

Risk of pneumonia associated with incident benzodiazepine use among community-dwelling adults with Alzheimer disease

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ABSTRACT

BACKGROUND: Knowledge regarding whether benzodiazepines and similarly acting non-benzodiazepines (Z-drugs) are associated with an increased risk of pneumonia among older adults is lacking. We sought to investigate this association among community-dwelling adults with Alzheimer disease, a condition in which both sedative/hypnotic use and pneumonia are common.

METHODS: We obtained data on all community-dwelling adults with a recent diagnosis of Alzheimer disease in Finland (2005–2011) from the Medication use and Alzheimer disease (MEDALZ) cohort, which incorporates national registry data on prescriptions, reimbursement, hospital discharges and causes of

death. Incident users of benzodiazepines and Z-drugs were identified using a 1-year washout period and matched with nonusers using propensity scores. The association with hospital admission or death due to pneumonia was analyzed with the Cox proportional hazards model and adjusted for use of other psychotropic drugs in a time-dependent manner.

RESULTS: Among 49 484 eligible participants with Alzheimer disease, 5232 taking benzodiazepines and 3269 taking Z-drugs were matched 1:1 with those not taking these drugs. Collectively, use of benzodiazepines and Z-drugs was associated with an increased risk of pneumonia (adjusted hazard ratio [HR]

1.22, 95% confidence interval [CI] 1.05–1.42). When analyzed separately, benzodiazepine use was significantly associated with an increased risk of pneumonia (adjusted HR 1.28, 95% CI 1.07–1.54), whereas Z-drug use was not (adjusted HR 1.10, 95% CI 0.84–1.44). The risk of pneumonia was greatest within the first 30 days of benzodiazepine use (HR 2.09, 95% CI 1.26–3.48).

INTERPRETATION: Benzodiazepine use was associated with an increased risk of pneumonia among patients with Alzheimer disease. Risk of pneumonia should be considered when weighing the benefits and risks of benzodiazepines in this population.

Alzheimer disease is the most common form of dementia, accounting for 60%–70% of all cases.^{1,2} In 2011, there were 35.6 million people with dementia globally, and the number is estimated to double every 20 years. Aging is the major risk factor for Alzheimer disease; thus, population aging is leading to major public health challenges related to dementia disorders. Dementia and Alzheimer disease result in frequent health care service utilization and substantial health care costs.³ Current drug therapy for Alzheimer disease has only modest efficacy.⁴ Behavioural and psychological symptoms of dementia are frequent^{5,6}

and often treated with psychotropic drugs,⁷ although these symptoms are not approved indications for most of these drugs. Use of benzodiazepines and similarly acting non-benzodiazepines (Z-drugs) is frequent among those with Alzheimer disease, and many patients use these drugs long term,⁸ although clinical care guidelines recommend only short-term use.^{5,6}

Incidence of pneumonia increases with age.⁹ Pneumonia is frequent and one of the leading causes of admission to hospital among adults with Alzheimer disease.¹⁰ Other risk factors include female sex, smoking, alcohol abuse, respiratory diseases and many other

comorbidities.¹¹ Dementia is also a risk factor for pneumonia-related death.^{12,13} Thus, it is important to recognize factors that increase the risk of pneumonia. Benzodiazepines are known to induce sedation, and more pronounced sedative effects are noticed among older adults because of pharmacodynamic changes.¹⁴ Sedation may lead to pneumonia by increased risk of aspiration.¹⁵

A nested case-control study in the United Kingdom evaluated benzodiazepine use and occurrence of pneumonia in people of all ages and found a 50% increased risk of pneumonia.¹⁶ However, another case-control study in the United States among older adults did not find an association between benzodiazepine use and pneumonia but reported an increased risk for opioid use.¹⁷ A recent population-based cohort study on benzodiazepine use found that it also was associated with adverse respiratory outcomes among older adults with chronic obstructive pulmonary disease (COPD).¹⁸

Our objective was to investigate whether benzodiazepine and Z-drug use is associated with risk of pneumonia among community-dwelling adults with a diagnosis of Alzheimer disease.

Methods

Setting

The Medication use and Alzheimer disease (MEDALZ) cohort included all community-dwelling adults with a diagnosis of Alzheimer disease ($n = 70\,718$) between 2005 and 2011 in Finland.¹⁹ These participants were identified from the Special Reimbursement Register (maintained by the Social Insurance Institution of Finland) that includes people with a diagnosis of chronic disease according to a predefined protocol. The protocol for Alzheimer disease includes a computed tomography or magnetic resonance imaging scan and confirmation of the diagnosis by a neurologist or geriatrician. The Social Insurance Institution of Finland, which grants special reimbursement, ensures that diagnostic criteria are met. Diagnosis was based on criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)²⁰ and DSM-IV (*Diagnostic and statistical manual of mental disorders*, 4th ed. Washington: American Psychiatric Association; 1994).

Data sources

Data for the cohort were collected from several nationwide registers in Finland: Prescription Register (for drug use, 1995–2012), Special Reimbursement Register (for comorbidities, 1972–2012) and Hospital Discharge Register (for pneumonia diagnoses and comorbidities, 1972–2012); and socioeconomic data since 1970 and causes of death (2005–2012) from Statistics Finland. The Prescription Register includes information on purchases of reimbursed drugs that are classified according to the Anatomic Therapeutic Chemical classification system.²¹ Some small packages (i.e., 10–30 tablets) of benzodiazepines and related drugs are not reimbursed; therefore, they are not captured in the database. However, reimbursement status is a strong driver of prescribing, because drugs without reimbursement status are more expensive. Data on drug use were restricted to community-dwelling

patients; drugs used during stays in hospital and public nursing homes are not recorded in the register.

