# Initial Cholinesterase Inhibitor Therapy Dose and Serious Events in Older Women and Men

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**OBJECTIVES:** To examine dose-related prescribing and short-term serious events associated with initiation of cholinesterase inhibitor (ChEI) therapy.
**DESIGN:** Retrospective, population-based cohort study.
**SETTING:** Ontario, Canada.
**PARTICIPANTS:** Women (n=47,829) and men (n=32,503) aged 66 and older who initiated a ChEI between April 1, 2010, and June 30, 2016.
**MEASUREMENTS:** All-cause serious events (emergency department (ED) visits, inpatient hospitalizations, death) within 30 days of ChEI initiation. Multivariable Cox proportional hazards models were used to estimate adjusted rates of serious events.
**RESULTS:** Overall, 4.8% of older adults were dispensed a lower-than-recommended ChEI starting dose, 87.9% a recommended dose, and 7.3% a higher-than-recommended starting dose. Eight thousand six hundred seventy-one (10.8%) individuals experienced a serious event within 30 days of initiating therapy, primarily ED visits (8,540, 10.6%). Relative to those initiated on a recommended starting dose, those initiated on a higher dose had a significantly increased rate of serious events (women adjusted hazard ratio (aHR) 1.50, 95% confidence interval (CI) =1.38–1.63; men aHR 1.31, 95% CI=1.19–1.45). Similar patterns were found for ED visits and inpatient hospitalizations but not death. The relative effect of higher-than-recommended starting dose dispensed vs. recommended starting dose dispensed was greater in women than it was in men: the number needed to harm was 22 (95% confidence interval (CI)=18–29) for women and 36 (95% CI= 26–61) for men.
**CONCLUSION:** Serious events immediately after initiation of ChEIs were associated with starting ChEI dose. This association was stronger in women. **J Am Geriatr Soc 66:1692–1699, 2018.**

**Key words: cholinesterase inhibitors; dose; serious events; women and men**

Globally, almost 50 million people live with dementia.[1] Cholinesterase inhibitors (ChEIs) are some of the only medications approved for the symptomatic management of Alzheimer's disease and related dementias. Accordingly, ChEI therapies are widely used despite evidence of limited efficacy[2–4] and known adverse events,[2] including gastrointestinal problems (abdominal pain, diarrhea, nausea, vomiting, anorexia, weight loss[2]), syncope, and dizziness.[5]

The adage "start low and go slow"[6] is a prescribing strategy accepted in geriatric medicine to minimize adverse events that individuals starting a new drug therapy experience because adverse events are often dose related and usually occur soon after drug initiation.[7] Despite this, randomized controlled trials, including those for ChEIs, seldom report dose-related risk of drug therapy.[8] Consequently, appropriate dose-related considerations are lacking in drug prescribing

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See related Editorial by Holly M. Holmes and Rajender R. Aparasu

DOI: 10.1111/jgs.15442



0002-8614/18/$15.00

guidelines, low doses of drugs are not manufactured, and older adults often split their pills to achieve the desired low dose.[9] The importance of "start low and go slow" may be magnified when prescribing for older women[6] because they are thought to be at greater risk of adverse events than men.[10,11]

Despite wide-spread use of ChEIs over 2 decades, little is known about the short-term effects of serious events associated with their initiation or how appropriate initial dose selection and consideration of sex differences may mitigate these events. We examined dose-related prescribing and short-term serious events associated with initiation of ChEI therapy in a large population-based cohort of older adults with dementia.

## METHODS

This was a population-based retrospective cohort study using administrative healthcare data from Ontario, Canada. Nine databases were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (Supplementary Appendix S1).

The Research Ethics Board of Sunnybrook Health Sciences Centre approved the study. This manuscript adheres to the Strengthening The Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies.[12]

We created a cohort of all community-dwelling Ontario residents aged 66 and older with dementia who were newly dispensed an oral ChEI (donepezil, galantamine, rivastigmine) between April 1, 2010, and June 30, 2016. New use was defined as the first ChEI dispensing date (index) in the accrual window and no ChEI in the 2 years before index. We used a validated administrative data algorithm based on diagnoses in hospital and physician records and prescription drug claims[13] to identify individuals with prevalent dementia.

