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ORIGINAL ARTICLE

Use of short-acting and long-acting hypnotics and the risk of fracture: a critical analysis of associations in a nationwide cohort

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Abstract

Summary Numerous observational studies suggest that hypnotics increase the risk of fractures, and long-acting hypnotics are suggested to be especially harmful. This study showed that the highest risk of fracture was found before start of treatment and remained after end of therapy, suggesting that the increased risk during treatment is influenced by other factors, such as underlying disease.

Introduction The purpose of this study was to evaluate associations between the use of short-acting and long-acting hypnotics and the risk of fracture.

Methods Four cohorts were formed from all individuals living in Sweden aged ≥ 50 years in 2005 ($n = 3{,}341{,}706$). In the first cohort, individuals prescribed long-acting propiomazine ($n = 233{,}609$) were matched 1:1 with controls. In the second cohort, individuals prescribed short-acting z-drugs (zopiclone, zolpidem, and zaleplon, $n = 591{,}136$) were matched 1:1 with controls. The third and fourth cohorts consisted of full sibling pairs with discordant propiomazine ($n = 83{,}594$) and z-drug ($n = 153{,}314$) use, respectively.

Results The risk of fracture was greatest among users of hypnotics in the 90 days before the initiation of treatment, both for propiomazine (odds ratio [OR], 2.52; 95% confidence interval [CI], 2.28–2.79) and z-drugs (OR, 4.10; 95% CI, 3.86–4.35) compared with that in matched controls. Furthermore, this risk was significantly reduced after the initiation of treatment with propiomazine (OR, 1.42; 95% CI, 1.27–1.60) and z-drugs (OR, 1.67; 95% CI, 1.56–1.80) and remained the first year following the last prescribed dose both for propiomazine (OR, 1.28, 95% CI, 1.21–1.36) and z-drugs (OR, 1.19, 95% CI, 1.16–1.23). The pattern was similar in the sibling cohorts, with the greatest risk of fracture seen in the 90 days before treatment with hypnotics was initiated.

Conclusion The use of short-acting and long-acting hypnotics is associated with an increased risk of fracture. This risk was highest before initiation of treatment and remained after end of therapy. The results suggest that the increased risk during treatment is influenced by other factors such as underlying disease.

Keywords Fractures · Hypnotics

Introduction

The ability to sleep decreases while insomnia increases in older individuals [1, 2]. These disturbances may result from normal age-related physiological changes, or they may be secondary to a variety of factors, such as underlying disease. Various drugs are commonly used to improve sleep disturbance. According to national registers, 33% of the population in Sweden aged at least 50 years has received at least one prescription for zopiclone, zolpidem, or zaleplon (z-drugs) [3], the drugs used most commonly for insomnia. However, according to recent practical guidelines of the American Academy of Sleep Medicine, the evidence for z-drugs and other drugs for sleeping disorders is weak [4]. Furthermore, the use of z-drugs and other hypnotics has been associated with unfavorable side effects, including drowsiness, gait impairment, reduced cognitive function [5], and an increased risk of fracture [6, 7]. Perhaps the most serious side effect

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associated with the use of hypnotics is hip fracture [8], as many of the patients lose independence and 25% die within the first year after the event [9].

Based on the risk of side effects, short-acting z-drugs are generally recommended over more long-acting hypnotics, such as benzodiazepines and neuroleptics [4, 10]. Z-drugs are also suggested to result in a more natural sleep pattern [11] and lack of tolerance and dependency compared with most other hypnotics [12]. However, to our knowledge, the risk of side effects associated with short-acting and long-acting hypnotics has not been compared in a randomized controlled study or large observational study. The association between hypnotics and fractures has also not been evaluated before therapy is started and after it is ended. The purpose of the present study was to compare the risks of fracture associated with the use of z-drugs and the long-acting hypnotic propiomazine. Another aim was to critically evaluate the association between hypnotic use and fracture.

Materials and methods

Data sources

This study was conducted with data from three Swedish databases: the Prescribed Drug Registry, the National Patient Registry (NPR), and the Cause of Death Registry. The Prescribed Drug Registry consists of records for all drug prescriptions filled at Swedish pharmacies since July 2005. The NPR includes records of all diagnoses made in inpatient care settings since 1987 and specialist outpatient care settings since 2001. The Cause of Death Registry contains data on causes and dates of death for all Swedish residents. These data were linked by Statistics Sweden using unique 10-digit civil registration numbers, which all Swedish residents have. Statistics Sweden also anonymized the data before receipt by the principal investigator (PN) and provided access to kinship and socioeconomic data, such as education, income, and early disability pension receipt. Diagnoses in the study cohorts were tracked in the NPR using International Classification of Diseases, 10th revision (ICD-10) codes (available since 1997). The present study was approved by the ethical committee of Umeå university, by the National Board of Health and Welfare and by Statistics Sweden.

