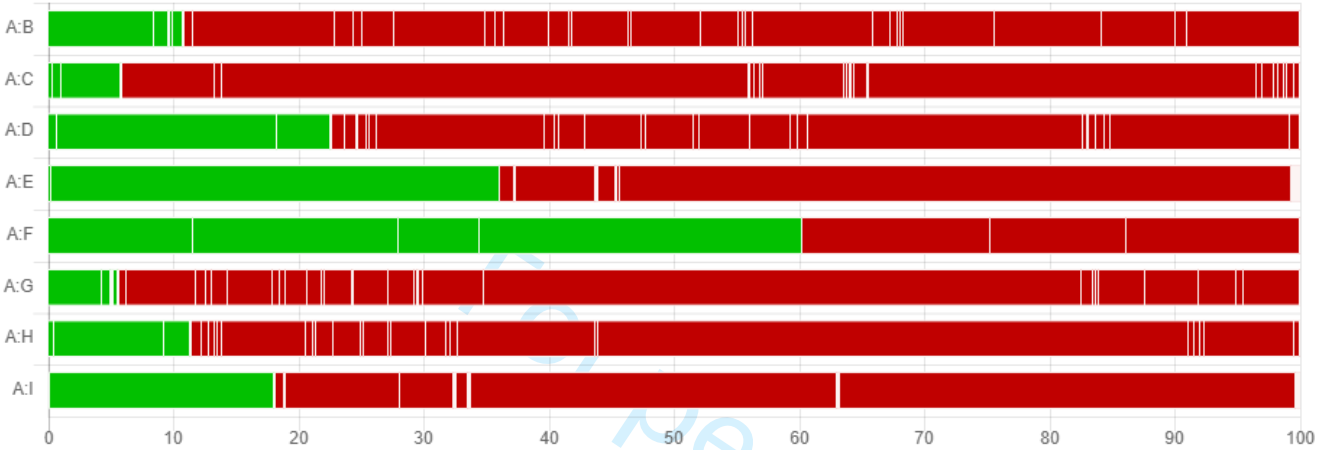
Interventions	
A:	PLAC
B:	DONE
C:	RIVA_O
D:	GALA
E:	RIVA_P
F:	MEMA
G:	DONE+MEMA
H:	GALA+MEMA
I:	RIVA_P+MEMA

MMSE outcome



AE outcome

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**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**

54

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

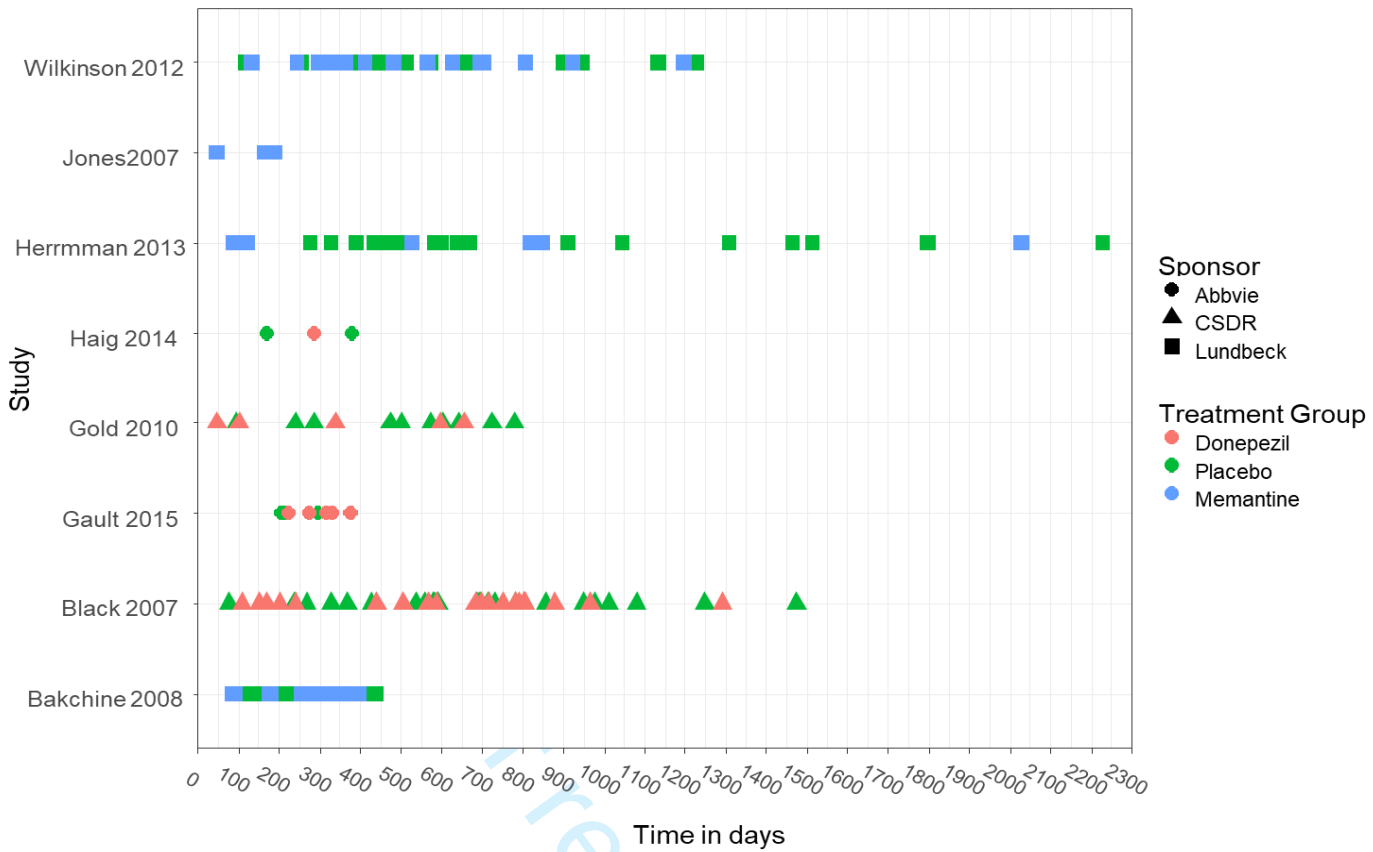
## Appendix 18: Study definitions for adverse events

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		

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3	Wilcock, 2003	World Health Organisation preferred terms	"monitoring for adverse events (classified according to WHO preferred terms) "
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5	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. "
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8	Wilkinson, 2002	NR	NR
9	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"
10			
11	Winblad, 2001	NR	NR
12	Winblad, 2006	COSTART	"We recorded all treatment emergent adverse events, coding them according to a modified COSTART dictionary. "
13			
14	Winblad, 2007	Determined by Investigator	"Safety evaluations included recording all adverse events, which were coded using a standard glossary."
15			
16	Zhang-Yi, 2005	NA	NA
17	Zhang, 2012	Determined by Investigator	"Serious adverse events considered to be possibly related to treatment occurred in one patient in each treatment arm"
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19	<b>Notes:</b> <sup>a</sup> Unpublished data, <sup>b</sup> Non-English studies		
20	<b>Abbreviations:</b> CR, companion report; NA, not applicable; NR, not reported.		
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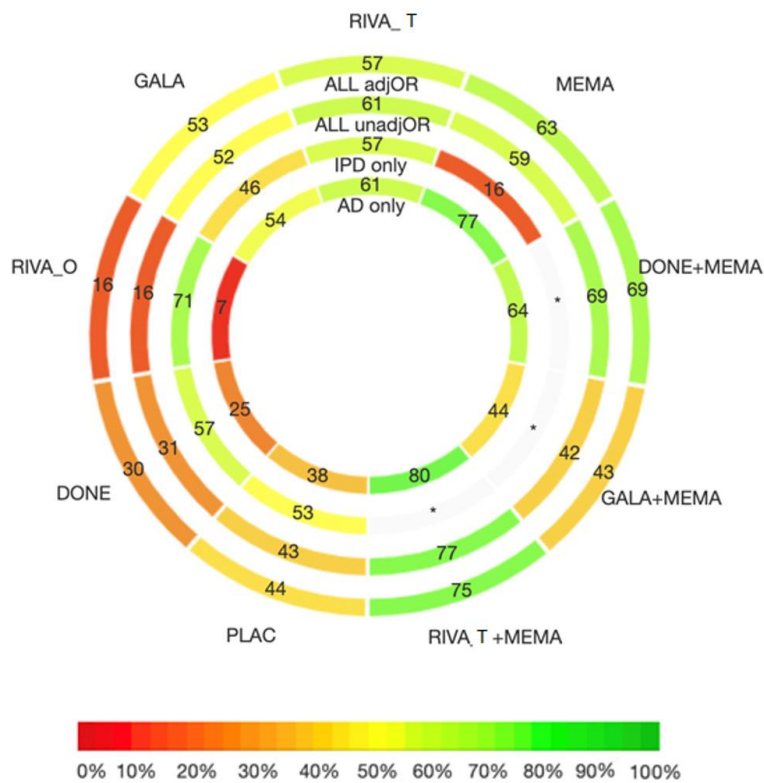
Appendix 19: Time taken to achieve at least an adverse event using individual patient data





**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.tw.
- 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.

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3 36 memantin\$.tw.  
4 37 memox.tw.  
5 38 namenda.tw.  
6 39 nimvastid.tw.  
7 40 nivalin\$.tw.  
8 41 "N-Methyl-D-aspartic acid receptor antagonist\$.tw.  
9 42 prometax.tw.  
10 43 razadyne.tw.  
11 44 reminyl.tw.  
12 45 rivastigmine.mp.  
13 46 exp Cholinesterase Inhibitors/  
14 47 Galantamine/  
15 48 Memantine/  
16 49 Galantamin.rn.  
17 50 Memantine.rn.  
18 51 Donepezil.rn.  
19 52 Donepezil Hydrochloride.rn.  
20 53 Rivastigmine.rn.  
21 54 or/21-53  
22 55 20 and 54  
23 56 exp Animals/ not (exp Animals/ and Humans/)  
24 57 55 and 56  
25 58 (comment or editorial or interview or news).pt.  
26 59 (letter not (letter and randomized controlled trial)).pt.  
27 60 57 not (58 or 59)  
28 61 (201111\* or 201112\* or 2012\* or 2013\* or 2014\*).ed.  
29 62 60 and 61  
30 63 alzheimer\$.mp.  
31 64 "benign senescent forgetfulness".mp.  
32 65 (cognit\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
33 disorder\$ or complain\$ or disturb\$)).mp.  
34 66 (cerebr\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or disorder\$ or  
35 complain\$ or disturb\$)).mp.  
36 67 (mental adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
37 disorder\$ or complain\$ or disturb\$)).mp.  
38 68 (ne?rocognit\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
39 disorder\$ or complain\$ or disturb\$)).mp.  
40 69 (ne?ro-cognit\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
41 disorder\$ or complain\$ or disturb\$)).mp.  
42 70 ((cognit\$ or memory or cerebral or brain) adj2 (improv\$ or enhanc\$ or perform\$ or  
43 process\$ or function\$ or rehabilitation or aid\$ or stimulat\$)).mp.  
44 71 cognition.ti.  
45 72 (confusion\$ or confused).tw.  
46 73 dement\$.mp.  
47 74 ("normal pressure hydrocephalus" and shunt\$.mp.  
48 75 "organic brain disease\$.mp.  
49 76 "organic brain syndrome".mp.  
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3 77 (presenil\$ or pre-senil\$ or senil\$.tw  
4 78 Alzheimer disease/  
5 79 cognitive defect/  
6 80 confusion/  
7 81 dementia/  
8 82 organic brain syndrome/  
9 83 or/63-82  
10 84 abixa.tw.  
11 85 aricept.tw.  
12 86 (acetylcholinesteraseadj inhibitor\$.tw.  
13 87 axura.tw.  
14 88 akatinol.tw.  
15 89 (anticholinesterase? or anti-cholinesterase?).tw.  
16 90 (cognitive adjenhanc\$.mp.  
17 91 (cholinesterase adj inhibitor\$.mp.  
18 92 ChEI.tw.  
19 93 donepezil.mp.  
20 94 ebixa.tw.  
21 95 eranz.tw.  
22 96 exelon.tw.  
23 97 galant?amin\$.tw.  
24 98 lycoremine.tw.  
25 99 memantin\$.tw.  
26 100 memox.tw.  
27 101 namenda.tw.  
28 102 nimvastid.tw.  
29 103 nivalin\$.tw.  
30 104 "N-Methyl-D-aspartic acid receptor antagonist\$.tw.  
31 105 prometax.tw.  
32 106 razadyne.tw.  
33 107 reminyl.tw.  
34 108 rivastigmine.mp.  
35 109 exp cholinesterase inhibitor/  
36 110 donepezil/ or donepezil plus memantine/  
37 111 galantamine/  
38 112 memantine/  
39 113 rivastigmine/  
40 114 357-70-0.rn.  
41 115 19982-08-2.rn.  
42 116 120011-70-3.rn.  
43 117 120014-06-4.rn.  
44 118 rivastigmine.rn.  
45 119 or/84-118  
46 120 83 and 119  
47 121 randomized controlled trial/ or controlled clinical trial/  
48 122 exp "clinical trial (topic)"/  
49 123 (randomi#ed or randomly or RCT\$1 or placebo\*).tw.  
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3 124 ((singl\* or doubl\* or trebl\* or tripl\*) adj (mask\* or blind\* or dumm\*)).tw.  
4 125 trial.ti.  
5 126 or/121-125  
6 127 120 and 126  
7 128 exp controlled clinical trial/  
8 129 exp "controlled clinical trial (topic)"/  
9 130 (control\* adj2 trial\*).tw.  
10 131 (nonrandom\* or non-random\* or quasi-random\* or quasi-experiment\*).tw.  
11 132 (nRCT or nRCTs or non-RCT\$1).tw.  
12 133 (control\* adj3 ("before and after" or "before after")).tw.  
13 134 time series analysis/  
14 135 (time series adj3 interrupt\*).tw.  
15 136 pretest posttest control group design/  
16 137 (pre- adj3 post-).tw.  
17 138 (pretest adj3 posttest).tw.  
18 139 controlled study/  
19 140 (control\* adj2 stud\$3).tw.  
20 141 control group/  
21 142 (control\$ adj2 group\$1).tw.  
22 143 or/128-142  
23 144 120 and 143  
24 145 cohort analysis/  
25 146 cohort.tw.  
26 147 retrospective study/  
27 148 longitudinal study/  
28 149 prospective study/  
29 150 (longitudinal or prospective or retrospective).tw.  
30 151 follow up/  
31 152 ((followup or follow-up) adj (study or studies)).tw.  
32 153 observational study/  
33 154 (observation\$2 adj (study or studies)).tw.  
34 155 population research/  
35 156 ((population or population-based) adj (study or studies or analys#s)).tw.  
36 157 ((multidimensional or multi-dimensional) adj (study or studies)).tw.  
37 158 exp comparative study/  
38 159 ((comparative or comparison) adj (study or studies)).tw.  
39 160 exp case control study/  
40 161 ((case-control\* or case-based or case-comparison) adj (study or studies)).tw.  
41 162 or/145-161  
42 163 120 and 162  
43 164 127 or 144 or 163  
44 165 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or  
45 nonhuman/ or exp vertebrate/  
46 166 exp humans/ or exp human experimentation/ or exp human experiment/  
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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  
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177 remove duplicates from 176  
178 177 use prmz [MEDLINE UNIQUE HITS]  
179 177 use emez [EMBASE UNIQUE HITS]  
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For peer review only



## PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Yes
<b>BACKGROUND</b>			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
<b>METHODS</b>			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
<b>RESULTS</b>			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
<b>DISCUSSION</b>			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
<b>OTHER</b>			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>



## PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: <b>Background:</b> main objectives <b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . <b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> <b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings. <b>Other:</b> primary source of funding; systematic review registration number with registry name.	3-4
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5, Appendix 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	6, Appendix 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6, Appendix 1

1	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	N/A (see published protocol)
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4	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, Appendix 1
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7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, Appendix 1
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11	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, Appendix 1
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14	<b>Geometry of the network</b>	<b>S1</b>	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	7, Appendix 1
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21	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6, Appendix 1
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25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	7, Appendix 1
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses; and</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>	7, Appendix 1
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40	<b>Assessment of Inconsistency</b>	<b>S2</b>	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	7, Appendix 1
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44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6, Appendix 1
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47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network; and</i></li> <li>• <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i></li> </ul>	7, Appendix 1
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## RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 – Figure 1
<b>Presentation of network structure</b>	<b>S3</b>	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	9 – Figure 2
<b>Summary of network geometry</b>	<b>S4</b>	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	7-8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8 – Table 1, Appendix 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	8-9 – Appendix 8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Appendices 6 and 10 (full data can be provided by the first author)
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	9-11 – Appendix 15
<b>Exploration for inconsistency</b>	<b>S5</b>	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	9 - Appendix 14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	9-11 - Appendix 12
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i> ).	9-11 - Appendices 16 and 17

<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	15

PICOS = population, intervention, comparators, outcomes, study design.

\* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

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**PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)**

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
<b>Title</b>			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
<b>Abstract</b>			
Structured summary	2	Provide a structured summary including as applicable:	3-4
		<b>Background:</b> state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		<b>Methods:</b> report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		<b>Results:</b> provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		<b>Discussion:</b> state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		<b>Other:</b> report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
<b>Introduction</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	5
<b>Methods</b>			

Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	5, Appendix 1
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	5-6, Appendix 1
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	6, Appendix 1
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	N/A (see published protocol)
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	6, Appendix 1
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study). If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	6, Appendix 1
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	6, Appendix 1

IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	Appendix 1
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	6, Appendix 1
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	7, Appendix 1
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): <ul style="list-style-type: none"> <li>• Use of a one-stage or two-stage approach.</li> <li>• How effect estimates were generated separately within each study and combined across studies (where applicable).</li> <li>• Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for.</li> <li>• Use of fixed or random effects models and any other model assumptions, such as proportional hazards.</li> <li>• How (summary) survival curves were generated (where applicable).</li> <li>• Methods for quantifying statistical heterogeneity (such as <math>I^2</math> and <math>\tau^2</math>).</li> <li>• How studies providing IPD and not providing IPD were analysed together (where applicable).</li> <li>• How missing data within the IPD were dealt with (where applicable).</li> </ul>	7, Appendix 1
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	Appendix 1
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	6, Appendix 1

Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	7, Appendix 1
<b>Results</b>			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	7 – Figure 1
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	8 – Table 1, Appendix 5
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	8-9, Appendices 5 and 10
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	8-9 – Appendix 8
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Appendices 6 and 10 (full data can be provided by the



			first author)
Results of syntheses	21	<p>Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.</p> <p>When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.</p> <p>Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.</p>	9-11 – Appendix 15
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	9-11 - Appendix 12
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	9-11 - Appendices 16 and 17
<b>Discussion</b>			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	11-13
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	13-14
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	13-14
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	12-13

Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	15

**A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.**

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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-053012.R3
Article Type:	Original research
Date Submitted by the Author:	17-Mar-2022
Complete List of Authors:	Veroniki, Areti; St. Michael's Hospital, Knowledge Translation Program; Imperial College London, Department of Surgery & Cancer, Faculty of Medicine Ashoor, Huda; St Michael's Hospital, Knowledge Translation Program Rios, Patricia; St Michael's Hospital, Knowledge Translation Program Seitidis, Georgios; University of Ioannina, Department of Primary Education Stewart, Lesley; University of York, Centre for Reviews and Dissemination Clarke, Mike; Queen's University Belfast, Northern Ireland Hub for Trials Methodology Research Tudur-Smith, Catrin; University of Liverpool, Department of Biostatistics Mavridis, Dimitris ; University of Ioannina, Department of Primary Education Hemmelgarn, Brenda; University of Alberta, Department of Medicine Holroyd-Leduc, Jayna; University of Calgary, Department of Medicine Straus, Sharon; St Michael's Hospital, Knowledge Translation Program; University of Toronto, Department of Geriatric Medicine Tricco, Andrea; St Michael's Hospital, Knowledge Translation Program; University of Toronto, Dalla Lana School of Public Health
<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Neurology
Keywords:	STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY, Dementia < NEUROLOGY

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4 **dementia: A systematic review with individual patient data network**  
5 **meta-analysis**  
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11 Areti Angeliki Veroniki<sup>1,2,\*</sup> PhD e-mail: [aretangeliki.veroniki@unityhealth.to](mailto:aretangeliki.veroniki@unityhealth.to)  
12 Huda M. Ashoor<sup>1</sup> BSc e-mail: [huda.ashoor@unityhealth.to](mailto:huda.ashoor@unityhealth.to)  
13 Patricia Rios<sup>1</sup> MSc e-mail: [patricia.rios@unityhealth.to](mailto:patricia.rios@unityhealth.to)  
14 Georgios Seitidis<sup>3</sup> MSc e-mail: [g.seitidis@uoi.gr](mailto:g.seitidis@uoi.gr)  
15 Lesley A. Stewart<sup>4</sup> PhD e-mail: [lesley.stewart@york.ac.uk](mailto:lesley.stewart@york.ac.uk)  
16 Mike Clarke<sup>5</sup> PhD e-mail: [m.clarke@qub.ac.uk](mailto:m.clarke@qub.ac.uk)  
17 Catrin Tudur Smith<sup>6</sup> PhD e-mail: [cat1@liverpool.ac.uk](mailto:cat1@liverpool.ac.uk)  
18 Dimitris Mavridis<sup>3</sup> PhD e-mail: [dmavridi@uoi.gr](mailto:dmavridi@uoi.gr)  
19 Brenda R. Hemmelgarn<sup>7</sup> PhD e-mail: [brenda.hemmelgarn@albertahealthservices.ca](mailto:brenda.hemmelgarn@albertahealthservices.ca)  
20 Jayna Holroyd-Leduc<sup>8</sup> MD e-mail: [jayna.holroyd-leduc@albertahealthservices.ca](mailto:jayna.holroyd-leduc@albertahealthservices.ca)  
21 Sharon E. Straus<sup>1,9</sup> MD e-mail: [sharon.straus@utoronto.ca](mailto:sharon.straus@utoronto.ca)  
22 Andrea C. Tricco<sup>1,10</sup> PhD e-mail: [andrea.tricco@unityhealth.to](mailto:andrea.tricco@unityhealth.to)  
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<sup>1</sup> Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

<sup>2</sup> Institute of Health Policy Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

<sup>3</sup> Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece

<sup>4</sup> Centre for Reviews and Dissemination, University of York, York, United Kingdom

<sup>5</sup> Northern Ireland Hub for Trials Methodology Research, Queen's University Belfast, Belfast, United Kingdom

<sup>6</sup> Department of Biostatistics, University of Liverpool, Block F, Waterhouse Building, 1-5 Brownlow Hill, Liverpool, L69 3GL, UK

<sup>7</sup> Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

<sup>8</sup> Department of Medicine, University of Calgary, Calgary, Alberta, Canada

<sup>9</sup> Department of Geriatric Medicine, University of Toronto, Toronto, Ontario, Canada

1  
2  
3 <sup>10</sup> Epidemiology Division & Institute of Health Policy, Management, and Evaluation, Dalla  
4 Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada  
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9

10 **\*Corresponding Author:**

11 Dr. Areti Angeliki Veroniki, MSc, PhD  
12 209 Victoria Street, East Building, Toronto, Ontario  
13  
14  
15 M5B 1T8, Canada

16  
17  
18 Phone: 416-564-5015; Fax: 416-564-5735;

19  
20 Email: [aretangeliki.veroniki@unityhealth.to](mailto:aretangeliki.veroniki@unityhealth.to)  
21  
22

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## 1 **Abstract**

2 Words: 377 (Max 300 words)

3 **Objective:** To examine the comparative efficacy and safety of cognitive enhancers by  
4 patient characteristics for managing Alzheimer's Dementia (AD).

