

Supplementary Material

Pharmacologic and Nutritional Interventions for Early Alzheimer's Disease: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

1. Search strategy

Search strategy for Embase (12463 items)

1. 'alzheimer disease'/exp
2. 'alzheimer disease':ti,ab
3. #1 OR #2
4. amnestic:ti,ab OR early:ti,ab OR mild:ti,ab OR preclinical:ti,ab OR asymptomatic:ti,ab OR prodromic:ti,ab OR prodromal:ti,ab
5. #3 AND #4
6. 'mild cognitive impairment'/exp
7. 'mild cognitive impairment':ti,ab
8. 'mci':ti,ab
9. #6 OR #7 OR #8
10. amnestic:ti,ab
11. #9 AND #10
12. #5 AND #11
13. trial*:ti,ab OR random*:ti,ab OR placebo*:ti,ab OR 'controlled clinical trial'/exp
14. #12 AND #13

Search strategy for PubMed (7656 items)

1. Alzheimer Disease [mh]
2. Alzheimer's disease[Title/Abstract]
3. #1 OR #2
4. early[Title/Abstract] OR mild[Title/Abstract] OR preclinical[Title/Abstract] OR asymptomatic[Title/Abstract] OR prodromic[Title/Abstract] OR prodromal[Title/Abstract]
5. #3 AND #4
6. Cognitive Dysfunction [mh]
7. Mild Cognitive Impairment[Title/Abstract]
8. MCI[Title/Abstract]
9. #6 OR #7 OR #8
10. Amnestic[Title/Abstract]
11. #9 AND #10
12. #5 OR #11
13. trial*[Title/Abstract] OR random*[Title/Abstract] OR placebo*[Title/Abstract]
14. #12 AND #13

Search strategy for Cochrane Library (5625 items)

1. [mh "Alzheimer Disease"]
2. "Alzheimer's disease":ti,ab
3. #1 OR #2
4. (early OR mild OR preclinical OR asymptomatic OR prodromic OR prodromal):ti,ab
5. #3 AND #4
6. [mh "Cognitive Dysfunction"]
7. "Mild Cognitive Impairment":ti,ab
8. MCI:ti,ab
9. #6 OR #7 OR #8
10. Amnestic:ti,ab
11. #9 AND #10
12. #5 OR #11

Search strategy for Clinicaltrial.gov (370 items)

("Alzheimer's disease" OR "Mild Cognitive Impairment") AND (amnestic OR early OR mild OR preclinical OR asymptomatic OR prodromic OR prodromal) AND *Studies with Results*

Supplementary Table 1. Study characteristics and patient demographics of included studies

