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Risk of death associated with new benzodiazepine use among persons with Alzheimer disease: A matched cohort study

Saarelainen Laura

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Title: Risk of death associated with new benzodiazepine use among persons with Alzheimer's disease – a matched cohort study

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Key points:

- New use of benzodiazepines and related drugs was associated with a 41 percent increase in risk of death in persons with Alzheimer's disease.
- The association with an increased risk of death was observed from the initiation of benzodiazepine and related drug use.
- Benzodiazepine use was associated with an increased risk of death whereas benzodiazepine-related drug use was not.

Authors: Laura Saarelainen ^{a,b}, Anna-Maija Tolppanen ^{b,c}, Marjaana Koponen ^{a,b}, Antti Tanskanen ^{d,e,f}, Jari Tiihonen ^{d,f,g}, Sirpa Hartikainen ^{a,b,h}, Heidi Taipale ^{a,b,d}

Institutions: *a) Kuopio Research Centre for Geriatric Care, University of Eastern Finland, Finland; b) School of Pharmacy, University of Eastern Finland, Finland; c) Research Centre for Comparative Effectiveness and Patient Safety, University of Eastern Finland, Finland; d) Department of Clinical Neuroscience, Karolinska Institutet, Sweden; e) Impact Assessment Unit, National Institute for Health and Welfare, Finland; f) Department of Forensic Psychiatry, Niuvanniemi Hospital, Finland; g) Stockholm County Council, Stockholm, Sweden; h) Department of Psychiatry, Kuopio University Hospital, Finland*

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Corresponding author:

Laura Saarelainen, MSc (Pharm)

Kuopio Research Centre of Geriatric Care, School of Pharmacy

University of Eastern Finland, PO Box 1627, 70211 Kuopio, Finland

Tel. +358503095536, Fax. +358-17-162 252

E-mail: laura.saarelainen@uef.fi

ABSTRACT

Objective

To investigate the risk of death associated with new benzodiazepine and related drug (BZDR) use in a nationwide cohort of persons with Alzheimer's disease (AD).

Methods

The register-based MEDALZ cohort, including all community-dwelling Finns diagnosed with AD during 2005-2011 (n=70,718), was utilized. Clinically verified AD diagnoses were obtained from the Special Reimbursement Register. Drug use periods were modelled from BZDR purchases, derived from the Prescription Register. To study new users, persons who had any BZDR use during the year preceding the AD diagnosis were excluded.

For each person initiating BZDR use (n=10,380), two nonusers (n=20,760) were matched on age, gender, and time since AD diagnosis. The outcome was 180-day mortality, and BZDR use was compared with nonuse with Cox regression. Multivariable analyses were adjusted for Charlson comorbidity index, socioeconomic position, hip fractures, psychiatric disorders, substance abuse, stroke, and other psychotropic drug use.

Results

During the follow-up, five excess deaths per 100 person-years occurred during BZDR use in comparison to nonuse, and mortality rates were 13.4 (95% confidence interval [CI]=12.2-

14.5) and 8.5 (95% CI=7.9-9.1), respectively. BZDR use was associated with an increased risk of death (adjusted hazard ratio=1.4 [95% CI=1.2-1.6]), and the association was significant from the initiation of use. Benzodiazepine use was associated with an increased risk of death whereas benzodiazepine-related drug use was not.

Conclusions

BZDR use was associated with an increased risk of death in persons with AD. Our results support treatment guidelines stating that nonpharmacological approaches should be the first-line option for symptomatic treatment of AD.

1. INTRODUCTION

The number of persons with Alzheimer's disease (AD) is increasing as the population globally is aging.¹ AD has been associated with a higher frequency of chronic comorbidities² as well as an increased risk of adverse health outcomes, including increased need of hospital and institutional care^{3,4}, hip fractures^{5,6}, and mortality^{4,7}, compared with other older persons. Therefore, persons with AD constitute a vulnerable population and the treatment of AD represents a major challenge to healthcare systems.