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

7 **Data Sources:** MEDLINE, EMBASE, Cochrane Methodology Register, CINAHL,  
8 Ageline and Cochrane Central Register of Controlled Trials up to March 2016.

9 **Participants:** 80 randomized controlled trials (RCTs) including 21,138 adults with AD,  
10 and 12 RCTs with IPD including 6,906 patients.

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

13 **Data extraction and Synthesis:** We requested IPD from authors, sponsors and data  
14 sharing platforms. When IPD were not available, we used aggregate data. We appraised  
15 study quality with the Cochrane risk-of-bias. We conducted a two-stage random-effects  
16 IPD-NMA, and assessed their findings using CINeMA (Confidence in Network meta-  
17 analysis).

18 **Primary and Secondary Outcomes:** We included trials assessing cognition with the  
19 Mini-Mental State Examination (MMSE), and adverse events (AEs).

20 **Results:** Our IPD-NMA compared 9 treatments (including placebo). Donepezil (mean  
21 difference [MD] = 1.41, 95% confidence interval [CI]: 0.51 to 2.32) and  
22 donepezil+memantine (MD = 2.57, 95% CI: 0.07 to 5.07) improved MMSE score (56  
23 RCTs, 11,619 participants; CINeMA score: moderate) compared with placebo. According  
24 to P-score, oral rivastigmine (odds ratio [OR] = 1.26, 95% CI: 0.82 to 1.94, P-score= 16%)  
25 and donepezil (OR = 1.08, 95% CI: 0.87 to 1.35, P-score= 30%) had the least favourable  
26 safety profile, but none of the estimated treatment effects were sufficiently precise when  
27 compared with placebo (45 RCTs, 15,649 patients; CINeMA score: moderate to high). For  
28 moderate to severe impairment, donepezil, memantine and their combination performed  
29 best, but for mild to moderate impairment donepezil and transdermal rivastigmine ranked  
30 best. Adjusting for MMSE baseline differences, oral rivastigmine and galantamine

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4 31 improved MMSE score, whereas when adjusting for comorbidities only oral rivastigmine  
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6 32 was effective.

7 33 **Conclusions:** The choice among the different cognitive enhancers may depend on patient's  
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9 34 characteristics. The MDs of all cognitive enhancer regimens except for single-agent oral  
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11 35 rivastigmine, galantamine, and memantine, against placebo were clinically important for  
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13 36 cognition (MD larger than 1.40 MMSE points), but results were quite imprecise. However,  
14  
15 37 two thirds of the published RCTs were associated with high risk of bias for incomplete  
16  
17 38 outcome data, and IPD were only available for 15% of the included RCTs.

18 39  
19 40 **Registration:** PROSPERO # CRD42015023507

20 41 **Funding:** This research was funded by the CIHR Drug Safety and Effectiveness Network  
21  
22 42 (grant number 137713).

23 43 **Keywords:** network meta-analysis; multiple treatments meta-analysis; individual  
24  
25 44 participant data; Nootropic Agents; Alzheimer Disease

### 26 27 28 29 30 45 **Strengths and limitations of this study**

- 31 46
- 32 47 • This is one of the most comprehensive systematic reviews and network meta-analysis  
33 48 of cognitive enhancers including individual patient data for Alzheimer's Dementia to  
34 49 produce treatment recommendations by patient characteristics.
  - 35 50 • We followed the methodologically rigorous guidelines in the Cochrane Handbook for  
36 51 systematic reviews, and the CINeMA quality assessment guidelines.
  - 37 52 • Access to individual patient data allowed us to 1) observe minor differences between  
38 53 the original published results and our re-analysis, potentially due to differences in  
39 54 imputation methods for missing data or because original studies have excluded some  
40 55 patients, and hence have used a smaller sample size, 2) overcome potential reporting  
41 56 bias, and 3) assess for potential effect modifiers that were not reported in the original  
42 57 publications (e.g., comorbidities, additional medications) and explore for treatment-by-  
43 58 covariate interactions on the patient-level.
  - 44 59 • Two thirds of the included RCTs, were associated with high risk of bias for incomplete  
45 60 outcome data due to attrition.
  - 46 61 • We were unable to include individual patient data for all RCTs (only 15% of the  
47 62 studies shared their individual patient data), highlighting potential availability bias.
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4 62 • Our literature searches were conducted 5 years ago and additional relevant studies may  
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6 63 be available. However, obtaining IPD in a timely manner was very challenging and  
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8 64 required more time than anticipated. Similar to all systematic reviews, the evidence  
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10 65 should be updated regularly.  
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For peer review only

## 66 Introduction

67  
68 Alzheimer's dementia (AD) is the most common type of dementia.<sup>1</sup> Patients living with AD have  
69 a lower quality of life due to deterioration in function, cognition, behavior, and mental health  
70 over time, as well as increased mortality.<sup>2</sup> Pharmacological treatment for AD predominantly  
71 consists of cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and the N-methyl-d-  
72 aspartate (NMDA) receptor antagonist, memantine. All three cholinesterase inhibitors and  
73 memantine are currently the only effective licensed treatments for dementia,<sup>3</sup> but their clinical  
74 effect can be small and there is no convincing evidence that they modify the disease process in  
75 AD.<sup>4</sup> Also, it is unclear whether galantamine, rivastigmine, or donepezil should be used by  
76 patients with severe AD, or whether memantine is the optimal treatment for severe AD.<sup>5</sup>

77  
78 In AD, disease severity and sex are potential effect modifiers. However, aggregate data and  
79 covariates of interest (e.g., sex, disease severity) are not consistently reported across randomized  
80 clinical trials (RCTs).<sup>6</sup> The use of IPD has several advantages, such as it allows for the  
81 exploration of the relationship between treatment effects and patient-level characteristics, and it  
82 overcomes restrictions in using the information reported in the publication among others. The  
83 aim of this study was to examine the comparative efficacy and safety of cognitive enhancers for  
84 patients with different characteristics, such as severities of AD and for females versus males  
85 through a systematic review and individual patient data (IPD) NMA. This systematic review was  
86 based on our previously published systematic review and aggregate data NMA.<sup>6</sup> NMA is an  
87 extension of standard meta-analysis synthesizing different sources of evidence from a network of  
88 RCTs comparing different treatments within a single model. NMA can provide treatment effect  
89 estimates for treatment comparisons that have not studied in a head-to-head study.

## 90 Methods

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92 We reported our results according to the Preferred Items for Systematic Reviews and Meta-  
93 analysis (PRISMA) Statement for NMA and PRISMA-IPD.<sup>7,8</sup>

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## 95 **Protocol**

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97 The research question and protocol were based on our previous systematic review and NMA.<sup>6</sup>  
98 We registered our systematic review protocol with the prospective register of systematic reviews  
99 (PROSPERO: CRD42015023507), and published our protocol.<sup>9</sup> Additional information is also  
100 provided in Additional File 1: Appendix 1 and Additional File 2. Herein, we briefly summarize  
101 our methods.

## 103 **Eligibility criteria**

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105 We updated our previous systematic review,<sup>6</sup> using similar population, interventions,  
106 comparators, study designs and time period (PICOST) criteria. The literature search was updated  
107 from January 2015 to March 2016. We included published and English RCTs that assessed  
108 cognition via the Mini-Mental State Examination (MMSE; efficacy and primary outcome) and/or  
109 adverse events (AE; safety outcome) in adults with Alzheimer's dementia.

## 111 **IPD collection process**

112  
113 We contacted the corresponding author followed by the next-in-order author, as presented in  
114 each eligible RCT, to obtain IPD. The author contact process was part of a RCT that our team  
115 conducted to assess methods that may optimize response rates for IPD retrieval.<sup>10</sup> We also  
116 contacted sponsors of eligible trials, as reported in the publications. We contacted industry  
117 sponsors only, as we were not able to locate contact information for the majority of non-industry  
118 sponsors (e.g., grants and university funding). If a study had multiple sponsors, we contacted all  
119 of them. To further facilitate IPD access, we contacted the Clinical Study Data Request  
120 (CSDR)<sup>11</sup> and Yale University Open Data Access (YODA) data sharing platforms.<sup>12</sup> If a data  
121 provider was unable to provide IPD we noted the reason.

## 123 **Risk of bias and quality appraisal**

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3 125 We appraised study quality using the Cochrane risk of bias tool.<sup>13</sup> To ensure data consistency<sup>8</sup>  
4 126 we compared IPD with aggregate data reported in the publication. We assessed whether  
5 127 randomization of patients was adequate (i.e., intervention and comparison groups were balanced  
6 128 for important patient characteristics), by comparing numbers and types of patients in each arm.  
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12 130 When at least 10 studies were available for each treatment against placebo, publication bias and  
13 131 small-study effects were examined visually using the comparison adjusted funnel plot under the  
14 132 fixed-effect model.<sup>3</sup> When a funnel plot asymmetry was detected, we performed the Copas  
15 133 selection for the treatment comparisons that were informed by at least 10 studies and for which  
16 134 asymmetry was evident in the funnel plot. We explored the possibility that this was due to  
17 135 publication bias,<sup>14</sup> and made moderate assumptions about the probability of publication of the  
18 136 smaller and larger (in terms of standard error) studies. We assumed that the smallest study had a  
19 137 probability of publication equal to 40-50% and the largest study had a probability of 80-90%.  
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22 138 Confidence in NMA findings was assessed for each outcome using CINeMA (Confidence in  
23 139 Network meta-analysis, see Additional File 1: Appendix 1 for more details).<sup>15</sup>  
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## 31 141 **Synthesis**

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34 143 We performed a descriptive analysis using frequencies and distributions of the characteristics of  
35 144 the included patients and treatments. For each outcome, we present the network geometry  
36 145 according to IPD availability. We conducted a two-stage IPD analysis, whereby data were  
37 146 analysed separately in each trial in the first stage and the trial parameter estimates were  
38 147 synthesised in a random-effects meta-analysis or NMA in the second stage.  
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45 149 The summary treatment effects are presented using the odds ratio (OR) or mean difference (MD)  
46 150 along with their corresponding CIs and prediction intervals (PIs).<sup>16</sup> We ranked the interventions  
47 151 for each outcome using the P-scores (and SUCRAs [surface under the cumulative ranking curve]  
48 152 in meta-regression analysis), and present them in a rank-heat plot.<sup>17,18</sup>  
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## 54 154 **Patient and public involvement**

55 155 Not applicable.  
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## 156 **Results**

### 157 **Literature search, study selection and IPD obtained**

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159 After screening 20,410 titles and abstracts and 1,968 full-text articles, 96 studies fulfilled the  
160 eligibility criteria; 80 unique studies and 16 companion reports (Figure 1a, Additional File 1:  
161 Appendix 2).

162  
163 (Figure 1 here)

164  
165 Of the 80 RCTs, 55 reported at least one industry-sponsored funder (i.e. 40 studies reported a  
166 single industry-sponsor and 15 multiple industry-sponsors). In the remaining studies, 9 were  
167 publicly-sponsored and 16 did not report any information about funding. We requested IPD by  
168 contacting the corresponding authors for 80 RCTs that included 21,138 participants. None of the  
169 original authors shared their IPD. Fifteen commercial sponsors were then contacted and 6 (40%)  
170 sponsors shared their data through proprietary sponsor-specific platforms. The 6 sponsors were  
171 contacted for 46 RCTs (14,580 participants), and we obtained IPD for 30% (14 RCTs, 8,007  
172 participants) of these RCTs (1,058 total waiting days up to March 9, 2020). The study flow for  
173 obtaining IPD is depicted in Figure 1b.

174  
175 We were able to include 12 (6,906 patients) of 14 RCTs in our NMA due to incompleteness of  
176 provided IPD (Additional File 1: Appendix 3). The number of studies with available/non-  
177 available IPD from each data provider along with reasons for non-availability of IPD are  
178 presented in Additional File 1: Appendix 4.

### 180 **Study and patient characteristics**

181  
182 Most included studies (33%) were multi-national. The mean age of patients ranged from 61 to 86  
183 years. The majority of the RCTs included patients with mild-moderate AD (56%), although the  
184 diagnostic criteria used for AD varied widely (Table 1). The most frequent longest duration of  
185 follow-up was 24 weeks (24 RCTs, 30%; Additional File 1: Appendix 5). Important patient  
186 characteristics, such as percent of male and dropout rates, were not balanced across groups in the

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3 187 RCTs with provided IPD (Additional File 1: Appendix 6). Comparing study and patient  
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5 188 characteristics of available and non-available IPD when a study was industry-sponsored, we  
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7 189 found differences in the year of study publication, study size, and absolute mean difference  
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9 190 (Additional File 1: Appendix 7).

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12 192 (Table 1 here)

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### 15 194 **Risk of bias and IPD integrity**

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18 196 Using the Cochrane risk-of-bias tool, allocation concealment was at low risk of bias for 43% and  
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20 197 blinding of participants and personnel was low for 64% of the RCTs (Additional File 1:  
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22 198 Appendix 8). One third of the RCTs had low risk of incomplete outcome data bias due to  
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24 199 attrition and almost two thirds had high potential risk of “other” bias, specifically, funding bias.  
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26 200 The other risk of bias item was scored as unclear for 32%. Overall risk of bias was comparable in  
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28 201 studies with available and unavailable IPD (Additional File 1: Appendix 9).

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30 203 All IPD provided were checked for consistency and results from published RCTs were  
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32 204 reproduced and provided in Additional File 1: Appendix 10. High dropout rates were observed in  
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34 205 the IPD; experiencing an adverse event was the most common reason for dropout. Despite the  
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36 206 high dropout rates observed in the individual studies, there was no indication of correlation  
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38 207 between age and dropout (Additional File 1: Appendix 11). Comparison-adjusted funnel plot for  
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40 208 MMSE suggested there is indication for small-study effects (see Additional File 1: Appendix  
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42 209 12). In contrast to the standard meta-analysis (MD=1·65 95% CI (0·16, 3·14)), the Copas  
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44 210 selection model estimated a pooled treatment effect for donepezil vs. placebo MD=1·87 95% CI  
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46 211 (1·55, 2·20) with between-study variance  $\tau^2=1·95$ , and correlation coefficient -0·45 (-0·76, -  
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48 212 0·01) reflecting the belief that the propensity for publication was associated with the observed  
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50 213 effect size.

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### 52 215 **Network meta-analysis**

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3 217 In both MMSE and AE outcomes, on average there were no important concerns regarding the  
4 218 transitivity and consistency assumptions (Additional File 1: Appendices 13 and 14; design-by-  
5 219 treatment interaction model MMSE:  $\chi^2= 4.36$ , 13 degrees of freedom (df), p-value= 0.987; AE:  
6 220  $\chi^2= 3.57$ , 6 df, p-value= 0.735). Below we present the main analysis results compared to  
7 221 placebo. Additional analyses are presented in Additional File 1: Appendix 15-16). The network  
8 222 geometry is presented in Figure 2.  
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15 224 (Figure 2 here)  
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## 18 226 **Cognition**

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21 228 The NMA for MMSE included 56 RCTs, 9 treatments (including placebo), and 11,619  
22 229 participants. Nine RCTs (3,625 patients) contributed IPD and 47 RCTs (7,994 patients)  
23 230 contributed aggregated data to the NMA. Two studies<sup>19,20</sup> did not report MMSE in the final  
24 231 publication, but in the retrieved IPD we were able to use data for this outcome.  
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### 30 233 *NMA of studies with IPD and aggregate data*

31 234  
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33 235 Studies in this NMA compared all available treatments. Donepezil (MD= 1.41, 95% CI: 0.51 to  
34 236 2.32) and donepezil+memantine (MD= 2.57, 95% CI: 0.07 to 5.07) were superior to placebo in  
35 237 terms of MMSE score (Additional File 1: Appendix 15). Transdermal rivastigmine (MD= 2.11,  
36 238 95% CI: -0.04 to 4.26), and the combinations donepezil+memantine, galantamine+memantine  
37 239 (MD= 2.24, 95% CI: -2.13 to 6.61), and transdermal rivastigmine+memantine (MD= 1.79, 95%  
38 240 CI: -1.70 to 5.27) were associated with a MD from placebo of more than 1.40 MMSE points. A  
39 241 previous study suggested a MD larger than 1.40 is a minimal clinically important difference  
40 242 (MCID).<sup>21</sup> However, the associated 95% CIs were quite imprecise spanning between a mean  
41 243 decrease below and a mean increase above the suggested MCID value (Figure 3a). However,  
42 244 donepezil+memantine had the highest likelihood of being the most effective in improving  
43 245 MMSE score (P-score range 79-80%, Figure 4). Confidence in NMA results was moderate  
44 246 (Additional File 1: Appendix 17).  
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54 247 (Figure 3 here)

55 248 (Figure 4 here)  
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*NMA of studies with aggregate data*

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252 Studies in this NMA compared all available treatments. Donepezil improved MMSE score  
253 significantly (MD= 1.55 95% CI: 0.41 to 2.68). Assuming an MCID of 1.40, results were in  
254 agreement with the NMA of IPD and aggregate data, and donepezil+memantine (MD= 2.71,  
255 95% CI: -0.17 to 5.60) was likely the most effective in improving MMSE score (P-score= 76%).

256

*NMA of studies with IPD*

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

264

*Additional analyses using IPD and aggregate data*

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267 Overall, additional analyses using both IPD and aggregate data were in agreement with the  
268 findings of the main analysis (Additional File 1: Appendix 16). Cognitive performance was  
269 better in patients with mild to moderate MMSE receiving donepezil (MD= 1.68 95% CI: 0.31 to  
270 3.06, P-score= 69%) and most likely when receiving transdermal rivastigmine (MD= 2.74 95%  
271 CI: -0.68 to 6.16, P-score= 81%). In patients with moderate to severe MMSE the combination  
272 donepezil+memantine improved MMSE score significantly (MD= 2.49 95% CI: 1.55 to 3.44, P-  
273 score=100%), but oral rivastigmine deteriorated MMSE score significantly (MD= -1.00 95% CI:  
274 -1.87 to -0.12, P-score= 4%). Donepezil (MD= 1.31 95% CI: 0.66 to 1.96, P-score= 78%) and  
275 memantine (MD=0.69 95% CI: 0.07 to 1.31, P-score= 59%) also performed well for patients  
276 with moderate to severe cognitive impairment.

