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

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Abstract

Purpose This study investigated prescriptions for sedative–hypnotics via data obtained from the Health Insurance Review and Assessment (HIRA) service.

Methods Data on sedative–hypnotic prescriptions from the HIRA service of the Republic of Korea were analyzed from 2011 to 2015. We included prescriptions for subjects > 18 years of age from hospitals and community healthcare centers. In addition, subgroup analyses with a subsample restricted to prescriptions from patients with diagnostic codes F510 (nonorganic insomnia) or G470 (insomnia) were performed. After analyzing the number of prescriptions by individual pharmacy items, the prescription codes were grouped as: (1) benzodiazepines; (2) non-benzodiazepines, including zolpidem; (3) antidepressants; and (4) antipsychotics. We calculated the monthly percent change in the number of prescriptions by drug group using Joinpoint regression.

Results Among the sedative–hypnotic groups, benzodiazepines were the most commonly prescribed drugs in Korea during the study period. As a single sedative–hypnotic item, zolpidem was the most frequently prescribed medication for patients with insomnia. Prescriptions for all groups of sedative–hypnotics increased significantly during the study period. When stratified by age group, antipsychotic prescriptions increased significantly by 0.19–0.21% per month among men and women aged 50–59 years and > 70 years. Prescriptions for antidepressants in 30–39-year-old men increased significantly by 0.20%.

Conclusions Benzodiazepine prescriptions as well as those for antipsychotics and antidepressants to treat insomnia increased during 2011–2015 in Korea. Monitoring the use of sedative–hypnotics at the national level is necessary, especially in the elderly population.

Keywords Sedatives · Hypnotics · Prescription · Insomnia

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Introduction

Insomnia is a common sleep disorder and is defined as difficulty initiating and maintaining sleep or waking up too early with daytime dysfunction according to the criteria of the International Classification of Sleep Disorders, Second Edition [1]. Approximately, one-third to one-half of the entire population experiences insomnia symptoms at least once in their lifetime [2]. The prevalence rates of an insomnia disorder meeting the diagnostic criteria are 10–20%, and insomnia follows a chronic course in 69% of individuals over a 1-year follow-up [3]. The prevalence of insomnia occurring at least two nights per week is 14.9% in Korea [4].

At least 80% of patients with major depression have insomnia-related symptoms [5]. An increased risk of accidents due to insomnia has also been reported. The risk of non-traffic accidents in patients with insomnia increased

2.4-fold compared with a control group [6]. Silvertsen et al. reported that insomnia was a strong predictor of persistent job disability for 6599 workers over a 4-year follow-up period [7].

The short-term use of sedative–hypnotics is helpful for chronic insomnia, and it should ideally be accompanied by behavioral therapy [8]. However, these drugs are not recommended for long-term treatment because of their abuse and dependence risk. The use of sedative–hypnotics has been associated with a fourfold higher mortality rate and increased cancer incidence among those prescribed high doses [9]. Several studies have suggested that the use of sedative–hypnotics is related with an increased risk for dementia [10, 11]. According to a cohort study based on National Health Insurance data conducted in Taiwan, patients with insomnia taking sedative–hypnotics had a higher risk of mental illness than those who do not take sedative–hypnotics [12].

Sedative–hypnotics are frequently used for suicide attempts in Korea. According to a study on suicide attempts in Korea, drug poisoning, mainly by hypnotics, was the most common suicide method, having been used in 1359 suicide attempts between May and December 2013 [13]. Currently, Korea's suicide rate is the highest among the Organization for Economic Cooperation and Development countries and is the second-highest suicide rate in the world, with nearly 30 deaths per 100,000 population [14]. Therefore, sedative–hypnotic use should be monitored with caution. The mean 1-year prevalence of benzodiazepine prescriptions was 23.7% of the entire population during 2007–2011 in Korea [15]. However, no extensive analysis of overall use of sedative–hypnotics, including benzodiazepines, has been performed.

