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Appendix

Acetylcholinesterase inhibitors combined with memantine for moderate to severe Alzheimer's disease: a meta-analysis

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Supplement 1 - Search strategies, conducted February 5th, 2018

Medline (OvidSP search):

Searches		Results
1	exp Memantine/	1993
2	Memantin*.ab,ti.	2844
3	Receptors, N-Methyl-D-Aspartate/ai, tu [Antagonists & Inhibitors, Therapeutic Use]	8025
4	methyl d aspartic acid.ab,ti.	1803
5	methyl d aspartate.ab,ti.	24537
6	Receptors, Glutamate/	6878
7	Excitatory Amino Acid Antagonists/tu [Therapeutic Use]	1944
8	receptor antagonism.ab,ti.	4107
9	receptor antagonist.ab,ti.	74603
10	receptor inhibitor.ab,ti.	2474
11	Receptor blocking agent.ab,ti.	721
12	axura.ab,ti.	9
13	ebixa.ab,ti.	20
14	Namenda*.ab,ti.	29
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	111125
16	exp Dementia/	143192
17	Dementia.ti,ab.	86177
18	Alzheimer Disease/	81052
19	Alzheimer.ti,ab.	23376
20	Cognition Disorders/	60171
21	(Dement or dementia or demenz or demenc*).ti,ab.	86234
22	((disorder* or decline or decay or impair* or loss* or deteriorat* or diminish* or insufficien* or degenerate* or frailty) and (cognit* or memory or mental* or thought* or cerebr* or senile)).ti,ab.	389386
23	Mini mental.ti,ab.	13477
24	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	538914
25	randomized controlled trial.pt.	452660
26	controlled clinical trial.pt.	92131
27	randomized.ab.	392146

28	randomised.ab.	78448
29	placebo.ab.	183166
30	clinical trials as topic.sh.	182408
31	randomly.ab.	278751
32	Random*.tw.	931333
33	trial.ti.	173206
34	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	1337539
35	15 and 24 and 34	1019

Medline (PubMed top up search)

(((((Memantine OR Memantin* OR N-Methyl-D-Aspartate receptor OR Glutamate receptor OR Excitatory Amino Acid Antagonists OR receptor antagonism OR receptor antagonist OR receptor inhibitor OR Receptor blocking agent OR Axura OR Ebixa OR Namenda))) AND ((Alzheimer OR Cognition Disorder OR Dement or dementia or demenz or demenc* OR ((disorder* or decline or decay or impair* or loss* or deteriorat* or diminish* or insufficien* or degenerate* or frailty) and (cognit* or memory or mental* or thought* or cerebral or senile)) OR Mini mental))) AND ((randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo OR clinical trials as topic OR random OR trial OR rct))) AND publisher[sb] 32 hits

EMBASE (Ovid search)

Searches		Results
1	exp amino acid receptor blocking agent/dt [Drug Therapy]	18763
2	exp Memantine/	9147
3	Memantin*.ab,ti.	4418
4	methyl d aspartic acid.ab,ti.	2014
5	methyl d aspartate.ab,ti.	27406
6	Receptors, Glutamate/	15528
7	receptor antagonism.ab,ti.	5171
8	receptor antagonist.ab,ti.	90893
9	receptor inhibitor.ab,ti.	3645
10	Receptor blocking agent.ab,ti.	940
11	axura.ab,ti.	13
12	ebixa.ab,ti.	32
13	Namenda*.ab,ti.	46
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	152471
15	exp Dementia/	302764
16	Dementia.ti,ab.	125572
17	Alzheimer Disease/	164928
18	Alzheimer.ti,ab.	31342
19	(Dement or dementia or demenz or demenc*).ti,ab.	125696
20	((disorder* or decline or decay or impair* or loss* or deteriorat* or diminish* or insufficien* or degenerate* or frailty) and (cognit* or memory or mental* or thought* or cerebr* or senile)).ti,ab.	563774
21	Mini mental.ti,ab.	20281
22	exp cognitive defect/	405810
23	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	840752
24	random$.tw. or placebo$.mp. or double-blind$.tw.	1506285
25	14 and 23 and 24	2898