In addition to cognitive impairment, AD involves also behavioral and psychological symptoms of dementia (BPSD) which are highly frequent in community-dwelling persons with AD,⁸ already at the early stages of the disease.⁹ Nonpharmacological options are the first-line treatment of BPSDs, and pharmacological options can be used if nonpharmacological treatment approaches have not been effective.¹⁰ Treatment of BPSDs is complex, as the evidence of pharmacological options' efficacy is scarce¹¹ and the risk of associated adverse outcomes is notable.¹⁰

Benzodiazepines and related drugs (BZDR) should be used in short-term or infrequent treatment of BPSDs, according to treatment guidelines.^{10,12} BZDR use increases considerably at the time of AD diagnosis¹³ and almost one-third of persons with AD use BZDRs after the diagnosis.¹⁴ However, there are only a few studies investigating adverse outcomes associated with BZDR use in persons with AD. BZDR use has been associated with an increased risk of hip fracture, stroke, and pneumonia in this population.¹⁵⁻¹⁷ The risk of these outcomes has been highest in the beginning of BZDR use. These adverse outcomes may predispose BZDR users to an increased risk of death. However, three studies investigating the association

between BZDR use and mortality in persons with dementia have ended up with varying results and conclusions, which may result from different methodologies.¹⁸⁻²⁰

There are no previous studies focusing specifically on community-dwelling persons with AD. Therefore, our aim in this study was to investigate all-cause 180-day mortality associated with BZDR use initiation in comparison to nonuse in a nationwide cohort of community-dwelling persons with AD.

2. METHODS

2.1. Cohort

We applied the Medication Use and Alzheimer's Disease (MEDALZ) cohort in this study.²¹ The cohort included all community-dwelling persons diagnosed with AD in Finland during 2005-2011 (n=70,718). All data were obtained from nationwide Finnish registers. Persons with AD were recognized from the Special Reimbursement Register which contains information on clinically verified diagnoses of chronic diseases. The validity of AD diagnoses in the Special Reimbursement Register has been demonstrated.²² The AD diagnoses were based on the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA)²³ as well as the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV)²⁴ criteria. The diagnosis criteria included symptoms consistent with mild to moderate AD and confirmation of diagnosis as well as exclusion of other diagnoses with imaging scans. All diagnoses were confirmed by a neurologist or a geriatrician and they were monitored by the Social Insurance

Institution (SII). The Special Reimbursement Register contained information on persons with all stages of AD.

No ethics approval or informed consent from the cohort was required by the Finnish legislation as the persons were not contacted and only pseudonymized data were utilized. Permissions for data use were received from the register maintainers.

2.2.Sources of data

Data on drug use were obtained from the Prescription Register which included information on all reimbursed drug purchases for all residents in Finland. We had information on MEDALZ study persons' purchases from 1995 to 2012. The register did not include information on drug use during hospital or institutional care as the drugs were provided by the public treatment facility during the stay. Data on clinically verified chronic diseases were obtained from the Special Reimbursement Register from 1972 to 2012. The diagnostic procedures were monitored by SII. Further, we obtained information on hospital stays from the Hospital Discharge Register. The information included hospital days of inpatient admissions as well as related procedures and diagnoses. Additionally, we defined institutionalization from decisions for long-term institutional care which were obtained from the SII. Finally, information on death dates from 2005 to 2012 was obtained from Statistics Finland.

2.3.Drug exposure

The Prescription Register data applied in this study included person identifier, anatomical therapeutic chemical (ATC) code of the substance, strength, formula, package size, purchase date, and the purchased amount.

We defined BZDRs as benzodiazepines (ATC classes N05BA and N05CD) and benzodiazepine-related drugs, i.e. ‘Z-drugs’ (N05CF). Benzodiazepines included diazepam, chlordiazepoxide, oxazepam, lorazepam, alprazolam, nitrazepam, and temazepam, whereas Z-drugs included zopiclone and zolpidem. As midazolam (N05CD08), triazolam (N05CD05), and zaleplon (N05CF03) were not reimbursed during the study period, they were not included in the analyses. We wanted to focus on BPSD treatment and, therefore, clobazam (N05BA09) was not included in BZDRs as its only indication was epilepsy.

