

Comparative Cognitive Effects of Cholinesterase Inhibitors Across Dementia Types: Meta-Analysis With Meta-Regression of RCTs

54F0978

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Cholinesterase inhibitors produce consistently larger cognitive gains in Lewy body/Parkinson's disease dementia than in Alzheimer's disease or vascular dementia, suggesting cholinergic deficit severity drives treatment response.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	Figures																				
Background: Cholinesterase inhibitors (ChEIs) are standard therapy in Alzheimer's disease (AD) and are increasingly prescribed in dementia with Lewy bodies or Parkinson's disease dementia (DLB/PDD) and vascular dementia (VaD). Knowledge gap: It remains unclear whether the differing severity of cholinergic deficits across these dementia types translates into distinct cognitive responses to ChEI therapy. Objective: To compare cognitive outcomes of licensed ChEI doses across AD, DLB/PDD, and VaD and to test diagnosis as a moderator of treatment effect via meta-regression.	Design: Meta-analysis of randomized controlled trials (RCTs) of licensed ChEIs in adults with AD, DLB/PDD, or VaD. Search: MEDLINE, Scopus, Web of Science, Embase, and CENTRAL were searched through May 2025. Outcome: Primary outcome was change in global cognition (MMSE, ADAS-Cog). Analysis: Standardized mean differences (SMDs) were pooled across instruments and mean differences (MDs) on dominant scales using random-effects models; meta-regression was fitted with diagnosis as a moderator.	Alzheimer's disease: All licensed ChEI doses produced small but consistent cognitive gains. Donepezil 5 mg and 10 mg improved global cognition (SMD 0.30 and 0.29). Galantamine 16-24 mg and rivastigmine 6-12 mg showed similar effects (SMD 0.31 and 0.95). DLB/PDD: Responses were consistently larger: donepezil 10 mg SMD 0.51; galantamine 16-24 mg SMD 1.28, with about 5 MMSE points gained (MD 5.00); rivastigmine 6-12 mg SMD 0.65. Meta-regression: Confirmed greater benefit in DLB/PDD than AD for donepezil 10 mg ($\beta = 0.21$ SMD units, $p = 0.034$) and for galantamine ($\beta = 4.28$ MMSE points, $p = 0.0004$-0.011). Vascular dementia: Donepezil 5 and 10 mg and rivastigmine produced small but statistically significant gains (SMD 0.27-0.47; MMSE MD 0.60-1.10), whereas galantamine showed little cognitive effect (SMD 0.06).	Gradient of response: Licensed ChEI doses yield modest-to-moderate cognitive benefits in AD and VaD, and possibly larger effects in DLB/PDD. Interpretation: This gradient may suggest that the severity of underlying cholinergic deficits influences ChEI efficacy. Clinical implication: Findings support prioritizing ChEIs in DLB/PDD, where cognitive responses appear most pronounced.	Cognitive efficacy of cholinesterase inhibitors aligns with underlying cholinergic pathology Standardized mean differences stratified by dementia subtype <table border="1"><caption>Approximate SMD values from the forest plot</caption><thead><tr><th>Dementia Subtype</th><th>Donepezil 5 mg</th><th>Donepezil 10 mg</th><th>Galantamine 16-24 mg</th><th>Rivastigmine 6-12 mg</th></tr></thead><tbody><tr><td>DLB/PDD</td><td>0.70</td><td>0.60</td><td>1.50</td><td>0.80</td></tr><tr><td>Alzheimer disease</td><td>0.30</td><td>0.29</td><td>0.31</td><td>0.95</td></tr><tr><td>Vascular dementia</td><td>0.27</td><td>0.47</td><td>0.06</td><td>1.10</td></tr></tbody></table> Legend: Donepezil 5 mg (blue circle), Donepezil 10 mg (light blue circle), Galantamine 16-24 mg (red square), Rivastigmine 6-12 mg (green diamond). Arrows indicate: Increasing severity of cortical cholinergic deficit (top) and Magnitude of cognitive response to cholinesterase inhibition (bottom).	Dementia Subtype	Donepezil 5 mg	Donepezil 10 mg	Galantamine 16-24 mg	Rivastigmine 6-12 mg	DLB/PDD	0.70	0.60	1.50	0.80	Alzheimer disease	0.30	0.29	0.31	0.95	Vascular dementia	0.27	0.47	0.06	1.10
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