CLINICAL INVESTIGATION

Low-Dose Trazodone, Benzodiazepines, and Fall-Related Injuries in Nursing Homes: A Matched-Cohort Study

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OBJECTIVES: To evaluate whether risk of fall-related injuries differs between nursing home (NH) residents newly dispensed low-dose trazodone and those newly dispensed benzodiazepines.

DESIGN: Retrospective, matched cohort study in linked, population-based administrative data. Matching was based on propensity score (± 0.2 standard deviations of the score as a caliper), age (± 1 year), sex, frailty status, and history of dementia. The derived propensity score included demographic characteristics, clinical comorbidities, cognitive and functional status, and risk factors for falls.

SETTING: All NHs in Ontario, Canada.

PARTICIPANTS: Propensity score–matched pairs of residents aged 66 and older who received a full clinical assessment between April 1, 2010, and March 31, 2015 (N=7,791).

MEASUREMENTS: Hospitalization (emergency department visit or acute care admission) for a fall-related injury within 90 days of exposure. Subdistribution hazard functions accounted for competing risk of death. Sensitivity analyses were used to examine falls resulting in hip or wrist fracture only, as well as different lengths of follow-up at 30, 60, and 180 days.

RESULTS: Cumulative incidence of a fall-related injury in the 90 days after index was 5.7% for low-dose trazodone users and 6.0% for benzodiazepine users (between-group change=–0.29, 95% confidence interval (CI)=–1.02–0.44]; hazard ratio=0.94, 95% CI=0.83–1.08). Findings were consistent across sensitivity analyses.

CONCLUSION: New use of low-dose trazodone was no safer with respect to a risk of a fall-related injury than new use of benzodiazepines. Additional studies to compare the effectiveness and risks of low-dose trazodone with those of a variety of psychotropic drug therapies are required in light of increasing trends in the use of trazodone in NHs. **J Am Geriatr Soc 00:1–9, 2018.**

Key words: fall-related injuries; trazodone; benzodiazepines; nursing home; pharmacoepidemiology

The use of benzodiazepines in nursing homes (NHs) has long been scrutinized because of known adverse events such as falls, fractures, and cognitive impairment, as well as concerns about dependency.[1–5] Benzodiazepines feature prominently in priority lists for deprescribing in older adults[6], and rates of benzodiazepine prescribing have been identified as important indicators of quality and safety of care.[7] In an attempt to reduce potentially inappropriate use, many jurisdictions publically report rates of psychotropic drugs—many having done so for longer than a decade.[8,9]

Several studies have recently reported decreasing trends in benzodiazepine use in older adults in community and NH settings.[10–12] It is unclear which factors are behind this pattern. The decline may be associated with better understanding of relative risks and benefits, but heightened awareness of guidelines and reporting might also result in prescribers searching for suitable substitutes.[13] Increased

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use of trazodone frequently accompanies decline in benzodiazepine use in NHs.[14] Studies report that trazodone is being used in doses well below those indicated for antidepressant therapy (<50% of the World Health Organization–defined daily dose) suggesting, perhaps, that trazodone is being used as a sedative for unapproved (off-label) indications—such as management of insomnia or treatment of behavioral and psychological symptoms of dementia (BPSD).[15,16]

A comprehensive review of off-label use of antidepressants in primary care reported that trazodone prescribed for insomnia was responsible for a significant proportion of prevalent off-label use.[17] These findings are notable, because there is limited randomized controlled trial or observational study evidence comparing the safety of low doses of trazodone with that of other psychotropic agents, particularly benzodiazepines.[18–22] Clinical trials have often been too small or too short to identify risks that are relatively infrequent, such as fall-related injuries. A recent review highlighted the dearth of comparative data for older adults and suggested that low-dose trazodone should be recommended for insomnia only if the individual has comorbid depression.[23] Consensus panels on dementia treatment have also concluded that there is not clear evidence for, or against, a recommendation for use of low-dose trazodone in BPSD,[24] and low-dose trazodone use has been linked to falls[25,26], nausea and vomiting,[23,27] and extrapyramidal symptoms[28].