CENTRAL

ID	Search	Hits
1	MeSH descriptor: [Memantine] explode all trees	279
2	Memantin*:ti,ab,kw	822
3	MeSH descriptor: [Receptors, N-Methyl-D-Aspartate] explode all trees	345
4	methyl-d-aspartic-acid:ti,ab,kw	46
5	methyl-d-aspartate:ti,ab,kw	931
6	MeSH descriptor: [Receptors, Glutamate] explode all trees	419
7	MeSH descriptor: [Excitatory Amino Acid Antagonists] explode all trees	466
8	receptor antagonism:ti,ab,kw	1099
9	receptor antagonist:ti,ab,kw	12338
10	receptor inhibitor:ti,ab,kw	8941
11	receptor blocking agent:ti,ab,kw	7360
12	axura:ti,ab,kw	1
13	ebixa:ti,ab,kw	5
14	namenda*:ti,ab,kw	7
15	or 1-14	23182
16	MeSH descriptor: [Dementia] explode all trees	4710
17	dementia*:ti,ab,kw	8115
18	MeSH descriptor: [Alzheimer Disease] explode all trees	2599
19	alzheimer:ti,ab,kw	7347
20	(Dement or dementia or demenz or demenc*):ti,ab,kw	8081
21	((disorder* or decline or decay or impair* or loss* or deteriorat* or diminish* or insufficien* or degenerate* or frailty) and (cognit* or memory or mental* or thought* or cerebr* or senile)):ti,ab,kw	48427
22	Mini mental:ti,ab,kw	3463
23	MeSH descriptor: [Cognition Disorders] explode all trees	3803
24	or 15-23	57173
25	15 and 24	1951
Limit “Trials”		1855

Supplement 2 – Hierarchy of extraction of eligible instruments or further explanations

The roman letters represent a hierarchy, which determined which instruments were considered with higher priority. Within each outcome, results were only extracted for the highest-ranking instrument that was available.

Outcome	Instrument/further explanations if necessary
Cognition	I. Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog)
	II. Mini-Mental State Examination (MMSE) score
	III. if I or II not reported: Severe Impairment Battery (SIB), Wechsler Memory Scale-Revised (WMS-R), Fuld Object-Memory Evaluation, Benton Visual Retention Test, Trail Making Test, Alzheimer's disease Cooperative Study-Clinical Global Impression of Change, Ten-Point Clock Drawing Test, Mental Function Impairment
Activities of daily living	I. Progressive Deterioration Scale,
	II. Alzheimer's Disease Cooperative Study activities of daily living inventory
	III. Caregiver Activity Survey
	VI. Nurses' Observation Scale for Geriatric Patients, Functional Independence Measure (FIM)
Clinical global impression	I. Clinician's Interview-Based Impression of Change (CIBIC)
	II. Clinical Global Impression of Change (CGI),
	III. Global Deterioration Scale (GDS)
Behavioural and psychological symptoms of dementia (BPSD)	I. Neuropsychiatric Inventory (NPI)
	II. if I. not reported: Behavioural Pathology in Alzheimer's disease, Cohen-Mansfield Agitation Inventory (CMAI)
Withdrawal from the study	Any patients declared as "discontinued" (for any reason), "lost to follow up," "withdrew consent," "no longer on study" or similar

Adverse events	Number of patients who experienced one or more adverse event
Caregiver Burden or distress	Any of the following: Neuropsychiatric Inventory of Caregiver Distress Scale (NPI-D), Resource Utilization in Dementia (RUD), Disability Assessment for Dementia (DAD)
Delay in nursing home placement	Outcome could either be reported as mean time to nursing home placement or as patients with a delay in nursing home placement based on a defined cut-off for delay; only applicable in case of ambulatory care
General quality of life	I. SF-36
	II. If I. not reported: Euroqol
* The roman letters represent a hierarchy, which determined which instruments were considered with higher priority. Within each outcome, results were only extracted for the highest-ranking instrument that was available.	