Study design and participants

We modelled when drug use started and ended (i.e., drug use period) with a previously used method (Prescriptions to drug use periods, PRE2DUP).^{8,22} We based our model on sliding averages of daily dose, and we modelled each Anatomic Therapeutic Chemical classification system code separately for each participant according to purchase regularity, taking into account admissions to hospital, stockpiling of drugs and changing dose as described previously.^{8,22}

We defined use of benzodiazepines and Z-drugs by the following Anatomic Therapeutic Chemical classification system codes: N05BA and N05CD for benzodiazepines and N05CF for Z-drugs. Benzodiazepines prescribed in this study included diazepam, nitrazepam, chlordiazepoxide, clobazam, oxazepam, alprazolam, lorazepam and temazepam, whereas Z-drugs included zopiclone and zolpidem. We modelled use of benzodiazepine and Z-drugs as “use of any of these drugs” by combining overlapping use periods of different drugs. Thus, patients were allowed to change from one drug to another if there were no breaks in drug availability. Similarly, we combined overlapping drug use periods when we modelled use of “any benzodiazepine” or “any Z-drug.”

We identified diagnoses of pneumonia from the Hospital Discharge and Causes of Death Registers, which represent hospital-treated pneumonia and pneumonia as a direct or underlying cause of death but excludes community-treated cases (not included in register-based data). We used the following ICD-10 (International Classifications of Diseases and Related Health Problems, 10th rev, World Health Organization, 1992) codes to define a diagnosis of pneumonia: J100, J110, J12, J13, J14, J15, J16, J18 and J690. Only the first recorded outcome (hospitalization or death due to pneumonia) for each person was considered after the date of the diagnosis of Alzheimer disease.

We excluded participants who were taking benzodiazepines or Z-drugs during the 1-year washout period before the date of diagnosis of Alzheimer disease, those who had more than 182 cumulative days in hospital and those who were in hospital for more than 90 days at the end of the washout period from all analyses. We also excluded participants who were in hospital or an institution during the entire follow-up period (Figure 1).

Statistical analysis

We conducted propensity score-matched analyses to compare participants who used benzodiazepines and Z-drugs with those who did not. Time since diagnosis of Alzheimer disease is a key factor that affects initiation of both benzodiazepines and Z-drugs, and risk of pneumonia. For this reason, we divided the follow-up time for the initiation of drug use into 3 sets by time passed since diagnosis: 0 to less than 1 year, 1 to less than 2 years and 2 or more years. We used logistic regression to derive 1 propensity score to predict initiation of benzodiazepine and another score to predict initiation of Z-drug within the prespecified time sets because initiators of these drugs may differ from each other in baseline covariates (Figure 2). Participants not tak-

ing these drugs were included in all time sets if censoring or an outcome event had not occurred before the start of the time set. More than 40 covariates (e.g., factors related to mental health that were strongly associated with use of benzodiazepines and Z-drugs, and markers of exacerbations of respiratory diseases) were included in the scores and measured before or at the start of the time sets. Descriptions of covariates are listed in Table 1, Table 2 and Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.160126/-/DC1).

Based on the estimated propensity scores, we conducted 1:1 nearest neighbour matching without replacement using 0.2 as a caliper width within the time sets, starting with those participants initiating use 2 or more years since the date of diagnosis.²³ We obtained 6 sets of matches that were merged together to form the matched study population, which excluded 44 participants who started benzodiazepines and 43 participants who started Z-drugs because they did not have a match. We evaluated similarity of matched patients taking these drugs and those