Donepezil, the first ChEI on the market, was approved in 1996[14] and has been available for more than 20 years.[14,15] Rivastigmine and galantamine are also approved for use in Ontario.

### Exposure: ChEI Dose

To examine the effect of initial dose on subsequent serious events, we calculated the daily dose of each new ChEI dispensed as a function of quantity of drug dispensed and strength. For example, the exposure of an individual dispensed a 7-day supply of 5-mg donepezil tablets and given 14 tablets is 10 mg/d of donepezil (5 mg twice a day). This approach has been used in prior studies.[16]

Three mutually exclusive starting dose categories were defined for each ChEI (Supplementary Appendix S2): lower than recommended, recommended, or higher than recommended.

### Outcome Measure: Serious Event

The primary outcome was any serious event occurring within 30 days of initiation of a ChEI, defined as emergency department (ED) visit, inpatient hospitalization, or death. Each event was analyzed separately as a secondary outcome.

This serious event definition was based on the guidelines in the International Conference on Harmonization (ICH) Clinical Safety Data Management: Definitions and Standards for Expedited Reporting[17] and has been used in our previous research.[18,19] The ICH defined a serious event as one that results in death, is life threatening, requires hospital admission, prolongs a hospital stay, or leads to persistent disability or incapacity. Our cohort was community dwelling, so prolonged hospitalization was not relevant. We extended the definition to include ED visits because these encounters often lead to hospital admissions and are serious events on their own.

In supporting analyses, we stratified serious events into "known" (previously reported) ChEI-related serious events and "other" serious events based on *International Classification of Diseases, Tenth Revision*, diagnosis codes for hospital and ED visits and Ontario Health Insurance Plan physician diagnosis codes (Supplementary Appendix S3).

The characteristics of our study cohort are described in Supplementary Appendix S4.

### Statistical Analyses

We examined the distribution of all baseline covariates between women and men and examined outcomes according to sex. We used a standardized difference (SDIF) of 0.10 (10%) to reflect an imbalance between groups.[20,21]

We used multivariable Cox proportional hazards models to examine the effects of ChEI dose on the outcome of any serious event and estimated the models separately in men and women. For all analyses, the recommended starting dose group was the reference, and individuals were censored on the date they changed the type of ChEI, or on the date they were prescribed a ChEI exceeding the highest recommended dose, or at the end of the 30-day follow-up period. ChEI use was measured as a time-dependent exposure. We measured the dose and duration of the prescribed drug dispensed to each individual during follow-up. If a new prescription was dispensed, we calculated and assigned a new dose for the individual.

Given recent guidelines highlighting the importance of examining drug outcomes according to sex, the primary focus was on sex-specific analyses, so all regression models were stratified according to sex. We used an iterative approach to identify relevant covariates for each model. Covariates that changed the effect size (hazard ratio) for the primary outcome by 2% or more were included in our final models.

Because we were interested in comparing sex interactions between women and men for each dose category (lower than recommended vs recommended, higher than recommended vs recommended), we used the beta coefficients and standard errors in the earlier sex-stratified models, used a z-test, and calculated 95% confidence intervals (CIs). The recommended starting dose was the reference.

Number needed to harm (NNH) was evaluated by taking the inverse of the absolute risk difference between the exposure groups (recommended starting dose as the reference). The 95% CI was calculated using a bootstrap method.[22]

Analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

**Table 1. Baseline Characteristics of Older Women and Men with Dementia Initiated on a Cholinesterase Inhibitor (ChEI)**

| Characteristic | Overall, N = 80,332 | Women, n = 47,829 | Men, n = 32,503 | Standardized Difference |
|---|---|---|---|---|
| ChEI type, n (%) | | | | |
| Donepezil | 62,091 (77.3) | 37,192 (77.8) | 24,899 (76.6) | 0.03 |
| Galantamine | 15,192 (18.9) | 9,090 (19.0) | 6,102 (18.8) | 0.01 |
| Rivastigmine | 3,049 (3.8) | 1,547 (3.2) | 1,502 (4.6) | 0.07 |
| ChEI dose, n (%) | | | | |
| Lower than recommended starting dose | 3,871 (4.8) | 2,675 (5.6) | 1,196 (3.7) | 0.09 |
| Recommended starting dose | 70,628 (87.9) | 41,851 (87.5) | 28,777 (88.5) | 0.03 |
| Higher than recommended starting dose | 5,833 (7.3) | 3,303 (6.9) | 2,530 (7.8) | 0.03 |
| Demographic | | | | |
| Age, mean ± standard deviation | 81.49 ± 6.57 | 82.02 ± 6.60 | 80.71 ± 6.44 | 0.20 |
| Low income, n (%) | 17,554 (21.9) | 12,477 (26.1) | 5,077 (15.6) | 0.26 |
| Urban residence, n (%) | 70,170 (87.3) | 42,118 (88.1) | 28,052 (86.3) | 0.05 |
| Time since first dementia documentation, n (%) | | | | |
| 0 days (diagnosed at cohort entry) | 46,292 (57.6) | 27,303 (57.1) | 18,989 (58.4) | 0.03 |
| 1–179 days | 17,035 (21.2) | 10,354 (21.6) | 6,681 (20.6) | 0.03 |
| 180–364 days | 4,606 (5.7) | 2,767 (5.8) | 1,839 (5.7) | 0.01 |
| 1–2 years | 4,412 (5.5) | 2,735 (5.7) | 1,677 (5.2) | 0.02 |
| ≥2 years | 7,987 (9.9) | 4,670 (9.8) | 3,317 (10.2) | 0.01 |
| Comorbidity (1-year look-back), n (%) | | | | |
| Aggregated diagnosis groups | | | | |
| 0–4 | 9,805 (12.2) | 6,418 (13.4) | 3,387 (10.4) | 0.09 |
| 5–9 | 35,411 (44.1) | 21,430 (44.8) | 13,981 (43.0) | 0.04 |
| ≥10 | 35,116 (43.7) | 19,981 (41.8) | 15,135 (46.6) | 0.10 |
| Chronic conditions | | | | |
| Acute myocardial infarction | 2,543 (3.2) | 1,282 (2.7) | 1,261 (3.9) | 0.07 |
| Asthma | 3,516 (4.4) | 2,250 (4.7) | 1,266 (3.9) | 0.04 |
| Angina pectoris | 1,315 (1.6) | 634 (1.3) | 681 (2.1) | 0.06 |
| Arrhythmia | 1,663 (2.1) | 792 (1.7) | 871 (2.7) | 0.07 |
| Cancer | 4,817 (6.0) | 2,233 (4.7) | 2,584 (8.0) | 0.14 |
| Diabetes mellitus | 26,082 (32.5) | 13,981 (29.2) | 12,101 (37.2) | 0.17 |
| Congestive heart failure | 7,119 (8.9) | 3,814 (8.0) | 3,305 (10.2) | 0.08 |
| Hypertension | 50,693 (63.1) | 30,934 (64.7) | 19,759 (60.8) | 0.08 |
| Liver disease | 2,274 (2.8) | 1,247 (2.6) | 1,027 (3.2) | 0.03 |
| Renal dysfunction | 9,271 (11.5) | 4,875 (10.2) | 4,396 (13.5) | 0.10 |
| Stroke | 2,380 (3.0) | 1,149 (2.4) | 1,231 (3.8) | 0.08 |
| Mood/anxiety disorder | 23,840 (29.7) | 15,640 (32.7) | 8,200 (25.2) | 0.17 |
| Concurrent drug therapy excluding ChEIs, n (%) | | | | |
| 0 (ChEI only) | 4,754 (5.9) | 2,752 (5.8) | 2,002 (6.2) | 0.02 |
| 1–4 | 35,899 (44.7) | 21,487 (44.9) | 14,412 (44.3) | 0.01 |
| 5–9 | 32,379 (40.3) | 19,355 (40.5) | 13,024 (40.1) | 0.01 |
| ≥10 | 7,300 (9.1) | 4,235 (8.9) | 3,065 (9.4) | 0.02 |
| Drug therapy to avoid in dementia, n (%) | | | | |
| Concurrent anticholinergic with an anticholinergic risk score ≥2 | 9,114 (11.3) | 5,771 (12.1) | 3,343 (10.3) | 0.06 |
| Concurrent benzodiazepine medication | 8,029 (10.0) | 5,397 (11.3) | 2,632 (8.1) | 0.11 |
| Concurrent antipsychotic medication | 7,118 (8.9) | 4,353 (9.1) | 2,765 (8.5) | 0.02 |
| Health system use (1-year look-back), n (%) | | | | |
| Family physician visit | 76,922 (95.8) | 45,734 (95.6) | 31,188 (96.0) | 0.02 |
| Specialist physician visit (neurologist, geriatrician, psychiatrist) | 33,380 (41.6) | 19,103 (39.9) | 14,277 (43.9) | 0.08 |
| Home care service received | 24,845 (30.9) | 15,765 (33.0) | 9,080 (27.9) | 0.11 |
| Previous emergency department visit | 39,809 (49.6) | 23,404 (48.9) | 16,405 (50.5) | 0.03 |
| Previous inpatient hospitalization | 17,815 (22.2) | 9,940 (20.8) | 7,875 (24.2) | 0.08 |