Supplement 3 – GRADE Summary of findings

Combination therapy compared to monotherapy with cholinesterase inhibitors for Alzheimer's Disease

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with monotherapy with cholinesterase inhibitors	Risk difference with combination therapy
Delay in nursing home placement -- Short-term follow-up (closest to 6 months) - not reported	-	-	-	-	-
Delay in nursing home placement - Long-term follow-up (>9 months) (NHP)	-	-	-	-	-
Cognition - Short-term follow-up (closest to 6 months)	2132 (7 RCTs)	⨁⨁◯◯ LOW [a,b]	-	-	SMD **0.20 higher** (0.05 higher to 0.35 higher)
Cognition - Long-term follow-up (≥ 9 months)	343 (2 RCTs)	⨁⨁◯◯ LOW [c,d]	-	-	SMD **0.08 higher** (-0.14 lower to 0.29 higher)
Activities of daily living - Short-term follow-up (closest to 6 months)	1784 (5 RCTs)	⨁⨁⨁◯ MODERATE [e]	-	-	SMD **0.1 higher** (-0.01 to 0.18 higher)
Activities of daily living - Long-term follow-up (≥ 9 months)	145 (1 RCT)	⨁⨁◯◯ LOW [f,g]	-	-	SMD **0.08 higher** (-0.25 lower to 0.40 higher)
Clinical Global Impression - Short-term follow-up (closest to 6 months)	1665 (4 RCTs)	⨁⨁⨁◯ MODERATE [h]	-	-	SMD **0.15 lower** (0.28 lower to 0.01 lower)
Clinical Global Impression - Long-term follow-up (≥ 9 months) - not reported	-	-	-	-	-
Behavioural and psychological symptoms of dementia - Short-term follow-up (closest to 6 months)	1949 (6 RCTs)	⨁⨁◯◯ LOW [b,i]	-	-	MD -3.07 **lower** (-6.53 lower to 0.38 higher)

Combination therapy compared to monotherapy with cholinesterase inhibitors for Alzheimer's Disease

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with monotherapy with cholinesterase inhibitors	Risk difference with combination therapy
Behavioural and psychological symptoms of dementia - Long-term follow-up (≥ 9 months) - not reported	-	-	-	-	-
Withdrawal - Short-term follow-up (closest to 6 months)	2092 (6 RCTs)	⨁⨁◯◯ LOW [j,k]	**RR 0.89** (0.72 to 1.11)	183 per 1.000	**20 fewer per 1.000** (51 fewer to 20 more)
Withdrawal - Long-term follow-up (≥ 9 months)	146 (1 RCT)	⨁◯◯◯ VERY LOW [c,l]	**RR 1.33** (0.49 to 3.65)	82 per 1.000	**27 more per 1.000** (42 fewer to 218 more)
Adverse events - Short-term follow-up (closest to 6 months)	1620 (4 RCTs)	⨁⨁◯◯ LOW [m,n]	**RR 1.05** (0.98 to 1.12)	661 per 1.000	**33 more per 1.000** (13 fewer to 79 more)
Adverse events - Long-term follow-up (≥ 9 months)	146 (1 RCT)	⨁◯◯◯ VERY LOW [g,o,p]	**RR 0.87** (0.67 to 1.14)	644 per 1.000	**84 fewer per 1.000** (212 fewer to 90 more)
Caregiver Burden or distress - Short-term follow-up (closest to 6 months)	25 (1 RCT)	⨁⨁◯◯ LOW [c,q]	-	-	MD **18.56 lower** (26.06 lower to 11.06 lower)
Caregiver Burden or distress - Long-term follow-up (≥ 9 months) - not reported	-	-	-	-	-
Quality of life - short term follow-up - not reported	-	-	-	-	-
Quality of life - long-term follow-up - not reported	-	-	-	-	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference; SMD: Standardised mean difference; RR: Risk ratio

Combination therapy compared to monotherapy with cholinesterase inhibitors for Alzheimer's Disease

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with monotherapy with cholinesterase inhibitors	Risk difference with combination therapy