Study cohorts

All persons aged ≥ 50 years on 31 December 2005 (n = 3,341,706) were considered for inclusion. We excluded individuals who filled prescriptions for propiomazine (n = 140,602, 4.3%) or z-drugs (n = 477,868, 14.3%) before 1 January 2007 to increase the likelihood that therapy began on the first recorded prescription date (data on prescriptions prior to July 2005 were unavailable). Thus, persons who filled prescriptions for propiomazine (n = 239,253, 7.2%) or z-drugs (n = 613,306, 18.4%) at least once between 1 January 2007 and 31 December 2016 were considered to be users. After excluding individuals with suspected inaccurate data, such as a fracture or drug dispensation recorded after a person's date of death, 237,396 propiomazine users and 604,457 z-drug users remained. Each user was matched with a non-user from the rest of the cohort based on birth year, birth month, sex, and Swedish or non-Swedish citizenship. Non-users who died before the corresponding users were dispensed their last doses of propiomazine or z-drugs were excluded and replaced with other non-users from the rest of the cohort. Unmatched individuals were excluded. This process yielded 233,609 propiomazine user/non-user pairs and 591,136 z-drug user/non-user pairs. The third and fourth cohorts consisted of all full sibling pairs from the total cohort with discordant propiomazine (n = 83,594) and z-drug use (n = 153,314), respectively. The baseline date for each pair was the date of treatment initiation. Sibling pairs in which the drug-naïve sibling died before baseline were excluded. The purpose of the subcohorts of siblings was to adjust for potential uncontrolled confounding due to familial and genetic factors that would not be captured in medical records.

Outcomes

The main study outcome was fracture (ICD-10 codes S22–S82, excluding S62 [fracture of the hand]). The Swedish NPR does not differentiate between new diagnoses and follow-up examination data. To avoid counting the same fracture more than once, only the first and last fractures in each individual were analyzed, and these events had to be separated by at least 365 days for the second diagnosis to be included. In sensitivity analyses, we also examined the secondary outcomes of hip fracture (ICD-10 code S72), stroke (ICD-10 codes I61–I64), and dementia (ICD-10 codes F00, F01, F039). NPR data have been validated in detail, with positive predictive values (PPVs) of 85–95% [13–15]. Notably, the PPV for hip fracture in this register exceeds 95% [16].

Statistical analysis

Baseline characteristics are presented as means and standard deviations, unless indicated otherwise. The baseline for each matched case-control pair was set as the date on which the user filled his or her first prescription.

To test whether the association between propiomazine or z-drug use and the risk of fracture diagnosis was time dependent, we evaluated Schoenfeld residuals using the estat phtest command in the Stata software (version 12.1; StataCorp LP, College Station, TX, USA). After determining that it was, we used flexible parametric models, which unlike Cox regression

models allow the inclusion of time-dependent covariates, for survival analyses. Retrospective and prospective fractures were analyzed independently using three degrees of freedom and knots at default positions [17]. The analyses were conditional, and thus adjusted for sex, age, and citizenship, but no other adjusting variable was used.

To investigate the magnitude of the association between drug use and fracture risk, conditional logistic regression models for six time frames were used. Associations were analyzed during days 1–90, 91–181, and 182–365 before and after the initiation of therapy. In each analysis, each pair in which a participant had a fracture or died in any time frame closer to the baseline date was excluded. Ninety days after the last prescription was filled, users and corresponding controls were excluded from further analyses. Finally, if not censored before, individuals were censored on 31 December 2016. The

Table 1 Baseline characteristics of the propiomazine study cohort

	Propiomazine users $n = 233,609$	Propiomazine non-users $n = 233,609$	P value
Age	69.2 ± 9.9	69.2 ± 9.9	
Civil status			< 0.001
Married	126,872 (54.3%)	139,114 (59.5%)	
Not married	29,080 (12.4%)	27,419 (11.7%)	
Divorced	50,577 (21.7%)	38,827 (16.6%)	
Widow/widower	27,148 (11.6%)	27,148 (11.6%)	
Missing data	268 (0.1%)	1024 (0.4%)	
Education			< 0.001
< 9 years Elementary school	37,936 (19.9%)	39,078 (20.6%)	
9 years Elementary school	19,958 (10.4%)	18,969 (10.0%)	
2 years Senior High school	62,156 (32.5%)	57,273 (30.2%)	
> 2 years Senior High school	21,045 (11.0%)	22,089 (11.7%)	
Post-secondary school	49,912 (26.1%)	52,145 (27.5%)	
Missing data	42,602 (18.2%)	44,055 (18.9%)	
Early retirement pension	44,731 (19.2%)	26,801 (11.5%)	< 0.001
Diagnoses at baseline			
Myocardial infarction	13,396 (5.7%)	9792 (4.2%)	< 0.001
Angina pectoris	21,024 (9.0%)	15,334 (6.6%)	< 0.001
Stroke	13,024 (5.6%)	8887 (3.8%)	< 0.001
Diabetes mellitus or diabetes drugs	29,749 (12.7%)	24,151 (10.3%)	< 0.001
Traumatic brain injury	11,302 (4.8%)	7253 (3.1%)	< 0.001
Cancer	51,835 (22.2%)	37,122 (15.9%)	< 0.001
Dementia or dementia drugs	7580 (3.2%)	4660 (2.0%)	< 0.001
Depression or antidepressants	99,195 (42.5%)	38,957 (16.7%)	< 0.001
Bipolar disease	3381 (1.4%)	659 (0.3%)	< 0.001
Alcoholic intoxication	12,524 (5.4%)	2547 (1.1%)	< 0.001
Opioid intoxication	967 (0.4%)	193 (0.1%)	< 0.001
Psychosis	1028 (0.4%)	323 (0.1%)	< 0.001
Renal failure	2058 (0.9%)	892 (0.4%)	< 0.001
Chronic obstructive pulmonary disease	10,602 (4.5%)	4837 (2.1%)	< 0.001
Rheumatoid arthritis	4450 (1.9%)	3582 (1.5%)	< 0.001
Chrohn's disease	1375 (0.6%)	967 (0.4%)	< 0.001
Colitis	2099 (0.9%)	1612 (0.7%)	< 0.001
Fracture	36,105 (15.5%)	28,750 (12.3%)	< 0.001
Drugs prescribed at least once			
Benzodiazepines	69,002 (29.5%)	25,943 (11.1%)	< 0.001
Glucocorticoids	55,235 (23.6%)	35,757 (15.3%)	< 0.001
Bisphosphonates	14,023 (6.0%)	10,400 (4.5%)	< 0.001
Levothyroxin	24,983 (10.7%)	19,922 (8.5%)	< 0.001