We applied the PRE2DUP drug use model to formulate drug use periods from the purchase-based register data for each drug and each person.²⁵ With this method, we obtained information on when each drug use period started and ended. This method accounts for regularity of drug purchases, hospital stays, and possible stockpiling of drugs. Overlapping benzodiazepine and Z-drug use periods were combined to receive any BZDR use periods, during which persons could switch substances as long as the use was continuous. For sub-analyses, we built benzodiazepine and Z-drug use periods separately as well. The validity of BZDR use periods based on the PRE2DUP method is good.²⁶

BZDR use was classified as use / nonuse and, further, the duration of BZDR use was classified in time windows from the initiation of use (1-30, 31-60, 61-90, 91-120, and 121-180 days). BZDR use was also classified in drug classes, i.e. benzodiazepine use and Z-drug

use. BZDR polypharmacy, i.e., use of benzodiazepines and Z-drugs concomitantly, was not investigated separately due to small number of BZDR users with polypharmacy.

2.4.Outcome

The outcome in this study was 180-day all-cause mortality.

2.5.Study setting

We applied a one-year washout period before the AD diagnosis to exclude prevalent BZDR users.²⁷ Therefore, all persons who had any BZDR use during the washout period were excluded from the study (Figure 1). Further, persons who were hospitalized / institutionalized for more than 50% of the washout period or who had an ongoing ≥ 90 days hospital stay at the end of the washout period were excluded.²⁸ Additionally, persons who were hospitalized / institutionalized throughout the study were excluded.

Each person initiating BZDR use after the AD diagnosis and by 31 December 2012, i.e., each incident BZDR user, was matched on the date of initiation with two nonusers, based on time since AD diagnosis (time frame: 90 days), age (time frame: 2 years), and gender (Figure 1). If the matched nonusers initiated BZDR use later, their follow-up as nonuser was censored.

The follow-up started from the index date which was defined as the date of BZDR use initiation in BZDR users or the corresponding matching date in nonusers. The follow-up ended at death, at the end of first BZDR use period, start of BZDR use in matched nonusers,

initiation of long-term hospitalization / institutionalization²⁸, after 180 days, or on December 31, 2012, whichever occurred first.

2.6. Covariates

The covariates obtained from registers included Charlson Comorbidity Index (CCI), socioeconomic position, and histories of chronic cardiovascular diseases, psychiatric disorders, substance abuse, stroke, antidepressant use, antipsychotic use, and opioid use. The collection and definitions of these covariates are described in Supplementary File 1.

2.7. Statistical analyses

Continuous covariates were reported with medians and interquartile ranges (IQR), and they were compared with the Mann-Whitney t-test. Categorical covariates were compared with chi square test.

We calculated the age-adjusted death rate per 100 person-years with 95% confidence intervals (CI) during BZDR use and nonuse. The risk of death was investigated during BZDR use, different durations of BZDR use, and during use of benzodiazepines and Z-drugs separately, in comparison to nonuse. The risk was analyzed with the Cox regression by taking into account the matched design. The associated risks were reported as hazard ratios (HR) with 95% CIs. In sub-analyses concerning benzodiazepine and Z-drug use separately, persons initiating BZDR use with concomitant use of these drugs, as well as their matched nonusers, were excluded. Further, in these sub-analyses, the follow-up was ended at the initiation of use of benzodiazepines and Z-drugs concomitantly.

In multivariable analyses, CCI, socioeconomic position²⁹, histories of hip fracture, psychiatric disorders, substance abuse²⁹, and stroke, as well as histories of antidepressant, antipsychotic, and opioid use were applied as covariates.

In sensitivity analyses, we performed intention-to-treat (ITT) analyses. In these analyses, the follow-up was not ended at the end of BZDR use or start of long-term hospitalization / institutionalization. Additionally, we performed subgroup analyses to investigate whether the observed risk of death was dependent on time since AD diagnosis.³⁰ The interaction between time since AD diagnosis (categorized as <180, 180-364, 365-729, 730-1094, and ≥ 1095 days) and BZDR use was investigated by including the corresponding interaction term in the Cox regression.