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. The study limitations were serious because risk of selection bias (allocation concealment) was unclear in 2 studies; risk of performance bias was unclear in 2 and high in 1 studies; risk of detection bias was unclear in 3 and high in 1 studies; risk of attrition bias was high in 7 studies; risk of reporting bias was unclear in 4 and high in 1 studies.
b. Inconsistency was serious because heterogeneity was high and remained unexplained by sensitivity analysis.
c. Imprecision was serious because the total sample size was below the optimal information size (OIS).
d. The study limitations were serious because risk of attrition bias was unclear in 1 study and high in 1 study; risk of reporting bias was high in 1 study.
e. The study limitations were serious because risk of performance bias was unclear in 1 and high in 1 studies; risk of detection bias was unclear in 2 and high in 1 studies; risk of attrition bias was high in 5 studies; risk of reporting bias was unclear in 3 studies.
f. The study limitation was serious because risk of attrition bias was high in 1 study.
g. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include no effect and a medium effect (0.5 SD) in favour of combination therapy; in addition the total sample size did appear lower than the optimal information size (OIS).
h. The study limitations were serious because risk of performance bias was unclear in 1 and high in 1 studies; risk of detection bias was unclear in 2 and high in 1 studies; risk of attrition bias was high in 4 studies; risk of reporting bias was unclear in 3 studies.
i. The study limitations were serious because risk of selection bias (allocation concealment) was unclear in 2 and high in 1 studies; risk of performance bias was unclear in 2 and high in 1 studies; risk of detection bias was unclear in 3 and high in 1 studies; risk of attrition bias was high in 6 studies; risk of reporting bias was unclear in 4 and high in 1 studies.
j. The study limitations were serious because risk of selection bias (allocation concealment) was unclear in 2 studies; risk of performance bias was unclear in 2 and high in 1 studies; risk of detection bias was unclear in 3 and high in 1 studies; risk of attrition bias was high in 2 studies; risk of reporting bias was unclear in 4 and high in 1 studies.
k. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include both no effect and appreciable benefit (relative risk increase greater than 25%) in favour of combination therapy.
l. The study limitation was very serious because risk of attrition bias was high in 1 study.
m. The study limitations were serious because risk of selection bias (random sequence generation and allocation concealment) was unclear in 1 study; risk of performance bias was unclear in 1 and high in 1 study; risk of detection bias was unclear in 2 and high in 1 studies; risk of attrition bias was high in 1 study; risk of reporting bias was unclear in 3 and high in 1 studies.
n. Indirectness was serious because most studies did not report on total adverse events, but treatment emergent adverse events only.
o. Indirectness was serious because the single study (DOMINO-AD 2012) did not report adverse events but reported on SAE including drug errors.

p. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include both no effect and appreciable benefit (relative risk increase greater than 25%) in favour of combination therapy. the total sample size was lower than the optimal information size (OIS).
q. The study limitations were serious because risk of selection bias (allocation concealment) was unclear in 1 study; risk of performance bias was unclear in 1 study; risk of detection bias was unclear in 1 study; risk of attrition bias was high in 1 study; risk of reporting bias was unclear in 1 study.

GRADE Summary of findings table

Combination therapy compared to monotherapy with memantine for Alzheimer's Disease					
Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with monotherapy with memantine	Risk difference with Should combination therapy
Delay in nursing home placement - Short -term follow-up (<9 months) - not reported	-	-	-	-	-
Delay in nursing home placement - Long -term follow-up (>9 months)	-	-	-	-	-
Cognition - Short-term follow-up (< 9 months)	234 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	-		MD **1.32 higher** (0.44 lower to 3.08 higher)
Cognition - Long-term follow-up (≥ 9 months)	146 (1 RCT)	⨁⨁◯◯ LOW [d,e]	-		MD **0.8 higher** (1.01 lower to 2.61 higher)
Activities of daily living - Short-term follow-up (< 9 months)	234 (2 RCTs)	⨁◯◯◯ VERY LOW [a,f,g]	-	-	SMD **0.06 higher** (0.55 lower to 0.68 higher)
Activities of daily living - Long-term follow-up (≥ 9 months)	146 (1 RCT)	⨁⨁◯◯ LOW [e,h]	-	-	SMD **0.22 higher** (0.1 lower to 0.55 higher)
Clinical Global Impression - Short-term follow-up (< 9 months) - not reported	-	-	-	-	-
Clinical Global impression - Long-term follow-up (≥ 9 months)New outcome - not reported	-	-	-	-	-
Behavioural and psychological symptoms of dementia - Short-term follow-up (< 9 months) - not reported	-	-	-	-	-