clogit command in the Stata software was used to fit maximum likelihood (fixed-effect) models to estimate odds ratios with the dichotomous dependent variable of interest, i.e., propiomazine or z-drug use. The likelihood was then calculated relative to each group, i.e., conditional likelihood was used. The first model was unadjusted, although adjusted for age, sex, and citizenship by design. The second model was adjusted for civil status (four categories), education (five categories), early retirement pension receipt, 17 diagnoses at baseline (all diagnoses listed in Tables 1 and 2, except fracture), and baseline use of four drugs. Associations in the year before baseline were adjusted for differences estimated at 1 year before baseline. Data from the sibling cohorts were analyzed in a similar fashion, but only fully adjusted models are presented. In the total matched cohorts, separate analyses were performed according to subgroups defined by sex, age group, depression diagnosis, use of certain medications, and receipt of one or several prescriptions for propiomazine or z-

Table 2 Baseline characteristics of the zopiclone/zolpidem/zaleplon study cohort

	Z users $n = 591{,}136$	Z non-users $n = 591{,}136$	P value
Age	72.1 ± 10.4	72.1 ± 10.4	
Civil status			< 0.001
Married	338,370 (57.2%)	346,646 (58.6%)	
Not married	61,674 (10.4%)	64,372 (10.9%)	
Divorced	106,265 (18.0%)	89,622 (15.2%)	
Widow/widower	83,741 (14.2%)	88,218 (14.9%)	
Missing data	792 (0.1%)	2112 (0.4%)	
Education			< 0.001
< 9 years Elementary school	100,218 (22.7%)	104,552 (23.9%)	
9 years Elementary school	41,970 (9.5%)	40,555 (9.3%)	
2 years Senior High school	135,816 (30.8%)	130,977 (29.9%)	
>2 years Senior High school	47,858 (10.9%)	49,747 (11.4%)	
Post-Secondary school	114,728 (26.0%)	112,074 (25.6%)	
Missing data	150,547 (25.5%)	153,232 (25.9%)	
Early retirement pension	79,674 (13.5%)	52,192 (8.9%)	< 0.001
Diagnoses at baseline			
Myocardial infarction	40,789 (6.9%)	26,589 (4.5%)	< 0.001
Angina pectoris	58,398 (9.9%)	40,031 (6.8%)	< 0.001
Stroke	42,676 (7.2%)	24,891 (4.2%)	< 0.001
Diabetes mellitus or diabetes drugs	82,255 (13.9%)	61,361 (10.4%)	< 0.001
Traumatic brain injury	24,790 (4.2%)	17,841 (3.0%)	< 0.001
Cancer	150,617 (25.5%)	96,394 (16.3%)	< 0.001
Dementia or dementia drugs	28,840 (4.9%)	13,799 (2.3%)	< 0.001
Depression or antidepressants	176,432 (29.8%)	74,690 (12.6%)	< 0.001
Bipolar disease	3381 (1.4%)	659 (0.3%)	< 0.001
Alcoholic intoxication	14,770 (2.5%)	5363 (0.9%)	< 0.001
Opioid intoxication	1088 (0.2%)	278 (0.05%)	< 0.001
Psychosis	1688 (0.3%)	620 (0.1%)	< 0.001
Renal failure	6203 (1.0%)	2121 (0.4%)	< 0.001
Chronic obstructive pulmonary disease	26,227 (4.4%)	10,974 (1.9%)	< 0.001
Rheumatoid arthritis	11,602 (2.0%)	8596 (1.5%)	< 0.001
Chrohn's disease	3087 (0.5%)	2025 (0.3%)	< 0.001
Colitis	4835 (0.8%)	3492 (0.6%)	< 0.001
Fracture	98,609 (16.7%)	77,028 (13.0%)	< 0.001
Drugs prescribed at least once			
Benzodiazepines	121,807 (20.6%)	49,236 (8.3%)	< 0.001
Glucocorticoids	144,844 (24.5%)	84,448 (14.3%)	< 0.001
Bisphosphonates	39,009 (6.6%)	27,654 (4.7%)	< 0.001
Levothyroxin	62,159 (10.5%)	50,290 (8.5%)	< 0.001

drugs. Unadjusted estimates are presented for all intervals in the subgroup analyses when the estimate for at least one interval was found to be unstable in fully adjusted models. The Stata software (versions 12.1 and 15.1) and SPSS software (version 23; IBM, Armonk, NY, USA) were used to fit the statistical models and to illustrate the results graphically. *P* values < 0.05 were considered to be significant.