3. RESULTS

3.1. Study persons

After the exclusion and matching, there were 10,380 persons initiating BZDR use and 20,760 matched nonusers in the study (Figure 1). The study follow-up consisted of 3,319.0 and 9,282.3 person-years in BZDR use and nonuse, respectively. The median age of the study population was 81.1 years and most of the population were female (Table 1). The median time between the date of AD diagnosis and index date was 445 days (IQR=166-903.5).

During the 180-day follow-up, the median duration of BZDR use was 121 days (IQR=40-180). In total, 6,438 persons initiated drug use with a benzodiazepine and 3,826 persons with

a Z-drug, while 116 persons initiated with concomitant use of these drugs. Incident BZDR use was associated with a lower socioeconomic position, higher frequency of history of opioid, antipsychotic, and antidepressant use, higher frequency of history of psychiatric disorders, substance abuse, and chronic cardiovascular diseases, as well as lower frequency of history of diabetes (Table 1).

3.2.All-cause mortality

In total, 440 persons died during BZDR use, whereas 785 persons died during nonuse (Table 2). The age-adjusted death rate during BZDR use was 13.4 (12.2-14.5) per 100 person-years and during nonuse 8.5 (7.9-9.1) per 100 person-years. BZDR use was associated with an increased risk of death (adjusted HR=1.41 [95% CI=1.23-1.62]). The association was significant from the initiation until 120 days of drug use. Benzodiazepine use was associated with a significantly increased risk of death whereas Z-drug use was not.

In ITT analyses, the risk estimate did not differ from main analyses (adjusted HR=1.40 [95% CI=1.25-1.57]) (Table 2). The subgroup analysis demonstrated that the observed risk of death was not dependent on time since AD diagnosis ($p=0.9470$ for the interaction).

4. DISCUSSION

Incident BZDR use was associated with an increased 180-day all-cause mortality among community-dwelling persons with AD in this study. This association was significant from the initiation and remained significant until four months of BZDR use. Benzodiazepine use was

associated with increased risk of death while Z-drug use was not. The sensitivity analyses confirmed our observation of associated risk increase.

Our observation of a 41% increase in the risk of death associated with BZDR use was higher than observations in the previous studies investigating persons with dementia.¹⁸⁻²⁰ In nursing home setting, the risk of 180-day mortality associated with BZDR use was slightly, but not significantly, higher than the risk associated with atypical antipsychotic use.¹⁹ In contrast, we compared the risk associated with BZDR use and nonuse, while antipsychotic use was applied as a covariate in multivariable analyses. Antipsychotic use has been associated with an increased risk of death in persons with dementia³¹ and BZDR use may not further increase the risk. Similarly with our study, Huybrechts *et al.*¹⁹ applied time-dependent BZDR use as exposure and investigated new users of BZDRs. The two other studies investigated mixed cohorts of persons with dementia in both community and nursing home settings.^{18, 20} Jennum *et al.*¹⁸ demonstrated a modestly increased risk of death associated with both benzodiazepine and Z-drug use in comparison to nonuse. On the contrary, Brännström *et al.*²⁰ demonstrated no risk increase during the first year and a significant risk decrease during the second year of follow-up, in comparison to nonuse. These studies involved both incident and prevalent users of drugs. Prevalent users are those who are more likely to tolerate BZDR use,²⁷ which partially explains the lower risk estimates compared with ours. In both studies, the exposure was defined in a cross-sectional manner from a baseline measurement, and the follow-up was 2-12 years. Therefore, the observations may have been affected by progression of dementia. Further, BZDR exposure might be susceptible to misclassification bias during the long follow-ups, as baseline users may discontinue and nonusers may initiate BZDR use during the study.³² These factors might also explain the risk decrease observed by Brännström *et al.*