The tendency to use sedative–hypnotics has been analyzed and monitored in the United States and Finland, and appropriate treatment for insomnia has been recommended [16, 17]. In Finland, the number of traditional hypnotic prescriptions, including aldehydes, benzodiazepines, piperidinedione derivatives, and melatonin receptor agonists, decreased during 2000–2010 in the annual wholesale database compiled by the Finnish Medicine Agency account of total national drug sales [16]. Ford et al. reported that the number of outpatients who visited for sleep problems increased significantly, and prescribed sleep medication also increased rapidly during 1999–2010 in the United States [17]. The aims of this study were to investigate the trend in sedative–hypnotic prescriptions during 2011–2015 in Korea. We hypothesized that the sedative–hypnotic prescriptions would increase with time, considering the previously studied sedative–hypnotic prescription trends.

Therefore, we evaluated the actual prescription trends for hypnotics using representative data of the entire Korean population. Because insomnia prevalence differs according

to gender and the side effects of sedative–hypnotics vary with age [18, 19], we examined the prescription trends in different hypnotic groups, age groups, and genders.

Methods

Setting

It is necessary to understand Korea's health insurance to understand the prescription trends for sedative–hypnotics in Korea. Korean National Health Insurance covers approximately 98% of the total population, and the Health Insurance Review and Assessment (HIRA) service database contains patient diagnoses, treatments, procedures, surgical histories, and prescription drug information [20]. HIRA data are generated when healthcare service providers submit a claim to be reimbursed for a service provided.

Study population

We used data from the 2011–2015 HIRA service of the Republic of Korea to evaluate prescriptions of pre-defined "sedative–hypnotics". We used information of the entire population in the HIRA claims database. Sedative–hypnotic prescriptions from hospital records, including both inpatient and outpatient clinics, were analyzed in the HIRA database regardless of the prescribing department. Prescriptions from community healthcare centers were included, amounting to 38,843,800 prescriptions of sedative–hypnotics. A subsample of patients with insomnia was defined with the data from subjects assigned diagnostic codes F51.0 (nonorganic insomnia) or G47.0 (insomnia) using the Korean Standard Classification of Diseases, Sixth Revision based on the International Classification of Diseases, Tenth Revision.

Assessment of medication use

Psychiatrists in Korea selected antidepressants, antipsychotics, and benzodiazepine with sedative effects to treat patients with insomnia. The sedative–hypnotics were categorized as (1) "benzodiazepines" (short-acting: triazolam, etizolam, and mexazolam; intermediate-acting: clonazepam, alprazolam, bromazepam, clotiazepam, and lorazepam; and long-acting: flunitrazepam, flurazepam, clobazam, clorazepate dipotassium, and diazepam), (2) "non-benzodiazepines" (zolpidem and zolpidem tartrate), (3) "antidepressants" (trazodone, amitriptyline, nortriptyline, and a low-dose formulation of mirtazapine), and (4) "antipsychotics" (low-dose formulation of quetiapine and chlorpromazine). A list of ATC codes for these drugs is provided in Electronic Supplementary Material (Supplementary Table S1).

We calculated the frequency of prescriptions issued over each 6-month period and divided by the mid-year population number to determine the time trends during 2011–2015. We initially grouped the individual medications by generic name, and the total number of prescriptions was calculated from January 2011 to June 2015. A subgroup analysis was performed according to age, group, and sex.

Statistical analysis

We plotted the annual total number of sedative–hypnotic prescriptions in the entire population and stratified by sex and age group. To assess the prescription trend in the insomnia patient subgroups, the number of total prescriptions was divided by the mid-year population of each half year and the trend was tested by linear regression. The mid-year population between 2011 and 2015 was obtained from the Korean statistics office [21]. Results of individual hypnotic prescriptions among insomnia patients were ranked and plotted separately by sex. We also calculated the monthly percent change in the number of prescriptions by medication group among insomnia patients using the Joinpoint Regression Program (v. 4.4.0.0; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, MD, USA) to distinguish the actual increase in the number of prescriptions in each subgroup. Subgroup analyses were conducted by sex and age group.

Results

Sedative–hypnotics prescriptions

Figure 1 shows the annual number of prescriptions for sedative–hypnotics according to the sex of subjects in the study population during 2011–2015. In the study population, the number of benzodiazepine prescriptions exceeded all other sedative–hypnotics in both men and women, and the absolute number of prescriptions tended to increase with time (Fig. 1). Intermediate-acting benzodiazepines were the most frequently prescribed drugs in men and women. Antipsychotics had the lowest frequency of prescriptions in women. The difference in prescription numbers between benzodiazepines and other sedative–hypnotics tended to increase during 2011–2015. The number of antipsychotic prescriptions increased by 224% in men (55,354 in 2011 and 124,105 in 2015) and 221% in women when the first half of 2015 was compared with the first half of 2011 (67,334 in 2011 and 148,988 in 2015) (Fig. 1).