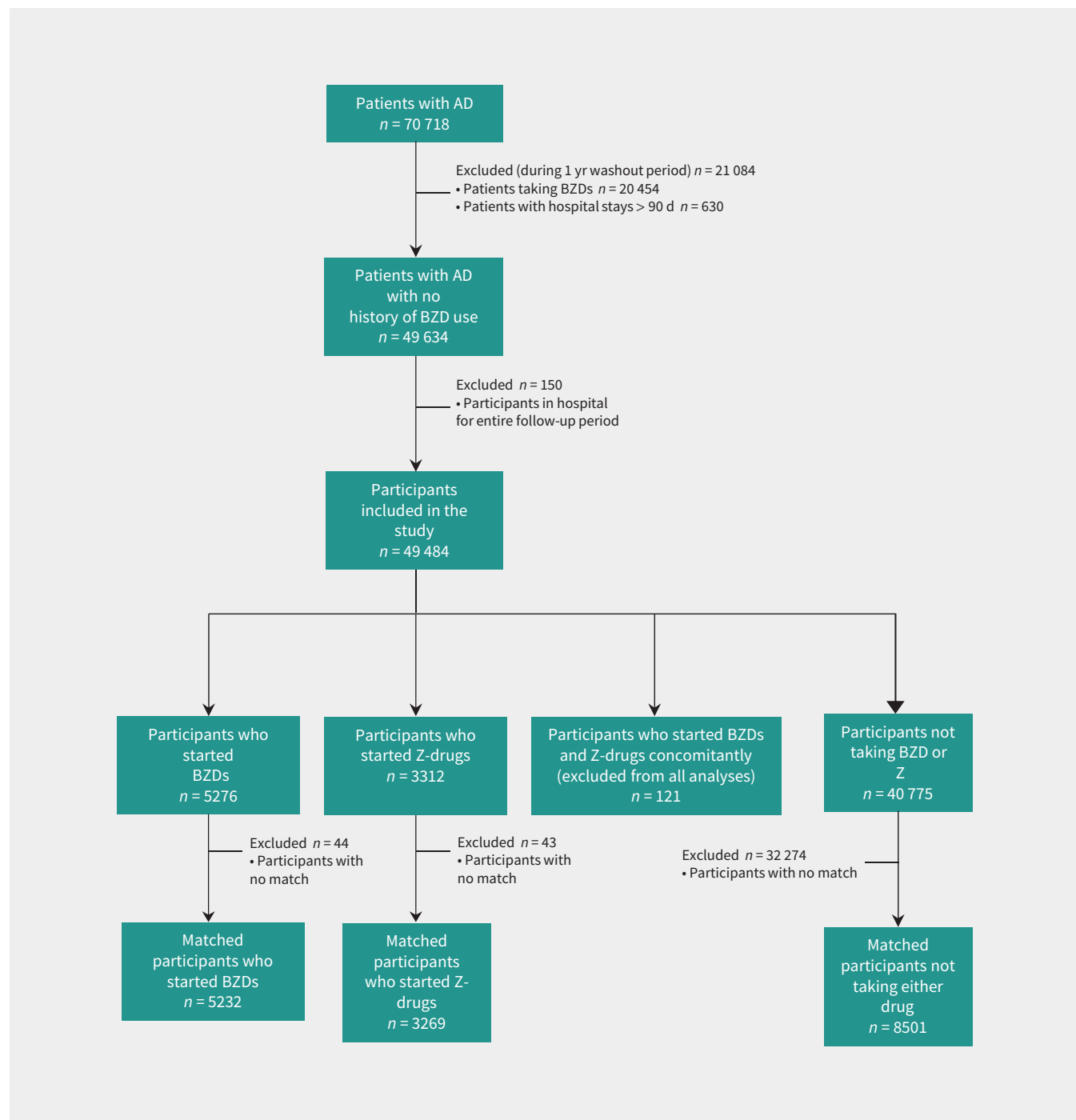


Figure 1: Flow chart showing selection of participants for the study. AD = Alzheimer disease, BZD = benzodiazepine, Z-drug = non-benzodiazepine similar in activity to benzodiazepine, BZDR = benzodiazepine and/or Z-drug.

not taking them using standardized difference, and we considered values greater than 10% to indicate meaningful imbalance between the groups.²⁴

We defined the index date as the start date of the time set when participants were matched with those not using the drugs (i.e., date of diagnosis, 1 yr after diagnosis or 2 yr after diagnosis). Follow-up for outcome events started at the index date for participants not using the drugs and at the initiation of use for those using the drugs. The follow-up ended when the participant was admitted to hospital or an institution for more than 90 days, upon death, discontinuation of use of benzodiazepines and Z-drugs, upon a switch between or concomitant use of benzodiazepines and Z-drugs, outcome of interest (pneumonia) or the end of study follow-up (Dec. 31, 2012), whichever occurred first.

We evaluated the effect of incident benzodiazepine use on risk of pneumonia using a Cox proportional hazards model, taking into account matching between those participants taking

benzodiazepines and those not taking them. We also analyzed how the risk of pneumonia varied by length of benzodiazepine and Z-drug use by using a time-dependent classification of duration of use — 30 days or less, 31 to 180 days, 181 to 365 days, 366 to 1095 days and more than 1095 days of use — and adding it as a time-dependent covariate in the main model.

To minimize the impact of other psychotropic drugs (antipsychotics, antidepressants and opioids) on the risk of pneumonia, we constructed a model with use of psychotropic drugs as a time-dependent covariate (instead of use at the index date). We conducted drug-substance-specific and higher versus lower dose analyses among those participants who initiated with monotherapy ($n = 8382$).

We performed secondary analyses by treating death due to causes other than pneumonia and a hospital stay of more than 90 days as competing risks for pneumonia in cause-specific hazards models.²⁵ In this method, we considered competing risks that prevent occurrence of pneumonia as censoring events.