Older persons, including the vulnerable persons with AD, are susceptible to adverse outcomes of BZDRs due to the age-related changes in pharmacodynamics and pharmacokinetics.³³ The changes increase the central nervous system effects of these drugs in older persons. Previous studies have demonstrated an increased risk of adverse outcomes associated with BZDR use, including hip fractures and respiratory outcomes, in older persons³⁴⁻³⁶ as well as in persons with AD.^{15, 17} Further, BZDR use has been associated with an increased risk of stroke in persons with AD.¹⁶ AD has been associated with increased mortality after hip fractures⁶ and pneumonia.³⁷ Further, stroke is a common cause of death in persons with AD.³⁸ Therefore, the observed association with an increased risk of death might result from these outcomes. However, a previous study did not demonstrate an association between BZDR use during hip fracture and one-year mortality after hip fracture.¹⁵ This may relate to the small number of BZDR users investigated in that study. Further research is needed to investigate the mechanism of BZDR-related mortality.

Contrary to our observations in persons with dementia, BZDR use has not been associated with an increased risk of death in community-dwelling older persons.^{35, 39-42} Those studies applied a cross-sectional definition of BZDR exposure based on a baseline measurement. The follow-up times ranged from 30 days to 12 years, and the risk of exposure misclassification bias increased with longer follow-up, similarly to the previous studies in persons with dementia. Two studies^{39, 40} excluded persons with dementia at baseline from their study populations. Another two studies^{35, 42} demonstrated a decreased risk of death associated with benzodiazepine use. However, the study by Patorno *et al.*⁴² had a selected sample as it consisted of persons with a private health insurance. Further, in the other study including persons with chronic obstructive pulmonary disease³⁵, an increased risk of death was observed in a sub-population with no exacerbations during the year before the study.

To our knowledge, the current study is the first one to investigate the risk of death associated with different durations of BZDR use in persons with dementia. We observed no association between BZDR use and risk of death after 120 days of drug use. This may result from selection related to tolerating BZDR use, since early phases of drug use are commonly associated with elevated risk of adverse effects²⁷ which might lead to discontinuation of treatment. Further, avoiding long-term hospital / institutional care might result in selection in our study, since the follow-up was censored at the beginning of long-term care. Thus, BZDR cannot be considered any safer during longer use.

Considering drug classes, we observed an increased risk of death associated with benzodiazepine use but not with Z-drug use. The previous study investigating the risk of death associated with benzodiazepine and Z-drug use in persons with dementia indicated slightly higher risk associated with benzodiazepine use as well, although also Z-drug use was associated with an increased risk of death.¹⁸ However, in both studies, the difference was small. Therefore, Z-drug use cannot be considered any safer than benzodiazepine use in persons with dementia regarding risk of death.

The strengths of the current study were related to the extensive dataset as the data in Finnish healthcare registers have been collected systematically for decades. Selection bias was minimal in this study as all persons with clinically verified AD diagnosis in Finland during 2005-2011 were included. The validity of these diagnoses has been demonstrated.²² Because information about the stage of the disease was not available in the register, we matched nonusers on time since AD diagnosis as this can be interpreted as a crude estimate of the disease progression. Further, age and gender were applied as matching variables to decrease

the differences between BZDR users and nonusers. Further, we could focus on first drug use periods of new BZDR users, i.e., apply the new-user design, decreasing selection bias because there were not any healthy survivors of BZDR use in this study.²⁷

Exposure misclassification bias was minimized by applying the PRE2DUP method throughout the follow-up to obtain time-dependent drug use status for each person in the study. The agreement between BZDR use periods and BZDR use according to an interview is good.²⁶ However, we did not have information on all BZDR purchases because some small packages of BZDRs were not reimbursed during the study period. Therefore, BZDR use may have been slightly underestimated and the observed hazard ratios may have been underestimated as well. The follow-up was up to 180 days in this study and, therefore, we cannot conclude anything on the long-term associations between BZDR use and mortality.

