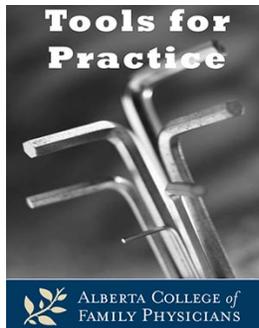


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## Cholinesterase inhibitors and treatment of Alzheimer's dementia

**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 review<sup>1</sup> of 13 trials (7,298 patients) and four other systematic reviews.<sup>2-5</sup> Data shown when  $\geq 2$  studies provide values, generally for common doses and follow-up  $\geq 6$  months.
    - ChEI vs. placebo statistically significant, but not clinically meaningful, mean change in cognition scores:
      - ADAS-Cog (out of 70): overall -2.37,<sup>1</sup> varying from -1.49 to -3.91, depending on study.<sup>1-5</sup>
      - MMSE (out of 30): overall 1.37, varying from -0.04 to 1.37, depending on study.<sup>1-3,5</sup>
    - Number who had clinically meaningful improvement:
      - ADAS-Cog  $>4$ : Number Needed to Treat (NNT) 6-18.<sup>3,4</sup>
      - Global clinical improvement: NNT 6-17.<sup>1-4</sup>
    - Harms:
      - Drop-out due to adverse events: Number Needed to Harm (NNH) 10 overall.<sup>1</sup>
      - Specific example with donepezil:<sup>2</sup> 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,<sup>6</sup> drop-outs analyzed like their cognition was stable,<sup>6,7</sup> poor description of randomization.<sup>2,6</sup>
- Meta-analyses: using single reviewers<sup>1-3</sup> or inclusion of biased studies.
- Dementia guidelines and reviews have ranged from supporting<sup>8,9</sup> to not supporting<sup>10,11</sup> their use.
- Three year non-profit community trial found no difference in institutionalization.<sup>12</sup> 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 months<sup>13</sup> 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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