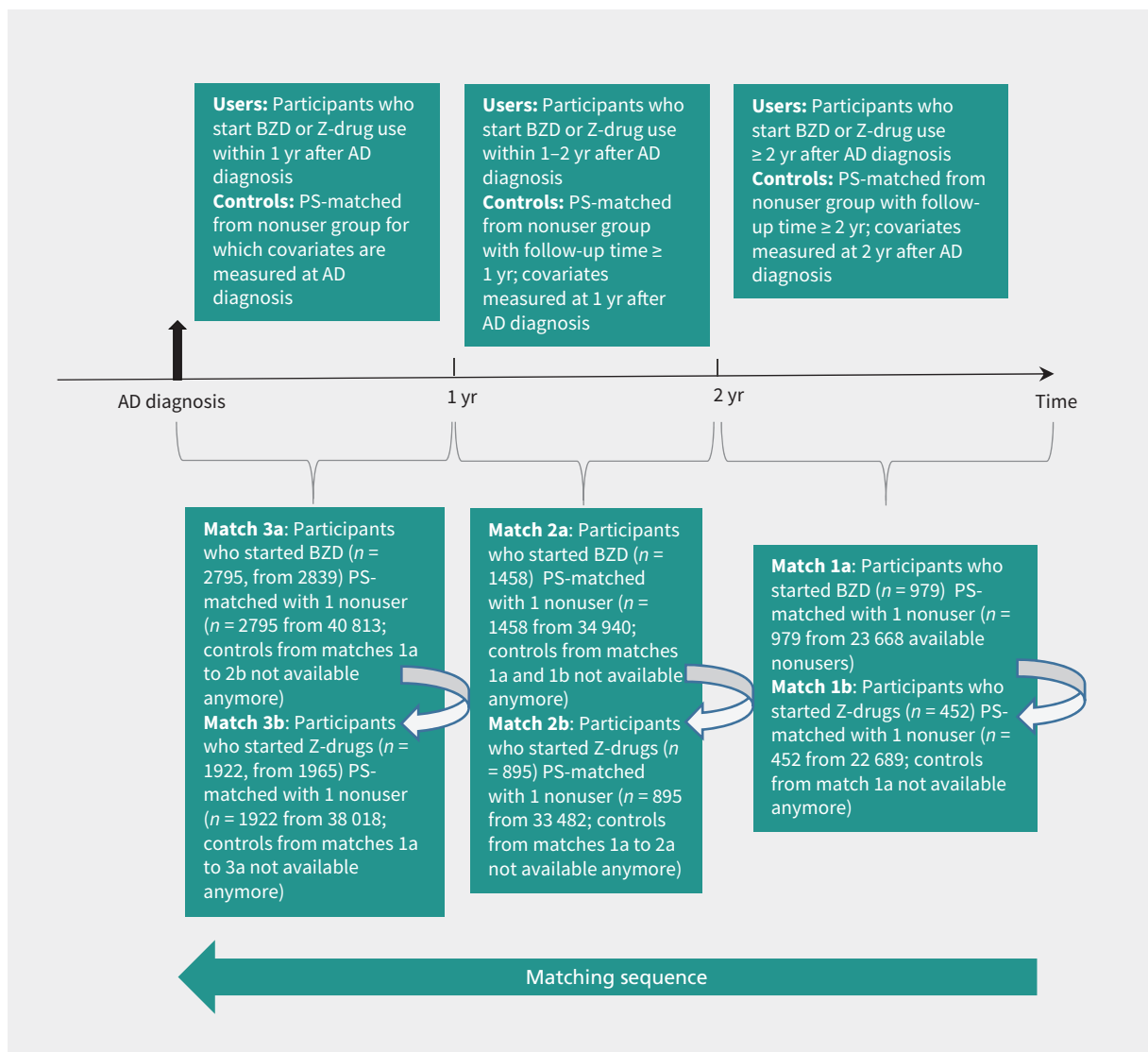


Figure 2: Process of propensity score matching for participants using benzodiazepines (BZDs) to those not using them and participants using Z-drugs (non-benzodiazepines similar in activity to benzodiazepines) to those not using them, by time-since-diagnosis of Alzheimer disease (AD). PS = propensity score.

Table 1 (part 1 of 2): Characteristics of participants taking benzodiazepines and those not taking benzodiazepines before and after propensity score matching

Characteristic	No. of participants (before PS matching), n (%)		Standardized difference before PS matching, %*	No. of patients (after PS matching), n (%)		Standardized difference after PS matching, %*
	No BZD use n = 40 775	BZD use n = 5276		No BZD use n = 5232	BZD use n = 5232	
Sex			1.2			1.6
Male	15 271 (37.5)	1945 (36.9)		1889 (36.1)	1928 (36.9)	
Female	25 504 (62.6)	3331 (63.1)		3343 (63.9)	3304 (63.1)	
Age, yr						
< 65	1472 (3.6)	248 (4.7)	5.5	178 (3.4)	217 (4.2)	3.9
65–74	7807 (19.2)	1066 (20.2)	2.7	875 (16.7)	904 (17.3)	1.5
75–84	22 508 (55.2)	2779 (52.7)	5.1	2832 (54.1)	2733 (52.2)	3.8
≥ 85	8988 (22.0)	1183 (22.4)	0.9	1347 (25.8)	1378 (26.3)	1.3
Socioeconomic position						
High	14 127 (34.7)	1654 (31.4)	7.0	1716 (32.8)	1644 (31.4)	3.0
Medium	23 698 (58.1)	3138 (59.5)	2.8	3030 (57.9)	3109 (59.4)	3.1
Low	2471 (6.1)	417 (7.9)	7.2	407 (7.8)	413 (7.9)	0.4
Unknown	479 (1.2)	67 (1.3)	0.9	79 (1.5)	66 (1.3)	2.1
Drug use ever before index date						
Antipsychotic	3837 (9.4)	1255 (23.8)	39.4	2193 (41.9)	1994 (38.1)	7.8
Benzodiazepine or Z-drug	8136 (20.0)	1649 (31.3)	26.1	1809 (34.6)	1615 (30.9)	7.9
Antidepressant	10 341 (25.4)	1855 (35.2)	21.4	2316 (44.3)	2176 (41.6)	5.4
Drug use at index date						
Antineoplastic drug	1363 (3.3)	150 (2.8)	2.9	171 (3.3)	167 (3.2)	0.4
Opioid	1100 (2.7)	198 (3.8)	6.0	295 (5.6)	277 (5.3)	1.5
Antipsychotic	2408 (5.9)	1283 (24.3)	53.2	2011 (38.4)	2040 (39.0)	1.1
Antidepressant	5462 (13.4)	1195 (22.7)	24.3	1553 (29.7)	1493 (28.5)	2.5
Proton pump inhibitor	3976 (9.8)	666 (12.6)	9.1	903 (17.3)	857 (16.4)	2.4
Antiepileptic	1405 (3.5)	239 (4.5)	5.5	310 (5.9)	294 (5.6)	1.3
Cardiovascular drug	29903 (73.3)	3841 (72.8)	1.2	4045 (77.3)	3935 (75.2)	4.9
Comorbidity						
Cardiovascular disease	19 633 (48.2)	2567 (48.7)	1.0	2694 (51.5)	2567 (49.1)	4.9
Chronic heart failure	11 332 (27.8)	1452 (27.5)	0.6	1586 (30.3)	1518 (29.0)	2.9
Cardiac arrhythmia	2748 (6.7)	360 (6.8)	0.3	362 (6.9)	363 (6.9)	0.1
Hypertension	12 005 (29.4)	1574 (29.8)	0.9	1680 (32.1)	1632 (31.2)	2.0
Stroke	3631 (8.9)	489 (9.3)	1.3	337 (6.4)	104 (2.0)	1.3
Diabetes	5430 (13.3)	571 (10.8)	7.7	641 (12.3)	591 (11.3)	3.0
Complicated diabetes	6631 (16.3)	708 (13.4)	8.0	778 (14.9)	709 (13.6)	0.0
Peripheral vascular disease	2005 (4.9)	247 (4.7)	1.1	258 (4.9)	249 (4.8)	0.8
Substance abuse	775 (1.9)	190 (3.6)	10.4	189 (3.6)	203 (3.9)	1.4
Previous hospital-treated fracture	7103 (17.4)	951 (18.0)	1.6	1085 (20.7)	1067 (20.4)	0.9
Any tumour	5178 (12.7)	662 (12.6)	0.5	668 (12.8)	660 (12.6)	0.5
Anemia	2695 (6.6)	311 (5.9)	3.0	345 (6.6)	321 (6.1)	1.9
Fluid and electrolyte disorder	1053 (2.6)	188 (3.6)	5.7	201 (3.8)	197 (3.8)	0.4
Epilepsy	808 (2.0)	106 (2.0)	0.2	135 (2.6)	125 (2.4)	1.2

