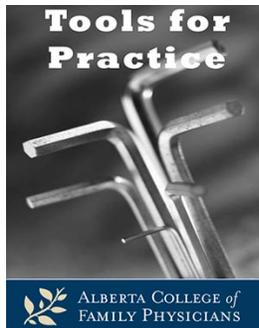


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Cholinesterase inhibitors and treatment of Alzheimer's dementia

Clinical Question: What are the benefits and harms of cholinesterase inhibitors (ChEI) for Alzheimer's dementia?

Bottom-line: Evidence for ChEI in Alzheimer's dementia is generally limited by small differences and high drop-out rates. Approximately one in ten patients show meaningful clinical improvement when treated for six months and ~1 in ten patients stop using the drug due to an adverse event.

Evidence:

- Over 20 meta-analyses are published on ChEI (donepezil, galantamine, rivastigmine) for Alzheimer's dementia.
 - Focus on Cochrane review¹ of 13 trials (7,298 patients) and four other systematic reviews.²⁻⁵ Data shown when ≥ 2 studies provide values, generally for common doses and follow-up ≥ 6 months.
 - ChEI vs. placebo statistically significant, but not clinically meaningful, mean change in cognition scores:
 - ADAS-Cog (out of 70): overall -2.37,¹ varying from -1.49 to -3.91, depending on study.¹⁻⁵
 - MMSE (out of 30): overall 1.37, varying from -0.04 to 1.37, depending on study.^{1-3,5}
 - Number who had clinically meaningful improvement:
 - ADAS-Cog >4 : Number Needed to Treat (NNT) 6-18.^{3,4}
 - Global clinical improvement: NNT 6-17.¹⁻⁴
 - Harms:
 - Drop-out due to adverse events: Number Needed to Harm (NNH) 10 overall.¹
 - Specific example with donepezil:² anorexia (NNH 17), diarrhea (NNH 10), nausea (NNH 11), vomiting (NNH 13), weight loss (NNH 18), and insomnia (NNH 24).

Context:

- Potential biases:

- Trials: drop-out rates up to 35% and often more among ChEI,⁶ drop-outs analyzed like their cognition was stable,^{6,7} poor description of randomization.^{2,6}
- Meta-analyses: using single reviewers¹⁻³ or inclusion of biased studies.
- Dementia guidelines and reviews have ranged from supporting^{8,9} to not supporting^{10,11} their use.
- Three year non-profit community trial found no difference in institutionalization.¹² Although anticipated to be a landmark study, there were multiple issues including <20% intended enrolment, >40% lost to follow-up in first year.
- Costs for three months¹³ are \$495 donepezil, \$130 galantamine, and \$135 rivastigmine.
- The large number of meta-analyses likely speaks more about people's willingness to accept the answer than the answer itself.

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Disclosure:

The authors have no conflicts to disclose.

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