



Remind me, do medications that target brain amyloid improve my dementia?

CLINICAL QUESTION

Are amyloid-targeting monoclonal antibodies safe and effective for mild cognitive impairment or Alzheimer's dementia?

BOTTOM LINE

Randomized controlled trials (RCTs) of monoclonal antibodies for patients with dementia or mild cognitive impairment found no clinically meaningful improvements in cognitive scores. These medications have a high risk of serious adverse effects and are costly. They should not be used at this time.

EVIDENCE

Placebo-controlled RCTs of patients with dementia or mild cognitive impairment due to Alzheimer's disease and amyloid deposits on PET scan. Mini-mental status exam (MMSE) ~26 unless indicated, 50-60% on dementia medications. Results statistically different unless indicated.

- Aducanumab: 2 RCTs, 3285 patients, terminated for futility.¹⁻³ Re-analysis found benefit in one dosage arm (10mg/kg) of one RCT. Outcomes at 18 months:
 - Clinical Dementia Rating-Sum of Boxes (CDR-SB) [scale 0-18, minimum clinically important difference=1-2]: 0.4 better with aducanumab, not clinically meaningful.⁴
 - MMSE: 0.6 better,¹ not clinically meaningful.⁴
 - Harms:^{2,5} Amyloid related imaging abnormalities (ARIA)
 - ARIA-E (brain edema): 35% versus 2.7% placebo; number needed to harm (NNH)=3.
 - ARIA-H (brain microhemorrhage): 21% versus 6.5% placebo; NNH=7.
- Lecanemab: 1795 patients.⁶ At 18 months:

- CDR-SB: 0.5 better with treatment.
- ARIA-H: 17% versus 9% placebo (NNH=13).
- ARIA-E: 13% versus 1.7% placebo (NNH=10).
- Infusion reactions: 26% versus 7.4% placebo (NNH=6).
- Stopped due to adverse events: 6.9% versus 2.9% (NNH=25).
- Donanemab: 1736 patients with early Alzheimer's (MMSE~22).⁷ At ~20 months:
 - CDR-SB: 0.7 better with treatment.
 - ARIA-E or H: 37% versus 15% placebo (NNH=5).
 - Stopped due to adverse events: 13.1% versus 4.3% (NNH=12).
 - Mortality: 1.9% versus 1.1% placebo: No statistics performed.
- Limitations: Multiple outcomes reported, often without statistical correction; other outcomes (example MMSE) missing; potential unblinding due to adverse events. Clinical importance of ARIAs is unclear. Work-up required additional investigation/ hospitalization.³
- Other RCTs demonstrate no meaningful benefit for crenezumab,⁸ solanezumab,^{9,10} and gantenerumab.¹¹
- Systematic review (14 RCTs): Amyloid-targeting medications do not improve dementia.¹²

CONTEXT

- No amyloid-targeting dementia medication currently approved in Canada.¹³
- Annual cost (not including infusion and other pre/post treatments): \$25,000-55,000 (US).^{2,13}
- Donepezil similar efficacy (1.1 MMSE improvement versus 0.6 Aducanumab), without serious harms.¹⁴

REFERENCES

1. Haeblerlein SB, Aisen PS, Barkhof F, *et al.* J Prev Alz Dis. 2022; 2(9):197-210.
2. Watt JA, Marple R, Hemmelgarn B, Straus SE. CMAJ. 2021;193:E1430-1. doi:10.1503/cmaj.211134.
3. Woloshin S, Kesselheim AS. JAMA Internal Medicine. Aug 2022; 182(8):892.
4. Andrews JS, Desai U, Kirson NY, *et al.* Alzheimers Dement. 2019; 5:354-63.
5. Salloway S, Chalkias S, Barkhof, F, *et al.* JAMA Neurol. Jan 1 2022; 79(1):13-21. doi:10.1001/jamaneurol.2021.4161.
6. van Dyck CH, Swanson CJ, Aisen P, *et al.* N Engl J Med. 2023; 388:9-21.
7. Sims JR, Zimmer JA, Evans CD, *et al.* JAMA. 2023; 330(6):512-527. doi:10.1001/jama.2023.13239.
8. Ostrowitzki S, Bittner T, Sink KM, *et al.* JAMA Neurol. 2022; 79(11):1113-1121. doi:10.1001/jamaneurol.2022.2909.
9. Honig LS, Vellas B, Woodward M, *et al.* N Engl J Med. 2018; 378:321-30.

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10. Sperling RA, Donohue MC, Raman R, *et al.* N Engl J Med. 2023; 389:1096-1107.
11. Safety and Efficacy Study of Gantenerumab in Participants With Early Alzheimer's Disease. clinicaltrials.gov (NCT03443973): Available at Clinicaltrials.gov. Accessed Dec 14, 2023.
12. Ackley SF, Zimmerman SC, Brenowitz WD, *et al.* BMJ. 2021; 372:n156. doi:http://dx.doi.org/10.1136/bmj.n156.
13. Watt JA, Isaranuwachai W, Grossman L, Straus SE. CMAJ. Oct 30 2023; 195:E1446-8.
14. Birks JS, Harvey RJ. Cochrane Database Syst Rev. 2018; Issue 6. Art. No.: CD001190. doi: 10.1002/14651858.CD001190.pub3.

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