Comparative Risk of Harm Associated with Zopiclone or Trazodone Use in Nursing Home Residents: a Retrospective Cohort Study in Alberta, Canada

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ABSTRACT

Background

There is growing evidence of harm associated with trazodone and nonbenzodiazepine sedative hypnotics (e.g., zopiclone); however, their comparative risk of harm is unknown.

Methods

We conducted a retrospective cohort study with linked health administrative data, which enrolled older (≥66 years old) nursing home residents living in Alberta, Canada, between December 1, 2009, and December 31, 2018; the last follow-up date was June 30, 2019. We compared the rate of injurious falls and major osteoporotic fractures (primary outcome) and all-cause mortality (secondary outcome) within 180 days of first prescription of zopiclone or trazodone with cause-specific hazard models and inverse probability of treatment weights to control for confounding; primary analysis was intention-to-treat and secondary analysis was per-protocol (i.e., residents censored if dispensed the other exposure drug).

Results

Our cohort included 1,403 residents newly dispensed trazodone and 1,599 residents newly dispensed zopiclone. At cohort entry, the mean resident age was 85.7 (standard deviation [SD] 7.4), 61.6% were female, and 81.2% had dementia. New zopiclone use was associated with similar rates of injurious falls and major osteoporotic fractures (intention-to-treat-weighted hazard ratio 1.15, 95% confidence interval [CI] 0.90-1.48; per-protocol-weighted hazard ratio 0.85, 95% CI 0.60-1.21) and all-cause mortality (intention-to-treat-weighted hazard ratio 0.96, 95% CI 0.79-1.16; per-protocol-weighted hazard ratio 0.90, 95% CI 0.66-1.23) compared to trazodone.

Conclusions

Zopiclone was associated with a similar rate of injurious falls, major osteoporotic fractures, and all-cause mortality compared to trazodone—suggesting one medication should not be used in lieu of the other. Appropriate prescribing initiatives should also target zopiclone and trazodone.

Key words: adverse drug event, trazodone, zopiclone, cohort studies

INTRODUCTION

Older adults living in nursing homes commonly experience neuropsychiatric symptoms such as sleep disturbances and agitation.[1] Pharmacologic interventions such as antipsychotics, antidepressants, benzodiazepines, and nonbenzodiazepines sedative hypnotics (i.e., z-drugs) are prescribed to treat these symptoms.[2] The pooled prevalence of chemical (e.g., antipsychotics, benzodiazepines) and physical (e.g., mittens, lap belt) restraint use in a systematic review of nursing home prevalence estimates was 32% and

33%, respectively.[3] Efficacious alternatives to chemical and physical restraints include massage therapy, music therapy, and multidisciplinary care plans; however, health-care provider knowledge of these interventions and resource limitations are perceived as barriers to their implementation.[4-6]

Time trend analyses conducted before the COVID-19 pandemic in Canada, the United States, and the United Kingdom suggested that antipsychotic and benzodiazepine use was stabilizing or decreasing, but use of alternative psychotropic medications such as antidepressants and anticonvulsants was increasing.[7-9] For example, 21.3% of older adults living in nursing homes in Ontario, Canada, were dispensed trazodone in 2013, compared to only 7.7% in 2002, which may have been in response to a growing body of literature describing harms associated with antipsychotic and benzodiazepine use, and initiatives targeting their appropriate prescribing. [10] From 2011 to 2014, 39.8% of older adults living in nursing homes in Oslo municipality, Norway, were prescribed nonbenzodiazepine sedative hypnotics (i.e., zopiclone or zolpidem); other studies have shown that nonbenzodiazepine sedative hypnotic use in people with dementia varies considerably by country.[2,11,12] Unlike benzodiazepines and antipsychotics, quality improvement work aimed at reducing potentially inappropriate prescribing of these alternative psychotropic medications has been limited.[13-15] This is important because there is growing evidence describing the risk of falls and fractures in older adults dispensed trazodone and nonbenzodiazepine sedative hypnotics (e.g., zopiclone). [16-18] Further, trazodone is associated with a similar risk of harm from injurious falls or fractures as benzodiazepines and atypical antipsychotics.[16,17]

Despite how commonly trazodone and zopiclone are prescribed in nursing homes, their comparative risk of harm in nursing home residents is unknown.[2,10] Our objective was to describe the risk of harm from injurious falls, fractures, and death associated with new use of zopiclone compared to new use of trazodone among older adults living in nursing homes in Alberta, Canada.

METHODS

This manuscript is reported in accordance with the STROBE (strengthening the reporting of observational studies in epidemiology) and RECORD-PE (reporting of studies conducted using observational routinely collected health data—pharmacoepidemiology) statements.[19, 20]

Setting and Data Sources

We created our cohort using linked health administrative databases in Alberta, Canada. Alberta has a largely publicly funded health-care system, in which individuals aged 65 years or older can access publicly funded nursing homes, when necessary, and receive universal coverage for physician services and most prescription medications. Between April 1, 2016, and March 31, 2017, there were 20,073 residents living in nursing homes in Alberta, and each resident received 10

different medications in the seven days before their Resident Assessment Instrument—Minimum Data Set, version 2.0 (RAI-MDS 2.0) assessment.[21] We linked patient-level data from these databases using each patient's health insurance program number: National Ambulatory Care Reporting System, Provincial Registry, Discharge Abstract Database, Practitioner Claims Database, Pharmacy Information Network, and the Alberta Continuing Care Information System (see Appendix A for database details). These databases are accurate and reliable.[22-24]