In light of limited evidence of the comparative safety of low-dose trazodone and benzodiazepines and to help support decisions associated with starting one drug over the other, the aim of this study was to use population-based data to compare the risk of emergency department (ED) visit or acute care admission for fall-related injuries in NH residents, using propensity score matching to address confounding.

METHODS

Study Design and Setting

We conducted a retrospective cohort study of NHs from Ontario, Canada; the provincial health system covers the majority of the cost of care, and access is centrally managed. The administrative datasets used in this study were linked using encoded identifiers at the individual level and analyzed at the Institute for Clinical Evaluative Sciences (Supplementary Table S1). Ethics approval was obtained from the research ethics board of Sunnybrook Health Sciences Centre, Ontario, Canada. This study is reported according to REporting of studies Conducted using Observational Routinely-collected Data guidelines (Supplementary Table S2).

Eligible Cohort

The Continuing Care Resident Reporting System database contains information on all NH residents; we identified 642,149 full assessments of residents aged 66 and older between April 1, 2010, and March 31, 2015. Data were collected using the Resident Assessment Instrument Minimum Data Set (RAI-MDS) version 2.0, a validated tool.[29] Assessments are mandatory, and trained healthcare staff administer them, with full assessments completed on admission, annually, and after any significant health status change. We excluded assessments at which no drugs were prescribed in the year before assessment (N=4,779, 0.7%) to ensure that residents had access to provincial drug insurance. Residents who were comatose or completely bedbound at assessment (N=18,531, 2.9%) or had received palliative care (N=22,941, 3.6%) in the 180 days before assessment were also excluded because the care plans and trajectories for these individuals differed. This resulted in 595,898 full assessments—corresponding to 169,595 residents—eligible for inclusion in the study.

Drug Exposure—Low-Dose Trazodone or Benzodiazepine

For all assessments, we extracted information on dispensed drug therapies from the Ontario Drug Benefit database to determine new users of low-dose trazodone and benzodiazepines. Within the Ontario Drug Benefit, the prevalence of trazodone dispensed to residents has increased over time, and that of benzodiazepines has decreased (Supplementary Figure S3). In our cohort, use was defined as receipt of an exposure drug within 7 days before or after an assessment (Supplementary Table S4). The initial dispensing date served as the index date from which to follow residents for outcomes. New users were required not to have filled a prescription for either exposure drug in the 90 days before the index date.

For use as an antidepressant, the typical dose of trazodone is a minimum of 150 mg/d, with most patients requiring between 300 and 600 mg/d.[30] Consistent with previous studies, we applied an average daily dose threshold of 150 mg or lower to define low dose, which has previously been shown to account for at least 97% of all trazodone prescriptions in NHs in Ontario.[14] Lorazepam was the most commonly prescribed benzodiazepine and was selected as the reference drug for dose equivalency (defined daily dose of lorazepam = 2.5 mg/d).[31] To facilitate comparisons of benzodiazepines, the defined daily dose thresholds for the remaining products were used to create lorazepam equivalency ratios, which were multiplied by the average daily dose for each resident to obtain lorazepam-equivalent doses (Supplementary Table S5), defined daily dose column. Supplementary Table S5 also lists low-dose benzodiazepine thresholds for the low-dose benzodiazepine subgroup which was considered in a secondary analysis. When a resident had multiple assessments, one was selected at random for analysis (Figure 1).

Outcomes

The primary outcome was a fall-related ED visit or acute care hospitalization (*International Classification of Diseases, Tenth Revision* (ICD-10) codes W00-W19 in any diagnostic code space). ED visits were ascertained from the Canadian Institute for Health Information National Ambulatory Care Reporting System and hospitalizations from the Discharge Abstract Database. Residents were followed for 90 days after index for the first occurrence of an outcome.