Results

Baseline characteristics

The characteristics of the matched cohorts based on propiomazine and z-drug use are presented in Tables 1 and 2, respectively. The mean ages at baseline in the propiomazine and z-drug cohorts were 69 and 72 years, respectively. In both cohorts, all baseline characteristics differed significantly between users and non-users. The greatest differences at baseline included higher prevalences of benzodiazepine use, glucocorticoid use, and depression or use of antidepressant drugs in propiomazine and z-drug users compared with non-users.

Fracture risk

The risks of fracture in the propiomazine cohort before and after the initiation of therapy are presented in Fig. 1. The risk associated with propiomazine use was greatest in the 90 days preceding the initiation of therapy (odds ratio [OR], 2.94; 95% confidence interval [CI], 2.73–3.16; Table 3). This risk was somewhat attenuated after adjustment for confounders (OR, 2.52; 95% CI, 2.28–2.79). In the first 90 days after initiation of therapy, this risk was reduced by more than half (OR, 1.42; 95% CI, 1.27–1.60) and the risk remained constant thereafter (Figs. 1 and 2, Table 3). The pattern was similar for hip fracture, with the greatest risk seen in the 90 days before the initiation of propiomazine use (Table 3). The pattern of greater fracture risk before than after the initiation of therapy was consistent in all subgroups defined according to age, certain diagnoses, and one or several prescriptions for propiomazine (Table 3). The risk of fracture after termination of therapy could be analyzed in 182,589 pairs, where one individual in each pair from the original cohort had previous use of propiomazine (Fig. 3). The first year after last prescribed dose, previous users still had an increased risk of fracture (OR, 1.28, 95% CI, 1.21–1.36), after adjustment for all confounders.

The risks of fracture in the z-drug cohort before and after the initiation of therapy are presented in Fig. 2. As in the propiomazine cohort, the risk associated with the use of z-drugs was greatest in the 90 days preceding therapy initiation (OR, 4.10; 95% CI, 3.86–4.35; Table 4). This increased risk was more than halved after the initiation of therapy (OR, 1.67; 95% CI, 1.56–1.80; Table 4), and the risk declined further with increasing follow-up time (Table 4). The pattern was similar for the outcome of hip fracture, with the greatest risk seen before the initiation of z-drug use (Table 4). The pattern of greater risk before than after the initiation of therapy was consistent in all subgroups defined according to age, certain diagnoses, and one or several prescriptions for z-drugs (Table 4). The risk of fracture after termination of therapy could be analyzed in 370,213 pairs, where one individual in each pair from the original cohort had previous use of z-drugs (Fig. 4). The first year after last prescribed dose, previous users still had an increased risk of fracture (OR, 1.20, 95% CI, 1.15–1.26), after adjustment for all confounders. Finally, individuals on the higher strength of the respective z-drug (10 mg, $n = 73{,}615$) had a lower risk of fracture than individuals on a lower strength ($n = 517{,}521$) both the year before

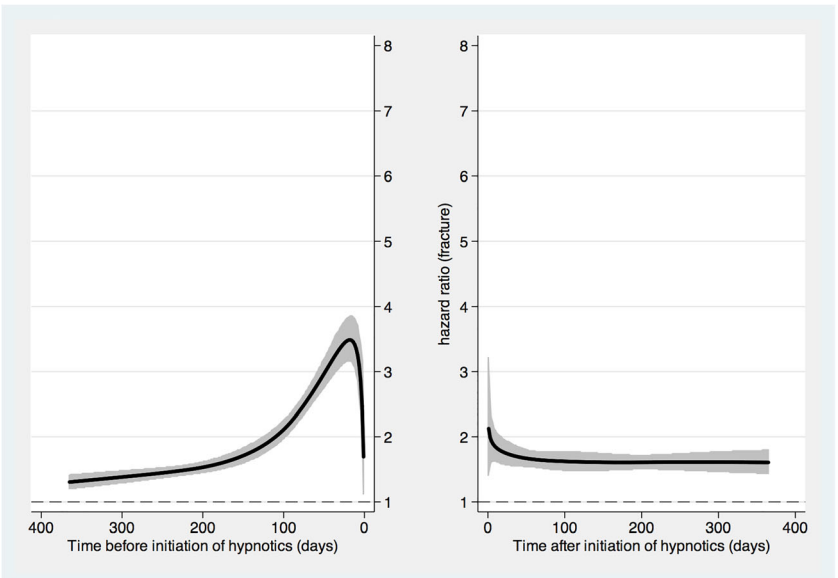

Fig. 1 Associations between propiomazine treatment initiation and fracture. Flexible parametric models for the matched cohort of propiomazine users and controls ($n = 467{,}218$). Conditional analyses were performed using four degrees of freedom and knots at default positions. The gray area represents the 95% confidence interval

