Syncope and Its Consequences in Patients With Dementia Receiving Cholinesterase Inhibitors

A Population-Based Cohort Study

Sudeep S. Gill, MD, MSc; Geoffrey M. Anderson, MD, PhD; Hadas D. Fischer, MD; Chaim M. Bell, MD, PhD; Ping Li, PhD; Sharon-Lise T. Normand, PhD; Paula A. Rochon, MD, MPH

Background: Cholinesterase inhibitors are commonly prescribed to treat dementia, but their adverse effect profile has received little attention. These drugs can provoke symptomatic bradycardia and syncope, which may lead to permanent pacemaker insertion. Drug-induced syncope may also precipitate fall-related injuries, including hip fracture.

Methods: In a population-based cohort study, we investigated the relationship between cholinesterase inhibitor use and syncope-related outcomes using health care databases from Ontario, Canada, with accrual from April 1, 2002, to March 31, 2004. We identified 19,803 community-dwelling older adults with dementia who were prescribed cholinesterase inhibitors and 61,499 controls who were not.

Results: Hospital visits for syncope were more frequent in people receiving cholinesterase inhibitors than in controls (31.5 vs 18.6 events per 1000 person-years; adjusted hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.57-1.98). Other syncope-related events were also more common among people receiving cholinesterase inhibitors compared with controls: hospital visits for bradycardia (6.9 vs 4.4 events per 1000 person-years; HR, 1.69; 95% CI, 1.32-2.15), permanent pacemaker insertion (4.7 vs 3.3 events per 1000 person-years; HR, 1.49; 95% CI, 1.12-2.00), and hip fracture (22.4 vs 19.8 events per 1000 person-years; HR, 1.18; 95% CI, 1.04-1.34). Results were consistent in additional analyses in which subjects were either matched on their baseline comorbidity status or matched using propensity scores.

Conclusions: Use of cholinesterase inhibitors is associated with increased rates of syncope, bradycardia, pacemaker insertion, and hip fracture in older adults with dementia. The risk of these previously underrecognized serious adverse events must be weighed carefully against the drugs' generally modest benefits.

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symptomatic bradycardia and syncope if these drugs are not recognized as potential precipitants of the episode. Furthermore, syncope can lead to fall-related injuries, including hip fractures. Patients with dementia who sustain hip fractures are at high risk of subsequent functional decline, institutionalization, and death.

It remains unclear how often drug-induced syncope and its consequences occur in older adults with dementia who are seen in routine clinical practice; many of these people were ineligible to participate in the RCTs evaluating cholinesterase inhibitors. The few postmarketing studies available on this topic are limited by small sample size. We therefore undertook a large, population-based cohort study to determine the relationship between cholinesterase inhibitor use and a spectrum of interrelated events, including hospital visits for (1) syncope, (2) bradycardia, (3) permanent pacemaker insertion, and (4) hip fracture. To demonstrate the consistency of our findings, we conducted secondary analyses in which drug users and control subjects were either matched according to the number of comorbid conditions they possessed or matched using propensity scores. To demonstrate the specificity of our findings for syncope-related outcomes, we also performed analyses to ensure the absence of any significant association between cholinesterase inhibitor use and 2 outcomes that were unlikely to be affected by exposure to these drugs (ie, pulmonary embolism and cataract extraction).

## METHODS

### DATA SOURCES

During the period of this study, Ontario, Canada, had a population of approximately 12 million people, of whom 1.4 million were 65 years or older. A universally funded health care program in Ontario covers nearly all physician services, medications, and hospital services for these seniors. Five administrative health care databases that track this population were linked to develop the study cohort. These databases included pharmacy records from the Ontario Drug Benefit program (ODB), emergency department records from the National Ambulatory Care Reporting System (NACRS), hospitalization records from the Canadian Institute for Health Information Discharge Abstract Database (DAD), physician billing information for inpatient and outpatient services from the Ontario Health Insurance Plan (OHIP), and basic demographic information and vital statistics from the Registered Persons Database (RPDB). Encrypted unique identifiers that are common between databases were used to link anonymous information on demographics and health services utilization for patients in our study. There is little basic information on patients missing in these databases because of administrative requirements. For example, the coding accuracy and completeness of drug claims in the ODB database is excellent, with an error rate of only 0.7%. The study was approved by ethics review boards at Sunnybrook Health Sciences Centre and Queen’s University.

