The long-term effect of benzodiazepine/hypnotics in old age

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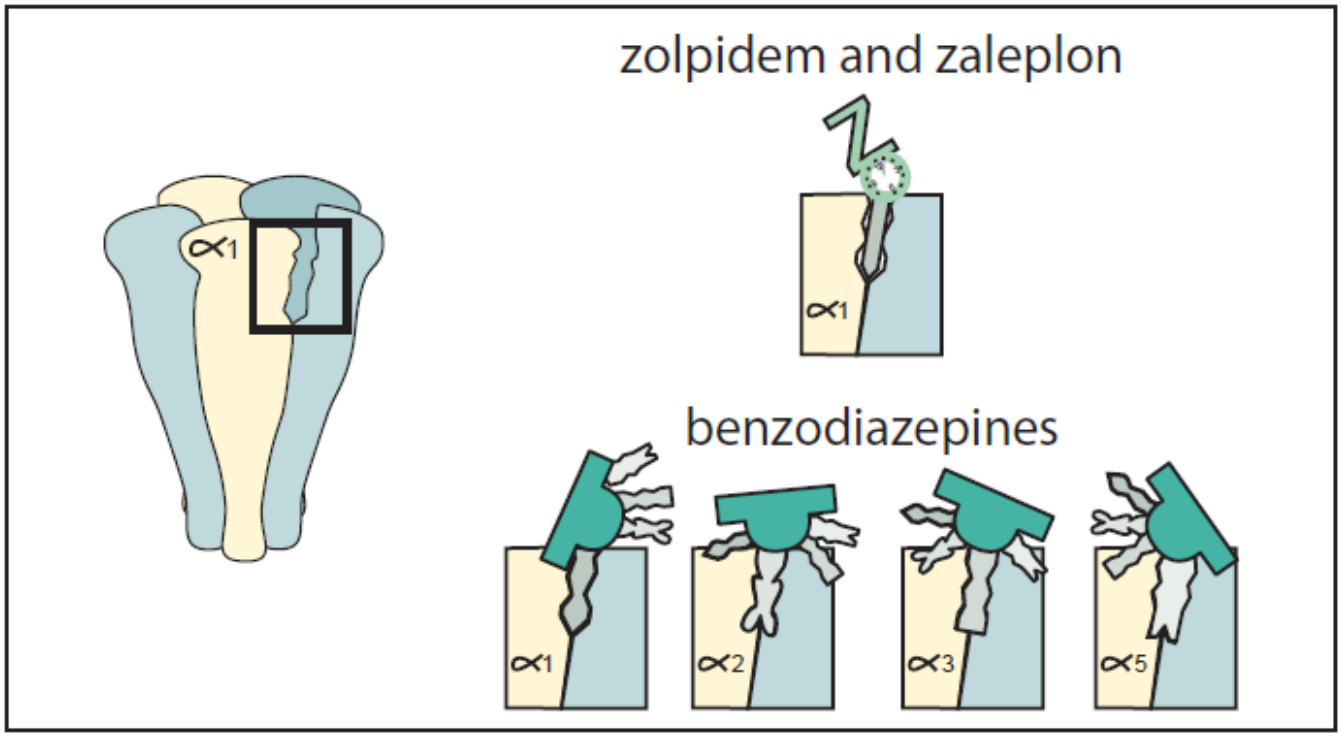
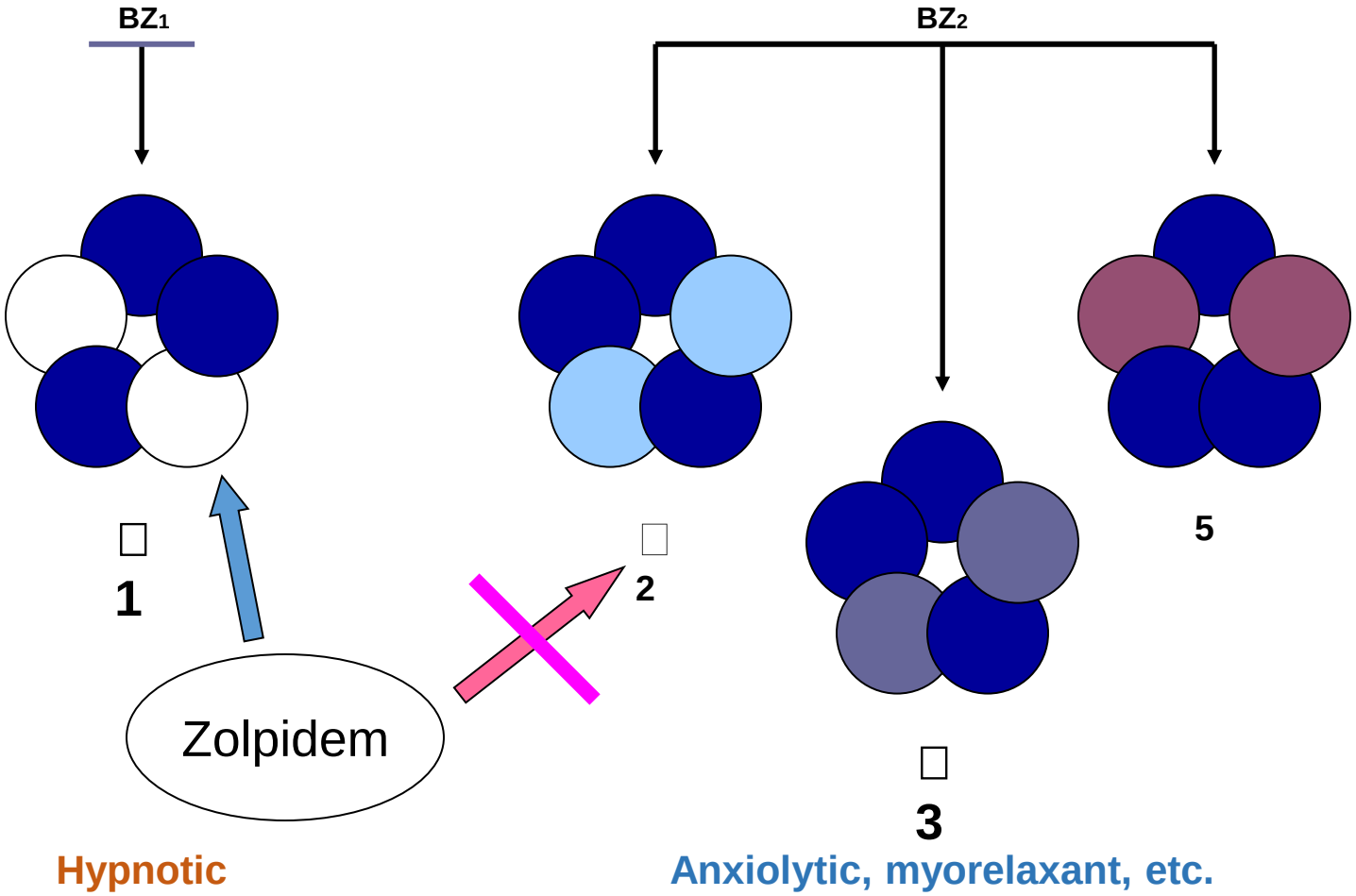
조철현

BDZs/NBRAs

- BZDs;
  - sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties → wide range of indications
- NBRAs (zolpidem, zopiclone, etc);
  - binds preferably to the alpha 1 subtype of the BZ receptor
  - produce sedation without interfering with other BZ properties



Putative functions of GABA-A receptor subtypes



Benavides et al. In Zolpidem, Freeman ed. Elsevier, 1996

Temporal trends in prescriptions of BDZs/NBRAs

- 1993–2010 waves of the National Ambulatory Medical Care Survey (NAMCS) in U.S.

- Prescribing of benzodiazepines (BZDs; e.g., alprazolam) and non-BZD receptor agonists (nBZRAs; e.g., zolpidem) increased from 1993 to 2010
- Growing trend observed for co-prescribing of BZDs and nBZRAs over same time period
- Prescribing of nBZRAs to patients with sleep disorders increased over this period while prescribing of BZDs to these patients declined

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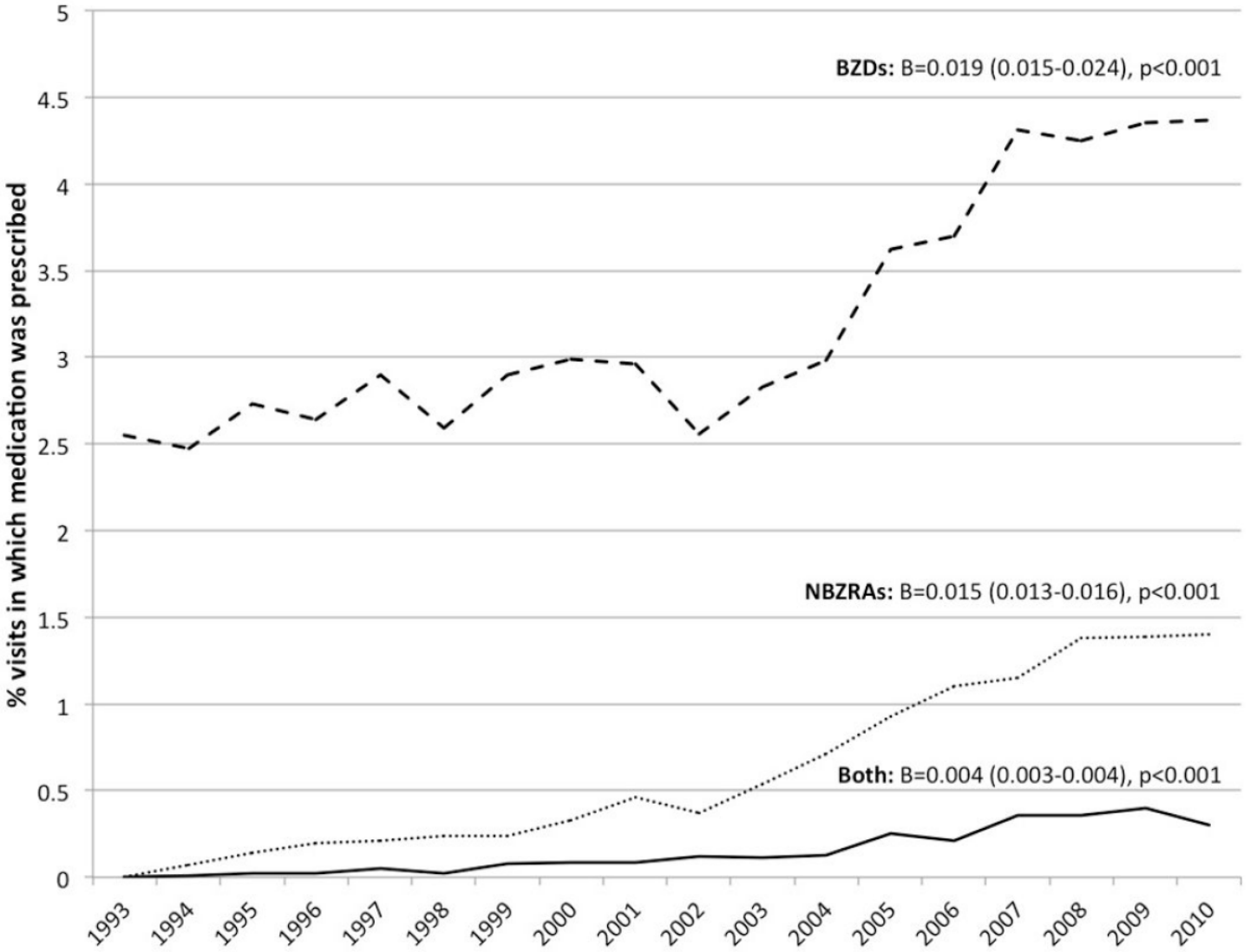
Temporal trends in prescriptions