Since healthcare registers do not contain information on clinical condition, we applied available data as proxies of BPSDs. These proxies included histories of psychotropic drug use and hospital-treated psychiatric disorders which could indicate having BPSDs. Both were more frequent in incident BZDR users. We applied these proxies in multivariable analyses to decrease potential confounding by indication related to treating BPSDs with BZDRs.

The sensitivity analyses strengthened the validity of our observations. We investigated the interaction between time since AD diagnosis and BZDR use because mortality rate is high in persons with AD.⁷ This analysis demonstrated that the risk of death associated with BZDR use was similar regardless of the time between AD diagnosis and index date. Further, we performed ITT analysis in which we assumed that BZDR use was continued during hospital / institutional care or until 180 days or 31 December 2012. With this analysis, the impact of

informative censoring, i.e. discontinuation of treatment or hospitalization due to adverse events of BZDR use,⁴³ was decreased.

BZDRs are commonly used in the symptomatic treatment of AD,^{14, 44, 45} although the evidence of their efficacy in BPSD treatment is insufficient.¹¹ Our observations highlight the importance of treatment guidelines, stating that nonpharmacological options should be the first-line treatment of BPSDs.^{10, 12}

5. CONCLUSION

It seems that benzodiazepine and related drug use is associated with an increased risk of death in persons with Alzheimer's disease. The observed 41% increase in the risk of death was mostly explained by the risk associated with benzodiazepine use. However, we would like to highlight that benzodiazepine-related drug use may not be any safer. We suggest higher threshold for prescribing benzodiazepines and related drugs to persons with Alzheimer's disease in clinical practice, as the risk increase seems to be significant from the initiation of benzodiazepine and related drug use. These results highlight the importance of nonpharmacological options as a first-line treatment of behavioral and psychological symptoms of dementia.

CONFLICTS OF INTEREST

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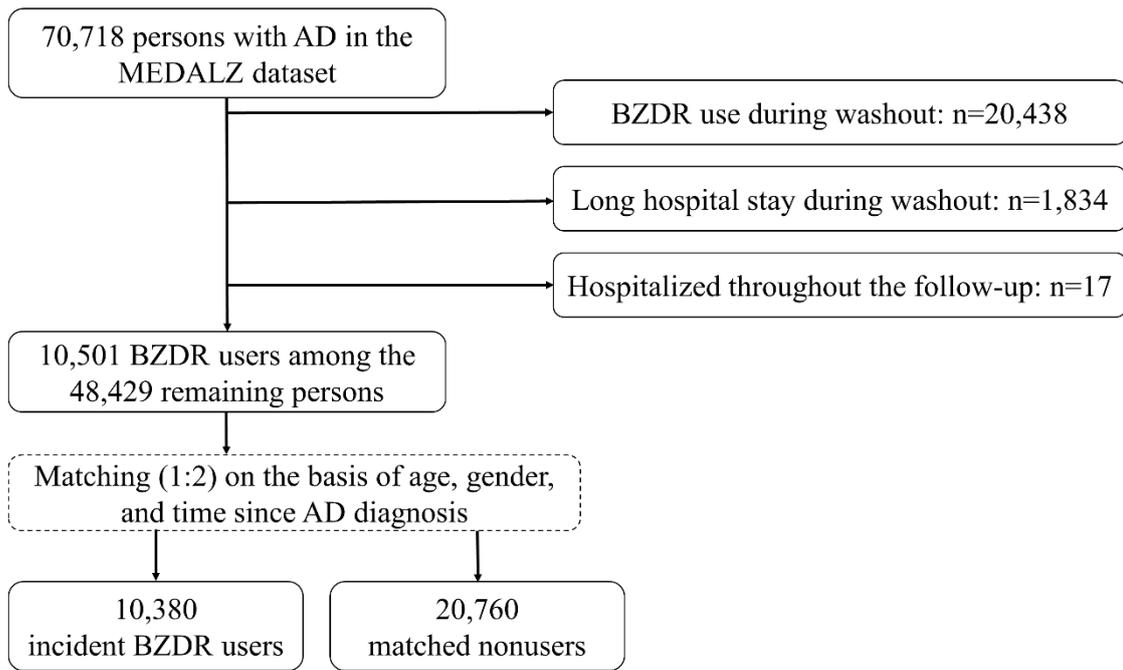