A more-restrictive secondary outcome examined fall-related ED visit or acute care hospitalization to those with a hip or wrist fracture as the most-responsible diagnosis(ICD-10 codes W00-W19 in any diagnostic code space with

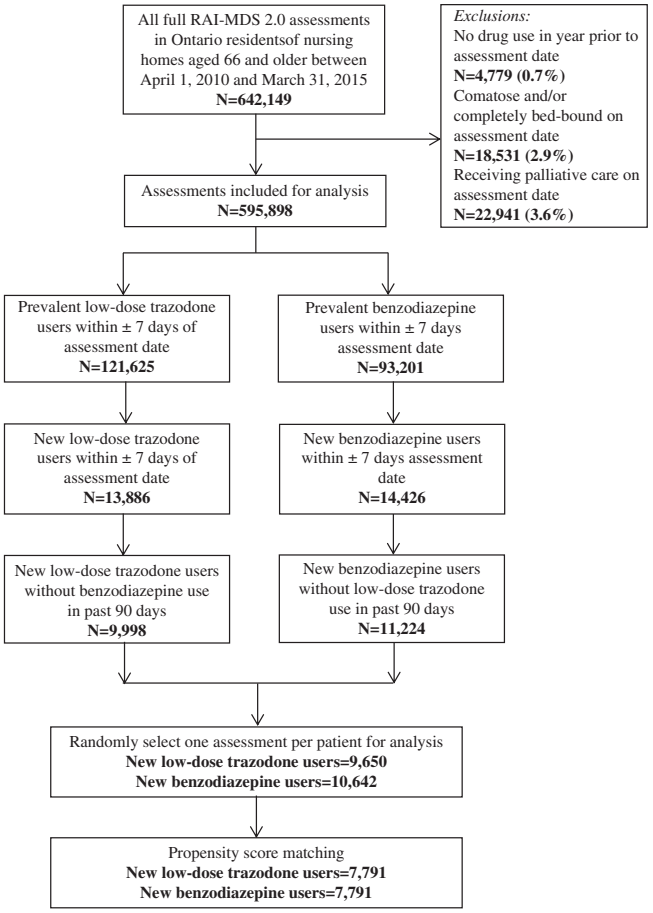

Figure 1. Flow diagram of creation of study cohort and drug exposure groups.

codes S72.0-S72.2, S52, and S62.0-S62.4 plus S62.8) within 90 days after index date. All of the fall definitions have been validated[32,33] with strong performance characteristics and used in prior research.[25]

Resident Characteristics

As in previous work,[5] we used assessment items from the RAI-MDS to calculate a validated frailty index for each resident; residents were considered frail if their frailty index score was 0.3 or greater. RAI-MDS data were also used to determine demographic information and specific clinical diagnoses, including Alzheimer's and related dementias (henceforth referred to as dementia). The RAI-MDS tool contains several validated scales that measure health status and function.[34–36] Historical ED visits, hospitalizations, physician visits, and dispensed drug therapies were counted to examine how frequently each resident interacted with the health system in the year before the index date. As a general measure of comorbidity, we calculated the number of Aggregated Diagnosis Group categories using the Johns Hopkins Adjusted Clinical Group Case-Mix System version 10.0 based on diagnoses in outpatient and inpatient records during the 2 years before admission.

To account for potential confounding variables in our propensity score, we identified concurrent drug therapies associated with risk of falls at index date from the Ontario Drug Benefit database. We also identified health conditions that may have predisposed residents to falls (e.g., dizziness on assessment) or a history of falls and fractures in the NH and ascertained whether residents had been assessed to be at medium to high risk of a future fall using the Falls Clinical Assessment Protocol in the RAI data. We identified all residents who had a fall that resulted in an ED visit or acute care hospitalization in the 5 years before the index date.

Statistical Analysis

Propensity score matching was used to compare residents with similar observed characteristics, all of whom were candidates for both exposure drug classes. A multivariable logistic regression model that included all measured resident characteristics was used to compute a resident-level propensity score for newly receiving low-dose trazodone. New users of low-dose trazodone were then matched to new users of benzodiazepines on the basis of age (±1 year), sex, frailty status (not frail vs frail), a history of dementia in the RAI-MDS data, and propensity score (±0.2 standard deviations of the score). A standardized difference of 10% or less for all resident characteristics was considered adequate balance.[37]