Percentage of visits involving BZDs and/or NBZRAs



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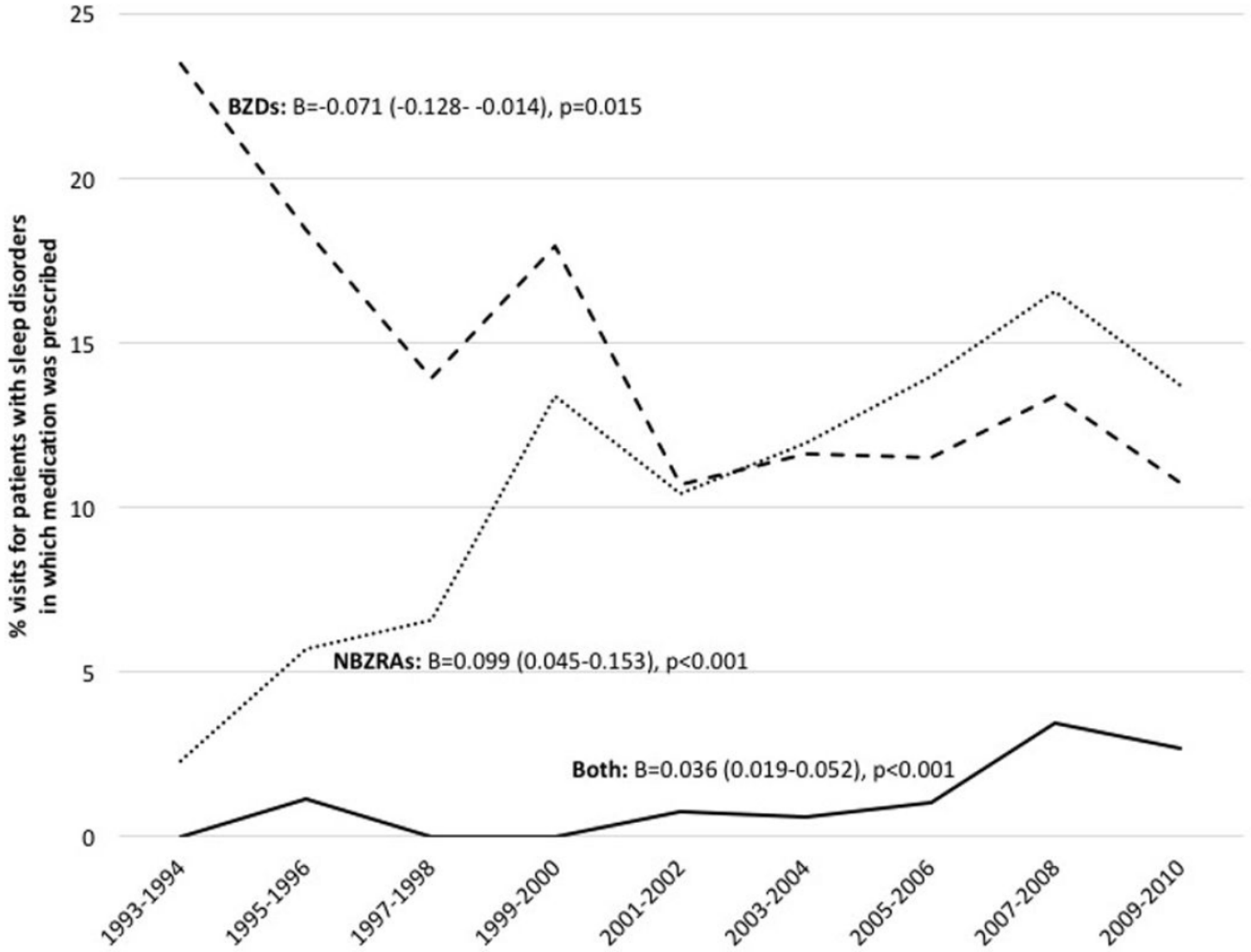
Temporal trends in prescriptions

Percentage of visits involving BDZs and/or NBZRAs for pts with sleep disorders



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Patient and visit characteristics of ambulatory healthcare office visits in which any sedative-hypnotic medications were prescribed.

Patient and Visit Characteristic	No BZD[a] nor nBZRA[b] visits n=494,220 n (%[c])	Any sedative-hypnotic visits n=21,898 n (%[c])	Comparison OR (95% CI)
Age			
<25 years	113,595 (25.8)	1,011 (3.6)	Ref.
25–44	114,405 (22.7)	5,864 (25.1)	**7.83 (7.05, 8.69)**
45–64	135,242 (26.4)	8,872 (40.5)	**10.89 (9.81, 12.09)**
65+	130,978 (25.0)	6,151 (30.8)	**8.73 (7.83, 9.73)**
Gender			
Female	282,846 (58.9)	14,331 (66.6)	Ref.
Male	211,374 (41.1)	7,567 (33.4)	**0.72 (0.69, 0.75)**
Race			
Non-Hispanic White	382,100 (76.2)	18,430 (83.5)	Ref.
Non-Hispanic Black	45,667 (9.6)	1,418 (7.0)	**0.66 (0.60, 0.73)**
Hispanic	46,417 (10.0)	1,495 (7.3)	**0.66 (0.59, 0.74)**
Other	20,036 (4.2)	555 (2.3)	**0.50 (0.42, 0.58)**
Diagnosis[d]			
Sleep	3,150 (0.6)	923 (5.3)	**9.21 (8.09, 10.48)**
Anxiety	8,540 (1.3)	4,773 (20.3)	**19.05 (17.69, 20.51)**
Mood	8,270 (1.0)	3,525 (11.0)	**11.82 (10.86, 12.88)**

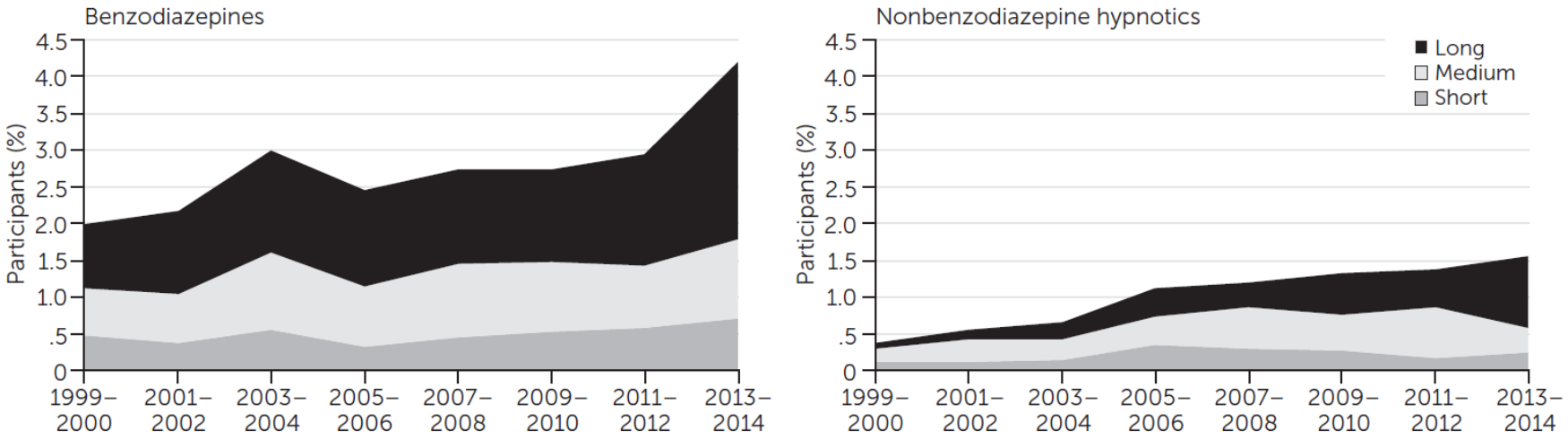
Pharmacoepidemiol Drug Saf. 2016

Comparison of patient and visit characteristics of ambulatory healthcare office visits involving benzodiazepines (BZD), non-benzodiazepine receptor agonists (nBZRA), and both classes (BZD+nBZRA).

Patient and Visit Characteristic	BZD[a] visits n=17,972 n (%[c])	nBZRA[b] visits n=3,042 n (%[c])	Comparison nBZRA vs. BZD visits OR (95% CI)	BZD+nBZRA visits n=884 n (%[c])	Comparison BZD+nBZRA vs. BZD visits OR (95% CI)
Age					
<25 years	889 (4.0)	108 (2.4)	Ref.	14 (1.6)	Ref.
25–44	4,923 (25.9)	672 (20.0)	1.31 (0.96, 1.79)	269 (29.4)	**2.87 (1.33, 6.19)**
45–64	7,072 (39.0)	1,363 (46.5)	**2.03 (1.50, 2.75)**	437 (48.3)	**3.14 (1.47, 6.71)**
65+	5,088 (31.2)	899 (31.2)	**1.71 (1.24, 2.35)**	164 (20.7)	1.68 (0.76, 3.70)
Gender					
Female	11,783 (66.9)	1,931 (64.3)	Ref.	617 (69.1)	Ref.
Male	6,189 (33.1)	1,111 (35.7)	**1.12 (1.00, 1.26)**	267 (30.9)	0.90 (0.71, 1.15)
Race					
Non-Hispanic White	15,202 (84.1)	2,471 (80.6)	Ref.	757 (83.1)	Ref.
Non-Hispanic Black	1,148 (6.9)	215 (7.3)	1.11 (0.91, 1.34)	55 (6.9)	1.01 (0.68, 1.52)
Hispanic	1,190 (7.0)	248 (8.6)	**1.28 (1.03, 1.61)**	57 (8.0)	1.15 (0.76, 1.75)
Other	432 (2.1)	108 (3.5)	**1.77 (1.24, 2.52)**	15 (2.1)	1.01 (0.51, 1.98)
Diagnosis[d]					
Sleep	455 (3.1)	408 (15.3)	**5.62 (4.66, 6.79)**	60 (8.3)	**2.83 (1.87, 4.29)**
Anxiety	4,263 (22.6)	248 (6.1)	**0.22 (0.19, 0.26)**	262 (31.0)	**1.54 (1.24, 1.91)**
Mood	2,877 (11.2)	388 (7.6)	**0.65 (0.55, 0.78)**	260 (22.0)	**2.24 (1.80, 2.80)**

Pharmacoepidemiol Drug Saf. 2016

Trends in short-term (less than six months), medium-term (six to 24 months), and long-term (more than 24 months) use of BDZs and nBDZ hypnotics, 1999–2014 in U.S.