### COHORT ASSEMBLY

We identified all Ontario residents aged 66 years or older with a prior diagnosis of dementia from April 1, 2002, through March 31, 2004. From this pool of subjects, we defined 2 cohorts: those who were new users of cholinesterase inhibitors and those who had not received any cholinesterase inhibitor prescriptions in the year prior to cohort entry. Cohort entry was defined as the date of the first dispensed cholinesterase inhibitor. Controls were required to have contact with a physician within the 3 months prior to cohort entry to ensure that they had access to health services. In addition, the control cohort was matched to the drug cohort by year and quarter of cohort entry to ensure that the cohorts were contemporaneous. We included only new users of cholinesterase inhibitors to reduce the potential for selection bias. Three drugs in this class are available through the ODB (donepezil, galantamine, and rivastigmine). Other dementia medications, including tacrine hydrochloride and memantine hydrochloride, were not licensed for use in Canada during the period of this study. Health Canada approved memantine in November 2004, and tacrine never received approval.

To improve comparability of the 2 cohorts, subjects had to meet the following 3 restriction criteria at the time of cohort entry: (1) evidence of a dementia diagnosis recorded in OHIP or DAD within the past 5 years, (2) community-dwelling status (ie, not residing in a long-term care facility at baseline), and (3) no hospitalizations for syncope within the past year. We excluded long-term care residents because we felt they might have different patterns of health services utilization (such as receiving on-site care for episodes of syncope rather than visiting a hospital). We excluded subjects with episodes of syncope in the past year to increase the likelihood that cholinesterase inhibitor use was the primary precipitant of outcomes following cohort entry.

### DRUG EXPOSURE AND DISCONTINUATION

We assumed that treatment with a cholinesterase inhibitor was discontinued and censored follow-up if the patient did not refill their prescription within 120 days of the prescription’s dispensation date. The ODB plan permits a maximum drug dispensation of 100 days’ supply, and prescriptions written for longer periods have the remaining days converted by the dispensing pharmacist into refills. Few patients were observed to switch from one cholinesterase inhibitor to another during the period of this study, and we did not examine outcomes for individual cholinesterase inhibitors.

### OUTCOMES

We examined first hospital visits for syncope (International Classification of Diseases and Related Health Problems, 10th Revision, Canada [ICD-10], code R35), as recorded in either the NACRS (ie, emergency department visits) or DAD (ie, hospital admissions). Preliminary data suggested that approximately 60% of patients assessed in emergency departments for syncope were not subsequently admitted to hospital, suggesting that reliance on hospital admission data alone would lead to an under-recognition of the true event rate. Other investigators have used similar approaches to identify episodes of syncope. Only the first hospital visit for syncope was counted as an event for patients who experienced recurrent syncope.

We also examined several related outcomes (Figure): hospital visits for bradycardia or complete atrioventricular block (ICD-10 codes R00.1 and I44.2), permanent pacemaker insertion (identified using DAD Canadian Classification of Health Interventions [CCI] codes), and hip fracture (ICD-10 codes S72.0, S72.1, S72.2, and S72.9). Hip fractures were excluded if they were pathological, associated with trauma, or associated with epilepsy. Bradycardia and atrioventricular block are potential mechanisms by which cholinesterase inhibitors can precipitate syncope, whereas pacemaker insertion and hip fracture are potential consequences of syncope. Other studies have used simi-
lar methods to examine the relationship between drug use and pacemaker insertion. The ICD-10 coding for hip fracture and the CCI coding for medical procedures in the DAD have been shown to be reliable sources of information with very high positive predictive values when validated against reabstracted health records.39

STATISTICAL ANALYSIS

We first calculated event rates for the cohorts, using the number of events per 1000 person-years for the 4 outcomes (syncope, bradycardia, permanent pacemaker insertion, and hip fracture). We conducted time-to-event analyses using Cox proportional hazards models to derive hazard ratios (HRs) and 95% confidence intervals (CIs) for each of the outcomes in cholinesterase inhibitor users vs control subjects. With each of these outcomes examined in a separate analysis, patients were observed until they experienced the outcome event of interest, discontinued drug therapy (for those in the drug cohort), initiated drug therapy (for those in the control cohort), died, or reached the end of the follow-up period (March 31, 2004). The proportional hazards assumption was confirmed in each model using an interaction term between the independent variable and time. Analyses were performed using SAS statistical software for UNIX (version 9.1; SAS Institute, Cary, North Carolina).