277

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



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3 281 suggested that oral rivastigmine improves MMSE score (MD= 0·88 95% CI: 0·31 to 1·45, P-  
4 282 score= 75%). Similarly, using IPD adjusted for cognitive impairment assessed with MMSE at  
5 283 baseline suggested that oral rivastigmine (MD= 0·88 95% CI: 0·31 to 1·45, P-score= 69%) and  
6 284 galantamine (MD= 0·76 95% CI: 0·34 to 1·18, P-score= 62%) improve MMSE score, but in a  
7 285 future study, results are only stable for galantamine.  
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13 287 Heterogeneity in NMA was high (between-study variance = 5·75, I<sup>2</sup>= 96%) compared also to the  
14 288 Rhodes et al.<sup>22</sup> empirical distribution (median 0.05, 95% range: 0·00 to 7·56). However,  
15 289 heterogeneity decreased importantly when excluding outliers (between-study variance = 0·59,  
16 290 I<sup>2</sup>= 73%), including only patients with moderate to severe AD (between-study variance = 0·18,  
17 291 I<sup>2</sup>= 44%), restricting to industry-sponsored trials (between-study variance = 0·16, I<sup>2</sup>= 43%), and  
18 292 using IPD only (between-study variance = 0·12, I<sup>2</sup>= 29%).  
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#### 25 294 *Adverse events*

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28 296 A NMA was conducted on adverse events (study definitions are provided in Additional File 1:  
29 297 Appendix 18) with 45 RCTs, 9 treatments (including placebo), and 15,649 patients (Figure 2b).  
30 298 In particular, 12 RCTs (6420 patients) contributed to the NMA using their IPD and 33 RCTs  
31 299 (9229 patients) using their data on their aggregated form. The time taken to achieve at least one  
32 300 AE was available in 8 studies with available IPD and ranged between 45 and 2228 days  
33 301 (Additional File 1: Appendix 19). Only one study included a patient with a AE occurring earlier  
34 302 than the trial opening and was excluded from the study.<sup>23</sup>  
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#### 42 304 *NMA of studies with IPD and aggregate data*

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45 306 Studies in this NMA compared all available treatments. According to P-score, oral rivastigmine  
46 307 had the least favourable safety profile regarding AE (OR= 1·26, 95% CI: 0·82 to 1·94, P-score=  
47 308 16%), followed by donepezil (OR= 1·08, 95% CI: 0·87 to 1·35, P-score= 30%) and  
48 309 galantamine+memantine (OR= 1·03, 95% CI: 0·45 to 2·39, P-score= 43%), yet in these  
49 310 comparisons the odds of experiencing an AE were imprecise and not importantly different from  
50 311 placebo (Figure 3b; Additional File 1: Appendices 16, 20). Confidence in NMA results ranged  
51 312 between moderate and high (Additional File 1: Appendix 17).  
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*NMA of studies with aggregate data*

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

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*NMA of studies with IPD*

321

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

325

*Additional analyses using IPD and aggregate data*

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328 Additional analyses using both IPD and aggregate data, showed that memantine was 0.61 times  
329 less likely to experience an AE than placebo when using study duration as a covariate, with an  
330 OR ranging from 0.37 to 0.93 (P-score= 88%). Restricting to low risk of bias for incomplete  
331 outcome data, galantamine was associated with significantly lower odds of a AE (OR= 0.69,  
332 95% CI: 0.50 to 0.97, P-score= 80%).

333

334 Heterogeneity in NMA was low (between-study variance = 0.04, I<sup>2</sup>= 22%) compared to the  
335 Turner et al.<sup>24</sup> empirical distribution (median 0.12, 95% range: 0.01 to 2.63). Heterogeneity  
336 decreased importantly when restricting to aggregate data (between-study variance = 0.00, I<sup>2</sup>=  
337 0%), low risk of bias for incomplete outcome data (between-study variance = 0.02, I<sup>2</sup>= 10%),  
338 patients with moderate to severe cognitive impairment (between-study variance = 0.00, I<sup>2</sup>= 0%),  
339 and when adjusting for study duration (between-study variance = 0.03), year of publication  
340 (between-study variance = 0.02), mean age (between-study variance = 0.02) or sex (between-  
341 study variance = 0.03).

**Discussion**

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3 344 We compared the efficacy and safety of cognitive enhancers regarding MMSE and AE outcomes  
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5 345 to update our previous systematic review<sup>6</sup> and included studies with both aggregate data and  
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7 346 IPD. Our results are in agreement with our previous systematic review,<sup>6</sup> and show that  
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9 347 donepezil+memantine, donepezil alone and transdermal rivastigmine were the most effective  
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11 348 treatments for improving MMSE score. However, heterogeneity was a major concern, which  
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13 349 requires careful consideration before suggesting the use of cognitive enhancers, and particularly  
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15 350 when the efficacy is not clear on the patient's characteristics. This was also captured by PIs, but  
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17 351 their interpretation requires caution due to evidence of funnel plot asymmetry in the MMSE  
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19 352 outcome. Overall, PIs are expected to include the true intervention effect expected in future  
20  
21 353 studies, and they incorporate an extra component of variance, specifically between-study  
22  
23 354 heterogeneity. In the absence of heterogeneity, confidence intervals and PIs are equal. According  
24  
25 355 to the P-score intervention ranking, both donepezil+memantine and transdermal rivastigmine had  
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27 356 a favourable safety profile regarding AE, whereas the therapy with the least favourable profile  
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29 357 was oral rivastigmine followed by donepezil. However, none of the estimated treatment effects  
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31 358 were sufficiently precise when cognitive enhancers were compared with the placebo group.  
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33 359 CINeMA suggested that within-study bias and reporting bias were the highest concerns for the  
34  
35 360 MMSE outcome, whereas within-study bias and imprecision of effect estimates were the highest  
36  
37 361 concerns for the AE outcome.

34 362  
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36 363 Overall, the choice among the different cognitive enhancers may depend on the patient's  
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38 364 characteristics. In participants with moderate to severe cognitive impairment (defined by  
39  
40 365 MMSE), a larger improvement in cognitive performance was observed for donepezil and  
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42 366 memantine, and their combination (donepezil+memantine), and these efficacy-related results are  
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44 367 expected to also be reflected when a future study becomes available. The least effective  
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46 368 cognitive enhancer in participants with moderate to severe cognitive impairment was oral  
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48 369 rivastigmine. For patients with mild to moderate impairments based on MMSE scores, donepezil  
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50 370 and transdermal rivastigmine were most likely the best performing cognitive enhancers. For  
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52 371 patients with moderate to severe cognitive impairment, cognitive enhancers were well tolerated.  
53  
54 372 For patients with mild to moderate cognitive impairment, all except for memantine and its  
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56 373 combination with transdermal rivastigmine, were associated with increased odds of an AE, yet  
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58 374 none of these results reached statistical significance. Overall, memantine was associated with

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3 375 lower odds of an AE than placebo, yet this was statistically significant only in the subnetwork  
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5 376 analysis including aggregate data (i.e., studies without IPD) and the meta-regression analysis  
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7 377 using study duration as a covariate. However, acknowledging for heterogeneity in the network,  
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9 378 PIs suggested that results are inconclusive and the odds of AE could not be differentiated  
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11 379 between memantine and placebo. Of note, the accuracy of AE reporting may be impacted by the  
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13 380 degree of cognitive impairment. Using IPD only and adjusting for MMSE baseline differences,  
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15 381 (as shown in Additional File 1: Appendix 16, Mean Difference: NMA of studies with IPD  
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17 382 adjusted for baseline cognitive impairment), oral rivastigmine and galantamine improved MMSE  
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19 383 score, whereas when adjusting for comorbidities only oral rivastigmine was effective, but results  
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21 384 can change in a future study. Considering a MCID equal to 1·40 points,<sup>21</sup> the MDs of all  
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23 385 cognitive enhancer regimens except for single-agent oral rivastigmine, galantamine, and  
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25 386 memantine, against placebo were clinically important for cognition, but these were associated  
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27 387 with high uncertainty. However, the 1·40 MMSE cut-off value is not a widely adopted MCID.  
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29 388 Also, high variability may be related to different populations included in the studies, such as  
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31 389 genetic profiles, race, and gender identity. Future studies should report this information to enable  
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33 390 exploration of population characteristics that would benefit more, with a clinically important  
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35 391 improvement, when using these treatments. Our results did not differ by participant  
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37 392 characteristics sex, age, and other medications, or by study characteristics, study duration and  
38  
39 393 year of publication. However, these findings might be due to low power since meta-regression  
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41 394 analyses depend on the number and size of studies, magnitude of the relationship between the  
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43 395 covariate and effect size, along with its precision and heterogeneity.<sup>25</sup>

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47 397 To the best of our knowledge, our study was the first to add IPD in a NMA of cognitive  
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49 398 enhancers for patients with Alzheimer's Dementia to produce treatment recommendations by  
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51 399 patient characteristics. We followed the methods guidelines in the Cochrane Handbook for  
52  
53 400 systematic reviews,<sup>26</sup> the reporting guidelines in the PRISMA-NMA and PRISMA-IPD  
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55 401 statements,<sup>7,8</sup> and the CINeMA quality assessment guidelines.<sup>15</sup> Compared to previous  
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57 402 systematic reviews, we included a larger number of studies and/or studies with shared IPD,  
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59 403 compared in a wider range of cognitive enhancers.<sup>6,27</sup> Our results are in agreement with previous  
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61 404 studies overall. Access to IPD allowed us to observe minor differences between the original  
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63 405 published results and our re-analysis. An explanation in these differences may be that many

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3 406 studies used the last-observation-carried-forward imputation method, whereas we used the  
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5 407 available case analysis when assessing MMSE. Another potential explanation might be that  
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7 408 original studies excluded some patients, and hence used a smaller sample size.  
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10 410 Comparing NMA, results between aggregate data and IPD were in agreement. The only  
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12 411 difference was observed in transdermal rivastigmine that was associated with a MCID of greater  
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14 412 than 1.40 MMSE points against placebo in the aggregate data NMA compared to the IPD NMA,  
15  
16 413 yet a statistically significant improvement was achieved in the IPD NMA. The inclusion of IPD  
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18 414 in our NMA, allowed us to overcome potential reporting bias and to include IPD for 1) a study  
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20 415 that we previously were unable to include since arm-level data were not reported in the RCT  
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22 416 publication,<sup>23</sup> and 2) two studies that did not report MMSE results in their publications.<sup>19,20</sup> The  
23  
24 417 use of IPD also allowed us to assess for potential effect modifiers that were not reported in the  
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26 418 original publications (e.g., comorbidities, additional medications) and explore for treatment-by-  
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28 419 covariate interactions on the patient-level. Several challenges were encountered during the IPD  
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30 420 request from sponsors, showing that repositories are not a panacea (Additional File 1: Appendix  
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32 421 21).  
33

34 422  
35 423 An important finding of our review is that the two thirds of the published RCTs, were associated  
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37 424 with high risk of bias for incomplete outcome data due to attrition, and the majority of these  
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39 425 RCTs used the last-observation-carried-forward technique for missing data. This approach may  
40  
41 426 bias results favouring cognitive enhancers, since the dropout rates were greater in the treatment  
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43 427 group compared to the placebo group in 63% of the included studies and because dementia is a  
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45 428 progressive disease. Of the 27 studies comparing treatment against placebo and reporting the  
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47 429 number of dropouts, 17 studies had a greater dropout rate in the treatment group (treatment  
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49 430 group: median dropout rate= 28% IQR [17% to 39%]; placebo group: median dropout rate= 21%  
50  
51 431 IQR [15% to 31%]). Last-observation-carried-forward is an inappropriate imputation method for  
52  
53 432 Alzheimer's Dementia studies, since it ignores expected deterioration of the patient's condition  
54  
55 433 and stabilizes the outcome at the value observed at the time of dropout (i.e., the last  
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57 434 observation).<sup>28</sup> Restricting to low risk of attrition bias studies, we found that galantamine was  
58  
59 435 significantly associated with decreased odds of experiencing an AE.  
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3 437 Our study has limitations worth mentioning. First, we were unable to include IPD for all eligible  
4 438 studies (only 15% of the included RCTs shared their IPD), highlighting potential availability bias  
5 439 for IPD. However, recent simulations have shown that combining IPD and aggregate data in a  
6 440 NMA can significantly improve precision, reduce bias, and increase information compared to  
7 441 NMA relying on aggregated data alone.<sup>29</sup> Second, missing data is a big concern in the published  
8 442 RCTs for AD. We found high rates of dropouts from experiencing an adverse event and the  
9 443 patients' characteristics that may increase the chances of such adverse reactions prior to  
10 444 administering these cognitive enhancers should further be explored. To assess the impact of  
11 445 missing data in our NMA, we applied the informative missingness of difference in means.<sup>30</sup>  
12 446 However, future studies should explore the characteristics of missing participants and specific  
13 447 adverse events. Third, the lack of studies in certain treatment comparisons may have affected the  
14 448 P-score calculation and treatment ranking. In particular, polytherapies were informed by  
15 449 maximum two studies, and ranking may have been in favour of the complex intervention group  
16 450 with the smaller number of studies.<sup>31</sup> For example, in MMSE the polytherapies including  
17 451 memantine in conjunction with one of the three treatments donepezil, galantamine, transdermal  
18 452 rivastigmine had a P-score  $\geq 60\%$ , but these all had wide 95% CIs for MD. As such, ranking  
19 453 should be interpreted with caution and along with the estimated effect sizes and their uncertainty  
20 454 measures. Fourth, the comparison-adjusted funnel plot for MMSE suggested there is an  
21 455 indication for small-study effects pointing to the treatment being better, and results should be  
22 456 interpreted with caution. This may also be related to the potential risk of funding bias, since the  
23 457 majority of the included studies were industry-sponsored and IPD were retrieved only from  
24 458 industry-sponsored studies favouring cognitive enhancers over placebo. Overall, MMSE score is  
25 459 only a surrogate maker for determining the impact of treatments on dementia. A full assessment  
26 460 that considers the potential impact of treatments on cognition, function and behavioural  
27 461 symptoms needs to be considered within the clinical context. Fifth, differences in patient  
28 462 characteristics, such as sex, were observed in the RCTs with provided IPD, which increased  
29 463 heterogeneity across studies. To account for these differences, we used the fully adjusted  
30 464 treatment effect estimates in the IPD analyses and the primary NMA analysis. Also, at the NMA  
31 465 level, we found that on average there were no important differences across treatment  
32 466 comparisons to threaten the transitivity assumption. Sixth, there are clinically important  
33 467 limitations associated with this review, including consistent definition of outcome measures

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3 468 across studies, a well-established MCID for the MMSE score, lack of consideration of drug  
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5 469 doses due to inconsistent reporting and data availability bias that we were unable to overcome  
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7 470 (15% of the studies shared their IPD). Future studies are needed to establish ranking efficacy in  
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9 471 drug doses and combination of interventions across different disease severity categories.  
10  
11 472 Seventh, the literature searches were conducted 5 years ago and additional relevant studies may  
12  
13 473 be available. However, obtaining IPD in a timely manner was very challenging and required  
14  
15 474 more time than anticipated (challenges to obtain IPD are outlined in Additional File 1: Appendix  
16  
17 475 21). Similar to all systematic reviews, the evidence should be updated regularly.<sup>32</sup>  
18

19 477 We expect that our findings will increase scientific knowledge, because people with Alzheimer's  
20  
21 478 Dementia require personalized medicine to optimize their healthcare. Well-conducted meta-  
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23 479 analyses of IPD are considered the 'gold-standard' and influence patient care since patient-level  
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25 480 data can be provided to facilitate tailored decision making. However, results from meta-analyses  
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27 481 of IPD are likely subject to retrieval bias and awareness of these limitations and their potential  
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29 482 impact on findings is required.  
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## 483 **Contributors**

484  
485 AAV, SES and ACT conceived and designed the study.  
486 AAV conducted the analyses, abstracted data, contacted sponsors, analysed data, interpreted  
487 results, appraised quality of results, and wrote a draft manuscript.  
488 GS conducted the analyses, appraised quality of results, and edited the manuscript.  
489 HMA coordinated the review, screened citations and full-text articles, abstracted data, appraised  
490 quality, cleaned the data, contacted sponsors, and edited the manuscript.  
491 PR helped coordinate the study, screened citations and full-text articles, extracted and  
492 categorized data, appraised quality, and edited the manuscript.  
493 SES and ACT interpreted results and edited the manuscript.  
494 ACT and HMA contacted authors. LAS, MC, CTS, DM, BRH, JHL provided input into the  
495 design, interpreted results, and edited the manuscript.  
496 All authors read and approved the final manuscript.

## 497 **Declaration of interests**

498  
499 The authors declare that they have no competing interests.

## 500 **Data sharing statement**

501 All data relevant to the study are included in the article or uploaded as supplementary  
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12  
13

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26 522 0/.

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5 539 University Open Data Access Project, which has an agreement with JANSSEN RESEARCH &  
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7 540 DEVELOPMENT, L.L.C.. The interpretation and reporting of research using this data are solely  
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18 546 **Ethical Approval Statement**

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21 547 Not applicable.  
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624

## 625 Figure Captions

626

627 **Figure 1.** Flow diagram for study inclusion in the review (a) and studies retrieved with  
628 individual patient data (b).

629

630 **Figure 2.** Network diagrams for (a) MMSE and (b) AE outcomes. The size of each node and line  
631 indicates the number of studies included in each treatment comparison. The number of studies  
632 per treatment comparison is presented on each edge, and the number of studies with individual  
633 patient data (IPD) is depicted in a parenthesis. Orange coloured edges are informed by both IPD  
634 and aggregate data, whereas black coloured edges are informed by aggregate data only.

635

636 **Figure 3.** Forest plot of network meta-analysis (NMA) results for all cognitive enhancers versus  
637 placebo in (a) MMSE outcome, and (b) AE outcome. NMA results are presented for i) aggregate  
638 data (AD) and fully adjusted results from studies with available individual patient data (IPD), ii)  
639 AD and crude results from studies with available IPD, iii) AD only (studies with available IPD  
640 are not included in the analysis), and iv) crude results from individual studies with individual  
641 patient data (IPD).

642

643 **Figure 4.** Rank-heat plot of P-scores for 9 treatments, including placebo, studied in randomized  
644 clinical trials with patients with Alzheimer's Dementia assessing MMSE. Circles from inside out  
645 present results for different network meta-analyses including: i) aggregate data (AD) only  
646 (studies with available IPD are not included in the analysis), ii) crude results from individual  
647 studies with individual patient data (IPD), iii) AD and crude results from studies with available  
648 IPD, and iv) AD and fully adjusted results from studies with available IPD. Numbers within each  
649 sector correspond to the P-score values as calculated in each model.