Table 1 (part 2 of 2): Characteristics of participants taking benzodiazepines and those not taking benzodiazepines before and after propensity score matching

Characteristic	No. of participants (before PS matching), n (%)		Standardized difference before PS matching, %*	No. of patients (after PS matching), n (%)		Standardized difference after PS matching, %*
	No BZD use n = 40 775	BZD use n = 5276		No BZD use n = 5232	BZD use n = 5232	
Respiratory comorbidity						
Asthma/COPD	3208 (7.9)	425 (8.1)	0.7	418 (8.0)	424 (8.1)	0.4
Any pulmonary disease	4302 (10.6)	572 (10.8)	0.9	591 (11.3)	570 (10.9)	1.3
Previous pneumonia 1 yr before diagnosis of Alzheimer disease	978 (2.4)	105 (2.0)	2.8	105 (2.0)	104 (2.0)	0.1
Hospital admission for asthma/COPD before (\leq 1 yr) index date	629 (1.5)	102 (1.9)	3.0	116 (2.2)	114 (2.2)	0.3
Antibiotic or oral corticosteroid use before (\leq 30 d) index date	4334 (10.6)	624 (11.8)	3.8	827 (15.8)	760 (14.5)	3.6
Theophylline use before (\leq 180 d) index date	331 (0.8)	58 (1.1)	3.0	50 (1.0)	58 (1.1)	1.5
β -Agonist use before (\leq 180 d) index date	1777 (4.4)	230 (4.4)	0.0	227 (4.3)	225 (4.3)	0.2
Use of inhaled anticholinergic before (\leq 180 d) index date	527 (1.3)	78 (1.5)	1.6	77 (1.5)	83 (1.6)	0.9
Use of inhaled corticosteroid before (\leq 180 d) index date	1395 (3.4)	169 (3.2)	1.2	170 (3.3)	148 (2.8)	2.5
Combined inhaled corticosteroid/long-acting β -agonist use before (\leq 180 d) index date	1457 (3.6)	181 (3.4)	0.8	180 (3.4)	196 (3.8)	1.6
Mental health-related comorbidity						
Schizophrenia	447 (1.1)	100 (1.9)	6.6	103 (2.0)	100 (1.9)	0.4
Depression or bipolar disorder	806 (2.0)	164 (3.1)	7.2	194 (3.7)	163 (3.1)	3.3
Psychosis	2044 (5.0)	510 (9.7)	17.9	552 (10.6)	513 (9.8)	2.5
Any admission to hospital for mental or behavioural disorders before (\leq 1 yr) index date	1535 (3.8)	330 (6.3)	11.4	2452 (46.9)	2380 (45.5)	2.8
Any psychiatric hospital admission before (\leq 1 yr) diagnosis of Alzheimer disease	6985 (17.1)	1456 (27.6)	25.3	364 (7.0)	327 (6.3)	2.9

Note: BZD = benzodiazepine, COPD = chronic obstructive pulmonary disease, PS = propensity score, Z-drug = nonbenzodiazepine drug with similar activity to benzodiazepine.
*Values > 10% were considered to indicate meaningful imbalance between groups.

Cause-specific hazard ratios (HRs) for both pneumonia and competing events were modelled separately, by applying the main Cox model for the event of interest and censoring all other observations. Proportional hazards assumptions were met for all the models. All the analyses were restricted to the first 1500 days of follow-up because of sparse data.

We performed all statistical analyses using SAS statistical software, version 9.3 (SAS Institute Inc.).

Data were de-identified before submission to the research team and, by Finnish law, no ethics committee approval was required.

Results

After applying exclusion criteria, we included 49 484 participants (mean age 80 [SD 7] yr, 62.7% were women; Figure 1) in our study cohort. From this cohort, we matched 5232 participants taking benzodiazepines (Table 1) and 3269 taking Z-drugs

(Table 2) with those not taking these drugs. After propensity score matching, we found no significant differences for those taking the drugs and those who were not in terms of comorbidities included. The median follow-up time for participants taking benzodiazepines was 134 (interquartile range [IQR] 85–422) days and 638 (IQR 306–1095) days for those not taking benzodiazepines. Corresponding values for participants taking or not taking Z-drugs were 100 (IQR 39–295) and 683 (IQR 366–1145) days, respectively.

During the period of benzodiazepine and Z-drug use, 8.10 pneumonias per 100 person-years (95% confidence interval [CI] 8.03–8.16) were diagnosed (Table 3). Use of benzodiazepines and Z-drugs was associated with an increased risk of pneumonia among participants with Alzheimer disease (adjusted HR 1.22, 95% CI 1.05–1.42) (Table 3). Benzodiazepine use was associated with an increased risk of pneumonia (adjusted HR 1.28, 95% CI 1.07–1.54), whereas use of Z-drugs was not (adjusted HR 1.10, 95% CI 0.84–1.44).