Figure 1. Flow chart. AD=Alzheimer’s disease, BZDR=benzodiazepine and related drug

Table 1. Characteristics of BZDR initiators and their matched nonusers

Variable	Incident BZDR users (n=10,380)	Matched nonusers (n=20,760)	p
Age at index date			
Median (IQR)	81.1 (76.4-85.2)	81.2 (76.5-85.2)	1.0000
Gender			
Female, n (%)	6,531 (62.9)	13,061 (62.9)	1.0000
Socioeconomic position			
			0.0094
Highest, n (%)	3,465 (33.4)	7,262 (35.0)	
Middle, n (%)	6,068 (58.5)	11,964 (57.6)	
Lowest, n (%)	716 (6.9)	1,288 (6.2)	
Unknown, n (%)	131 (1.3)	246 (1.2)	
History of drug use			
Opioid use, n (%)	984 (9.5)	1,334 (6.4)	<0.0001
Antipsychotic use, n (%)	3,074 (29.6)	2,434 (11.7)	<0.0001
Antidepressant use, n (%)	3,021 (29.1)	3,627 (17.5)	<0.0001
History of comorbidities			
Hip fracture, n (%)	557 (5.4)	1,091 (5.3)	0.6806
Stroke, n (%)	1,053 (10.1)	1,946 (9.4)	0.0298

Psychiatric disorders, n (%)	1,674 (16.1)	2,342 (11.3)	<0.0001
Substance abuse, n (%)	327 (3.2)	395 (1.9)	<0.0001
Active cancer treatment, n (%)	547 (5.3)	1,018 (4.9)	0.1633
Asthma / COPD, n (%)	880 (8.5)	1,645 (7.9)	0.0914
Chronic cardiovascular diseases, n (%)	5,124 (49.4)	9,991 (48.1)	0.0393
Diabetes, n (%)	1,261 (12.2)	2,759 (13.3)	0.0046
Rheumatic diseases, n (%)	420 (4.1)	878 (4.2)	0.4461
Severe renal failure, n (%)	18 (0.2)	39 (0.2)	0.7785
Charlson comorbidity index			0.2649
0, n (%)	6,101 (58.8)	12,283 (59.2)	
1, n (%)	2,768 (26.7)	5,596 (27.0)	
≥2, n (%)	1,511 (14.6)	2,881 (13.9)	
Reason for ending follow-up			<0.0001
Death, n (%)	440 (4.2)	785 (3.8)	
End of follow-up (180 days), n (%)	3,779 (36.4)	16,810 (81.0)	

Institutionalization, n		
(%)	487 (4.7)	805 (3.9)
End of BZDR use, n (%)	5,206 (50.2)	0
Start of BZDR use, n (%)	0	997 (4.8)
31 December 2012, n		
(%)	468 (4.5)	1,363 (6.6)

BZDR=benzodiazepine and related drug; COPD=chronic obstructive pulmonary

disease; IQR= interquartile ranges

Table 2. Death rates and risk of death associated with BZDR use in persons with Alzheimer's disease

Exposure	Number of persons	Number of deaths	Person-years	Age-adjusted death rate per 100 person-years	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Nonuse	20,760	785	9,282.3	8.5 (7.92-9.05)	reference	reference
Main analysis						
BZDR use	10,380	440	3,319.0	13.4 (12.23-14.53)	1.56 (1.38-1.77)	1.41 (1.23-1.62)
Duration of BZDR use (days)						
1-30	10,380	95	829.30	11.5 (9.33-13.60)	1.73 (1.32-2.28)	1.63 (1.22-2.16)
31-60	9,592	97	665.18	14.7 (12.03-17.30)	1.72 (1.31-2.27)	1.52 (1.15-2.03)
61-90	7,281	101	578.73	17.5 (14.45-20.55)	1.91 (1.45-2.53)	1.68 (1.25-2.25)
91-120	6,765	80	527.39	15.2 (12.17-18.27)	1.69 (1.25-2.29)	1.64 (1.20-2.25)
121-180	6,091	67	718.37	9.6 (7.45-11.79)	1.03 (0.76-1.39)	0.91 (0.66-1.24)
Drug classes†						