Table 3 Odds ratios (ORs) for fracture in propiomazine users relative to non-users. Associations are presented for intervals before and after the index date (start of treatment in users), adjusted for confounders according to civil status, education, early retirement pension receipt, diagnoses, and drug use, as presented in Table 1

	Before index date			After index date		
	365–182 days OR, 95% CI)	181–91 days OR, 95% CI)	90–1 days OR, 95% CI	1–90 days OR, 95% CI)	91–181 days OR, 95% CI)	182–365 days OR, 95% CI)
Total cohort, not adjusted ($n = 467,218$)	1.40, 1.33–1.49	1.83, 1.69–1.98	2.94, 2.73–3.16	1.71, 1.58–1.82	1.60, 1.43–1.79	1.62, 1.48–1.76
Outcome of fracture adjusted for all confounders	1.26, 1.16–1.36	1.55, 1.39–1.74	2.52, 2.28–2.79	1.42, 1.27–1.60	1.23, 1.04–1.46	1.34, 1.21–1.49
According to subgroups at baseline adjusted for all confounders						
Women ($n = 267,078$)	1.13, 1.03–1.25	1.38, 1.20–1.57	1.90, 1.68–2.15	1.24, 1.08–1.43	1.14, 0.97–1.33	1.19, 1.06–1.35
Men ($n = 200,140$)	1.60, 1.38–1.86	2.15, 1.73–2.68	4.42, 3.66–5.35	1.86, 1.52–2.29	1.93, 1.50–2.50	1.82, 1.50–2.23
< 65 years ($n = 177,356$)	1.23, 1.07–1.40	1.42, 1.17–1.71	2.33, 1.95–2.78	1.41, 1.16–1.73	1.28, 0.97–1.68	1.50, 1.19–1.82
65–80 years ($n = 216,614$)	1.28, 1.15–1.42	1.64, 1.41–1.90	2.67, 2.34–3.05	1.51, 1.31–1.75	1.27, 1.04–1.55	1.44, 1.22–1.69
> 80 years ($n = 73\ 248$)	1.37, 1.23–1.51[a]	1.83, 1.69–1.98[a]	2.94, 2.74–3.16[a]	1.57, 1.38–1.78[a]	1.69, 1.37–2.08[a]	1.41, 1.20–1.64[a]
Individuals with depression ($n = 34,238$)	1.09, 0.82–1.44	1.28, 0.88–1.85	1.63, 1.14–2.33	1.18, 0.82–1.70	1.34, 0.62–2.88	1.83, 1.12–2.99
Individuals on glucocorticoids ($n = 19,514$)	1.33, 1.03–1.72[a]	2.24, 1.55–3.24[a]	1.93, 1.42–2.64[a]	1.26, 0.92–1.73[a]	1.57, 0.93–2.64[a]	1.25, 0.82–1.89[a]
Individuals on benzodiazepines ($n = 16,878$)	1.48, 1.17–1.88[a]	2.00, 1.47–1.72[a]	2.75, 2.03–3.73[a]	1.42, 1.05–1.92[a]	1.42, 0.91–2.22[a]	1.29, 0.90–1.86[a]
1 prescription of propiomazine ($n = 207,466$)	1.06, 0.72–1.58[a]	1.50, 0.91–2.46[a]	2.29, 1.42–3.70[a]	1.44, 1.29–1.62[a]	No observations	No observations
> 1 prescription of propiomazine ($n = 259,752$)	1.26, 1.13–1.40	1.65, 1.41–1.92	2.53, 2.19–2.92	1.61, 1.36–1.90	1.25, 1.05–1.49	1.42, 1.24–1.62
Sibling pairs discordant for use of propiomazin ($n = 83,594$)						
Outcome of fracture adjusted for all confounders	1.10, 0.91–1.33	1.40, 1.11–1.75	2.84, 2.19–3.67	1.76, 1.35–2.29	1.45, 1.03–2.05	1.82, 1.37–2.41
Other outcomes adjusted for all confounders ($n = 467,218$)						
Hip fracture	1.46, 1.14–1.88	2.22, 1.63–3.02	5.54, 4.17–7.36	1.75, 1.27–2.41	1.27, 0.77–2.10	1.76, 1.17–2.63
Stroke[b]	1.97, 1.58–2.47[a]	4.42, 3.32–5.89[a]	8.95, 6.80–11.76[a]	1.69, 1.29–2.21[a]	0.95, 0.66–1.37[a]	1.45, 1.06–1.98[a]
Dementia[b]	1.83, 1.49–2.26	2.06, 1.54–2.75	2.79, 2.19–3.54	2.11, 1.62–2.75	2.11, 1.54–2.91	1.52, 1.23–1.87

[a] Unadjusted models presented because of unstable estimates in fully adjusted models

[b] Only subjects with no diagnosed dementia or stroke, respectively, at baseline were included