Study	Participant characteristics	Study design and registration	Intervention	Control	No of Patients	Follow-up
van Dyck 2023 [1]	Early AD; amyloid positive; age range 50-90; male 47.7%; MMSE 22-30; CDR 0.5 or 1	Phase 3, NCT03887455	Lecanemab (10 mg/kg biweekly)	Placebo	1,734	18 months
Sims 2023 [2]	Early AD; amyloid positive; age range 60-85; male 42.6%; MMSE 20-28; CDR 0.5 or 1	Phase 3, NCT04437511	Donanemab	Placebo	1,736	19 months
Florian 2023 [3]	Early AD; amyloid positive; age range 55-85; male 48.3%; MMSE 22-30; CDR 0.5	Phase 2, NCT02880956	Tilavonemab	Placebo	453	24 months
Sperling 2023 [4]	Preclinical AD; amyloid positive; age range 65-85; male 40.6%; MMSE 25-30; CDR 0	Phase 3, NCT02008357	Solanezumab	Placebo	1,147	18 months
Berry 2023 [5]	Early AD; amyloid positive; age range 50-90; male 48.5%; MMSE 22-28; CDR 0.5 or 1	Phase 2b, NCT01767311	Lecanemab (10 mg/kg biweekly)*	Placebo	390	18 months
Teng 2022 [6]	Early AD; amyloid positive; age range 50-80; male 44.3%; MMSE 20-30; CDR 0.5 or 1	Phase 2, NCT03289143	Semorinemab	Placebo	422	18 months
EMERGE 2022 [7]	Early AD; amyloid positive; age range 50-85; male 48.5%; MMSE 24-30; CDR 0.5	Phase 3, NCT02484547	Aducanumab	Placebo	1,638	19 months
ENGAGE 2022 [7]	Early AD; amyloid positive; age range 50-85; male 48.5%; MMSE 24-30; CDR 0.5	Phase 3, NCT02477800	Aducanumab	Placebo	1,647	19 months
CREAD 2022 [8]	Early AD; amyloid positive; age range 50-85; male 40.6%; MMSE \geq 22; CDR 0.5 or 1	Phase 3, NCT02670083	Crenezumab	Placebo	813	25 months
CREAD2 2022 [8]	Early AD; amyloid positive; age range 50-85; male 43.4%; MMSE \geq 22; CDR 0.5 or 1	Phase 3, NCT03114657	Crenezumab	Placebo	806	25 months
Mintun 2021 [9]	Early AD; amyloid positive; age range 60-85; male 46.7%; MMSE 20-28	Phase 2, NCT03367403	Donanemab	Placebo	272	18 months
Sperling 2021 [4]	Preclinical AD; amyloid positive; age range 60-85; male 38.8%; MMSE (mean) 28.2; CDR 0	Phase 2b/3, NCT02569398	Atabecestat	Placebo	557	6 months
Salloway 2021 [10]	Dominantly inherited AD; male 53.3%; MMSE (mean) 26.8; CDR 0-1	Phase 2/3, NCT01760005	Gantenerumab	Placebo	92	12 months
Salloway 2021 [10]	Dominantly inherited AD; male 43.3%; MMSE (mean) 26.8; CDR 0-1	Phase 2/3, NCT01760005	Solanezumab	Placebo	90	12 months

Prins 2021 [11]	Mild AD; amyloid positive; age range 55-85; male 50.3%; MMSE 20-28; CDR 0.5 or 1	Phase 2, NCT03402659	Neflamapimod	Placebo	161	6 months
Wessels 2020 [12]	Early AD; amyloid positive; age range 55-85; male 46.9%; MMSE 20-30; CDR 0.5 or 1	Phase 2/3, NCT02245737	Lanabecestat	Placebo	2,218	24 months
Wessels 2020 [12]	Early AD; amyloid positive; age range 55-85; male 40.6%; MMSE 20-26; CDR 0.5 or 1	Phase 3, NCT02783573	Lanabecestat	Placebo	1,722	18 months
Howard 2020 [13]	Mild AD; age \geq 50; male 55.7%; MMSE 24-30	ISRCTN16105064	Minocycline	Placebo	544	24 months
Craft 2020 [14]	Amnesic MCI or early AD; age range 55-85; male 53.6%; MMSE \geq 20; CDR 0.5 or 1	Phase 2/3, NCT01767909	Insulin	Placebo	289	12 months
Gibson 2020 [15]	Amnesic MCI; amyloid positive; age \geq 60; male 41.4%; MMSE \geq 21; CDR 0.5 or 1	Phase 2a, NCT02292238	Benfotiamine	Placebo	70	12 months
Egan 2019 [16]	Prodromal AD; amyloid positive; age range 50-85; male 52.8%; MMSE 24-30	Phase 3, NCT01953601	Verubecestat	Placebo	1,454	24 months
van Dyck 2019 [17]	Mild AD; amyloid positive; age range 55-85; male 54.7%; MMSE 18-26	Phase 2a, NCT02167256	Saracatinib	Placebo	159	12 months
Tian 2019 [18]	Amnesic MCI; male 51.2%; MMSE 24-30; CDR 0.5	NR	Qinggongshoutao	Placebo	244	12 months
Tian 2019 [18]	Amnesic MCI; male 46.6%; MMSE 24-30; CDR 0.5	NR	Ginkgo biloba extract	Placebo	174	12 months
Frolich 2019 [19]	Prodromal AD: amyloid positive; age \geq 55; male 44.5%; MMSE \geq 24; CDR 0.5 or 1 Mild AD: amyloid positive; age \geq 55; male 50.5%; MMSE 18-26; CDR \geq 1	Phase 2, NCT02240693 and NCT0233907	BI409306	Placebo	457	3 months
Forlenza 2019 [20]	Amnesic MCI; age \geq 60	Phase 2, NCT01055392	Lithium	Placebo	61	24 months
Padala 2018 [21]	Mild AD; age \geq 55; male 100%; MMSE 18-29	Phase 4, NCT00495820	Methylphenidate	Placebo	60	3 months
Honig 2018 [22]	Mild AD; amyloid positive; age range 55-90; male 42.2%; MMSE 20-26	Phase 3, NCT01900665	Solanezumab	Placebo	2,129	18 months
Soininen 2017 [23]	Prodromal AD; age range 55-85; male 49.5%; MMSE \geq 24	NTR1705	LipiDiDiet	Placebo	311	24 months
Kile 2017 [24]	Amnesic MCI; age range 50-84; male 42.9%; MMSE 24-30; CDR 0 or 0.5	Phase 2, NCT01300728	IVIG	Placebo	49	24 months
Tian 2017 [18]	Amnesic MCI; age range 55-80; male 41.6%; MMSE 24-30	Phase 3, NCT01451749	Shenwu capsules	Donepezil	322	6 months
Ostrowitzki 2017 [25]	Prodromal AD; amyloid positive; age range 50-85; male 43.2%; MMSE \geq 24; CDR 0.5	Phase 3, NCT01224106	Gantenerumab	Placebo	797	24 months
Fujino 2017 [26]	Mild AD; age range 60-85; male 38.6%; MMSE 20-27	UMIN000014945	Plasmalogen	Placebo	285	6 months
Luchsinger 2016 [27]	Amnesic MCI; age range 55-90; male 50%; MMSE \geq 20; CDR 0.5	Phase 2, NCT00620191	Metformin	Placebo	80	12 months