Study Design

In this retrospective cohort study, the date of a new prescription for oral trazodone or zopiclone between December 1, 2009, and December 31, 2018, was our index date. We included nursing home residents, aged 66 years or older, who received a full RAI-MDS 2.0 assessment within 45 days before our index date. The RAI-MDS 2.0 is a validated assessment tool that records information about residents' health status (e.g., independence in activities of daily living and cognitive impairment severity). [25] Choosing assessments within 45 days of the index date ensured a close temporal association between drug exposure and residents' current health status. Our observation window was 180 days, which balanced the time required for event accrual against a need to minimize residual confounding over time. The maximum follow-up date was June 30, 2019. We excluded residents from our cohort if they: 1) did not have a complete Resident Assessment Instrument—Minimum Data Set, version 2.0 assessment within 45 days prior to cohort entry; 2) had an invalid identifying number or died on or before the index date; 3) had no drug claims in the year prior to cohort entry; 4) were dispensed trazodone or zopiclone in the 180 days prior to cohort entry; 5) were newly dispensed both trazodone and zopiclone on the index date; 6) received palliative care services in the 180 days prior to cohort entry; or 7) were dispensed trazodone at a dose greater than 300 mg/day or zopiclone at a dose greater than 15 mg/day (see Figure 1).

We defined our primary outcome as a composite of fall-related emergency department visit (i.e., injurious fall) or major osteoporotic fracture, defined as a hip, pelvis, humerus, or forearm fracture (see Appendix B).[26] These outcomes are identified with a high positive predictive value in administrative databases and high level of agreement during medical chart re-abstraction.[22,26,27] Our secondary outcome was all-cause mortality. Where numbers permitted, we planned to report primary outcome components (i.e., fall, hip fracture, major osteoporotic fracture) as secondary outcomes. See Appendix A for all International Classification of Diseases, Tenth Revision (ICD-10) codes used to define residents' baseline characteristics and study outcomes.[22,23,26]

Statistical Analysis

We summarized categorical baseline characteristics as frequencies (and percentages) and compared across exposure groups with chi-square tests. We summarized continuous baseline characteristics as means (and SDs) and compared

across exposure groups with independent *t*-tests. We reported the proportion of residents missing data for individual baseline characteristics.

We derived inverse probability of treatment weights from an estimated propensity score, which we derived by regressing exposure status on baseline covariates (see Appendix B for covariates), including medications dispensed in the year before cohort entry. In our study, the propensity score was the probability that a resident would be dispensed trazodone or zopiclone, conditional on their baseline characteristics.[28] We included missing values for categorical variables as an additional category. There were no missing values for continuous variables. We modeled the average treatment effect because we could foresee any cohort member potentially receiving either exposure drug and we wished to understand the average effect of treatment in the entire cohort.[29] Treatment weights were inspected for outlying values (greater than 50).[30] Crude (i.e., unweighted) and weighted cause-specific hazard ratios comparing outcome rates associated with zopiclone or trazodone use were derived from cause-specific hazards models, because we wanted to understand the association between our exposure and outcome rate in residents who had not yet had an outcome and were, therefore, at risk of having an outcome.[31] Weighted cause-specific hazards models were adjusted for all baseline characteristics for which there were statistically significant differences (i.e., *p*<.05) between exposure groups. We verified that hazard ratios did not vary over time, and we used robust standard errors to account for within-subject homogeneity in outcomes induced by weighting.[32]

Our primary analyses were based on an intention-to-treat principle (i.e., residents who were newly dispensed either exposure drug remained in the cohort even if they were dispensed the other exposure drug during the follow-up period); residents were followed until the first of the outcome of interest, death, or 180 days after index date. In secondary analyses, we censored residents who were dispensed the other exposure drug during the 180-day follow-up period (i.e., per protocol). We reported weighted incidence rates as the number of events per 100 person-years. Where numbers permitted, we planned to conduct subgroup analyses based on residents' age, sex, dementia severity, and concurrent antipsychotic prescription. Analyses were conducted with SAS (version 9.4; Cary, NC) and STATA SE (version 13.0; StataCorp LP, College Station, TX).

Ethics Approval

We obtained ethics approval for this study from the University of Alberta Research Ethics Board (Pro00091328).
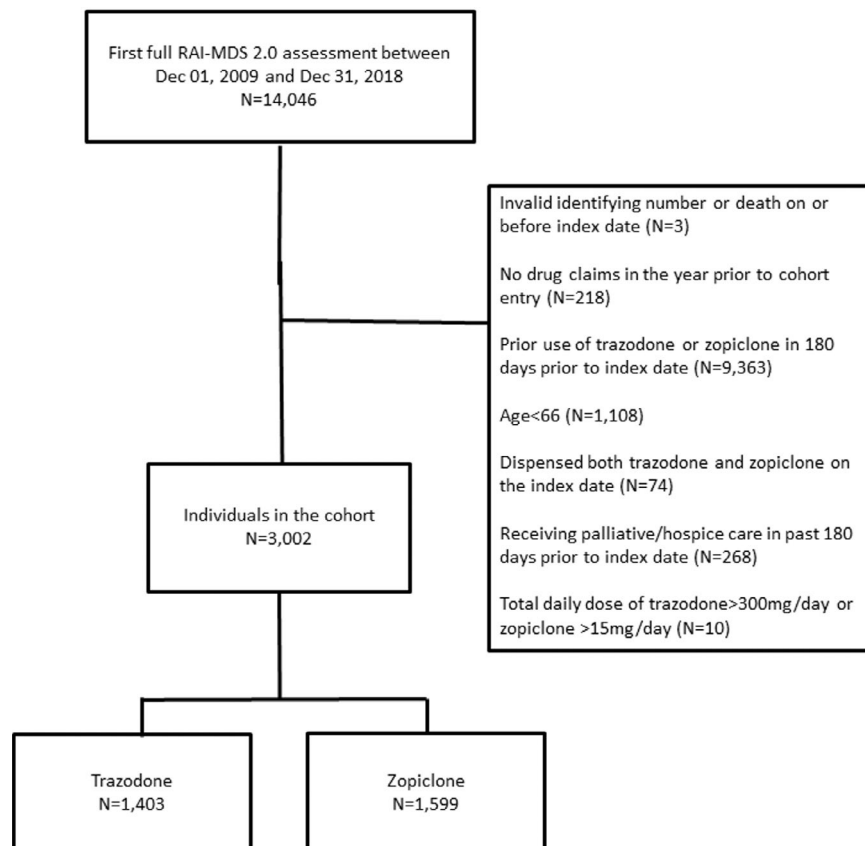
N = number; RAI-MDS 2.0 = Resident Assessment Instrument – Minimum Data Set, version 2.0.