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650 **Tables**

651

<b>Table 1· Study and patient characteristics</b>		
	<b>AD (N=80)</b>	<b>IPD (N=12)</b>
<b>Total # participants</b>	21,138	5839
<b>Longest duration of follow-up in weeks: mean (range)</b>	28·28 (8 - 208)	29·33 (12 - 104)
<b>Mean number of patients (range)</b>	264·23 (14 - 2,045)	486·58 (123 - 2,045)
<b>Mean age in years (range)</b>	74·64 (61 - 85·7)	73·94 (70·4 - 78)
<b>Mean % Female (range)</b>	61·35 (3 - 89)	62·76 (53·68 - 81)
<b>Country of conduct: frequency (%)</b>		
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)	-
United Kingdom	6 (7·50)	1 (8·33)
United States	15 (18·75)	-
Multi-national	26 (32·50)	9 (75·00)
<b>Interventions examined: frequency*</b>		
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)
<b>Effectiveness outcomes reported: frequency*</b>		
Mini-Mental State Examination	57 (71·25)	6 (50·00)
Adverse Events	46 (57·50)	12 (100·00)
<b>Funding</b>		
Industry-sponsored	48 (60·00)	12 (100·00)
Publicly-sponsored†	9 (11·25)	-
Mixed	7 (8·75)	-
Not Reported	16 (20·0)	-
<b>Severity of Alzheimer's dementia: frequency (%)</b>		
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)
<b>Diagnostic criteria for Alzheimer's dementia: frequency*</b>		
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)
Magnetic Resonance Imaging/Computerized Tomography	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)

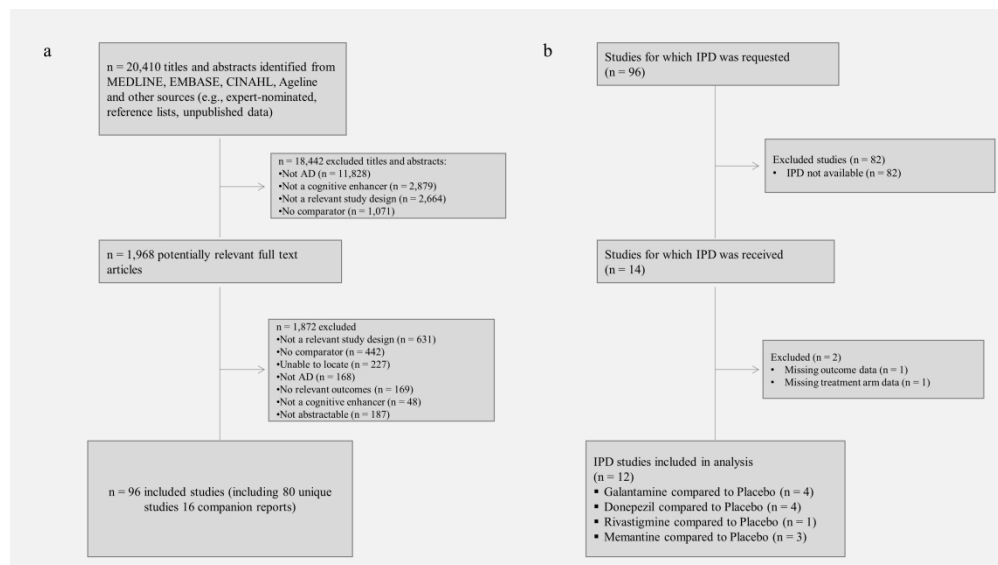
**Abbreviations:** -, not applicable

\* 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

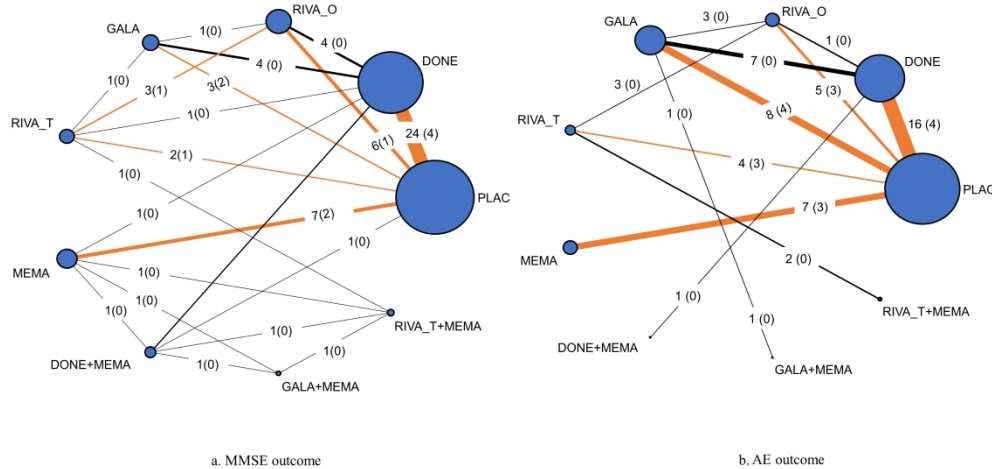
652



25 Figure 1. Flow diagram for study inclusion in the review (a) and studies retrieved with individual patient data  
26 (b).

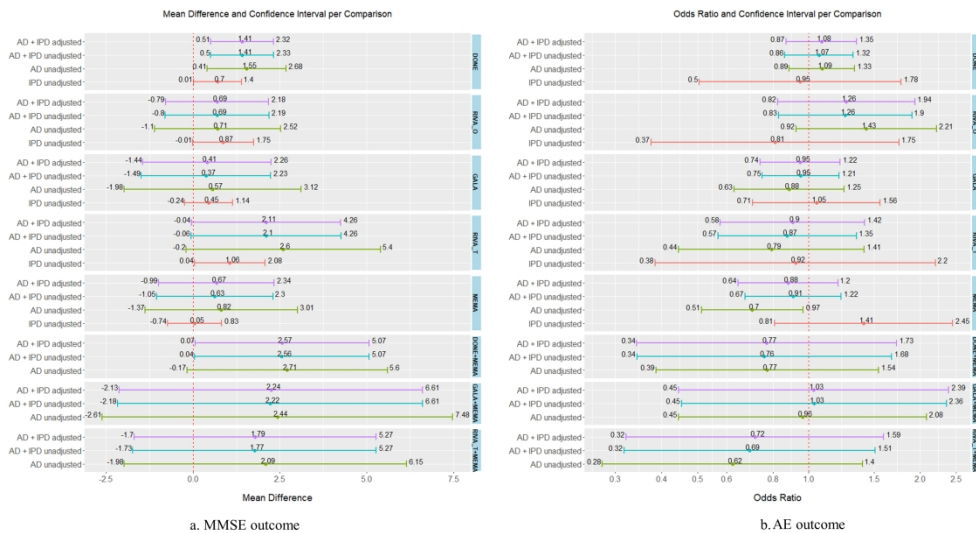
27 338x190mm (300 x 300 DPI)





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.

338x190mm (300 x 300 DPI)



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 individual patient data (IPD).

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Figure 4. Rank-heat plot of P-scores for 9 treatments, including placebo, studied in randomized clinical trials with patients with Alzheimer’s Dementia assessing MMSE. 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.

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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***

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## 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,<sup>4</sup> 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.<sup>10</sup> 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:<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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

1  
2  
3 corresponding comparison-specific effect (obtained from standard meta-analysis) against the corresponding  
4 study-specific standard error. We used the fixed effect model for the standard meta-analysis performed for each  
5 treatment comparison, ordered treatments chronologically according to year of availability in Canada, and used  
6 only treatment comparisons versus placebo. We used the *netfunnel* command in Stata to produce the  
7 comparison-adjusted funnel plot.<sup>4</sup>  
8

9 For imprecision, we considered a MD=1.4 and a OR=1 as a clinically important size of effect for  
10 MMSE and AE, respectively, and followed the CINeMA guidelines for exploring whether statistical  
11 significance and clinical importance coincide. Similarly, heterogeneity and incoherence (i.e. inconsistency) were  
12 assessed by following the standard CINeMA approach.  
13

14 CINeMA assesses the credibility of the NMA results and heterogeneity examining the range of both  
15 confidence intervals (CIs; which do not capture heterogeneity) and prediction intervals (PIs; which capture  
16 heterogeneity) in relation to their equivalence. If a PI includes values that lead to a different conclusion than an  
17 assessment based on the corresponding CI, then this suggests that there is considerable heterogeneity. PIs are  
18 expected to include the true intervention effects in future studies with characteristics similar to the existing  
19 studies, and they incorporate the extent of between-study heterogeneity.<sup>5,6</sup> In the presence of considerable  
20 heterogeneity, they are wide to include intervention effects with different implications for practice. However,  
21 caution is needed in the interpretation of results in the presence of funnel plot asymmetry, since PIs are based on  
22 the assumption of a normal distribution for the study-specific effects and as such they may be problematic if the  
23 data do not follow a normal distribution.  
24

### 25 *Statistical Analysis*

26 We performed a descriptive analysis using frequencies and percentages of the discrete characteristics of  
27 the included patients and treatments of the eligible studies. We explored the distributions of the continuous  
28 patient characteristics per outcome and treatment group using means and standard deviations. For studies not  
29 providing outcome results for a certain outcome, we presented distributions of the available and requested  
30 patient characteristics, whenever available. Outliers for each patient characteristic were also explored in each  
31 study dataset using boxplots. We also recorded the number of missing participants per treatment group and  
32 overall. We compared the characteristics of the unavailable and the available by the sponsors' studies. In  
33 particular, we explored whether these were well-conducted according to overall risk of bias, and compared  
34 distributions of mean participant age, publication year, study duration, study size, percent male, and magnitude  
35 of treatment effect, to assess for potential bias in IPD sharing. We conducted a two-stage analysis for both  
36 standard meta-analysis and NMA. The network geometry was explored through the presentation of network  
37 plots.  
38

### 39 *First stage*

40 All IPD from included studies were first aggregated to study-level summary statistics using each  
41 sponsor's portal. The use of different platforms and failure to obtain IPD from all studies restricted us from  
42 combining IPD in a one-stage analysis. For each separate study with IPD available, we fitted a logistic  
43 regression model for the binary outcome and a linear regression model for the continuous outcome. For MMSE,  
44 we considered the longest duration of follow-up per study (most frequently at week 24). In the shared IPD,  
45 when we were unable to make a judgement on first and last date of visit per patient, we used the older coded  
46 date and the newest coded date as baseline and final value for each patient respectively.  
47

48 Initially, we did not adjust for any of the patient characteristics provided, but in a subsequent analysis  
49 we included patient-level covariates with as many interaction terms in the model as the patient characteristics  
50 were provided (considering only the ones we have asked for). For each study, we obtained the adjusted odds  
51 ratio (OR) for binary data and adjusted mean difference (MD) for continuous data, along their corresponding  
52 95% CI. We adjusted for any of the following variables that were available in each study: age, sex, severity of  
53 Alzheimer's disease (e.g., baseline Mini-Mental State Examination [MMSE] level), presence of behavioural  
54 disturbance, comorbidity, and other medications. The first stage of the IPD analyses were conducted in  
55 RStudio,<sup>7</sup> which was available in data providers. Additional medications and comorbid conditions were grouped  
56 into broader categories according to their clinical relevance to increase power in our analysis (e.g., grouped  
57 medications as anti-psychotics, anti-depressants, and cognitive enhancers, as well as comorbid conditions as  
58 psychiatric, neurological, and cardiac disorders). Eligible studies with insufficient data to derive a pairwise  
59 estimate for NMA were summarized descriptively without performing a statistical analysis.  
60

1  
2  
3 We applied an available case analysis for each study, since we were unable to install R packages in  
4 most sponsor-specific platforms, and hence we applied a consistent approach across all IPD datasets. We  
5 explored the impact of missing data during the second stage of analysis. Reasons for missing participants and  
6 time taken to have an adverse event were captured (when available).  
7

8 We synthesized IPD at the first stage in four different proprietary sponsor-specific platforms. Analyses  
9 were conducted in the RStudio using different R versions<sup>7</sup> according to what was provided in each sponsor's  
10 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  
11 Lundbeck.  
12

### 13 *Second stage*

14  
15 Since we were not successful in obtaining IPD for all eligible studies, we combined both IPD and  
16 aggregate data in a single meta-analysis or NMA model. Both IPD and aggregate data studies shared the same  
17 amount of heterogeneity. In both meta-analysis and NMA models, we combined the adjusted IPD estimates with  
18 the aggregate data (main analysis). As a secondary analysis, we combined the unadjusted estimates from retrieved  
19 IPD with the evidence provided by the aggregated data studies in a joint NMA model. A common-within network  
20 between-study variance was assumed across comparisons for all NMA models.<sup>8</sup> We estimated the between-study  
21 variance using the DerSimonian and Laird<sup>9</sup> method and compared it with the relevant distributions provided by  
22 Turner et al<sup>10</sup> and Rhodes et al<sup>11</sup> to assess heterogeneity. We also calculated  $I^2$  on the NMA level to quantify  
23 overall heterogeneity and inconsistency in each outcome.  
24

25 To assess the validity of the transitivity assumption for each outcome, we assessed the distribution of  
26 potential effect modifiers (e.g., age, sex) across treatment comparisons in each network.<sup>12-14</sup> We visually inspected  
27 similarity and assessed whether these characteristics were likely to modify the treatment effect. We evaluated the  
28 consistency assumption using the design-by-treatment interaction model<sup>15,16</sup> and the loop-specific method.<sup>17,18</sup> In  
29 the presence of statistically significant inconsistency, we checked the data for discrepancies and if none were  
30 identified, we planned to conduct subgroup NMA or network meta-regression analysis adjusting for potential  
31 variables influencing the results.  
32

33 We conducted additional NMA analyses for all potential effect modifiers requested from data  
34 providers. If relevant data were not available in the IPD, we used aggregate data of the relevant publications.  
35 Additional NMA analyses included: 1) subgroup analysis for industry vs. publicly sponsored studies, for studies  
36 with available IPD vs. studies with aggregate data (unadjusted estimates), and for AD severity, classified  
37 according to MMSE scores using the National Institute for Health and Care Excellence categories: mild (21–  
38 24), moderate (10–20), severe (<10),<sup>19</sup> 2) network meta-regression accounting for study duration, year of  
39 publication, mean age, and sex (% of male participants) effect modifiers separately and assuming a common  
40 regression coefficient across comparisons (studies with aggregate data were used only; studies with available  
41 IPD were pooled in a NMA separately adjusted for available covariates at first stage), 3) sensitivity analysis  
42 including studies with low risk of bias for allocation concealment and incomplete outcome data items, as these  
43 items may have an important impact on the meta-analysis results according to our previous NMA,<sup>20</sup> and 4) the  
44 'informative missingness difference of means' (IMDoM) imputation method<sup>21</sup> for MMSE for the aggregate data  
45 studies to assess the impact of missing data in our NMA. In all additional NMA analyses, we used the adjusted  
46 effect estimates derived from the IPD within-study analysis and the aggregate data extracted from the eligible  
47 publications. Network meta-regression was performed in a Bayesian setting using OpenBUGS version 3.2.3,  
48 non-informative priors for all parameters in the model and a half-normal prior for the between standard  
49 deviation. We compared the results of the additional models by evaluating the treatment effect estimates and  
50 ranking statistics, as well as monitoring the reduction in the between-study variance.  
51

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

Meta-analysis and NMA at the 2<sup>nd</sup> stage were conducted in the RStudio using R version 3.6.2 and the *meta*<sup>28</sup> and *netmeta*<sup>29</sup> 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<sup>1</sup> of 859 participants comparing transdermal rivastigmine vs. placebo included only IPD for the placebo arm. Another study<sup>2</sup> 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 cm<sup>2</sup> group, 287 to the rivastigmine patch 10 cm<sup>2</sup> 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

<sup>1</sup>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.

<sup>2</sup>Wilkinson D, Murray J. Galantamine: a randomized, double-blind, dose comparison in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2001; 16(9): 852-7.



## 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
	Johansen, 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/Allergan	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-Padullés, 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

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2							
3	Kano, 2013;	Japan	30; 28	Donepezil, Donepezil + Memantine ; MMSE	NA	Not reported; August 2011; Not reported	No; NR
4							
5	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
6							
7	Likitjaroen, 2012	Germany	25; 26	Galantamine, Placebo; MMSE	Publicly- sponsored + Industry- sponsored	Not reported; September 2006; Not reported	No; Do not own data
8							
9	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
10							
11	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
12							
13	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
14							
15	Mazza, 2006	Italy	51; 24	Donepezil, Placebo/No treatment; MMSE	NA	Not reported; March 2003; 1:1:1	No; NR
16							
17	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
18							
19	Moretti, 2014	Italy	20; 78	Rivastigmine Patch, Rivastigmine Oral; MMSE	NA	Not reported; Not reported; Not reported	No; NA
20							
21	Mowla, 2007	Iran	81; 12	Rivastigmine, Placebo/No treatment; MMSE	Publicly- sponsored	Not reported; Not reported; Not reported	No; NA
22							
23	Nakamura, 2011	Japan	855; 24	Rivastigmine, Placebo/No treatment; MMSE, AEs, Vomiting, Nausea, Diarrhea	Industry- sponsored	Not reported; January 2007; Not reported	Yes; NA
24							
25	Nakano, 2001	Japan	35; 48	Donepezil, Placebo/No treatment; MMSE	NA	Not reported; Not reported; Not reported	No; NR
26							
27	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
28							
29	Pakdaman H, 2015	Iran	198; 68.8	Donepezil, Galantamine, Rivastigmine; MMSE, ADAS-cog, Mortality,	Industry- sponsored	Not reported; Not reported; Not reported	No; NR
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			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 Britain, 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

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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

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## 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

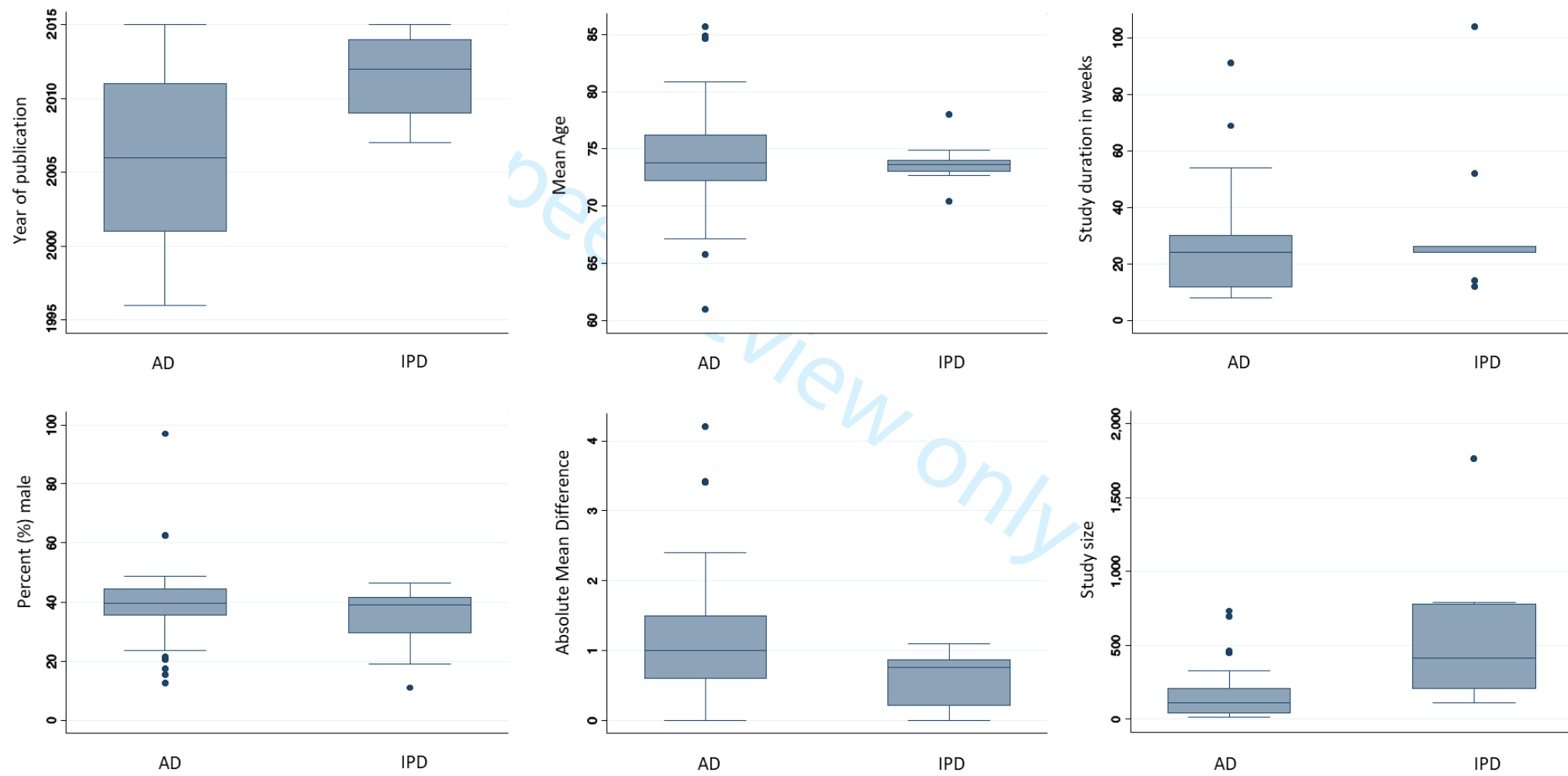
† The MMSE final value comes from visit 8 (last available visit in IPD). MMSE was not reported in study publication

**Abbreviations:** AD, Alzheimer's Dementia; IPD, individual patient data; MMSE, Mini-Mental State Examination; NR, not reported; N/A, not applicable; AE, adverse event