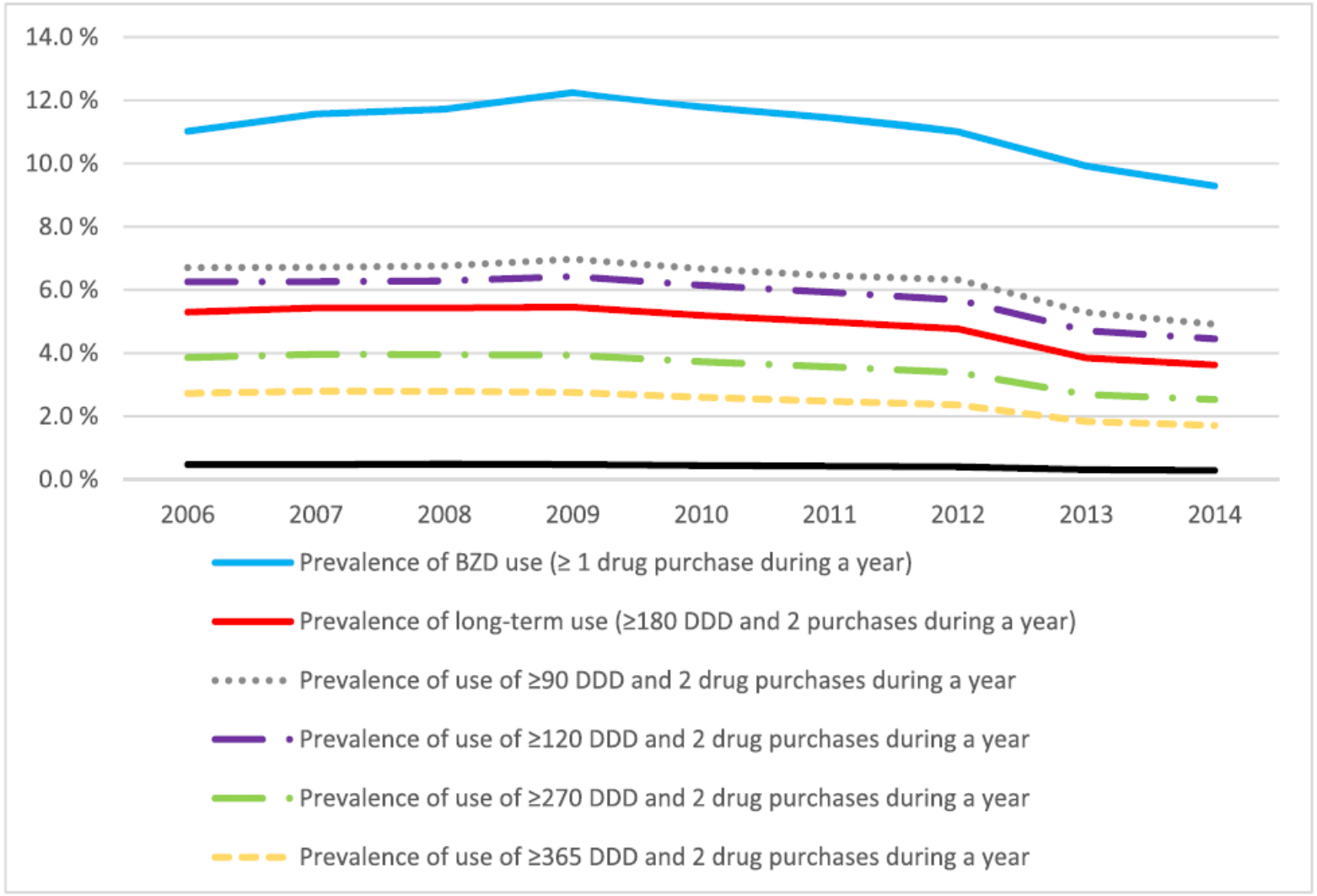


The observed increases in BZD and nBDZ hypnotic use in recent years may be attributable to growth in long-term use.

Monitoring of long-term BZD and nBDZ hypnotics use, particularly in vulnerable patients (for example, older adults), may be important for understanding the reasons for changing patterns of use of these medications and prevention of potential adverse health outcomes associated with their use.

Psychiatric Services in Advance, 2017

Trends in use, long-term use, and high-dose use of benzodiazepines and conducted sensitivity analyses (dotted lines) among the Finnish adult population



Pharmacoepidemiol Drug Saf. 2018

The prevalence of use, long-term use, and high-dose use of the most commonly used benzodiazepines in 2014 among Finnish adults and the proportion of long-term users among all users of active substance

Active Substance	The Prevalence of BZD Use (%)	The Prevalence of Long-Term[a] Use (%)	The Proportion of Long-Term[a] Users Among All Active Substance Users, (%)	The Proportion of High-Dose[b] Users Among All Active Substance Users, (%)	Female Users Among All Long-Term Users, (%)	Users of ≥ 65 Years Old Among All Long-Term Users, (%)
Anxiolytics by Active Substances						
Oxazepam	1.9	0.4	20.7	0.6	56.3	41.7
Diazepam	0.8	0.3	41.9	5.8	40.0	23.9
Alprazolam	0.7	0.3	40.5	7.9	49.0	28.0
Clonazepam	0.5	0.3	62.7	16.7	47.4	24.6
Hypnotics by active substances						
Zopiclone	4.1	1.8	42.8	0.6	61.9	66.6
Zolpidem	1.8	0.6	30.2	0.5	63.9	49.3

[a]≥180 defined daily doses (DDDs) and 2 drug purchases bought cumulatively during a calendar year.

[b]≥1000 DDDs and 2 drug purchases bought cumulatively during a calendar year.

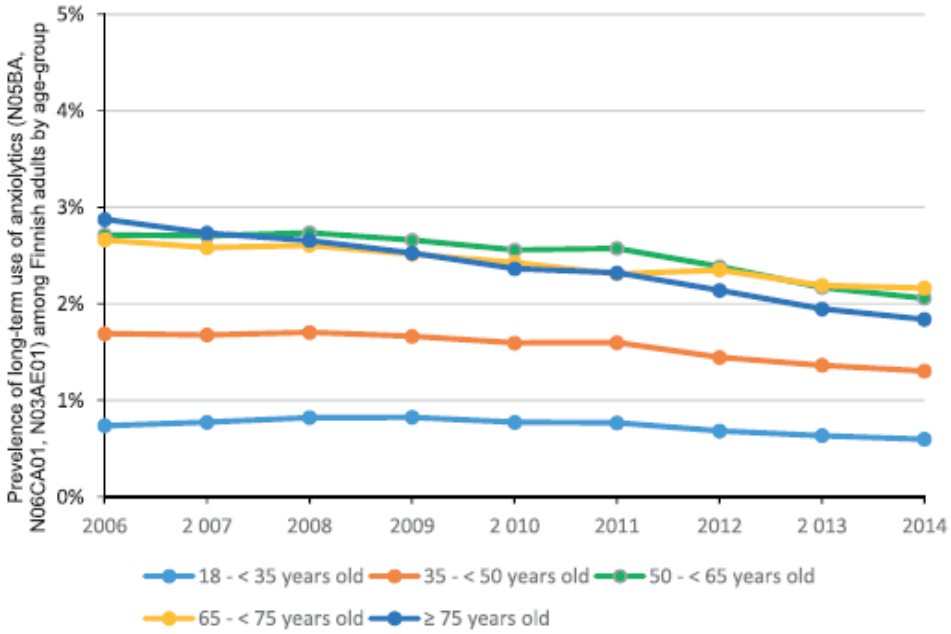
Mean persistence rates of benzodiazepine use among incident users 3, 5, 7, and 9 years after treatment start

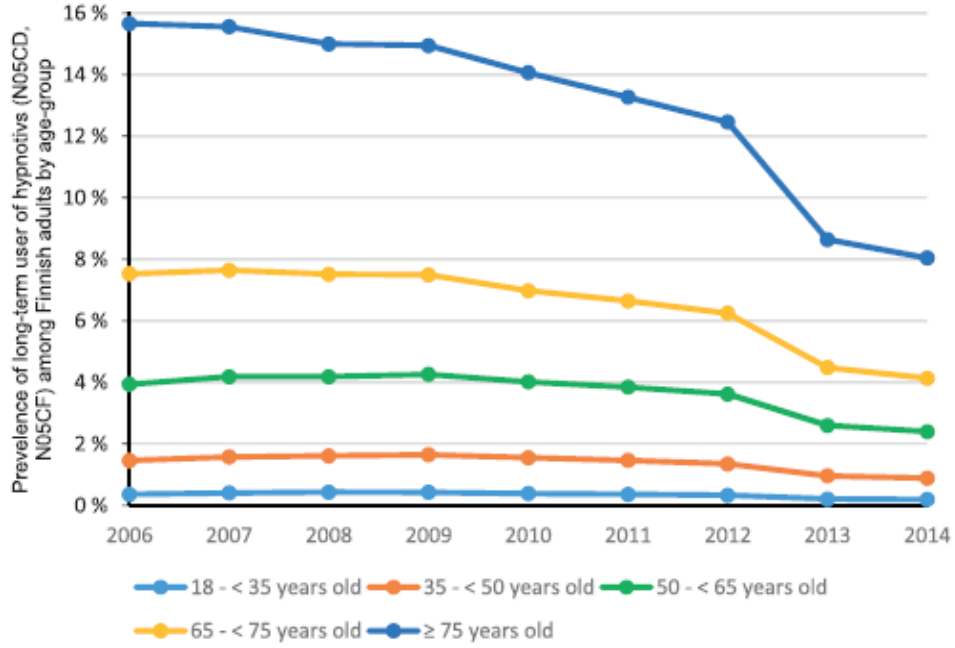
Incident Users of	Initially %	3 Years Mean (SD) %	5 Years Mean (SD) %	7 Years Mean (SD) %	9 Years Mean %
Clonazepam[b] (n = 34 114)	100	34.5 (3.5)	25.1 (4.3)	20.6 (4.8)	21.2
Temazepam[a] (n = 76 067)	100	40.6 (3.7)	26.7 (3.4)	18.6 (NA)	NA
Zopiclone (n = 387 437)	100	29.3 (5.6)	20.6 (3.9)	16.0 (3.0)	14.1
Zolpidem (n = 214 608)	100	23.8 (3.7)	15.4 (2.1)	11.2 (1.7)	10.8
Oxazepam (n = 208 142)	100	23.8 (4.9)	15.3 (4.1)	11.5 (3.6)	10.9
Diazepam (n = 88 920)	100	24.9 (3.7)	14.6 (3.4)	11.0 (2.2)	9.1
Alprazolam i (n = 79 223)	100	19.4 (7.6)	11.7 (3.4)	9.2 (0.5)	7.5

[a]Temazepam was withdrawn from the national reimbursement system in February 2013. Therefore, it was censored at the end of 2012.

[b]Clonazepam use for nonepilepsy indications.