FIGURE 1. Flow diagram of cohort creation

RESULTS

We included 3,002 residents in our study cohort: 1,403 residents were newly dispensed trazodone, and 1,599 residents were newly dispensed zopiclone (Figure 1). The median total daily dose of zopiclone was 7.5 mg (interquartile range 3.75 mg to 7.5 mg) and trazodone was 25 mg (interquartile range 25 mg to 50 mg). There were no outlying inverse probability of treatment weights. After applying inverse probability of treatment weights, exposure groups were similar at baseline (Table 1 and Table B1 in Appendix B). The mean age of residents on the date of cohort entry was 85.7 (SD 7.4), 61.6% were female, and 81.2% had a diagnosis of dementia.

In both intention-to-treat and per-protocol analyses, residents newly dispensed zopiclone experienced a similar rate of falls and major osteoporotic fractures compared to residents newly dispensed trazodone (crude hazard ratio 0.89, 0.70 to 1.13; intention-to-treat-weighted hazard ratio 1.15, 95% CI 0.90 to 1.48; per-protocol-weighted hazard ratio 0.85, 95% CI 0.60 to 1.21) (Table 2). Similarly, residents newly dispensed zopiclone experienced a similar rate of all-cause mortality compared to residents newly dispensed trazodone (crude hazard ratio 0.96, 95% CI 0.82 to 1.13; intention-to-treat-weighted hazard ratio 0.96, 95% CI 0.79 to 1.16; per-protocol-weighted hazard ratio 0.90, 95% CI 0.66 to 1.23) (Table 2). We did not conduct subgroup analyses because there were too few outcomes in exposure groups.

DISCUSSION

In our cohort of older nursing home residents, we found a similar rate of injurious falls, major osteoporotic fractures, and death in residents newly dispensed trazodone or zopiclone. Our findings are important because trazodone is associated with a similar risk of injurious falls and fractures compared to benzodiazepines and atypical antipsychotics, and these outcomes are common and important to residents and the health-care system: the mean incidence of falls in nursing homes is 1.5 falls per bed per year and 4% of falls result in a fracture.[16,17,33] Further, our findings provide direct estimates of the comparative risk of harm associated with trazodone or zopiclone use, which will inform quality improvement initiatives and highlight potential dangers associated with medication substitution as clinicians are discouraged from administering certain medications without having access to feasible and evidence-based alternatives.

There is mounting evidence of harm associated with trazodone and zopiclone use in older adults.[16-18] Trazodone is associated with a similar risk of harm from injurious falls or fractures as benzodiazepines or atypical antipsychotics.[16,17] Similarly, a systematic review and meta-analysis describing harms associated with nonbenzodiazepine sedative hypnotic use in older adults identified an increased risk of fractures and injuries, but it did not identify an increased risk of falls associated with their use.[18] However, a subsequent cohort study by Westerlind and colleagues identified an increased risk of falls associated with zopiclone or zolpidem use.[34] Our findings bridge the gap between these bodies of literature to show that trazodone and zopiclone are associated with a similar risk of harm in nursing home residents. Further, our findings, combined with the work of others, demonstrate that trazodone, zopiclone, atypical antipsychotics, and benzodiazepines are all associated with a similar risk of harm from injurious falls and fractures in this patient population.[16,17]

Unlike benzodiazepines and antipsychotics, there has been less research directed at reducing the potentially inappropriate prescribing of alternative psychotropic medications, such as trazodone and nonbenzodiazepines sedative hypnotics (i.e., z-drugs), despite growing evidence of harm associated these alternative psychotropic medications.[13-15,35] A multi-hospital study demonstrated that a sedative-hypnotic reduction quality improvement bundle, which consisted of order set changes, audit feedback, pharmacist-enabled medication reviews, sleep hygiene, daily sleep huddles, and education, decreased benzodiazepine and nonbenzodiazepine sedative hypnotic use.[35] Other potentially efficacious interventions that could be implemented instead of psychotropic medications include multidisciplinary care, massage and touch therapy, outdoor activities, and cognitive stimulation. However institution- and individual-level barriers, including perceived lack of effectiveness, lack of knowledge of the dangers associated with psychotropic medication use, inadequate staffing, and clinician attitudes towards neuropsychiatric symptom management, prevent their widespread use.[6,36-40] Institution-level (e.g., hospitals, non-profit organizations, nursing homes) policies that 1) establish an interprofessional team responsible for psychotropic medication stewardship; 2) agree on psychotropic medication appropriateness criteria, educate care staff; 3) inform and involve family and friend carers; 4) establish a regular medication review process; 5) discontinue potentially inappropriate medications; and 6) implement nonpharmacologic interventions are needed to ensure that inappropriate administration of psychotropic medications is minimized, and feasible nonpharmacologic alternative interventions are available.[41]

Our study has limitations. The nonrandomized study design means there are potential residual confounders that could influence our results; however, we 1) used comprehensive RAI-MDS 2.0 data containing information about resident health status, including functional and cognitive impairment; 2) restricted our cohort to a population of older nursing home residents (in Alberta, Canada, where residents are supported in completing basic and instrumental activities of daily living, which ensures they receive medications); and 3) utilized a propensity score to balance between-group differences. We also limited our definition of falls to those requiring transfer to hospital (i.e., injurious falls), which means our reported estimate of falls or major osteoporotic fractures per 100 person-years is likely an underestimate of true incidence.