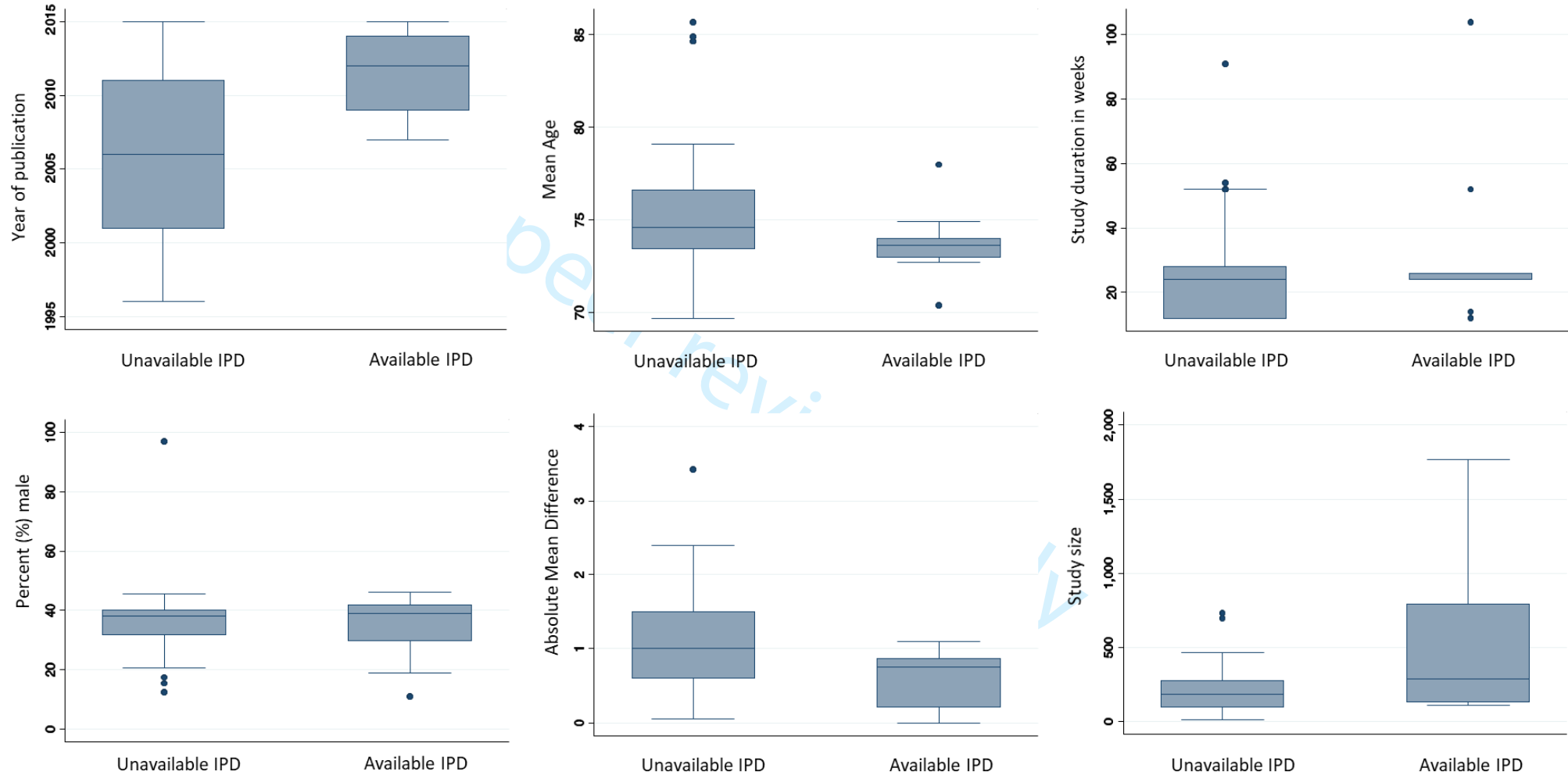
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Appendix 7: Comparison of studies with shared IPD with (a) all remaining studies and (b) studies for which sponsors claimed unavailable IPD. AD: aggregate data; IPD: individual patient data

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 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-Padullas, 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:

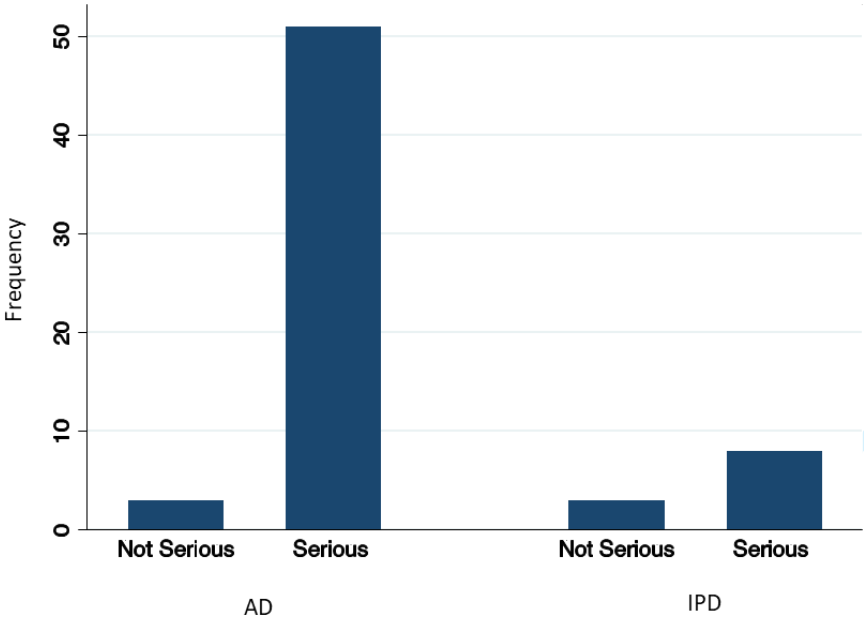
- A potential source of bias related to the specific study design used; or
- A conflict of interest related to funding source; or
- An author was an employee of the drug company that sponsored the study; or
- Been claimed to have been fraudulent; or
- Other potential biases.

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

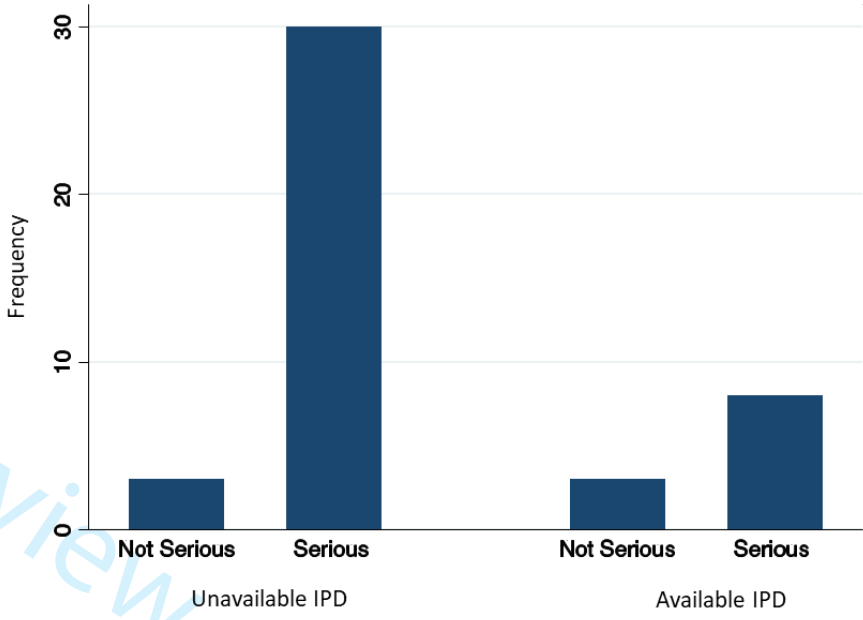
- Insufficient information to assess whether an important risk of bias exists; or
- Insufficient rationale/evidence that an identified problem would introduce bias; or
- Funding by drug company, but conflicts were not described

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**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**

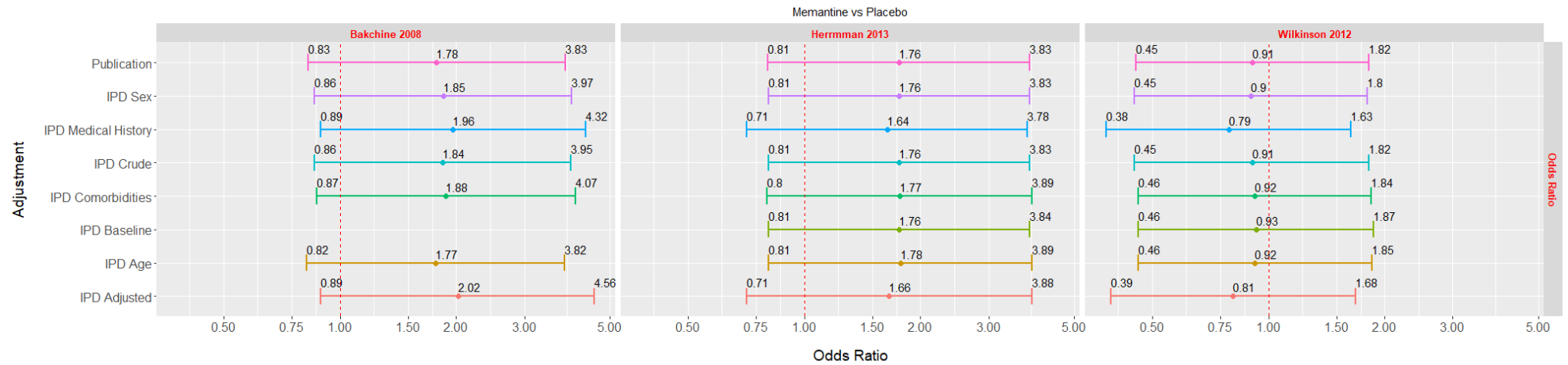
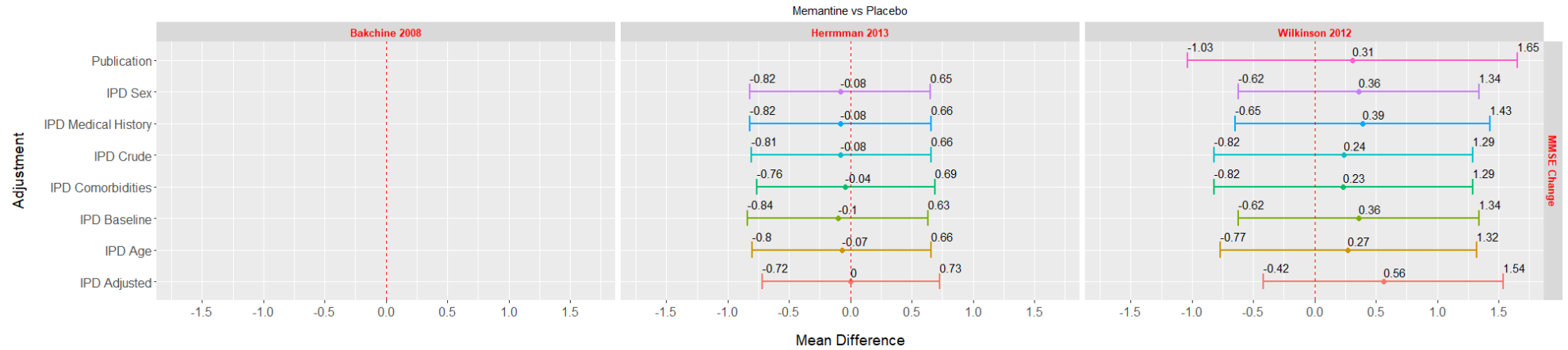


a. Comparison of studies with shared IPD with all remaining studies (irrespective type of sponsor)

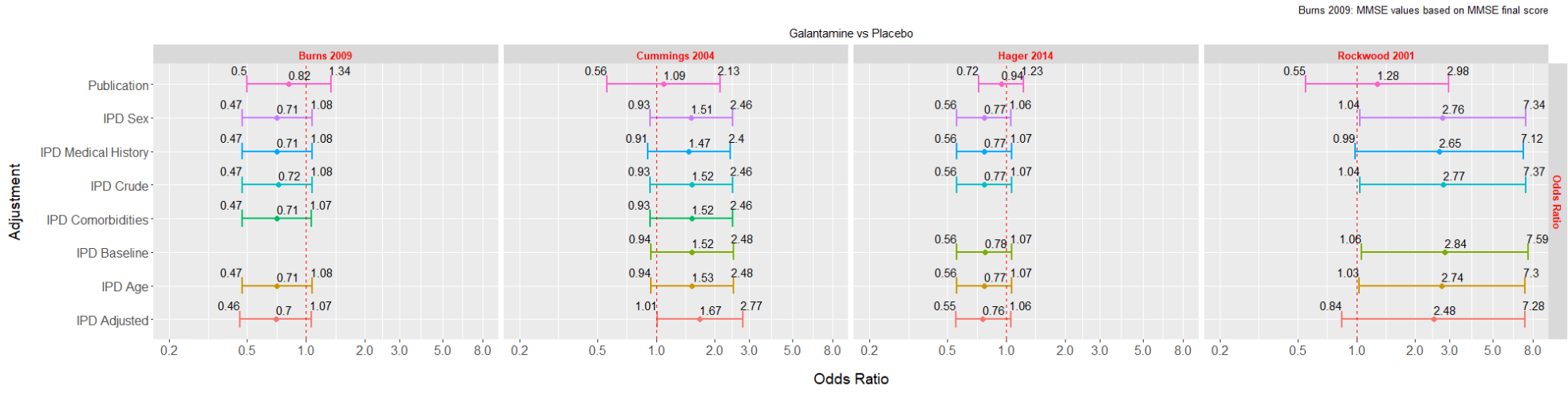
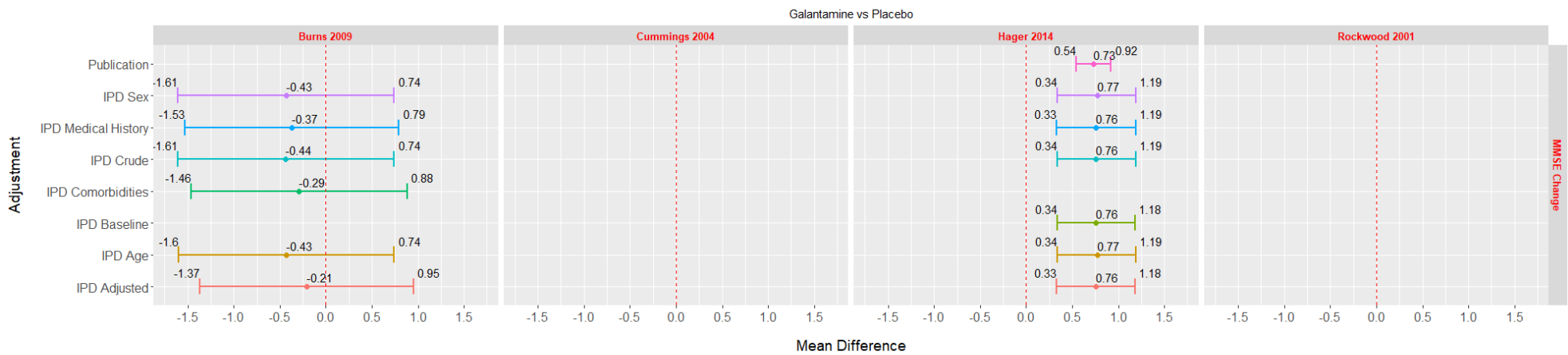


b. Comparison of studies with available and unavailable IPD (industry-sponsored studies only)

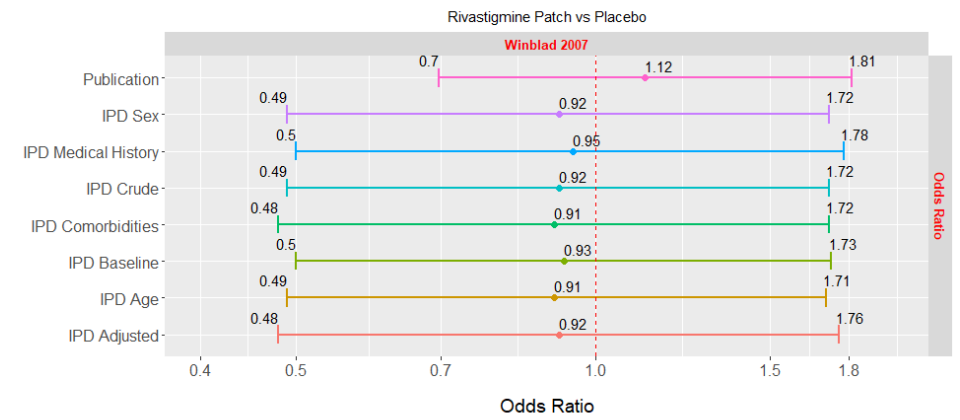
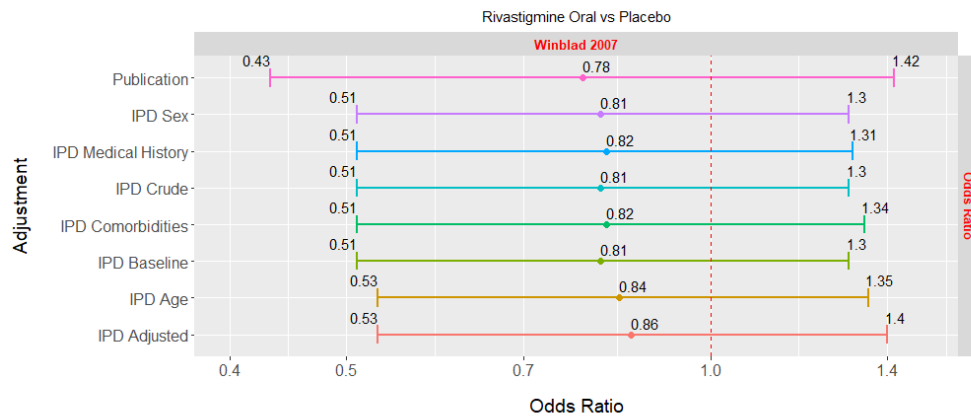
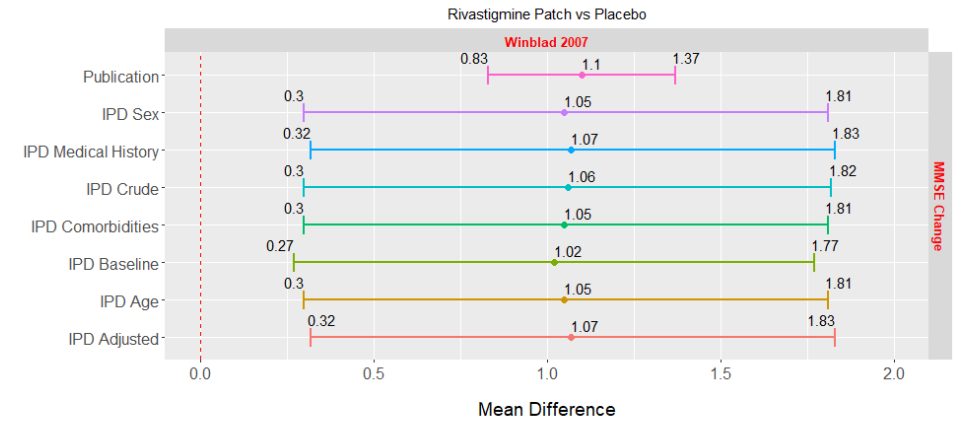
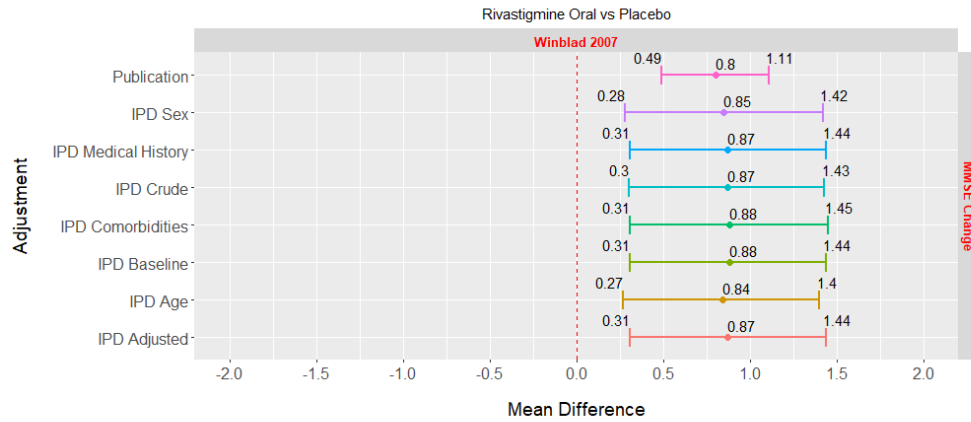
Appendix 10: Study-specific effect sizes calculated from shared IPD and published data. IPD: individual patient data