PRIMARY ANALYSIS

For each of the 4 outcomes we used risk adjustment to account for differences in baseline risk. The covariates in our models included factors that would influence the development of or recognition of syncope or the related outcomes. For the syncope and bradycardia outcomes, the covariates included demographic factors (such as age and sex), use of antiarrhythmic drugs or other drugs with negative chronotropic effects, presence of coronary artery disease, aortic stenosis, atrial fibrillation or other cardiac conduction disorders, previous insertion of a permanent pacemaker or implantable cardioverter defibrillator, and the Charlson comorbidity index score.39 For the pacemaker outcome, covariates included demographic factors, use of antiarrhythmic drugs or other drugs with negative chronotropic effects, and the presence of atrial fibrillation or other cardiac conduction disorders. For the pacemaker outcome, we excluded subjects who had previously received a permanent pacemaker or implantable cardioverter defibrillator. For the hip fracture outcome, covariates included demographic factors, the Charlson comorbidity index score, history of hip fracture, and use of drugs that influence fracture risk (hormone replacement therapy; bisphosphonates; raloxifene hydrochloride; thiazide diuretic agents; steroids; benzodiazepines; and anticonvulsant, antidepressant, antipsychotic, and antiparkinsonian agents).

To assess the possibility of biased ascertainment of outcomes, we compared the number of emergency department visits in the year prior to cohort entry made by new users of cholinesterase inhibitors with those made by controls.

ADDITIONAL ANALYSES

To demonstrate the consistency of our findings, we conducted several complementary analyses. We reanalyzed our results by matching subjects from the drug cohort with up to 3 individuals from the control cohort. Matching was based on the burden of comorbid disease as measured by a modified version of the Charlson comorbidity index that excluded the point for presence of dementia. Subjects were matched on having 0, 1, or 2 or more points on this modified comorbidity index.

RESULTS

We developed a third set of results by matching subjects using a propensity score. The propensity score is the probability of receiving treatment for an individual with specific prognostic factors. It is a scalar summary of all observed confounders. The rationale and methods underlying the use of propensity scores are detailed elsewhere.31,32 We computed a propensity score for new receipt of a cholinesterase inhibitor by developing a logistic regression model with 34 covariates describing patient characteristics. Covariates were selected based on guidance from recent studies.33,34 Table 1 lists many of the characteristics included in the propensity score. After an assessment of the balance of measured covariates between cholinesterase inhibitor users and non-user controls, we used the resulting predicted probabilities as propensity scores and matched each drug user with up to 3 controls. Matching involved a caliper width (ie, interval for successful match) of 0.6 of the standard deviation of the log odds of the propensity score. This method has been demonstrated to remove approximately 90% of the bias from measured confounders.35

Finally, to assess the specificity of our findings we examined the associations between cholinesterase inhibitor use and either subsequent hospitalization for pulmonary embolism (ICD-10 codes I26.x) or subsequent cataract extraction (OHIP ophthalmologist procedure code E140). The goal was to confirm the absence of associations where none would be plausibly expected. Confirming negative findings in these analyses provides support for the notion that the cholinesterase inhibitor users and controls in our study were similar in terms of their access to care (eg, cataract extraction) and vulnerability to unrelated diseases (eg, pulmonary embolism).

For the primary analysis, we identified 19803 new users of cholinesterase inhibitors (13641 receiving donepezil; 3448, galantamine; and 2714, rivastigmine) and 61499 control subjects. The 2 cohorts had comparable baseline characteristics (Table 1), including similar proportions with pacemaker insertions in the 5 years prior to cohort entry (1.6% of drug cohort vs 1.8% of controls). Emergency department utilization in the year prior to cohort entry was also similar in the cholinesterase inhibitor and control cohorts (Table 2).