We found that zopiclone use was associated with a similar rate of injurious falls, major osteoporotic fractures, and all-cause mortality compared to trazodone in older nursing

TABLE 1.
Baseline characteristics of a cohort of older adults dispensed trazodone or zopiclone (number [n] =3,002)

Characteristic	Trazodone (n=1403)	Zopiclone (n=1599)	Crude p value	Weighted p value
Demographics				
Year of cohort entry, n (%)				
2010	93 (6.6)	275 (17.2)		
2011	103 (7.3)	216 (13.5)		
2012	112 (8.0)	222 (13.9)		
2013	144 (10.3)	188 (11.8)	<.01	.01
2014	135 (9.6)	169 (10.6)		
2015	204 (14.5)	170 (10.6)		
2016	179 (12.8)	134 (8.4)		
2017	203 (14.5)	121 (7.6)		
2018	230 (16.4)	104 (6.5)		
Age at cohort entry, mean (SD)	85.8 (7.3)	85.6 (7.5)	.44	.35
Female, n (%)	859 (61.2)	991 (62.0)	.67	.11
Weight (kg), mean (SD)	65.9 (39.0)	68.3 (44.4)	.02	.64
Dependency in ADLs, mean (SD)	5.7 (0.7)	5.6 (0.8)	<.01	.09
Health-care Utilization				
Prescriptions in last year, mean (SD)	12.6 (6.8)	14.2 (7.5)	<.01	.97
Emergency department visits in last year, n (%)	905 (64.5)	1149 (71.9)	<.01	.22
Psychiatrist visits in last year, n (%)	451 (32.2)	315 (19.7)	<.01	.20
Geriatrician visits in last year, n (%)	30 (2.1)	21 (1.3)	.08	.23
Hospitalization in last 30 days, n (%)	71 (5.1)	127 (7.9)	<.01	.02
Medications Use in the Past Year				
Antihypertensives, n (%)	793 (56.5)	1028 (64.3)	<.01	<.01
Antidepressants, n (%)	603 (43.0)	652 (40.8)	.22	.46
Anticonvulsants, n (%)	194 (13.8)	282 (17.6)	<.01	.88
Antipsychotics, n (%)	601 (42.8)	474 (29.6)	<.01	.07
Cholinesterase inhibitors, n (%)	292 (20.8)	255 (16.0)	<.01	.57
Antiarrhythmics, n (%)	496 (35.4)	712 (44.5)	<.01	.65
Antiparkinsonian agents, n (%)	101 (7.2)	126 (7.9)	.48	.31
Osteoporosis medications, n (%)	235 (16.8)	328 (20.5)	<.01	.65
Diuretics, n (%)	378 (26.9)	569 (35.6)	<.01	.76
Opioids, n (%)	173 (12.3)	240 (15.0)	.03	.61
Antilipemics, n (%)	444 (31.7)	547 (34.2)	.14	.81
Medical History				
Atrial fibrillation/flutter, n (%)	548 (39.1)	791 (49.5)	<.01	.94
Cerebrovascular disease, n (%)	271 (19.3)	378 (23.6)	<.01	.82
Delusions or hallucinations, n (%)	122 (8.7)	82 (5.1)	<.01	.11
Dementia, n (%)	1261 (89.9)	1177 (73.6)	<.01	.04
Falls, n (%)	400 (28.5)	441 (27.6)	.57	.94
Major osteoporotic fracture, n (%)	293 (20.9)	377 (23.6)	.08	.53
Unsteady gait[a], n (%)	1308 (93.2)	1532 (95.8)	<.01	.51
Hypertension, n (%)	1012 (72.1)	1267 (79.2)	<.01	.49
Parkinsonism, n (%)	115 (8.2)	143 (8.9)	.47	.37
Psychotic disorder, n (%)	83 (5.9)	98 (6.1)	.81	.77
Wheelchair ambulation[b], n (%)	863 (61.5)	1080 (67.5)	<.01	.49

TABLE 1. Continued

Characteristic	Trazodone (n=1403)	Zopiclone (n=1599)	Crude p value	Weighted p value
Performance Scales				
Cognitive performance scale, n (%)				
mild	284 (20.2)	674 (42.2)	<.01	.15
moderate	841 (59.9)	721 (45.1)		
severe	278 (19.8)	204 (12.8)		
Aggressive behavior scale, n (%)				
none	473 (33.7)	887 (55.5)	<.01	.17
mild-moderate	591 (42.1)	540 (33.8)		
severe	339 (24.2)	172 (10.8)		
Depression rating scale, n (%)				
no depressive symptoms	744 (53.0)	1018 (63.7)	<.01	.47
depressive symptoms	659 (47.0)	581 (36.3)		

[a]<1% missing data.
[b]4% missing data.
ADL = activities of daily living; kg = kilogram; n = number; SD = standard deviation.