Zhang 2016 [28]	Amnestic MCI; age range 50-80; male 46.7%; MMSE \geq 24	Phase 2, ChiCTR-TRC-12003073	Bushen capsule	Donepezil	60	24 months
Zhang 2015 [29]	Mild AD; age range 50-85; male 38.2%; CDR 1	ChiCTR-TRC-12002846	Yishen Huazhuo decoction	Donepezil	144	6 months
Coric 2015 [30]	Prodromal AD; age range 45-90; male 43.7%; MMSE 24-30; CDR 0.5	Phase 2, NCT00890890	Avagacestat	Placebo	263	24 months
Lin 2014 [31]	Early AD; age range 50-90; male 38.3%; MMSE 17-26; CDR 0.5 or 1	NR	Benzoate	Placebo	60	6 months
Morimoto 2013 [32]	Amnestic MCI; age range 55-85; male 46.5%; MMSE \geq 24	Phase 2, NCT00422981	Davunetide	Placebo	144	3 months
Scheltens 2012 [33]	Mild AD; age \geq 50; male 51.0%; MMSE \geq 20	NTR1975	Souvenaid	Placebo	259	6 months
Miao 2012 [34]	Amnestic MCI; age range 40-85; male 41.5%; MMSE 19-30; CDR 0.5	NR	Chinese herbal medicine	Donepezil	130	3 months
Zhao 2012 [35]	Amnestic MCI; age range 60-85; male 35.4%; CDR 0.5	NR	Ginkgo biloba extract	Placebo	113	6 months
Scheltens 2010 [36]	Mild AD; age \geq 50; male 50.0%; MMSE 20-26	ISRCTN72254645	Souvenaid	Placebo	212	3 months
Green 2009 [37]	Mild AD; age \geq 55; male 49.1%; MMSE 20-26	Phase 3, NCT00105547	Tarenflurbil	Placebo	1,649	18 months
Lannfelt 2008 [38]	Early AD; age \geq 55; male 50%; MMSE 20-26; CDR 0.5 or 1	Phase 2a, NCT00471211	PBT2	Placebo	78	3 months
Kessler 2008 [39]	Mild AD; age range 50-80; MMSE $<$ 25	Phase 2, NCT00608946	Copper	Placebo	68	12 months
Gomez-Isla 2008 [40]	Amnestic MCI; age \geq 60; male 33.9%; MMSE \geq 24	NR	Triflusal	Placebo	257	18 months
Petersen 2005 [41]	Amnestic MCI; age range 55-90; male 54.5%; MMSE 24-30; CDR 0.5	NR	Donepezil	Placebo	512	36 months
Petersen 2005 [41]	Amnestic MCI; age range 55-90; male 53.5%; MMSE 24-30; CDR 0.5	NR	Vitamin E	Placebo	516	36 months
Seltzer 2004 [42]	Early AD; age range 50-92; male 46.4%; MMSE 21-26; CDR 0.5 or 1	NR	Donepezil	Placebo	153	6 months
Salloway 2004 [43]	Amnestic MCI; age range 55-90; male 57.8%; MMSE \geq 24; CDR 0.5	NR	Donepezil	Placebo	270	6 months
Van Gool 2001 [44]	Early AD; male 42.3%	NR	Hydroxychloroquine	Placebo	168	18 months
NCT00476008 [45]	Mild AD; age \geq 60; male 65.1%; MMSE \geq 23	Phase 4, NCT00476008	Memantine	Placebo	43	12 months
NCT02956486 [46]	Early AD; amyloid positive; age range 50-85; male 48.9%; MMSE \geq 24; CDR 0.5	Phase 3, NCT02956486	Elenbecestat	Placebo	2,204	24 months
NCT02080364 [47]	Mild AD; age \geq 50; male 54.1%; MMSE 21-26; CDR 0.5 or 1	Phase 3, NCT02080364	Azeliragon	Placebo	875	18 months
NCT02791191 [48]	Mild AD; age range 55-85; male 39.2%; MMSE 20-26	Phase 2, NCT02791191	LY3202626	Placebo	316	12 months
NCT02727699 [49]	Mild AD; age \geq 50; male 42.7%; MMSE 20-26; CDR 0.5 or 1	Phase 2, NCT02727699	Xanamem™	Placebo	185	3 months
NCT03518073 [50]	Early AD; age range 60-85; male 47.2%	Phase 2, NCT03518073	LY3303560	Placebo	360	23 months