Pharmacoepidemiol Drug Saf. 2018



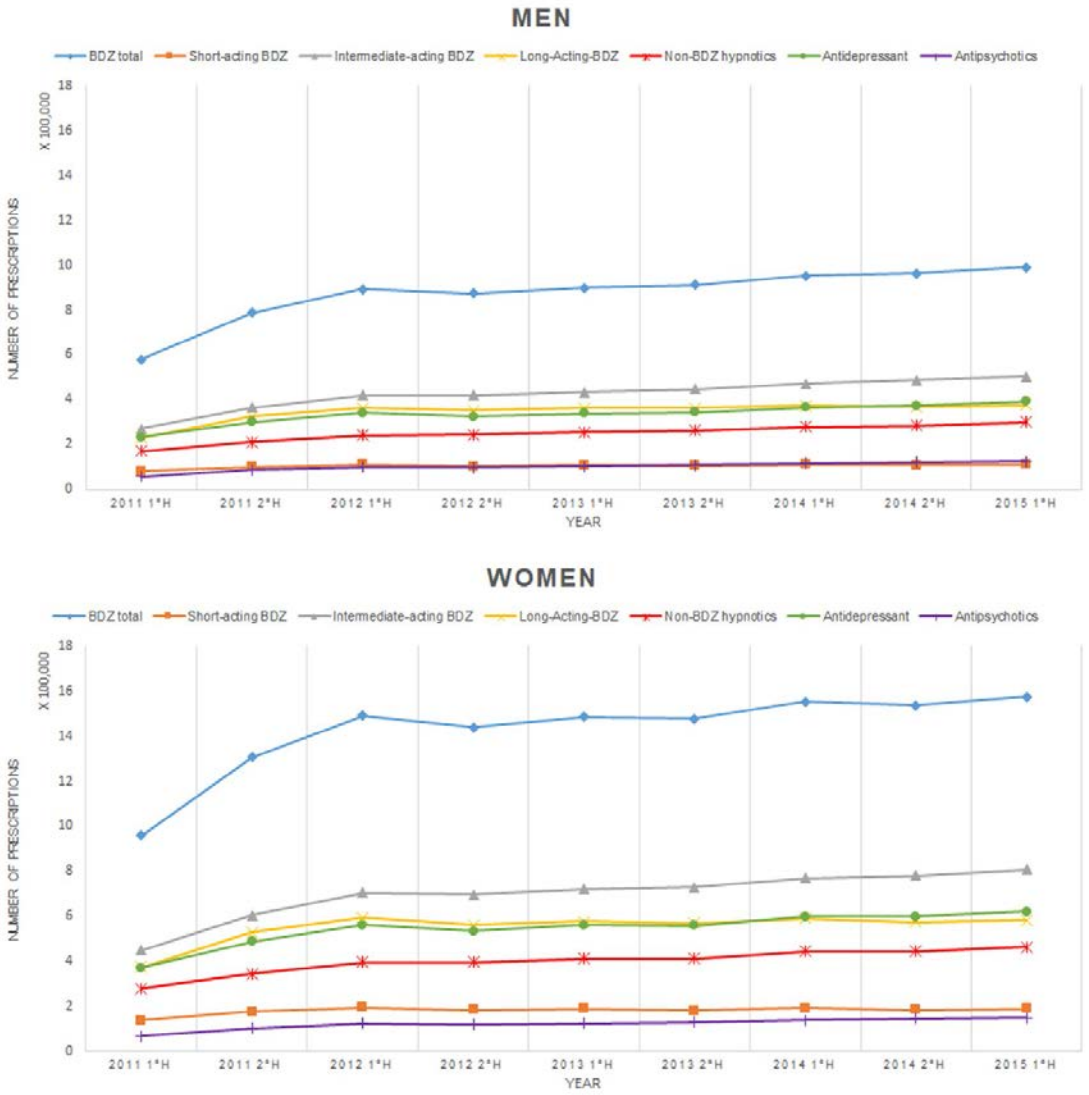


Prevalence of long-term use of anxiolytic and hypnotic benzodiazepines by age-group among the Finnish adult population

Pharmacoepidemiol Drug Saf. 2018

In Korea

Trends in prescriptions for sedative–hypnotics among Korean adults: a nationwide prescription database study for 2011–2015

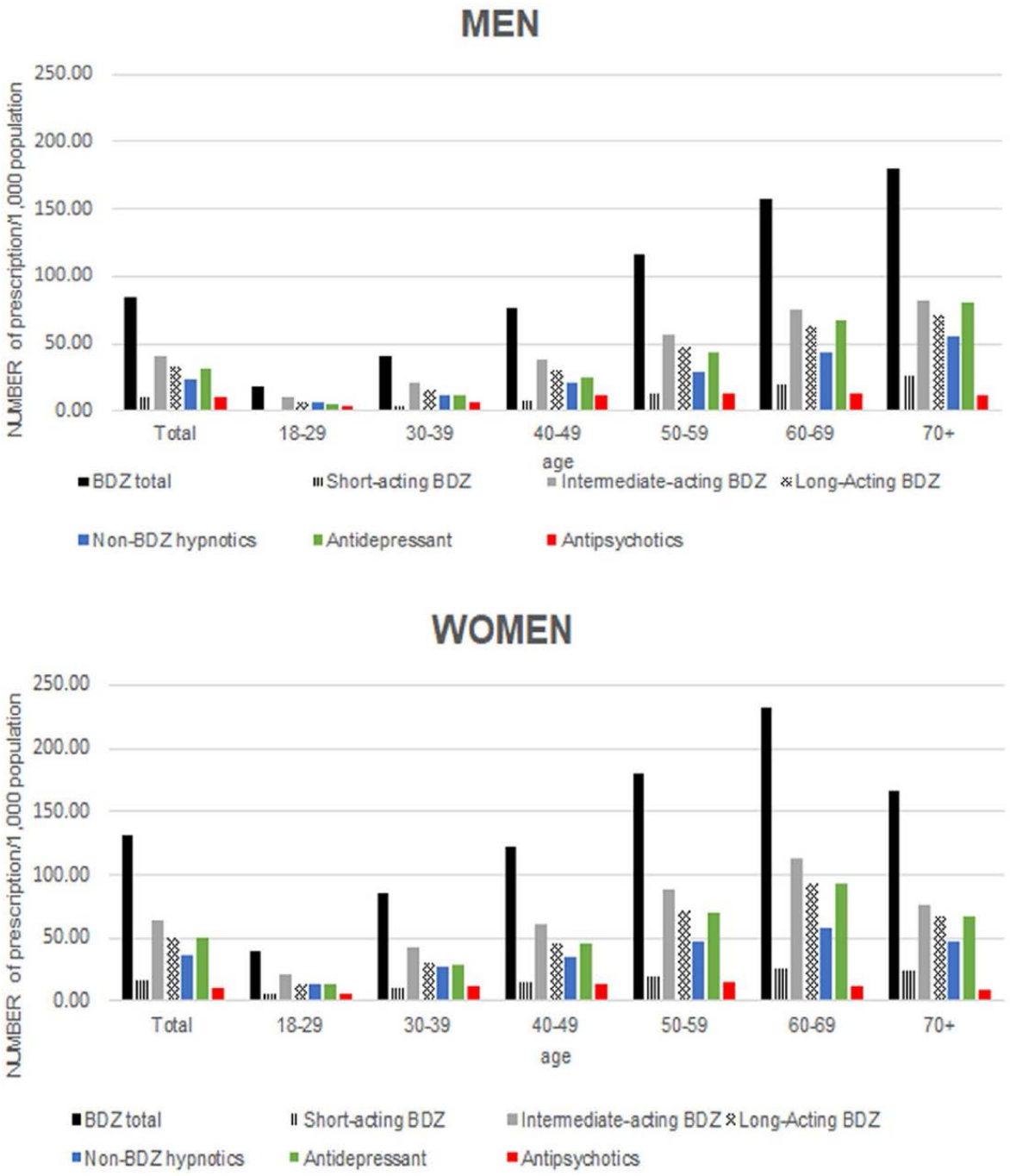


In Korea

The number of prescriptions for sedative–hypnotics commonly used for patients with insomnia, Health Insurance Review and Assessment Service, 2011–2015

Rank	Men		Women	
	Name	No. of prescriptions	Name	No. of prescriptions
1	Zolpidem	2,228,938	Zolpidem	3,589,251
2	Lorazepam	1,888,665	Diazepam	2,763,452
3	Diazepam	1,659,183	Alprazolam	2,571,917
4	Flunitrazepam	1,381,965	Lorazepam	2,500,784
5	Alprazolam	1,302,737	Flunitrazepam	2,123,646
6	Trazodone	894,579	Triazolam	1,557,864
7	Triazolam	811,476	Trazodone	1,416,119
8	Amitriptyline	765,967	Amitriptyline	1,329,288
9	Quetiapine fumarate	475,788	Quetiapine fumarate	859,834
10	Clonazepam	457,624	Bromazepam	848,512
11	Bromazepam	385,834	Clonazepam	644,447
12	Chlorpromazine	259,804	Imipramine HCl	404,059
13	Flurazepam	253,314	Nortriptyline HCl	386,750
14	Imipramine HCl	238,116	Flurazepam	340,215
15	NortryptilineHCl	160,523	Zolpidem tartrate	173,767
16	Zolpidem tartrate	131,805		

In Korea



Prevalence of grouped sedative–hypnotic prescriptions by age group for the entire Korean population, Health Insurance Review and Assessment Service, 2011–2015.

Sleep Medicine Reviews, Vol. 4, No. 1, pp 5–20, 2000

SLEEP MEDICINE reviews

REVIEW ARTICLE

Chronic hypnotic use: deadly risks, doubtful benefit

Daniel F. Kripke

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"미국에서 수면진정제를 처방 받은 이들 중 약 2/3는 장기 투약을 하며, 이는 평균 5년 또는 그 이상이다."

- 투약 초기에는 효과가 있을 수 있지만, 내성이 생기기 시작하면 수면진정제의 장기 투약은 수면을 오히려 악화시킴

- The mortality hazard
  - 한달 간 30회 수면제 투약 – 하루 담배 1~2갑 흡연

Risk of Major Injury

Falls

- increase the risk of falls by inducing muscle-relaxation and ataxia *(Bourin M, 2010)*
- The risk is probably the highest at treatment introduction
- 58.9 % of them had experienced one or more falls during the year *(Tu K, 2007)*
- BZD-related hypnotics consumption could expose to a similar risk, with the highest risk found among people aged 85 or over *(Holm E, 2012)*

Risk of Car Accident

- Older adults have altered motor reflexes → more sensitive to the psychomotor effects of medication
- If combined with alcohol → warning
- associated with a 60–80 % increase in the risk of traffic accidents, and co-ingestion of alcohol increases the risk by 7.7 times *(Dell'osso B, 2011)*

Benzodiazepines and Risk of Hip Fractures in Older People

- The epidemiological evidence strongly suggests that the use of benzodiazepines by older people increases their risk of hip fracture by at least 50%.
- There was no evidence that the risk of hip fracture differed between short- and long-acting benzodiazepines. People using higher doses of benzodiazepines and those who had recently started using benzodiazepines were at the highest risk of hip fracture.