Combination therapy compared to monotherapy with memantine for Alzheimer's Disease

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with monotherapy with memantine	Risk difference with Should combination therapy
Behavioural and psychological symptoms of dementia - Long-term follow-up (≥ 9 months) - not reported - not reported	-	-	-	-	-
Withdrawal - Short-term follow-up (< 9 months) - not reported	-	-	-	-	-
Withdrawal - Long-term follow-up (≥ 9 months)	149 (1 RCT)	⨁◯◯◯ VERY LOW [e,i]	**RR 0.56** (0.25 to 1.23)	197 per 1.000	**87 fewer per 1.000** (148 fewer to 45 more)
Adverse events - Short-term follow-up (< 9 months)	88 (1 RCT)	⨁◯◯◯ VERY LOW [j,k]	**RR 1.40** (0.60 to 3.27)	227 per 1.000	**91 more per 1.000** (91 fewer to 516 more)
Adverse events - Long-term follow-up (≥ 9 months)	149 (1 RCT)	⨁◯◯◯ VERY LOW [e,l,m]	**RR 1.07** (0.80 to 1.43)	526 per 1.000	**37 more per 1.000** (105 fewer to 226 more)
Caregiver Burden or distress - Short-term follow-up (< 9 months) - not reported	-	-	-	-	-
Caregiver Burden or distress - Long-term follow-up (≥ 9 months) - not reported	-	-	-	-	-
Quality of life - short term follow-up (< 9 months) - not reported	-	-	-	-	-
Quality of life - long-term follow-up (≥ 9 months) - not reported	-	-	-	-	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference; SMD: Standardised mean difference; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. The study limitations were serious because risk of selection bias (random sequence generation and allocation concealment) was unclear in 1 study; risk of detection bias was unclear in 1 study; risk of performance bias was unclear in 1 study; risk of attrition bias was high in 1 study; risk of reporting bias was unclear in 1 study.
b. Inconsistency was serious because heterogeneity was high.
c. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include no effect and an MCID of 2.1 (MMSE) in favour of combination therapy; this is consistent with: the standardized effect estimate (0.38 [0.11, 0.65]) is sufficiently wide to include no effect and a medium effect (0.5 SD). In addition, the total sample size was lower than the optimal information size (OIS)
d. Imprecision was serious because the total sample size was lower than the optimal information size (OIS).
e. The study limitation was serious because risk of attrition bias was high in 1 study.
f. Inconsistency was serious because heterogeneity was high and the individual point estimates varied into different directions
g. Imprecision was very serious because the 95% CI of the effect estimate is sufficiently wide to include a 0.5 SD either in favour or against combination therapy.
h. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include no effect and a 0.5 SD in favour of memantine and because the total sample size was lower than the optimal information size (OIS).
i. Imprecision was very serious because the 95% CI of the effect estimate is sufficiently wide to include both no effect and an appreciable benefit (relative risk increase greater than 25%) of combination therapy. In addition the event rate was too low.
j. The study limitations were serious because risk of selection bias (random sequence generation and allocation concealment) was unclear in 1 study; risk of performance bias was unclear in 1 study; risk of detection bias was unclear in 1 study; risk of reporting bias was unclear in 1 study.
k. Imprecision was very serious because the 95% CI of the effect estimate is sufficiently wide to include appreciable harm or benefit (relative risk increase greater than 25%) of combination therapy.
l. Indirectness was serious because the single study (DOMINO-AD 2012) did not report adverse events but reported on SAE including drug errors.
m. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include both no effect and an appreciable harm (relative risk increase greater than 25%) of combination therapy. In addition the event rate was too low.