Prescriptions for insomnia patients

All types of sedative–hypnotic prescriptions for insomnia patients increased significantly during the study period (all P trend < 0.001) (Table 1). In the first half of 2011, the total number of prescriptions was 2,568,249 and the number of prescriptions increased gradually. Up to 4,410,804 prescriptions were filed in the first half of 2015, which was a 170% increase compared with those in the first half of 2011. The number of prescribed sedative–hypnotics for women was higher than that for men. Among women, 1,592,452 prescriptions for sedative–hypnotics were issued in the first half of 2011, and the number of prescriptions increased rapidly to 2,690,416 prescriptions issued in the first half of 2015. Among men, 975,797 prescriptions were issued for sedative–hypnotics in the first half of 2011, which increased to 1,720,388 issued in the first half of 2015.

Table 2 shows the most commonly prescribed sedative–hypnotics for patients with insomnia. Zolpidem was the most commonly used medication in male and female patients with insomnia. Prescriptions for zolpidem were 1.6 times more frequent in women than in men. Lorazepam was the second most frequently prescribed insomnia drug in men, and the fourth most frequent in women.

Trends in prescriptions by age

We investigated the number of prescriptions by age group (Fig. 2). Benzodiazepines were used more frequently as age increased. The number of prescriptions of benzodiazepines, non-benzodiazepine hypnotics, and antidepressants increased with age in men. The number of prescriptions for antipsychotics increased until the age of 59 years, but decreased after age of 60 years in men. In women, prescriptions for all medications increased until the 60s, but decreased slightly after 70 years of age.

The prevalence of prescriptions for sedative–hypnotics in men < 30 years and > 70 years differed by 3–16 fold. Specifically, the prevalence of prescriptions for short-acting benzodiazepines and antidepressants was 16 times higher in men > 70 years old compared with men < 30 years old.