Reference	Year	Country and time period	Sample size	Results[a]
Cohort studies				
Cummings et al.[16]	1995	USA 1986–1988	9516 subjects, 192 cases	**1.6 (1.1–2.4)**
Population-based case-control studies				
Ray et al.[17]	1989	Canada 1977–1985[b]	4501 cases, 24 041 controls	$t_{1/2}$ <24h: 1.1 (0.9–1.3); $t_{1/2}$ >24h: **1.7 (1.5–2.0)**
Cumming and Klineberg[18]	1993	Australia 1990–1991	209 cases, 207 controls	**1.6 (1.0–2.5)**
Herings et al.[19]	1995	Netherlands 1986–1992[b]	493 cases, 1311 controls	**1.6 (1.2–2.1)**; $t_{1/2}$ <24h: **1.5 (1.1–2.0)**; $t_{1/2}$ >24h: 1.3 (0.7–2.4)
Wang et al.[20]	2001	USA 1993–1995[b]	1222 cases, 4888 controls	**1.5 (1.2–1.8)**; short-acting: **1.5 ($p < 0.05$)**; long-acting: 1.3 ($p > 0.05$)
Case-control studies of hip fractures only in nursing homes				
Sgadari et al.[21]	2000	USA 1992–1996[b]	9752 cases, 38 564 controls	1.1 (1.0–1.2); $t_{1/2}$ <24h: 1.1 (1.0–1.2); $t_{1/2}$ >24h: 1.2 (1.0–1.5)
Case-control studies of hip fractures only in hospitals				
Lichtenstein et al.[22]	1994	Canada 1983–1985	129 cases, 234 controls	**2.1 (1.1–3.8)**

CNS Drugs 2003

Long-Term Use of Zolpidem Increases the Risk of Major Injury

- first prescription for zolpidem between January 1, 2000, and December 31, 2009

TABLE 2. Incidence of Major Injury (Head Injury or Fracture Requiring Hospitalization) and Hazard Ratio Measured for Study Cohort According to Doses of Zolpidem by Using Multivariate Cox Proportional Hazards Regression Analysis[a,b]

Variable	No. of events	PYs	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)
Comparison cohort	120	32,689	36.71	Reference value	Reference value
Zolpidem user cohort	49	8159	60.05	1.64 (1.17-2.28)	1.67 (1.19-2.34)
Dosage (mg/y)					
≤70	6	3641	16.48	0.45 (0.20-1.02)	0.48 (0.21-1.09)
71-800	26	3562	73.0	1.99 (1.30-3.04)	2.04 (1.32-3.13)
801-1600	8	482	165.96	4.52 (2.21-9.24)	4.37 (2.12-9.01)
>1600	9	475	189.54	5.16 (2.62-10.16)	4.74 (2.38-9.42)
P value for trend				<.001	<.001

[a]HR = hazard ratio; PY = person-year; rate = incidence rate, per 10,000 person-years.

[b]Adjusted for diabetes, sleep disorder, alcohol-related disorders, urinary incontinence, chronic arthritis, antihypertensive drugs, antidepressant drugs, and antipsychotic drugs.

TABLE 3. Incidence of Subsequent Injury and Hazard Ratio Measured for Zolpidem User and Comparison Cohorts by Using Multivariate Cox Proportional Hazards Regression Analysis[a,b]

Variable	Comparison cohort (n=32,752)			Zolpidem user cohort (n=8188)			Adjusted HR (95% CI)
	No. of events	PYs	Rate	No. of events	PYs	Rate	
Age							
18-54 y	90	27,562	32.65	37	6880	53.78	1.70 (1.15-2.51)
≥55 y	30	5127	58.51	12	1279	93.83	1.57 (0.78-3.13)
Sex							
Female	49	15,964	30.69	19	3985	47.67	1.60 (0.93-2.75)
Male	71	16,726	42.45	30	4174	71.88	1.72 (1.11-2.67)
Comorbidity							
Without any comorbidity	96	26,772	35.86	29	5310	54.62	1.54 (1.02-2.33)
Sleep disorder							
No	120	31,555	38.03	43	7188	59.82	1.56 (1.10-2.22)
Yes	0	1134	0	6	971	61.78	—
Alcohol-related disorders							
No	119	32,628	36.47	48	8114	59.16	1.67 (1.19-2.35)
Yes	1	61	163.71	1	46	218.58	2.06 (0.10-43.23)
Antidepressant drugs							
No	120	32,671	36.73	49	8111	60.41	1.67 (1.19-2.34)
Yes	0	18	0	0	48	0	—
Antipsychotic drugs							
No	115	31,076	37.01	42	7471	56.22	1.59 (1.11-2.28)
Yes	5	1614	30.98	7	688	101.68	3.18 (0.98-10.28)

[a]HR = hazard ratio; PY = person-year; rate = incidence rate, cases per 10,000 person-years.

[b]Adjusted for diabetes, sleep disorder, alcohol-related disorders, urinary incontinence, chronic arthritis, antihypertensive drugs, antidepressant drugs, and antipsychotic drugs.

Ming-May Lai, 2014

Medical Consequences

Respiratory Failure

- in the context of chronic obstructive pulmonary disease (COPD)
- associated with an increased risk of several serious adverse respiratory outcomes among older adults with COPD
- the relative risk was 1.92 (95 % CI [1.69–2.18]) for pneumonia and 1.45 (95 % CI [1.36–1.54]) for respiratory exacerbations *(Vozoris NT, 2014)*

Delirium

- known to worsen delirium states, especially in the elderly *(Anand A, 2012)*
- The reported prevalence of delirium among elderly hospitalized patients ranges from 14 to 56 %, and almost a third appears to be drug-induced *(Lorenzl S, 2012)*

Mobidity & Mortality associated with hypnotic use

- Controlling for age, men were 3.18 times as likely to die within 6 years if they reported using prescription sleeping pills 30 times per month, and women were 2.82 times more likely to die.

The mortality hazard associated with taking prescription sleeping pills 30 times in the past month is similar to the hazard of smoking 1–2 packs of cigarettes per day.

Both long and short sleep were associated with increased mo rtality

Daniel F. Kripke, 2000

Morbidity & mortality associated with hypnotic use

- Geisinger Health System (GHS)
- between January 2002 and January 2007
- 10,529 patients who received hypnotic prescriptions and 23,676 matched controls with no hypnotic prescriptions

Table 1 Characteristics of study participants

	Non-users	Any hypnotic users	Zolpidem	Temazepam
N	23 674	10 531	4338	2076
% Female*	62.7	63.9	64.8	60.0
Age (years, mean±SD)*	53.6 ±16.6	54.0±16.9	54.0±17.1	53.7±17.2
Years of observation (mean±SD)	2.50±1.43	2.49±1.39	2.34±1.33	2.51±1.37
Comorbidity classes (mean ±SD)***	1.06±1.27	1.53±1.55	1.49±1.54	1.53±1.52
Died during observation (% deceased)***	295 (1.2)	638 (6.1)	265 (6.1)	143 (6.9)

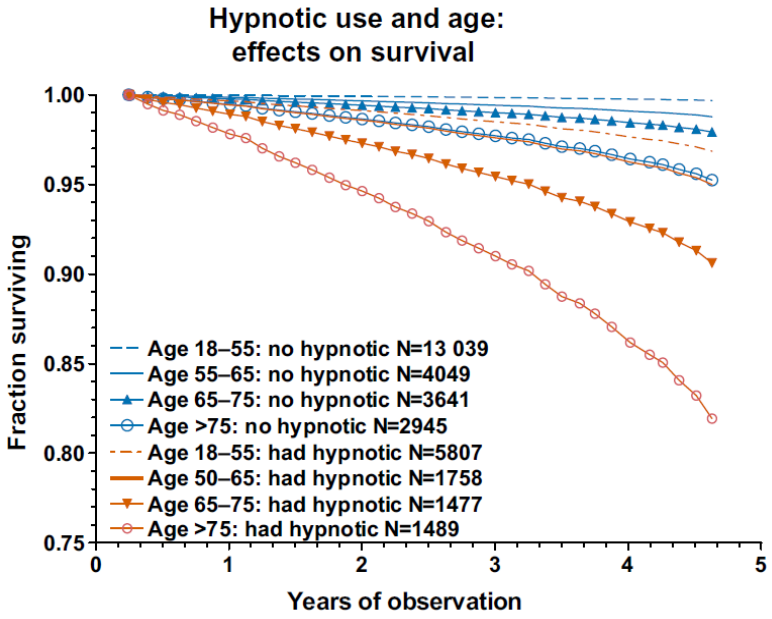
Table 2 Comorbid diagnoses of non-users and users of hypnotics (percentages of total group)

Comorbidity	Non-users	Any hypnotic users	Zolpidem	Temazepam
Asthma***	6.6	11.3	10.9	11.3
Cerebrovascular disease***	3.8	6.2	5.9	6.1
Coronary heart disease***	9.4	14.5	14.1	15.8
Chronic kidney disease***	0.9	1.7	1.5	1.9
COPD***	5.5	9.1	8.8	8.8
Cardiovascular disease, all***	14.1	21.4	21.1	22.3
Dementia	0.6	0.6	0.7	0.2
Diabetes***	14.6	17.9	17.8	18.5
Heart failure***	3.2	6.6	6.6	6.6
Hypertension***	37.5	42.8	41.9	43.9
Obesity***	6.7	10.5	9.6	10.0
Reflux and peptic disease***	15.0	27.9	26.9	26.3
Peripheral vascular disease***	2.1	3.9	4.0	3.7

BMJ Open 2012

Table 3 HRs for deaths and for cancers with dose–response analyses

Hypnotic	Deaths		Cancers	
	p Value	HR (95% CI)	p Value	HR (95% CI)
Any hypnotic: doses/year	<0.001		<0.001	
No hypnotics, N=23 676	Reference		Reference	
0.4–18 pills/year, mean 8, N=3491	<0.001	3.60 (2.92 to 4.44)	0.086	0.86 (0.72 to 1.02)
18–132 pills/year, mean 57, N=3548	<0.001	4.43 (3.67 to 5.36)	0.022	1.20 (1.03 to 1.40)
>132 pills/year, mean 469, N=3490	<0.001	5.32 (4.50 to 6.30)	<0.001	1.35 (1.18 to 1.55)
Zolpidem only: mg/year	<0.001		0.035	
No zolpidem or other hypnotics, N=23 671	Reference		Reference	
Zolpidem 5–130 mg/year, mean 60, N=1453	<0.001	3.93 (2.98 to 5.17)	0.095	0.79 (0.60 to 1.04)
Zolpidem 130–800 mg/year, mean 360, N=1456	<0.001	4.54 (3.46 to 5.95)	0.585	1.07 (0.83 to 1.39)
Zolpidem >800 mg/year, mean 3600, N=1427	<0.001	5.69 (4.58 to 7.07)	0.023	1.28 (1.03 to 1.59)
Temazepam only: mg/year	<0.001		<0.001	
NO temazepam or other hypnotics, N=23 674	Reference		Reference	
Temazepam 1–240 mg/year, mean 98, N=798	<0.001	3.71 (2.55 to 5.38)	0.003	0.48 (0.30 to 0.77)
Temazepam 240–1640 mg/year, mean 683, N=613	<0.001	4.15 (2.88 to 5.99)	0.024	1.44 (1.05 to 1.98)
Temazepam >1640 mg/year, mean 7777, N=665	<0.001	6.56 (5.03 to 8.55)	<0.001	1.99 (1.57 to 2.52)



The red curves represent the fact that a higher percentage of hypnotic users died during the observation periods and fewer survived. Each curve was adjusted for covariates except age (which shared excessive colinearity with the age-based categories) and was adjusted for comorbidity strata.