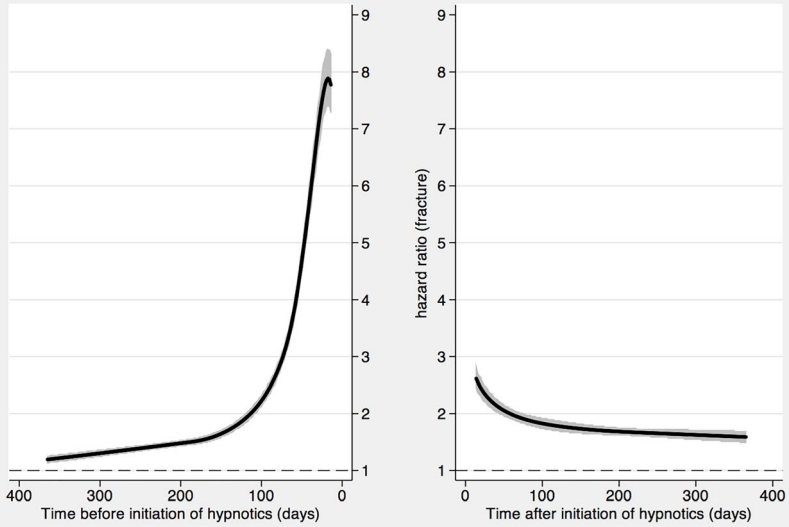

Fig. 2 Associations between z-drug treatment initiation and fracture. Flexible parametric models for the matched cohort of z-drug users and controls (n = 1,182,272). Conditional analyses were performed using five degrees of freedom and knots at default positions. The gray area represents the 95% confidence interval

(OR, 0.82, 95% CI, 0.77–0.88) and after initiation of therapy (OR, 0.90, 95% CI, 0.84–0.97), after adjustment of all confounders.

Sensitivity analysis results

The risk patterns associated with fracture in propiomazine users and z-drug users were tested in several sensitivity analyses. In the first analysis, the risk was investigated in the two subcohorts of sibling pairs with discordant drug use. The patterns associated with drug use in the sibling cohorts were similar to those in the main cohort, with the greatest risk of fracture seen before treatment was initiated (Tables 3 and 4). Finally, we investigated the risks of stroke and dementia associated with use of the drugs of interest. The patterns were similar to those observed for the outcome of fracture, with the greatest risk seen before the initiation of treatment with propiomazine and z-drugs (Tables 3 and 4).

Discussion

This study showed that the initiation of treatment with propiomazine and z-drugs is associated strongly with an increased risk of fracture. However, this risk was even higher before initiation of therapy. The strength of associations increased from 1 year before the baseline date, peaked close to this date, and then fell after the initiation of treatment with hypnotics. The associations had similar patterns in siblings, women and men, different age groups, and different subgroups

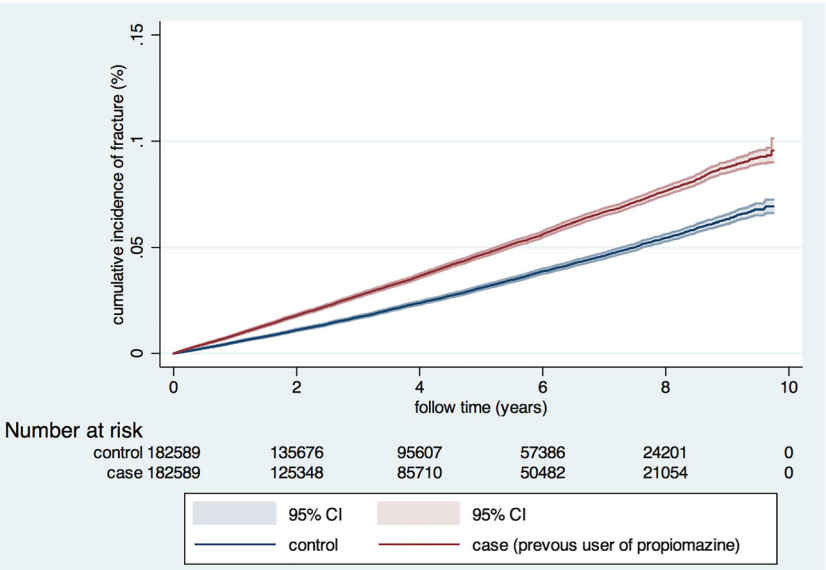

Fig. 3 Associations between previous propiomazine use and fracture after end of therapy. Kaplan-Meier curve for the outcome of fracture in previous users of propriomazine and corresponding controls. Cumulative incidence of fracture and 95% confidence intervals (95% CI) are presented

Table 4 Odds ratios (ORs) for fracture in users of zolpidem/zopiclone/zaleplon (z-drug) users relative to non-users. Associations are presented for intervals before and after the index date (start of treatment in users), adjusted for confounders according to civil status, education, early retirement pension receipt, diagnoses, and drug use, as presented in Table 1