Monthly percent change in prescriptions by sedative–hypnotic type

A monthly percent change analysis of sedative–hypnotic type revealed a significant increase in prescriptions in all medication groups for all ages between 2011 and 2015 (Table 3) ($p < 0.05$). Specifically, prescriptions for antidepressants increased by 0.78% and 0.80% in men and women, respectively. Antipsychotics also increased significantly by 1.36% and 1.40% in men and women,
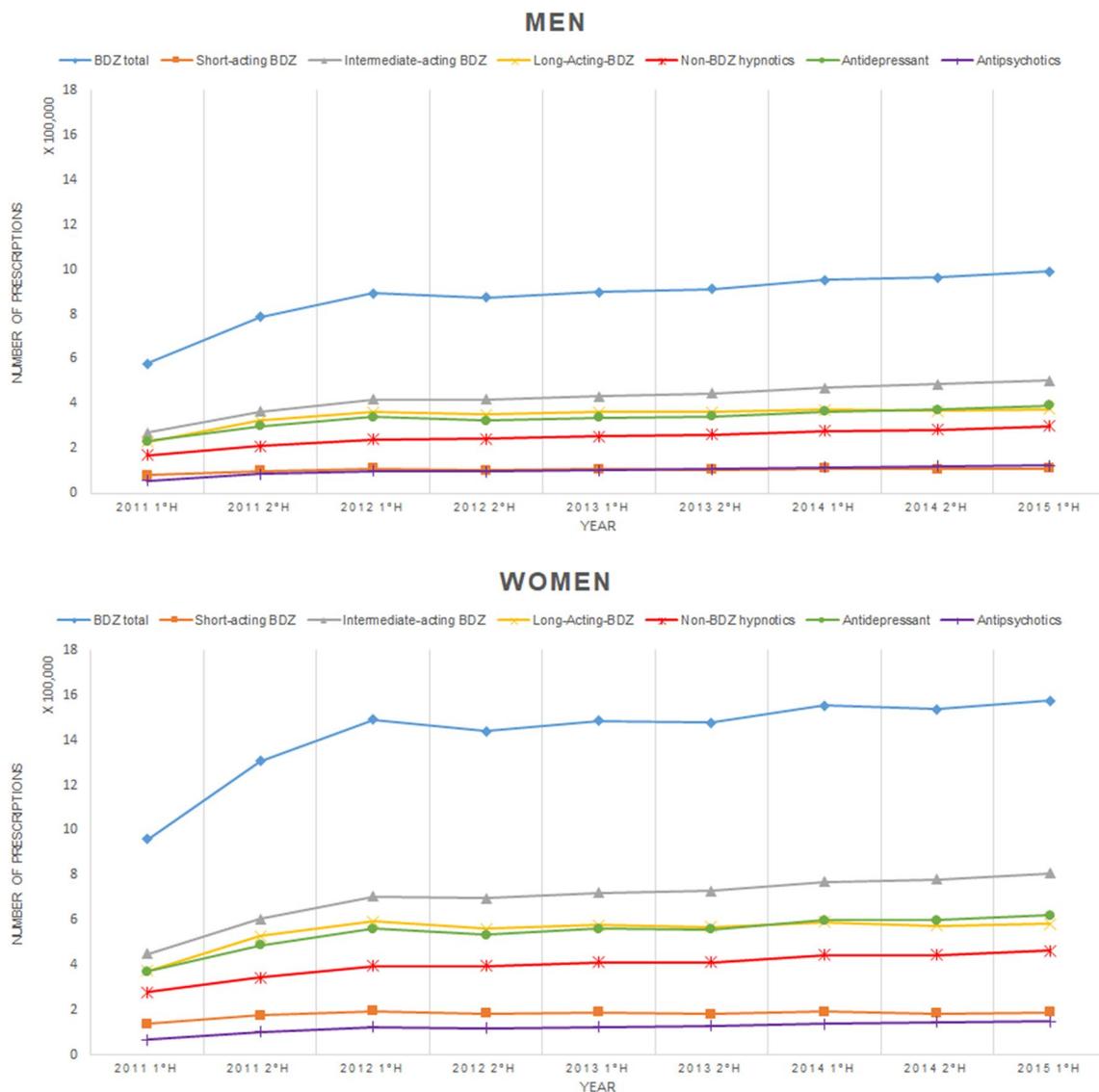
Fig. 1 Annual number of prescriptions for sedative–hypnotics in the entire Korean population according to sex, Health Insurance Review and Assessment Service, 2011–2015. Sedative–hypnotics were categorized as benzodiazepines (BDZ; short-acting, intermediate-acting, and long-acting), non-benzodiazepines (zolpidem and zolpidem tartrate), antidepressants (trazodone, amitriptyline, nortriptyline, and a low-dose formulation of mirtazapine), and antipsychotics. Analysis by year was divided into the first half and the second half

respectively ($p < 0.05$). The subgroup analysis according to age showed that antipsychotic prescriptions increased significantly by 0.21% in men in the 50–59-year range and by 0.20% in those > 70 years (both $p < 0.05$). Antipsychotic prescriptions increased significantly by 0.19% and 0.20% in women with insomnia aged 50–59 years and > 70 years, respectively ($p < 0.05$). A significant increase of 0.20% in antidepressant use was detected in men aged 30–39 years ($p < 0.05$). In contrast, a significant decrease of 0.04% was observed in short-acting benzodiazepine prescriptions in women aged 18–29 years ($p < 0.05$).

Discussion

Benzodiazepines were the most frequently prescribed medication in the Korean population-based National Health Insurance claims in the HIRA database. Zolpidem was the most widely prescribed medication among patients with insomnia. In addition, the number of benzodiazepine and zolpidem prescriptions increased significantly between 2011 and 2015. Consistent with prior studies that evaluated sedative–hypnotic use, we found an increasing prevalence of overall sedative–hypnotic prescriptions over time.