TABLE 2.
Intention-to-treat and per-protocol analyses of the comparative risk of (i) fall or major osteoporotic fracture and (ii) all-cause mortality for new users of zopiclone vs. trazodone within 180 days

	Trazodone (n=1,403)	Zopiclone (n=1,599)
Injurious fall or major osteoporotic fracture		
Events per 100 person-yrs (95% CI)		
Intention-to-treat	17.5 (17.3,17.7)	17.7 (17.5,17.8)
Per protocol	9.83 (9.70,9.95)	7.48 (7.37,7.59)
Hazard ratio (95% CI)		
Crude	1 (ref)	0.89 (0.70, 1.13)
Intention-to-treat	1 (ref)	1.15 (0.90, 1.48)
Per protocol	1 (ref)	0.85 (0.60, 1.21)
All-cause Mortality		
Events per 100 person-yrs (95% CI)		
Intention-to-treat	38.8 (38.6,39.1)	38.4 (38.2,38.7)
Per protocol	13.4 (13.3,13.6)	15.5 (15.3,15.6)
Hazard ratio (95% CI)		
Crude	1 (ref)	0.96 (0.82,1.13)
Intention-to-treat	1 (ref)	0.96 (0.79, 1.16)
Per protocol	1 (ref)	0.90 (0.66, 1.23)

CI = confidence interval; HR = hazard ratio; n = number; ref = reference.

home residents. Our findings suggest that quality improvement initiatives should target trazodone and nonbenzodiazepine sedative hypnotic use in older adults, in addition to benzodiazepine and antipsychotic use; trazodone and zopiclone, despite their potential for harm, are not currently targeted by many of these initiatives.[2,10,14,35,42] Our findings, combined with earlier research, suggest that 1) trazodone, zopiclone, benzodiazepines, and atypical antipsychotics are all similarly harmful in older adults with respect to a risk of falling or sustaining a fracture; 2) trazodone and zopiclone should also be targeted by quality improvement initiatives to decrease their inappropriate use; 3) further comparative safety research is needed on other psychotropic medications to inform decision-making for patients and caregivers that will help them understand the risks and benefits of choosing pharmacologic or non-pharmacologic interventions for reducing neuropsychiatric

symptoms; and, 4) greater resources should be dedicated to implementing feasible nonpharmacologic interventions to antipsychotics and benzodiazepines in nursing homes so we can avoid inappropriate substitution of potentially harmful alternative medications.[16-18,34]

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CONFLICT OF INTEREST DISCLOSURES

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APPENDIX A. Variable definitions used for cohort creation

Variable	Database Source	Codes	Algorithm
		DEMOGRAPHICS	
Age	Provincial Registry	NA	patient's age at index date
Sex	Provincial Registry	NA	patient's sex at index date
Year of cohort entry	PIN	NA	year of index date
Weight	Alberta CCIS	K2B	from most recent non-missing RAI assessment prior to index date
Receiving palliative care	CIHI-DAD Practitioner Registry Alberta CCIS	ICD10: Z515 or patserv=58 03.05I, 03.05T, 03.05U P1AO=1	any code in past 180 days prior to index date
Wheelchair ambulation	Alberta CCIS	G5B=1, G5C=1, G5D=1	any 1 code from RAI assessment ≤45 days prior to index date
		MEDICAL HISTORY	
Alcohol use	CIHI-DAD Practitioner Registry	ICD9: 303,305 ICD10: E244, E512, F10, G312, G621, G721, I426, K292, K70, K860, T510, X45, X65, Y15, Y573, Z502, Z714, Z721 291, 303	any 1 code any 2 codes
Atrial fibrillation/flutter	CIHI-DAD or NACRS Practitioner Registry PIN	ICD9: 427.31, 427.32 ICD10: I48 427, 49.98X see "Antiarrhythmics" and "Anticoagulants"	1 CIHI-DAD/NACRS code OR 1 PIN claim for "Antiarrhythmics" (****correction: instead of 1 PIN claim) OR 1 practitioner registry claim for cardioversion [Z437] OR (PIN claim for anticoagulant + 1 practitioner registry code)
Cerebrovascular disease	CIHI-DAD Alberta CCIS	ICD10: 160.x (exclude 160.8), 161.x, 163.x (exclude 163.6), H34.1, 164.x, H34.0, G45.x (exclude G45.4) I1U	any 1 code in DAD most responsible diagnosis position any 1 code
Delusions/hallucinations	Alberta CCIS	J1E=1, J1I=1	any 1 code (from most immediately antecedent RAI assessment prior to index date)
Dementia	CIHI-DAD Practitioner Registry PIN Alberta CCIS	ICD9: 46.1, 290.0, 290.1, 290.2, 290.3, 290.4, 294.x, 331.0, 331.1, 331.5, 331.82 ICD10: F00x, F01x, F02x, F03x, G30x 290, 331 see "Cholinesterase Inhibitors" I1V=1, I1R=1, P1AN=1	3 Practitioner registry codes at least 30 days apart in a 2 year period OR 1 PIN claim OR 1 CIHI-DAD code any 1 code
Depression	CIHI-DAD Practitioner Registry Alberta CCIS	ICD10: F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.8, F32.9, F33.0, F33.1, F33.2, F33.3, F33.41, F33.42, F33.8, F33.9, F34.1, F34.8, F34.9, F38.0, F38.1, F38.8, F39, F41.2 311 I1GG=1	any 1 code ≥1 psychiatrist codes OR ≥2 family physician codes within 2 years for any ICD10 depression diagnoses in CIHI-DAD (see above) any 1 code