We compared the risk of our primary outcome in the two exposure groups using subdistribution hazard models to account for the competing risk of death[38], because mortality was high in this care setting. Marginal models using a robust sandwich-type estimator were used to account for the matched nature of the data.[39] Residents were followed in an intention-to-treat fashion whereby switching drug exposure groups and discontinuation were permitted, but individuals remained in their initial assignment group. We also conducted stratified analyses according to sex, frailty status, and history of dementia diagnosis because all of these factors have been suggested as important effect modifiers of drug-outcome associations.[40–43]

In sensitivity analyses, we altered length of follow-up time after index date for the primary outcome (30, 90, and 180 days) and investigated the secondary outcome. We conducted a sensitivity analysis whereby residents were censored on the date they received the other exposure drug or the date they stopped using the index exposure drug. The latter allowed for a 2-week grace period from the end of the previous claim, which was estimated using days supplied. Finally, we repeated the propensity score matching process and statistical analyses to compare a cohort of low-dose trazodone users with a subgroup of low-dose benzodiazepine users.

Analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). All statistical tests were 2-tailed, and we defined $P<.05$ as statistically significant.

RESULTS

Characteristics of Matched Cohort

We identified residents who were new users of low-dose trazodone (n=9,650) and benzodiazepines (n=10,642) within 7 days before or after clinical assessment in the study period. New low-dose trazodone users were less likely to be female, had a higher prevalence of dementia, and had been

Table 1. Baseline Characteristics of Ontario Nursing Home Residents Dispensed Low-Dose Trazodone or a Benzodiazepine: April 1, 2010, to March 31, 2015