NCT03721705 [51]	Mild AD; age range 55-85; male 38.4%	Phase 3, NCT03721705	Renew NCP-5	Placebo	190	6 months
NCT03131453 [52]	Preclinical AD; amyloid positive; age range 60-75; male 37.1%	Phase 2/3, NCT03131453	CNP520	Placebo	1,144	6 months
NCT02565511 [53]	Preclinical AD; age range 60-75; male 32.3%; MMSE \geq 24	Phase 2/3, NCT02565511	CAD106	Placebo	65	6 months
NCT02565511 [53]	Preclinical AD; age range 60-75; male 56.1%; MMSE \geq 24	Phase 2/3, NCT02565511	CNP520	Placebo	412	6 months

AD, Alzheimer's disease; CDR, Clinical Dementia Rating scores; MMSE, Mini-Mental State Examination; NR, not reported

* Only data from a subgroup with a dosage of 10 mg/kg was extracted.

Supplementary Table 2. Risk of bias for included randomized controlled trials

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
van Dyck 2023	Low	Low	Low	Low	Low	Low
Sims 2023	Low	Low	Low	Low	Low	Low
Florian 2023	Low	Low	Low	Low	Low	Low
Sperling 2023	Low	Low	Low	Low	Low	Low
Berry 2023	Low	Low	Low	Low	Low	Low
Teng 2022	Low	Low	Low	Low	Low	Low
EMERGE 2022	Low	Low	Low	Low	Low	Low
ENGAGE 2022	Low	Low	Low	Low	Low	Low
CREAD 2022	Low	Low	Low	Low	Low	Low
CREAD2 2022	Low	Low	Low	Low	Low	Low
Mintun 2021	Low	Low	Low	Low	Low	Low
Sperling 2021	Low	Low	Some concern	Low	Low	Some concern
Salloway 2021 (Gantenerumab)	Low	Low	Low	Low	Low	Low
Salloway 2021 (Solanezumab)	Low	Low	Low	Low	Low	Low
Prins 2021	Low	Low	Low	Low	Low	Low
Wessels 2020 (AMARANTH)	Low	Low	Low	Low	Low	Low
Wessels 2020 (DAYBREAK-ALZ)	Low	Low	Low	Low	Low	Low
Howard 2020	Low	Low	Low	Low	Low	Low
Craft 2020	Low	Low	Low	Low	Low	Low
Gibson 2020	Low	Low	Low	Low	Low	Low
Egan 2019	Low	Low	Low	Low	Low	Low
van Dyck 2019	Low	Low	Low	Low	Low	Low
Tian 2019 (Qinggongshoutao)	Low	Low	Low	Low	High	High
Tian 2019 (Ginkgo biloba extract)	Low	Low	Low	Low	High	High