APPENDIX A. Continued

Variable	Database Source	Codes	Algorithm
		MEDICAL HISTORY continued	
Diabetes mellitus	CIHI-DAD	ICD9: 250.x	any 1 code
	Practitioner Registry	250	any 2 codes in a 2-year period
	Alberta CCIS	I1a=1	any 1 code
Injurious falls	NACRS or CIHI-DAD	ICD10: W00-W19	Any 1 code in last year prior to index date
Hearing impairment	Alberta CCIS	C1=1,2,or3; C2A=1;C2B=1;C2C=1	Any 1 code
Heart failure	CIHI-DAD	ICD9: 428	Any 1 code
		ICD10: I500, I501, I509	Any 1 code
	Practitioner Registry	428	Any 1 code + 2nd claim from CIHI-DAD or practitioner registry in 1 year
	Alberta CCIS	I1f=1	Any 1 code
Hypertension	Practitioner Registry	ICD9: 401x, 402x, 403x, 404x, 405x ICD10: I10x, I11x, I12x, I13x, I15x	Any 2 outpatient codes within 3 years
	CIHI-DAD	ICD9: 401x, 402x, 403x, 404x, 405x ICD10: I10x, I11x, I12x, I13x, I15x	
	Alberta CCIS	I1i=1	Any 1 code
Ischemic heart disease	Practitioner Registry	410, 412, 413, 48.12, 48.13, 48.14, 48.15, 51.61C, 51.59B, 51.59D, 51.59E, 51.59F	Any 2 codes (with 1 being in a hospital or emergency room setting) in a 1 year period
	CIHI-DAD	CCI: 1IJ50, 1IJ57GQ, 1IJ76	Any 1 code
Kidney disease (chronic)	Alberta CCIS	P1AB=1	any 2 codes
Liver disease (chronic)	Alberta CCIS	I1TT=1	any 1 code
Major Osteoporotic Fracture	CIHI-DAD	ICD10: S321, S322, S323, S324, S325, S327, S328, S422, S432, S424, S720, S721; CCI 1VA53, 1VA73, 1VA74, 1VA80, 1VC73, 1VC74	any 1 code
	Practitioner Registry	91.00A-E, 91.01, 91.04A-C, 91.08L, 91.08J, 91.10, 91.14, 91.30, 91.31, 91.34	any 2 codes
	Alberta CCIS	J4C, I1M	any 1 code
Malignancy	Alberta CCIS	I1RR=1, P1AA=1, P1AH=1	any 1 code
Myocardial Infarction	CIHI-DAD or NACRS	ICD9: 410, 412 ICD10: I21, I22, I25.2	any 3 practitioner registry codes in 1 year (with at least one being by a specialist [i.e., not a family doctor] OR within a hospital or emergency room) + any one CIHI-DAD code
	Practitioner Registry	ICD9: 410, 412 ICD10: I21, I22, I25.2	
Osteoporosis	CIHI-DAD	ICD9: 733.01-733.09	any 1 code in 5 years prior to index date
		ICD10: M80, M81, M82	
	PIN	See "Osteoporosis Medications"	any 1 code
	Practitioner Registry	733	any 1 code in 5 years prior to index date
	Alberta CCIS	I1O=1	any 1 code

APPENDIX A. Continued

Variable	Database Source	Codes	Algorithm
MEDICAL HISTORY continued			
Parkinsonism	CIHI-DAD	ICD9: 332.0, 332.1 ICD10: G20, G21.0, G21.1, G21.2, G21.3, G21.4, G21.8, G21.9, G22, F02.3	don't use; algorithm is best with Practitioner Registry codes - many other algorithms if needed
	Practitioner Registry	332	any 2 practitioner registry codes in 1 year separated by 30 days
	Alberta CCIS	I1AA=1	any 1 code
Peripheral vascular disease	Alberta CCIS	I1J=1	any 1 code
Psychoses (chronic)	CIHI DAD	ICD10: F20, F25, F29	any 1 CIHI-DAD code or 2 practitioner registry codes within 5 years
	Practitioner Registry	295, 298	
	Alberta CCIS	I1II=1	any 1 code
Rheumatoid arthritis	CIHI-DAD	ICD9: 714 ICD10: M05-M06	any 1 code
	Practitioner Registry	714	any 3 codes with ≥1 by a specialist (specialist = rheumatologist, internist, or orthopedic surgeon) within 2 years
Seizure disorder	CIHI-DAD	ICD9: 345 ICD10: G40.x, G41.x	any 1 code
	Practitioner Registry	345	3 codes separated by 30 days
	Alberta CCIS	I1CC=1	any 1 code
Unsteady gait	Alberta CCIS	J1N=1, G5A=1, G6B=1, G6C=1, G6D=1, G6E=1	any 1 code
Visual impairment	Alberta CCIS	D1=1,2,3,or 4; D2A=1;D2B=1;D3=1	any 1 code
HEALTH-CARE UTILIZATION[a]			
Number of inpatient hospitalizations	CIHI-DAD	NA	Use %getdadsds to pull all hospitalization admissions (parameter source = inpat; parameter refdate = admdate) in the year prior to index date. To exclude hospital transfers, only keep one hospitalization record for each unique hospitalization episode (variable epi). Count the number of inpatients admissions for each cohort member.
Number of drugs prescribed	PIN	NA	Use %getodb to pull all ODB records (including records without the LTC flag) in the year prior to index date. Count the number of unique dins for each cohort member.
Number of emergency room visits	NACRS	NA	Use %getnacrs to pull all unscheduled ED records (parameter inclscheduled = F) in the year prior to index date. Exclude records that constitute a transfer from one ED to another ED (where From_Type = 'E'). Count the number of ED visits for each cohort member.
Number of geriatrician visits	Practitioner Claims	SPECNAM = ("GERIATRICS")	Count only one visit per person per day per physician. For each patient, sum the total number of visits made in the past year.