	Unmatched			Propensity Score Matched		
Characteristic	New Low-Dose Trazodone Users, n=9,650	New Benzodiazepine Users, n=10,642	Standardized Difference	New Low-Dose Trazodone Users, n=7,791	New Benzodiazepine Users, n=7,791	Standardized Difference
Demographic						
Age, mean±SD	84.1 ± 7.2	83.5 ± 7.6	0.08	83.9 ± 7.1	83.9 ± 7.1	0
Female, n (%)	5,815 (60.3)	7,092 (66.6)	0.13	4,977 (63.9)	4,977 (63.9)	0
New admission on assessment date, n (%)	7,911 (82.0)	7,658 (72.0)	0.24	6,160 (79.1)	6,143 (78.8)	0.01
Clinical diagnoses, n (%)						
Diabetes	2,562 (26.5)	2,733 (25.7)	0.02	2,017 (25.9)	1,990 (25.5)	0.01
Congestive heart failure	1,351 (14.0)	1,520 (14.3)	0.01	1,076 (13.8)	1,080 (13.9)	0
Hypertension	6,242 (64.7)	6,757 (63.5)	0.02	5,000 (64.2)	4,990 (64.0)	0
Stroke or transient ischemic attack	2,415 (25.0)	2,492 (23.4)	0.04	1,867 (24.0)	1,855 (23.8)	0
Alzheimer's disease and related dementia	6,671 (69.1)	6,153 (57.8)	0.24	5,066 (65.0)	5,066 (65.0)	0
Emphysema, chronic obstructive pulmonary disease, asthma	1,749 (18.1)	2,018 (19.0)	0.02	1,426 (18.3)	1,454 (18.7)	0.01
Depression	2,253 (23.3)	2,649 (24.9)	0.04	1,848 (23.7)	1,887 (24.2)	0.01
Arthritis	3,860 (40.0)	4,283 (40.2)	0.01	3,118 (40.0)	3,106 (39.9)	0
Osteoporosis	2,373 (24.6)	2,849 (26.8)	0.05	1,989 (25.5)	2,043 (26.2)	0.02
Health status						
Frail, n (%)	4,954 (51.3)	5,190 (48.8)	0.05	3,796 (48.7)	3,796 (48.7)	0
Aggressive Behavior Scale score, mean±SD	1.7 ± 2.5	1.7 ± 2.5	0.03	1.7 ± 2.5	1.7 ± 2.5	0.01
Activities of daily living						
Independent (with and/or without supervision)	876 (9.1)	1,140 (10.7)	0.05	785 (10.1)	795 (10.2)	0
Limited assistance	1,439 (14.9)	1,671 (15.7)	0.02	1,233 (15.8)	1,253 (16.1)	0.01
Extensive assistance	4,906 (50.8)	4,794 (45.0)	0.12	3,751 (48.1)	3,773 (48.4)	0.01
Total dependence	2,429 (25.2)	3,037 (28.5)	0.08	2,022 (26.0)	1,970 (25.3)	0.02
Cognitive function, n (%)						
Intact or borderline intact	1,953 (20.2)	2,975 (28.0)	0.18	1,796 (23.1)	1,841 (23.6)	0.01
Mild impairment	1,867 (19.3)	1,922 (18.1)	0.03	1,529 (19.6)	1,523 (19.5)	0
Moderate impairment	4,628 (48.0)	4,240 (39.8)	0.16	3,462 (44.4)	3,452 (44.3)	0
Severe impairment	1,202 (12.5)	1,505 (14.1)	0.05	1,004 (12.9)	975 (12.5)	0.01
Health system use in past year, mean±SD						
ED visits	2.0 ± 2.5	2.0 ± 2.4	0.03	2.0 ± 2.5	2.0 ± 2.5	0
Primary care physician visits	33.6 ± 30.2	29.5 ± 29.0	0.14	31.1 ± 27.8	30.6 ± 29.5	0.02
Unique drug therapies	14.4 ± 9.7	15.8 ± 9.7	0.14	14.9 ± 9.9	15.0 ± 9.4	0.01
Number of aggregated diagnosis groups in past 2 years, n (%)						
0–5	1,284 (13.3)	1,748 (16.4)	0.09	1,114 (14.3)	1,176 (15.1)	0.02
6–10	3,313 (34.3)	3,503 (32.9)	0.03	2,752 (35.3)	2,579 (33.1)	0.05
≥11	5,053 (52.4)	5,391 (50.7)	0.03	3,925 (50.4)	4,036 (51.8)	0.03
Concurrent drug therapy use, n (%)						
Antipsychotic	3,515 (36.4)	3,733 (35.1)	0.03	2,816 (36.1)	2,812 (36.1)	0
Antidepressant	3,942 (40.8)	4,485 (42.1)	0.03	3,246 (41.7)	3,240 (41.6)	0
Cholinesterase inhibitor	2,810 (29.1)	2,635 (24.8)	0.1	2,187 (28.1)	2,194 (28.2)	0
Opioid	1,845 (19.1)	2,814 (26.4)	0.18	1,649 (21.2)	1,694 (21.7)	0.01
Risk factors for falls, n (%)						
Visual impairment	1,300 (13.5)	1,458 (13.7)	0.01	1,046 (13.4)	1,028 (13.2)	0.01
Hearing impairment	1,438 (14.9)	1,467 (13.8)	0.03	1,106 (14.2)	1,125 (14.4)	0.01
Unsteady gait	4,265 (44.2)	4,517 (42.4)	0.04	3,372 (43.3)	3,449 (44.3)	0.02

Table 1 (Contd.)

Characteristic	Unmatched			Propensity Score Matched		
	New Low-Dose Trazodone Users, n=9,650	New Benzodiazepine Users, n=10,642	Standardized Difference	New Low-Dose Trazodone Users, n=7,791	New Benzodiazepine Users, n=7,791	Standardized Difference
Dizziness or vertigo	227 (2.4)	314 (3.0)	0.04	192 (2.5)	202 (2.6)	0.01
Delusions or hallucinations	579 (6.0)	607 (5.7)	0.01	460 (5.9)	452 (5.8)	0
Shortness of breath	747 (7.7)	1,067 (10.0)	0.08	645 (8.3)	668 (8.6)	0.01
Dehydrated or insufficient fluid intake	675 (7.0)	873 (8.2)	0.05	558 (7.2)	540 (6.9)	0.01
Fall in past 180 days	4,654 (48.2)	4,802 (45.1)	0.06	3,607 (46.3)	3,658 (47.0)	0.01
Fracture in past 180 days	937 (9.7)	1,028 (9.7)	0	743 (9.5)	752 (9.7)	0
Assessed as medium to high risk for future falls	2,449 (25.4)	2,624 (24.7)	0.02	1,895 (24.3)	1,975 (25.3)	0.02
ED visit or acute care hospitalization for fall-related injury in past 5 years	5,122 (53.1)	5,664 (53.2)	0	4,135 (53.1)	4,133 (53.0)	0

Abridged version; full table available in Supplementary Table S6.
SD=standard deviation; ED=emergency department.