Table 2 (part 1 of 2): Characteristics of participants taking Z-drugs and those not taking Z-drugs before and after propensity score matching

Characteristic	No. of participants (before PS matching), n (%)		Standardized difference before PS matching, %	No. of participants (after PS matching), n (%)		Standardized difference after PS matching, %*
	No Z-drug use n = 40 775	Z-drug use n = 3312		No Z-drug use n = 3269	Z-drug use n = 3269	
Sex			2.6			1.9
Male	15 271 (37.5)	1200 (36.2)		1161 (35.5)	1190 (36.4)	
Female	25 504 (62.6)	2112 (63.8)		2108 (64.5)	2079 (63.6)	
Age, yr						
< 65	1472 (3.6)	111 (3.4)	1.4	96 (2.9)	100 (3.1)	0.7
65–74	7807 (19.2)	644 (19.4)	0.8	523 (16.0)	546 (16.7)	1.9
75–84	22 508 (55.2)	1888 (57.0)	3.6	1799 (55.0)	1841 (56.3)	2.6
≥ 85	8988 (22.0)	669 (20.2)	4.5	851 (26.0)	782 (23.9)	4.9
Socioeconomic position						
High	14 127 (34.7)	1156 (34.9)	0.5	1160 (35.5)	1140 (34.9)	1.3
Medium	23 698 (58.1)	1892 (57.1)	2.0	1851 (56.6)	1866 (57.1)	0.9
Low	2471 (6.1)	225 (6.8)	3.0	219 (6.7)	224 (6.9)	0.6
Unknown	479 (1.2)	39 (1.2)	0.0	39 (1.2)	39 (1.2)	0.0
Drug use ever before index date						
Antipsychotic	3837 (9.4)	474 (14.3)	15.2	699 (21.4)	682 (20.9)	1.3
Benzodiazepine or Z-drug	8136 (20.0)	1235 (37.3)	39.1	1227 (37.5)	1196 (36.6)	2.0
Antidepressant	10 341 (25.4)	1155 (34.9)	20.8	1356 (41.5)	1271 (38.9)	5.3
Drug use at index date						
Antineoplastic drug	1363 (3.3)	106 (3.2)	0.8	128 (3.9)	114 (3.5)	2.3
Opioid	1100 (2.7)	124 (3.7)	5.9	192 (5.9)	174 (5.3)	2.4
Antipsychotic	2408 (5.9)	393 (11.9)	21.1	540 (16.5)	560 (17.1)	1.6
Antidepressant	5462 (13.4)	645 (19.5)	16.5	753 (23.0)	747 (22.9)	0.4
Proton pump inhibitor	3976 (9.8)	459 (13.9)	12.8	597 (18.3)	572 (17.5)	2.0
Antiepileptic	1405 (3.5)	169 (5.1)	8.2	198 (6.1)	193 (5.9)	0.6
Cardiovascular drug	29 903 (73.3)	2528 (76.3)	6.9	2564 (78.4)	2559 (78.3)	0.4
Comorbidity						
Cardiovascular disease	19 633 (48.2)	1652 (49.9)	3.5	1622 (49.6)	1633 (50.0)	0.7
Chronic heart failure	11 332 (27.8)	917 (27.7)	0.2	941 (28.8)	928 (28.4)	0.9
Cardiac arrhythmia	2748 (6.7)	256 (7.7)	3.8	223 (6.8)	254 (7.8)	3.7
Hypertension	12 005 (29.4)	1004 (30.3)	1.9	1030 (31.5)	1012 (31.0)	1.2
Stroke	3631 (8.9)	312 (9.4)	1.8	226 (6.9)	51 (1.6)	2.4
Diabetes	5430 (13.3)	403 (12.2)	3.4	409 (12.5)	423 (12.9)	1.3
Complicated diabetes	6631 (16.3)	529 (15.9)	1.0	516 (15.8)	524 (16.0)	0.0
Peripheral vascular disease	2005 (4.9)	185 (5.6)	3.0	184 (5.6)	183 (5.6)	0.1
Substance abuse	775 (1.9)	96 (2.9)	6.5	103 (3.2)	104 (3.2)	0.2
Previous hospital-treated fracture	7103 (17.4)	635 (19.2)	4.5	670 (20.5)	697 (21.3)	2.0
Any tumour	5178 (12.7)	461 (13.9)	3.6	491 (15.0)	461 (14.1)	2.6
Anemia	2695 (6.6)	246 (7.4)	3.2	238 (7.3)	252 (7.7)	1.6
Fluid and electrolyte disorders	1053 (2.6)	97 (2.9)	2.1	102 (3.1)	97 (3.0)	0.9
Epilepsy	808 (2.0)	61 (1.8)	1.0	61 (1.9)	65 (2.0)	0.9

Table 2 (part 2 of 2): Characteristics of participants taking Z-drugs and those not taking Z-drugs before and after propensity score matching