## RESULTS

The cohort included 80,332 community-dwelling older adults with dementia (47,829 (59.5%) women, 32,503 (40.5%) men) (Table 1). Women were more likely than men to be older (mean age 82.0 vs 80.7, SDIF = 0.20) and eligible for a low-income subsidy on their drug coverage (26.1% vs 15.6%, SDIF=0.26). More than half (57.1% women, 58.4% men, SDIF = 0.03) had their first documentation of dementia at the time ChEI therapy was initiated.

The most frequently dispensed ChEI was donepezil (77.8% women, 76.6% men), followed by galantamine (19.0% women, 18.8% men) and rivastigmine (3.2%

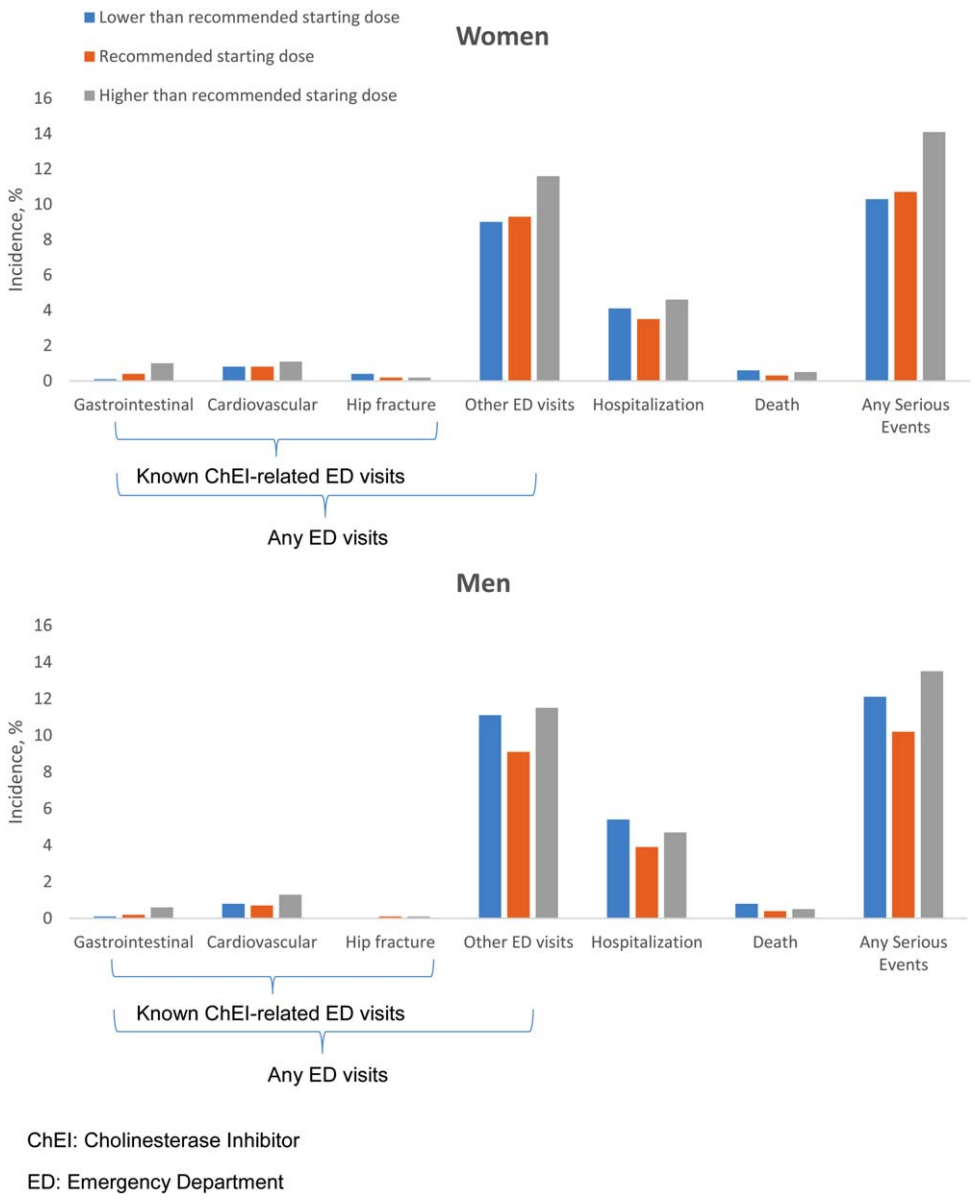


**Figure 1.** Distribution of any serious event within 30 days of cohort entry according to sex.

women, 4.6% men). The majority (87.5% women, 88.5% men) were dispensed these therapies at the recommended starting dose. Overall, 4.8% of older adults were dispensed a ChEI at a lower-than-recommended starting dose (5.6% women, 3.7% men) and 7.3% a higher-than-recommended starting dose (6.9% women, 7.8% men).

Concurrent use of drug therapy was common, with 49.4% of women and 49.5% of men receiving 5 or more concurrent drug therapies. Concurrent dispensing of drug therapies that should be avoided in dementia was also frequent. Women received concurrent benzodiazepines more frequently than men (11.3% vs 8.1%, SDIF=0.11).

## Risk of Serious Events

Eight thousand six hundred seventy-one (10.8%) individuals experienced a serious event within 30 days of initiating a ChEI (Figure 1). There were no statistically significant differences between women and men in the risk of developing a serious event (10.9% vs 10.6%). Serious events included ED visit (10.8% women, 10.4% men), inpatient hospitalization (3.6% women, 4.0% men), and death (0.4% women, 0.4% men)). Of those who experienced at least one ED visit, 32.6% of women and 37.4% of men had a subsequent hospitalization and a further 2.2% of women and 2.4% of men died.

Overall, 12.0% of ED visits were for known ChEI-related events, and these differed between women and men (13.0% vs 10.4%, P<.001). Of these, gastrointestinal illnesses accounted for 4.2% in women and 2.2% in men (P<.001), cardiovascular illnesses 7.2% in women and 7.5% in men (P=.84), and hip fracture 1.8% in women and 1.0% in men (P<.001).