Table 1 Trends in prescriptions for sedative–hypnotics among patients with insomnia, Health Insurance Review and Assessment Service, 2011–2015

		2011 Jan–June	2011 July–Dec	2012 Jan–June	2012 July–Dec	2013 Jan–June	2013 July–Dec	2014 Jan–June	2014 July–Dec	2015 Jan–June	P trend
Total	No. of total prescriptions	2,568,249	3,439,099	3,937,163	3,829,900	3,975,374	4,006,349	4,237,823	4,261,218	4,410,804	<0.001
	No. of total prescriptions/1000 people/1 year[a]	51.12	68.46	78.03	75.91	78.47	79.08	83.32	83.78	86.42	
Men	No. of total prescriptions	975,797	1,306,875	1,487,880	1,459,675	1,513,257	1,544,258	1,625,524	1,654,445	1,720,388	<0.001
	No. of total prescriptions/1000 people/1 year[a]	38.82	51.99	58.96	57.84	59.74	60.97	63.95	65.09	67.47	
Women	No. of total prescriptions	1,592,452	2,132,224	2,449,283	2,370,225	2,462,117	2,462,091	2,612,299	2,606,773	2,690,416	<0.001
	No. of total prescriptions/1000 people/1 year[a]	63.45	84.96	97.12	93.99	97.19	97.19	102.67	102.45	105.33	

[a] The number of prescriptions was divided by the size of the mid-year population, and the first half of 2015 was divided into the June 2015 population. Trends in prescriptions were assessed by linear regression

In the United States, Ford et al. reported a large increase in prescriptions for non-benzodiazepine sleep medications (~ 350%), benzodiazepine receptor agonists (~ 430%), and any sleep medication (~ 200%) from 1999 to 2010 in the National Ambulatory Medical Care Survey [17]. In the current study, all types of sedative–hypnotic prescriptions increased by 170% in the first half of 2015 compared with the first half of 2011.

Bertisch et al. analyzed prescribed insomnia medication trends for 1999–2010 using data from the National Health and Nutrition Examination Survey [22]. They found that the prevalence of all medications commonly used to treat insomnia increased significantly from 2.0% during 1999–2000 to 3.5% during 2009–2010 in 906 participants. That study was different from our study as it was conducted through surveys about prescription medications rather than objective data at the national level as in our study. They reported that 3% of adults > 20 years of age took medications used commonly for insomnia over the past month; Z-medications, such as eszopiclone, zaleplon, and zolpidem, were the most commonly used. The strongest independent predictor of insomnia medication use was increased age, female sex, and higher income. Pillai et al. reported that the use of over-the-counter (OTC) medications as sleep aids was higher in females than that in males in a cohort study of patients with insomnia [23]. Of 649 participants with insomnia, the prevalence of OTC medication use for sleeping purposes was 29.6% in women and 19.6% in men. We also found that older women had an increased likelihood of receiving a sedative–hypnotic prescription compared with men.

In the entire population and in patients with insomnia, the number of prescriptions increased remarkably during 2011–2012. It is possible that the number of patients with insomnia actually increased during this period. In addition, the insurance policy was changed in March 2011, and the insomnia diagnosis (F51, G47) must be registered to enable insurance benefits for zolpidem. Because this study limited the subgroup analysis of patients with insomnia diagnoses, this change in insurance policy may have affected the rapidly increasing zolpidem prescription rate during 2011–2012. However, it was significant that prescriptions increased steadily even after 2012.

In the first half of 2015, antipsychotic prescriptions for males increased 224% (55,354 in 2011 and 124,105 in 2015), and those for females increased 221% (67,334 in 2011 and 148,988 in 2015), compared with the first half of 2011. A similar result was reported in Finnish data, as Kronholm et al. found that use of quetiapine for its sedative effect increased from 2002 to 2010. In another cross-sectional prescriber survey study, sedation was given as one reason among others in 441 participants (20.1%) and as the sole reason in 266 participants (12.1%) when second-generation antipsychotics were prescribed; quetiapine was the

Table 2 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	Nortryptiline HCl	160,523	Zolpidem tartrate	173,767
16	Zolpidem tartrate	131,805		