APPENDIX A. Continued

Variable	Database Source	Codes	Algorithm
HEALTH-CARE UTILIZATION[a] *continued*			
Number of psychiatrist visits	Practitioner Claims	SPECNAM = ("PSYCHIATRY")	Count only one visit per person per day per physician. For each patient, sum the total number of visits made in the past year.
PERFORMANCE SCALES			
Cognitive performance scale	Alberta CCIS	B1=0,1; B4=0,1,2,3; G1h=0,1,2; B2a=0,1; C4=0,1,2,3	from RAI assessment ≤45 days prior to index date
Dependency in ≥1 activities of daily living (ADL)	Alberta CCIS	G1a=1,2,3, or 4; G1b=1,2,3, or 4; G1c=1,2,3, or 4; G1d=1,2,3, or 4; G1e=1,2,3, or 4; G1f=1,2,3, or 4; G1g=1,2,3, or 4; G1h=1,2,3, or 4; G1i=1,2,3, or 4; G1j=1,2,3, or 4; G2=1,2,3 or 4	any 1 code equal to 1, 2, 3, or 4 from (one of G1a,G1b,G1c,G1d,G1e, G1f) OR G1g, G1h, G1i, G1j, G2 (from RAI assessment ≤30 days prior to index date)
Dependency in ADLs (mean, SD)	Alberta CCIS	G1a=1,2,3, or 4; G1b=1,2,3, or 4; G1c=1,2,3, or 4; G1d=1,2,3, or 4; G1e=1,2,3, or 4; G1f=1,2,3, or 4; G1g=1,2,3, or 4; G1h=1,2,3, or 4; G1i=1,2,3, or 4; G1j=1,2,3, or 4; G2=1,2,3 or 4	if (G1a=1,2,3, or 4) OR (G1b=1,2,3, or 4) OR (G1c=1,2,3, or 4) OR (G1d=1,2,3, or 4) OR (G1e=1,2,3, or 4) OR (G1f=1,2,3, or 4) then patient is dependent for mobility (mobility=1); if G1g=1,2,3, or 4 then dressing=1; if G1h=1,2,3, or 4 then eating=1; if G1i=1,2,3, or 4 then toilet=1; if G1j=1,2,3, or 4 then hygiene=1; if G2=1,2,3 or 4 then bathing=1; sum of mobility + dressing + eating + toilet + hygiene + bathing = dependency in ADLs (from RAI assessment ≤30 days prior to index date)
Depression symptom scale	Alberta CCIS	E1a=0,1,2; E1d=0,1,2; E1f=0,1,2; E1h=0,1,2; E1i=0,1,2; E1l=0,1,2; E1m=0,1,2	from RAI assessment ≤45 days prior to index date
Aggressive behaviour scale	Alberta CCIS	E4b=0,1,2,3; E4c=0,1,2,3; E4d=0,1,2,3; E4e=0,1,2,3	from RAI assessment ≤45 days prior to index date
OUTCOMES			
Major osteoporotic fracture	NACRS or CIHI-DAD	ICD 10: S321, S322, S323, S324, S325, S327, S328, S422, S432, S424, S720, S721; CCI 1VA53, 1VA73, 1VA74, 1VA80, 1VC73, 1VC74	admission date (admdate) is within 180 days following index date; combine NACRS and DAD records and keep the record for the first (earliest) fracture within the 180 day follow-up period.
	Practitioner Claims	91.00A-E, 91.01, 91.04A-C, 91.08L, 91.08J, 91.10, 91.14, 91.30, 91.31, 91.34	any 2 codes within the 180 day follow-up period
Injurious fall	NACRS or CIHI-DAD	ICD 10: W00-W19	admission date (admdate) is within 180 days following index date; combine NACRS and DAD records and keep the record for the first (earliest) fall within the 180 day follow-up period.

[a]For all hospitalizations using DAD defined above, use:
DAD source: inpatient; Diagnosis type: All diagnosis types except where specifically indicated otherwise;
Exclude suspected diagnoses.

Data Sources
The Alberta Continuing Care Information System (CCIS) contains comprehensive information about residents of nursing homes, including their functional dependence, severity of cognitive impairment, and symptoms relating to depression and pain. Dispensed prescription medications were identified in the Pharmacy Information Network (PIN). The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) was used to identify all inpatient hospitalizations. The National Ambulatory Care Reporting System (NACRS) database was used to identify all emergency department visits. All information relating to physician payment claims was obtained from the Practitioner Claims database. All patient demographic information (including date of death, if appropriate) was obtained from the Provincial Registry.

APPENDIX B.

TABLE B1.

Complete baseline characteristics of a cohort of older adults dispensed trazodone or zopiclone (number [n] =3,002)