Relationship of Zolpidem and Cancer Risk

the National Health Insurance system of Taiwan, about 10 years

TABLE 2. HRs (95% CIs) for the Association Between Specific Cancers and Zolpidem Use: Results of Cox Proportional Hazards Regression Analysis[a]

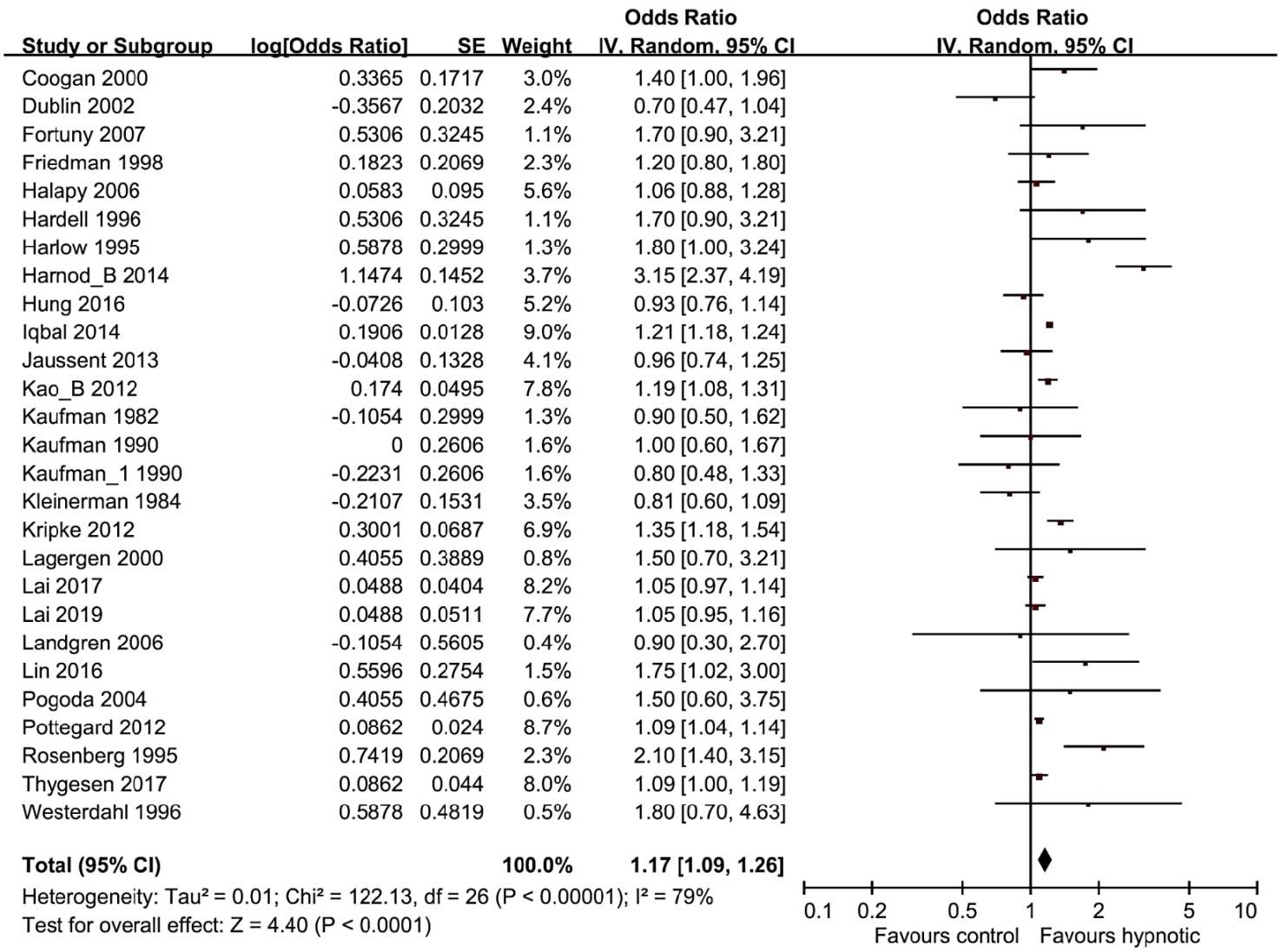
	All[b]			Women[c]			Men[c]		
Variable	Zolpidem cohort	Nonzolpidem cohort	HR (95% CI)	Zolpidem cohort	Nonzolpidem cohort	HR (95% CI)	Zolpidem cohort	Nonzolpidem cohort	HR (95% CI)
Overall	1047	2924	1.68 (1.55-1.82)[d]	512	1473	1.67 (1.49-1.87)[d]	535	1451	1.70 (1.52-1.91)[d]
Oral cancer	47	94	2.36 (1.57-3.56)[d]	7	16	1.89 (0.70-5.07)	40	78	2.48 (1.58-3.89)[d]
Esophagus cancer	21	46	1.95 (1.07-3.55)[e]	2	4	2.11 (0.35-12.7)	19	42	1.91 (1.02-3.61)[e]
Stomach cancer	53	207	1.28 (0.92-1.79)	21	87	1.22 (0.71-2.09)	32	120	1.32 (0.86-2.03)
Colorectal cancer	109	490	1.04 (0.83-1.32)	63	251	1.13 (0.83-1.53)	46	239	0.96 (0.67-1.37)
Liver cancer	177	408	1.81 (1.48-2.22)[d]	62	168	1.42 (1.03-1.96)[e]	115	240	2.12 (1.64-2.75)[d]
Lung cancer	142	386	1.64 (1.32-2.03)[d]	49	156	1.31 (0.91-1.89)	93	230	1.85 (1.40-2.45)[d]
Breast cancer[f]	99	259	1.84 (1.40-2.42)[d]	99	259	1.84 (1.40-2.42)[d]			
Cervical cancer[f]	28	110	1.62 (1.00-2.62)	28	110	1.62 (1.00-2.62)			
Prostate cancer[g]	59	160	1.39 (0.99-1.95)				59	160	1.39 (0.99-1.95)
Endometrial cancer[f]	7	40	1.20 (0.47-3.03)	7	40	1.20 (0.47-3.03)			
Bladder cancer	40	110	1.60 (1.06-2.41)[e]	12	34	1.66 (0.79-3.50)	28	76	1.54 (0.94-2.52)
Kidney cancer	39	76	2.18 (1.41-3.36)[d]	27	41	2.54 (1.47-4.40)[d]	12	35	1.68 (0.81-3.49)
Other cancers	226	538	2.16 (1.81-2.58)[d]	135	307	2.31 (1.83-2.91)[d]	91	231	1.98 (1.50-2.62)[d]

TABLE 4. Cox Proportional Hazards Regression Analysis Measured HRs (95% CIs) of Cancers by Zolpidem Dosage in Association With Using Zolpidem Alone and Using Both Zolpidem and Benzodiazepine[a]

	Overall		Zolpidem only		Zolpidem and benzodiazepine		
Zolpidem, mg/y	No. of events/ No. of patients	HR (95% CI)	No. of events/ No. of patients	HR (95% CI)	No. of events/ No. of patients	HR (95% CI)	*P* value
0	2924/59,800	1.00 (Reference)	1316/35,336	1.00 (Reference)	1608/24,464	1.47 (1.36-1.59)[b]	<.001
1-29	188/4578	0.99 (0.85-1.15)	32/1211	0.92 (0.65-1.31)	156/3367	1.45 (1.23-1.72)[b]	.04
30-299	413/5381	1.90 (1.70-2.13)[b]	35/419	3.15 (2.25-4.41)[b]	378/4962	2.64 (2.34-2.99)[b]	.50
≥300	446/4990	2.38 (2.12-2.67)[b]	23/161	6.24 (4.13-9.43)[b]	423/4829	3.30 (2.91-3.75)[b]	.049

Mayo Clin Proc. 2012

Forest plot of BDZs/Z-drugs use and the risk of cancer



Medicina 2020

Potentially Increased Risk of Cancer

- possible associations between BZD consumption and the risk of cancer (brain, colorectal, and lung) or benign brain tumors

- The γ-aminobutyric acid transmission, that is activated by the BZDs, could play a role in cell proliferation and cell differentiation, but the underlying biological mechanisms remain unclear *(Harnod T, 2013; Iqbal U, 2015)*

Verdoux H. et al., 2005; Tveito M. et al., 2014

Mobidity & Mortality associated with hypnotic use

Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards

- UK General Practice Research Database
- A retrospective, matched cohort study of 34,727 patients first prescribed anxiolytic or hypnotic drugs, or both, between 1998 and 2001, and 69 418 patients matched by age, sex, and practice with no prescriptions for such drugs (controls)
- Patients were followed-up for a mean of 7.6 years (range 0.1-13.4 years)

DDDs	No of patients	Age adjusted hazard ratio (95% CI)	P value	Fully adjusted* hazard ratio (95% CI)	P value
All study drugs:					
0	63 717	1.00		1.00	
1-30	5142	1.46 (1.35 to 1.57)	<0.001	1.45 (1.35 to 1.56)	<0.001
31-60	1873	2.02 (1.82 to 2.23)	<0.001	1.94 (1.76 to 2.16)	<0.001
61-90	659	2.27 (1.94 to 2.66)	<0.001	1.87 (1.59 to 2.19)	<0.001
≥91	910	3.14 (2.80 to 3.52)	<0.001	2.63 (2.34 to 2.95)	<0.001
Any DDDs	8584	1.83 (1.73 to 1.92)	<0.001	1.75 (1.65 to 1.85)	<0.001
Benzodiazepines only:					
Any DDDs	4964	1.88 (1.76 to 2.02)	<0.001	1.81 (1.68 to 1.94)	<0.001
Z drugs only:					
Any DDDs	1715	1.94 (1.72 to 2.17)	<0.001	1.78 (1.58 to 2.01)	<0.001
Other study drugs only:					
Any DDDs	1317	1.63 (1.45 to 1.82)	<0.001	1.57 (1.40 to 1.76)	<0.001

*Age, sex, physical health problems (arthritis, asthma, cancer, ischaemic heart disease, stroke, chronic obstructive pulmonary disease, diabetes, epilepsy, gastrointestinal disorders, hypertension, musculoskeletal disorders, anxiety disorders, sleep disorders), other (non-anxiety) psychiatric disorders, and prescriptions for non-study drugs.

BMJ 2014

Cognitive Consequences

- Older adults → prone to the anterograde amnesia induced by BZDs and BZD-related hypnotics
  - Esp. at high dosages

- Findings regarding the association between BZD/nBDRA use and long-term cognitive impairment

  → still debated

- Conflicting evidence regarding BZD use as a risk factor for Alzheimer's disease

Curr Psychiatry Rep 2016

Dementia and Long-Term Use of Benzodiazepine

All subjects were aged 45 and older and enrolled in the National Health Insurance Research Database in Taiwan, 1997–2004

TABLE 2. The Benzodiazepines Exposure Status and the Risk of Dementia

	Unadjusted OR[a]	95% CI	Adjusted OR[a,b]	95% CI
Benzodiazepines with zolpidem and zopiclone				
Long-term benzodiazepine user	2.37	2.00–2.81	1.34	1.09–1.64
Cumulative dosage of BZD use				
Cumulative dose <90 DDD	1.00	Reference	1.00	Reference
90 DDD ≤ cumulative dose <180 DDD	1.74	1.34–2.25	1.28	0.97–1.68
Cumulative dose ≥180 DDD	2.46	2.07–2.93	1.39	1.12–1.73
p trend[c]		<0.001		<0.001
Cumulative period of BZD use				
Using period <90 days	1.00	Reference	1.00	Reference
90 days ≤ using period <180 days	1.73	1.32–2.27	1.38	1.03–1.83
Using period ≥180 days	2.48	2.10–2.94	1.45	1.18–1.79
p trend[c]		<0.001		0.003
Benzodiazepines without zolpidem and zopiclone				
Long-term benzodiazepine user	2.24	1.88–2.67	1.24	1.01–1.53
Cumulative dosage of BZD use				
Cumulative dose <90 DDD	1.00	Reference	1.00	Reference
90 DDD ≤ cumulative dose <180 DDD	1.49	1.14–1.94	1.07	0.80–1.42
Cumulative dose ≥180 DDD	2.35	1.97–2.81	1.32	1.05–1.64
p trend[c]		<0.001		0.017
Cumulative period of BZD use				
Using period <90 days	1.00	Reference	1.00	Reference
90 days ≤ using period <180 days	1.58	1.19–2.08	1.25	0.93–1.67
Using period ≥180 days	2.43	2.05–2.88	1.43	1.16–1.77
p trend[c]		<0.001		<0.001
Psychiatric comorbidity				
Mood disorders	3.77	2.96–4.82	2.54[d]	1.93–3.33
Anxiety disorders	1.89	1.59–2.25	1.18[d]	0.97–1.45
Psychotic-related disorders	8.51	4.58–15.78	5.13[d]	2.64–9.98
Alcohol-related disorders	2.14	0.77–5.95	1.55[d]	0.52–4.67
Medical comorbidity				
Hypertension	1.73	1.47–2.05	1.16[d]	0.96–1.39
Diabetes	1.43	1.20–1.71	1.10[d]	0.91–1.34
Dyslipidemia	1.28	1.07–1.53	0.99[d]	0.81–1.21
Cerebrovascular disorders	3.56	3.01–4.20	2.94[d]	2.46–3.52