Fig. 2 Prevalence of grouped sedative–hypnotic prescriptions by age group for the entire Korean population, Health Insurance Review and Assessment Service, 2011–2015. Prevalence was calculated as the number of prescriptions/1000 population × mid-year population of that period (June 2013). BDZ: benzodiazepine
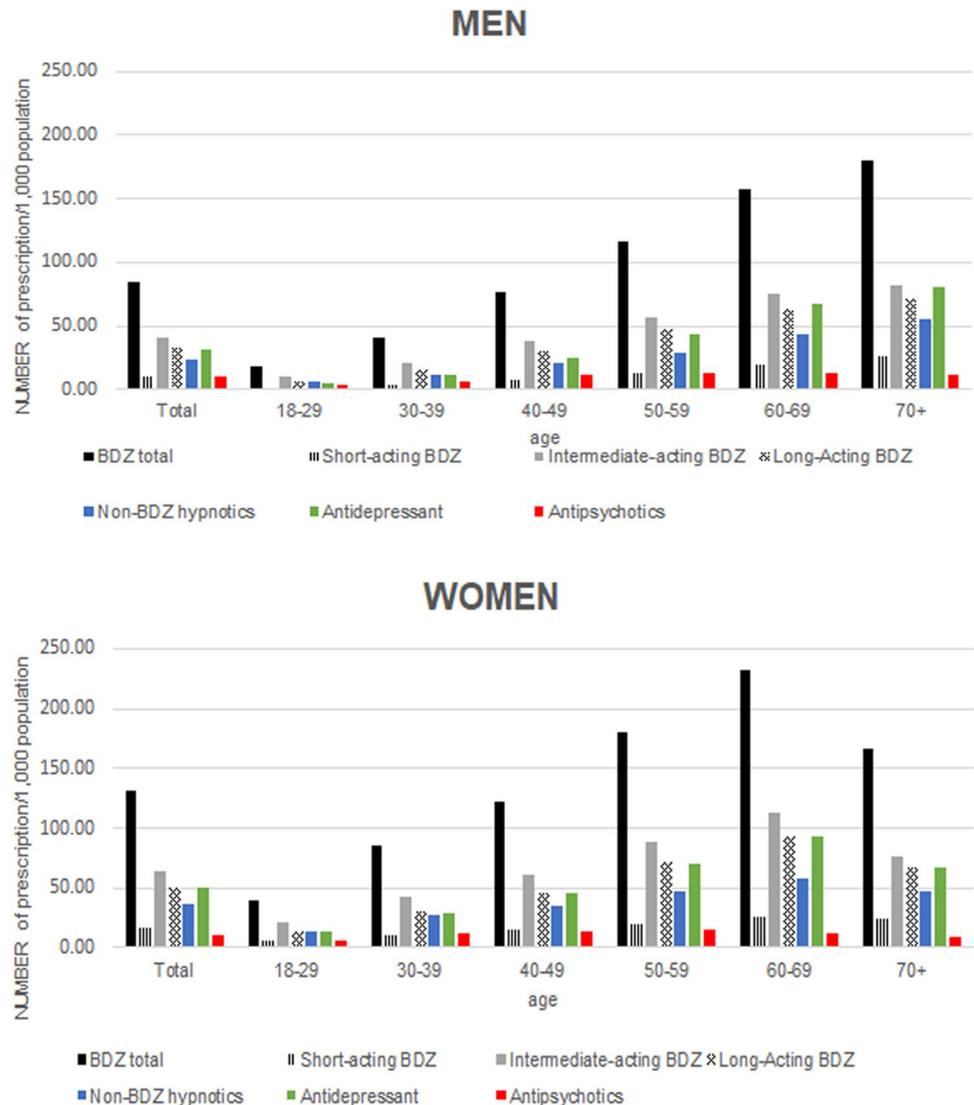
Table 3 Monthly percent change in prescriptions stratified by age among patients with insomnia, Health Insurance Review and Assessment Service, 2011–2015