Characteristic	No. of participants (before PS matching), n (%)		Standardized difference before PS matching, %	No. of participants (after PS matching), n (%)		Standardized difference after PS matching, %*
	No Z-drug use n = 40 775	Z-drug use n = 3312		No Z-drug use n = 3269	Z-drug use n = 3269	
Respiratory comorbidity						
Asthma/COPD	3208 (7.9)	284 (8.6)	2.6	278 (8.5)	283 (8.7)	0.6
Any pulmonary disease	4302 (10.6)	355 (10.7)	0.5	352 (10.8)	357 (10.9)	0.5
Previous pneumonia 1 yr before diagnosis of Alzheimer disease	978 (2.4)	60 (1.8)	4.1	52 (1.6)	59 (1.8)	1.7
Admission to hospital for asthma/COPD before (\leq 1 yr) index date	629 (1.5)	67 (2.0)	3.6	72 (2.2)	69 (2.1)	0.6
Antibiotic or oral corticosteroid use before (\leq 30 d) index date	4334 (10.6)	383 (11.6)	3.0	476 (14.6)	467 (14.3)	0.8
Theophylline use before (\leq 180 d) index date	331 (1.0)	19 (0.6)	2.9	16 (0.5)	19 (0.6)	1.3
β -Agonist use before (\leq 180 d) index date	1777 (4.4)	175 (5.3)	4.3	173 (5.3)	176 (5.4)	0.4
Use of inhaled anticholinergic before (\leq 180 d) index date	527 (1.3)	41 (1.2)	0.5	42 (1.3)	44 (1.4)	0.5
Use of inhaled corticosteroid before (\leq 180 d) index date	1395 (3.4)	136 (4.1)	3.6	119 (3.6)	119 (3.6)	0.0
Combined inhaled corticosteroid/long-acting β -agonist use before (\leq 180 d) index date	1457 (3.6)	126 (3.8)	1.2	135 (4.1)	134 (4.1)	0.2
Mental health-related comorbidity						
Schizophrenia	447 (1.1)	39 (1.2)	0.8	44 (1.4)	39 (1.2)	1.4
Depression or bipolar disorder	806 (2.0)	100 (3.0)	6.7	102 (3.1)	100 (3.1)	0.4
Psychosis	2044 (5.0)	249 (7.5)	10.4	249 (7.6)	242 (7.4)	0.8
Any admission to hospital for mental or behavioural disorders before (\leq 1 yr) index date	1535 (3.8)	157 (4.7)	4.8	956 (29.2)	973 (29.8)	1.1
Any psychiatric hospital admission before (\leq 1 yr) diagnosis of Alzheimer disease	6985 (17.1)	645 (19.5)	6.1	160 (4.9)	154 (4.7)	0.9
Note: COPD = chronic obstructive pulmonary disease, PS = propensity score, Z-drug = non-benzodiazepine drug with similar activity to benzodiazepine. *Values > 10% were considered to indicate meaningful imbalance between groups.						

We found results similar to the main analysis for time-dependent adjustment of other psychotropic drugs (Table 3). Among those participants taking benzodiazepines, the increased risk was only observed at the start of use (first 30 d, HR 2.09 [95% CI 1.26–3.48]). To further explore possible prevalent user bias, we conducted additional analyses separately categorizing those participants with the shortest duration of use (\leq 7 d). We found that the risk of pneumonia among participants taking benzodiazepines was attenuated and no longer statistically significant for the first 7 days of use (adjusted HR 1.83, 95% CI 0.68–4.96) but was still significant between 8 and 30 days of use (adjusted HR 2.06, 95% CI 1.14–3.75). Risk of pneumonia was not affected by type of drug, and higher doses were associated with a larger HR than lower doses; however, in both cases, CIs were wide, which limited our conclusions (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.160126/-/DC1).

In the secondary analyses, participants taking benzodiazepine and Z-drugs had an increased risk of death due to other causes and stays in hospital of more than 90 days (HR 1.13, 95% CI 1.03–1.25) (Table 4).

Interpretation

Use of benzodiazepines and Z-drugs was associated with an increased risk of pneumonia among patients with Alzheimer disease. The risk was highest at the start of treatment, and benzodiazepine use was associated with an increased risk of pneumonia, whereas the association with Z-drug use did not reach significance. However, the results are not sufficient to support a conclusion that Z-drugs would be safer than benzodiazepines for patients with Alzheimer disease, because our study was not designed for a direct

comparison of the these groups. Furthermore, differing physician attitudes toward benzodiazepine and Z-drug prescribing²⁶ would complicate comparisons between drug groups. Both drugs have similar mechanisms of action and adverse effects,²⁷ which often are pronounced in older patients because of age-related changes in pharmacokinetics and pharmacodynamics.^{14,28,29} Benzodiazepines and Z-drugs have prolonged elimination half-lives in older patients, which may lead to accumulation of the drug.

One possible explanation for the increased risk of pneumonia associated with benzodiazepine use may be related to the more pronounced sedative effects of these drugs in this population. Sedation may increase risk of aspiration,¹⁵ which may lead to pneumonia. In addition, sedation is more pronounced at the start of use before tolerance develops. This supports the results of duration of use indicating that the higher risk is only at the start of drug use.

An increased risk of pneumonia is an important finding to consider in treatment of patients with Alzheimer disease. Benzodiazepines and Z-drugs are frequently prescribed for this population, and

long-term use is typical.^{8,30} Pneumonia often leads to admission to hospital,¹⁰ and patients with dementia are at increased risk of death related to pneumonia.^{12,13} Although our findings need further research and confirmation, the increased risk of pneumonia should be considered when benzodiazepines and Z-drugs are prescribed to older adults with Alzheimer disease.

Our results concur with a large case-control study on benzodiazepine use and pneumonia in the United Kingdom that reported a 50% increase in the risk among patients of all ages.¹⁶ In our study, benzodiazepine use was associated with a 30% increased risk of pneumonia. Another smaller case-control study found no association between benzodiazepine use and pneumonia among older adults, which may have been related to the small sample size for this study.¹⁷

Some researchers have suggested that benzodiazepines and Z-drugs may suppress the immune system and consequently induce adverse respiratory effects.^{17,31} In 2014, a population-based cohort study in Ontario reported that benzodiazepine use was associated with respiratory exacerbations and visits to

Table 3: Risk of pneumonia using propensity score matching for risk of pneumonia among participants taking and not taking benzodiazepines and Z-drugs

