Long-term Effects of Cholinesterase Inhibitors on Cognitive Decline and Mortality

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Study Question
Does the cognitive benefit of cholinesterase inhibitors (ChEIs) used in routine settings persist over the long term in patients with Alzheimer dementia (AD) and is their use associated with decreased risk of severe dementia and death?

What Is Known and What This Paper Adds
Few studies have examined long-term cognitive outcomes for ChEI-treated patients. This study provides Class III evidence that for patients with AD, ChEIs decrease long-term cognitive decline and risk of death, and that galantamine decreases the risk of severe dementia.

Methods
For this retrospective cohort study, data from the Swedish Dementia Registry were used to assemble a cohort of 11,652 patients with AD who initiated ChEI treatment ≤3 months after their AD diagnoses and a cohort of 5,826 patients who did not take ChEIs. Patient registration occurred between 2007 and 2017, and follow-up data were available up to October 2018, that is up to 5 years. Propensity scores were used to match each nonuser of ChEIs to 2 ChEI users. The 2 cohorts were compared in terms of cognitive trajectory (as measured with the Mini-Mental State Examination [MMSE]) using mixed-effects repeated-measures models, and the risks of death or severe dementia (MMSE <10) were analyzed using Cox proportional-hazards models.

Results and Study Limitations
Relative to the nonusers, ChEI users had slower annual MMSE score declines (mean difference, 0.13 points/y; 95% confidence interval [CI], 0.06–0.20 points/y). ChEI users also had lower risks of death (hazard ratio [HR], 0.73; 95% CI, 0.69–0.77). Galantamine users in particular had lower risks of death and severe and enjoyed the greatest decreases in cognitive decline rates. These findings are Class III evidence that ChEI usage reduces long-term cognitive decline and mortality risks for patients with AD. The present study’s limitations include high attrition rates, the possibility of ChEI users discontinuing ChEI usage, and a focus on Sweden, which may limit generalizability to dissimilar countries.

Study Funding and Competing Interests
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Table Treatments Effects of Galantamine

<table>
<thead>
<tr>
<th>Outcome metric</th>
<th>Outcome value (95% CI) for galantamine users</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR for mortality</td>
<td>0.71 (0.65–0.76)</td>
</tr>
<tr>
<td>HR for severe dementia</td>
<td>0.69 (0.47–1.00)</td>
</tr>
<tr>
<td>Reduction in MMSE score declines</td>
<td>0.18 points/y (0.07–0.28 points/y)</td>
</tr>
</tbody>
</table>

Outcomes for galantamine users when compared with matched nonusers of ChEIs.
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