Frolich 2019	Low	Low	Low	Low	Some concern	Some concern
Forlenza 2019	Low	Low	Some concern	Low	Low	Some concern
Padala 2018	Low	Some concern	Low	Low	Low	Some concern
Honig 2018	Low	Low	Low	Low	Low	Low
Soinininen 2017	Low	Low	Low	Low	Low	Low
Kile 2017	Low	Low	Low	Low	Low	Low
Tian 2017	Low	Low	High	Low	Low	High
Ostrowitzki 2017	Low	Low	Low	Low	Low	Low
Fujino 2017	Low	Low	Low	Low	Low	Low
Luchsinger 2016	Low	Low	Low	Low	Low	Low
Zhang 2016	High	Low	Low	Low	Low	High
Zhang 2015	Low	Low	Low	Low	High	High
Coric 2015	Low	Low	Low	Low	Low	Low
Lin 2014	Low	Low	Low	Low	Some concern	Some concern
Morimoto 2013	Low	Low	Low	Low	Low	Low
Scheltens 2012	Low	Low	Low	Low	Low	Low
Miao 2012	Low	Low	Low	Low	High	High
Zhao 2012	Some concern	High	High	High	Some concern	High
Scheltens 2010	Low	Low	Low	Low	Low	Low
Green 2009	Low	Low	Low	Low	Low	Low
Lannfelt 2008	Low	Low	Low	Low	Low	Low
Kessler 2008	High	Low	High	Low	Low	High
Gomez-Isla 2008	Some concern	Low	Some concern	Low	High	High
Petersen 2005 (Donepezil)	Low	Low	Low	Low	Some concern	Some concern
Petersen 2005 (Vitamin E)	Low	Low	Low	Low	Some concern	Some concern
Seltzer 2004	Low	Low	Low	Low	Some concern	Some concern
Salloway 2004	Low	Low	Low	Low	Some concern	Some concern
Van Gool 2001	Low	Low	Low	Low	Some concern	Some concern
NCT00476008	Some concern	Low	High	Low	Low	High

NCT02956486	Some concern	Low	Low	Low	Low	Some concern
NCT02080364	Some concern	Low	Low	Low	Low	Some concern
NCT02791191	Some concern	Low	Low	Low	Low	Some concern
NCT02727699	Some concern	Low	Low	Low	Low	Some concern
NCT03518073	Some concern	Low	Low	Low	Low	Some concern
NCT03721705	Some concern	Low	Low	Low	Low	Some concern
NCT03131453	Low	Low	Low	Low	Some concern	Low
NCT02565511 (CAD106)	Low	Low	Low	Low	Some concern	Low
NCT02565511 (CNP520)	Low	Low	Low	Low	Some concern	Low