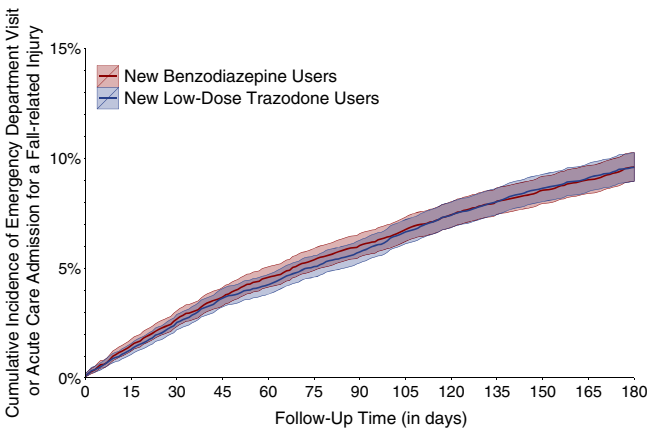

Figure 2. Cumulative incidence functions for fall-related injuries in Ontario nursing homes residents dispensed low-dose trazodone benzodiazepines between April 1, 2010, and March 31, 2015.

dispensed fewer overall medications, including opioids, than new benzodiazepine users (Table 1; see Supplementary Table S6 for all measured characteristics). The majority of residents had been newly admitted to a NH; this was not surprising, given that admission is often a time of medication reconciliation, and our focus was on new use. The unadjusted proportion of fall-related ED visits or acute care hospitalizations before matching was 5.8% in new trazodone users and 5.5% in new benzodiazepine users. Although not directly comparable because of the nature of our study design, a random sample of assessed residents with no history of either drug had a slightly lower risk of falls (4.1%) than the present study cohort (data not shown).

Propensity score matching produced 7,791 analytical pairs of new low-dose trazodone and new benzodiazepine users. The drug exposure groups were well balanced, as standardized differences of less than 10% for all measured resident characteristics indicated; including high baseline rates of use of other antidepressants, antipsychotics, and opioids. Mortality in the 90 days after the index date was high for both groups: 9.2% for new low-dose trazodone users and 10.3% for new benzodiazepine users. Median dose for trazodone users was 50.0 mg/d (interquartile range (IQR) 25.0–51.7 mg/d); the 95th percentile for use was 107.1 mg/d and demonstrated few users near the 150-mg/d threshold. Lorazepam (76.6%) was the most common benzodiazepine product identified in the matched pairs, followed by oxazepam (11.5%). Median dose for benzodiazepine users was 1.07 mg/d lorazepam equivalents (IQR 0.75–2.14 mg/d).

Fall-Related ED or Acute Care Hospitalization within 90 Days

Figure 2 illustrates the cumulative incidence of our primary outcome in the 90 days after index for low-dose trazodone (5.7%) and benzodiazepine (6.0%) users. The difference in fall-related injury between the two groups was not significant (–0.29%, 95% confidence interval (CI)=–1.02–0.44%) (Table 2). After accounting for competing risk of death, there was no significant association between risk of our primary outcome (hazard ratio (HR)=0.95, 95% CI=0.83–1.08, P=.43) and having been prescribed low-dose trazodone as opposed to a benzodiazepine. There was no significant association between low-dose trazodone use and fall-related injury in any stratified analysis either. Differences in risk between men and women, frail and not frail, and those with and without a history of dementia were not significant.