Subjects with dementia had higher cumulative dose, longer duration of BZDs exposure, and more likelihood to be long-term BZDs users

The Association Between the Use of Zolpidem and the Risk of Alzheimer's Disease Among Older People

A retrospective cohort study using data from 2001 to 2011 from the National Health Insurance Research Database

Study group	Hazard ratio (95% CI)
Non-zolpidem use (n = 3,461)	Reference
Zolpidem use (n = 3,461)	1.35 (0.85–2.13)
By zolpidem cumulative dosage in one year since initiation	
Non-user	Reference
<28 cDDD	0.71 (0.32–1.54)
28–90 cDDD	1.31 (0.71–2.42)
91–180 cDDD	1.20 (0.47–3.09)
>180 cDDD	2.97 (1.61–5.49)
Zolpidem users	
<28 cDDDs	Reference
28–90 cDDDs	1.84 (0.78–4.34)
91–180 cDDDs	1.69 (0.55–5.17)
>180 cDDDs	4.18 (1.77–9.86)

The use of a high cumulative dose of zolpidem was associated with an increased risk of Alzheimer's disease among older people living in Taiwan.
Caution when considering long-term use of zolpidem in older patients

J Am Geriatr Soc 2017

Associations of Benzodiazepines, Z-Drugs, and Other Anxiolytics With Subsequent Dementia in Patients With Affective Disorders

the Danish National Patient Registry - affective disorder between 1996 and 2015

Measure	All Drugs		Benzodiazepines		Z-Drugs		Long-Acting Drugs		Short-Acting Drugs		Other Drugs	
	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95%	Hazard ratio	95% CI
Cohort study (2–20.1 years of follow-up)												
Number of prescriptions												
None	1		1		1		1		1		1	
1–2	0.94	0.84, 1.04	1.00	0.92, 1.09	0.95	0.88, 1.03	0.99	0.91, 1.08	0.96	0.88, 1.04	0.94	0.77, 1.16
3–25	0.95	0.87, 1.03	0.97	0.90, 1.04	0.95	0.88, 1.02	0.98	0.92, 1.06	0.98	0.91, 1.05	1.13	0.86, 1.47
26 (maximum)	0.95	0.87, 1.04	0.95	0.87, 1.04	0.98	0.87, 1.09	1.01	0.91, 1.11	0.98	0.89, 1.07	0.96	0.43, 2.15
Total defined daily dose												
None	1		1		1		1		1		1	
Lowest third	0.99	0.84, 1.03	0.99	0.90, 1.08	0.96	0.87, 1.05	0.95	0.86, 1.03	0.99	0.90, 1.08	0.97	0.76, 1.24
Middle	0.95	0.86, 1.03	0.97	0.89, 1.05	0.92	0.84, 1.00	1.02	0.93, 1.11	0.94	0.84, 1.02	1.02	0.78, 1.36
Highest third	0.94	0.86, 1.03	0.97	0.89, 1.04	0.98	0.90, 1.00	1.00	0.92, 1.08	0.98	0.89, 1.05	1.00	0.72, 1.40
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Nested case-control study (2 years before index date, 1995)												
Number of prescriptions												
None	1		1		1		1		1		1	
1–2	1.23	1.12, 1.35	1.16	1.06, 1.26	1.11	1.03, 1.20	1.07	0.99, 1.16	1.20	1.10, 1.31	1.09	(0.94–1.26)
3–25	1.01	0.95, 1.07	1.06	1.00, 1.13	0.98	0.92, 1.04	1.08	1.01, 1.15	1.05	0.99, 1.11	0.88	(0.74–1.05)
26 (maximum)	0.87	0.82, 0.93	0.94	0.88, 1.00	0.84	0.79, 0.90	0.91	0.84, 0.97	0.90	0.84, 0.96	0.51	0.37, 0.69
Total defined daily dose												
None	1		1		1		1		1		1	
Lowest third	1.08	1.01, 1.15	1.08	1.01, 1.15	1.25	1.17, 1.35	1.05	0.95, –1.13	1.11	(1.05–1.19)	1.15	0.97, 1.36
Middle	0.99	0.92, 1.05	1.07	1.00, 1.14	1.07	0.98, 1.14	1.10	1.02, 1.12	0.97	(0.87–1.10)	0.86	0.71, 1.03
Highest third	0.83	0.77, 0.88	0.91	0.85, 0.91	0.92	0.86, 1.00	0.92	0.85, 0.98	0.86	0.80, 0.92	0.73	0.66, 0.88

This large cohort study did not reveal associations between use of benzodiazepines or Z-drugs and subsequent dementia, even when exposures were cumulated or divided into long- and short-acting drugs.

AJP in Advance 2019

Uncertain Association Between Benzodiazepine Use and the Risk of Dementia

retrospective cohort study, using a nationwide healthcare database of South Korea (2002~2016)

	Age-Sex Exact-Matched Cohort*		PS-Matched Cohort*	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Benzodiazepine users vs nonusers†				
Strict outcome definitions				
Restricted to secondary diagnosis and treatment for dementia‡	2.19 (2.06–2.33)	1.96 (1.84–2.09)	2.08 (1.94–2.23)	2.07 (1.93–2.21)
Diagnosis from tertiary hospital and treatment for dementia§	2.35 (2.18–2.53)	2.08 (1.92–2.25)	2.21 (2.03–2.40)	2.19 (2.02–2.39)
Other instrumental definitions				
≥1 diagnosis and treatment for dementia‖	2.23 (2.11–2.36)	2.00 (1.89–2.12)	2.11 (1.99–2.24)	2.10 (1.97–2.23)
≥1 inpatient or 2 outpatient diagnosis or treatment for dementia**	2.13 (2.05–2.22)	1.90 (1.82–1.98)	2.01 (1.91–2.10)	2.01 (1.92–2.10)
Dementia diagnosis or treatment for dementia††	2.14 (2.06–2.22)	1.90 (1.82–1.97)	2.02 (1.93–2.11)	2.00 (1.91–2.10)
Benzodiazepine users vs antidepressant users‡‡				
Strict outcome definitions				
Restricted to secondary diagnosis and treatment for dementia‡	0.96 (0.71–1.29)	1.07 (0.79–1.44)	0.95 (0.67–1.35)	0.94 (0.67–13.4)
Diagnosis from tertiary hospital and treatment for dementia§	0.84 (0.59–1.19)	0.96 (0.67–1.38)	0.92 (0.60–1.41)	0.92 (0.61–1.41)
Other instrumental definitions				
≥1 diagnosis and treatment for dementia‖	0.86 (0.66–1.11)	0.97 (0.74–1.26)	0.90 (0.66–1.23)	0.90 (0.66–1.23)
≥1 inpatient or 2 outpatient diagnosis or treatment for dementia**	0.88 (0.72–1.07)	1.01 (0.82–1.23)	1.00 (0.79–1.26)	1.00 (0.79–1.26)
Dementia diagnosis or treatment for dementia††	0.80 (0.67–0.96)	0.91 (0.75–1.09)	0.90 (0.72–1.12)	0.90 (0.72–1.11)

We observed a 23% increase in the risk of dementia in benzodiazepine users, compared with that in nonusers, over a mean follow-up period of 5.5 years (HR 1.23, 95% CI 1.14-1.32).
When new-users of antidepressants were used as the active comparator, no increase in the risk of dementia with benzodiazepines was observed over 7 years (HR 1.01, 95% CI 0.81-1.27).

A significant association was observed between benzodiazepine use and the risk of dementia, compared with nonusers. However, a null or negative association was observed with the use of the active comparator, suggesting the absence of a causal association between dementia and benzodiazepine use.

JAMDA, 2019

SCIENTIFIC REPORTS
nature research

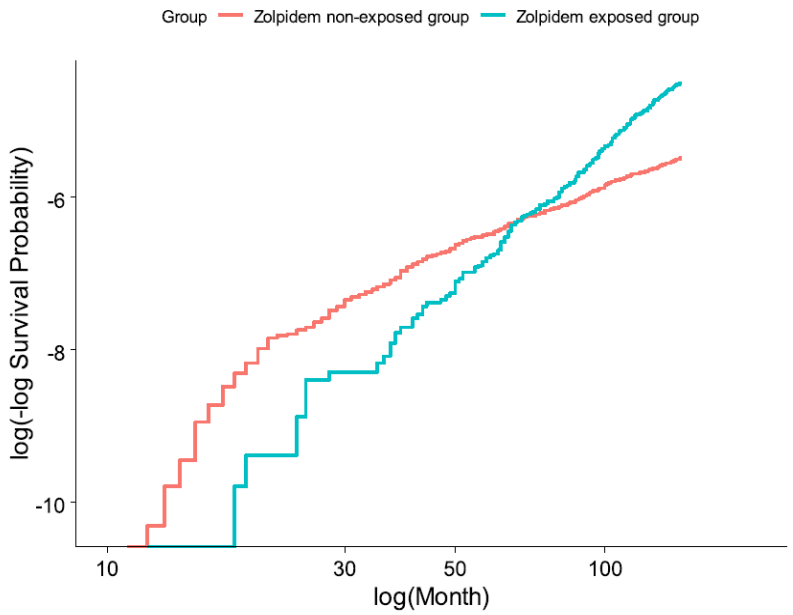
OPEN

Temporal association between zolpidem medication and the risk of suicide: A 12-year population-based, retrospective cohort study

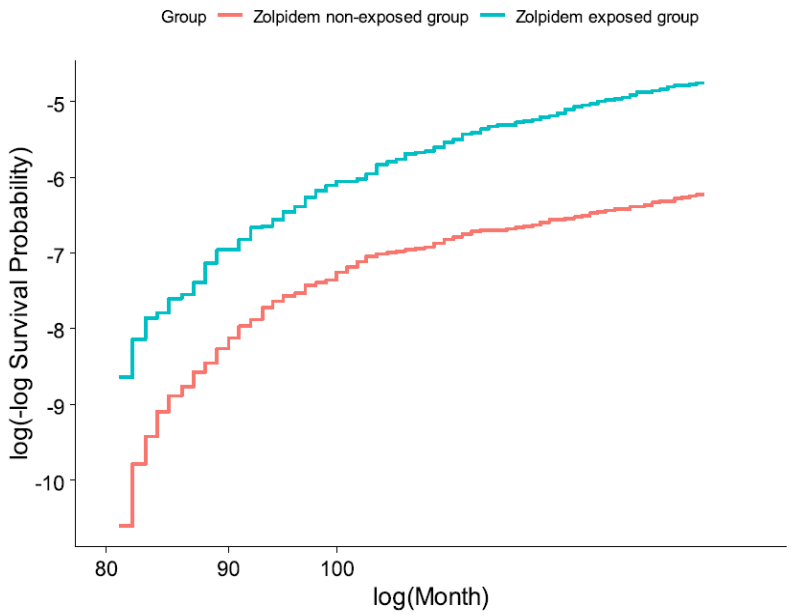
Chul-Hyun Cho[1,2,3], Hee-Jung Jee[4], Yoon-Ju Nam[5], Hyonggin An[4], Leen Kim[3,5] & Heon-Jeong Lee[3,5*]

- 건강보험공단 표본코호트, 2002년 1월 ~ 2013년 12월
- 총 1,125,691명에 대한 12년 동안의 약물처방 및 진단명 데이터베이스 등을 이용하여 데이터 클리닝 수행
- 10세 미만 제외
- 888,739명 대상 후향적 분석

A.