In absolute terms, women were more at risk of gastrointestinal (0.5% vs 0.2%) and hip fracture–related (0.2% vs 0.1%) ED visits than men and equally likely to have

**Table 2. Effect of Cholinesterase Inhibitor Use on Risk of Serious Event According to Dosage**

| | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | Serious | HR (95% CI) | | Serious | HR (95% CI) | |
| Group | Event, n (%) | Unadjusted | Adjusted[1] | Event, n (%) | Unadjusted | Adjusted[2] |
| Any serious event | | | | | | |
| Lower than recommended starting dose | 275 (10.3) | 0.91 (0.78–1.06) | 0.82 (0.70–0.95) | 145 (12.1) | 1.03 (0.84–1.28) | 0.90 (0.73–1.11) |
| Recommended starting dose | 4,494 (10.7) | Reference | Reference | 2,949 (10.2) | Reference | Reference |
| Higher than recommended starting dose | 466 (14.1) | 1.55 (1.43–1.69) | 1.50 (1.38–1.63) | 342 (13.5) | 1.35 (1.22–1.49) | 1.31 (1.19–1.45)[3] |
| Any ED visit | | | | | | |
| Lower than recommended starting dose | 275 (10.3) | 0.92 (0.79–1.07) | 0.83 (0.71–0.96) | 143 (12.0) | 1.05 (0.85–1.30) | 0.92 (0.74–1.14) |
| Recommended starting dose | 4,442 (10.6) | Reference | Reference | 2,890 (10.0) | Reference | Reference |
| Higher than recommended starting dose | 455 (13.8) | 1.54 (1.41–1.68) | 1.49 (1.37–1.62) | 335 (13.2) | 1.36 (1.22–1.50) | 1.32 (1.19–1.46) |
| Any inpatient hospitalization | | | | | | |
| Lower than recommended starting dose | 110 (4.1) | 1.03 (0.80–1.33) | 0.89 (0.69–1.14) | 65 (5.4) | 1.20 (0.87–1.65) | 1.00 (0.72–1.38) |
| Recommended starting dose | 1,453 (3.5) | Reference | Reference | 1,109 (3.9) | Reference | Reference |
| Higher than recommended starting dose | 152 (4.6) | 1.39 (1.20–1.62) | 1.31 (1.12–1.52) | 119 (4.7) | 1.15 (0.97–1.37) | 1.10 (0.93–1.31) |
| Death | | | | | | |
| Lower than recommended starting dose | 15(0.6) | 1.08 (0.44–2.64) | 0.88 (0.36–2.17) | 9 (0.8) | 1.32 (0.49–3.60) | 1.13 (0.41–3.06) |
| Recommended starting dose | 141(0.3) | Reference | Reference | 114 (0.4) | Reference | Reference |
| Higher than recommended starting dose | 17 (0.5) | 1.22 (0.73–2.02) | 1.14 (0.69–1.90) | 13 (0.5) | 0.88 (0.50–1.55) | 0.85 (0.48–1.50) |
| Any known cholinesterase inhibitor–related ED visit or hospitalization | | | | | | |
| Lower than recommended starting dose | 36 (1.3) | 1.07 (0.75–1.53) | 0.96 (0.67–1.37) | 13 (1.1) | 1.00 (0.56–1.78) | 0.87 (0.49–1.54) |
| Recommended starting dose | 610 (1.5) | Reference | Reference | 335 (1.2) | Reference | Reference |
| Higher than recommended starting dose | 79 (2.4) | 1.88 (1.54–2.28) | 1.87 (1.54–2.27) | 50 (2.0) | 1.51 (1.18–1.93) | 1.51 (1.18–1.93) |

[1]Adjusted for age at index, Johns Hopkins Aggregated Diagnosis Groups (ADGs), home care use, recent hospitalization, recent emergency department (ED) visit, and number of concurrent drugs used.
[2]Adjusted for age at index, ADGs, renal disease, cardiologist consultation, specialist consultation, home care use, recent hospitalization, recent ED visit, number of concurrent drugs used, and concurrent use of antipsychotic medication.
[3]The interaction between starting dose and sex was significant ($p<.05$).
HR = hazard ratio; CI = confidence interval.

cardiovascular-related ED visits (Figure 1, Supplementary Appendix S5).

