### ADVERSE EFFECTS

**Sympathetic Adverse Effects**

- Adverse effects of cholinesterase inhibitors used in Alzheimer’s disease include cardiac disorders (bradycardia, conduction disorders) that can cause malaise and syncope.
- A cohort study compared 20,000 patients who received a cholinesterase inhibitor for dementia with a control group of untreated dementia patients. Cholinesterase inhibitor therapy was associated with statistically significant increases in hospitalisations for syncope or bradycardia, pacemaker insertion, and hip fracture.
- In practice, cholinesterase inhibitors have little more than a placebo effect and do not justify exposing patients to these risks.

### Syncope with Cholinesterase Inhibitors

Three cholinesterase inhibitors, donepezil, galantamine and rivastigmine, are widely used as symptomatic treatment for Alzheimer’s disease (1-3). Yet their efficacy is minimal and transient, and none of these drugs has been shown to prevent disease progression (1).

**Bradycardia with syncope.** The adverse effects of these drugs include cardiac disorders (bradycardia and conduction disorders) that can cause malaise and syncope. The risk is increased by coadministration of drugs that reduce their elimination or provoke the same adverse effects (a)(3).

The risks of bradycardia and syncope associated with cholinesterase inhibitors were expected on the basis of their pharmacological properties and confirmed by pharmacovigilance studies (4). A 2009 case-control study showed that the risk of bradycardia in patients receiving cholinesterase inhibitors was not adequately taken into account: more than half of the patients treated with these drugs who were admitted to hospital for bradycardia were retreated with the same drug class after discharge (5,6).

**Hospitalisation, Pacemaker Insertion, Fractures.** A Canadian cohort study conducted from April 2002 through March 2004 analysed data concerning 19,803 patients aged at least 66 years who had received donepezil, galantamine or rivastigmine for dementia, and 61,499 untreated controls with dementia (7). There was a statistically significant increase in hospitalisation for syncope among patients who received a cholinesterase inhibitor (3.15 versus 18.6 events per 1000 person-years; adjusted relative risk 1.76; 95% confidence interval (95% CI) 1.57 to 1.98), as well as hospitalisation for bradycardia (6.9 versus 4.4 per 1000 person-years; adjusted relative risk 1.69; 95% CI: 1.32 to 2.15) (7).

Serious consequences of syncope and bradycardia were more frequent in the patients who received a cholinesterase inhibitor, in terms of pacemaker insertion (4.7 versus 3.3 per 1000 person-years; adjusted relative risk 1.49; 95% CI: 1.12 to 2.00) and hip fracture (22.4 versus 19.8 per 1000 person-years; adjusted relative risk 1.18; 95% CI 1.04 to 1.34) (7).

In practice: avoid cholinesterase inhibitors. The minimal benefits of cholinesterase inhibitors, beyond a placebo effect, do not justify exposing patients to the risk of syncope and bradycardia, and their consequences (pacemaker insertion, hip fracture). These drugs should simply be avoided and the emphasis placed on non-drug management, however difficult.

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**Selected references from Prescrire’s literature search.**

5. Prescrire Editorial Staff “Bradycardia due to cholinesterase inhibitors: identify adverse effects and take them into account” Prescrire Int 2011; 30 (115): 95.