

Comparative Safety of Cholinesterase Inhibitors and Memantine for Dementia: A GRADE-Assessed Network Meta-Analysis

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Memantine is the safest dementia therapy with no significant increase in adverse events versus placebo, while higher-dose cholinesterase inhibitor formulations carry the greatest risk of harm.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES																														
Background: Cholinesterase inhibitors (ChEIs) and memantine are standard therapies for dementia, but little is known about the comparative safety profile of their different doses and formulations. Rationale: Clinicians need head-to-head safety data, not just efficacy data, to individualize treatment choice and minimize harm. Objective: We conducted this network meta-analysis to synthesize evidence from RCTs on the safety and tolerability of ChEIs and memantine in dementia.	Design: PRISMA-compliant systematic review and network meta-analysis of 100 RCTs (n=36,691) Search: PubMed, Scopus, Embase, Web of Science, and CENTRAL were searched for RCTs of ChEIs and memantine in dementia. Outcomes: All adverse events (AEs), serious AEs, discontinuations due to AEs, and seven specific AE categories (GIT, CNS, cardiovascular, psychological, sleep, falls, skin). Certainty: GRADE was used to assess the certainty of evidence for each outcome.	Memantine: The safest treatment overall, with no significant increase versus placebo in overall AEs (RR 1.03), GIT AEs (RR 1.05), discontinuations (RR 1.10), or serious AEs; a dose-specific analysis showed a signal for CNS AEs. ChEIs overall: Donepezil (RR 1.11), galantamine (RR 1.16), rivastigmine (RR 1.22), and the donepezil patch (RR 1.40) significantly increased overall AEs versus placebo. Higher-dose formulations: Showed the greatest harm: donepezil 23 mg (RR 1.77), galantamine 36 mg (RR 1.22), and rivastigmine 17.4 mg patch (RR 1.35). Agent-specific patterns: Oral rivastigmine carried the highest GIT AE risk (RR 2.94) and was most strongly associated with CNS AEs (RR 2.27); donepezil was uniquely linked to sleep disturbances (RR 2.06), cardiovascular AEs (23 mg: RR 2.50), and skin AEs among oral agents (RR 2.63). Rivastigmine patches, despite ranking safest for serious AEs, still increased discontinuations (RR 1.82-2.17). <table><tr><th>Outcome Category</th><th>👍 BEST OPTION (Lowest Risk)</th><th>👎 WORST OPTION (Highest Risk)</th></tr><tr><td>Total adverse events</td><td>Memantine ER 28 mg [Low Certainty] RR 0.98 (0.81-1.19) possibly similar to a placebo.</td><td>Donepezil 23 mg [Moderate Certainty] RR 1.77 (1.52-2.05) probably increases total AEs.</td></tr><tr><td>Serious adverse events</td><td>Rivastigmine 4.6 mg patch [High Certainty] RR 0.62 (0.39-0.98) reduces SAEs.</td><td>Galantamine 32 mg [Moderate Certainty] RR 1.40 (0.84-2.31) probably has little or no effect on SAEs.</td></tr><tr><td>Discontinuation due to AEs</td><td>Memantine 20 mg [Low Certainty] RR 1.04 (0.87-1.24) possibly similar to a placebo.</td><td>Donepezil 23 mg [Moderate Certainty] RR 3.57 (2.61-4.88) probably greatly increases discontinuation.</td></tr><tr><td>GI-related AEs</td><td>Memantine 20 mg [Low Certainty] RR 1.00 (0.80-1.26) Possibly similar to a placebo.</td><td>Donepezil 23 mg [Moderate Certainty] RR 4.33 (2.60-7.21) Probably greatly increases GI AEs.</td></tr><tr><td>CNS-related AEs</td><td>Rivastigmine 9.5 mg patch [Low Certainty] RR 0.89 (0.69-1.15) Possibly similar to placebo.</td><td>Galantamine 36 mg [Moderate Certainty] RR 2.16 (1.44-3.23) Probably doubles CNS AEs.</td></tr><tr><td>Cardiovascular adverse events</td><td>Rivastigmine 4.6 mg patch [Moderate Certainty] RR 0.79 (0.16-4.02) Probably has little to no effect compared with a placebo.</td><td>Donepezil 23 mg [High Certainty] RR 2.51 (1.08-6.83) increases cardiovascular AEs.</td></tr><tr><td>Psychological disturbances</td><td>Memantine 20 mg [Moderate Certainty] RR 0.87 (0.68-1.10) Probably similar to a placebo.</td><td>Galantamine 36 mg [Low Certainty] RR 7.66 (0.97-60.7) Harm with high-dose galantamine is possibly present, but very uncertain.</td></tr><tr><td>Sleep disturbances</td><td>Memantine 20 mg [Moderate Certainty] RR 0.97 (0.65-1.48) Probably similar to placebo.</td><td>Galantamine 36 mg [Low Certainty] RR 8.98 (1.12-68.3) Possibly increases sleep problems.</td></tr><tr><td>Falls</td><td>Memantine ER 28 mg [Moderate Certainty] RR 0.81 (0.62-1.06) Probably similar to placebo.</td><td>Donepezil 5 mg [High Certainty] RR 1.43 (1.03-1.98) Probably increases falls.</td></tr></table> Figure 1: Diagram of ChEIs differential effect sizes from pairwise meta-analysis across dementia types	Outcome Category	👍 BEST OPTION (Lowest Risk)	👎 WORST OPTION (Highest Risk)	Total adverse events	Memantine ER 28 mg [Low Certainty] RR 0.98 (0.81-1.19) possibly similar to a placebo.	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Practical guidance: Low-dose rivastigmine patches may better suit patients prone to GI events, with counseling on skin reactions. Evidence certainty: Certainty of evidence ranged from low to high across outcomes, assessed using GRADE.	Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2018. McShane R, et al. Memantine for dementia. Cochrane Database Syst Rev. 2019. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev. 2006. Birks JS, Grimley Evans J. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev. 2015. CONTACT Moaz Elsayed Abouelmagd Negida Academy, Medical Research Group of Egypt Email: moaz.s.sayed@gamil.com ALZHEIMER'S ASSOCIATION AAIC 26
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