Supplementary Table 3. GRADE assessment

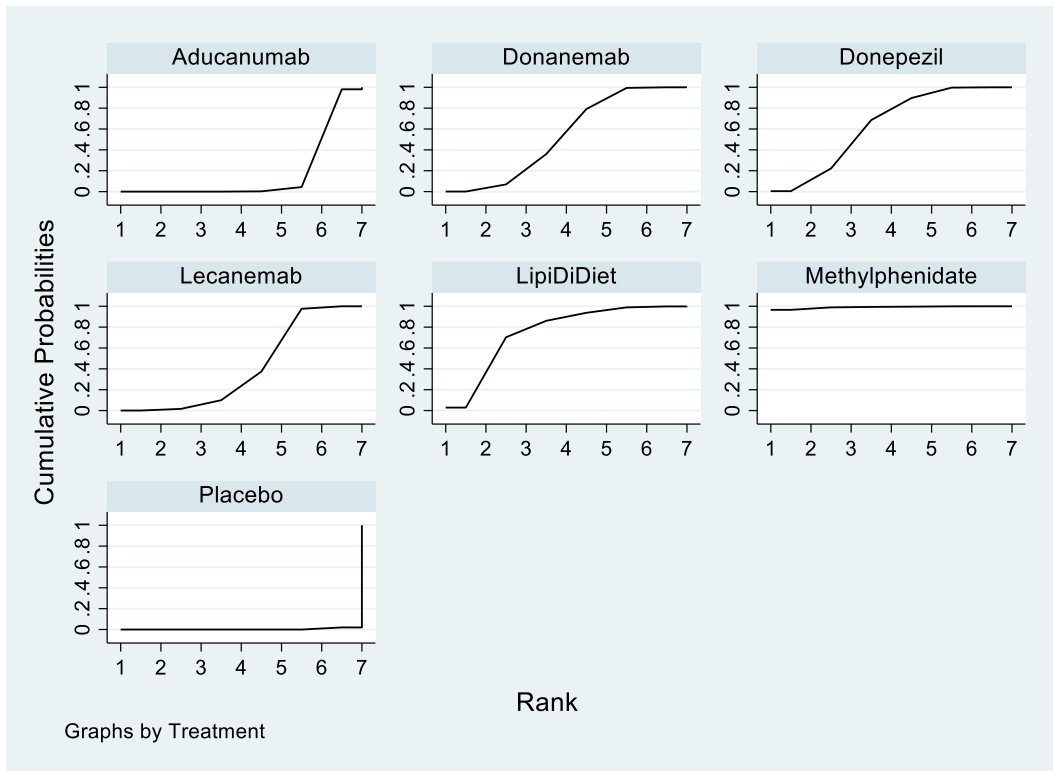
Outcomes	Quality assessment								No. of trial	Effects	GRADE
	Study limitations	Inconsistency	Indirectness	Imprecision	Reporting bias	Large effect	Dose response	Other Factors			
The change in the cognitive scores (compared with placebo)											
Aducanumab	<i>Not serious</i>	Very serious	<i>Not serious</i>	<i>Not serious</i>	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	2	SMD -0.078 (-0.150, -0.005)	Low
Donanemab	<i>Not serious</i>	<i>Not serious</i>	<i>Not serious</i>	<i>Not serious</i>	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	2	SMD -0.239 (-0.343, -0.134)	High
Donepezil (6 months)	Serious	<i>Not serious</i>	Serious	<i>Not serious</i>	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	3	SMD -0.279 (-0.410, -0.149)	Low
Lecanemab	<i>Not serious</i>	<i>Not serious</i>	<i>Not serious</i>	<i>Not serious</i>	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	2	SMD -0.194 (-0.279, -0.108)	High
LipiDiDiet	<i>Not serious</i>	<i>Not serious</i>	Serious	Serious	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	1	SMD -0.365 (-0.589, -0.140)	Low
Methylphenidate	<i>Not serious</i>	<i>Not serious</i>	Serious	Serious	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	1	SMD -0.938 (-1.477, -0.399)	Low
Ginkgo biloba extract	Very serious	Very serious	<i>Not serious</i>	Serious	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	2	SMD -0.765 (-1.427, -0.103)	Very low
Qinggongshoutao	Very serious	<i>Not serious</i>	<i>Not serious</i>	Serious	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	1	SMD -1.177 (-1.474, -0.881)	Very low
The change in the cognitive scores (compared with donepezil)											
Bushen capsule	Very serious	<i>Not serious</i>	<i>Not serious</i>	Serious	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	1	SMD -0.698 (-1.219, -0.176)	Very low
Chinese herbal medicine	Very serious	<i>Not serious</i>	<i>Not serious</i>	Serious	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	1	SMD 0.131 (-0.365, 0.626)	Very low
Shenwu capsule	Very serious	<i>Not serious</i>	<i>Not serious</i>	Serious	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	1	SMD 0.022 (-0.210, 0.254)	Very low
Yishen Huazhuo decoction	Very serious	<i>Not serious</i>	<i>Not serious</i>	Serious	<i>Not serious</i>	<i>None</i>	<i>None</i>	<i>None</i>	1	SMD -0.403 (-0.733, -0.073)	Very low