Sponsor: LUNDBECK

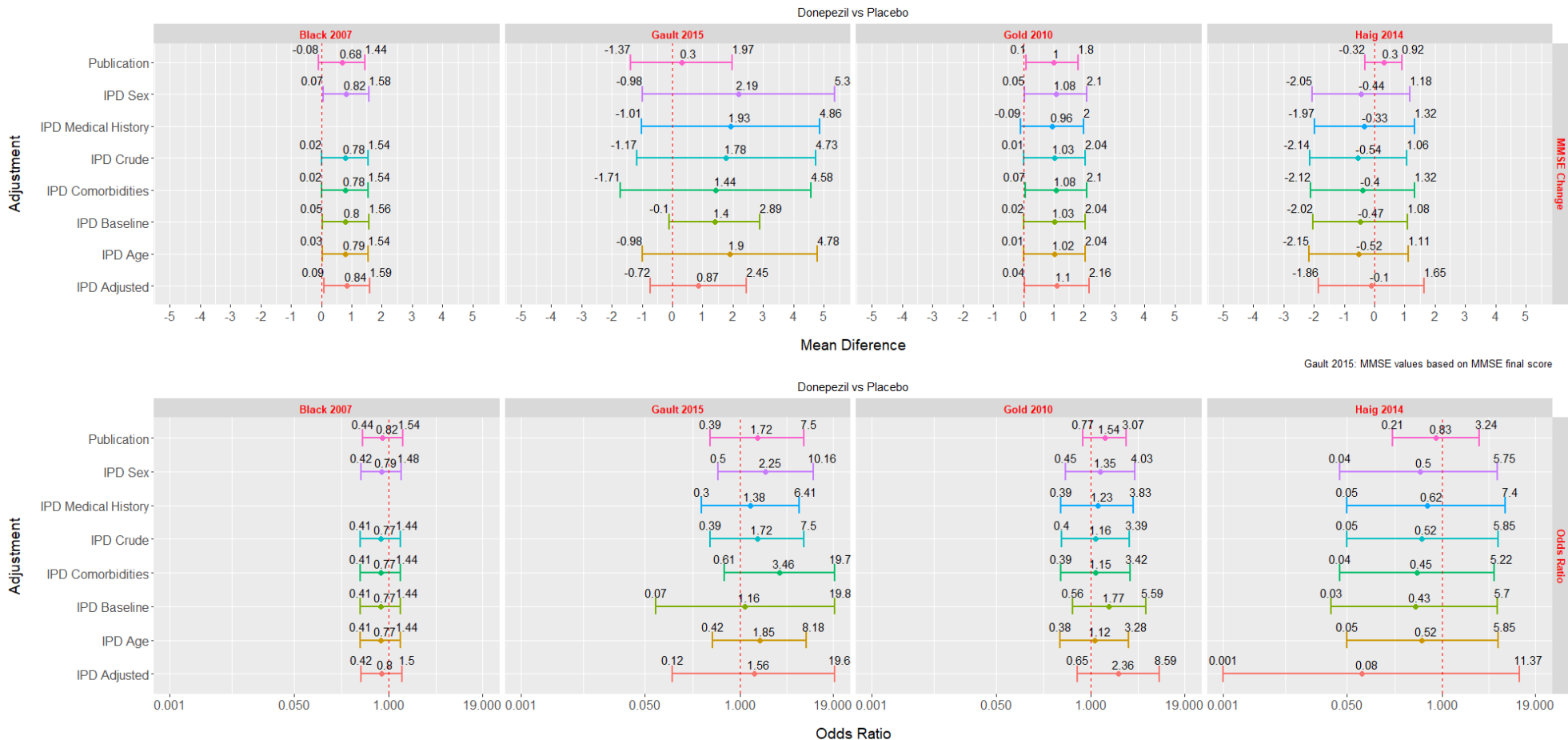


Sponsor: YODA



Sponsor: CSDR Novartis

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Sponsor: CSDR, ABBVIE

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 assesment we did not have access to these data.

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3 **Abbreviations:** IPD sex, regression analysis adjusting for sex; IPD medical history, regression analysis adjusting for medical history; IPD crude, analysis with no  
4 adjustments; IPD comorbidities, regression analysis adjusting for comorbidities; IPD baseline, regression analysis adjusting for MMSE baseline; IPD age, regression analysis  
5 adjusting for age; IPD adjusted, regression analysis adjusting for all available variables (we only considered those that we initially requested from sponsor)  
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**Appendix 11: Correlation between participant age and dropout in studies with IPD.** IPD: individual patient data

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

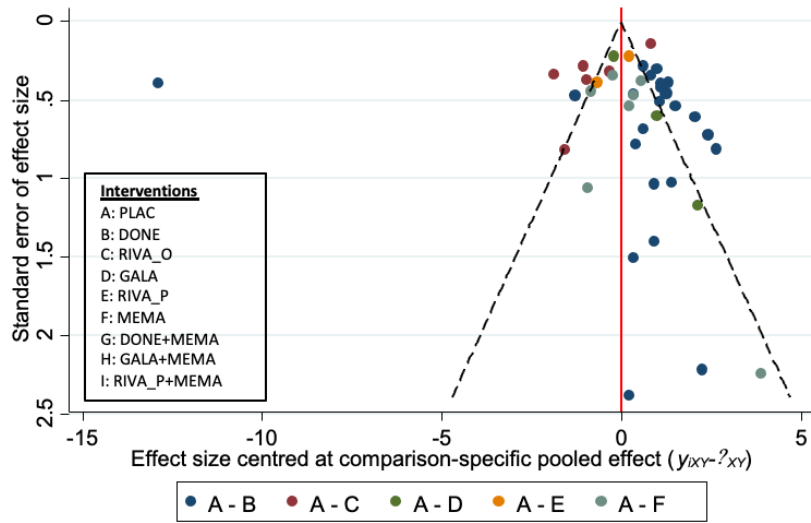
\* We were unable to assess this correlation for studies obtained through YODA and AbbVie, since at the time of this assessment we did not have access to these data

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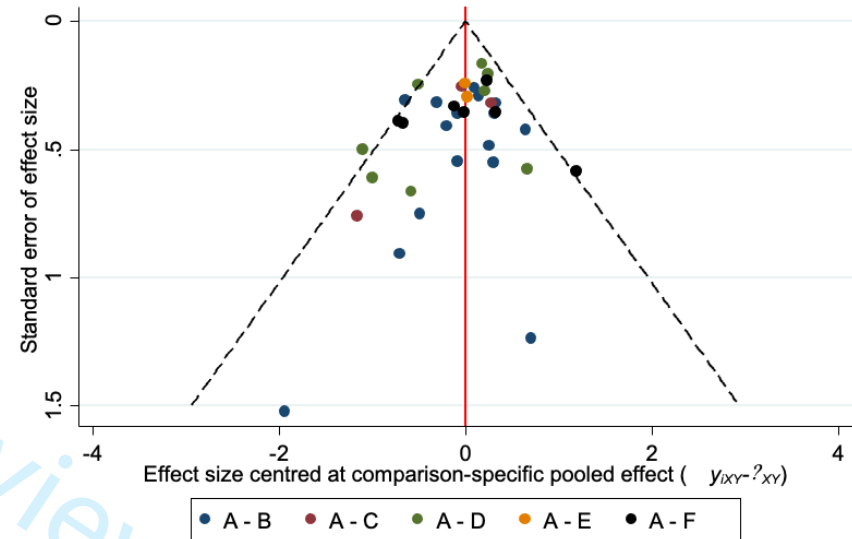
Appendix 12: Comparison Adjusted Funnel plot (all treatments vs placebo)

(a) MMSE



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

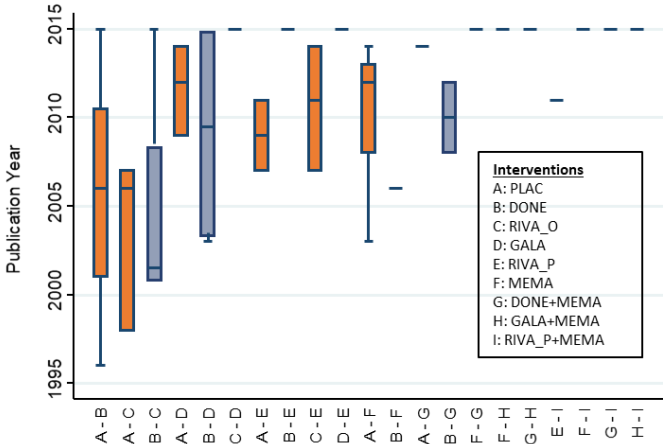
(b) Adverse Events



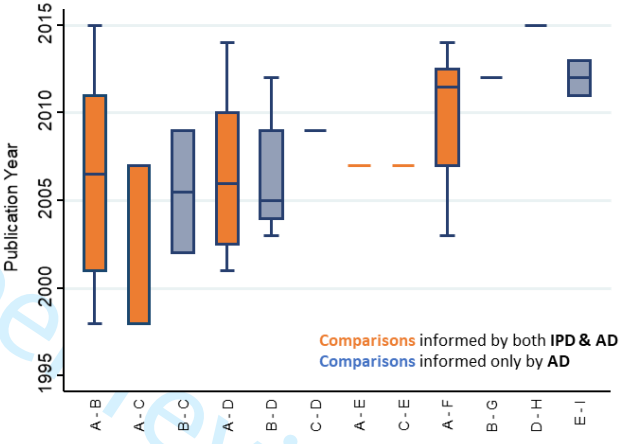
Note: Comparisons including only one study (when present) have been excluded

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

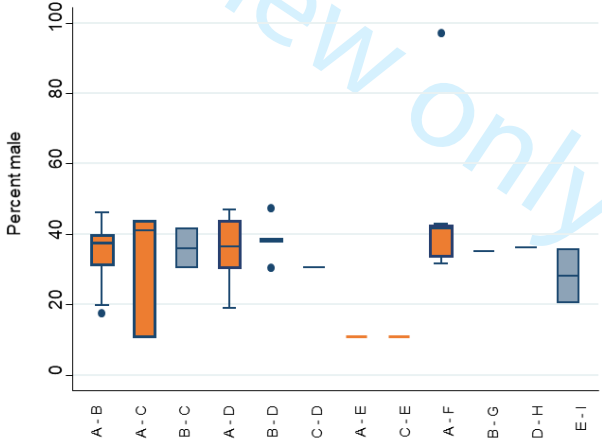
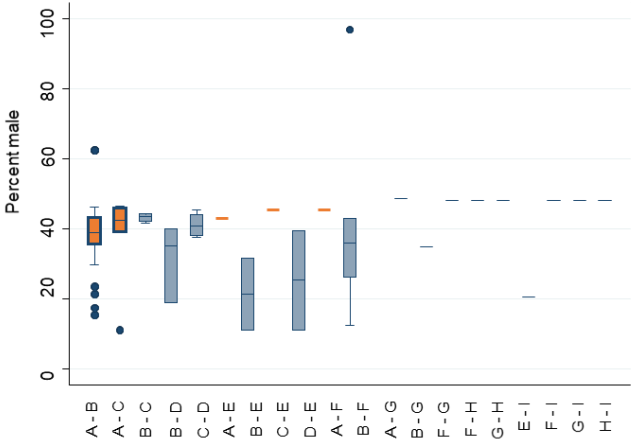
(a) MMSE



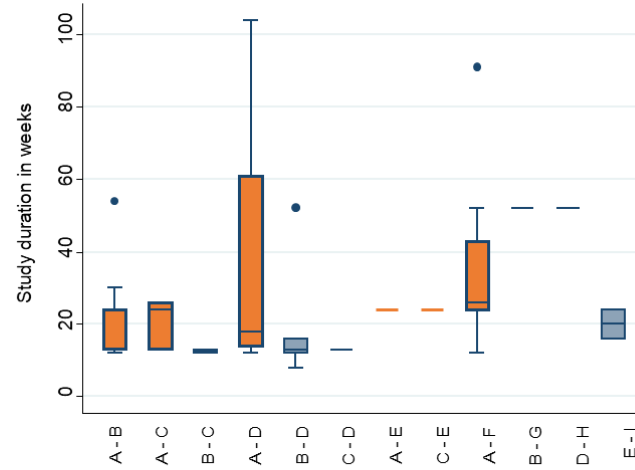
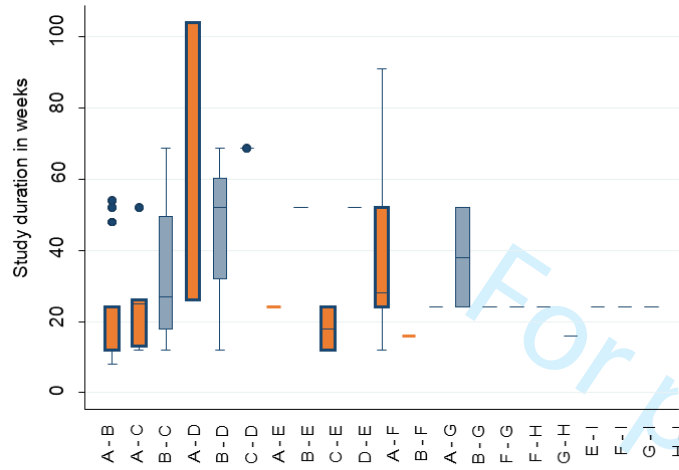
(b) Adverse Events



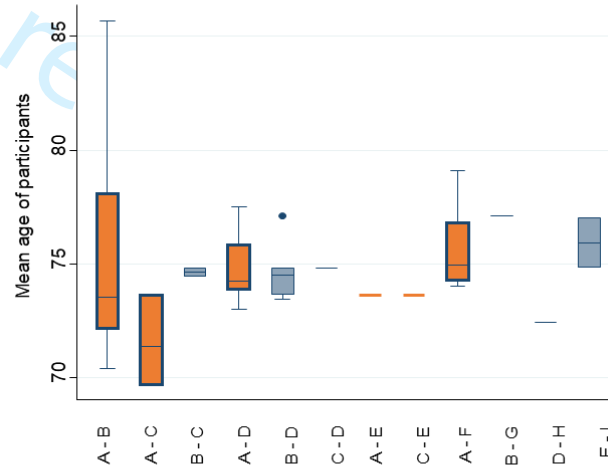
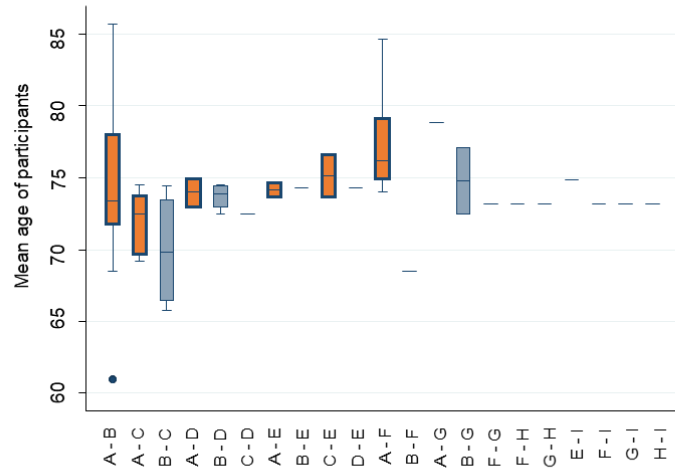
a. Publication year



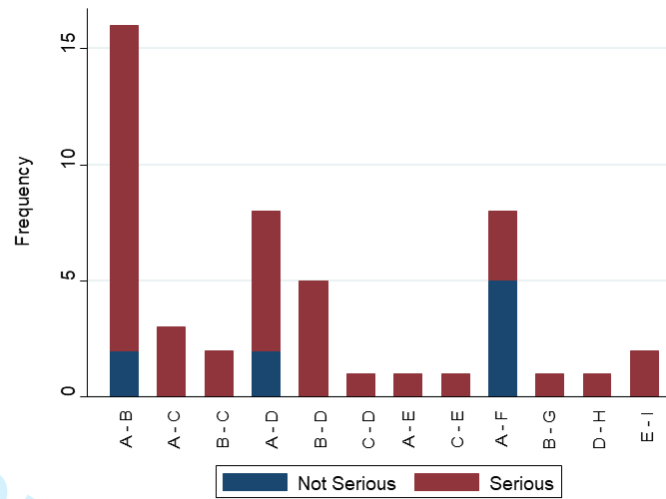
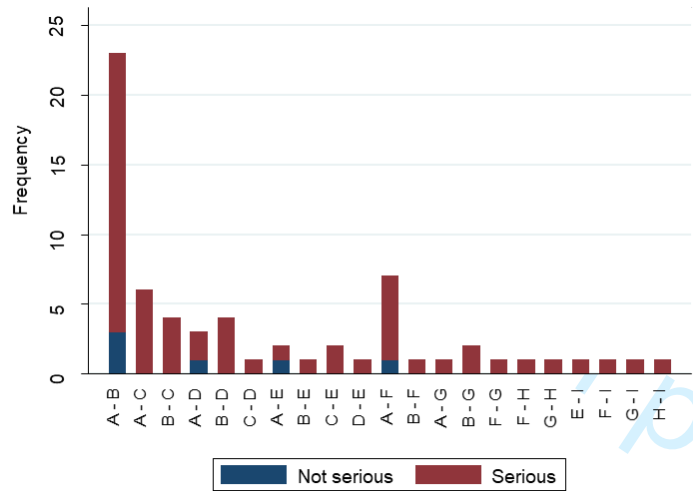
b. Percentage male



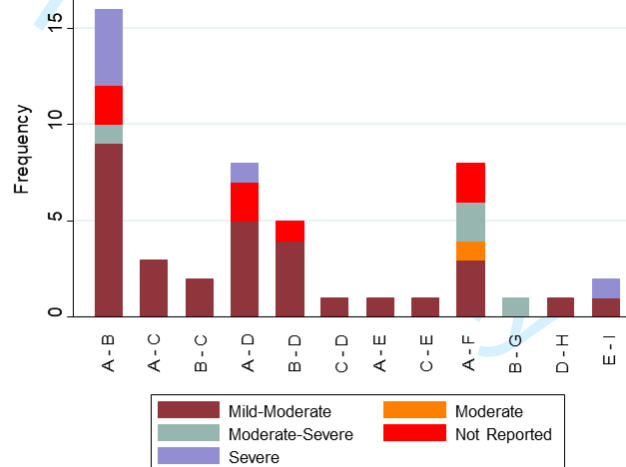
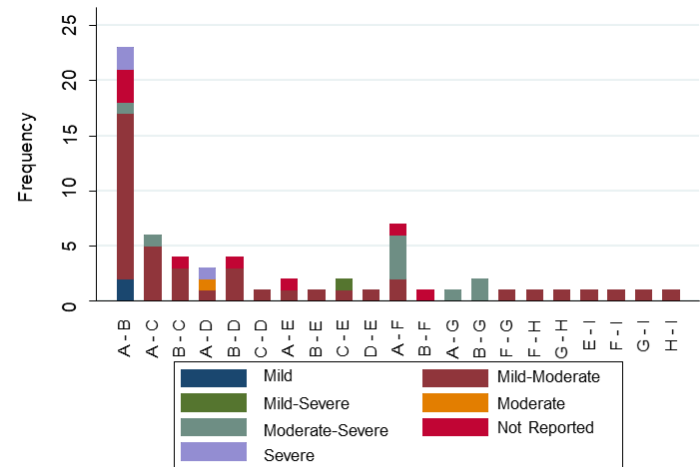
c. Study duration



d. Mean participant age



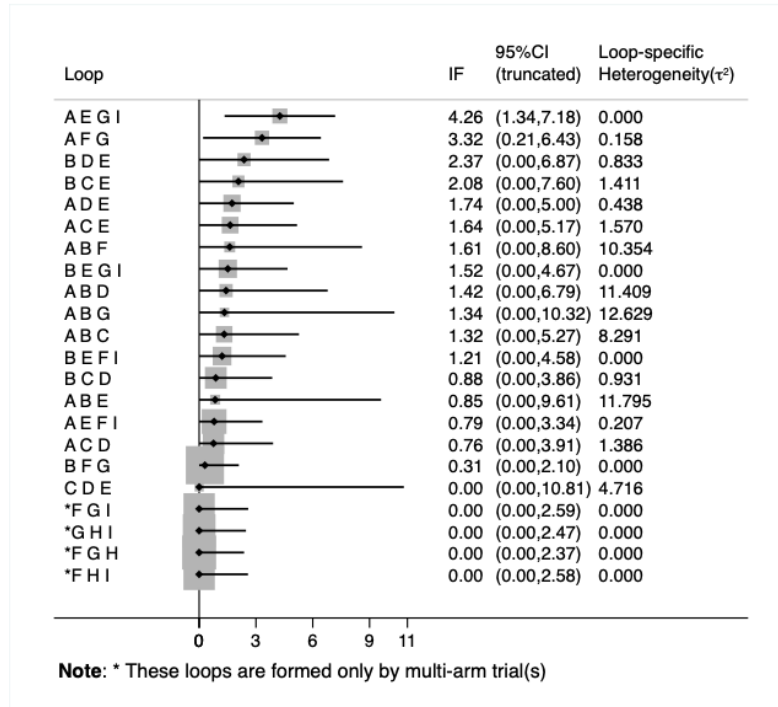
e. Overall Risk of Bias



f. Alzheimer's Dementia Severity

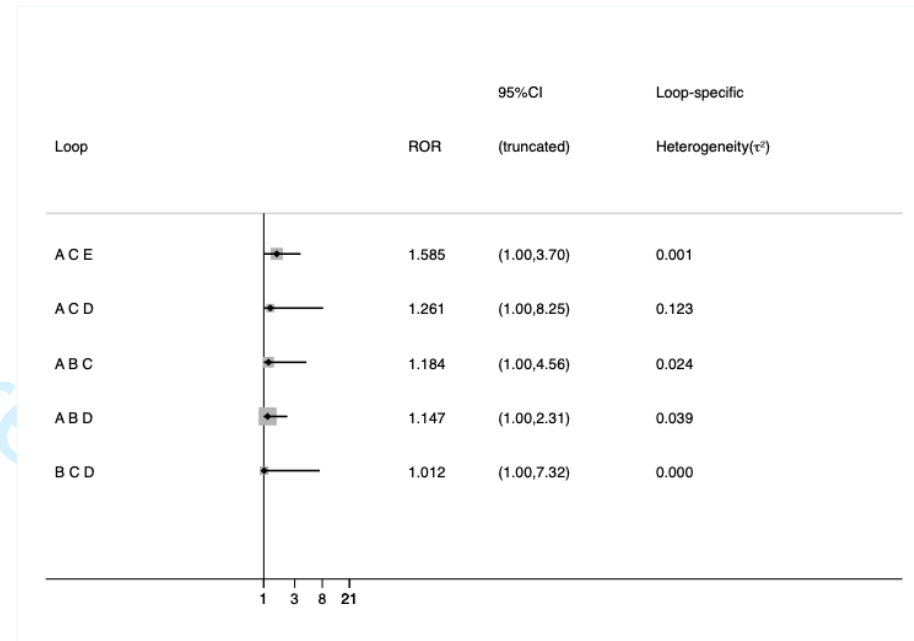
Appendix 14: Consistency Assessment – Loop-specific approach (using adjusted treatment effects)