Hospital visits for syncope were more frequent in people receiving cholinesterase inhibitors than in controls (31.5 vs 18.6 events per 1000 person-years; adjusted HR, 1.76; 95% CI, 1.57-1.98). Syncope-related outcomes were also more common among people receiving cholinesterase inhibitors compared with controls: hospital visits for bradycardia (6.9 vs 4.4 events per 1000 person-years; HR, 1.69; 95% CI, 1.32-2.15), permanent pacemaker insertion (4.7 vs 3.3 events per 1000 person-
years; HR, 1.49; 95% CI, 1.12-2.00), and hip fracture (22.4 vs 19.8 events per 1000 person-years; HR, 1.18; 95% CI, 1.04-1.34) (Table 3).

In the comorbidity-matched analyses, 14324 drug users (72.3%) were each matched to 3 control subjects, and the remaining 5479 drug users were each matched...
to 2 controls. In these analyses conducted with subjects matched on their baseline burden of comorbid disease, results were consistent with those in the primary analysis (Table 4).

In the analysis involving propensity-based matching, 12,891 drug users (65.1%) were each matched to 4 control subjects, 6811 drug users (34.4%) were matched to 2 controls, and the remaining 101 drug users (0.5%) were each matched to 1 control. Propensity-based matching produced results that were consistent with those from the primary analysis and comorbidity-based matching (Table 4).

We confirmed the absence of any relationship between cholinesterase inhibitor use and the 2 outcomes we anticipated would be unrelated to drug use. Specifically, cholinesterase inhibitor use was not significantly associated with either subsequent hospitalization for pulmonary embolism (HR, 0.97; 95% CI, 0.55-1.72) or subsequent cataract extraction (HR, 1.00; 95% CI, 0.91-1.10).

### Table 4. Outcomes From Additional Analyses (Matching on Comorbidity Scores or Propensity Scores)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Matching on Comorbidity Scores</th>
<th>Matching on Propensity Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>Unadjusted (HR) 1.71 (1.49-1.96)</td>
<td>Adjusted (HR) 1.81 (1.57-2.10)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Unadjusted (HR) 1.72 (1.27-2.32)</td>
<td>Adjusted (HR) 2.08 (1.47-2.96)</td>
</tr>
<tr>
<td>Permanent pacemaker insertion(d)</td>
<td>Unadjusted (HR) 1.57 (1.10-2.23)</td>
<td>Adjusted (HR) 1.72 (1.17-2.54)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>Unadjusted (HR) 1.20 (1.03-1.39)</td>
<td>Adjusted (HR) 1.21 (1.03-1.43)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

d Up to 3 control cohort subjects matched to each drug cohort subject, with matching based on comorbidity score (0, 1, or ≥2 points).

Our findings are generally consistent with the limited published research on this topic. Schneider suggested that drug-related syncope might lead to more injuries in people prescribed cholinesterase inhibitors; our results now bolster these suspicions. The risk of syncope found in our study is similar to results of a review by Birks of RCTs (odds ratio [OR], 1.90; 95% CI, 1.09-3.33). However, the review’s wider CI reflects the fact that data on syncope were pooled from 5 RCTs with a total of only 2206 subjects. Similar limitations affect the risks presented for accidental injury (OR, 1.35; 95% CI, 0.86-2.10) and fracture (OR, 0.96; 95% CI, 0.53-1.74) in the review by Birks. Although these risks seem insignificant, imprecise estimates were unavoidable in this review because data could only be pooled from the few trials reporting on these outcomes. Thus, the overall number of events was small. Vandenbroucke and Psaty highlight the many challenges of assessing harm in meta-analyses of RCTs. Newer RCTs not yet included in Birks’ review also involve too few adverse events to permit definitive conclusions, but some of these trials have reported a slight excess of accidental injuries and fractures in subjects receiving cholinesterase inhibitor treatment. Few postmarketing studies have been published on this topic, and most represent small case series or case reports. As a result, many clinicians do not recognize the potential for syncope-related adverse events with these drugs, and prescribing patterns vary widely in patients with cardiovascular conditions.

Cholinesterase inhibitors are thought to work by reducing inactivation of the neurotransmitter acetylcholine, thereby increasing its activity in the synaptic cleft. This action is not limited to the central nervous system; well-documented peripheral cholinergic effects include nau-

**COMMENT**

This population-based study identifies increased risks of syncope, bradycardia, permanent pacemaker insertion, and hip fracture in community-dwelling older adults who received cholinesterase inhibitors. To our knowledge, this is the first large study to focus on the risk of syncope with these commonly prescribed medications, and the first to document a link to pacemaker insertion and hip fracture. Although our study is observational, the relationships we found are biologically plausible, the cohorts were comparable at baseline, the results were consistent in the primary analysis and 2 sets of matched analyses, and we confirmed the absence of potentially spurious associations with unrelated outcomes.