## Dose-Related Serious Events

Serious events were dose related (Table 2). Women and men dispensed a higher-than-recommended starting dose were significantly more likely to have a serious event than those dispensed a recommended starting dose. Women dispensed a higher-than-recommended starting dose were 50% more likely than those dispensed a recommended dose to have a serious event (adjusted hazard ratio (aHR)=1.50, 95% CI=1.38–1.63), and men dispensed a higher-than-recommended starting dose were approximately one-third more likely to have a serious event (aHR=1.31, 95% CI=1.19–1.45).

For the specific secondary outcomes, this heightened rate was present for both women and men for any ED visit, and for women only for any inpatient hospitalization. This dose-related rate was not associated with death for either sex. The pattern of a greater dose-related risk was also demonstrated for known ChEI-related events in women and men. (Figure 1). Figure 1 illustrates the same data for hospitalizations, death, and any serious event.

Women dispensed a lower-than-recommended starting dose had a lower rate of serious events (aHR=0.82, 95% CI=0.70–0.95) than those dispensed a recommended starting dose. This association was not present in men.

### *Comparison of Women and Men*

The relative effect of higher-than-recommended starting dose dispensed vs. recommended starting dose dispensed was greater in women than it was in men. ($z=2.01$, $p=.04$). No interaction was observed at the lower-than-recommended starting dose.

### *Number Needed to Harm*

Twenty-two women (95% CI=18–29) prescribed a ChEI at a higher-than-recommended dose (compared to recommended starting dose) resulted in 1 woman having a serious event within 30 days. For men, the NNH was 36 (95% CI=26–61) (Supplementary Appendix S6).

## DISCUSSION

We examined new use of ChEI therapy by older adults and evaluated the dose-related development of serious events according to sex to better understand drug safety. Our data suggest that short-term harm is relatively common and occurs soon after drug therapy is initiated. Within 30 days, almost 11% of ChEI users had an event serious enough to result in an ED visit, inpatient hospitalization, or death. Our data are among the first to suggest that these serious events are dose related.

Our study shows the importance of following the geriatric medicine maxim of "start low and go slow" to promote drug safety.[6] Starting low is particularly important when initiating a modestly effective symptomatic therapy such as a ChEI for which there is seldom urgency to initiate the drug at its full dose. For donepezil, this means that older adults are given a dose lower than the manufactured dose and as such may split their pills. Pill splitting is a practice that has been well documented in older adults.[23] This is even more important when adverse events are dose related, and ChEI prescribing guidance recommends upward titration[24] to accrue benefit. ChEIs produce cholinergic adverse events, especially if the dose is increased too quickly.[25] Some clinical guidance suggests that ChEI therapy should be started at lower-than-recommended starting doses[25,26] (e.g., donepezil at 2.5 mg) and the initial dose maintained for several months,[27] particularly in frail adults. This strategy is important because serious events precipitate drug discontinuation, and these drugs are one of the only drug classes available to manage dementia. When possible, the dose should be titrated to achieve a therapeutic, tolerated dose.

Women dispensed higher-than-recommended starting doses were 50% more likely to develop serious events than those dispensed a recommended starting dose. In contrast, men dispensed a higher-than-recommended starting dose were 31% more likely to develop serious events than those dispensed a recommended starting dose. Dispensing a lower-than-recommended dose to women may protect against serious events. Product labelling information for ChEI acknowledges that adverse events are higher in persons of low body weight. Women generally weigh less than men, and this may predisposes women to adverse events. Our findings were consistent with product monograph information [28] that found clinical trials drug discontinuation rates to be dose-related and twice as likely in women. The importance of this sex difference is magnified because women live longer than men, so more women develop dementia and therefore may use these therapies.

Our study suggests substantial co-prescribing of drugs that should be avoided with dementia, because they exacerbate cognitive impairment[29] and, in so doing, mitigate the modest benefit of the ChEI. A drug therapy with strong anticholinergic properties had already been dispensed to almost 11% of individuals, more frequently women. The prescribing of a ChEI to treat drug-related adverse events is a diagnostic error and may lead to a prescribing cascade,[30–32] underlining the importance of identifying medications that may contribute to confusion for deprescribing (tapering or discontinuing) before adding a ChEI therapy.[33]

Our study is among the first to describe the development of serious events associated with the use of ChEIs at a population level according to sex. Although we report on known ChEI-related events, we also report on other serious events that may go unrecognized. A case of head trauma associated with use of ChEI therapy has been described; a man developed gastrointestinal upset after initiation of ChEI therapy and self-medicated using bismuth, which led to salicylate toxicity, a fall, and an intensive care unit admission not attributed to the ChEI therapy.[34] By capturing all serious events, we aimed to identify previously unrecognized events associated with these therapies.