	Before index date			After index date		
	365–182 days OR, 95% CI)	181–91 days OR, 95% CI)	90–1 days OR, 95% CI	1–90 days OR, 95% CI)	91–181 days OR, 95% CI)	182–365 days OR, 95% CI)
Total cohort, not adjusted (n = 1,182,272)	1.32, 1.28–1.37	1.84, 1.75–1.93	4.98, 4.78–5.20	2.22, 2.13–2.33	1.82, 1.72–1.94	1.65, 1.57–1.72
Outcome of fracture adjusted for all confounders	1.22, 1.15–1.28	1.50, 1.40–1.62	4.10, 3.86–4.35	1.67, 1.56–1.80	1.43, 1.30–1.57	1.33, 1.25–1.43
According to subgroups at baseline adjusted for all confounders						
Women (n = 679,590)	1.11, 1.04–1.18	1.31, 1.20–1.42	3.41, 3.18–3.66	1.48, 1.36–1.61	1.34, 1.20–1.50	1.29, 1.19–1.40
Men (n = 502,682)	1.51, 1.37–1.66	2.06, 1.80–2.37	6.11, 5.47–6.84	2.23, 1.94–2.57	1.70, 1.40–2.06	1.42, 1.24–1.63
< 65 years (n = 331,614)	1.16, 1.05–1.28	1.38, 1.20–1.58	3.03, 2.70–3.41	1.36, 1.18–1.57	1.33, 1.10–1.61	1.16, 1.01.1.32
65–80 years (n = 564,074)	1.24, 1.16–1.32	1.57, 1.43–1.71	4.43, 4.12–4.78	1.76, 1.61–1.93	1.41, 1.26–1.59	1.43 1.32–1.56
> 80 years (n = 286,584)	1.31, 1.09–1.59	1.51, 1.15–1.97	6.49, 5.12–8.22	2.27, 1.75–2.95	2.40, 1.52–3.77	1.03, 0.76–1.40
Individuals with depression (n = 47,322)	1.04, 0.81–1.34	1.52, 1.03–2.23	4.84, 3.46–6.77	2.42, 1.68–3.58	1.93, 1.13–3.30	1.93, 1.37–2.71
Individuals on glucocorticoids (n = 46,098)	1.02, 0.80–1.29	1.89, 1.29–2.79	3.85, 2.85–5.19	2.12, 1.51–2.97	1.59, 0.95–2.66	1.69, 1.16–2.45
Individuals on benzodiazepines (n = 22,796)	1.21, 1.01–1.46[a]	1.64, 1.27–2.11[a]	4.13, 3.29–5.18[a]	2.06, 1.62–2.62[a]	1.87, 1.34–2.61[a]	1.87, 1.45–2.41[a]
1 prescription of z-drugs (n = 345,054)	1.23, 1.12–1.35	1.55, 1.36–1.76	4.50, 4.06–4.99	1.73, 1.52–1.97	No observations	No observations
> 1 prescription of z-drugs (n = 837,218)	1.21, 1.14–1.29	1.48, 1.36–1.61	3.92, 3.64–4.22	1.67, 1.53–1.82	2.61, 2.15–3.16	2.22, 1.92–2.56
Sibling pairs discordant for use of z drugs (n = 153,314)						
Outcome of fracture adjusted for all confounders	1.37, 1.20–1.56	1.59, 1.33–1.90	4.73, 3.99–5.62	1.53, 1.28–1.83	1.23, 0.95–1.58	1.47, 1.24–1.74
Other outcomes adjusted for all confounders						
Hip fracture (n = 1,182,272)	1.45, 1.26–1.65	2.33, 1.94–2.79	10.96, 9.43–12.74	2.29, 1.92–2.73	1.96, 1.56–2.46	1.88, 1.59–2.22
Stroke[b]	2.97, 2.58–2.47[a]	5.66, 4.84–6.62[a]	14.14, 12.40–16.15[a]	2.53, 2.24–2.86[a]	2.21, 1.86–2.61[a]	2.07, 1.82–2.36[a]
Dementia[b]	2.48, 2.20–2.78	2.96, 2.52–3.48	5.31, 4.61–6.13	3.90, 3.31–4.59	2.45, 2.08–2.87	1.90, 1.69–2-15

[a] Unadjusted models presented because of unstable estimates in fully adjusted models

[b] Only subjects with no diagnosed stroke or dementia, respectively, at baseline were included

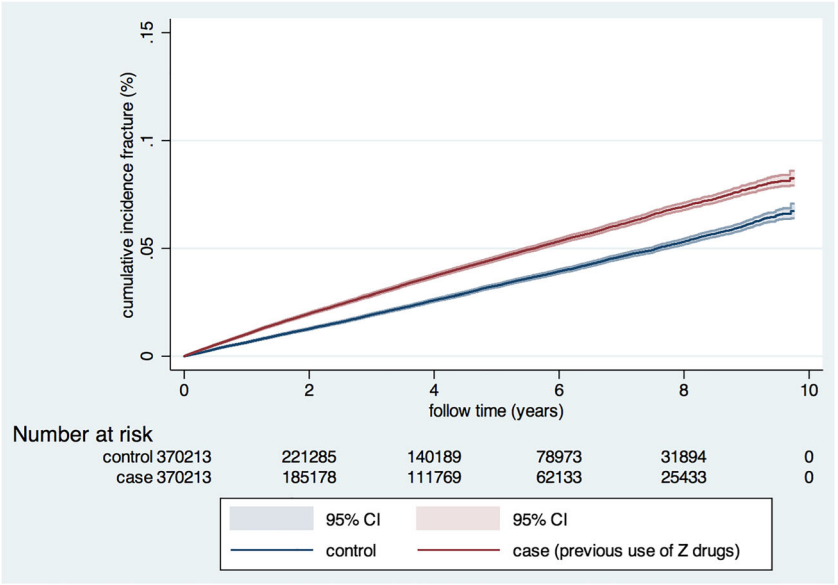

Fig. 4 Associations between previous z-drug use and fracture after end of therapy. Kaplan-Meier curve for the outcome of fracture in previous users of z-drugs and corresponding controls. Cumulative incidence and 95% confidence intervals (95% CI) are presented

defined according to certain diagnoses and use of certain drugs. It is also of interest that the association remained in the first year after therapy was ended for both propriomazine and the z-drugs. Finally, the patterns were similar in sensitivity analyses for the outcomes of stroke and dementia.