The impact of these adverse events on patient outcomes merits serious concern for several reasons. First, emergency department assessments and hospitalizations are costly and expose cognitively impaired older patients to further risks. Second, the prognosis following hip fracture in older patients with dementia is grim. Finally, although the retrospective nature of our study did not allow us to judge the appropriateness of individual procedures, RCTs have questioned the role of pacemaker insertion to treat neurocardiogenic syncope. This invasive procedure can involve serious complications, including venous thrombosis, pericardial tamponade, and infection. We speculate that bradycardia and further episodes of syncope might have been prevented in some subjects if their cholinesterase inhibitors had been discontinued. As a result of these multiple consequences of syncope, the impact of cholinesterase inhibitor treatment on overall health care costs may be currently underestimated, and the cost-effectiveness of these drugs remains debatable. Prescription of cholinesterase inhibitors is steadily rising in many countries, in part owing to expanding indications, including severe Alzheimer disease and non-Alzheimer dementia. Despite the fact that RCTs have failed to establish benefits from the use of these drugs to treat mild cognitive impairment, many physicians report prescribing them off-label for patients with this condition.

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Many patients in our study assume syncope is exclusively the result of exposure to a cholinesterase inhibitor. Many older adults with dementia are particularly susceptible to syncope and fall-related injuries; Kenny et al found that neurocardiovascular instability is highly prevalent in this population, and treatment with cholinesterase inhibitors may worsen these deficits.

Physicians caring for people with dementia should be alert to the risks we document herein. Treatment decisions need to be individualized and should involve a discussion with patients and their caregivers about the expected benefits and potential risks of treatment. In clinical practice, syncope represents a common presenting symptom that can be provoked by many conditions. Clinicians evaluating a patient with syncope should be open to the possibility that several potential contributors could exist, and they should not immediately assume syncope is exclusively the result of exposure to a cholinesterase inhibitor. Many patients in our study had additional risk factors for syncope. Clinicians must also appreciate that drug-induced syncope does not always occur immediately after treatment with the drug is started. The timing of adverse events relative to initiation of cholinesterase inhibitor treatment may be influenced by several factors, including the slow upward dose titration commonly recommended for these drugs, potential drug-drug interactions, and periodic development of other factors (such as hypovolemia) that might contribute to neurocardiogenic syncope.

Our study has potential limitations. First, all observational studies are vulnerable to residual confounding and hidden bias. Although we used a variety of techniques to assess for these possibilities, we cannot rule out residual confounding by unknown or unmeasured factors. Our ability to control for differences in the cohorts was limited to the variables recorded in the administrative databases. Nonetheless, observational studies that focus on unrecognized adverse drug effects often provide credible results. Second, we did not compare event rates for individual cholinesterase inhibitors, but the 3 drugs we studied are thought to possess similar benefits and risks. Third, we did not examine dose-response relationships, in part because these drugs are started at low doses and only gradually increased to target doses. Fourth, the only fall-related injury we examined was hip fracture. Further research is required to determine associations between drug exposure and other fall-related injuries including fractures at other sites, closed head injuries, and motor vehicle crashes. Finally, we excluded patients with a recent history of syncope to make it more likely that the drugs were the main contributor to events following cohort entry. Further research is needed to establish the safety of these drugs in patients with prior syncopal episodes.

Additional research is needed to confirm our findings. The best approach may require combining evidence from RCTs and observational studies because many RCTs provide inadequate data on adverse events. Older adults with dementia are vulnerable to adverse drug effects, and future RCTs evaluating treatments targeted to this population should therefore provide comprehensive documentation of common and serious outcomes such as falls (syncopal or otherwise) and injuries.

In conclusion, use of cholinesterase inhibitors is associated with increased rates of syncope, bradycardia, pacemaker insertion, and hip fracture in older adults with dementia. The risk of these previously underrecognized serious adverse events must be carefully weighed against the drugs’ generally modest benefits.
stry of Health and Long-term Care, the Institute for Clinical Evaluative Sciences, or the funding sources is intended or should be inferred.

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REFERENCES