SMD, standardized mean difference; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

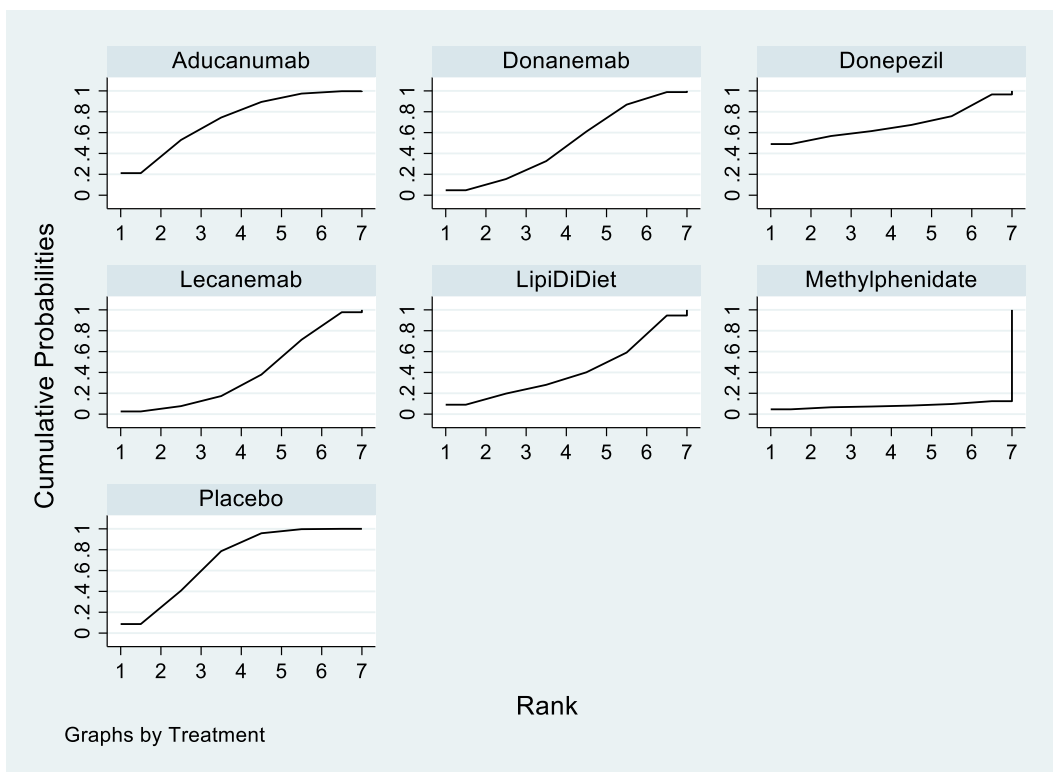
Supplementary Table 4. League tables of serious adverse events (relative risk with 95% confidence intervals).

Methylphenidate						
4.13 (0.49, 34.77)	LipDiDiet					
5.29 (0.55, 51.09)	1.28 (0.47, 3.46)	Donepezil				
4.46 (0.55, 36.20)	1.08 (0.67, 1.74)	0.84 (0.34, 2.10)	Donanemab			
4.19 (0.52, 34.12)	1.02 (0.62, 1.65)	0.79 (0.32, 1.99)	0.94 (0.70, 1.26)	Lecanemab		
4.93 (0.61, 39.97)	1.19 (0.74, 1.92)	0.93 (0.37, 2.32)	1.11 (0.85, 1.45)	1.18 (0.89, 1.56)	Aducanumab	
4.83 (0.60, 38.89)	1.17 (0.76, 1.81)	0.91 (0.37, 2.23)	1.08 (0.89, 1.32)	1.15 (0.93, 1.43)	0.98 (0.82, 1.18)	Placebo

Supplementary Figure 1. Treatment ranking probabilities for the change in the cognitive scores



Supplementary Figure 2. Treatment ranking probabilities for serious adverse events.



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