(a) MMSE



Design-by-treatment interaction model:  
 $\chi^2$  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:  
 $\chi^2$  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
<b>Mini-Mental State Examination (MMSE)*†</b>								
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
<i>Common within-network between-study variance <math>\tau^2 = 5.75</math>, <math>I^2 = 96\%</math> (96%, 97%)</i>								
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>								
<b>Adverse Events (AEs)*<sup>‡</sup></b>								
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 vs Donepezil	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
<i>Common within-network between-study variance <math>\tau^2 = 0.04</math>, <math>I^2 = 22\%</math> (0%, 48%)</i>						
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>						

\* 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

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Appendix 16: Network subgroup and meta-regression analysis results

Treatment Comparison	NMA estimate	95% CI	95%PI	P-score
<b>Mini-Mental State Examination (MMSE)†</b>				
<b>Mean Difference: Aggregate data and crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 5.81, I^2 = 96\%</math> (96%, 97%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.42 (13, 0.986, 7.44)</i>				
<b>Mean Difference: Aggregate data results**</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 7.66, I^2 = 97\%</math> (96%, 97%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.92 (11, 0.972, 8.76)</i>				
<b>Mean Difference: Crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.12, I^2 = 29\%</math> (0%, 71%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Mean Difference: Low Risk of Bias for Allocation Concealment*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 13.82, I^2 = 98\%</math> (98%, 99%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.13 (3, 0.99, 19.10)</i>				
<b>Mean Difference: Low risk of bias for Incomplete Data*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 1.16, I^2 = 79\%</math> (65%, 88%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 12.15 (3, 0.007, 0.863)</i>				
<b>Mean Difference: Publicly-Sponsored Studies*</b>				
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

<i>Common within-network between-study variance: <math>\tau^2 = 81.93</math>, <math>I^2 = 99\%</math> (99%, 100%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.05 (1, 0.815, 116.71)</i>				
<b>Mean Difference: Industry-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.16</math>, <math>I^2 = 43\%</math> (15%, 62%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 8.06 (7, 0.327, 0.16)</i>				
<b>Mean Difference: Studies with Mild to Moderate cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 9.67</math>, <math>I^2 = 97\%</math> (97%, 98%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.22 (9, 0.96, 13.28)</i>				
<b>Mean Difference: Studies with Moderate to Severe cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.18</math>, <math>I^2 = 44\%</math> (0%, 75%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.60 (1, 0.11, 0.11)</i>				
<b>Mean Difference: Excluding outlier studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.59</math>, <math>I^2 = 73\%</math> (64%, 79%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 10.60 (13, 0.64, 0.61)</i>				
<b>Accounting for missing outcome data - Informative Missingness Difference of Means<sup>§</sup></b>				
Donepezil vs Placebo	1.42	0.51 to 2.33	0.51 to 2.33	0.59 <sup>  </sup>
Rivastigmine oral vs Placebo	0.45	-1.09 to 1.99	-1.09 to 1.99	0.30 <sup>  </sup>
Galantamine vs Placebo	0.19	-1.78 to 2.17	-1.78 to 2.17	0.25 <sup>  </sup>
Rivastigmine transdermal vs Placebo	2.37	-0.03 to 4.79	-0.03 to 4.79	0.76 <sup>  </sup>
Memantine vs Placebo	0.60	-1.09 to 2.42	-1.09 to 2.42	0.36 <sup>  </sup>
Donepezil + Memantine vs Placebo	2.55	0.09 to 5.01	0.09 to 5.01	0.80 <sup>  </sup>
Galantamine + Memantine vs Placebo	2.26	-2.03 to 6.56	-2.03 to 6.56	0.68 <sup>  </sup>
Rivastigmine transdermal + Memantine vs Placebo	1.81	-1.66 to 5.28	-1.66 to 5.28	0.61 <sup>  </sup>
Placebo (reference)				0.16 <sup>  </sup>
<i>Common within-network between-study variance: <math>\tau^2 = 5.47</math><sup>  </sup></i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.45 (11, 0.955, 6.45)</i>				
<b>Mean Difference: Meta-regression, Trial Mean Age<sup>**</sup></b>				
Donepezil vs Placebo	1.53	0.52 to 2.53	-3.17 to 6.27	0.50 <sup>††</sup>
Rivastigmine oral vs Placebo	0.80	-0.84 to 2.44	-4.15 to 5.79	0.37 <sup>††</sup>
Galantamine vs Placebo	0.60	-1.63 to 2.83	-4.57 to 5.72	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.53	0.06 to 4.98	-2.72 to 7.80	0.75 <sup>††</sup>
Memantine vs Placebo	0.79	-1.18 to 2.74	-4.33 to 5.85	0.37 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.66	0.09 to 5.19	-2.70 to 7.97	0.87 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.39	-2.02 to 6.84	-4.14 to 8.83	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.05	-1.53 to 5.59	-3.83 to 7.94	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
Regression coefficient	0.03	-0.14 to 0.20		
<i>Common within-network between-study variance: <math>\tau^2 = 5.50</math></i>				
<i>3.72 to 8.51</i>				

<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.92 (11, 0.972, 8.76)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for Age</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.12</math>, <math>I^2 = 29\%</math> (0%, 71%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: Meta-regression, Percent of Male Participants**</b>				
Donepezil vs Placebo	1.62	0.58 to 2.65	-3.40 to 6.61	0.62 <sup>††</sup>
Rivastigmine oral vs Placebo	0.73	-0.90 to 2.35	-4.30 to 5.81	0.37 <sup>††</sup>
Galantamine vs Placebo	0.62	-1.65 to 2.89	-4.75 to 5.93	0.25 <sup>††</sup>
Rivastigmine Transdermal vs Placebo	2.51	0.01 to 5.04	-2.78 to 7.94	0.75 <sup>††</sup>
Memantine vs Placebo	0.66	-1.47 to 2.77	-4.54 to 5.88	0.25 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.52	-0.40 to 5.45	-3.09 to 8.17	0.75 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.27	-2.28 to 6.83	-4.37 to 8.90	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	1.98	-1.67 to 5.65	-4.02 to 7.99	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
<i>Regression coefficient</i>	0.01	-0.05 to 0.06		
<i>Common within-network between-study variance: <math>\tau^2 = 5.73</math>, 3.83 to 8.84</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.72 (10, 0.959, 8.97)</i>				
<b>Mean difference: NMA of studies with IPD adjusted for Percent of Male Participants</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.13</math>, <math>I^2 = 32\%</math> (0%, 72%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for cognitive impairment, assessed with MMSE at baseline</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 79%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for comorbidities</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 67%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: NMA of studies with IPD adjusted for other medications</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.17</math>, <math>I^2 = 35\%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (one closed loop with a single multi-arm trial)</i>				
<b>Mean Difference: Meta-regression, Study Duration**</b>				
Donepezil vs Placebo	1.66	0.67 to 2.66	-3.12 to 6.32	0.62 <sup>††</sup>
Rivastigmine oral vs Placebo	0.80	-0.77 to 2.37	-4.14 to 5.69	0.37 <sup>††</sup>
Galantamine vs Placebo	0.47	-1.75 to 2.68	-4.64 to 5.66	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.38	-0.04 to 4.83	-2.87 to 7.56	0.75 <sup>††</sup>
Memantine vs Placebo	0.67	-1.27 to 2.58	-4.35 to 5.79	0.25 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.67	0.18 to 5.16	-2.60 to 7.97	0.88 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.43	-1.94 to 6.79	-3.94 to 8.81	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.13	-1.40 to 5.63	-3.62 to 7.87	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>

<i>Regression coefficient</i>	0.02	-0.01 to 0.06		
<i>Common within-network between-study variance: <math>\tau^2 = 5.40</math></i>	3.63 to 8.29			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>				
<b>Mean Difference: Meta-regression, Year of Publication**</b>				
Donepezil vs Placebo	1.53	0.51 to 2.54	-3.27 to 6.31	0.50 <sup>††</sup>
Rivastigmine oral vs Placebo	0.66	-1.01 to 2.32	-4.31 to 5.65	0.25 <sup>††</sup>
Galantamine vs Placebo	0.60	-1.65 to 2.85	-4.65 to 5.83	0.25 <sup>††</sup>
Rivastigmine transdermal vs Placebo	2.59	0.09 to 5.12	-2.73 to 7.95	0.75 <sup>††</sup>
Memantine vs Placebo	0.89	-1.05 to 2.80	-4.17 to 5.90	0.38 <sup>††</sup>
Donepezil + Memantine vs Placebo	2.82	0.19 to 5.44	-2.57 to 8.21	0.88 <sup>††</sup>
Galantamine + Memantine vs Placebo	2.59	-1.93 to 7.16	-3.98 to 9.12	0.75 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	2.21	-1.49 to 5.95	-3.81 to 8.24	0.75 <sup>††</sup>
Placebo (reference)				0.12 <sup>††</sup>
<i>Regression coefficient</i>	-0.02	-0.17 to 0.14		
<i>Common within-network between-study variance: <math>\tau^2 = 5.53</math></i>	3.71 to 8.48			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 4.36 (13, 0.987, 7.35)</i>				
<b>Adverse Events (AEs)‡</b>				
<b>Odds Ratio: Aggregate data and crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.04</math>, <math>I^2 = 20\%</math> (0%, 47%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.58 (6, 0.733, 0.05)</i>				
<b>Odds Ratio: Aggregate data results**</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 42%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.29 (4, 0.682, 0.01)</i>				
<b>Odds Ratio: Crude results from studies with available individual patient data</b>				
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
<i>Common within-network between-study variance <math>\tau^2 = 0.10</math>, <math>I^2 = 48\%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: Low Risk of Bias for Allocation Concealment*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.08</math>, <math>I^2 = 37\%</math> (0%, 64%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.19 (3, 0.53, 0.1)</i>				
<b>Odds Ratio: Low Risk of Bias for Incomplete Data*</b>				
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

<i>Common within-network between-study variance: <math>\tau^2 = 0.02</math>, <math>I^2 = 10\%</math> (0%, 50%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 0.00 (1, 0.95, 0.04)</i>				
<b>Odds Ratio: Publicly-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = N/A</math> (each comparison includes a single study)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: Industry-Sponsored Studies*</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.05</math>, <math>I^2 = 25\%</math> (0%, 50%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.68 (6, 0.72, 0.07)</i>				
<b>Odds Ratio: Studies with Mild to Moderate cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.09</math>, <math>I^2 = 29\%</math> (0%, 57%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.29 (5, 0.66, 0.13)</i>				
<b>Odds Ratio: Studies with Moderate to Severe cognitive impairment, assessed with MMSE at baseline *</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.00</math>, <math>I^2 = 0\%</math> (0%, 72%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 2.90 (1, 0.09, 0.00)</i>				
<b>Odds Ratio: NMA of studies with IPD – available case analysis</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.13</math>, <math>I^2 = 50\%</math> (0%, 77%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, heterogeneity): N/A (no closed loops)</i>				
<b>Odds Ratio: Meta-regression, Trial Mean Age*</b>				
Donepezil vs Placebo	1.13	0.88 to 1.43	0.68 to 1.86	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.52	0.89 to 2.53	0.77 to 3.04	0.00 <sup>††</sup>
Galantamine vs Placebo	0.91	0.60 to 1.30	0.52 to 1.59	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.84	0.39 to 1.58	0.34 to 1.80	0.75 <sup>††</sup>
Memantine vs Placebo	0.74	0.48 to 1.07	0.39 to 1.26	0.75 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.92	0.38 to 1.89	0.33 to 2.15	0.62 <sup>††</sup>
Galantamine + Memantine vs Placebo	0.99	0.37 to 2.27	0.33 to 2.55	0.50 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.73	0.24 to 1.70	0.22 to 1.87	0.87 <sup>††</sup>
Placebo (reference)				0.37 <sup>††</sup>
<i>Regression coefficient (log-scale)</i>	-0.03	-0.08 to 0.02		
<i>Common within-network between-study variance: <math>\tau^2 = 0.02</math></i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for Age</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.10</math>, <math>I^2 = 48\%</math> (0%, 76%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				

<b>Odds Ratio: Meta-regression, Percent of Male Participants**</b>				
Donepezil vs Placebo	1.12	0.87 to 1.44	0.64 to 2.01	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.71	0.97 to 2.92	0.83 to 3.67	0.00 <sup>††</sup>
Galantamine vs Placebo	0.93	0.62 to 1.36	0.49 to 1.77	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.89	0.39 to 1.79	0.34 to 2.05	0.63 <sup>††</sup>
Memantine vs Placebo	0.64	0.37 to 1.00	0.29 to 1.21	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.88	0.35 to 1.88	0.30 to 2.13	0.63 <sup>††</sup>
Galantamine + Memantine vs Placebo	1.13	0.39 to 2.58	0.36 to 2.95	0.38 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.77	0.24 to 1.93	0.21 to 2.13	0.88 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
<i>Regression coefficient (log-scale)</i>	0.00	0.00 to 0.02		
<i>Common within-network between-study variance: <math>\tau^2 = 0.03</math></i>	0.00 to 0.23			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for Percent of Male Participants</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.11</math>, <math>I^2 = 51\%</math> (0%, 77%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for cognitive impairment, assessed with MMSE at baseline</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.16</math>, <math>I^2 = 52\%</math> (0%, 80%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for comorbidities</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.12</math>, <math>I^2 = 44\%</math> (0%, 77%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: NMA of studies with IPD adjusted for other medications</b>				
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
<i>Common within-network between-study variance: <math>\tau^2 = 0.11</math>, <math>I^2 = 51\%</math> (0%, 78%)</i>				
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): N/A (no closed loops)</i>				
<b>Odds Ratio: Meta-regression, Study Duration**</b>				
Donepezil vs Placebo	1.12	0.87 to 1.43	0.63 to 1.95	0.25 <sup>††</sup>
Rivastigmine oral vs Placebo	1.76	1.00 to 2.99	0.88 to 3.68	0.00 <sup>††</sup>
Galantamine vs Placebo	0.92	0.62 to 1.36	0.50 to 1.69	0.50 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.87	0.39 to 1.70	0.34 to 1.96	0.63 <sup>††</sup>
Memantine vs Placebo	0.61	0.37 to 0.93	0.31 to 1.13	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.76	0.29 to 1.69	0.26 to 1.90	0.75 <sup>††</sup>
Galantamine + Memantine vs Placebo	0.98	0.34 to 2.26	0.30 to 2.53	0.50 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.75	0.25 to 1.81	0.23 to 1.97	0.75 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
<i>Regression coefficient (log-scale)</i>	0.00	0.00 to 0.01		
<i>Common within-network between-study variance: <math>\tau^2 = 0.03</math></i>	0.00 to 0.22			
<i>Design-by-treatment interaction model for inconsistency <math>\chi^2</math> (d.f., P-value, <math>\tau^2</math>): 3.57 (6, 0.735, 0.06)</i>				
<b>Odds Ratio: Meta-regression, Year of Publication**</b>				
Donepezil vs Placebo	1.05	0.79 to 1.38	0.61 to 1.77	0.38 <sup>††</sup>
Rivastigmine oral vs Placebo	1.68	0.98 to 2.77	0.85 to 3.37	0.00 <sup>††</sup>
Galantamine vs Placebo	0.91	0.61 to 1.32	0.50 to 1.64	0.63 <sup>††</sup>
Rivastigmine transdermal vs Placebo	0.92	0.40 to 1.84	0.36 to 2.04	0.63 <sup>††</sup>
Memantine vs Placebo	0.73	0.46 to 1.05	0.38 to 1.28	0.88 <sup>††</sup>
Donepezil + Memantine vs Placebo	0.88	0.35 to 1.83	0.31 to 2.15	0.75 <sup>††</sup>

Galantamine + Memantine vs Placebo	1.24	0.43 to 2.85	0.39 to 3.25	0.25 <sup>††</sup>
Rivastigmine transdermal + Memantine vs Placebo	0.88	0.24 to 2.24	0.24 to 2.42	0.75 <sup>††</sup>
Placebo (reference)				0.38 <sup>††</sup>
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 $\chi^2$ (d.f., P-value, $\tau^2$ ): 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)

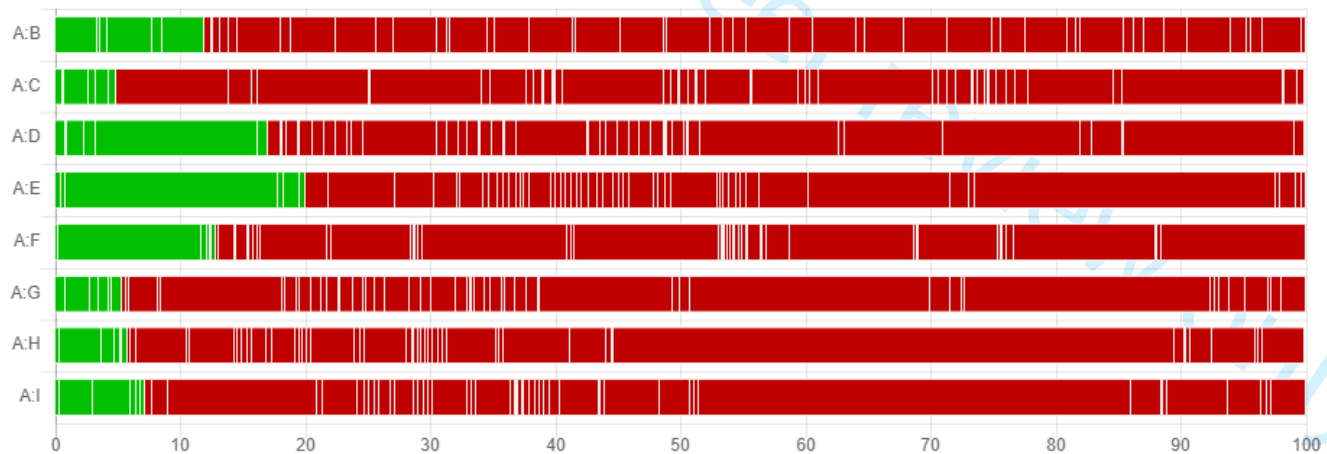
†† Analyses were conducted in OpenBUGS, and SUCRA values were calculated instead of P-scores