	Overall	Age (years)					
		18–29	30–39	40–49	50–59	60–69	70+
Men							
BDZ hypnotics							
Short-acting BDZ	0.41*	0.02	0	0.01	0.05	0.05	0.09
Intermediate-acting BDZ	1.03*	0.1	0.1	0.1	0.13	0.12	0.14
Long-acting BDZ	0.70*	0.05	0.06	0.07	0.1	0.07	0.09
Non-BDZ hypnotics	0.98*	0.06	0.09	0.1	0.13	0.12	0.13
Antidepressant	0.78*	0.07	0.2*	0.06	0.1	0.09	0.11
Antipsychotics	1.36*	NA	0.1	NA	0.21*	0.19	0.2*
Women							
BDZ hypnotics							
Short-acting BDZ	0.38*	− 0.04*	0.02	0.03	0.06	0.05	0.08
Intermediate-acting BDZ	0.98*	0.05	0.09	0.1	0.12	0.12	0.14
Long-acting BDZ	0.62*	0.01	0.06	0.06	0.09	0.08	0.08
Non-BDZ hypnotics	0.87*	0.02	0.08	0.09	0.12	0.12	0.12
Antidepressants	0.80*	0.01	0.07	0.08	0.1	0.1	0.12
Antipsychotics	1.40*	0.07	0.13	0.15	0.19*	0.2	0.2*

BDZ benzodiazepine

*p value < 0.05

most frequently used drug in this class [24]. In a study of off-label prescriptions for low-dose quetiapine (≤ 100 mg/day) for insomnia in the Netherlands, a significant increase in the number of quetiapine prescriptions was observed between 1999 and 2012 [25].

A marked increase in the use of the antidepressant mirtazapine was reported by a Finnish study. Direct comparisons are difficult because our results were based on person-years, but we found a similar increasing trend in antidepressant prescriptions for men in their 30s. In the Finnish study, the prescriptions for traditional sedative–hypnotics, including benzodiazepines and barbiturates, decreased, but in our study, prescriptions for sedative–hypnotics, including benzodiazepine, increased. This is an important point, as some people may abuse these medications. Official guidelines are available in Finland to treat insomnia in clinical practice [26]. According to these insomnia guidelines, the cognitive behavioral method is the first-line option, and the use of hypnotics for acute insomnia should not exceed 2 weeks. Non-pharmacological treatments, such as cognitive behavioral therapy, are not covered by insurance in Korea; therefore, cognitive behavioral therapy is not often tried in Korean patients with insomnia. Non-benzodiazepine sedative–hypnotics used in other countries, such as ramelteon and eszopiclone, have not been introduced in Korea, so the probability that benzodiazepines would be prescribed is higher. In addition, comorbidity with other psychiatric disorders, such as an anxiety or a mood disorder, must be considered, as a sedative–hypnotics may have been prescribed to treat these disorders. It is also possible that the overall number of sedative–hypnotic prescriptions increased as public acceptance of sedative–hypnotics increased. In research on the public awareness of sleep disorders in Korea, the most popular search engine returned higher scores for "insomnia" than for "dementia" [27]. As the public's awareness of insomnia increases, it is possible that interest in sedative–hypnotics has also increased.

The overall sedative–hypnotic prescription rate increased significantly with age, and the antipsychotic prescription rate has also increased in the elderly population > 70 years. These findings suggest that a sensate sedative–hypnotic monitoring system is particularly warranted among the vulnerable elderly population.

A limitation of this study is that we used data based on insurance diagnostic codes, which may differ from the actual diagnosis (i.e., the diagnostic code may not be reliable). We evaluated the number of prescriptions, but we do not know if or when the patients actually took the prescribed medication. There is also a lack of information on the actual number of patients prescribed, the duration of the prescriptions, and the prescribed interval. Further studies will need to analyze prescription data, including specific information on individual drug use patterns, such as the prescribed interval and actual use.

Despite this shortcoming, our analysis included close to the entire population of Korea, and we conducted a subgroup analysis by age, sex, and medication group. Investigating time trends in sedative–hypnotics is important to identify the potential risks of sedative–hypnotics and monitor the use of sedative–hypnotics at the national level.

Conclusions

Zolpidem was the most frequently prescribed drug for treating insomnia, and the total number of sedative–hypnotic prescriptions increased significantly during 2011–2015, among patients with insomnia and the entire population. Prescriptions for antipsychotics and antidepressants tended to increase during 2011–2015. In the United States and Finland, prescriptions for traditional sedative–hypnotics, such as benzodiazepines, are declining, whereas they are increasing in Korea. These results will be a reference for more robust monitoring of sedative–hypnotic use in Korea.

Compliance with ethical standards

Conflict of interest On behalf of all of the authors, the corresponding author states that there are no conflicts of interest.

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