Benzodiazepine use	6,438	312	2,153.2	14.3 (12.80-15.71)	1.76 (1.51-2.06)	1.59 (1.35-1.88)
Z-drug use	3,826	112	1,005.1	10.7 (8.88-12.60)	1.17 (0.92-1.48)	1.06 (0.83-1.35)
Intention-to-treat analyses						
Nonuse	20,760	809	9,426.40	8.55 (7.99-9.10)	reference	reference
BZDR use	10,380	624	4,778.8	13.03 (12.09-13.97)	1.54 (1.39-1.71)	1.40 (1.25-1.57)

* Adjusted for Charlson Comorbidity Index, socioeconomic position, histories of hip fracture, psychiatric disorders, substance abuse, and stroke, as well as histories of antidepressant, antipsychotic, and opioid use.

† In drug class analyses, 116 persons were excluded because they initiated BZDR use with polypharmacy

BZDR=benzodiazepine and related drug; CI=confidence interval; HR=hazard ratio

Supplementary file 1.

Covariates collected from the Special Reimbursement Register since 1972 until the index date included diabetes, asthma, chronic obstructive pulmonary disease (COPD), disseminated connective tissue diseases as well as rheumatoid arthritis and other comparable conditions, and severe renal failure. Additionally, data on heart failure, coronary artery disease, hypertension, and arrhythmia were obtained to define history of chronic cardiovascular diseases at the index date.

Covariates collected from the Hospital Discharge Register since 1972 until the index date included histories stroke, substance abuse, and hip fracture. Stroke was defined as hospital-treated stroke (ICD-10 codes I60-I64). Substance abuse was defined as diagnosis of mental and behavioral disorders because of psychoactive substance use (F10-F19) or alcoholic pancreatitis (K86.0), or substance abuse as a reason for hospital admission. Hip fracture was defined as hospital-treated hip fracture (S72.0, S72.1, and S72.2). Additionally, we defined history of psychiatric disorders at least 5 years before AD diagnosis to exclude prodromal symptoms of AD. These diagnoses included schizophrenia, schizotypal or delusional disorders (F20-29), bipolar disorder (F30-31), and depression (F32-39). Corresponding ICD-9 and ICD-8 codes were applied as well.

Active cancer treatment was defined from the year preceding the index date. This covariate included any cancer (ICD-10 codes C00-C97) as a main or a side diagnosis in the Hospital Discharge Register or purchases of antineoplastics or immunomodulating agents in the Prescription Register during the 12 months preceding the index date.¹

A modified Charlson Comorbidity Index (CCI) at index date was computed from histories of chronic heart failure (score=1), coronary artery disease (score=1), diabetes (score=1), asthma or COPD (score=1), disseminated connective tissue diseases as well as rheumatoid arthritis and other comparable conditions (score=1), severe renal failure (score=2), and active cancer treatment (score=2).^{2, 3} CCI scores were categorized as 0, 1, and ≥ 2 .

Data on antipsychotic (ATC code N05A, excluding lithium and prochlorperazine), antidepressant (N06A), and opioid (N02A) purchases were obtained from the Prescription Register. Drug use periods were modelled with the PRE2DUP method and histories of antipsychotic, antidepressant, and opioid use were defined from the year preceding the index date.

Socioeconomic position was defined as the highest position recorded for study persons in their middle age (45-55 years old) in population census. The position was categorized to four classes (high, medium, low, unknown), according to definitions by Statistics Finland. The highest class included entrepreneurs and higher clerical workers, medium class lower clerical workers and employees, and the lowest class unemployed, retired and students. The class 'unknown' included persons with unknown socioeconomic class as well as persons with missing data at Statistics Finland (approximately 5% of the cohort).

Supplementary references:

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