Appendix 17: CINeMA results

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

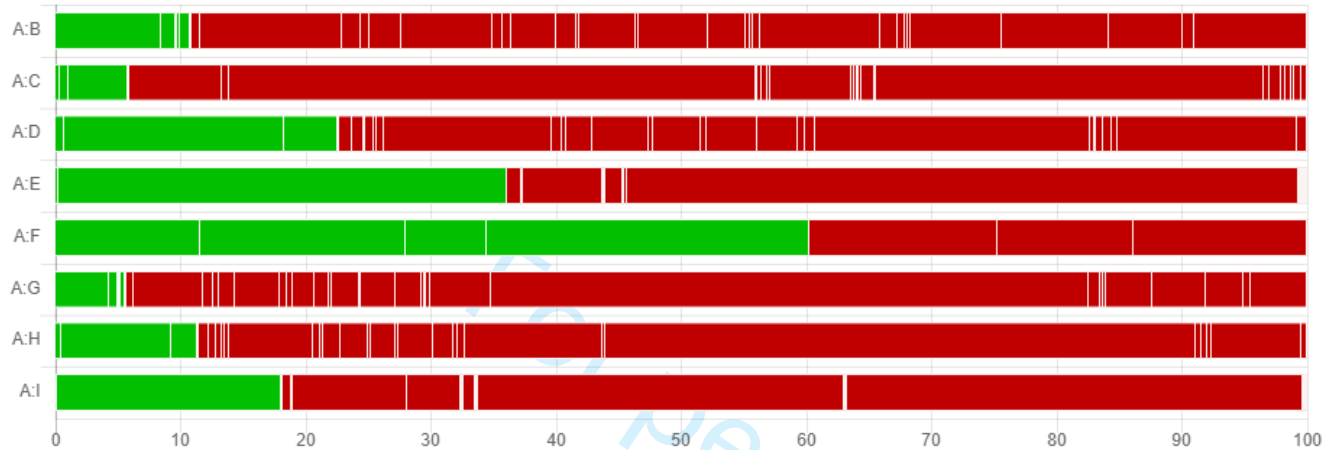
- Interventions**
- A: PLAC
  - B: DONE
  - C: RIVA\_O
  - D: GALA
  - E: RIVA\_P
  - F: MEMA
  - G: DONE+MEMA
  - H: GALA+MEMA
  - I: RIVA\_P+MEMA

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**

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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

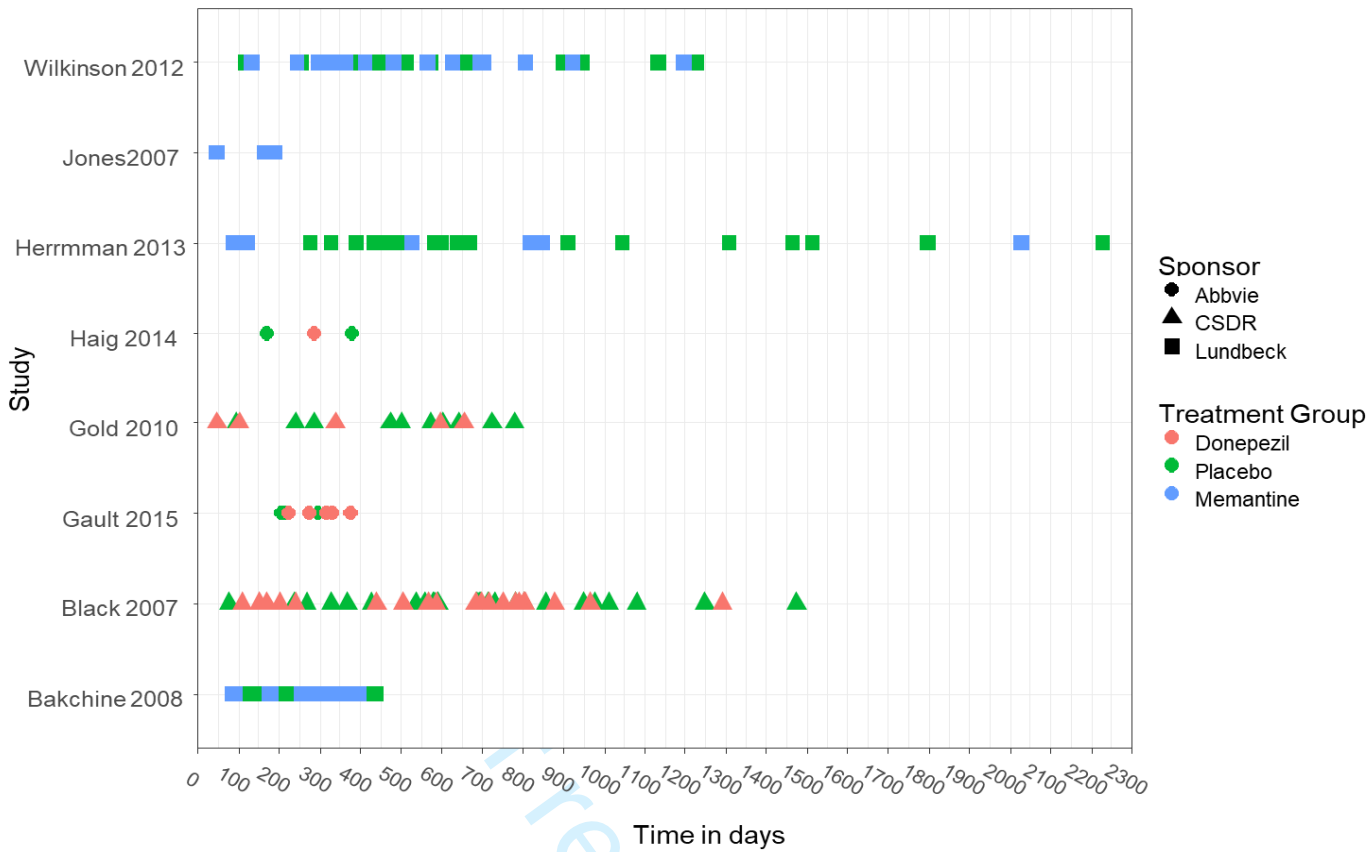
## Appendix 18: Study definitions for adverse events

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"

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3	Homma, 1998	NR	NR
4	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). "
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9	Hong, 2006	NR	NR
10	Howard, 2007	NA	NA
11	Howard, 2012	NR	NR
12	Hu, 2006	NA	NA
13	Johannsen, 2006	NA	NA
14	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"
15			
16	Kadir, 2008	NA	NA
17	Kano, 2013	NA	NA
18	Karaman, 2005	NA	NA
19	Likitjaroen, 2012	NA	NA
20	Lorenzi, 2011	NA	NA
21	Maher-Edwards, 2011	Determined by Investigator	"Eight subjects experienced nonfatal serious AEs; all were considered unrelated to the study drug"
22	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"
23	Mazza, 2006	NA	NA
24	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. "
25			
26	Moretti, 2014	NA	NA
27	Mowla, 2007	NA	NA
28	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. "
29			
30			
31	Nakano, 2001	NA	NA
32	Nordberg, 2009	Determined by Investigator	"Safety and tolerability were monitored throughout the study by recording all adverse events (AEs). "
33			
34	Pakdaman H, 2015	NA	NA
35	Peng, 2005	NA	NA
36	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"
37			
38	Peters O, 2015	NR	NR
39	Reisberg, 2003	NR	NR
40	Rockwood, 2001	World Health Organisation preferred terms	"adverse events (classified according to World Health Organisation preferred terms)."
41			
42	Rockwood, 2006	NR	NR
43	Rogers, 1996		
44	Rogers, 1998	COSTART	"Events, recorded using investigator terminology, were grouped and coded into common terms using a modified COSTART dictionary"
45			
46	Rogers, 1998	COSTART	"Events, recorded using investigator terminology, were grouped and coded into common terms using a modified COSTART dictionary. "
47			
48	Saxton, 2012	Determined by Investigator	"Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were recorded at all post-Screening study visits"
49	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"
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51	Schmidt, 2008	NA	NA
52	Seltzer, 2004	NA	NA
53	Shao, 2015	NA	NA
54	Shimizu, 2015	NA	NA
55	Sole-Padulles, 2013	NA	NA
56	Tariot, 2000	World Health Organisation preferred terms	"adverse events (classified according to World Health Organization Preferred Term). "
57			
58	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. "
59			
60	Thomas, 2001		

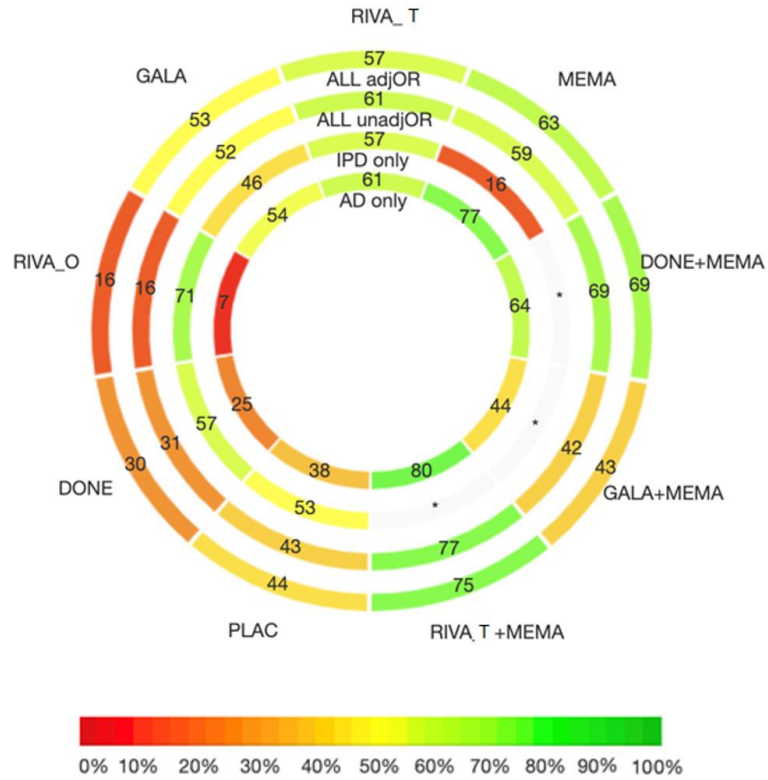
1	Wilcock, 2003	World Health Organisation preferred terms	"monitoring for adverse events (classified according to WHO preferred terms) "
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3	Wilkinson, 2001	Determined by Investigator	"All adverse events were recorded, regardless of the considered relationship to treatment. All details of adverse events and their outcomes were recorded including severity and relationship to treatment. Serious adverse events were documented separately. "
4			
5	Wilkinson, 2002	NR	NR
6	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"
7			
8	Winblad, 2001	NR	NR
9	Winblad, 2006	COSTART	"We recorded all treatment emergent adverse events, coding them according to a modified COSTART dictionary. "
10	Winblad, 2007	Determined by Investigator	"Safety evaluations included recording all adverse events, which were coded using a standard glossary."
11	Zhang-Yi, 2005	NA	NA
12	Zhang, 2012	Determined by Investigator	"Serious adverse events considered to be possibly related to treatment occurred in one patient in each treatment arm"
13	<b>Notes:</b> <sup>a</sup> Unpublished data, <sup>b</sup> Non-English studies		
14	<b>Abbreviations:</b> CR, companion report; NA, not applicable; NR, not reported.		
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**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.tw.  
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.

- 1  
2  
3 36 memantin\$.tw.  
4 37 memox.tw.  
5 38 namenda.tw.  
6 39 nimvastid.tw.  
7 40 nivalin\$.tw.  
8 41 "N-Methyl-D-aspartic acid receptor antagonist\$.tw.  
9 42 prometax.tw.  
10 43 razadyne.tw.  
11 44 reminyl.tw.  
12 45 rivastigmine.mp.  
13 46 exp Cholinesterase Inhibitors/  
14 47 Galantamine/  
15 48 Memantine/  
16 49 Galantamin.rn.  
17 50 Memantine.rn.  
18 51 Donepezil.rn.  
19 52 Donepezil Hydrochloride.rn.  
20 53 Rivastigmine.rn.  
21 54 or/21-53  
22 55 20 and 54  
23 56 exp Animals/ not (exp Animals/ and Humans/)  
24 57 55 and 56  
25 58 (comment or editorial or interview or news).pt.  
26 59 (letter not (letter and randomized controlled trial)).pt.  
27 60 57 not (58 or 59)  
28 61 (201111\* or 201112\* or 2012\* or 2013\* or 2014\*).ed.  
29 62 60 and 61  
30 63 alzheimer\$.mp.  
31 64 "benign senescent forgetfulness".mp.  
32 65 (cognit\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
33 disorder\$ or complain\$ or disturb\$)).mp.  
34 66 (cerebr\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or disorder\$ or  
35 complain\$ or disturb\$)).mp.  
36 67 (mental adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
37 disorder\$ or complain\$ or disturb\$)).mp.  
38 68 (ne?rocognit\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
39 disorder\$ or complain\$ or disturb\$)).mp.  
40 69 (ne?ro-cognit\$ adj2 (impair\$ or declin\$ or deficit\$ or degenerat\$ or deteriorat\$ or los\$ or  
41 disorder\$ or complain\$ or disturb\$)).mp.  
42 70 ((cognit\$ or memory or cerebral or brain) adj2 (improv\$ or enhanc\$ or perform\$ or  
43 process\$ or function\$ or rehabilitation or aid\$ or stimulat\$)).mp.  
44 71 cognition.ti.  
45 72 (confusion\$ or confused).tw.  
46 73 dement\$.mp.  
47 74 ("normal pressure hydrocephalus" and shunt\$.mp.  
48 75 "organic brain disease\$.mp.  
49 76 "organic brain syndrome".mp.  
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3 77 (presenil\$ or pre-senil\$ or senil\$.tw  
4 78 Alzheimer disease/  
5 79 cognitive defect/  
6 80 confusion/  
7 81 dementia/  
8 82 organic brain syndrome/  
9 83 or/63-82  
10 84 abixa.tw.  
11 85 aricept.tw.  
12 86 (acetylcholinesteraseadj inhibitor\$.tw.  
13 87 axura.tw.  
14 88 akatinol.tw.  
15 89 (anticholinesterase? or anti-cholinesterase?).tw.  
16 90 (cognitive adjenhanc\$.mp.  
17 91 (cholinesterase adj inhibitor\$.mp.  
18 92 ChEI.tw.  
19 93 donepezil.mp.  
20 94 ebixa.tw.  
21 95 eranz.tw.  
22 96 exelon.tw.  
23 97 galant?amin\$.tw.  
24 98 lycoremine.tw.  
25 99 memantin\$.tw.  
26 100 memox.tw.  
27 101 namenda.tw.  
28 102 nimvastid.tw.  
29 103 nivalin\$.tw.  
30 104 "N-Methyl-D-aspartic acid receptor antagonist\$.tw.  
31 105 prometax.tw.  
32 106 razadyne.tw.  
33 107 reminyl.tw.  
34 108 rivastigmine.mp.  
35 109 exp cholinesterase inhibitor/  
36 110 donepezil/ or donepezil plus memantine/  
37 111 galantamine/  
38 112 memantine/  
39 113 rivastigmine/  
40 114 357-70-0.rn.  
41 115 19982-08-2.rn.  
42 116 120011-70-3.rn.  
43 117 120014-06-4.rn.  
44 118 rivastigmine.rn.  
45 119 or/84-118  
46 120 83 and 119  
47 121 randomized controlled trial/ or controlled clinical trial/  
48 122 exp "clinical trial (topic)"/  
49 123 (randomi#ed or randomly or RCT\$1 or placebo\*).tw.  
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3 124 ((singl\* or doubl\* or trebl\* or tripl\*) adj (mask\* or blind\* or dumm\*)).tw.  
4 125 trial.ti.  
5 126 or/121-125  
6 127 120 and 126  
7 128 exp controlled clinical trial/  
8 129 exp "controlled clinical trial (topic)"/  
9 130 (control\* adj2 trial\*).tw.  
10 131 (nonrandom\* or non-random\* or quasi-random\* or quasi-experiment\*).tw.  
11 132 (nRCT or nRCTs or non-RCT\$1).tw.  
12 133 (control\* adj3 ("before and after" or "before after")).tw.  
13 134 time series analysis/  
14 135 (time series adj3 interrupt\*).tw.  
15 136 pretest posttest control group design/  
16 137 (pre- adj3 post-).tw.  
17 138 (pretest adj3 posttest).tw.  
18 139 controlled study/  
19 140 (control\* adj2 stud\$3).tw.  
20 141 control group/  
21 142 (control\$ adj2 group\$1).tw.  
22 143 or/128-142  
23 144 120 and 143  
24 145 cohort analysis/  
25 146 cohort.tw.  
26 147 retrospective study/  
27 148 longitudinal study/  
28 149 prospective study/  
29 150 (longitudinal or prospective or retrospective).tw.  
30 151 follow up/  
31 152 ((followup or follow-up) adj (study or studies)).tw.  
32 153 observational study/  
33 154 (observation\$2 adj (study or studies)).tw.  
34 155 population research/  
35 156 ((population or population-based) adj (study or studies or analys#s)).tw.  
36 157 ((multidimensional or multi-dimensional) adj (study or studies)).tw.  
37 158 exp comparative study/  
38 159 ((comparative or comparison) adj (study or studies)).tw.  
39 160 exp case control study/  
40 161 ((case-control\* or case-based or case-comparison) adj (study or studies)).tw.  
41 162 or/145-161  
42 163 120 and 162  
43 164 127 or 144 or 163  
44 165 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or  
45 nonhuman/ or exp vertebrate/  
46 166 exp humans/ or exp human experimentation/ or exp human experiment/  
47 167 165 not 166  
48 168 164 not 167  
49 169 editorial.pt.  
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3 170 letter.pt.not (letter.pt. and randomized controlled trial/)  
4 171 168 not (169 or 170)  
5 172 (2011112\* or 2011113\* or 201112\* or 2012\* or 2013\* or 2014\*).dd.  
6 173 171 and 172  
7 174 62 use prmz  
8 175 173 use emez  
9 176 174 or 175  
10 177 remove duplicates from 176  
11 178 177 use prmz [MEDLINE UNIQUE HITS]  
12 179 177 use emez [EMBASE UNIQUE HITS]  
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For peer review only



## PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Yes
<b>BACKGROUND</b>			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
<b>METHODS</b>			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
<b>RESULTS</b>			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
<b>DISCUSSION</b>			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
<b>OTHER</b>			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

## PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: <b>Background:</b> main objectives <b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . <b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> <b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings. <b>Other:</b> primary source of funding; systematic review registration number with registry name.	3-4
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5, Appendix 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	6, Appendix 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6, Appendix 1

1	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	N/A (see published protocol)
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4	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, Appendix 1
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7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, Appendix 1
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11	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, Appendix 1
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14	<b>Geometry of the network</b>	<b>S1</b>	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	7, Appendix 1
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21	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6, Appendix 1
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25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	7, Appendix 1
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses; and</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>	7, Appendix 1
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40	<b>Assessment of Inconsistency</b>	<b>S2</b>	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	7, Appendix 1
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44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6, Appendix 1
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47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network; and</i></li> <li>• <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i></li> </ul>	7, Appendix 1
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## RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 – Figure 1
<b>Presentation of network structure</b>	<b>S3</b>	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	9 – Figure 2
<b>Summary of network geometry</b>	<b>S4</b>	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	7-8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8 – Table 1, Appendix 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	8-9 – Appendix 8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Appendices 6 and 10 (full data can be provided by the first author)
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	9-11 – Appendix 15
<b>Exploration for inconsistency</b>	<b>S5</b>	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	9 - Appendix 14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	9-11 - Appendix 12
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i> ).	9-11 - Appendices 16 and 17

1	<b>DISCUSSION</b>			
2	Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	11-13
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6	Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	13-14
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14	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
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18	<b>FUNDING</b>			
19	Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	15
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PICOS = population, intervention, comparators, outcomes, study design.

\* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

## PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
<b>Title</b>			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
<b>Abstract</b>			
Structured summary	2	Provide a structured summary including as applicable:	3-4
		<b>Background:</b> state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		<b>Methods:</b> report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		<b>Results:</b> provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		<b>Discussion:</b> state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		<b>Other:</b> report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
<b>Introduction</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	5
<b>Methods</b>			

Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	5, Appendix 1
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	5-6, Appendix 1
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	6, Appendix 1
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	N/A (see published protocol)
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	6, Appendix 1
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study). If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	6, Appendix 1
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	6, Appendix 1

IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	Appendix 1
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	6, Appendix 1
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	7, Appendix 1
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): <ul style="list-style-type: none"> <li>• Use of a one-stage or two-stage approach.</li> <li>• How effect estimates were generated separately within each study and combined across studies (where applicable).</li> <li>• Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for.</li> <li>• Use of fixed or random effects models and any other model assumptions, such as proportional hazards.</li> <li>• How (summary) survival curves were generated (where applicable).</li> <li>• Methods for quantifying statistical heterogeneity (such as <math>I^2</math> and <math>\tau^2</math>).</li> <li>• How studies providing IPD and not providing IPD were analysed together (where applicable).</li> <li>• How missing data within the IPD were dealt with (where applicable).</li> </ul>	7, Appendix 1
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	Appendix 1
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	6, Appendix 1

Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	7, Appendix 1
<b>Results</b>			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	7 – Figure 1
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	8 – Table 1, Appendix 5
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	8-9, Appendices 5 and 10
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	8-9 – Appendix 8
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Appendices 6 and 10 (full data can be provided by the

			first author)
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	9-11 – Appendix 15
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	9-11 - Appendix 12
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	9-11 - Appendices 16 and 17
<b>Discussion</b>			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	11-13
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	13-14
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	13-14
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	12-13

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Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	15

**A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.**

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