Characteristic	Trazodone (n=1403)	Zopiclone (n=1599)	Crude p Value	Weighted p Value
DEMOGRAPHICS				
Year of cohort entry, n (%)				
2010	93 (6.6)	275 (17.2)		
2011	103 (7.3)	216 (13.5)		
2012	112 (8.0)	222 (13.9)		
2013	144 (10.3)	188 (11.8)		
2014	135 (9.6)	169 (10.6)	<.01	.01
2015	204 (14.5)	170 (10.6)		
2016	179 (12.8)	134 (8.4)		
2017	203 (14.5)	121 (7.6)		
2018	230 (16.4)	104 (6.5)		
Age at cohort entry, mean (SD)	85.8 (7.3)	85.6 (7.5)	.44	.35
Female, n (%)	859 (61.2)	991 (62.0)	.67	.11
Weight (kg), mean (SD)	65.9 (39.0)	68.3 (44.4)	.02	.64
Dependency in ≥1 ADLs, n (%)	1001 (99.9)	1592 (99.6)	.22	.33
Dependency in ADLs, mean (SD)	5.7 (0.7)	5.6 (0.8)	<.01	.09
HEALTH-CARE UTILIZATION				
Prescriptions in last year, mean (SD)	12.6 (6.8)	14.2 (7.5)	<.01	.97
Emergency department visits in last year, n (%)	905 (64.5)	1149 (71.9)	<.01	.22
Psychiatrist visits in last year, n (%)	451 (32.2)	315 (19.7)	<.01	.2
Geriatrician visits in last year, n (%)	30 (2.1)	21 (1.3)	.08	.23
Inpatient hospitalizations in 30 days prior to exposure drugs, n (%)	780 (55.6)	1035 (64.7)	<.01	.04
Hospitalization in 30 days prior to exposure drugs, n (%)	71 (5.1)	127 (7.9)	<.01	.02
Nursing home admission in 30 days prior to exposure drugs, n (%)	509 (36.3)	560 (35.0)	.47	.05
MEDICATIONS				
Antihypertensives, n (%)	793 (56.5)	1028 (64.3)	<.01	<.01
Anticoagulants, n (%)	256 (18.3)	364 (22.8)	<.01	.71
Antidepressants, n (%)	603 (43.0)	652 (40.8)	.22	.46
Anticonvulsants, n (%)	194 (13.8)	282 (17.6)	<.01	.88
Antipsychotics, n (%)	601 (42.8)	474 (29.6)	<.01	.07
Cholinesterase inhibitors, n (%)	292 (20.8)	255 (16.0)	<.01	.57
Memantine, n (%)	66 (4.7)	26 (1.6)	<.01	.69
Antiplatelet agents, n (%)	583 (41.6)	733 (45.8)	.02	.37
Antiarrhythmics, n (%)	496 (35.4)	712 (44.5)	<.01	.65
Antiparkinsonian agents, n (%)	101 (7.2)	126 (7.9)	.48	.31
Osteoporosis medications, n (%)	235 (16.8)	328 (20.5)	<.01	.65
Diuretics, n (%)	378 (26.9)	569 (35.6)	<.01	.76
Glucocorticoids, n (%)	109 (7.8)	169 (10.6)	<.01	.42
Hormone therapies, n (%)	42 (3.0)	41 (2.6)	.47	0.86
Antihyperglycemic medications, n (%)	240 (17.1)	299 (18.7)	.26	.39
NSAIDs, n (%)	100 (7.1)	147 (9.2)	.04	.65
Opioids, n (%)	173 (12.3)	240 (15.0)	.03	.61
Antilipemics, n (%)	444 (31.7)	547 (34.2)	.14	.81
Acid reflux medications, n (%)	550 (39.2)	725 (45.3)	<.01	.03
Urinary incontinence treatments, n (%)	250 (17.8)	352 (22.0)	<.01	<.01

TABLE B1. Continued

Characteristic	Trazodone (n=1403)	Zopiclone (n=1599)	Crude p Value	Weighted p Value
MEDICAL HISTORY				
Alcohol use disorder, n (%)	90 (6.4)	82 (5.1)	.13	.06
Atrial fibrillation/flutter, n (%)	548 (39.1)	791 (49.5)	<.01	.94
Cerebrovascular disease, n (%)	271 (19.3)	378 (23.6)	<.01	.82
Delusions or hallucinations, n (%)	122 (8.7)	82 (5.1)	<.01	.11
Depression, n (%)	634 (45.2)	723 (45.2)	.99	.89
Dementia, n (%)	1261 (89.9)	1177 (73.6)	<.01	.04
Diabetes mellitus, n (%)	384 (27.4)	464 (29.0)	.32	.45
Injurious falls, n (%)	400 (28.5)	441 (27.6)	.57	.94
Major osteoporotic fracture, n (%)	293 (20.9)	377 (23.6)	.08	.53
Heart failure, n (%)	251 (17.9)	420 (26.3)	<.01	.51
Unsteady gait[a], n (%)	1308 (93.2)	1532 (95.8)	<.01	.51
Hearing impairment[b], n (%)	710 (50.6)	792 (49.5)	.56	.06
Myocardial Infarction, n (%)	42 (3.0)	102 (6.4)	<.01	<.01
Hypertension, n (%)	1012 (72.1)	1267 (79.2)	<.01	.49
Chronic liver disease, n (%)	10 (0.7)	12 (0.8)	.90	.97
Malignancy[b], n (%)	108 (7.7)	109 (6.8)	.35	.52
Parkinsonism, n (%)	115 (8.2)	143 (8.9)	.47	.37
Peripheral vascular disease[b], n (%)	45 (3.2)	75 (4.7)	.04	.83
Psychotic disorder, n (%)	83 (5.9)	98 (6.1)	.81	.77
Rheumatoid arthritis, n (%)	21 (1.5)	32 (2.0)	.30	.27
Seizure disorder, n (%)	52 (3.7)	65 (4.1)	.61	.62
Visual impairment[b], n (%)	1148 (81.8)	1299 (81.2)	.68	.59
Wheelchair ambulation[b], n (%)	863 (61.5)	1080 (67.5)	<.01	.49
Charlson comorbidity index, mean (SD)	2.5 (2.1)	3.1 (2.5)	<.01	.1
PERFORMANCE SCALES				
Cognitive performance scale, n (%)				
mild	284 (20.2)	674 (42.2)	<.01	.15
moderate	841 (59.9)	721 (45.1)		
severe	278 (19.8)	204 (12.8)		
Aggressive behavior scale, n (%)				
none	473 (33.7)	887 (55.5)	<.01	.17
mild-moderate	591 (42.1)	540 (33.8)		
severe	339 (24.2)	172 (10.8)		
Depression rating scale, n (%)				
no depressive symptoms	744 (53.0)	1018 (63.7)	<.01	.47
depressive symptoms	659 (47.0)	581 (36.3)		

[a]<1% missing data.

[b]4% missing data.

ADL = activities of daily living; kg = kilogram; NSAIDs = nonsteroidal anti-inflammatory drugs; n = number; SD = standard deviation.