Follow-Up Time and Secondary Analyses

The results of the primary analysis were also robust to shorter and longer follow-up periods after the index date

Table 2. Association Between Initial Drug Exposure and Fall-Related Injuries for Ontario Nursing Home Residents Dispensed Low-Dose Trazodone or a Benzodiazepine, Overall and According to Subgroup: April 1, 2010, to March 31, 2015

Analysis	Matched Pairs Analyzed, n	Cumulative Incidence of Falls, %		Difference in Outcomes, % (95% CI)	Hazard Ratio (95% CI)[1]	P-Value
		New Low-Dose Trazodone Users	New Benzodiazepine Users			
Primary analysis: Fall-related ED visit or acute care hospitalization within 90 days	7,791	5.74	6.03	–0.29 (–1.02–0.44)	0.95 (0.83–1.08)	.43
Stratification groups						
Sex						
Female	4,977	5.71	6.31	–0.60 (–1.53–0.33)	0.90 (0.77–1.06)	.21
Male	2,814	5.79	5.54	0.25 (–0.96–1.46)	1.05 (0.84–1.30)	.68
Frailty (frailty index score)						
Prefrail or not frail (<0.3)	3,995	5.10	5.51	–0.41 (–1.39–0.57)	0.92 (0.76–1.12)	.41
Frail (≥0.3)	3,796	6.40	6.59	–0.19 (–1.30–0.92)	0.97 (0.82–1.16)	.76
Dementia						
No	2,725	4.59	5.39	–0.80 (–1.95–0.35)	0.84 (0.66–1.07)	.17
Yes	5,066	6.36	6.38	–0.20 (–0.96–0.92)	1.00 (0.86–1.16)	.98
Sensitivity analyses on follow-up time, days						
30	7,791	2.53	2.68	–0.15 (–0.64–0.34)	0.94 (0.77–1.14)	.54
60	7,791	4.24	4.58	–0.34 (–0.99–0.31)	0.93 (0.80–1.08)	.31
180	7,791	9.59	9.60	–0.01 (–0.93–0.90)	1.00 (0.90–1.10)	.96
Secondary analyses						
Fall-related (with hip or wrist fracture diagnosis) ED visit or acute care hospitalization within 90 days	7,791	1.22	1.54	–0.32 (–0.68–0.04)	0.79 (0.60–1.04)	.09
Censoring on exposure drug discontinuation or switching	7,791	5.97	5.92	0.05 (–1.01–1.11)	0.96 (0.82–1.14)	.67
New low-dose trazodone vs new low-dose benzodiazepine subgroup	4,958	5.71	5.79	–0.08 (–1.00–0.83)	0.99 (0.84–1.16)	.86

[1]Low-dose trazodone (with benzodiazepine serving as reference drug).
CI=confidence interval; ED=emergency department.

(Table 2). For the secondary outcome, there was a trend toward a lower risk of fall-related injury in low-dose trazodone users than in benzodiazepine users, but the difference was not significant (HR=0.79, 95% CI=0.60–1.04, P=.09). The results of our primary analysis were also robust to censoring residents upon switching or discontinuing their initial exposure drugs (HR=0.96, 95% CI=0.82–1.14) and to an analysis in which new low-dose trazodone users were matched with new low-dose benzodiazepine users (HR=0.99, 95% CI=0.84–1.16, P=.86).

DISCUSSION

We compared the risk of fall-related injuries in NH residents newly exposed to low-dose trazodone with that of those newly exposed to benzodiazepines. Our data show that new use of low-dose trazodone was no safer with respect to fall-related injuries. Within 90 days, the risk of a fall-related injury was 5.7% for low-dose trazodone and 6.0% for benzodiazepines (difference not statistically significant).

The rising use of trazodone in NHs is consistent with emerging patterns for antidepressants more broadly.[44] An accompanying concern is that these drug therapies are being used for indications for which they have not been approved (off-label use).[45] A recent study identified trazodone use for insomnia as the most common off-label use for antidepressants in primary care; trazodone accounted for 26.2% of off-label antidepressant prescriptions despite no apparent evidence base.[17] In general, in the absence of robust scientific evidence, off-label use of drug therapies has been shown to be associated with risk of adverse drug events.[46]