### Limitations

It is likely that this study underestimates the extent of adverse events that older adults newly initiated on ChEIs experience because we considered only serious events, not all events. People may present to their primary care provider to manage adverse events and discontinue ChEIs. As such, our results provide a conservative estimate. Observational studies using health administrative data are at risk of bias because of confounding.[35] For example, other high-risk medications could have been initiated at the same time as the ChEI or shortly thereafter. To limit this possibility, our study compared new users of ChEI therapy and accounted for other risk factors in our models. We used a 30-day follow-up period to minimize this potential situation that other high-risk medications could have been initiated at the same time as the ChEI or shortly thereafter. Our study focuses on ChEI therapy. We recognize that dose-related adverse events and sex differences may occur with many different drug therapies. As such, our results may apply more broadly. Our findings may not extrapolate to transdermal rivastigmine (patch) because this dosage form was not included in the analysis.

Our findings are important for prescribers, individuals, and caregivers who are deciding to initiate ChEIs. Our data may help people weigh the relative risks and benefits of initiating a ChEI in their circumstance. Our results indicate that the practice of initiating a ChEI at a higher-than-recommended starting dose may compromise safety. Although the trend of lower rate of serious events for older adults dispensed a lower-than-recommended starting dose was not statistically significant, our findings support the initiation of the ChEI at a lower-than-recommended starting dose, particularly for women. Our data may provide additional information to assist clinicians in determining the risk:benefit ratio for ChEI therapy and underscore the importance of clinical follow-up after initiation of treatment.

## CONCLUSION

Serious events immediately after initiation of ChEIs were associated with the starting dose of ChEI. This association was stronger in women than men.

## ACKNOWLEDGMENTS

Dr. Rochon holds the Retired Teachers of Ontario Chair in Geriatric Medicine at the University of Toronto.

We thank IMS Brogan, Inc. for use of their Drug Information Database.

Parts of this material are based on data that the Canadian Institute for Health Information (CIHI) compiled and provided, but the analyses, conclusions, opinions, and statements expressed in the material are those of the authors and not necessarily of CIHI.

This study was supported by the Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by the Institute for Clinical Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred.

Parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred.

**Financial Disclosure**: This study was supported by a grant from Physicians Services Incorporated (PSI 2015–16).

**Conflict of Interest**: Dr. Nathan Herrmann has received research support from Lundbeck, Roche, and Axovant and consultation fees from Merck, Lilly, Astellas, and Mediti. Dr. Austin is supported by a Career Investigator Award from the Heart and Stroke Foundation.

**Author Contributions**: PAR: study concept. PAR, SEB: supervision. PAR, AG, SEB: study design. VG: data acquisition. PAR, AG, WW, LZ, PCA, VG, AA, SN, SEB: data analysis and interpretation. PAR: drafting manuscript. All authors: critical revision for important intellectual content, approval of final version of manuscript.

**Sponsor's Role**: The sponsors had no role in the design, conduct, reporting of the study, or the decision to submit the manuscript for publication.

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## SUPPORTING INFORMATION

**Appendix S1.** Methods—Population Data Sources and Exclusion Criteria

**Appendix S2.** Methods—Dose Categories of Cholinesterase Inhibitor Therapy

**Appendix S3.** Methods—Known Cholinesterase Inhibitor (ChEI) related Events

**Appendix S4.** Methods—Characteristics of Older Adults

**Appendix S5.** Results—Serious Events in the 30 Days After Cholinesterase Inhibitor Initiation for Women and Men

**Appendix S6.** Results—Number Need to Harm (NNH) of Serious Event by Dosage Level

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