The associations after the initiation of therapy between hypnotic use and fracture confirm the results of previous observational studies of the use of other neuroleptics [18–21] and those of meta-analysis of z-drug use [6, 7]. However, to our knowledge, no previous large observational study has critically evaluated this association by also analyzing the risk of fracture before the initiation of therapy and after end of therapy. In our study cohorts, the risk of fracture was greatest in the last 3 months before the initiation of treatment. This risk was significantly higher than after the initiation of therapy, and the pattern was true for all four cohorts analyzed. This was especially true for the short-acting z-drugs, and the results strongly suggest that the association found between hypnotic use and fracture after initiation of therapy is not causal. Thus, the greater risk of fracture before beginning treatment with hypnotics probably explains the greater risk of fracture after treatment initiation. This explanation is supported by the fact that the associations remained after therapy with hypnotics was ended. This is also supported by the greater prevalence of all considered diseases in users of hypnotics. Yet, disease severity is not indicated in the registry data used, which likely contribute to residual confounding in the present study, as in other observational studies. Finally, register studies cannot measure factors such as general frailty, which increases the risks of many outcomes, including fracture [22]. Our results may represent real-life situations in which individuals have conditions that influence sleep, according to our results a fracture, and are prescribed hypnotics to improve accompanying sleep disorders because of fracture occurrence. These patients would have a greater risk of a new fracture, not necessarily because of hypnotic use, but due to existing conditions that increase the risks of falling and fracture. During treatment with hypnotics, the underlying condition may improve and the patients' fracture risk is reduced compared to before therapy was started. Another less likely explanation for the main results is that different underlying factors influence the risk of fracture before and after the initiation of treatment with hypnotics. If so, it would still be difficult to explain the remaining increased risk after therapy is terminated, and the fact that a higher strength of z-drugs was associated with lower risk of fracture. It is of interest that we found a quite similar association between antidepressants and fractures in a recent study [23], drugs that previously also have been associated with an increased risk of fractures [24, 25].

We further evaluated the causality of the association between hypnotic use and fracture in sensitivity analyses. In particular, we evaluated the associations between hypnotic use and the outcomes of stroke and dementia. In these analyses, the patterns of association with hypnotic use were similar to that seen for fracture, with the greatest risk observed before the start of treatment. With respect to causality, hypnotic use could theoretically increase the risk of stroke [26, 27], although the results of the present study strongly suggest that the association after the initiation of therapy represents residual confounding and reverse causality. Irrespectively, hypnotic use cannot cause dementia within weeks after the initiation of treatment. Instead, undiagnosed early dementia was likely present in this cohort in the period before the initiation of therapy [28]; this condition is often accompanied by anxiety and depression, resulting in decreased sleep quality.

Despite the obvious pitfalls associated with the evaluation and comparison of side effects of different drugs using observational data, cohort studies are often used for this purpose. In

a well-cited study of the risks of side effects of different types of antidepressants [29], selective serotonin inhibitors were associated with greater risks of falls and other side effects compared with tricyclic antidepressants. Another aim of the present study was to critically evaluate any difference in fracture risk after the initiation of propiomazine and z-drug use. If only the risk after the initiation of therapy was assessed, z-drug use would be associated with slightly greater risks not only of fracture, but also of stroke and dementia. However, examination of the associations also before treatment initiation shows that the associations after baseline likely reflect the increased risk before the initiation of therapy, and thus residual confounding and reverse causality.

Several limitations of this study should be considered. The registry-based nature of the study resulted in the lack of some important information, such as whether and how often patients took the medications they had obtained at pharmacies. In addition, no information was available on confounders such as physical activity, eating habit, weight, or smoking habit. Chronic obstructive pulmonary disease data were available as a surrogate for smoking, but this surrogate is inexact. Alcohol intoxication data were available as a surrogate for excessive alcohol use, but this surrogate is also inexact. Information was also lacking for some other drugs of potential interest, such as benzodiazepines, neuroleptics, histamine H1 blockers, melatonin, and antiepileptics. Although access to data on more confounders and more accurate estimation thereof would be of interest, such differences would not likely have changed the results of this study, as the risk of fracture was compared before and after the initiation of treatment. The strengths of the present study include the examination of a nationwide cohort and the lack of data loss during follow-up, both of which increase the external validity of the results.

In conclusion, this study showed that use of hypnotics is associated with a greater risk of fracture after the age of 50 years in the Swedish population. However, this increased risk is not likely to be causal, as the risk of fracture was greater before than after the initiation of treatment and remained similar after end of therapy. Given these results, similar investigation of reported associations between the use of other drugs and fracture, such neuroleptics other than propiomazine, would be of interest. Finally, the results of the present study emphasize the importance of not making inferences based on observational data.

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Compliance with ethical standards

Conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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