Low-dose trazodone is not highlighted in many prescribing guidelines for older adults, such as the Beers Criteria[47], not because of evidence demonstrating safety, but because of a lack of studies demonstrating harm. In the face of limited scientific evidence[19–22], our finding that individuals exposed to low-dose trazodone were at risk of fall-related hospitalizations similar to that of those receiving benzodiazepines is troubling. The overall incidence of falls in NH residents has been reported at 12%, and the incidence of fall-related fractures at 2%[48], but this risk varies based on age, sex, and functional ability.[49] In our study, close to 80% of individuals were newly admitted to the NH, which probably elevated the underlying baseline risk of falls in our analysis. We specifically chose a comparative effectiveness study design to help protect against selection biases present in studies comparing drug with no drug.[50]

The use of psychotropic drug therapies is strongly associated with risk of falls.[51] Benzodiazepines are a common cause of falls in older adults,[52,53] and our estimates for the incidence of fall-related injuries in benzodiazepine users were of a similar magnitude. We also report a fall-related injury risk for low-dose trazodone similar to that found in a recent study[25] that demonstrated a number needed to harm of 50 (i.e., on average 50 residents need to be exposed to cause harm in one resident) in trazodone users compared with nonusers. Our findings suggest that, similar to benzodiazepines, there might be risks associated with low-dose trazodone, but even though trazodone was not found to protect against falls in the current study, it may (or may not) offer benefits that benzodiazepines do not with respect to dependence, risk of withdrawal, and impaired cognition. The median dose of benzodiazepines in our study was low and might contribute to our finding of no difference. Furthermore, a certain percentage of those dispensed benzodiazepines may not have received the stated dose as a single bedtime dose but instead may have been receiving that daily dose divided throughout the day for an indication other than insomnia.

An alternative, but related, concern for NHs is whether public reporting for rates of prescribing has resulted in pressure on institutions and healthcare providers to search for clinically suitable substitutes. This phenomenon has been described for other drug therapies[54] and highlights a consequence of focusing on single drugs instead of broader strategies to optimize prescribing. For psychotropic drugs, which feature prominently on potentially inappropriate medication lists and for which variations are frequently publically (often in the media) reported, this can be important. The rise in use of low-dose trazodone may be a result of substitution—for benzodiazepines or antipsychotics (or both). In our study, concurrent use of antipsychotics was balanced across exposure groups; even before propensity matching, so the growing use of low-dose trazodone merits additional research on efficacy and safety.

Strengths and Limitations

Our study has a number of strengths. We examined prescribing of low-dose trazodone in population-based data using a robust study design to address confounding. We also acknowledge some limitations to our study. First, it is likely that we underestimated the extent of fall-related injuries because we focused on falls resulting in ED visits or acute care hospitalizations. Second, substitution of low-dose trazodone for benzodiazepines has been suggested based on recent trends but has not been directly demonstrated. We did not have direct information on the reason for new drug exposure. Finally, observational studies using health administrative data are at risk of bias due to confounding. To limit this possibility, our study used propensity score matching to compare new users of low-dose trazodone with new users of benzodiazepines. In addition, the comprehensiveness of data available from the RAI-MDS allowed for better control of measured confounders than is possible in traditional administrative data studies. Nevertheless, although we controlled for measured characteristics, unmeasured bias is still possible, and additional studies are required.

CONCLUSION

Low-dose trazodone is no safer than benzodiazepines in protecting against fall-related ED visits or hospitalizations. Given rising trends in use of low-dose trazodone in NHs, greater vigilance related to off-label prescribing is recommended.

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Author Contributions: SB, MC, AI, CM: Study concept and design. JG, MC: statistical analysis. SB, MC: writing the manuscript. All authors: interpretation and critical appraisal. SB and MC had full access to the study databases and are the guarantors of the study.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Description of Ontario health administrative data sources included in this study

Table S2. RECORD statement

Figure S3. Trends in the prevalence of trazodone and benzodiazepines dispensed to residents of nursing homes in Ontario from January 1, 2007 to March 31, 2015, by quarter year

Table S4. Drug therapies eligible for study inclusion based on Ontario Drug Benefit Program formulary

Table S5. Average daily dose thresholds and low-dose thresholds for each benzodiazepine product included in this study

Table S6. Baseline characteristics of Ontario residents of nursing homes dispensed low-dose trazodone compared to a benzodiazepine between April 1, 2010 and March 31, 2015. *Full version.

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