Comparison	No. of participants included	No. of cases of pneumonia	Person-years of follow-up	No. of diagnoses of pneumonia per 100 person-years (95% CI)	PS-matched HR (95% CI)	PS-matched and time-dependent adjustment for other psychotropic drugs HR (95% CI)*,†,‡
Any benzodiazepine and Z-drug use						
No use of benzodiazepines or Z-drugs	8501	1135	17 967	6.32 (6.28–6.35)	Ref.	Ref.
Use of benzodiazepines or Z-drugs	8501	566	6993	8.10 (8.03–8.16)	1.24 (1.07–1.43)	1.22 (1.05–1.42)
Benzodiazepine use						
No use of benzodiazepines or Z-drugs	5232	713	10 846	6.57 (6.53–6.62)	Ref.	Ref.
Use of benzodiazepines	5232	394	4629	8.51 (8.43–8.60)	1.31 (1.10–1.56)	1.28 (1.07–1.54)
Interval of benzodiazepine use, d						
0–30	5232	46	421	10.92 (10.60–11.23)	2.09 (1.26–3.48)	
31–180	4856	124	1398	8.87 (8.71–9.02)	1.27 (0.96–1.67)	
181–365	2207	77	930	8.28 (8.09–8.46)	1.16 (0.80–1.69)	
366–1095	1468	117	1534	7.63 (7.49–7.76)	1.23 (0.85–1.76)	
≥ 1096	322	30	360	8.33 (8.04–8.64)	1.40 (0.44–4.41)	
Z-drug use						
No use of benzodiazepines or Z-drugs	3269	422	7121	5.92 (5.87–5.98)	Ref.	
Use of Z-drugs	3269	172	2363	7.28 (7.17–7.39)	1.11 (0.86–1.43)	1.10 (0.84–1.44)
Interval of Z-drug use, d						
0–30	3269	24	257	9.34 (9.27–9.41)	1.60 (0.84–3.05)	
31–180	2719	51	665	7.67 (7.46–7.88)	0.88 (0.59–1.32)	
181–365	1044	29	440	6.60 (6.36–6.84)	1.14 (0.64–2.02)	
366–1095	708	53	794	6.67 (6.43–6.91)	1.19 (0.67–2.13)	
≥ 1096	189	15	216	6.95 (6.76–7.13)	1.75 (0.51–5.98)	

Note: CI = confidence interval, HR = hazard ratio, PS = propensity score, Z-drug = non-benzodiazepine drug with similar activity to benzodiazepine.

*Main analyses in time-dependent model, HR (95%CI): antipsychotic use, 1.18 (0.90–1.54); antidepressant use, 0.79 (0.62–1.02); and opioid use, 2.23 (1.50–3.31).

†Benzodiazepine analyses in time-dependent model, HR (95% CI): antipsychotic use, 1.22 (0.88–1.68); antidepressant use, 0.83 (0.61–1.14); and opioid use, 2.09 (1.32–3.35).

‡Analyses of Z-drugs in time-dependent model, HR (95%CI): antipsychotic use, 1.10 (0.67–1.81); antidepressant use, 0.71 (0.46–1.11); and opioid use, 2.60 (1.25–5.42).

Table 4: Cause-specific hazard ratios, by competing outcomes

Outcome	HR (95% CI)		
	Benzodiazepine and Z-drug use	Benzodiazepine use only	Z-drug use only
Pneumonia risk	1.24 (1.07–1.43)	1.31 (1.10–1.56)	1.11 (0.86–1.43)
Death due to other causes and hospital stays > 90 d	1.13 (1.03–1.25)	1.15 (1.02–1.29)	1.09 (0.91–1.30)

Note: CI = confidence interval, HR = hazard ratio.

the emergency department for COPD or pneumonia among older adults with COPD.¹⁸ A study involving a cohort of patients with asthma in the UK showed increased odds of exacerbations and death among those patients taking benzodiazepines.³¹

Limitations

We investigated the association of benzodiazepine and Z-drug use with a diagnosis of pneumonia in a large nationwide cohort that included patients with a clinically verified diagnosis of Alzheimer disease. For this reason, our results are generalizable to community-dwelling older adults with Alzheimer disease. We restricted analyses to incident use because prevalent users are more likely to have developed tolerance to drug effects. We also restricted the analyses to incident pneumonia cases to exclude the possibility of multiple admissions to hospital because of the same occurrence of pneumonia. With propensity-score matched design and by taking into account time-since-diagnosis, we were able to control for the main measured confounders. However, as in all observational studies, unmeasured confounders may still exist. For example, register-based data lack information on smoking, which is a predictor of pneumonia.³² The covariates we selected (e.g., psychotropic drug use, asthma/COPD, previous pneumonia, lower socioeconomic status and history of substance abuse) likely captured some of the variation in smoking status. We also conducted analyses to reduce the impact of other psychotropic drugs on risk of pneumonia by adjusting for their time-dependent use.

The participants in our study were either admitted to hospital with pneumonia or died of pneumonia. We did not include cases of pneumonia treated through home care. Therefore, our results represent the most severe infections. The limitations also include lack of information on indications for drug use (including presence and severity of behavioural symptoms) and severity of Alzheimer disease, both of which may affect the start of drug use and incidence of pneumonia. We controlled for time-since-diagnosis as a crude measure of severity.

Drug use was based on data recorded in the Prescription Register in Finland. Benzodiazepine use based on data from the Prescription Register was previously validated in a population-based intervention study.³³ Our study may underestimate benzodiazepine use, because smaller packages of these drugs were not reimbursed. We used a mathematical modelling method (PRE2DUP) to construct drug-use periods.²² This allowed us to use time-dependent exposure in our analyses.

Conclusion

Benzodiazepine use was associated with a 30% increase in the relative risk of pneumonia among patients with Alzheimer disease compared with patients not using the drug. Benefits and risks of the use of benzodiazepines should be carefully considered for patients with Alzheimer disease and include risk of pneumonia. Accumulating evidence that use of benzodiazepines and Z-drugs is associated with respiratory adverse effects suggests that future studies examine the possible pharmacologic mechanisms.

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