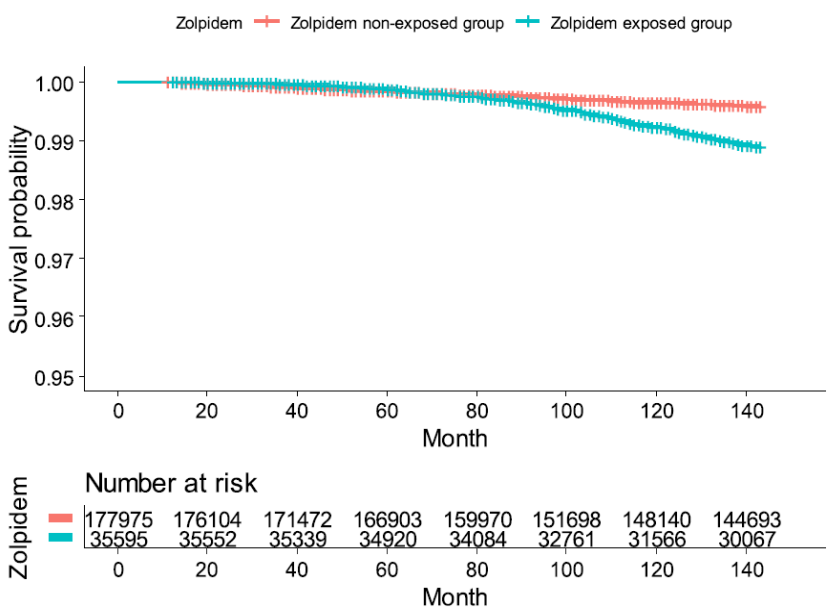
B.



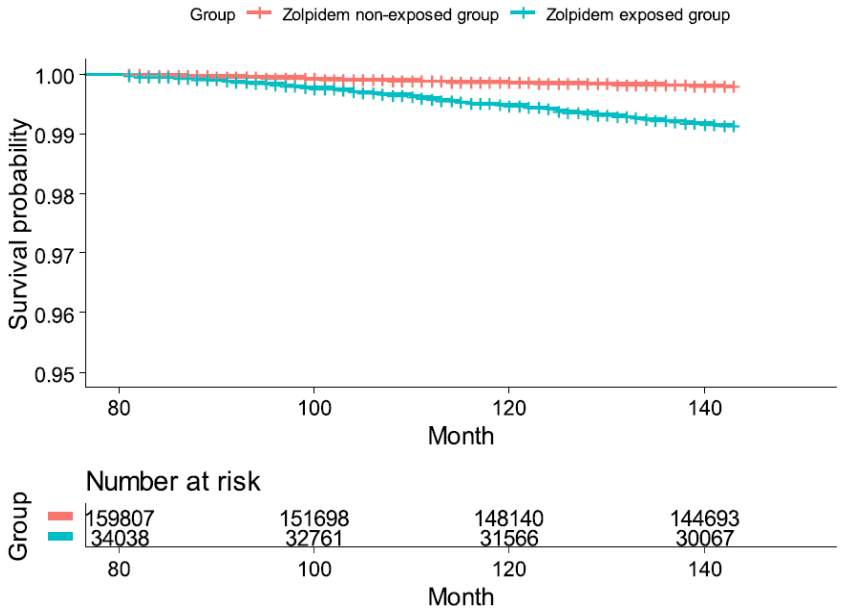
The graph of a Kolmogorov-type supremum test to assess the proportional hazard assumption to suicides between the zolpidem exposed group (ZEG) and zolpidem non-exposed group (ZNG). In verification of the proportional hazard assumption, the risk curves of the ZEG and the ZNG of the current data crossed at the 80-month time point, confirming that the proportional risk assumption had been violated (**A**). The proportional risk assumption is verified only on the second divided time-period of more than 80 months (**B**).

Scientific Reports, 2020

A.



B.



The graph of a Kaplan-Meier survival plot of suicide between the zolpidem exposed group (ZEG) and zolpidem non-exposed group (ZNG). Survival probability related only to suicides is presented between the ZEG and ZNG on whole time period (**A**) and the time period of more than 80 months (**B**).

Scientific Reports, 2020

The temporal association between zolpidem medication and the risk of suicide in the two divided time-period intervals (less than 80 months and more than 80 months from the date of the initial exposure of the zolpidem exposed group (ZEG)): Cox proportional hazards regression analysis.

Variable		Unadjusted HR				Adjusted HR			
		HR	95% C.I		P-value	HR	95% C.I		P-value
Zolpidem medication	> 80 months	4.32	3.67	5.09	<0.001	**2.01**	**1.58**	**2.56**	**<0.001**
	≤ 80 months	1.14	0.90	1.44	0.283	0.83	0.61	1.11	0.206

The comparison of the frequency of the chronic zolpidem medication group between suicide and control groups according to the cumulative prescription duration of 6 months or one year, respectively

Chronic zolpidem medication exposure: the cumulative prescription duration (≥ 6 months or ≥ one year)	Suicide group (N (%))	Non-suicide group (N (%))	P-value
The cumulative zolpidem prescription duration ≥ 6 months			
Yes	103 (1.32%)	7708 (98.68%)	0.002
No	258 (0.93%)	27526 (99.07%)	
The cumulative zolpidem prescription duration ≥ one year			
Yes	62 (1.41%)	4339 (98.59%)	0.005
No	299 (0.96%)	30895 (99.04%)	

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수면제 복용과 인지기능장애 발병의 연관성에 대한 연구

				Univariate			Multivariate	
분류	변수	N	(%)	OR	95% CI	p-value	OR	95% CI
수면진정제	zolpidem	325,559	(79.51)	1.034	(1.01,1.06)	0.0022	0.675	(0.65,0.70)
	lorazepam	369,120	(90.15)	0.525	(0.51,0.54)	<.0001	1.336	(1.30,1.37)
	alprazolam	347,937	(84.98)	0.825	(0.81,0.84)	<.0001	0.929	(0.90,0.96)
	triazolam	393,125	(96.01)	0.594	(0.57,0.62)	<.0001	1.260	(1.21,1.32)
	diazepam	356,644	(87.10)	0.379	(0.37,0.39)	<.0001	2.594	(2.53,2.66)
	bromazepam	406,638	(99.31)	0.687	(0.63,0.75)	<.0001	0.956	(0.86,1.06)
	clonazepam	381,162	(93.09)	0.279	(0.27,0.29)	<.0001	2.858	(2.77,2.95)
	chlordiazepoxide	408,982	(99.89)	0.946	(0.74,1.20)	0.6477		
	etizolam	391,134	(95.53)	0.823	(0.79,0.86)	<.0001	0.950	(0.91,0.99)
주요질환	악성신생물	385,724	(94.21)	1.121	(1.08,1.16)	<.0001	0.838	(0.81,0.87)
	심장질환	367,351	(89.72)	0.778	(0.76,0.80)	<.0001	1.171	(1.14,1.21)
	뇌혈관질환	333,932	(81.56)	0.957	(0.94,0.98)	<.0001	1.055	(1.03,1.08)
	폐렴	377,632	(92.23)	0.55	(0.54,0.57)	<.0001	1.641	(1.59,1.69)
	당뇨병	350,535	(85.61)	0.957	(0.93,0.98)	0.0003	0.984	(0.96,1.01)
	만선 하기도 질환	337,186	(82.35)	0.771	(0.76,0.79)	<.0001	1.102	(1.08,1.13)
	간질환	342,063	(83.54)	0.934	(0.91,0.96)	<.0001	0.936	(0.91,0.96)
	고혈압성질환	333,175	(81.37)	1.045	(1.02,1.07)	0.0001	0.871	(0.85,0.89)
정신질환	Schizophrenic spectrum disorders	391,077	(95.51)	0.223	(0.22,0.23)	<.0001	3.107	(3.00,3.22)
	Major depressive disorder	319,456	(78.02)	0.706	(0.69,0.72)	<.0001	1.113	(1.09,1.14)
	Bipolar disorder	381,162	(93.09)	0.248	(0.24,0.26)	<.0001	3.219	(3.13,3.32)
	Anxiety	314,659	(76.85)	0.702	(0.69,0.72)	<.0001	0.949	(0.93,0.97)
	Substance use	402,935	(98.36)	0.897	(0.84,0.96)	0.0007	0.741	(0.69,0.80)
	Insomnia	309,975	(75.71)	0.894	(0.88,0.91)	<.0001	1.015	(0.98,1.05)
	Other mental disorders	314,264	(76.75)	2.058	(2.01,2.11)	<.0001	2.592	(2.53,2.66)

In preparation

Discussion

- 수면진정제와 outcome
  - 연관성?
  - 인과관계?

- 수면진정제의 오남용의 위험성
  - 의존과 금단증상의 위험성
  - 장기투약이 매우 흔함

- 불면증상과 우울증상의 공존: common

  → 수면진정제만 투약 시, 우울증상과 자살(사고, 시도, 사망)를 악화시킬 수 있음

Mayo Clin Proc. 2016;91(3):308-315

Discussion

- 불면증상의 위험성
  - 불면증상 그 자체로 다양한 증상의 악화를 유발함
  - Hopelessness, Executive function, emotional regulation, neurotransmitter system
  - Insomnia → (A,B,C, etc) → Outcome
  - Insomnia? vs. Hypnotics?
  - "Hypnotics do not substantially improve objective sleep or objective daytime performance and have no known objective benefits for any aspect of general health" *(F1000Research 2016, 5:918)*
  - "Addition of an FDA-approved hypnotic to an antidepressant will improve the overall rates of response to the antidepressant" *(J Clin Sleep Med 2010)*

Discussion

- 불면/불안 증상을 호소하는 환자에 대한 면밀한 평가와 통합적 진료
  - 정확한 증상에 대한 평가
  - 증상에 맞는 투약 조절

- 불면/불안증상 치료를 위한 효과적이고 적합한 치료 방법
  - 인지행동치료 기반 접근과 적절한 투약
  - 우울증상 및 불면에 CBT-I *(Journal of Clinical Sleep Medicine, 7, 645-652)*

- 수면진정제 초기 투약 시, 치료 계획에 대한 수립 필요
  - 수면진정제의 오남용, 수면진정제의 장기복용의 관리가 반드시 필요
  - 부작용에 대한 교육을 통해 관련 위험성 조기 관리 필요

- 연구결과 해석에 유의
  - 인과관계
  - 수면진정제 자체? 수면진정제를 장기복용하는 사람들의 어떤 특성?
  - Further fine research